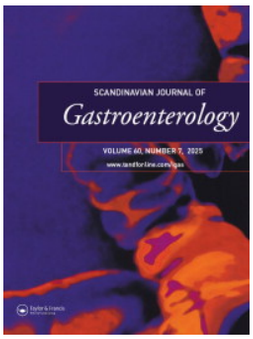

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RESEARCH ARTICLE

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Spondyloarthritis features in IBD patients: prevalence, referral trends and clinical implications. A questionnaire-based study

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ABSTRACT

Objectives: This study examines the prevalence of spondyloarthritis (SpA) features in patients with inflammatory bowel disease (IBD) and their rates of referral to rheumatologists.

Material and methods: A questionnaire was administered to 2087 IBD patients (≥18 years) in Sweden, assessing demographics, medications and SpA features based on the ASAS and ESSG classification criteria. Patient that met our self-reported adapted criteria are referred to as suspected SpA.

Results: Among the 1032 respondents, 59.1% met our questionnaire-based adapted SpA criteria. However, depending on different criteria (based on adapted ASAS, ESSG, peripheral or axial symptoms) only 24.3–44.0% of these patients had been referred to a rheumatologist. Patients with suspected SpA had higher usage of immunomodulators (42.8–48.8% vs. 37.0%), biologics (27.1–32.4% vs. 14.9%) and steroids (58.1–64.8% vs. 46.2%) compared to those without suspected SpA. Additionally, suspected SpA patients reported a higher incidence of active colitis (30.4–40.4% vs. 11.8%). Logistic regression analysis identified significant associations between suspected axial SpA and factors such as age, smoking, psoriasis, anterior uveitis and a high P-SCCAI score (≥5). Female gender and BMI ≥30 kg/m^2 were linked to suspected peripheral SpA.

Conclusion: The study highlights a significant prevalence of self-reported SpA in IBD patients, with many remaining undiagnosed and un-referred to rheumatologists. These findings emphasize the need for greater awareness and improved collaboration between gastroenterologists and rheumatologists for better SpA management in IBD patients.

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Crohn's disease; inflammatory back pain; inflammatory bowel disease; psoriasis; spondyloarthritis; ulcerative colitis

Introduction

Inflammatory bowel disease (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), is an immune-mediated inflammatory disorder that primarily affects the gastrointestinal (GI) tract. However, extraintestinal manifestations (EIMs) are common among individuals with IBD such as peripheral or axial spondyloarthritis (SpA), episcleritis, uveitis, scleritis, erythema nodosum, pyoderma gangrenosum, sweet syndrome, primary sclerosing cholangitis and oral or metastatic manifestations of CD [1–3]. Among these, SpA is considered the most prevalent. SpA is characterized by inflammation of the joints and/or entheses, and it can be categorized as either axial or peripheral SpA, depending on the predominant clinical presentation [4]. In addition, extra-musculoskeletal manifestations (EMMs) are common in SpA typically including IBD, uveitis and psoriasis [5].

There is substantial evidence indicating a significant delay in the diagnosis of SpA, both in the general population [6] and in patients with IBD [7]. This delay in diagnosis increases the risk of long-term disability due to inadequate management and treatment. Furthermore, early initiation of treatment has been associated with better clinical outcomes, underscoring the importance of timely identification of SpA in this patient population [8]. This is particularly relevant as treatment guidelines differ depending on whether a patient with IBD also has SpA [9].

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Given the complexity of diagnosing and managing SpA in IBD patients, effective collaboration between gastroenterologists and rheumatologists is essential. However, there is uncertainty regarding the extent to which patients with IBD and suspected SpA are referred to a rheumatologist [7,10]. Additionally, there is a paucity of studies addressing the prevalence of individual SpA features in IBD patients, with existing literature reporting a wide range of prevalence estimates for axial and peripheral SpA. For example, a recent systematic review and meta-analysis found the prevalence of axial SpA and peripheral SpA in IBD patients to range from 1% to 46% and 1% to 43% respectively [8]. Notably, only a small proportion of these studies focused on the prevalence of specific SpA features [11].

The primary aim of this questionnaire-based study was to assess the prevalence of individual self-reported SpA features in IBD patients and determine the proportion of patients with suspected peripheral SpA and axial SpA according to our questionnaire-based adapted Assessment of SpondyloArthritis international Society (ASAS) [4] and European Spondyloarthritis Study Group (ESSG) classification criteria [12]. A secondary aim was to investigate the extent to which these patients had been referred to a rheumatologist. Additionally secondary objectives included comparing IBD patients with and without suspected SpA, in terms of patient characteristics, reported disease activity and medical treatment usage.

Materials and methods

The study was designed as a cross-sectional survey utilizing questionnaires.

Study group

Patients with IBD were identified through the Swedish National Quality Registry for Inflammatory Bowel Disease (SWIBREG) [13]. All patients in SWIBREG have a confirmed diagnosis of IBD made by a gastroenterologist. The registry covers approximately 90% of IBD patients in the Region of Västernorrland and Umeå, Sweden. In this study, eligible participants included IBD patients residing in Västernorrland or Umeå, age 18 years or older.

Questionnaires

From October 2018 to August 2020, a total of 2087 eligible patients were sent a questionnaire by mail. Non-respondents received a reminder questionnaire two to four months after the initial mailing. The questionnaires collected tata on the following: age, gender, body mass index (BMI) in kg/m^2, smoking status, comorbidities, medications, previous referral to a rheumatologist, features of SpA and IBD disease activity. The questionnaire is found in Supplementary Material.

Assessment of SpA features

The questionnaire included questions to assess the presence of the following SpA features: arthritis, enthesitis, dactylitis, anterior uveitis, psoriasis, inflammatory back pain (IBP) and family history of SpA. Specifically, questions addressing arthritis, enthesitis and dactylitis were as follows:

- 'Have you experienced joint swelling that has been diagnosed by a doctor?'
- 'Have you experienced pain in your Achilles tendon or under your heel that emerged spontaneously/without obvious reason?'
- 'Have you experienced swelling of an entire finger or toe, so called sausage finger/toe?'.

