Risk factors for diagnosis of psoriatic arthritis, psoriasis, rheumatoid arthritis, and ankylosing spondylitis: A set of parallel case-control studies

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ABSTRACT

Objective: To compare potential risk factors for the diagnosis of psoriatic arthritis (PsA), psoriasis, rheumatoid arthritis (RA), and ankylosing spondylitis (AS).

Methods: Four parallel case-control studies were conducted within The Health Improvement Network using data between 1994 and 2015. Patients with PsA, psoriasis, RA, or AS were identified using validated code lists and matched to controls on age, sex, practice, and year. Risk factors were selected in the time prior to diagnosis. Multivariable logistic regression models were constructed for each disease using automated stepwise regression to test potential risk factors.

Results: Patients with incident PsA (N=7,594), psoriasis (N=111,375), RA (N=28,341), and AS (N=3, 253) were identified and matched to 75,930, 1,113,345, 282,226, and 32,530 controls, respectively. Median diagnosis age was 48 (IQR 38-59), 41 (31-54), 43 (31-54), and 60 (48-71), respectively. In multivariable models, there were some shared and some differing risk factors across all 4 diseases: PsA was associated with obesity, pharyngitis, and skin infections; PsA and psoriasis were associated with obesity and moderate alcohol intake; PsA and AS were associated with uveitis; and PsA and RA were associated with preceding gout. Both RA and AS were associated with current smoking, former moderate drinking, anemia, osteoporosis, and inflammatory bowel disease. All shared former or current smoking as a risk factor; statin use was inversely associated with all 4 diseases.

Conclusion: Shared and different risk factors for PsA, psoriasis, RA, and AS were identified. Statin use was inversely associated with all 4 conditions.

Psoriasis is a chronic inflammatory skin disease, and psoriatic arthritis (PsA), rheumatoid arthritis (RA), and axial spondyloarthritis (axSpA) (which includes ankylosing spondylitis (AS)) are chronic forms of inflammatory arthritis.[1-4] Together, these diseases affect up to 2 to 4% of the adult population. Each of these diseases is associated with reduced quality of life, economic burden,[5,6] and comorbidities such as cardiovascular disease.[7,8] The early diagnosis of inflammatory arthritis is critical to improving outcomes.[9] In fact, many patients have joint damage within the first year of onset.[10] Additionally, patients treated earlier in their disease course respond better to therapy and may have overall improved long-term outcomes.[3,11] To achieve earlier disease identification, the development of risk scores to optimize screening methods is essential.

One way to identify patients who may be “high risk” is to identify a set of codes or diagnoses in medical records that are associated with the subsequent diagnoses of PsA, psoriasis, RA, and/or axSpA.[12] Once such codes are established, a sufficient number of codes/diagnoses could trigger a notification to the medical care team through the electronic medical record itself. However, as with any screening test, a set of risk factors that would denote a “high risk” patient must be both sensitive (capable of picking up the majority of patients who are likely to develop the disease) and specific (false positives are minimized so that resources are not dedicated to following individuals who do not have the disease). Given the complexity and heterogeneity of these diseases, achieving an appropriate specificity for such a test is particularly challenging.[13] Therefore, it is crucial to better understand whether risk factors are specific to a rheumatologic disease (i.e., PsA) or more broadly applicable to patients who may develop another inflammatory arthritis or chronic disease (i.e., psoriasis, RA, or axSpA). A first step in this process is to understand what factors are present prior to diagnosis that should raise a clinician’s suspicion that an inflammatory disease is present.

Rheumatic diseases, because of their systemic inflammatory component, are associated with several shared comorbidities.[14] For example, PsA, psoriasis, RA, and axSpA have all been associated with an increased risk for cardiovascular outcomes.[4,15,16] Additionally, these diseases may have some shared genetic factors.[17-20] Likewise, these inflammatory conditions may have shared environmental risk factors. While individual clinical risk factors for the development of inflammatory diseases have been identified, to date, no studies have compared risk factors across multiple inflammatory diseases or examined whether risk factors for PsA are similarly associated with related disorders.[21] This study aimed to compare the strength of the association between selected potential risk factors for the development of PsA, psoriasis, RA, and axSpA and to determine which risk factors are specific for PsA or shared with these other diseases.

