Manuscript title	**THE IMPACT OF SPONDYLOARTHRITIS AND JOINT SYMPTOMS ON HEALTH-RELATED QUALITY OF LIFE AND FATIGUE IN IBD PATIENTS. RESULTS FROM A POPULATION-BASED INCEPTION COHORT (20-YEAR FOLLOW-UP IN THE IBSEN STUDY)**
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Summary: Ongoing joint pain and back pain was associated with reduced quality of life and fatigue in IBD patients after 20 years of disease, while spondyloarthritis without ongoing joint symptoms did not have a negative impact on these patient-reported outcomes.

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Abstract

Background: Patients with inflammatory bowel disease (IBD) often suffer from musculoskeletal manifestations. Health-related quality of life (HRQoL) and fatigue are known to be associated with IBD activity as well as musculoskeletal complaints. The aim of this study was to determine the association between spondyloarthritis, arthralgia or back pain and the patient-reported outcomes of HRQoL and fatigue in IBD patients 20 years after their diagnosis.

Methods: The IBSEN cohort was followed prospectively for 20 years. At the 20-year follow-up the patients answered detailed questionnaires regarding rheumatological manifestations, intestinal symptoms, HRQoL and fatigue. Multiple regression analyses were used to evaluate associations between spondyloarthritis or joint symptoms and HRQoL or fatigue. Gender, IBD diagnosis and age were included in all the multiple regression models, in addition to other clinically relevant confounders.

Results: In total, 441 patients (94%) completed the questionnaires at the 20-year follow-up. The criteria for spondyloarthritis (axial or peripheral) were fulfilled in 158 patients (36%), current back pain during the previous three months was reported by 79 patients (18%) and current arthralgia by 178 patients (40%). Current back pain and arthralgia were independently associated with lower HRQoL, higher levels of fatigue and chronic fatigue. A diagnosis of spondyloarthritis was not associated with reduced HRQoL or fatigue when adjusted for possible confounders.

Conclusions: Current joint symptoms in IBD patients 20 years after diagnosis were associated with poorer HRQoL, higher levels of fatigue and chronic fatigue, while spondyloarthritis did not impact HRQoL or fatigue negatively in this cohort.

Keywords: IBD, arthritis, spondyloarthritis, quality of life, fatigue

Introduction

Numerous studies have shown that inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is associated with reduced health-related quality of life (HRQoL) and increased fatigue compared to the general population, even after many years of disease [1 2]. In addition to increased intestinal disease activity, which is one of the most commonly reported factors [3-5], studies have reported associations between musculoskeletal symptoms and reduced HRQoL [6 7] and higher levels of fatigue [8].

Many IBD patients suffer from musculoskeletal manifestations, such as arthralgia and back pain [9 10]. Some of these fulfil specific criteria for defined rheumatological diagnoses, including spondyloarthritis (SpA), which is a chronic disease that can be classified as either peripheral SpA or axial SpA, depending on the predominance and location of the symptoms [11]. The symptoms of SpA may be continuous or fluctuating [12]. SpA can have a negative impact on HRQoL and fatigue [7 8 13]. We have previously shown that arthralgia was associated with reduced HRQoL in IBD patients [14]. Thus, it might be expected that a diagnosis of SpA and, similarly, general symptoms such as arthralgia or back pain with or without a specific SpA diagnosis can be associated with sustained impaired HRQoL and higher levels of fatigue. Long-term studies on how the burden of ongoing rheumatic manifestations impact IBD patients are missing.

The aim of this study was to determine the association between SpA, arthralgia or back pain and the patient-reported outcomes of HRQoL and fatigue as well as chronic fatigue in IBD patients 20 years after their diagnosis.

Materials and methods

Patients and study design

From 1 January 1990 to 31 December 1993 all newly diagnosed cases of IBD in four counties in south-eastern Norway were included in the IBSEN study (the Inflammatory Bowel South-Eastern Norway study) [15]. The patients were followed with pre-scheduled follow-up visits at years 1, 5, 10 and 20, which included clinical examinations, interviews, laboratory tests, colonoscopies and detailed questionnaires. Further details are described elsewhere [16 17].

At the 5-year follow-up, 80% of the patients underwent a thorough rheumatological assessment [18 19]. At the 20-year follow-up, all participants were asked to complete patient-reported questionnaires, which included generic and disease-specific HRQoL instruments, a fatigue instrument and a detailed questionnaire on musculoskeletal symptoms and rheumatological diagnoses [17 20].

Rheumatological assessment

The patients were classified as having SpA if they fulfilled the criteria for axial or peripheral SpA according to the Assessment of Spondyloarthritis International Society (ASAS) criteria (Fig.1 and 2) [21 22]. The diagnosis was based on the cumulative results from the 5-year follow-up and the rheumatological questionnaire at the 20-year follow-up, thus representing the entire disease course, regardless of what time during the disease course the symptoms necessary for fulfilling the diagnosis had been present. Other specific musculoskeletal symptoms were reported at the 20-year follow-up, including arthralgia and back pain. Arthralgia was defined as the sensation of daily joint pain the previous three months without specification of joint localisation. Patients with registered inflammatory joint disease such as arthritis were not excluded from this group. Thus, arthralgia presented in the current study is the patients' feeling of joint pain itself, regardless of objective findings. Daily back pain during the previous three months was reported by the patients and registered regardless of known inflammatory back disease [20].