For patients with back pain, the questions assessed: age of onset, duration, insidious onset, morning stiffness, improvement with exercise, improvement with rest and nocturnal pain. A family history of SpA was defined as presence of any of the following conditions in a first- or second degree relative: ankylosing spondylitis, psoriasis, anterior uveitis, IBD, or reactive arthritis.

Assessment of IBD disease activity

IBD disease activity was assessed using the Patient Simply Clinical Colitis Index (P-SCCAI) [14]. The P-SCCAI include questions about bowel frequency during the day and night, urgency of defecation, presence of diarrhea or blood in the stool, general well-being and extra-intestinal manifestations, including arthropathy, anterior uveitis and skin conditions. The P-SCCAI is validated only for patients with UC but was in this study also used for patients with CD. We did not use the validated (for CD) Harvey Bradshaw index because it includes a physical examination parameter (abdominal mass). Patients with a P-SCCAI score of 0–4 were categorized as 'remission', while those with scores of 5–19 were classified as having 'active colitis' [14].

Assessment of non-steroidal anti-inflammatory drug (NSAID) intake

NSAID use was assessed with the following questions:

- 'If you have had musculoskeletal pain in the past year, did you use NSAIDs to relieve the pain? (Yes/No)'
- 'Did you experience a negative effect on your IBD symptoms from NSAID use? (Yes/No)'
- 'How effective were NSAIDs in relieving your musculoskeletal pain? (Very good effect/Good effect/Minor effect/No effect)'

Classification of axial SpA, peripheral SpA and inflammatory back pain

The suspected SpA definition was based on the self-reported data from the questionnaires. Suspected SpA was defined according to the ASAS classification criteria, non-imaging arm [15,16] and the ESSG [12] criteria, adaption due to the questionnaire-based nature of the study. In the ASAS criteria, HLA-B27 and CRP were excluded due to lack of access to laboratory results. In the ESSG, we classified all patients with a self-reported diagnosis of peripheral arthritis as having 'peripheral SpA', regardless of whether the arthritis was asymmetric or predominantly affecting the lower limbs. Below are all criteria presented in detail.

Our detailed questionnaire-based adapted criteria are as follows:

- Axial SpA (ASAS criteria):
  - Back pain for ≥3 months, with age of onset <45 years and
  - At least one of the following: IBP according to ASAS criteria (≥4 of the following: age at onset <45 years; insidious onset; improvement with exercise; no improvement with rest; nocturnal pain); arthritis; enthesitis; dactylitis; psoriasis; good response to NSAIDs; family history of SpA.
- Axial SpA (ESSG criteria):
  - Inflammatory back pain (according to Calin criteria, ≥4 of the following: age at onset <45 years; duration of pain >3 months; insidious onset; associated with morning stiffness; improvement with exercise) and
  - At least one of the following: positive family history; psoriasis; IBD; urethritis, cervicitis, or acute diarrhea within one month prior to arthritis; alternating buttock pain; enthesopathy; sacroiliitis.
- Peripheral SpA (ASAS criteria):
  - Arthritis, enthesitis and/or dactylitis,
  - Absence of IBP according to ASAS and
  - At least one of the following: psoriasis; IBD; preceding infection; HLA-B27; uveitis; sacroiliitis on imaging; or ≥2 of the following: arthritis; enthesitis; dactylitis; previous IBP; positive family history of SpA.
- Peripheral SpA (ESSG criteria):
  - Peripheral arthritis and
  - At least one of the following: positive family history; psoriasis; IBD; urethritis, cervicitis, or acute diarrhea within one month before arthritis; alternating buttock pain; enthesopathy; sacroiliitis.

Statistical analysis

Data from the questionnaires were analyzed in IBM SPSS Statistics version 26.0 (IBM, Armonk, NY, USA). Descriptive statistics are presented as absolute number with percentages or as means with standard deviation (SD). Chi-square test or Fisher's Exact Test were used for categorical data comparisons and independent t-test for continuous variables. To account for potential confounders, logistic regression was performed with suspected axial and suspected peripheral SpA (fulfilled both ASAS and ESSG criteria) as the dependent variables. Independent variables included gender BMI ≥30 kg/m^2, Crohn's disease, smoking status (never/ever), psoriasis, anterior uveitis and active colitis. All tests were two-tailed, with $p \leq .05$ considered statistically significant. Multiple testing adjustments were not applied.

Results

Characteristics of responding patients

The response rate was 1032 out of 2069 (49.9%). The characteristics for the responding patients with UC and CD patients are presented separately in Table 1.

SpA manifestations in patients with IBD

The frequency of various SpA manifestations was analyzed for the entire cohort of IBD patients, as well as for UC and CD separately (Table 2). Self-reported anterior uveitis and dactylitis were significantly more common in patients with CD, whereas psoriasis was significantly more prevalent among patients with UC.

Patients with IBD with suspected SpA

As shown in Table 2, 610 out of 1032 responding patients (59.1%) met the criteria for either axial or

Table 1. Characteristics of responding patients with inflammatory bowel disease (IBD), divided into ulcerative colitis (UC) and Crohn's disease (CD) patients.

	UC, $n=592$	CD, $n=440$
Gender		
Men	303 (51.2%)	196 (44.5%)
Women	285 (48.1%)	243 (55.2%)
Mean age, years	54.1 (SD 14.6)	55.12 (SD 16.5)
Body mass index, kg/m^2	26.3 (SD 4.6)	26.0 (SD 5.3)
IBD medications, current or previous		
5-ASA[a]	563 (95.1%)	236 (53.6%)
Immunomodulators[b]	168 (28.4%)	261 (59.3%)
Biologics[c]	78 (13.2%)	150 (34.1%)
Steroids[d]	279 (47.1%)	270 (61.4%)
IBD medications, current		
5-ASA[a]	392 (66.2%)	66 (15.0%)
Immunomodulators[b]	78 (13.2%)	123 (28.0%)
Biologics[c]	40 (6.8%)	97 (22.0%)
Steroids[e]	78 (13.2%)	95 (21.6%)
Smoking		
Never	322 (54.4%)	214 (48.6%)
Previous	216 (36.5%)	179 (40.7%)
Current	50 (8.4%)	47 (10.7%)
Unknown/missing	4 (0.7%)	0 (0.0%)

[a]Balsalazide sodium, mesalamine, olsalazine or sulfasalazine.
[b]6-Mercaptopurine, azathioprine or methotrexate.
[c]Adalimumab, golimumab, infliximab or vedolizumab.
[d]Budesonide or oral cortisone treatment >3 months.
[e]Budesonide or oral cortisone treatment.

peripheral SpA according to the adapted ASAS or ESSG classification criteria. The overlap between patients with suspected SpA according to these criteria is presented in Figure 1. Figure 2 and Figure 3 further subdivide the patients with IBD classified with suspected SpA by age categories.

