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Original Article

Association Between Inflammatory Bowel Disease and Spondyloarthritis: Findings from a Nationwide Study in Sweden

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Abstract

Background and Aims: Inflammatory bowel disease [IBD] has been associated with spondyloarthritis [SpA], but population-based estimates are scarce. Here we compare the occurrence of SpA before and after a diagnosis of IBD with the general population, overall and by IBD subtype and age.

Methods: We used a nationwide register-based cohort study of 39 203 patients diagnosed with IBD during 2006-2016, identified from Swedish registers and gastrointestinal biopsy data, and 390 490 matched reference individuals from the general population. Conditional logistic regression models were used to estimate odds ratios [ORs] for a prior [prevalent] SpA diagnosis and conditional Cox regression to calculate hazard ratios [HRs] for a subsequent [incident] SpA diagnosis in IBD patients.

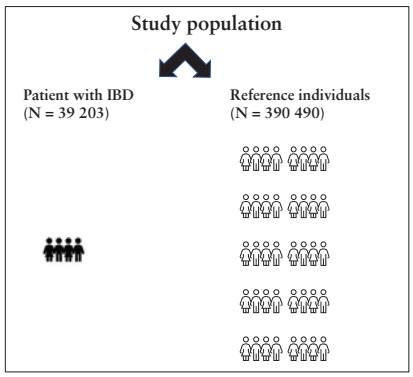
Results: IBD patients were more likely to have prevalent SpA at IBD diagnosis [2.5%] compared with reference individuals [0.7%] with an OR of 3.48 [95% CI: 3.23, 3.75]. They also more often received an incident diagnosis of SpA; during 23 341 934 person-years of follow-up in IBD patients, there were 1030 SpA events [5.0/1000 person-years] compared with 1524 SpA events in the reference group [0.72/1000 person-years], corresponding to an HR of 7.15 [95% CI: 6.60, 7.75]. In subgroup analyses, associations were most pronounced among patients with Crohn's disease ([OR = 5.20; 95% CI: 4.59, 5.89], and [HR = 10.55; 95% CI: 9.16, 12.15]) and paediatric onset IBD ([OR = 3.63; 95% CI: 2.35, 5.59] and [HR = 15.03; 95% CI: 11.01, 20.53]).

Conclusions: IBD patients more frequently experience SpA both before and after the diagnosis of IBD compared with the general population, supporting evidence of a shared pathophysiology. The variation in SpA comorbidity, across IBD subtypes and age groups, calls for targeted approaches to facilitate timely diagnosis and intervention.

Key Words: Inflammatory bowel diseases; spondyloarthritis; epidemiology; population-based study

Graphical Abstract

Association between inflammatory bowel disease and spondyloarthritis: findings from a nationwide study in Sweden



Conclusions

Patients with inflammatory bowel disease (IBD) more frequently experience spondyloarthritis (SpA) both before and after the diagnosis of IBD compared to the general population. The variation in SpA comorbidity across IBD subtypes and age-groups, calls for targeted approaches to facilitate timely diagnosis and intervention.

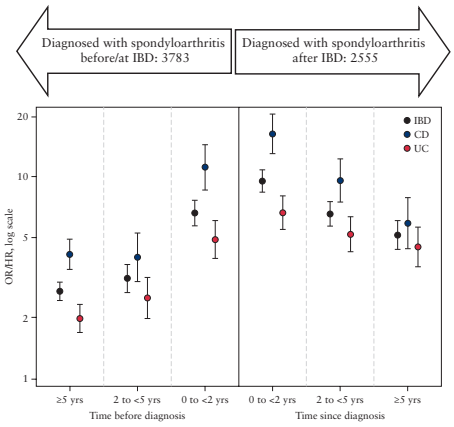


Figure 1. Associations of inflammatory bowel disease with prevalent spondyloarthritis are presented as odds ratios and associations with incident spondyloarthritis are presented as hazard ratios for inflammatory bowel disease overall (in black), and separately for Crohn's disease (in blue) and ulcerative colitis (in red). Error bars indicate 95% confidence intervals.

	OR (95% CI)	HR (95% CI)
Inflammatory bowel disease	3.48 (3.23–3.75)	7.15 (6.60–7.75)
Subtype		
Crohn's disease	5.20 (4.59–5.89)	10.55 (9.16–12.15)
Ulcerative colitis	2.62 (2.35–2.93)	5.47 (4.86–6.15)
Age group		
<18 years	3.63 (2.35–5.59)	15.03 (11.01–20.53)
18–60 years	3.85 (3.51–4.21)	7.48 (6.82–8.20)
>60 years	2.82 (2.46–3.22)	4.09 (3.30–5.07)

Table 1. Association of inflammatory bowel disease with prevalent and incident spondyloarthritis, overall and by subtype and age at diagnosis.

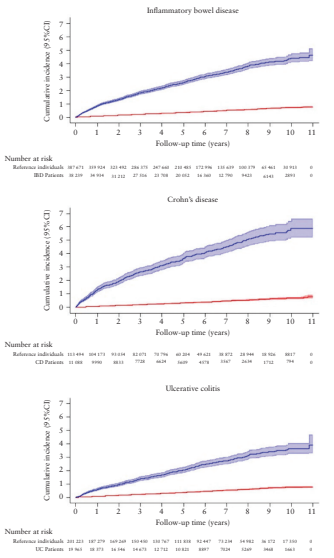


Figure 2. Cumulative incidence of spondyloarthritis in patients with inflammatory bowel disease (in blue) and reference individuals (in red), estimated using the Kaplan-Meier method with time since index date.

