

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

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1 **Title Page**

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

4

5 **Short title:**

6 Inflammatory Bowel Disease risk in associated skin disorders

7

8 **Summary:**

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

12

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40 **Author Contributions**

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

44 **Ethics**

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

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

51

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53

54 **Conflict of Interest:** KN reports a grant from AstraZeneca, and personal fees from Sanofi, MSD and  
55 Boehringer Ingelheim, outside the submitted work. NT reports grants from Dr. Falk, MSD, AstraZeneca  
56 and Pfizer. Other authors have no conflicts of interest to declare.

57

58 **Data Availability statement:**

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

61

62 **Abbreviations:**

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

## 66 Abstract

### 67 Introduction

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

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

### 73 Methods

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

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

### 79 Results

80 7,447 subjects with D-EIMs (74% female, median age 38 (IQR 24-65) years) were matched to 29,297  
81 subjects without D-EIMs. 131 (1.8%) subsequent IBD diagnoses were observed in those with D-EIMS  
82 compared to 65 (0.2%) in those without. Median time to IBD diagnosis was 205 (IQR 44-661) days in  
83 those with D-EIMs and 1,594 (693-2,841) in those without. The adjusted HR for later diagnosis of IBD  
84 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  
85 disease 8.54 (5.74-12.70), $p<0.001$ . Subjects with psoriasis had a 34% increased risk of a subsequent  
86 IBD diagnosis compared to matched controls (1.34 (1.20-1.51),  $p<0.001$ ).

87 4,043 subjects with an incident EN diagnosis were included in the prediction model cohort with 87  
88 (2.2%) diagnosed with IBD within 3-years. The model had a bias-corrected c-statistic of 0.82 (95% CI  
89 0.78-0.86).

### 90 Conclusions

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

## 94 Introduction

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

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

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

121

## 122 Materials and methods

### 123 Data source

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

### 133 Study Design

#### 134 Cohort study

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

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

149 Subjects were followed from their index date until the first of the following events (exit date): death;  
150 subject left the practice; last data collection from their practice; study end date (25<sup>th</sup> September  
151 2019); diagnosed with CD or UC. Subjects with a code for both UC and CD were allocated to one  
152 based on the frequency of coding. For those with equal coding frequency, the earliest diagnosis date  
153 and the latest IBD subtype was used.

#### 154 Prediction model

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

#### 158 Validation

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

164

#### 165 Statistical analysis

##### 166 Cohort study

167 The time from index date to a later diagnosis of IBD in those with and without a baseline D-EIM were  
168 presented as median time to combined IBD, UC and CD diagnoses with accompanying interquartile  
169 range (IQR). Log-rank tests were used to compare time to IBD diagnosis between those with  
170 (exposed) and without (unexposed) D-EIMs. Cox proportional hazard models, with time to  
171 subsequent diagnosis of IBD as the time-metric, were produced to assess the adjusted hazard ratio



172 (aHR) of IBD diagnoses in participants with D-EIM compared to matched unexposed subjects.  
173 Adjusted HRs were produced for IBD (combined), UC and CD outcomes. For EN and PG, aHRs were  
174 produced only for combined IBD diagnoses due to relatively few IBD diagnoses in these secondary  
175 analyses. For psoriasis, aHRs were produced for IBD (combined), UC and CD outcomes. Hazard ratios  
176 were adjusted for age at index; sex; smoking status; body mass index (BMI); Townsend level of  
177 deprivation (quintiles); Charlson comorbidity score; within 6-month of EIM diagnosis (prior to an IBD  
178 diagnosis) coding of anaemia (<11.9g/dL for females and <12.9g/dL for males), abdominal pain,  
179 loperamide prescription, diarrhoea or lower gastrointestinal bleeding. Smoking status was  
180 dichotomised into current smokers and non-smokers with missing data for smoking status  
181 considered non-smokers, a method that has been previously validated<sup>23</sup>. Missing data for Townsend  
182 deprivation were considered a separate category. The proportional hazards assumption was  
183 assessed using log-log plots and the Schoenfeld residuals test. Cumulative incidence plots were  
184 produced to demonstrate the cumulative risk of IBD diagnosis over time.