Comparisons of patients with and without suspected SpA

Both suspected peripheral and suspected axial SpA, according to the definitions in this study, were significantly more common in women compared to men. Patients with suspected axial SpA according to adapted ASAS criteria were significantly younger than those without SpA. Additionally, patients with suspected SpA had higher BMI and had more often a history of smoking compared to those without suspected SpA (Table 3). Among patients with CD, current smoking was more prevalent in those with suspected SpA compared to those without with the following differences: peripheral SpA according to our adapted ASAS criteria: 11.2% versus 4.8%, $p=.024$; axial SpA according to our adapted ASAS criteria: 19.8% versus 4.8%, $p<.001$; peripheral SpA according to our adapted ESSG criteria: 14.1% versus 4.8%, $p=.006$; axial SpA according to our adapted ESSG criteria: 21.4% versus 4.8%, $p<.001$. No significant difference in smoking prevalence was observed between patients with UC with and without suspected SpA (peripheral SpA according to our adapted ASAS criteria: 9.2% versus 7.8%, $p=.642$; axial SpA according to our adapted ASAS criteria: 7.5% versus 7.8%, $p=.852$; peripheral SpA according to our adapted ESSG criteria: 6.1% versus 7.8%, $p=.501$; axial SpA according to our adapted ESSG criteria: 8.4% versus 7.8%, $p=.891$).

Table 2. The proportion of patients with inflammatory bowel disease (IBD) with manifestations of spondyloarthritis (SpA) and the proportion of IBD patients who fulfilled our adapted classification criteria for SpA according to the assessment of SpondyloArthritis International Society (ASAS) and the European Spondyloarthritis Study Group (ESSG), respectively.

Manifestation	Patients with IBD (all patients), $n=1032$	Patients with ulcerative colitis (UC) patients, $n=592$	Patients with Crohn´s disease (CD) patients, $n=440$	p Value, UC vs CD
Peripheral arthritis	252 (24.4%)	131 (22.1%)	121 (27.5%)	*.047*
Anterior uveitis	79 (7.7%)	30 (5.1%)	49 (11.1%)	*<.001*
Swelling of an entire finger or toe	125 (12.1%)	59 (10.0%)	66 (15.0%)	*.014*
Sporadic pain in the Achilles tendon	200 (19.4%)	114 (19.3%)	86 (19.5%)	.908
Sporadic pain under the heel	283 (27.4%)	153 (25.8%)	130 (29.5%)	.188
Psoriasis	85 (8.2%)	59 (10.0%)	26 (5.9%)	*.018*
Heredity for SpA[a]	493 (47.8%)	279 (47.1%)	214 (48.6%)	.631
Good effect of NSAID on back pain	200 (19.4%)	110 (18.6%)	90 (20.5%)	.451
Inflammatory back pain according to ASAS	199 (19.3%)	104 (17.6%)	95 (21.6%)	.105
Inflammatory back pain according to Cailin	269 (26.1%)	143 (24.2%)	126 (28.6%)	.105
Type of spondyloarthritis				
Suspected peripheral spondyloarthritis (ASAS)[b]	358 (34.7%)	206 (34.8%)	152 (34.5%)	.933
Suspected axial spondyloarthritis (ASAS)[c]	250 (24.2%)	134 (22.6%)	116 (26.4%)	.167
Suspected peripheral spondyloarthritis (ESSG)[d]	252 (24.4%)	131 (22.1%)	121 (27.5%)	*.047*
Suspected axial spondyloarthritis (ESSG)[e]	269 (26.1%)	143 (24.2%)	126 (28.6%)	.105
No spondyloarthritis[f]	422 (40.9%)	254 (42.9%)	168 (38.2%)	.127

[a]Heredity for ankylosing spondylitis, reactive arthritis, psoriasis, anterior uveitis, or IBD.
[b]IBD patients with peripheral arthritis, enthesitis, or dactylitis, but without inflammatory back pain (IBP) according to the ASAS criteria for IBP.
[c]IBD patients with back pain with a duration of ≥3 months that debuted <45 years of age and with ≥1 additional SpA feature.
[d]IBD patients with peripheral arthritis.
[e]IBD patients with inflammatory back pain according to the Calin criteria.
[f]IBD patients who do not fulfill the criteria for peripheral or axial SpA according to the ASAS or the ESSG criteria.

Medical therapy for IBD

Patients with suspected peripheral or axial SpA were more likely to report current or previous use of