Materials and Methods

Study Design: In this study, 4 separate case-control studies were conducted in parallel. Data from 1994 to 2015 were extracted from The Health Improvement Network (THIN), a general practitioner database in the United Kingdom.

Cases and Controls: Cases were identified with at least 1 code for PsA, psoriasis, RA, or AS using validated code lists[22-25] and matched to up to 10 controls from the general population without these diseases based on age (within 2.5 years), sex, practice, and year of diagnosis (controls were required to be in the practice on the diagnosis date and were assigned the same “diagnosis date”). (Note that codes for AS are used as there are not specific codes for axSpA). Diagnosis was established based on the first of these diagnoses for this analysis. We required at least 12 months of follow-up prior to diagnosis. Controls were excluded if they ever developed 1 of the 4 diseases.

Risk Factor Time Period: Potential risk factors were assessed from the latest of time of enrollment into a THIN practice or the practice’s initiation of Vision software until the diagnosis date for cases or the assigned diagnosis date for controls (assigned based on the matched case’s diagnosis date). Unequal follow-

up time was addressed by comparing the matched control's first date of observation to that of the case. If the first date of observation was more than 180 days before that of the case, the control's first date of observation was shortened to fit within the 180-day window. We selected this time window as it would theoretically allow for at least one additional visit given that the match date was when the case had a visit.

Exposures/Potential Risk Factors: Potential risk factors were derived from an extensive code list of over 100 covariates including common comorbidities, infections, trauma, and a more limited number of medications (e.g., statins) that were selected based on a review of the literature or a relationship to other known risk factors (e.g., obesity and hyperlipidemia in the case of statins). These code lists were derived either from validated code lists or, when no prior code list existed, agreement on the code list was established between 2 reviewers. Only hypothesized risk factors with a prevalence of ≥1% were included in the final models and tables. Risk factors that had multiple values (e.g., body mass index, smoking, alcohol) were assessed closest to the end of follow-up. The full list of potential risk factors can be found in **Supplementary Table 1**.

Statistical Analysis: Univariable logistic regression was used to screen risk factors for association with the disease of interest. A multivariable logistic regression model was constructed for each disease using the significant risk factors. Automated stepwise regression was used to arrive at the final model ($p<0.05$ to enter and $p<0.05$ to be removed). All analyses were performed in SAS statistical software. C-statistics are reported with each model. Because of the large number of patients, confidence intervals were small and statistical differences were easily identified. Thus, we denoted in tables those with a stronger association (OR>1.25 or OR<0.8). This cutoff was arbitrarily chosen as it is symmetric, and we felt these were more clinically meaningful risks. In a sensitivity analysis, we ran each stepwise regression model again in each sex separately to qualitatively compare models, looking for a potential effect modification by sex.

Ethical Approval: This study was considered exempt by the University of Pennsylvania Institutional Review Board (Protocol #815997) and approved by the THIN Scientific Review Committee.

Patient and Public Involvement: Patients were not involved in this study. This study was considered exempt by the University of Pennsylvania Institutional Review Board.

Results

In this study, 7,594 incident PsA cases, 111,375 incident psoriasis cases, 28,341 incident RA cases, and 3,253 incident AS cases were identified and matched to 75,930, 1,113,345, 282,226, and 32,530 controls, respectively. The median age at diagnosis was 48.3 (IQR 38-59), 40.7 (31-54), 43.1 (31-54), and 59.9 (48-71), respectively (**Table 1**). Sex was balanced in PsA and psoriasis but more female in RA (68%) and more male in AS (70%). Mean follow-up time ranged from 6.4-7.2 years and was slightly longer among controls (**Table 1**). The prevalence of additional covariates tested is shown in **Supplementary Table 1**.

In univariable logistic regression models by disease, previously identified risk factors for diagnosis of the 4 diseases were replicated including obesity, uveitis, and trauma for PsA; smoking for RA; and inflammatory bowel disease (IBD) and uveitis for AS (**Supplementary Table 2**).