1. Introduction

Inflammatory bowel disease [IBD], encompassing Crohn's disease and ulcerative colitis, represents a chronic inflammatory disease entity that mainly affects the gastrointestinal tract.[1] Extraintestinal manifestations, however, frequently occur and may involve different organ systems.[2] Among the most common extraintestinal manifestations are spondyloarthritis [SpA], here defined as ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis, reactive arthritis, and undifferentiated spondyloarthritis diagnosis.[3–6] This group of rheumatic diseases share a similar clinical presentation with involvement of the spine, sacroiliac joints, peripheral arthritis, and frequently also enthesitis.[7] Both IBD and SpA are also highly heritable diseases, and genome-wide and family-based association studies have demonstrated evidence of a shared genetic basis between IBD and SpA.[8–11]

Comorbidity with SpA has been associated with disability and decreased quality of life in IBD patients.[12–14] In some IBD patients, these complications of SpA can lead to greater morbidity than the typical gastrointestinal symptoms for IBD.[15–17] Even though lower back pain is commonly reported by IBD patients with SpA, early symptoms related to SpA may be mild and not always recognisable. However, an early diagnosis of SpA is important since a delayed diagnosis may potentially lead to a more severe disease course and poor treatment responses in patients with SpA.[18] There is also some evidence suggesting that use of some SpA therapies, such as anti-IL-17A [secukinumab], in patients with ankylosing spondylitis or psoriatic arthritis comorbidity may trigger the onset and activation of IBD, even though the strength of this association is unknown.[19]

SpA and IBD appear to co-occur in the same families and some overlap has been reported in genetic risk loci,[9,11] but the temporal nature of the association between IBD and SpA overall and specific subgroups is largely unknown. This is because existing evidence mainly comes from cross-sectional studies[20] which do not provide information on temporality, i.e., whether an increased occurrence of SpA was already present at the time of IBD diagnosis and how the risk of SpA evolves over time after IBD diagnosis. Previous data further suggest that the pattern of SpA comorbidity may be different for patients with Crohn's disease and ulcerative colitis, and may also vary by age at diagnosis,[20] but this has not been studied systematically using longitudinal data.

Identifying the temporal association between IBD and SpA overall and in specific subgroups can provide insight into the actual nature of this association and could inform the development of timely and targeted strategies for diagnosis and management of SpA among IBD patients. Therefore, the aim of this study was to assess the temporal association between IBD and SpA using data from a nationwide cohort, and to examine whether this association varies according to IBD subtype and age at diagnosis.

2. Methods

2.1. Study population

This study is based on data from Swedish national registers, details of which can be found in the [Supplementary Methods]. Each resident in Sweden is assigned a unique personal identity number which allows data linkage across the registers used here. We used the National Patient Register [NPR] and the nationwide Epidemiology Strengthened by Histopathology Reports in Sweden [ESPRESSO] cohort[21] to identify patients diagnosed with IBD in Sweden between January 1, 2006, and December 31, 2016, and followed until December 31, 2017. The NPR holds information on hospital admissions since 1964, with national coverage since 1987. From 2001, data on non-primary outpatient visits have also been recorded. The ESPRESSO cohort consists of gastrointestinal histopathology

records obtained between 1965 and 2017 from Sweden's 28 pathology departments. The period of this study [2006-2016] was chosen to reflect modern diagnostic criteria and provide sufficient coverage of inpatient and outpatient data. For inclusion in this study, patients had to have at least two International Classification of Diseases [ICD] codes for a diagnosis of IBD, or one ICD code plus a colorectal biopsy report with a morphology code suggestive of IBD, from the Swedish NPR and the ESPRESSO from January 1, 2006, to December 31, 2016, [Supplementary Table 1]. Information on IBD treatment was retrieved through linkage with the Swedish IBD Quality Register [SWIBREG], Swedish Prescribed Drug Register and NPR, based on Anatomical Therapeutic Classification [ATC] codes [Supplementary Table 2].

Each patient with IBD was matched with up to 10 reference individuals from the Swedish Total Population Register.[22] Reference individuals had to be free of IBD when their index case received the first IBD diagnosis [i.e., index date]. Matching was performed with replacement, and matching variables consisted of birth year, sex, residential area and calendar year. The requirement of two diagnostic listings for a diagnosis of IBD with the first diagnosis as the start of follow-up confers a survival advantage to individuals with IBD in analysis. To avoid possible bias resulting from this immortal time in IBD patients, reference individuals who died or emigrated before the second diagnosis date of their index case were excluded from analysis [n = 1098] [Supplementary Figure 1].

2.2. Spondyloarthritis

Diagnoses of SpA were identified from the Swedish NPR. For this study, we extracted the first in- or outpatient diagnosis based on relevant ICD-codes [9th and 10th revisions, applying to diagnoses made from 1987 to 1997 and from 1997 onwards, respectively] for SpA and for the phenotypic subtypes of SpA, including ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis, reactive arthritis and undifferentiated spondyloarthritis diagnosis [Supplementary Table 3]. This means that prevalent cases of SpA could be identified from 1987 and onwards.