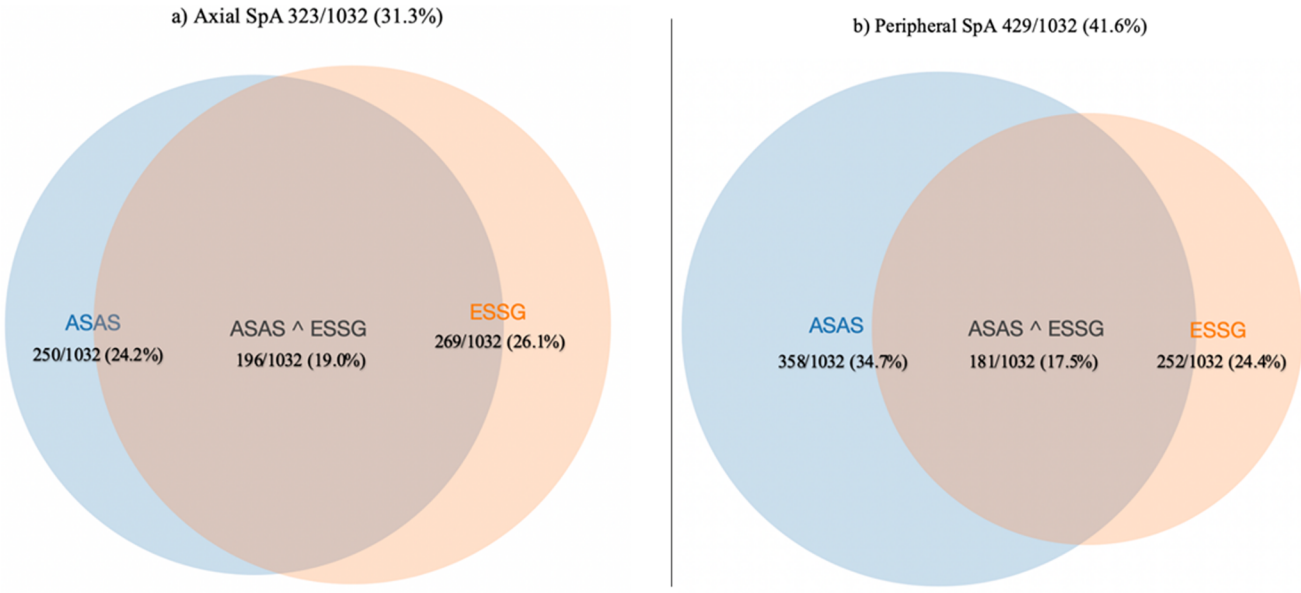

Figure 1. Venn diagrams of patients with inflammatory bowel disease (IBD) with suspected (a) axial spondyloarthritis (axSpA) and (b) peripheral spondyloarthritis (pSpA) according to our adapted Assessment of SpondyloArthritis International Society (ASAS) and European Spondyloarthritis Study Group (ESSG) criteria.

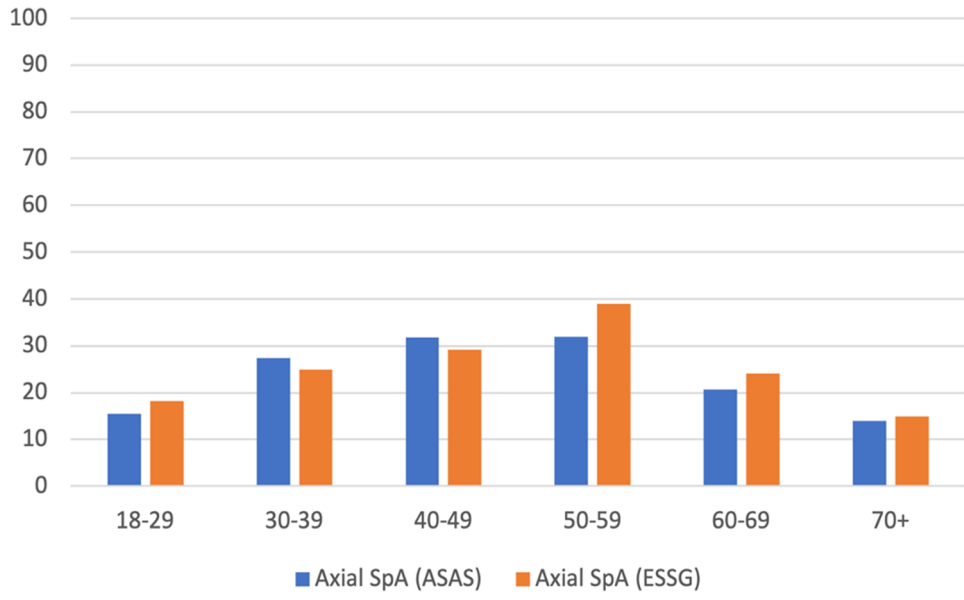

Figure 2. Proportion of patients with inflammatory bowel disease (IBD) with suspected axial and peripheral spondyloarthritis (SpA), subdivided into age categories (years).

immunomodulators, biologics and steroids compared to those without suspected SpA. The current use of biologics was more common in patients with suspected axial SpA, though there were no significant differences in the use of other IBD medications (Table 3).

Extraintestinal manifestations and rheumatic comorbidities

As detailed in Table 3, patients with suspected SpA had a significantly higher prevalence of psoriasis compared to those without suspected SpA, representing 67 out of 85 (78.8%) of all psoriasis diagnoses in the IBD cohort. They also exhibited a higher prevalence of anterior uveitis.

Referral to a rheumatologist

A significantly higher proportion of patients with suspected SpA had been referred to a rheumatologist compared to those without suspected SpA (Table 4). However, more than half of those fulfilling our adapted