In multivariable analyses, there were some shared and some differing risk factors across all 4 diseases (**Table 2**). PsA was associated with alcohol use (OR 1.67, 95% CI: 1.45-1.93), obesity (1.64, 95% CI: 1.52-1.76), a previous diagnosis of gout (2.19, 95% CI: 1.92-2.50), pharyngitis (1.23, 95% CI: 1.12-1.35), skin infection (1.37, 95% CI: 1.27,1.46), and trauma (1.22, 95% CI: 1.03-1.44). Psoriasis was associated with smoking (OR 1.60, 95% CI: 1.58-1.63), obesity (1.27, 95% CI: 1.25-1.30), alcohol (1.27, 95% CI: 1.23-1.32), prior myocardial infarction (1.43, 95% CI: 1.33-1.53), and trauma to bone (1.29, 95% CI: 1.20-1.39). RA was associated with smoking (OR 1.56, 95% CI: 1.51-1.61), coronary artery disease (1.28, 95% CI: 1.12-1.47), anemia (1.26, 95% CI: 1.20-1.34), a prior diagnosis of gout (1.67, 95% CI: 1.55-1.79), osteoporosis (1.43, 95% CI:

1.32-1.55), IBD (1.56, 95% CI: .1.37-1.78), and trauma to the joint (1.25, 95% CI: 1.18-1.32). Finally, AS was associated with current smoking (OR 1.31, 95% CI: 1.16-1.48), former drinking (1.51, 95% CI: 1.21-1.88), anemia (1.57, 95% CI: 1.25-1.98), osteoporosis (2.93, 95% CI: 2.00-4.29), uveitis (37.93, 95% CI: 27.42-52.58), IBD (5.46, 95% CI: 4.12-7.23), and gastrointestinal infection (1.32, 95% CI: 1.05-1.66).

There were also multiple shared risk factors among certain diseases (**Table 3**). Both PsA and psoriasis diagnoses were associated with obesity and moderate alcohol intake, PsA and AS diagnoses were associated with uveitis, and PsA and RA were associated with preceding gout diagnoses and a history of former moderate alcohol intake. Psoriasis and RA were associated with smoking (current and former) and myocardial infarction. Psoriasis and AS were associated with current smoking. Both RA and AS were associated with current smoking, former moderate drinking, anemia, osteoporosis, and IBD. PsA, psoriasis, and RA shared former smoking as a risk factor, and psoriasis, RA, and AS shared current smoking as a risk factor. Finally, statin use was inversely associated with all 4 diseases.

When models were generated separately by sex, the findings were generally similar although there were some differences (**Supplementary Table 3**). The only factors that were significantly different were that anemia was not statistically associated with AS in women but continued to be associated with AS in men. Finally, current smoking was positively associated with PsA in women but negatively associated in men in this case-control study.

Discussion

In this hypothesis-generating study, we aimed to understand similarities and differences in potential risk factors for PsA, psoriasis, RA, and AS and to better understand the specificity of these risk factors for the individual diseases. We conducted a broad sweep of potential risk factors that have a prevalence of at least 1% in the population, which are common enough to be useful to identify

patients within an electronic medical record setting. Overall, infections, lifestyle factors, and metabolic disease were commonly identified across the conditions, though with differential strength. Additionally, patients with PsA and RA had commonly received a diagnosis for gout or joint trauma prior to receiving a diagnosis of PsA or RA. Finally, statin use was negatively associated with the development of any 1 of the 4 diseases. This set of parallel case-control studies identifies some shared and some differing risk factors between these groups and is among the first studies to compare risk factors between groups.

Lifestyle factors, including smoking and alcohol consumption, were commonly identified as risk factors across different diseases though the strength of association was variable. Smoking has long been associated with RA but has a mixed association with PsA.[17,26] Interestingly, there were sex differences in the impact of smoking on the development of PsA with men less impacted than women. Because smoking status was defined closest to diagnosis date, the differences in whether someone was an ex-smoker or current smoker may be less meaningful. Instead, these data suggest that being a smoker at any point increased the risk for inflammatory disease compared to the general population.

Metabolic risk factors, in particular obesity in psoriasis and PsA, and myocardial infarction in psoriasis and RA, were also identified. Obesity has been consistently identified as a risk factor for psoriatic disease[13] but has not been as consistently associated with RA.[17] Additionally, cardiovascular morbidity and mortality are known to be associated with these systemic inflammatory conditions.[7,8,15] These results suggest these associations exist prior to diagnosis and may further suggest that the inflammatory disease is ongoing well before diagnosis.[27] In addition, the results also suggest negative associations between diabetes and the rheumatological diseases, which is surprising given the comorbidity and autoimmune associations. This relationship may be due to a protective effect of diabetes medications (metformin or thiazolidinediones) directly through decreased inflammation or indirectly through the improvement of lifestyle factors.[28-30] Because many of the cardiometabolic diseases travel

together, there was the potential for collinearity. We explored the insertion and removal of individual risk factors using an alternative modeling approach (purposeful selection) and there was minimal impact on the final models (sensitivity analysis not shown).