2.3. Statistical analysis

The temporal association between IBD and SpA was assessed in two separate analyses: 1] the association with having prior SpA [i.e., prevalent SpA] was estimated using conditional logistic regression to produce odds ratios [ORs] with the matching group as stratum variable; and 2] the association with future or incident SpA was estimated using hazard ratios [HRs] derived from Cox proportional hazards models. In these latter models, follow-up was defined from the index date [i.e., first IBD diagnosis date] until the end of the study, death, emigration, or SpA diagnosis, whichever came first. Individuals with prevalent SpA were excluded from these Cox models, and reference individuals who later developed IBD after the index date were censored at their IBD diagnosis date. As for the analysis of prevalent SpA, HRs were conditioned on the matched set. To assess the temporal association in more detail, we estimated ORs and HRs during specific periods before and after the index date [<2 years, 2 to 5 years, >5 years]. Besides HRs, we also provide prevalence estimates and cumulative incidence estimates based on the Kaplan-Meier method.

All analyses were repeated for Crohn's disease and ulcerative colitis separately and stratified by sex and age at diagnosis [paediatric onset <18 years, adult onset:18-60 years, and late onset IBD >60 years]; p-values for interaction terms were derived from ordinary logistic and Cox regression, including all matching factors as covariates in the models. Interaction terms were entered to these models and likelihood-ratio tests were used to test consistency of associations across subgroups of age and sex.

Since SpA represents a cluster of different rheumatic phenotypes, we also evaluated associations with each SpA type separately [ankylosing spondylitis, psoriatic/enteropathic arthritis, reactive arthritis, and undifferentiated SpA/sacroiliitis].

We further conducted stratified analyses by calendar period of IBD diagnosis [2006-2010 and 2011-2016] to explore if changing diagnostic criteria and treatment options over time might have impacted on our results. In these analyses, follow-up was restricted to 5 years to allow equal time periods of follow-up. To examine whether associations varied depending on IBD treatment, we also report HRs comparing patients treated with an anti-TNF agent, an immunomodulator, combination therapy with an anti-TNF and an immunomodulator, or none of these drugs with their matched reference individuals. In these analyses, follow-up was defined from the index date or the date of treatment initiation if treatment succeeded the date of IBD diagnosis. Follow-up was defined from the same date in corresponding matched reference individuals. All analyses were performed in Stata, 16.1 version.

2.4. Ethical considerations

The study was approved by the Regional Ethics Committee in Stockholm in 2015 [approval numbers: 2007/785-31/5; 2011/1509-32; 2012/601-32; 2015/0004-31; 2015/615-32; 2015/1030-32; 2016/191-31/2; 2014/1287-31/4]. Informed consent was waived due to the strict registry-based nature of the study.[23]

3. Results

We identified 39 203 IBD patients [51% female] during the study period [Table 1; Supplementary Figure 1], who were matched to 390 490 IBD-free reference individuals from the general population. The mean [standard deviation; SD] age at IBD diagnosis was 41.3 [20.5] years; 22.6% were aged >60 years, and 10.6% were aged less than 18 years. In patients with IBD, median [interquartile range; IQR] time interval between the first and second diagnostic listing of IBD was 0.08 [0.29] years. Median [IQR] observation period before the diagnosis of IBD was 23.6 [5.6] years.

3.1. Association of IBD with prevalent and incident SpA

SpA was more frequently observed in IBD patients than in the general population, regardless of temporal order. At the time of diagnosis of IBD, the prevalence of SpA was 2.5% [n = 964] in patients with IBD and 0.7% [n = 2819] in matched reference individuals, corresponding to an OR of 3.48; 95% CI: 3.23, 3.75 [Table 2]. During a median [IQR] follow-up period of 3.9 [3.0] years, 1030 patients with IBD [5.0/1000 person-years] and 1524 [0.72/1000 person-years] matched reference individuals received a diagnosis of SpA, yielding an HR of 7.15 [95% CI: 6.60, 7.75] [Table 2]. Overall, higher magnitudes of associations were observed for Crohn's disease than for ulcerative colitis, both before (OR = 5.20 [95% CI: 4.59,

5.89] vs OR = 2.62 [95% CI: 2.35, 2.93]] and after diagnosis [HR = 10.55 [95% CI: 9.16, 12.15] vs HR = 5.47 [95% CI: 4.86, 6.15]) [Table 2]. Figure 1 presents the temporal association in more detail with effect estimates in specific time intervals.

Associations with SpA peaked around the time of IBD diagnosis but remained statistically significant >5 years before and after this date [Figure 1; Supplementary Table 4]. Cumulative incidence curves of SpA in IBD patients and matched reference individuals are presented in Figure 2 with corresponding estimates at specific time points of follow-up in Supplementary Table 5. The 5- and 10-year cumulative incidence of SpA in IBD patients was 2.6% [95% CI: 2.4, 2.8] and 4.4% [95% CI:4.1, 4.8], respectively, compared with 0.4% [95% CI: 0.3, 0.4] and 0.7% [95% CI:0.7, 0.8], respectively, in the reference population. Consistent with the relative risk pattern, absolute differences in risk were larger for Crohn's disease than ulcerative colitis [Supplementary Tables 6 and 7].