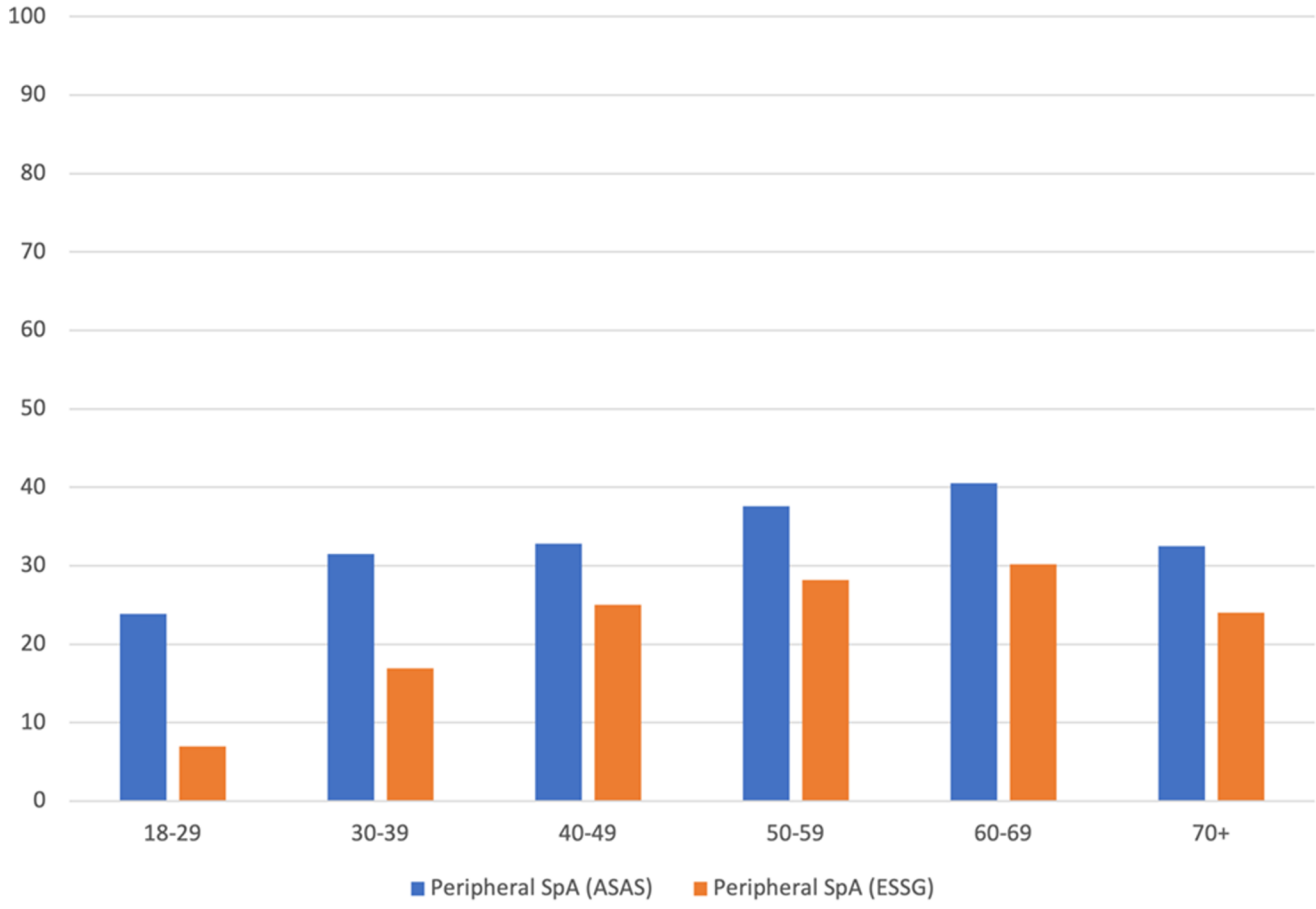

Figure 3. Proportion of patients with inflammatory bowel disease (IBD) with suspected peripheral spondyloarthritis (SpA), subdivided into age categories (years).

criteria for peripheral SpA and nearly two-thirds of those meeting our adapted criteria for axial SpA had not been referred to a rheumatologist.

Among all IBD patients, 191 had been referred to a rheumatologist, while 835 had not. Compared to patients not referred, a significantly higher proportion of those referred to a rheumatologist had used immunomodulators (53.9% vs. 38.9%, $p < .001$), biologics (40.8% vs. 18.0%, $p < .001$) and steroids (67.5% vs. 50.2%, $p < .001$). Additionally, patients referred to a rheumatologist were more likely to report current use of various analgesics, including NSAIDs (9.9% vs. 4.4%, $p = .002$), paracetamol (29.8% vs. 11.0%, $p < .001$), amitriptyline (4.7% vs. 2.2%, $p = .046$) and opioids (8.9% vs. 2.8%, $p < .001$).

Medical treatment for pain

Patients with suspected SpA reported significantly higher use of NSAIDs, paracetamol and opioids compared to those without suspected SpA. Furthermore, patients with suspected axial SpA and suspected peripheral SpA (according to ESSG criteria) were more likely to report a negative impact of NSAID use on their IBD symptoms compared to those without suspected SpA (Table 3). Despite this, a high proportion of patients across all groups reported adequate pain relief from NSAID use (95.0% in the not suspected SpA group, 96.0–99.3% in the suspected SpA groups).

IBD disease activity

Among UC patients, 21.5% ($n = 127$) had active colitis, and among CD patients, 27.5% ($n = 121$) had active colitis. Patients with suspected SpA (peripheral and axial) had a significantly higher prevalence of active colitis compared to those without suspected SpA (Table 3).

Logistic regression analyses

Logistic regression analyses, adjusting for potential confounders, were performed to identify factors associated with suspected axial and suspected peripheral SpA (based on fulfilling both our adapted ASAS and ESSG criteria). Significant associations with suspected

Table 3. Medical treatment, comorbidities and inflammatory bowel disease (IBD) activity in patients with IBD classified with suspected and without suspected peripheral and axial spondyloarthritis (pSpA and axSpA) according to our adapted assessment of SpondyloArthritis International Society (ASAS) and European Spondyloarthritis Study Group (ESSG) criteria (ESSG) criteria.