HRQoL and fatigue

HRQoL was assessed at the 20-year follow-up with the Norwegian version of the Inflammatory Bowel Disease Questionnaire (N-IBDQ) [23] and the 36-item Short Form Health Survey (SF-36) [24]. For evaluation of all aspects of HRQoL, it is recommended to use the generic SF-36 form and the disease specific IBDQ form in combination [25]. Fatigue was evaluated with the fatigue questionnaire (FQ) [26].

SF-36

The SF-36 is a generic HRQoL instrument containing 36 questions, sub-grouped into eight different domains, covering both physical and mental measures [24]. The eight domains are as follows: Physical Functioning (PF), Role limitation due to Physical Health (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role limitations due to Emotional problems (RE), and Mental Health (MH). The raw scale scores are transformed into a 0 – 100 scale, with a higher score representing a better HRQoL. The SF-36 has been translated to Norwegian and validated in the Norwegian population [27].

N-IBDQ

The IBDQ is a disease-specific questionnaire for IBD patients. The Norwegian version of the IBDQ (N-IBDQ) has been translated and validated previously in the IBSEN study [23]. The questionnaire consists of 32 items graded on a 7-point Likert scale from 1 (a very severe problem) to 7 (not a problem), with a total score ranging from 32 to 224. A higher score indicates a better HRQoL. The patients who had undergone colectomy were excluded from the N-IBDQ analyses (n=54), since N-IBDQ includes items that are not relevant for colectomised patients.

Fatigue Questionnaire (FQ)

The FQ, developed by Chalder et al. [26], was intended to measure fatigue in epidemiological studies. It contains 11 items measuring physical and mental fatigue, as well as two additional questions that measures the duration and extent of fatigue symptoms. The responses to each item are scored on a Likert scale from 0-3, and the total fatigue score ranges from 0 to 33, with a higher score indicating higher levels of fatigue. The FQ score can also be dichotomised, so that each question with a score of 0 or 1 are given a new score of 0, and each question with a score of 2 or 3 are given a new score of 1, thus producing a score from 0 to 11. Chronic fatigue is defined as a dichotomised score ≥4 with a symptom duration of ≥6 months. The questionnaire has been translated and validated in Norwegian [26 28].

IBD activity

The patients reported intestinal symptoms/activity in the past two weeks prior to the 20-year follow-up as 1) “no complaints/symptoms”; 2) “some symptoms (get by without problems with daily activities/functioning)”; 3) “a lot of symptoms (trouble with daily activities/functioning, for instance sick leave)”; and 4) “severe symptoms (cannot perform daily activities/sick leave or hospitalised)”. These were further dichotomised into “no complaints/symptoms” and “current intestinal symptoms”. Disease activity was assessed with the Harvey-Bradshaw index (HBI) [29] for the CD patients and the Simple Clinical Colitis Activity Index (SCCAI) [30] for the UC patients (UC patients who had undergone colectomy were excluded from the SCCAI analyses). A score of ≤4 on the HBI was interpreted as clinical remission and <2.5 for the SCCAI, the latter as defined by Higgins et al [31]. The disease activity indices were associated with the variable “current intestinal symptoms” in the present study population and were thus excluded from the multiple linear regression analysis to avoid multicollinearity (see calculations in the appendix). Ongoing medication with corticosteroids (prednisolone) at the 20-year follow-up was chosen as a proxy for intestinal disease activity. No association was found between the variable “current intestinal symptoms”

and “use of prednisolone at the 20-year follow-up”, and thus, both variables were included from the linear regression analyses.

Demographics

Demographic data were patient-reported. Working status was dichotomised into working or studying and not working (unemployed, retired, disabled and housewives). Education level was dichotomised as ≥12 years or <12 years. Relationship status was categorised as living alone or living together/married. Since both “education level” and “relationship status” were independently and significantly associated with “working status”, only “working status” was included in the multiple regression analyses to avoid multicollinearity (calculations are shown in the appendix).

Statistical analyses

Continuous variables are presented as the median and range, and categorical variables are presented as counts and percentages. Linear regression models were fitted separately for each of the domains of the SF-36, the N-IBDQ total score and the FQ total score. All analyses were adjusted for sex, age at the 20-year follow-up and type of diagnosis (UC or CD). The remaining selected independent variables that had a p-value <0.1 in the univariate linear regression analyses for the respective HRQoL and fatigue scores were included in the multiple linear regression models. The results are given as unstandardised estimates of beta with 95% CI intervals and standardised beta coefficients (data not shown). The independent variables included in the multiple linear regression analyses were chosen based on results from previously published articles, including the results from the 10-year follow-up [32 33] and 20-year follow-up [34 35] from the IBSEN study. In addition to our rheumatological variables of interest, we chose to include variables related to demographics or disease activity previously

shown to be associated with reduced HRQoL and/or increased fatigue in the statistical models.

Logistic regression was used to estimate the odds for chronic fatigue. Selected variables that reached $p<0.1$ in univariate analyses were fitted into multiple logistic regression models. To avoid overfitting, we restricted the number of included variables to <8. The results are expressed as odds ratios (OR) with 95% confidence intervals.

Due to multiple testing, p-values <0.01 were considered statistically significant for all statistical analyses, and all tests were two-sided. The analyses were performed using SPSS version 25.