Another intriguing finding in this study was the association between statin use and a decreased likelihood of having inflammatory disease. Previous studies have found a decreased risk for the development of RA in statin users.[17,31] Our findings suggest that this decreased risk is not unique to RA but rather extends to other inflammatory conditions. However, further studies are needed to better understand this relationship. It may be that patients who receive statins are different in other ways. For example, they may be receiving better preventative care or may have differences in lifestyle factors.

Infections have long been suspected to be associated with the development of autoimmune disease,[32] and patients often cite infections as triggers for their disease. In our study, we found that pharyngitis and skin infections were significantly associated with the development of PsA, and gastrointestinal infections were associated with the development of AS. These findings are intriguing as prior studies have linked streptococcus and/or staphylococcus infections with the development of psoriasis.[33] Additionally, gastrointestinal infections (in particular shigella, salmonella, and campylobacter) have previously been linked to the development of reactive arthritis.[34] Eder et al. previously identified “infections requiring antibiotics” as a risk factor associated with the development of PsA.[35] Thus, these results not only support previous theories of pathophysiologic triggers related to these diseases but also demonstrate some commonalities between diseases. Finally, interestingly, influenza was negatively associated with the development of inflammatory arthritis. The rationale for this association is not clear. To date, only 1 study to our knowledge has addressed influenza and the risk for RA. In this ecological study, there was not an apparent association.[36] It may be that patients who had influenza had better primary care follow-up or other competing risks, or patients

who were observed more closely received the influenza vaccine and were also more likely to have diagnoses such as 1 of these inflammatory diseases. Cohort studies are needed to better study the association between these infections and the development of inflammatory arthritis or psoriasis.

The results of this study should be considered in light of some limitations. First, the use of an electronic health record, while practical, relies on codes placed by healthcare professionals, meaning codes for certain diagnoses (or risk factors) may be missing and thus there may be misclassification of both the exposures and outcomes.[37] This may have affected the results of the study. We assume this to be non-differential misclassification, meaning that the estimates would be biased toward the null[37] and the misclassification would not lead to excessive Type I error.[38] However, this is also the 'real world' and mimics the way similar algorithms would be built within the medical record to identify patients at increased risk for development of these inflammatory conditions. Furthermore, missed diagnoses of inflammatory arthritis have been demonstrated to be common, at least among patients with PsA and likely the other groups as well, potentially influencing the results of this study.[39] In addition, the definition of incident diagnosis required 1 year of time in the practice prior to diagnosis. It is possible, however, that patients may have had the disease ongoing for a period of time prior to diagnosis. The case-control design is a limitation in that these inflammatory diseases may be ongoing for many years prior to diagnosis, and thus risk factors may represent disease features or signs of disease rather than being causal. In fact, many patients who later were diagnosed with RA or PsA were first given diagnoses of trauma or gout, suggesting the disease was ongoing but not yet labeled correctly well before the diagnosis was finally made. Similarly, AS diagnoses were associated with uveitis and IBD, which are known comorbidities of AS. However, the associations are still valuable in identifying the earliest features of a syndrome and have clinical utility in prompting suspicion for other manifestations.

Despite these limitations, this study also has strengths. This study was a first step toward identifying potential risk factors for all 4 diseases using a wide-based approach to identify all possible associations. Furthermore, the value of this study is strengthened by the use of a large cohort of patients, the previous

validation of codes, the use of a primary care electronic medical record dataset, and the replication of previous risk factors, which support the external validity of these results. Finally, there are relatively few studies that have addressed risk factors for AS.[16]