Basic characteristics	No SpA, $n=422$	Suspected pSpA (ASAS), $n=358$	Suspected AxSpA (ASAS), $n=250$	Suspected pSpA (ESSG), $n=252$	Suspected AxSpA (ESSG), $n=269$
Mean age, years	54.9 (SD 17.2)	55.8 (SD 14.4) $p=.454$	52.3 (SD 13.2) $p=.037$	57.3 (SD 12.7) $p=.068$	53.2 (SD 13.2) $p=.161$
Women	179 (42.4%)	214 (59.8%) $p=<.001$	138 (55.2%) $p=.001$	158 (62.7%) $p=<.001$	141 (52.4%) $p=.010$
Mean BMI, kg/m^2	25.2 (SD 4.2)	27.1 (SD 5.0) $p<.001$	27.0 (SD 5.5) $p<.001$	27.3 (SD 5.1) $p<.001$	27.1 (SD 5.5) $p<.001$
Current smoker	28 (6.7%)	36 (10.1%) $p=.083$	33 (13.4%) $p=.004$	25 (10.0%) $p=.125$	39 (14.5%) $p=.001$
Never smoked	238 (56.4%)	168 (46.9%) $p=.008$	118 (47.2%) $p=.021$	117 (46.4%) $p=.012$	124 (46.1%) $p=.008$
IBD medications, current or previous					
5-ASA[a]	321 (76.1%)	280 (78.2%) $p=.478$	199 (79.6%) $p=.290$	199 (79.0%) $p=.385$	205 (76.2%) $p=.966$
Immunomodulators[b]	156 (37.0%)	158 (44.1%) $p=.042$	122 (48.8%) $p=.003$	117 (46.4%) $p=.015$	115 (42.8%) $p=.129$
Biologics[c]	63 (14.9%)	97 (27.1%) $p=<.001$	81 (32.4%) $p=<.001$	76 (30.2%) $p=<.001$	73 (27.1%) $p=<.001$
Steroids[d]	195 (46.2%)	208 (58.1%) $p=<.001$	162 (64.8%) $p=<.001$	158 (62.7%) $p=<.001$	162 (60.2%) $p=<.001$
IBD medications, current					
5-ASA[a]	187 (44.3%)	159 (44.4%) $p=.976$	111 (44.4%) $p=.982$	98 (38.9%) $p=.168$	111 (41.3%) $p=.430$
Immunomodulators[b]	87 (20.6%)	66 (18.4%) $p=.445$	56 (22.4%) $p=.585$	44 (17.5%) $p=.316$	52 (19.3%) $p=.681$
Biologics[c]	42 (10.0%)	50 (14.0%) $p=.083$	44 (17.6%) $p=.004$	36 (14.3%) $p=.089$	45 (16.7%) $p=.009$
Steroids[e]	72 (17.1%)	56 (15.6%) $p=.594$	51 (20.4%) $p=.279$	45 (17.9%) $p=.792$	44 (16.9%) $p=.809$
Comorbidities					
Psoriasis	18 (4.3%)	37 (10.3%) $p<.001$	33 (13.2%) $p<.001$	36 (14.3%) $p<.001$	32 (11.9%) $p<.001$
Anterior uveitis	13 (3.1%)	32 (8.9%) $p=<.001$	43 (17.2%) $p=<.001$	39 (15.5%) $p=<.001$	40 (14.9%) $p=<.001$
Referred to a rheumatologist	19 (4.5%)	87 (24.3%) $p=<.001$	95 (38.0%) $p=<.001$	111 (44.0%) $p=<.001$	99 (36.8%) $p=<.001$
IBD disease activity					
Active colitis (P-SCCAI score ≥5)	50 (11.8%)	109 (30.4%) $p=<.001$	101 (40.4%) $p=<.001$	88 (34.9%) $p=<.001$	108 (40.1%) $p=<.001$
Pain medications					
NSAID[f]	121 (28.7%)	145 (40.5%) $p=<.001$	113 (45.2%) $p=<.001$	117 (46.4%) $p=<.001$	124 (46.1%) $p=<.001$
NSAID[g]	9 (2.1%)	24 (6.7%) $p=.002$	21 (8.4%) $p<.001$	28 (11.1%) $p<.001$	23 (8.6%) $p<.001$
Paracetamol[g]	28 (6.6%)	61 (17.0%) $p=<.001$	66 (26.4%) $p=<.001$	57 (22.6%) $p=<.001$	69 (25.7%) $p=<.001$
Amitriptyline[g]	8 (1.9%)	13 (3.6%) $p=.182$	10 (4.0%) $p=.137$	8 (3.2%) $p=.305$	6 (2.2%) $p=.787$
Gabapentin[g]	8 (1.9%)	6 (1.7%) $p=>.99$	7 (2.8%) $p=.433$	4 (1.6%) $p=>.99$	7 (2.6%) $p=.597$
Opioids[g]	6 (1.4%)	19 (5.3%) $p=.003$	25 (10.0%) $p=<.001$	22 (8.7%) $p=<.001$	19 (7.1%) $p=<.001$
	No SpA, $n=121$	Suspected pSpA (ASAS), $n=145$	Suspected AxSpA (ASAS),, $n=113$	Suspected pSpA (ESSG), $n=117$	Suspected AxSpA (ESSG), $n=124$
The effect of NSAID intake on IBD symptoms					
Negative effect on IBD symptoms	15 (12.4%)	27 (18.6%) $p=.166$	27 (23.9%) $p=.022$	29 (24.8%) $p=.014$	32 (25.8%) $p=.008$
No negative effect on IBD symptoms	79 (65.3%)	84 (57.9%) $p=.220$	51 (45.1%) $p=.002$	61 (52.1%) $p=.039$	58 (46.8%) $p=.004$
Unsure of the effect on IBD symptoms	27 (22.3%)	34 (23.4%) $p=.827$	34 (30.1%) $p=.176$	27 (23.1%) $p=.888$	34 (27.4%) $p=.356$

Notes: Disease activity was measured according to the patient simply clinical colitis index (P-SCCAI). The different suspected SpA groups are compared with the non-suspected-SpA group.

[a]Balsalazide sodium, mesalamine, olsalazine or sulfasalazine.

[b]6-Mercaptopurine, azathioprine or methotrexate.

[c]Adalimumab, golimumab, infliximab or vedolizumab.

[d]Budesonide or oral cortisone treatment >3 months.

[e]Budesonide or oral cortisone treatment.

[f]Reported intake during the last year.

[g]Reported current intake.

Table 4. Univariate and multivariate logistic regression analyses, showing patients with inflammatory bowel disease (IBD) and suspected spondyloarthritis (SpA) as the dependent variable.