Results

Four hundred seventy of the eligible 599 patients (78%) from the IBSEN cohort participated at the 20-year follow-up. Of those, 94% (n=441) completed the patient-reported rheumatic questionnaires (Fig. 3), including 365 patients who had undergone the rheumatological assessment at the 5-year follow-up. No significant differences in demographics or disease characteristics were found between the patients who did or did not complete the questionnaires [17]. Demographics and IBD characteristics are shown in Table 1.

The ASAS criteria for SpA (Fig. 1 and 2) were fulfilled by 158 patients (36%), of whom 35 were defined as axial SpA and 123 as peripheral SpA (Fig. 3) [17 20]. Current arthralgia was reported by 178 patients (40%) and current back pain by 79 patients (18%). There was substantial overlap between the patients with SpA and those reporting current arthralgia and back pain, as 59 % of the patients with SpA also reported current arthralgia or back pain (Fig. 4a). There was also overlap between the patients reporting current intestinal symptoms, arthralgia and back pain, which is depicted in Fig. 4b.

SF-36

In univariate linear regression analyses, SpA was associated with reduced scores in the SF-36 RP, BP, BP, GH and SF domains (Table 2). After adjusting for possible confounders (sex, age at the 20-year follow-up, diagnosis (UC/CD), current intestinal symptoms, working status, prednisolone use at the 20-year follow-up) in the multiple regression models, this association was no longer statistically significant (Table 3a, for the full version see Appendix). Current arthralgia and back pain were both independently associated with reduced scores in all of the SF-36 domains in univariate linear regression analyses. In the multiple linear regression analyses, the association with back pain remained statistically significant for the following SF-36 domains: PF, RP, BP, VT and SF (all $p<0.01$). Similarly, for arthralgia, the adjusted association remained statistically significant for the following SF-36 domains: RP, BP, GH, VT, SF and RE (all $p<0.01$) (Table 3a).

N-IBDQ

SpA was not associated with the total N-IBDQ score in any of the analyses (Table 2 and 3a). Both current arthralgia and back pain were associated with the total N-IBDQ score in univariate analyses and when adjusted for the following variables in multiple linear regression analyses: sex, age at the 20-year follow-up, diagnosis (UC/CD), current intestinal symptoms, working status, and prednisolone use at the 20-year follow-up (Table 3a).

Fatigue questionnaire (FQ)

SpA was not associated with a higher level of fatigue or chronic fatigue in any analyses (Tables 2 and 3a). Current arthralgia and back pain were associated with a higher level of fatigue in univariate and multiple linear regression analyses (Table 3a). In a multiple logistic regression model, both current arthralgia and back pain were independently associated with higher odds for chronic fatigue when adjusted for the possible confounders: sex, age at the 20-

year follow-up, diagnosis (UC/CD), current intestinal symptoms, and working status (Table 3b).

Discussion

In this large population-based IBD cohort in which the patients were followed for 20 years after their first diagnosis, current daily back pain and arthralgia were independently associated with lower HRQoL, higher levels of fatigue and chronic fatigue. A diagnosis of SpA was not associated with reduced HRQoL or fatigue when adjusted for possible confounders.

HRQoL

SpA was associated with reduced scores in several of the SF-36 domains in univariate analyses, but these associations disappeared when adjusted for selected confounders (Table 3a, for the full version see Appendix). Previous studies have reported reduced HRQoL in patients with both axial and peripheral SpA [7 13], but these studies reported findings among patients without concurrent IBD. Thus, SpA in IBD patients might be presented differently than in patients without IBD. The lack of association between the SpA diagnosis and the HRQoL outcomes (Table 3a) in the current study might partly be explained by the method, with SpA reported as accumulated findings over the 20-year period, while HRQoL was reported as a cross-sectional value at the 20-year follow-up. Another explanation can be that the patients suffering from SpA had adapted to their symptoms over time, so-called response shift, and thus, the burden of joint symptoms in patients with SpA would not affect the patients' HRQoL outcomes as much as at the onset of symptoms.

We found that a high burden of joint symptoms, presented either as current arthralgia or current back pain had a strong association to reduced HRQoL (Table 3a). This is in accordance with Van der Have et al. [36], who investigated IBD patients at an outpatient clinic in the Netherlands, and reported that patients with back pain or arthralgia had lower HRQoL

compared to those without. Furthermore, arthralgia in IBD patients was also associated with reduced HRQoL at the 5-year follow-up in the IBSEN study, although arthralgia presented in the article included only patients with non-inflammatory joint pain [14]. The overall proportion of patients with arthralgia was high in the current study (40%), which can partly be explained by the ageing IBD cohort. Our data revealed a substantial overlap between the patients with SpA and those reporting current arthralgia or back pain at the time of the 20-year follow-up (Fig. 4a). Thus, the absence of association between SpA and the SF-36 domains in multiple regression analyses after inclusion of possible confounders, including current arthralgia and back pain, implies that ongoing symptom burden affects the HRQoL outcomes more than the underlying SpA diagnosis itself. IBD patients with SpA can experience fluctuations in joint symptoms and even be asymptomatic [37], and the lack of association between SpA and HRQoL might also be due to that several of the patients were asymptomatic or had inactive disease at the time of the 20-year follow-up.