185

#### 186 Prediction model

187 Multivariable logistic regression was used to establish a prediction model for IBD diagnosis within 3-  
188 years in subjects presenting with a new diagnosis of EN. Only those with an IBD diagnosis within 3-  
189 years or those who had a minimum of 3-years follow up were included in the development cohort.  
190 Backwards stepwise elimination was used to select variables with an elimination alpha-to-remove p-  
191 value of 0.20. Sex, age (categorical), and smoking status were included due to their clinical  
192 importance. Candidate predictors recorded within 6 months of EN diagnosis included the following:  
193 anaemia, abdominal pain, weight loss, lower gastrointestinal bleeding, loperamide prescription and  
194 diarrhoea (prior to an IBD diagnosis). A receiver operating characteristic (ROC) curve with  
195 accompanying c-statistic was used to assess model discrimination; calibration was assessed using the  
196 Hosmer-Lemeshow test for goodness of fit. A complete case analysis was performed where subjects  
197 with missing values were excluded. Of explored predictors, only BMI had missing values. Subjects  
198 without BMI values were therefore excluded for the complete case analysis. To further assess

199 missingness, multiple imputation of missing BMI values was performed, producing 10 imputed  
200 datasets. The models were well calibrated in both the complete case analysis and when subjects  
201 with missing BMI values were also included. Multiple imputation had minimal impact upon the  
202 discrimination of the model as assessed by the AUROC c-statistic. All subjects were therefore  
203 included in the prediction model development with a missing category for BMI included. Internal  
204 validation of the prediction model was performed through bootstrapping by resampling the dataset  
205 (with replacement) 200 times and comparing the resulting average of the area under the ROC curve  
206 from the bootstrap samples to the original model.

207 Analyses were performed using Stata version 16.0 and p-values <0.05 were considered statistically  
208 significant<sup>24</sup>.

## 209 Results

### 210 Study subjects

211 Following exclusions (Figure 1), 7,447 subjects with D-EIMs were identified: 74% female and a  
212 median age of 38 (IQR 24-65) years. D-EIM subjects were age, sex and general practice-matched to  
213 29,297 subjects without D-EIMs. The median follow-up time for subjects was five and half years,  
214 with a total of 47,377 person-years (py) of follow-up in D-EIM subjects and 185,889 py in those  
215 without D-EIMs. Cohort characteristics are shown in Table 1.

### 216 Risk of inflammatory bowel disease in subjects with dermatological conditions

217 Among D-EIM subjects, 131 (1.8%) diagnoses of IBD (33 UC and 98 CD) were observed compared to  
218 65 (0.2%) (30 UC and 35 CD) in matched subjects without D-EIMs. The median time to subsequent  
219 diagnosis of IBD from D-EIM diagnosis (index date) was 205 (IQR 44-661) days compared to 1,594  
220 (693-2,841) days for subjects without D-EIMs. For UC the median time to diagnosis was 231 (43-  
221 1,230) days and 1,544 (551-2359) days respectively, and for CD 159 (47-598) days and 1,690 (915-  
222 2,962) days respectively. For IBD, UC and CD, the log-rank test p was <0.001. Following adjustment,  
223 the hazard ratio for an IBD diagnosis in D-EIM subjects compared to matched subjects without D-  
224 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  
225 8.54 (5.74-12.70), p<0.001 (Table 2; full models are shown in Appendix 3). Figure 2 shows the  
226 cumulative incidence plot for IBD diagnoses in subjects with D-EIMs compared to those without.

### 227 Risk of inflammatory bowel disease in erythema nodosum and pyoderma 228 gangrenosum

229 The characteristics of D-EIM and matched subjects without D-EIM in these subgroup analyses  
230 together with full Cox models are shown in Appendices 4 and 5 respectively. 6,329 subjects with  
231 incident EN were identified with 5,917 remaining once tuberculosis, sarcoidosis and sulfasalazine use  
232 had been removed. 327 individuals with pre-existing IBD were then excluded (Figure 1). Following  
233 exclusions, 5,590 EN subjects (79% female, median age 38 (23-52)) were matched to 22,039 subjects  
234 without EN, contributing 36,324 and 139,304 py of follow-up, respectively. 104 (1.9%) IBD diagnoses  
235 (23 UC and 81 CD) were observed in subjects with EN and 53 (0.2%) (23 UC and 32 CD) in those