	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Patients with IBD with suspected axial SpA[a]		
Gender (female reference[b])	1.09 (0.80–1.49)	0.93 (0.66–1.30)
Age	1.01 (1.00–1.02)	*1.02 (1.01–1.04)*
Crohn's disease[c]	0.81 (0.59–1.10)	0.97 (0.69–1.37)
BMI ≥30 kg/m^2	*1.52 (1.03–2.22)*	1.44 (0.96–2.16)
Current/previous smoker	*1.39 (1.02–1.90)*	*1.51 (1.06–2.15)*
Psoriasis	*2.14 (1.32–3.48)*	*1.78 (1.05–3.02)*
Anterior uveitis	*4.40 (2.74–7.06)*	*4.48 (2.67–7.52)*
Active colitis[d]	*2.95 (2.12–4.11)*	*2.51 (1.76–3.57)*
Patients with IBD with suspected peripheral SpA[e]		
Gender (female reference[b])	*1.64 (1.18–2.28)*	*1.58 (1.12–2.21)*
Age	0.98 (0.97–0.99)	0.98 (0.97–0.99)
Crohn's disease[c]	0.83 (0.60–1.15)	0.97 (0.69–1.35)
BMI ≥30 kg/m^2	*1.64 (1.12–2.42)*	*1.57 (1.05–2.33)*
Current/previous smoker	*1.68 (1.21–2.33)*	1.35 (0.95–1.92)
Psoriasis	1.19 (0.68–2.08)	1.02 (0.57–1.83)
Anterior uveitis	1.67 (0.98–2.85)	1.45 (0.82–2.56)
Active colitis[d]	*1.64 (1.15–2.33)*	1.38 (0.95–2.00)
Patients with IBD with suspected axial or peripheral SpA[f]		
Gender (female reference[b])	*1.82 (1.41–2.33)*	*1.63 (1.24–2.13)*
Age	1.00 (1.00–1.01)	1.01 (1.00–1.02)
Crohn's disease[c]	0.82 (0.64–1.06)	0.94 (0.72–1.25)
BMI ≥30 kg/m^2	*2.06 (1.45–2.93)*	*1.91 (1.32–2.76)*
Current/previous smoker	*1.37 (1.07–1.76)*	1.22 (0.92–1.63)
Psoriasis	*2.77 (1.62–4.73)*	*2.65 (1.45–4.83)*
Anterior uveitis	*3.82 (2.08–7.01)*	*3.12 (1.66–5.88)*
Active colitis[d]	*3.55 (2.53–5.00)*	*2.91 (2.03–4.16)*

[a]According to both our modified ASAS and ESSG criteria for axial SpA.
[b]Men was coded 0 and women was coded 1.
[c]CD was coded 0 and UC was coded 1.
[d]Patient Simply Clinical Colitis Index (P-SCCAI) score ≥5.
[e]According to both our modified ASAS and ESSG criteria for peripheral SpA.
[f]According to any of our modified ASAS or ESSG criteria for axial or peripheral SpA.

axial SpA included age, current/previous smoking, comorbid psoriasis, comorbid anterior uveitis and a high Patient Simple Clinical Colitis Index (P-SCCAI) score (≥5). Female gender and BMI ≥30 kg/m^2 were significantly associated with suspected peripheral SpA (Table 4).

Analysis of non-responders

Among the 1037 non-respondents, the proportion of UC patients was higher than that of CD patients, though this difference was not statistically significant (UC: $n=601$; CD: $n=436$; $p=.074$). Non-responders were significantly younger than the responding patients (mean age 48.5 years [SD 22.6] vs. 54.6 years [SD 15.4], $p<.001$). A higher proportion of men (54.3%) compared to women (45.7%) were non-responders ($p=.013$).

When including both responding and non-responding patients and assuming no SpA features in the non-responders, the prevalence of specific SpA features in the non-responders was as follows: 3.8% for anterior uveitis, 4.1% for psoriasis, 6.0% for dactylitis, 9.5% for inflammatory back pain (IBP) according to ASAS criteria, 12.9% for IBP according to Calin criteria, 9.6% for Achilles tendinitis, 12.1% for peripheral arthritis, 13.6% for plantar fasciitis and 23.6% for SpA heredity.

Discussion

Signs of SpA are frequently observed in patients with IBD, but the prevalence and defining characteristics of IBD patients with associated SpA remain incompletely understood. In this questionnaire-based study, we aimed to determine the proportion of IBD patients who meet our adapted versions of the ASAS [4] and ESSG classification criteria for peripheral SpA and axial SpA [12].

Among the responding IBD patients, 24–26% fulfilled our adapted criteria for axial SpA and 24–35% met our adapted criteria for peripheral SpA, depending on the criteria used. We chose to use both our adapted ASAS and ESSG criteria to find out if they demonstrated similar results in this setting. The agreement between the criteria was highest in axial SpA. These findings confirm that SpA features are common in patients with IBD and suggest that the prevalence may be higher than previously anticipated. In the most recent systematic review examining SpA prevalence in patients with IBD, the median prevalence for axial SpA and peripheral SpA was reported as 5% and 16%, respectively [11]. Given the adapted nature of the classification criteria in our study, we consider the patients with IBD fulfilling these adapted criteria as having suspected associated SpA.

Our study also provides valuable insights into specific self-reported SpA manifestations. Compared to a meta-analysis by Karreman et al. we observed a higher prevalence of dactylitis (12.1% vs 0–5%) and peripheral arthritis (24.4% vs. 13%), while the prevalence of enthesitis was within the range presented in the meta-analysis (19.4% for Achilles' tendinitis and 27.4% for plantar fasciitis compared to 1–54%) [17]. The meta-analysis included studies with a mix of clinical evaluations, medical records and self-reported data,

which were highly heterogeneous. Notably, when the meta-analysis focused only on questionnaire-based studies, the reported prevalence was slightly higher and more in line with our findings – 5.8% for dactylitis [18], 5.6–11.1% for peripheral arthritis [19,20] and 16.8% for enthesitis [18,19].

Geographic differences in the prevalence of SpA are well-established, with higher estimates in Northern Arctic communities, including Sweden [21], which may partly explain the relatively high frequency of reported SpA features in our study. Furthermore, the average age of our participants was 10–15 years older than those in other studies, which may have contributed to the increased self-reported prevalence of SpA features.

Approximately one-third of patients with suspected SpA had been referred to a rheumatologist, a proportion that aligns with findings from previous studies [22]. A recent systematic review of referral criteria suggested that patients with IBD exhibiting symptoms such as chronic low back pain, dactylitis, enthesitis, or peripheral joint pain/swelling should be referred to a rheumatologist [23]. Our results underscore the need for a proactive screening of SpA in IBD patients, as only a subset of those with suspected SpA had received appropriate referral. One possible explanation for the low referral rate is insufficient awareness among gastroenterologists and primary care physicians regarding the comorbidity of IBD and SpA, as well as limited focus on musculoskeletal symptoms during routine consultations. Given the complexity of modern treatments for both IBD and SpA, a more holistic approach, incorporating both gastrointestinal and musculoskeletal symptoms, could benefit patients during treatment decision-making.