Fatigue

While SpA was not associated with more fatigue in the current study, both the current symptoms of arthralgia and back pain were (Table 3a). These symptoms were also associated with higher odds for chronic fatigue. In general, few studies have reported on the associations between musculoskeletal symptoms/diagnoses and fatigue in IBD patients, and comparison to the available studies is hampered by differences in diagnostic criteria and fatigue instruments. SpA in patients without IBD has been associated with high levels of fatigue in previous studies. Stebbings et al. [8] reported high levels of fatigue in patients with axial SpA in a cross-sectional study in New Zealand, and Chauffier et al. [38] found high levels of fatigue in SpA patients in France. The lack of association between SpA and fatigue in the current study might

be explained by the fact that SpA was diagnosed over a 20-year period and fatigue as a cross-sectional value at the 20-year follow-up, in the same way as the HRQoL outcomes.

In line with the current study, Villoria et al. [39] found an association between joint pain in IBD outpatients in Spain and increased fatigue, and Salvetti et al. [40] found that patients with chronic low back pain without concurrent IBD reported higher levels of fatigue compared to the estimates from the background population in Brazil.

Clinical interpretation of the results

To the best of our knowledge, a specific cut-off for the clinically meaningful threshold of the separate SF-36 domains has not been published for IBD in general, but Coteur et al. have published a minimal clinically important difference (MCID) for CD patients [41]. According to these thresholds, current back pain reached a clinically important difference in the multiple linear regression analyses for the PF, RP and BP domains, while current arthralgia reached the threshold for the BP, GH and VT domains (data not shown), supporting a clinical impact on HRQoL.

To further assess the impact of the joint symptoms on the HRQoL outcomes, we compared the estimated standardised beta-coefficients (weighted coefficients) for each of the variables "current intestinal symptoms", "current back pain" and "current arthralgia" (data not shown). The strength of the association between these three variables and the separate SF-36 domains was similar, indicating a comparable impact of joint symptoms and the intestinal symptoms/IBD activity on HRQoL.

A clinically meaningful change in the disease-specific IBDQ score has been suggested at 16 points for the overall score [42 43]. In our multiple linear regression model, "current intestinal symptoms" reached this threshold with a B value of -21 (95 % CI: -26, -16), but back pain and arthralgia did not, despite the results being statistically significant. This is not surprising,

considering that the IBDQ is a disease-specific HRQoL instrument that measures IBD symptoms, and can also explain why a diagnosis of SpA was not associated with the N-IBDQ.

To our knowledge, no studies are published with a given threshold to predict a clinically meaningful difference for the continuous FQ score in IBD patients, but both arthralgia and back pain were independently associated with chronic fatigue in the current study, indicating a clinical impact.

Strengths and limitations

The current study is based on data from a well-characterised population-based cohort of IBD patients, who have been followed closely over 20 years since their IBD diagnosis, with an overall very good patient adherence and completeness of the clinical data.

The SpA diagnosis is based on a set of the current internationally accepted criteria (the ASAS criteria) following objective findings and clinical symptoms, and partly based on patient-reported questionnaires. This could have led to an overestimation of the number of patients with this diagnosis, but as the results were based on the ASAS criteria, we believe that they were as close as possible to a reliable diagnosis. Repeated rheumatological assessments at each follow-up in the IBSEN study would have been superior to the current method, but this was not feasible. Validated patient-reported outcome measure instruments and activity indices were used which strengthens the results.

We did not stratify on the type of IBD diagnosis in the current study, but this variable was included in all multiple regression analyses, and the results showed that the IBD diagnosis had little or no impact on the HRQoL and fatigue outcomes in this context.

Conclusions

IBD patients with current arthralgia and back pain reported reduced HRQoL, higher levels of fatigue and more chronic fatigue compared to IBD patients without these symptoms 20 years after their IBD diagnosis. SpA did not have a negative impact on HRQoL or fatigue in this cohort when adjusted for possible confounders, including ongoing joint symptoms. A closer cooperation between gastroenterologists and rheumatologists for patients with a shared intestinal and rheumatological disease burden might lead to better treatment and follow-up.

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Author contributions

The authors Alvilde M. Ossum, Øyvind Palm, Milada Cvancarova, Bjørn Moum and Marte L. Høivik were involved in the study conceptualisation and design. The authors Alvilde M. Ossum, Øyvind Palm, Tomm Bernklev, Jørgen Jahnsen, Bjørn Moum and Marte L. Høivik all contributed to the acquisition of data. The authors Alvilde M. Ossum, Øyvind Palm, Milada Cvancarova, Bjørn Moum and Marte L. Høivik also interpreted the data and drafted the manuscript, and the statistical analyses were performed by Alvilde M. Ossum and Milada Cvancarova. All authors reviewed and provided critical revisions, and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria

and that no others meeting the criteria have been omitted. The guarantor of the study is Bjørn Moum.

Conflicts of interest

Marte L. Høivik has received lecture fees from Takeda, MSD, Meda and Abbvie, research grants from Ferring, Tillots, Pfizer and Takeda, and advisory board fees from Takeda. Jørgen Jahnsen has served as a speaker, consultant or advisory board member for AbbVie, Astro Pharma, Boerhinger Ingelheim, BMS, Celltrion, Ferring, Hikma, Janssen, Meda, MSD, Napp Pharma, Orion Pharma, Pfizer, Pharmacosmos, Takeda, Tillotts and Sandoz.

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Figure legends

Fig. 1. The Assessment of Spondyloarthritis International Society (ASAS) criteria for axial spondyloarthritis (SpA).