236 without EN. Median time to IBD diagnosis was 151 (42-615) days for EN subjects compared to 1,618  
237 (728-2,895) days for those without EN (log-rank test  $p < 0.001$ ). For UC the median time to diagnosis  
238 was 224 (28-1,230) days for EN subjects and 1,620 (1079-2,841) days for those without, and for CD,  
239 the median time to a diagnosis was 133 (44-552) days for subjects with EN and 1,549 (460-3,315)  
240 days for those without EN (log-rank test  $p < 0.001$  for both CD and UC). The adjusted hazard ratio for  
241 an IBD diagnosis in subjects with EN compared to matched subjects without EN was 6.49 (4.62-9.11),  
242  $p < 0.001$  (Table 2).

243 In the PG study, 1,143 subjects with incident PG were identified prior to exclusions, with 166 having  
244 a pre-existing IBD diagnosis (Figure 1). In the PG subgroup analysis, 977 subjects with PG (60%  
245 female and median age 57 (39-73) years) were matched to 3,852 subjects without PG, contributing  
246 5,301 and 23,963 py of follow-up time, respectively. 21 (2.1%) IBD diagnoses (10 UC and 11 CD) were  
247 observed in subjects with PG compared to 11 (0.3%) (6 UC and 5 CD) in those without PG. Median  
248 time to IBD diagnosis was 392 (127-1,323) days for subjects with PG compared to 1,890 (1,111-  
249 4,626) days for those without PG (log-rank test  $p < 0.001$ ). For UC the median time to diagnosis was  
250 405 (77-3,327) days for PG subjects and 2,816 (1,426-4,146) days for those without PG, and for CD  
251 the median time to a diagnosis was 282 (101-946) days for subjects with PG and 2,529 (1,890-5,948)  
252 days for those without PG (log-rank test  $p < 0.001$  for both CD and UC). The adjusted hazard ratio for  
253 an IBD diagnosis in PG was 6.27 (2.84-13.86),  $p < 0.001$  (Table 2).

#### 254 [Risk of inflammatory bowel disease in psoriasis](#)

255 In the psoriasis study, 121,195 subjects with incident psoriasis and without a pre-existing IBD  
256 diagnosis were identified (53% female and median age 45 (29-61) years). Psoriasis subjects were  
257 matched to 476,281 controls by age and sex; subjects with psoriasis and matched controls  
258 contributed 759,831 and 2,895,686 py of follow-up time, respectively. Characteristics of subjects  
259 with and matched subjects without psoriasis are shown in Appendix 6. 407 (0.3%) IBD diagnoses  
260 (398 UC and 178 CD) were observed in subjects with psoriasis compared to 1090 (0.2%) (692 UC and  
261 398 CD) in those without psoriasis. Median time to IBD diagnosis was 1,502 (604-2,646) days for

262 subjects with psoriasis compared to 1,366 (623-4,536) days for those without psoriasis. For UC the  
263 median time to diagnosis was 1,378 (558-2,410) days for psoriasis subjects and 1,315 (588-2,462)  
264 days for those without psoriasis, and for CD the median time to a diagnosis was 1,743 (626-2,905)  
265 days for subjects with psoriasis and 1,481 (721-2,583) days for those without psoriasis (log-rank tests  
266 for IBD and CD were  $p < 0.001$ , and for UC  $p = 0.002$ ). The aHR for an IBD diagnosis in psoriasis was  
267 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),  
268  $p < 0.001$ ) (Table 2).

### 269 Prediction model

270 5,590 EN subjects were identified with 4,043 eligible for inclusion in the prediction model  
271 development cohort based on sufficient follow up time or an IBD diagnosis within 3-years of EN  
272 diagnosis. 87 (2.2%) had the outcome of an IBD diagnoses within 3-years (79% CD). Characteristics of  
273 EN subjects with and without an IBD diagnosis by 3-years after EN diagnosis are shown in Table 3.  
274 Those with an IBD diagnosis were younger (median age 25 (IQR 19-35) and 37 (24-52) years  
275 respectively,  $p < 0.001$ ) but no significant difference was seen by sex between the groups,  $p = 0.384$ .  
276 Smoking was more common in IBD subjects though not significant at the 5% level (23% compared to  
277 16%,  $p = 0.067$ ) and there was a higher proportion within the lowest body mass index category ( $< 25$   
278  $\text{kg/m}^2$ ) – 48% compared to 31% in those not diagnosed with IBD,  $p = 0.003$ . When those diagnosed  
279 with IBD within 6-months of an EN diagnosis (64%) were compared to those diagnosed with IBD later  
280 than 6-months there was no statistical difference between the two groups for coding of anaemia,  
281 abdominal pain and diarrhoea.