3.2. Stratified analyses by age and sex

Results of stratified analyses by age at diagnosis and sex are presented in Table 3. Overall, relative risk estimates tended to be more pronounced in patients with an early disease onset, irrespective of IBD subtype, and were particularly high after the diagnosis of IBD. For patients with IBD, HRs decreased gradually in magnitude with increasing age at diagnosis (p for interaction <0.001; HRs for SpA =15.03 [95% CI: 11.01, 20.53] in patients aged <18 years, 7.48 [95% CI: 6.82, 8.20] in patients aged 18 to 60 years, and 4.09 [95% CI: 3.30, 5.07] in patients aged >60 years). Absolute differences in risk of SpA were also greater among younger than older IBD patients, although differences in absolute risk were not notably different between those aged <18 years and 18-60 years. Compared with the reference population, differences in 5-year cumulative incidence were 2.2% [95% CI: 1.7, 2.7], 2.6% [95% CI: 2.4, 2.8], and 1.2% [95% CI: 0.9, 1.5], respectively, in patients aged <18 years, 18-60 years, and older than 60 years at diagnosis of IBD [Supplementary Table 7]. Whereas ORs tended to be greatest among younger IBD patients, differences in prevalence estimates increased with increasing age [Supplementary Table 8]. Stratified analyses by sex revealed no differences in ORs between male and female patients at the time of diagnosis of IBD [p for interaction = 0.91], but somewhat higher magnitude of HRs [p for interaction = 0.05] and greater absolute risk differences were observed in females compared with males in the period following diagnosis [Table 3; Supplementary Tables 7 and 8].

3.3. Analyses by SpA type

Separate analyses for each SpA type demonstrated that associations with prevalent SpA were most pronounced for ankylosing spondylitis (OR = 4.93 [95% CI: 4.29, 5.65]) and

Table 1. Descriptive characteristics of the study population.

	IBD patients % [*N*]	Reference individuals % [*N*]
Inflammatory bowel disease	39 203	390 490
Crohn's disease	11 471	114 249
Ulcerative colitis	20 359	202 742
Sex		
Male	49.3 [19 340]	49.3 [192 612]
Female	50.7 [19 863]	50.7 [197 878]
Age at diagnosis/ index date		
<18 years	10.6 [4173]	10.7 [41 782]
18-60 years	66.8 [26 189]	66.8 [261 356]
>60 years	22.6 [8841]	22.4 [87 352]
Mean age at diagnosis of IBD [SD]	41.3 [20.5]	41.2 [20.5]
Calendar period of IBD diagnosis		
≤2010	38.0 [14 912]	-
>2010	61.9 [24 291]	-

IBD, inflammatory bowel disease; SD, standard deviation; *N*, number.

Table 2. Association of inflammatory bowel disease with prevalent and incident spondyloarthritis.

	N SpA/*N* total		OR [95% CI]	*N* SpA/*N* total		HR [95% CI]
	IBD patients	Reference individuals		IBD patients	Reference individuals	
Inflammatory bowel disease	964/39 203	2819/390 490	3.48 [3.23, 3.75]	1030/38 239	1524/387 671	7.15 [6.60, 7.75]
Crohn's disease	383/11 471	755/114 249	5.20 [4.59, 5.89]	401/11 088	407/113 494	10.55 [9.16, 12.15]
Ulcerative colitis	394/20 359	1519/202 742	2.62 [2.35, 2.93]	439/19 965	838/201 223	5.47 [4.86, 6.15]

Associations of IBD with prevalent and incident SpA are represented by odds ratios and hazard ratios, respectively, comparing IBD patients with matched reference individuals.
SpA, spondyloarthritis; IBD, inflammatory bowel disease; OR, odds ratio; HR, hazard ratio; CI, confidence interval; *N*, number.