Fig. 2. The Assessment of Spondyloarthritis International Society (ASAS) criteria for peripheral spondyloarthritis (SpA).

Fig. 3. Flow chart of the participants in the IBSEN (the Inflammatory Bowel South-Eastern Norway) study. UC=ulcerative colitis. CD=Crohn's disease.

Fig. 4a: Patients with a diagnosis of SpA (spondyloarthritis) and those reporting current arthralgia and back pain at the time of the 20-year follow-up.

Fig. 4b: Patients reporting current intestinal symptoms, arthralgia and back pain at the 20-year follow-up.

	Univariate		Multivariate	
Variable	**OR**	**95 % CI**	**OR**	**95 % CI**
Gender *Ref=males*	1.92	1.20, 3.06	1.53	0.89, 2.62
Diagnosis *Ref=ulcerative colitis*	1.38	0.86, 2.22	1.14	0.65, 1.99
Age at 20-year follow-up *Per year continuous*	0.99	0.97, 1.01	0.97	0.95, 1.00
SpA *Ref=without SpA*	1.29	0.81, 2.05	-	
Current arthralgia *Ref=no arthralgia*	3.64	2.23, 5.96	2.68*	1.54, 4.65
Current back pain *Ref=no back pain*	3.60	2.12, 6.13	2.69*	1.46, 4.96
Current intestinal symptoms *Ref=no intestinal symptoms*	2.19	1.37, 3.51	1.52	0.88, 2.63
Work status *Ref=work/studying*	2.25	1.41, 3.59	1.90	1.04, 3.48
Prednisolone use at the 20-year follow-up *Ref=prednisolone use at the follow-up*	1.13	0.41, 3.11	-	

Table 3b. Multiple logistic regression model for chronic fatigue. Estimated odds ratio (OR) with 95 % confidence intervals (CI). Chronic fatigue was defined as a dichotomised FQ score ≥4 with a symptom duration of ≥6 months. * = p-value<0.01

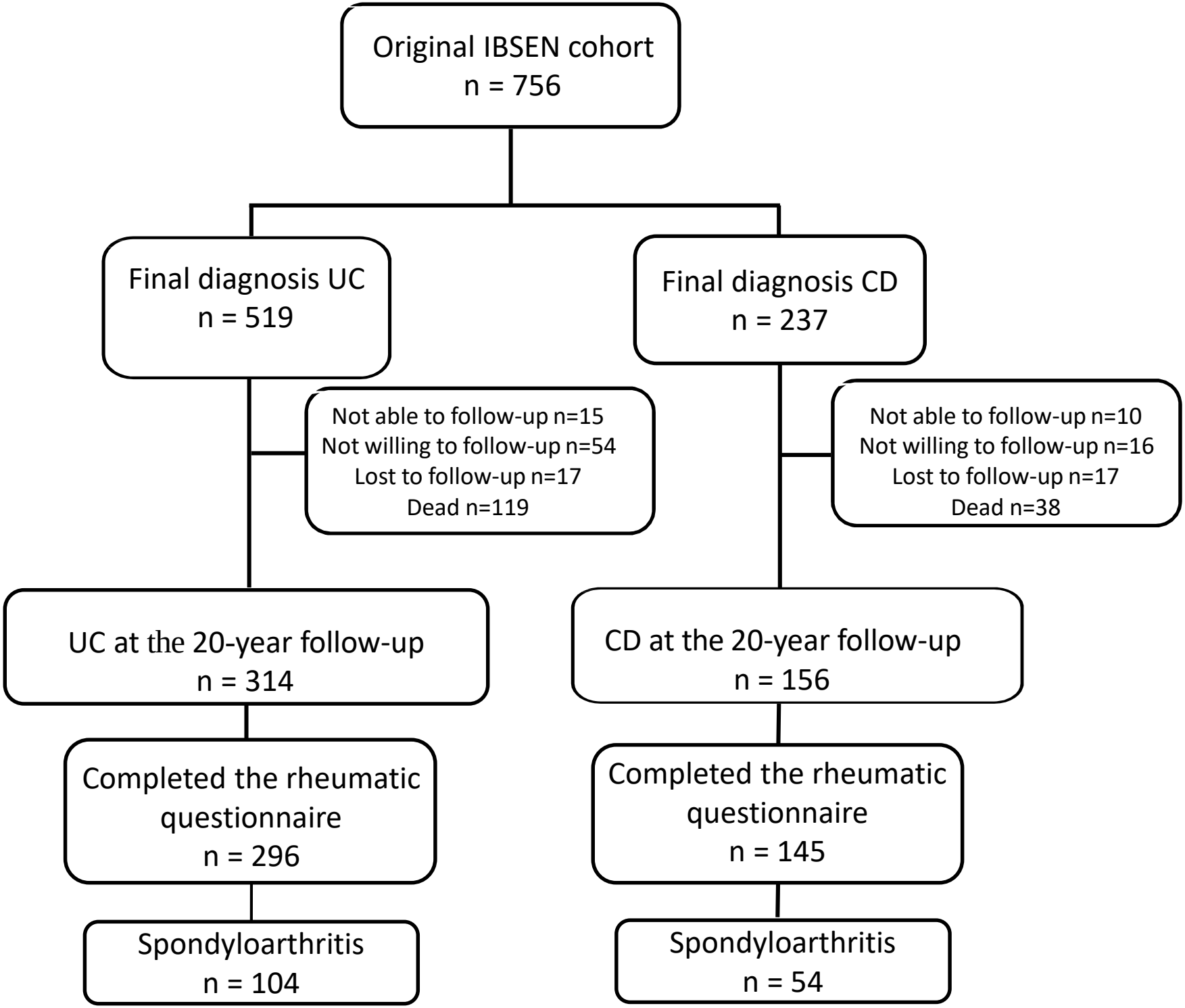
	Spondyloartritis	Current arthralgia	Current back pain	Current intestinal symptoms
Physical Function		-4.1 (-7.4;-0.9)[c]	**-14.2 (-18.3;-10.1)[a]**	**-4.5 (-7.6;-1.3)[b]**
Role Physical		**-15.0 (-22.0;-8.1)[a]**	**-18.7 (-27.3;-10.0)[a]**	**-14.1 (-20.8;-7.4)[a]**
Bodily Pain	-5.0 (-9.0;-1.0)[c]	**-16.0 (-20.1;-11.9)[a]**	**-20.2 (-25.3;-15.1)[a]**	**-11.8 (-15.7;-7.9)[a]**
General Health		**-11.3 (-15.7;-6.9)[a]**	-5.7 (-11.1;-0.2)[c]	**-7.1 (-11.3;-2.8)[b]**
Vitality		**-9.3 (-13.4;-5.3)[a]**	**-7.9 (-13.0;-2.8)[b]**	**-9.4 (-13.3;-5.4)[a]**
Social Functioning		**-9.1 (-13.7;-4.4)[a]**	**-8.2 (-14.1;-2.4)[b]**	**-8.1 (-12.6;-3.6)[a]**
Role Emotional		**-11.9 (-18.9;-4.9)[b]**	-9.6 (-18.4;-0.8)[c]	
Mental Health		-3.5 (-6.8;-0.2)[c]	-4.5 (-8.6;-0.3)[c]	
N-IBDQ total score		**-7.1 (-11.8;-2.5)[b]**	**-9.3 (-15.0;-3.5)[b]**	**-21.0 (-25.6;-16.5)[a]**
Fatigue Questionnaire total score		**2.7 (1.7;3.7)[a]**	**1.9 (0.7;3.2)[b]**	**1.8 (0.8;2.7)[a]**