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

288 model fit. The receiver operating characteristic (ROC) curve, shown in Figure 3, produced an area  
289 under the curve (AUC) c-statistic of 0.83 (0.78-0.87). Following internal validation by bootstrapping,  
290 resampling the dataset 200 times, the mean difference between the original AUC and AUC in each  
291 bootstrap sample was 0.01. This produces a bias-corrected c-statistic value of 0.82 (95%CI 0.78-  
292 0.86).

293 A probability calculator was produced to determine the likelihood of an IBD diagnosis within the EN  
294 cohort using the following examples: 1) A female, 34-year-old, non-smoker with a body mass index  
295 (BMI) of 21 kg/m<sup>2</sup> and a within 6-month history of anaemia and abdominal pain would have a 7%  
296 risk of IBD being diagnosed within 3 years of her EN diagnosis. 2) A male, 17-year-old, current  
297 smoker with a BMI of 24 kg/m<sup>2</sup> and a history of abdominal pain and diarrhoea would have a 43% 3-  
298 year IBD diagnosis risk. 3) A female, 49-year-old, current smoker with a BMI of 30 kg/m<sup>2</sup> and a  
299 history of diarrhoea and abdominal pain would have an 11% risk of IBD diagnosis within 3 years. A  
300 nomogram for the prediction model is shown in appendix 7.

## 301 Discussion

302 In this study, we have shown that subjects with a D-EIM but without a recorded diagnosis of IBD, are  
303 at greater risk of later being diagnosed with IBD than matched subjects without a D-EIM. A  
304 subsequent diagnosis of IBD in those with a new dermatological EIM diagnosis was recorded at a  
305 median of 205 days after D-EIM diagnosis with 50% of cases recorded between 44 and 661 days. A  
306 substantial number of new IBD diagnoses were therefore not made until more than a year following  
307 an EIM diagnosis. Considering dermatological EIMs usually present when bowel disease is active, our  
308 findings might suggest a missed diagnostic opportunity. Although these skin manifestations may  
309 accompany bowel activity, they do not always relate to disease extent or severity<sup>25-27</sup> and as such it  
310 is plausible that symptoms of IBD may not have manifested themselves clinically. That being said, in  
311 the prediction model presented, 55% of participants with EN who were later diagnosed with IBD had  
312 a record of either anaemia, abdominal pain, loperamide prescription, diarrhoea or lower  
313 gastrointestinal bleeding at the time of dermatological EIM diagnosis, compared to only 18% of non-  
314 IBD diagnosed subjects. We found a predominance of CD diagnoses in exposed subjects with EIM,  
315 which is in keeping with previous observations that EIMs are more common in those with CD. This  
316 was also observed, though the numbers were small, in the PG cohort, whereas others have shown  
317 an predominant association with UC in this condition<sup>8,28,29</sup>.

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

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

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

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



351 Aphthous stomatitis (ApS) and Sweet's syndrome (SS) were not studied individually but made up a  
352 significant minority (9% and 3% respectively) of the individuals with dermatological EIMs. ApS is  
353 common, with a fifth of people suffering from these lesions, although diagnostic criteria and  
354 populations studied have resulted in a wide variation in prevalence<sup>38</sup>. ApS is seen in 7-10% of  
355 patients with IBD in observational studies, with CD subjects predominating<sup>8,28</sup>. It is likely that ApS,  
356 especially milder forms, are under-reported. When reviewed separately, only 4 (0.6%) participants  
357 with ApS were later diagnosed with IBD, three quarters of which were CD. Sweet's syndrome  
358 (otherwise known as febrile neutrophilic dermatosis) is a rare condition characterised by fever,  
359 neutrophilia and skin lesions. It may be drug induced, present as a paraneoplastic phenomenon or  
360 be termed "classical" and associated with IBD, streptococcal pharyngitis, pregnancy or may appear  
361 in isolation<sup>32</sup>. Little is known about its prevalence, with the published literature dominated by case  
362 reports, however, it predominantly affects females which was also the case in the present study  
363 (62% female)<sup>39</sup>. Only two (1%) individuals with SS were later diagnosed with IBD. Although their  
364 Charlson comorbidity scores were both 0, making malignant causes less likely, it remains challenging  
365 to comment further on this rare syndrome, other than to say that vigilance for IBD should be  
366 exercised if SS is encountered in the absence of an alternative cause.