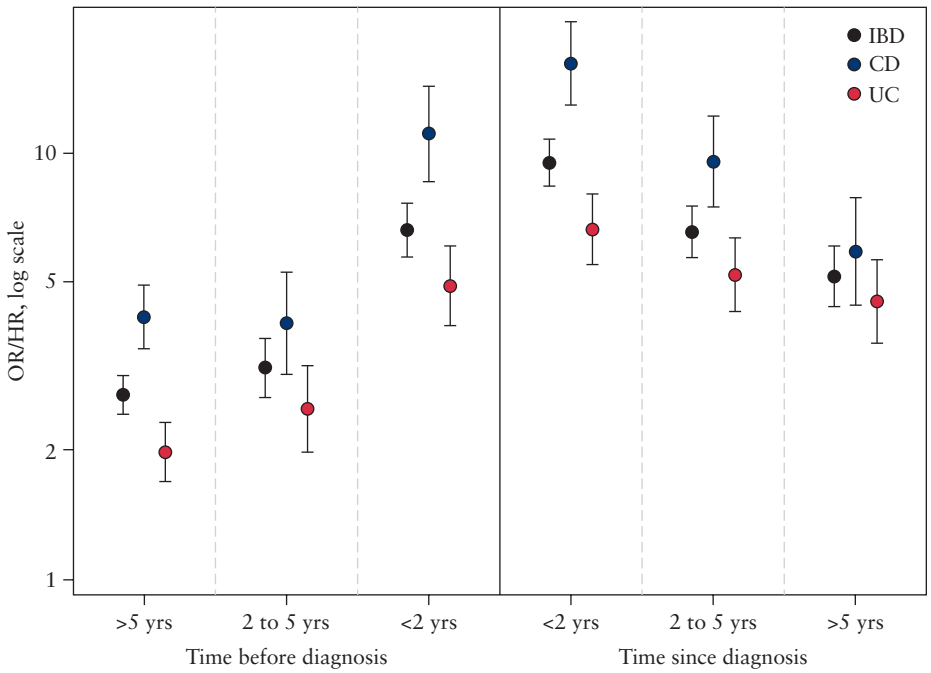


Figure 1. Associations between IBD and SpA during different time periods before and after IBD diagnosis. Associations with prevalent SpA are presented as ORs; associations with incident IBD are presented as HRs. Estimates were obtained from analyses using matched reference individuals from the general population as comparator and are split by prespecified time intervals before and after the index date. ORs and HRs are presented for IBD overall [in black], and separately for Crohn's disease [in blue] and ulcerative colitis [in red]. Error bars indicate 95% confidence intervals. OR, odds ratio; HR, hazard ratio; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; SpA, spondyloarthritis.

undifferentiated SpA/sacroiliitis (OR = 4.02 [95% CI: 3.52, 4.58]), and weakest for reactive arthritis (OR = 2.60 [95% CI: 2.17, 3.12]) [Table 4]. The pattern of association with each SpA type was somewhat different in the period following the diagnosis of IBD, with associations being strongest for incident psoriatic/enteropathic arthritis (HR = 12.00 [95% CI: 10.76, 13.38]) and weakest for incident reactive arthritis (HR = 3.39 [95% CI: [2.63, 4.37]) [Table 4].

3.4. Other analyses

Sensitivity analyses showed that associations with prevalent and incident SpA were not materially different by calendar period of IBD diagnosis [Supplementary Table 9; and Figure 2]. Restricting our analyses to the first 5 years after IBD diagnosis, HRs of SpA were also of similar magnitude in patients diagnosed with IBD in 2006-2010 (HR = 7.65 [95% CI: 6.69, 8.75]) vs 2011-2016 (HR = 8.35 [95% CI: 7.33, 9.50]). Results of analyses by IBD medication are presented in Supplementary Table 10. The magnitude of the HR for SpA was greatest in patients receiving anti-TNF treatment, either as monotherapy (HR = 27.87 [95% CI: 13.06, 59.50]) or in combination with an immunomodulator (HR = 21.28 [95% CI: 17.40, 26.02]).

4. Discussion

In this large population-based cohort study, we found that compared with a general population comparison group, IBD patients have a higher SpA prevalence and incidence. The association of IBD with SpA was most pronounced in the period 2 years before to 2 years after the diagnosis of IBD but did not vanish in the preceding or following years. Overall, higher magnitude associations with SpA were observed for Crohn's disease than for ulcerative colitis. Stratified analyses by age further indicated that the relative risk of SpA was most pronounced for paediatric onset IBD [<18 years], whereas the greatest risk differences in absolute terms were seen among paediatric and adult [18-60 years] onset IBD.

4.1. Comparison with previous literature

To our knowledge, this is the first population-based study examining the temporal association between SpA and incident IBD compared with reference individuals in the general population. Overall, the prevalence of SpA among IBD patients in our study [2.5%] falls within the lower range of prevalence estimates reported by others [1-22%].[24–33] Comparison with existing literature is, however, challenging, as most previous studies were not population-based but used small cohorts of selected IBD patients at outpatient clinics or referral centres.[29,30,33] Another explanation for the substantial variation in the reported occurrence of SpA in IBD lies in the different diagnostic criteria used across studies. We are aware of two previous studies examining the incidence of SpA in a population-based cohort of IBD patients. The cumulative incidence of SpA at 10 years reported in these North American studies [6.7% in Crohn's disease and 4.8% in ulcerative colitis] agrees with the estimates reported herein.[31,32]

Consistent with data from some previous studies, the association between IBD and SpA was most pronounced among patients with Crohn's disease[25,28,31,32] and patients diagnosed at a younger age.[20] In the present study, differences in cumulative incidence estimates were also more prominent in patients with Crohn's disease [as compared with ulcerative colitis] and patients aged <18 years and 18-60 years at diagnosis, whereas the magnitude of difference in prevalence estimates was most pronounced in patients diagnosed at an older age [>60 years].