Table 3a. The variables spondyloarthritis, current arthralgia, current back pain and current intestinal symptoms in the multiple linear regression models for the eight domains of the SF-36 (the 36-item Short Form Health Survey), the N-IBDQ (the Norwegian Inflammatory Bowel Disease Questionnaire) total score and the Fatigue Questionnaire total score. The additional included possible confounders in the regression models were: sex, diagnosis (CD/UC), age at the 20-year follow-up, working status, and prednisolone use at the 20-year follow-up. The values are presented as estimates of B coefficients with 95 % confidence intervals.

[a] = $p<0.001$, [b] =$p<0.01$, [c] =$p<0.05$. p-values <0.01 were considered statistically significant and are marked in bold. Only the results with p-values<0.05 are included in the table.

	Physical Function	Role Physical	Bodily Pain	General Health	Vitality	Social Functioning	Role Emotional	Mental Health	N-IBDQ total score	Fatigue Questionnaire total score
Female sex	**-7.4 (-4.3;-10.5)[a]**	**-8.9 (-2.4;-15.4)[b]**	**-5.3 (-1.4;-9.1)[b]**		**-8.3 (-4.4;-12.1)[a]**	-4.5 (-0.1;-8.9)[c]	-7.6 (-1.0;-14.2)[c]	-3.8 (-0.7;-6.9)[c]	**-6.4 (-1.9;-10.8)[b]**	**1.7 (2.6;0.8)[a]**
Diagnosis CD		-7.0 (-13.9;-0.1)[c]			-5.1 (-9.1;-1.0)[c]					
Age at the 20-year follow-up	**-0.4 (-0.5;-0.2)[a]**		0.2 (0.0;0.4)[c]	**0.3 (0.1;0.5)[b]**	**0.4 (0.2;0.6)[a]**	0.2 (0.0;0.5)[c]	**0.5 (0.2;0.9)[b]**	0.2 (0.0;0.3)[c]	**0.4 (0.2;0.6)[b]**	**-0.1 (-0.1;-0.0)[b]**
Spondylo-arthritis			-5.0 (-9.0;-1.0)[c]							
Current arthralgia	-4.1 (-7.4;-0.9)[c]	**-15.0 (-22.0;-8.1)[a]**	**-16.0 (-20.1;-11.9)[a]**	**-11.3 (-15.7;-6.9)[a]**	**-9.3 (-13.4;-5.3)[a]**	**-9.1 (-13.7;-4.4)[a]**	**-11.9 (-18.9;-4.9)[b]**	-3.5 (-6.8;-0.2)[c]	**-7.1 (-11.8;-2.5)[b]**	**2.7 (1.7;3.7)[a]**
Current back pain	**-14.2 (-18.3;-10.1)[a]**	**-18.7 (-27.3;-10.0)[a]**	**-20.2 (-25.3;-15.1)[a]**	-5.7 (-11.1;-0.2)[c]	**-7.9 (-13.0;-2.8)[b]**	**-8.2 (-14.1;-2.4)[b]**	-9.6 (-18.4;-0.8)[c]	-4.5 (-8.6;-0.3)[c]	**-9.3 (-15.0;-3.5)[b]**	**1.9 (0.7;3.2)[b]**
Current intestinal symptoms	**-4.5 (-7.6;-1.3)[b]**	**-14.1 (-20.8;-7.4)[a]**	**-11.8 (-15.7;-7.9)[a]**	**-7.1 (-11.3;-2.8)[b]**	**-9.4 (-13.3;-5.4)[a]**	**-8.1 (-12.6;-3.6)[a]**			**-21.0 (-25.6;-16.5)[a]**	**1.8 (0.8;2.7)[a]**
Unemployed/not studying	**-9.6 (-5.9;-13.3)[a]**	**-19.4 (-11.5;-27.3)[a]**	**-8.6 (-3.9;-13.3)[a]**	**-13.2 (-8.2;-18.1)[a]**	**-6.7 (-2.1;-11.4)[b]**	**-8. 1 (-2.8;-13.4)[b]**	**-16.4 (-8.3;-24.4)[a]**	-5.0 (-1.2;-8.8)[c]	**-10.7 (-5.4;-16.0)[a]**	1.4 (2.5;0.3)[c]
Prednisolone use at the 20-year follow-up						-10.6 (-20.4;-0.8)[c]				