In summary, the goal of this paper was to identify potential predictors that could be used within an electronic medical record to detect patients who may be at higher risk of developing these inflammatory conditions. We performed a set of parallel case control studies to address this question and identified potential risk factors across inflammatory diseases and some that were different between diseases. Inclusion of all four diseases was important in order to consider whether such algorithms should be designed to identify patients across these conditions or whether individual algorithms for each disease type should be tested. This was a hypothesis generating study; the goal was not to identify causal or etiologic associations (the case-control design also limits this ability). Future cohort studies are needed to further explore the causal effects of the identified predictors. Additionally, these future studies will examine the positive predictive value of combinations of these risk factors in identifying patients with early inflammatory disease. Such combinations of risk factors can then be used in trials to enroll high-risk patients in intervention studies aiming to prevent disease.[40,41]

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Table 1. Baseline Characteristics

		PsA	PsA Controls	Psoriasis	Psoriasis Controls	RA	RA Controls	AS	AS Controls
N		7594	75930	111375	1113345	28341	283226	3253	32530
Age	**Median (IQR)**	48.3 (38.1 - 58.6)	48.2 (38.0 - 58.6)	43.1 (28.3 - 59.7)	43.1 (28.2 - 59.6)	59.9 (48.0 - 71.1)	59.9 (48.0 - 71.0)	40.7 (31.7 – 54.3)	40.8 (31.6 - 54.2)
Sex	**Female N (%)**	3883 (51.1%)	38830 (51.1%)	58155 (52.2%)	581356 (52.2%)	19342 (68.2%)	193342 (68.3%)	979 (30.1%)	9790 (30.1%)
BMI	**Mean (SD)**	29.2 +/- 6.4	27.9 +/- 6.0	27.6 +/- 6.3	27.3 +/- 6.1	27.5 +/- 6.2	27.5 +/- 6.0	27.0 +/- 5.6	27.6 +/- 5.7
Time observed (years)	**Median (IQR)**	7.2 (3.6 - 11.4)	7.7 (4.1 - 11.9)	6.7 (3.3 - 10.6)	7.2 (3.8 - 11.1)	6.4 (3.0 - 10.7)	6.9 (3.5 - 11.2)	6.4 (2.9 - 10.9)	6.9 (3.4 - 11.4)

Controls were matched on age, sex, practice, and calendar year.

Abbreviations: PsA: psoriatic arthritis; RA: rheumatoid arthritis; AS: ankylosing spondyloarthritis; N: number; IQR: interquartile range; BMI: body mass index; SD: standard deviation.

Table 2. Multivariable logistic regression models by disease

	PsA	Psoriasis	RA	AS
Risk Factor	**OR (95_CI)**	**OR (95_CI)**	**OR (95_CI)**	**OR (95_CI)**
Current Smoker	1.01 (0.93, 1.09)	1.45 (1.42, 1.48)**	1.43 (1.37, 1.49)**	1.31 (1.16, 1.48)**
Former Smoker	1.53 (1.43, 1.63)**	1.60 (1.58, 1.63)**	1.56 (1.51, 1.61)**	1.18 (1.06, 1.33)*
Current Drinker	1.24 (1.08, 1.42)*	1.27 (1.23, 1.32)**	0.89 (0.84, 0.95)*	1.14 (0.94, 1.38)
Former Drinker	1.67 (1.45, 1.93)**	1.45 (1.39, 1.50)**	1.36 (1.27, 1.45)**	1.51 (1.21, 1.88)*
Overweight (BMI 25-30)	1.23 (1.14, 1.32)**	1.14 (1.12, 1.17)**	1.01 (0.97, 1.04)	
Obese (BMI>30)	1.64 (1.52, 1.76)**	1.27 (1.25, 1.30)**	1.07 (1.03, 1.11)*	
Hyperlipidemia		1.07 (1.04, 1.10)**		
Hypertension		1.09 (1.07, 1.12)**		
Diabetes	0.89 (0.80, 0.98)	0.85 (0.82, 0.87)**	0.86 (0.82, 0.90)**	0.77 (0.64, 0.94)*
Myocardial Infarction		1.43 (1.33, 1.53)**	1.20 (1.07, 1.35)*	
CAD			1.28 (1.12, 1.47)*	
Statin Use	0.53 (0.48, 0.57)**	0.60 (0.59, 0.62)**	0.46 (0.44, 0.47)**	0.59 (0.50, 0.69)**
Anemia	1.15 (1.01, 1.31)	0.77 (0.74, 0.81)**	1.26 (1.20, 1.34)**	1.57 (1.25, 1.98)**
Acne		0.84 (0.81, 0.87)**		
Anxiety		0.90 (0.87, 0.92)**	0.83 (0.78, 0.87)**	
Depression		0.94 (0.92, 0.96)**		
Cancer	0.65 (0.60, 0.71)**	0.75 (0.73, 0.77)**		0.74 (0.64, 0.86)**
Gout	2.19 (1.92, 2.50)**	1.06 (1.01, 1.12)*	1.67 (1.55, 1.79)**	
Thyroid Disease	1.19 (1.04, 1.36)*	1.18 (1.13, 1.22)**	1.39 (1.31, 1.47)**	
Osteoporosis		1.12 (1.05, 1.20)*	1.43 (1.32, 1.55)**	2.93 (2.00, 4.29)**
Uveitis	3.79 (2.77, 5.18)**			37.97 (27.42, 52.58)**
General Eye Complaints+	0.62 (0.56, 0.68)**	0.69 (0.67, 0.71)**	0.68 (0.65, 0.71)**	
Inflammatory Bowel Disease			1.56 (1.37, 1.78)**	5.46 (4.12, 7.23)**
Diarrhea		0.93 (0.90, 0.95)**	0.93 (0.89, 0.98)*	
Infection: GI				1.32 (1.05, 1.66)*
Infection: GU		1.09 (1.05, 1.14)**		
Infection: Influenza	0.56 (0.52, 0.60)**	0.50 (0.49, 0.51)**	0.55 (0.53, 0.57)**	0.49 (0.43, 0.55)**