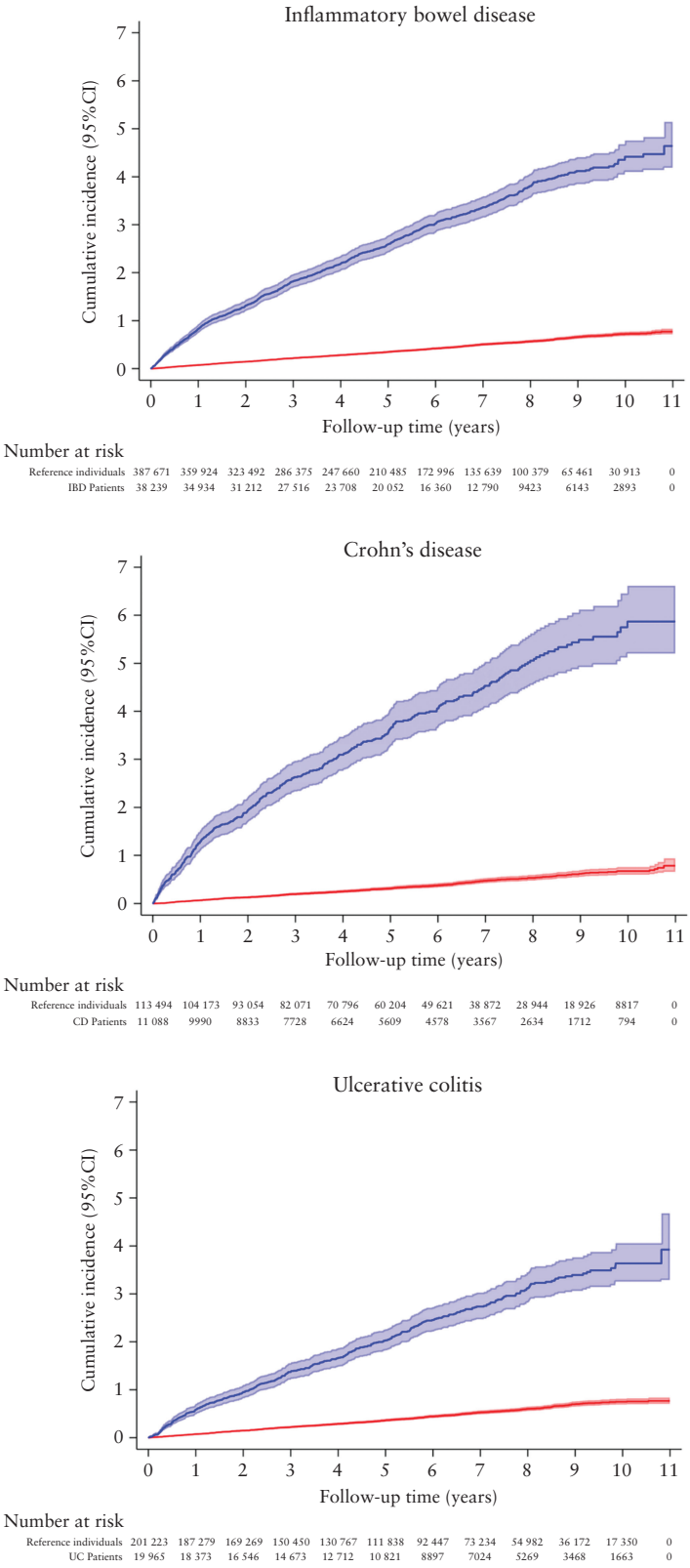


Figure 2. Cumulative incidence of SpA in IBD patients, also by subtypes and matched reference individuals from the general population. Cumulative incidence curves of SpA in IBD patients [in blue] and reference individuals from the general population [in red] were estimated using the Kaplan-Meier method with time since index date as underlying time scale. Shaded areas represent 95% confidence intervals. IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; CI, confidence interval; SpA, spondyloarthritis.

Our study confirms the previously reported absence of sex-predilection for joint manifestations, including SpA, at the time of IBD diagnosis.[33] However, the association with SpA after the time of diagnosis of IBD differed by sex, and differences in cumulative incidence estimates of SpA were somewhat higher in female IBD patients compared with male patients.

Table 3. Association of inflammatory bowel disease with prevalent and incident spondyloarthritis, stratified analyses by age and sex

	N SpA/*N* total		OR [95% CI]	*N* SpA/*N* total		HR [95% CI]
	IBD patients	Reference individuals		IBD patients	Reference individuals	
Inflammatory bowel disease						
Age group						
<18 years	28/4173	77/41 782	3.63 [2.35, 5.59]	102/4145	71/41 705	15.03 [11.01, 20.53]
18-60 years	656/26 189	1738/261 356	3.85 [3.51, 4.21]	806/25 533	1129/259 618	7.48 [6.82, 8.20]
>60 years	280/8841	1004/87 352	2.82 [2.46, 3.22]	122/8561	324/86 348	4.09 [3.30, 5.07]
p interaction			<0.001			<0.001
Sex						
Female	493/19 340	1419/192 612	3.53 [3.18, 3.92]	578/18 847	792/191 193	7.78 [6.98, 8.68]
Male	471/19 863	1400/197 878	3.43 [3.09, 3.82]	452/19 392	732/196 478	6.47 [5.75, 7.30]
p interaction			0.91			0.05
Crohn's disease						
Age group						
<18 years	17/1688	28/16 899	5.94 [3.25, 10.85]	42/1671	31/16 871	14.14 [8.75, 22.86]
18-60 years	266/7525	475/75 164	5.78 [4.96, 6.73]	311/7259	307/74 689	10.81 [9.19, 12.70]
>60 years	100/2258	252/22 186	3.97 [3.13, 5.03]	48/2158	69/21 934	7.62 [5.19, 11.17]
p interaction			0.10			0.11
Sex						
Female	200/5820	413/57 984	4.95 [4.17, 5.88]	243/5620	219/57 571	12.15 [10.06, 14.67]
Male	183/5651	342/56 265	5.50 [4.58, 6.60]	158/5468	188/55 923	8.77 [7.07, 10.88]
p interaction			0.44			0.07
Ulcerative colitis						
Age group						
<18 years	8/1592	31/15 984	2.62 [1.20, 5.72]	37/1584	30/15 953	13.33 [8.11, 21.89]
18-60 years	267/14 101	975/140 660	2.76 [2.41, 3.17]	350/13 834	633/139 685	5.72 [5.01, 6.53]
>60 years	119/4666	513/46 098	2.34 [1.91, 2.86]	52/4547	175/45 585	3.16 [2.30, 4.33]
p interaction			0.32			<0.001
Sex						
Female	193/9944	747/99 004	2.61 [2.22, 3.06]	238/9751	434/98 257	5.71 [4.87, 6.71]
Male	201/10 415	772/103 738	2.64 [2.26, 3.09]	201/10 214	404/102 966	5.20 [4.38, 6.18]
p interaction			0.68			0.40