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

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

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

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

403 considered in future research. It is clear that delays in the diagnosis of IBD can lead to unfavourable  
404 outcomes with increased hospitalisation, potential exposure to an avoidable surgical risk and  
405 significant costs<sup>14,42,43</sup>.

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

420

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

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547

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

	Exposed subjects with any associated dermatological condition	Controls
<b>Number of subjects</b>	7,447	29,297
<b>Median py of follow-up (IQR)</b>	5.5 (2.3-9.6)	5.4 (2.3-9.5)
<b>Median age (IQR)</b>	38 (24-56)	38 (23-54)
<b>Age category, n (%)</b>		
<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)
<b>Female sex, n (%)</b>	5,533 (74)	21,785 (74)
<b>Townsend deprivation quintile, n (%)</b>		
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)
<b>Charlson comorbidity score, n (%)</b>		
0	4888 (66)	21804 (74)
1	1706 (23)	5361 (18)
>/=2	853 (12)	2132 (7)
<b>Smoking status, n (%)</b>		
current smoker	1152 (15)	5128 (18)
non- smoker	6295 (85)	24169 (82)
<b>Body mass index, n (%)</b>		
<25 kg/m <sup>2</sup>	2340 (31)	9539 (33)
25-30 kg/m <sup>2</sup>	1656 (22)	5991 (20)
>30 kg/m <sup>2</sup>	1498 (20)	4251 (15)
missing	1953 (26)	9516 (32)
<b>Anaemia<sup>†‡</sup>, n (%)</b>	941 (13)	947 (3)
<b>Abdominal pain<sup>†</sup>, n (%)</b>	190 (3)	600 (2)
<b>Lower gastrointestinal bleeding<sup>†</sup>, n (%)</b>	83 (1)	164 (1)
<b>Loperamide prescription<sup>†</sup>, n (%)</b>	139 (2)	212 (1)
<b>Diarrhoea<sup>†</sup>, n (%)</b>	240 (3)	503 (2)

py: person years

IQR: Interquartile range

<sup>†</sup> coded within 6 months of Index date

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



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

	aHR	[95% Conf. Interval]		p-value
<b>Any associated dermatological condition</b>				
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
<b>Erythema Nodosum</b>				
Inflammatory bowel disease	6.49	4.62	9.11	<0.001
<b>Pyoderma Gangrenosum</b>				
Inflammatory bowel disease	6.27	2.84	13.86	<0.001
<b>Psoriasis</b>				
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**

	<b>IBD diagnosis (87)</b>	<b>No IBD diagnosis (5,486)</b>
<b>Median age (IQR)</b>	25 (19-35)	37 (24-52)
<b>Age category, n (%)</b>		
<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)
<b>Female sex, n (%)</b>	72 (79)	3,122 (79)
<b>Smoking status, n (%)</b>		
current smoker	20 (23)	622 (16)
non- smoker	67 (77)	3334 (84)
<b>Body mass index, n (%)</b>		
<25 kg/m <sup>2</sup>	42 (48)	1217 (31)
25-30 kg/m <sup>2</sup>	14 (16)	908 (23)
>30 kg/m <sup>2</sup>	9 (10)	795 (20)
Missing	22 (25)	1036 (26)
<b>Anaemia<sup>†‡</sup>, n (%)</b>	28 (32)	44 (11)
<b>Abdominal pain<sup>†</sup>, n (%)</b>	9 (10)	104 (3)
<b>Lower gastrointestinal bleeding<sup>†</sup>, n (%)</b>	3 (3)	42 (1)
<b>Loperamide prescription<sup>†</sup>, n (%)</b>	7 (8)	55 (1)
<b>Diarrhoea<sup>†</sup>, n (%)</b>	24 (27)	113 (3)