Regarding sex differences, we found that female gender was associated with suspected peripheral SpA, a result that contrasts with some earlier studies indicating that peripheral SpA affects both sexes equally [24,25]. However, previous research has identified female sex as a risk factor for undifferentiated SpA in IBD patients [26]. Interestingly, our study did not find significant association between female gender and suspected axial SpA.

The association between smoking and suspected SpA in IBD patients has been noted in prior studies [27]. In our study, patients with suspected axial SpA were more likely to have a history of smoking, while no such association was observed in patients with suspected peripheral SpA. We also found that patients with Crohn's disease (CD) and suspected SpA were more likely to be smokers compared to those without SpA, a finding not observed in ulcerative colitis (UC) patients. Smoking has been linked to more severe and active SpA [27], which may explain these findings.

Our study also revealed that patients with IBD and suspected SpA were more likely to be treated with immunomodulators, biologics and glucocorticoids. This may reflect the more severe IBD course in these patients, which increases their likelihood of developing extraintestinal manifestations (EIMs) [28]. Additionally, the use of biologic agents could contribute to the onset or exacerbation of SpA-related symptoms [29], as tumor necrosis factor (TNF)-α inhibitors, for example, have been shown to both induce and worsen psoriasis in IBD patients [30]. This is consistent with other studies that have found associations between biologic therapy and SpA in IBD patients [26,31].

Our study also found that nearly half of the patients meeting our adapted SpA criteria (and 28% of those without suspected SpA) reported NSAID use due to musculoskeletal pain within the last year. This is particularly important because NSAIDs can elevate faecal calprotectin levels, a marker commonly used to monitor IBD activity [32] and have been linked to clinical relapse in IBD patients [33]. The higher prevalence of NSAID use in the suspected SpA groups may reflect greater musculoskeletal pain, but it is noteworthy that the suspected SpA groups also reported a higher prevalence of adverse effects on IBD symptoms due to NSAID use. This suggests that IBD patients with SpA may experience greater benefits from NSAID intake despite the potential side effects. Alternatively, these patients could be more sensitive to NSAID-induced complications due to higher IBD disease activity.

In addition to NSAIDs, the use of other analgesics, such as paracetamol and opioids, was more prevalent among patients with suspected SpA, further indicating increased pain and potential issues with pain management. Previous research has highlighted the increased use of opioids in patients with axial SpA [34], which may contribute to suboptimal therapeutic outcomes when combined with a reduction in the prescription of recommended therapies like TNF-α inhibitors [35].

Patients with IBD who were referred to a rheumatologist had more severe disease, as indicated by higher rates of immunomodulator, biologic, steroid and analgesic use. Regarding IBD and EIMs, certain EIMs may occur independently of intestinal inflammation (i.e., axial SpA and polyarticular peripheral SpA), while other EIMs (i.e., pauciarticular or Type I peripheral SpA and episcleritis) often occur in parallel with IBD activity [3]. However, in our study, the patients with IBD and suspected associated axial SpA were also significantly more likely to have active colitis. Moreover, an active disease has been identified as a risk factor for EIMs in CD patients [28], which is in line with our results that suggest that patients with IBD classified

with suspected associated SpA are approximately three to four times more likely to suffer from an active colitis according to P-SCCAI compared to IBD patients without suspected SpA.

We identified several factors associated with suspected SpA in IBD patients, including female gender, BMI ≥30 kg/m^2, psoriasis, anterior uveitis and a high P-SCCAI score. This is in line with previous studies linking female gender and smoking as risk factors for SpA in IBD [26,36]. Notably, psoriasis and anterior uveitis were stronger predictors of suspected axial SpA than peripheral SpA, indicating a distinct pathophysiological relationship between these manifestations and axial disease.

While our study provides valuable insights, several limitations should be acknowledged. The most significant limitation is that the criteria used to classify 'suspected SpA' were based on self-reported data and did not include laboratory or imaging findings, as required by the original ASAS and ESSG classification criteria. To assess SpA symptoms and features, we employed questionnaire items that correspond to the different variables in ASAS and ESSG classification criteria [9,12,13] (Supplementary Material). However, the questionnaires used in this study has not previously been validated. Instead, we relied on adapted criteria that lack validation in clinical settings and have not been employed in prior studies. This should be taken into considerations when interpreting our findings. The use of self-reported data may also result in overestimation of certain SpA manifestations. Moreover, the response rate was moderate, and the respondents were generally older and more likely to be female compared to non-respondents, which may limit the generalizability of our results. Another limitation is the use of P-SCCAI to assess colonic disease activity in all patients, including those with CD, despite the index being validated primarily for UC. Additionally, we did not incorporate other clinical indicators relevant for CD, such as abdominal pain and the presence of an abdominal mass, in our evaluation of disease activity. Finally, the study lacked objective markers of intestinal inflammation, such as faecal calprotectin levels or endoscopic indices.

However, the strengths of our study include the large sample size and the inclusion of both UC and CD patients, which enhances its applicability.

In conclusion, our study found a higher prevalence of both suspected axial and peripheral SpA in IBD patients than previously reported. However, only one-third of these patients had been referred to a rheumatologist. This highlights the need for gastroenterologists to more proactively screen for SpA features in IBD patients and to strengthen collaboration with rheumatologists. Recognizing and diagnosing SpA in IBD patients may also influence treatment decisions and improve overall patient management.

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Ethical approval

The regional ethic committee in Umeå, Sweden, (Dnr 2018-269-31 M), approved the study. The study has been carried out in accordance with the Helsinki Declaration. All participants gave written informed consent prior to their inclusion in the study.

Author contributions

CRediT: **Nina Pettersson**: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing – original draft; **Fredrik Kragbjerg**: Conceptualization, Formal analysis, Investigation, Writing – review & editing; **Arvid Hamrin**: Investigation, Resources, Writing – review & editing; **Helena Forsblad-d'Elia**: Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – review & editing; **Pontus Karling**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Data availability statement

Selected data are available from the corresponding author on reasonable request.

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