Associations of IBD with prevalent and incident SpA are represented by odds ratios and hazard ratios, respectively, comparing IBD patients with matched reference individuals. Probability values [*p*-values] for interaction were derived from ordinary logistic and Cox regressions, including all matching factors as covariates in the models. Interaction terms were entered to these models and likelihood ratio tests were used to test consistency of associations across subgroups of age and sex.
SpA, spondyloarthritis; IBD, inflammatory bowel disease; OR, odds ratio; HR, hazard ratio; CI, confidence interval; *N*, number.

Among the various subtypes of SpA, comorbidity with ankylosing spondylitis and enteropathic arthritis is well-recognised in patients with IBD.[31,32,34] Of all SpA types, we found that associations with IBD were most pronounced for ankylosing spondylitis and psoriatic/enteropathic arthritis and weakest for reactive arthritis, an inflammatory arthritis typically triggered by a gastrointestinal infection.[2]

4.2. Potential mechanisms

The fact that the association with SpA was observed both before and after the diagnosis of IBD supports previous research demonstrating a shared genetic susceptibility between IBD and SpA.[8–11] In general, we observed stronger associations for Crohn's disease than ulcerative colitis. These findings may indicate that shared genetic susceptibility between IBD and SpA differs by IBD subtype, and agrees with reported stronger co-heritability between ankylosing spondylitis and Crohn's disease [40%] than ulcerative colitis [33%].[35,36] Besides shared genetic factors, both diseases may also have environmental risk factors in common. A decreased gut bacterial diversity has not only been reported in the faecal and mucosal microbiomes of patients with IBD, but also in patients with SpA.[37–41] Also, a poor vitamin D status has been linked to both diseases.[42,43] Therefore, further studies are needed to disentangle the relative contribution of potential shared environmental and genetic risk factors between IBD and SpA.

4.3. Strengths and limitations

Strengths of this study include the large sample size and the population-based design with prospectively recorded data in routine medical practice and complete follow-up, which minimises information and selection biases. These strengths also increase the generalisability of our findings. Access to the ESPRESSO database helped to accurately define the date of first diagnosis of IBD, that is the index date, and to shorten the time period to fulfil the criteria for IBD. The linkage of the NPR with the ESPRESSO database, also ensured the inclusion of the vast majority of incident patients with IBD in Sweden during the study period. In this study, we also assessed the occurrence of SpA in subgroups of IBD patients and at various

Table 4. Association of inflammatory bowel disease with prevalent and incident spondyloarthritis subtypes, overall and by inflammatory bowel disease subtype.

SpA subtype	At the index date			After the index date		
	N total/*N* SpA [%]			*N* total/*N* SpA [%]		
	Patients	Reference individuals	OR [95% CI]	Patients	Reference individuals	HR [95% CI]
Ankylosing spondylitis						
IBD	304/39 203	618/390 490	4.93 [4.29, 5.65]	176/38 899	288/389 872	6.35 [5.25, 7.67]
CD	157/11 471	153/114 249	10.32 [8.25, 12.91]	76/11 314	75/114 096	10.64 [7.69, 14.73]
UC	99/20 359	347/202 742	2.85 [2.28, 3.56]	70/20 260	153/202 395	4.67 [3.51, 6.22]
Undifferentiated SpA/sacroiliitis						
IBD	315/39 203	789/390 490	4.02 [3.52, 4.58]	318/38 888	549/389 701	5.89 [5.13, 6.78]
CD	132/11 471	216/114 249	6.16 [4.96, 7.66]	115/11 339	155/114 033	7.78 [6.09, 9.95]
UC	121/20 359	446/202 742	2.72 [2.22, 3.32]	145/20 238	308/202 296	4.72 [3.87, 5.76]
Psoriatic/ enteropathic arthritis						
IBD	324/39 203	1091/390 490	2.97 [2.63, 3.37]	725/38 879	622/389 399	12.00 [10.76, 13.38]
CD	113/11 471	303/114 249	3.74 [3.01, 4.65]	301/11 358	149/113 946	20.47 [16.77, 24.98]
UC	141/20 359	582/202 742	2.42 [2.01, 2.91]	302/20 218	355/202 160	8.77 [7.51, 10.25]
Reactive arthritis						
IBD	149/39 203	573/390 490	2.60 [2.17, 3.12]	81/39 054	242/389 917	3.39 [2.63, 4.37]
CD	56/11 471	143/114 249	3.92 [2.88, 5.35]	31/11 415	67/114 106	4.71 [3.07, 7.24]
UC	66/20 359	297/202 742	2.22 [1.70, 2.90]	37/20 293	128/202 445	2.90 [2.01, 4.18]