<sup>†</sup> coded within 6 months of Index date

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

IBD: Inflammatory bowel disease

IQR: Interquartile range

552

553 **Table 4. Multivariable logistic regression prediction model**  
 554 **Factors associated with diagnosis of inflammatory bowel disease within 3 years of an erythema**  
 555 **nodosum diagnosis**

	$\beta$ -Coefficient	Odds Ratio	[95% Conf. Interval]		P value
<b>Sex</b>					
Male (reference)		1.00			
Female	0.04	1.04	0.56	1.93	0.90
<b>Age Category</b>					
<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
<b>Smoking Status</b>					
current smoker (reference)		1.00			
non smoker	-0.40	0.67	0.38	1.17	0.16
<b>Body mass index</b>					
<25 kg/m <sup>2</sup> (reference)		1.00			
25-30 kg/m <sup>2</sup>	-0.59	0.55	0.29	1.06	0.07
>30 kg/m <sup>2</sup>	-0.92	0.40	0.19	0.85	0.02
Missing	-0.74	0.48	0.24	0.94	0.03
<b>Anaemia<sup>†‡</sup></b>					
no (reference)		1.00			
yes	1.41	4.11	2.48	6.79	0.00
<b>Abdominal pain<sup>†</sup></b>					
no (reference)		1.00			
yes	0.92	2.51	1.06	5.96	0.04
<b>Diarrhoea<sup>†</sup></b>					
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