Table 3a. The independent variables included in the multiple linear regression models for the eight domains of the SF-36 (the 36-item Short Form Health Survey), the N-IBDQ (the Norwegian Inflammatory Bowel Disease Questionnaire) total score and the Fatigue Questionnaire total score. The values are presented as estimates of B coefficients with 95 % confidence intervals. [a] = p<0.001, [b] =p<0.01, [c] =p<0.05. p-values <0.01 were considered statistically significant and are marked in bold. Only the results with p-values<0.05 are included in the table.


Original IBSEN cohort
n = 756
Final diagnosis UC
n = 519
Final diagnosis CD
n = 237
Not able to follow-up n=15
Not willing to follow-up n=54
Lost to follow-up n=17
Dead n=119
Not able to follow-up n=10
Not willing to follow-up n=16
Lost to follow-up n=17
Dead n=38
UC at the 20-year follow-up
n = 314
CD at the 20-year follow-up
n = 156
Completed the rheumatic questionnaire
n = 296
Completed the rheumatic questionnaire
n = 145
Spondyloarthritis
n = 104
Spondyloarthritis
n = 54

ASAS criteria for Axial Spondyloarthritis (SpA)

In patients with ≥ 3 months back pain and onset < 45 years

Sacroiliitis on imaging
AND
≥ 1 SpA feature

OR

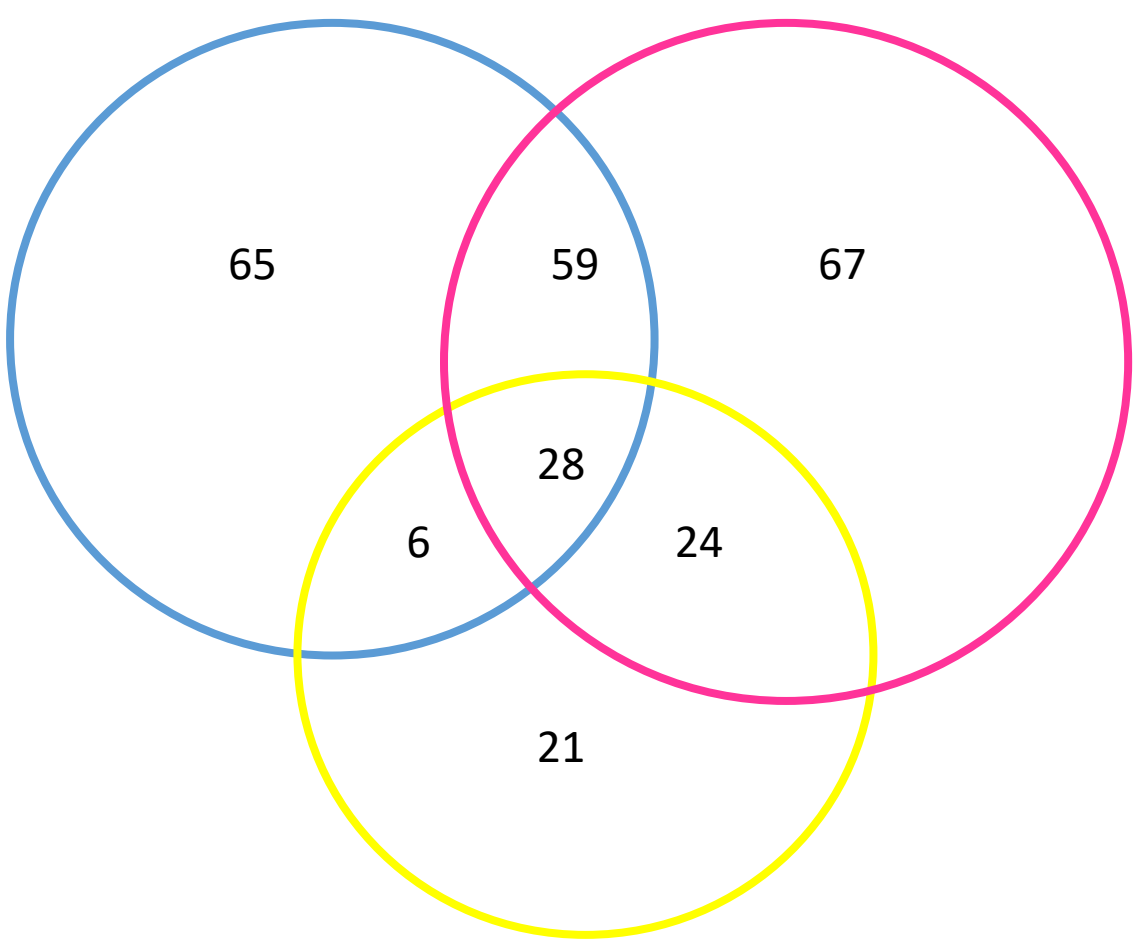
HLA-B27 positive
AND
≥ 2 other SpA features