Associations of IBD with prevalent and incident SpA are represented by odds ratios and hazard ratios, respectively, comparing IBD patients with matched reference individuals.
SpA, spondyloarthritis; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; OR, odds ratio; HR, hazard ratio; CI, confidence interval; *N*, number.

time points in relation to the diagnosis of IBD. Such analyses are essential for guiding clinicians regarding risk stratification and disease management. We have previously also demonstrated that age at diagnosis of IBD can be accurately defined from the NPR.[44] Information on risk estimates of SpA in patients with IBD, on an absolute scale, has also been requested by the Swedish patient organisation.[45]

Our study also has some limitations. First, due to the register-based study design, we were not able to confirm diagnoses by reviews of medical records and cannot rule out misclassifications of IBD and SpA. However, we have previously shown that the positive predictive value [PPV] for IBD with two or more relevant ICD codes in the NPR is 93% [95% CI:87, 97][46] and 95%[47] with one patient register record documenting IBD and a colorectal biopsy showing inflammation. The PPV for ankylosing spondylitis has been reported to be 70% for the modified New York criteria, 89% for any set of SpA criteria,[48] and 63-92%[49] for psoriatic arthritis. Also, there are different protocols for diagnosing SpA and diagnostic delays often occur, so some individuals may have had symptoms of SpA without being diagnosed.[50] However, we anticipate misclassification of IBD and SpA to be non-differential [i.e., degree of misclassification is independent of the outcome/exposure], and in most instances such misclassification will only bias estimates towards the null. Apart from this, we were unable to examine the specific effect of medical surveillance and diagnostic intensity, but we acknowledge that the peak of SpA diagnosis around IBD diagnosis might very well be an effect of diagnostic intensity and frequent contacts with health care because of severe disease activity or disease onset. However, we consider it unlikely that such bias entirely explains the associations observed, given the increased occurrence of SpA even 5 years beyond the diagnosis of IBD. Second, although our analyses addressed confounding by demographic factors, we cannot rule out residual confounding by other environmental factors not captured by the Swedish registers. Third, we did not examine the occurrence of SpA in patients with IBD-unclassified as this group of patients was too small for meaningful analysis. Also we had limited power in some subgroup analyses, such as in patients with paediatric IBD, but still 173 patients with paediatric onset IBD developed SpA during follow-up. When examining the association of IBD treatments with subsequent risk of SpA, we defined exposure as drug use from the date of treatment initiation. Whereas this strategy does not fully capture all relevant drug exposures and changes in exposure over time, it provides some insight into how risks vary in different patient groups. However, the observed effect estimates for the different treatments should be interpreted with caution, since our cohort was not specifically tailored to address the influence of treatment and these results may be confounded by differences in disease characteristics and severity. Last, the short study period [2006-2016] limited our possibility to address temporal changes in effect estimates by calendar period.

4.4. Implications

Patients with IBD who have joint symptoms should be examined for a potential SpA diagnosis. This recommendation is relevant both at the initial diagnostic work-up of patients with suspected IBD and during the follow-up of patients diagnosed with IBD. Higher magnitude of associations was observed for Crohn's disease than for ulcerative colitis, both on the relative and the absolute scale, indicating the importance for physicians to routinely ask questions about musculoskeletal complaints, especially in patients with Crohn's disease. Even though relative risk estimates of SpA were most pronounced in paediatric onset IBD, differences in absolute risk of SpA after the time of IBD diagnosis were not notably different between those aged <18 years and 18-60 years. Furthermore, clinicians should be aware that a diagnosis of SpA may also precede the onset of IBD and that gastrointestinal symptoms among patients with SpA may indicate a need for ileocolonoscopy to rule out an IBD diagnosis.

In conclusion, the associations observed between IBD and SpA, regardless of temporal order, support the existence of a common aetiology for both diseases. Based on the observed variation in SpA comorbidity across subtypes of IBD, sex, and age groups at diagnosis, our results call for targeted approaches to facilitate timely diagnosis and intervention.

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Conflict of Interest

JFL coordinates a study on behalf of the Swedish IBD quality register [SWIBREG]. This study has received funding from Janssen corporation. OO has been PI on projects at Karolinska Institutet partly financed by investigator-initiated grants from Janssen and Ferring, and also reports a grant from Pfizer in the context of a national safety monitoring programme. None of those studies have any relation to the present study. Karolinska Institutet also has received fees for OO's lectures and participation on advisory boards from Janssen, Ferring, Takeda, and Pfizer regarding topics that are not related to the present study. JA reports grants from AbbVie, AstraZeneca, BMS, Eli Lilly, MSD, Pfizer, Roche, Samsung Bioepis, Sanofi, and UCB outside the submitted work. SM has received financial support for research from AstraZeneca, Roche, and Novartis, advisory board: IQVIA, lecture fee [s]: Teva. JH served as speaker and/or advisory board member for AbbVie, Celgene, Celltrion, Dr. Falk Pharma and the Falk Foundation, Ferring, Hospira, Janssen, MEDA, Medivir, MSD, Olink Proteomics, Pfizer, Prometheus Laboratories, Sandoz/Novartis, Shire, Takeda, Thermo Fisher Scientific, Tillotts Pharma, Vifor Pharma, UCB, and received grant support from Janssen, MSD, and Takeda.

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Data Availability

The data underlying this article cannot be shared publicly due to privacy of individuals who participated in the study.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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