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

556

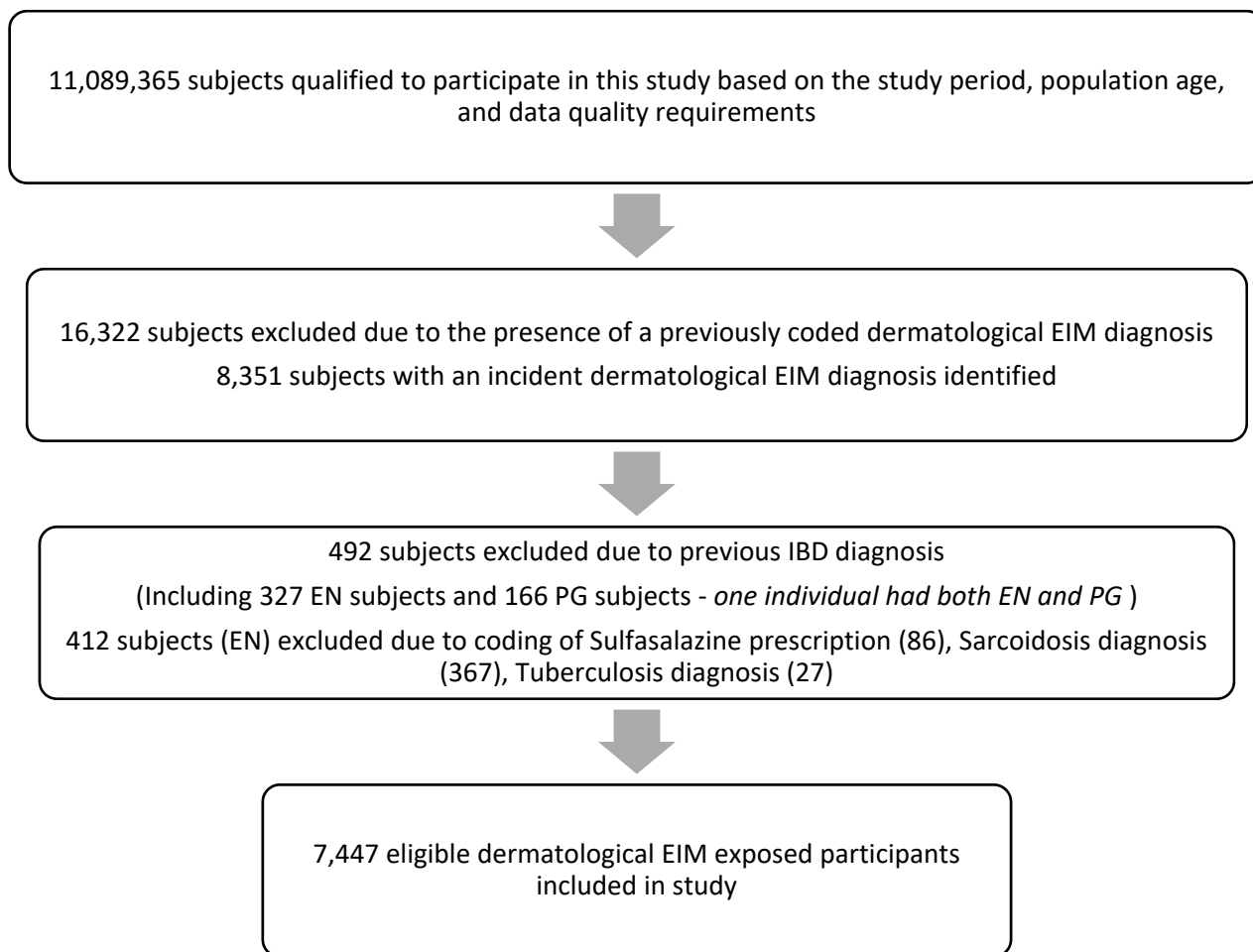


Figure 1. Consort flow chart.

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

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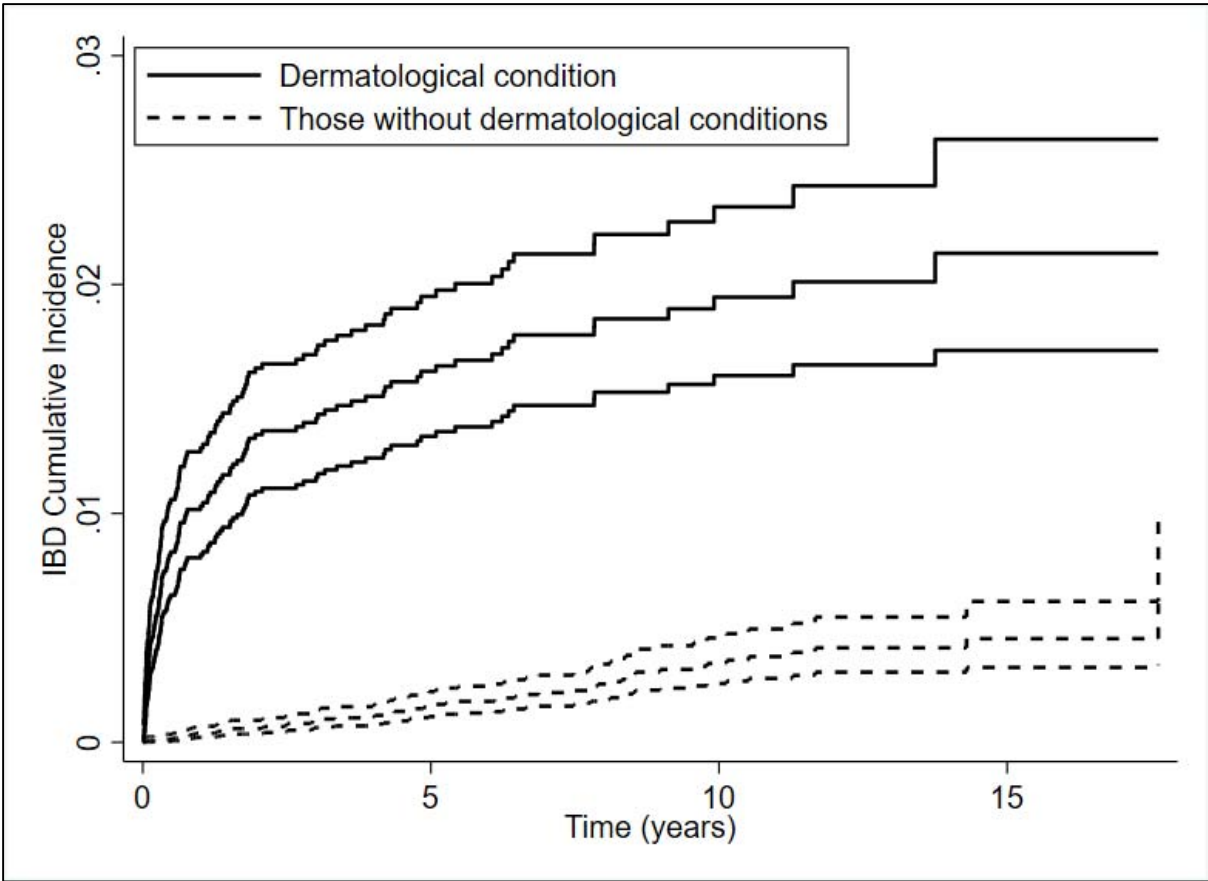


Figure 2. Cumulative incidence (with 95% confidence intervals) of IBD (inflammatory bowel diseases) in subjects with dermatological conditions and those without.