SpA features:

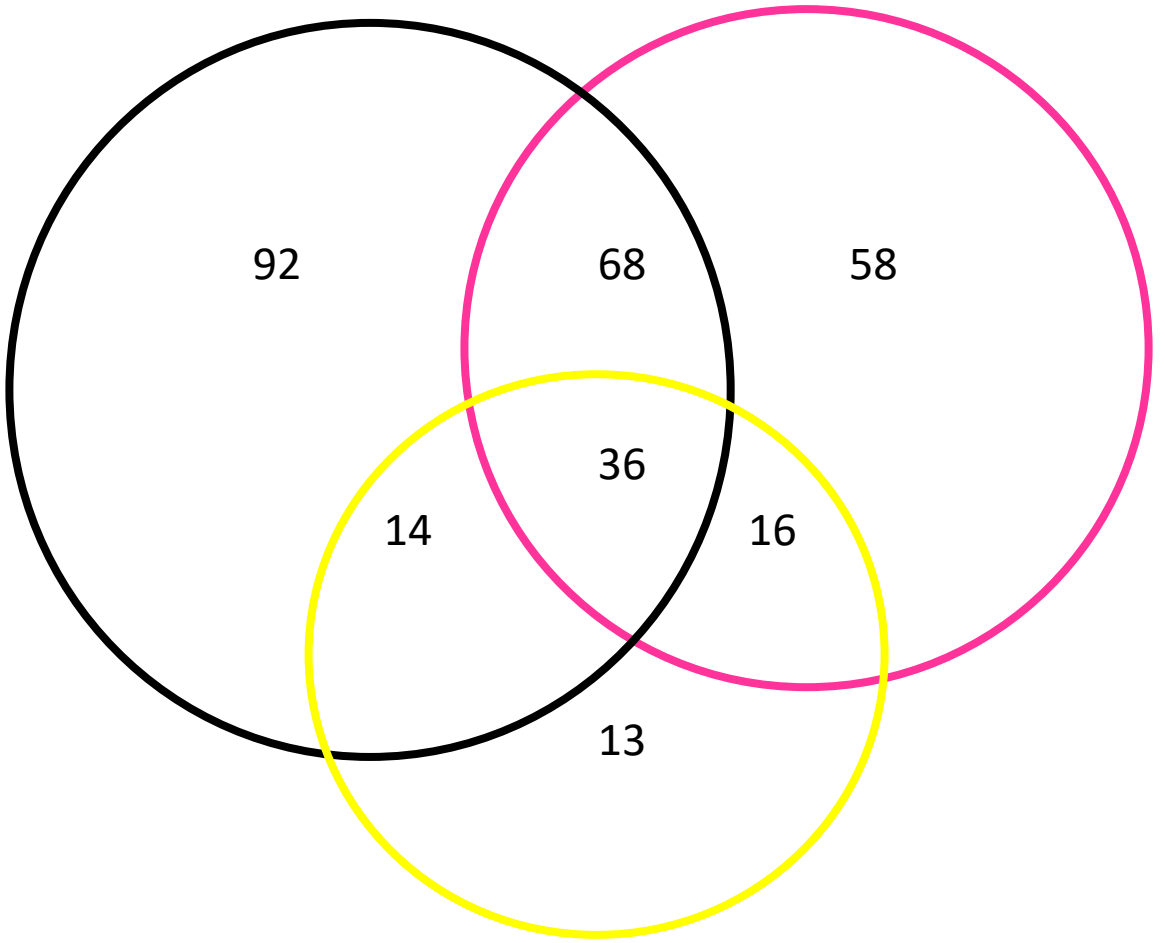
- Inflammatory back pain
- Arthritis
- Enthesopathy (heel)
- Uveitis
- Psoriasis
- IBD
- Good response to NSAIDs
- Family history of SpA
- HLA-B27
- Elevated CRP

Sacroiliitis on imaging:

- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- Definite radiographic sacroiliitis according to the modified New York criteria


Spondyloarthritis n=158
Current arthralgia n=178
65
59
67
28
6
24
21
Current back pain n=79

A


Current intestinal symptoms n=210
Current arthralgia n=178
92
68
58
36
14
16
13
Current back pain n=79

B

Peripheral Arthritis and/or Enthesitis and/or Dactylitis
PLUS

≥ 1 SpA feature

- Uveitis
- Psoriasis
- Crohn's/colitis
- Preceding infection
- HLA-B27
- Sacroiliitis on imaging

OR

≥ 2 other SpA features

- Arthritis
- Enthesitis
- Dactylitis
- Inflammatory back pain
- Family history of SpA