Infection: Pharyngitis	1.23 (1.12, 1.35)**	1.10 (1.08, 1.13)**	1.15 (1.09, 1.22)**	
Infection: Skin	1.37 (1.28, 1.46)**	1.15 (1.13, 1.18)**	0.96 (0.92, 0.99)*	0.82 (0.71, 0.94)*
Trauma: Hand	1.22 (1.03, 1.44)		1.37 (1.25, 1.50)**	
Trauma: Joint	1.21 (1.10, 1.32)**	1.03 (1.01, 1.06)	1.25 (1.18, 1.32)**	
Trauma: Foot			1.11 (1.02, 1.20)*	
Trauma: Bone		1.29 (1.20, 1.39)**		
Trauma: Skin		1.11 (1.07, 1.15)**		
Trauma: Lower Extremity			0.85 (0.77, 0.93)*	
Trauma: Nerve			0.72 (0.63, 0.81)**	
Fracture	0.84 (0.75, 0.93)*	0.70 (0.65, 0.75)**	0.72 (0.68, 0.76)**	

Empty cells indicate that the factor was not statistically significant and thus was removed from the multivariable model.

In this analysis, we only included risk factors with a prevalence of >1% in the control population. Highlighted in yellow are risk factors with an effect size >1.25 and a significant association with p-value<0.01. Highlighted in blue are risk factors with an effect size of <.8 and a significant association with p-value<0.01.

*/** p-values <0.001 have 2 asterisks and <0.02 have one asterisk.

+General eye complaints were a broad category that included vision loss, blurry vision, retinal artery occlusion, and referral to ophthalmology.

Abbreviations: PsA: psoriatic arthritis; RA: rheumatoid arthritis; AS: ankylosing spondylitis; OR: odds ratio; CI: confidence interval; BMI: body mass index; CAD: coronary artery disease; GI: gastrointestinal; GU: genitourinary.

Table 3. Summary of unique and shared risk factors positively associated with diagnosis of PsA, psoriasis, RA, and AS

	PsA	Psoriasis	RA	AS
PsA	Overweight Pharyngitis Skin Infections	Former Smoking Obesity Alcohol		
Psoriasis	Obesity Alcohol Former Smoking	Myocardial infarction Bone trauma		
RA	Gout Joint Trauma Hand Trauma	Smoking (current and former) Myocardial infarction/Coronary Artery Disease	Thyroid disease	
AS	Uveitis	Current Smoking	Current smoker Former drinker Anemia Osteoporosis IBD	Gastrointestinal infection

Abbreviations: PsA: psoriatic arthritis; RA: rheumatoid arthritis; AS: ankylosing spondylitis; IBD: inflammatory bowel disease.