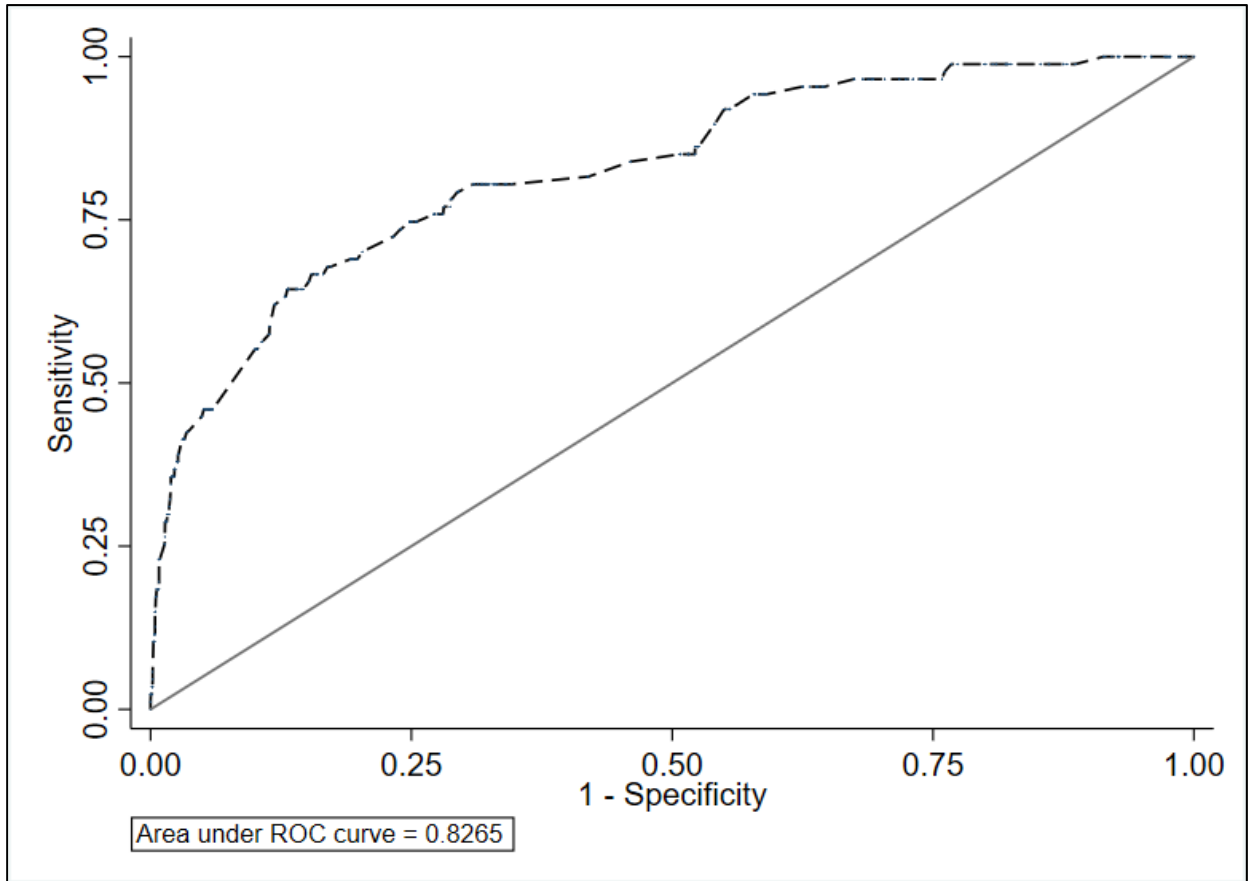


Figure 3. Receiver operating characteristic (ROC) curve of diagnostic ability of prediction model to detect an inflammatory bowel disease diagnosis within 3-years of an erythema nodosum diagnosis.