RHEUMATOLOGY

Rheumatology 2021;60:4121–4129
doi:10.1093/rheumatology/keaa888
Advance Access publication 6 January 2021

Original article

The changing states of fibromyalgia in patients with axial spondyloarthritis: results from the British Society of Rheumatology Biologics Register for Ankylosing Spondylitis

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Abstract

Objectives. To identify factors associated with FM development and recovery in patients with axial SpA (axSpA).
Methods. The British Society of Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS) recruited patients with axSpA from 83 centres in a prospective study. FM was diagnosed using the self-reported Fibromyalgia Survey Diagnostic Criteria from 2015. Measures of axSpA disease activity and clinical findings were recorded at regular intervals. We identified predictors for FM development and recovery between yearly visits using uni- and multivariable logistic regression models.
Results. A total of 801 participants, 247 (30.8%) female, had two or more visits and were eligible for inclusion. A total of 686 participants did not have FM at baseline, of whom 45 had developed FM at follow-up, while 115 participants had FM at baseline, of whom 77 had recovered at follow-up. A high baseline BASDAI score [odds ratio (OR) 1.27 (95% CI 1.08, 1.49)] and Widespread Pain Index (WPI) [OR 1.14 (95% CI 1.02, 1.28)] were significantly associated with FM development in the final multivariable model. A low baseline BASFI score [OR 0.68 (95% CI 0.53, 0.86)] and WPI [OR 0.84 (95% CI 0.720, 0.97)] and starting a TNF inhibitor [OR 3.86 (95% CI 1.54, 9.71)] were significantly associated with FM recovery.
Conclusion. High levels of disease activity and the presence of widespread pain is associated with the development of FM in patients with axSpA, while low levels of the same variables and starting a TNF inhibitor are associated with recovery from FM. The presence of comorbid FM should be considered in patients with persistent high axSpA disease activity and widespread pain.

Key words: spondyloarthritis, fibromyalgia, trajectories, disease activity

Rheumatology key messages

- In patients with axial spondyloarthritis (axSpA), comorbid fibromyalgia (FM) is not usually a permanent state.
- High levels of axSpA disease activity are associated with developing FM.
- Patients with low levels of axSpA disease activity or who experience a change in disease activity through starting a TNF inhibitor are more likely to recover from FM.

Introduction

Axial SpA (axSpA) is a chronic inflammatory disease associated with the presence of HLA-B27 [1]. AxSpA may affect the sacroiliac joints, spine and peripheral joints and the pathological process leads to the formation of new bone. Most untreated patients will eventually suffer from limited mobility of the spine that may cause pain and physical dysfunction [1, 2]. AS is a form of axSpA that can be diagnosed by the modified New York

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Submitted 8 April 2020; accepted 14 November 2020

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(mNY) criteria [3]. The mNY criteria require radiological evidence of sacroiliitis. In recent years the Assessment of SpondyloArthritis international Society (ASAS) has developed classification criteria for axSpA that do not require sacroiliitis to be visible on conventional radiographs [4]. FM is a disorder of pain perception characterized by widespread pain and fatigue. There are many additional symptoms, including lack of concentration, autonomic dysfunction and abdominal pain [5]. In the general population, FM should be diagnosed promptly and patients should be offered treatment for the condition [6].

The estimated prevalence of coexisting FM in axSpA is 14% (95% CI 8, 20) according to a recent meta-analysis [7]. The identification of comorbid FM in patients with axSpA could be especially important in the current treat-to-target era, as the presence of FM may interfere with the patient's self-assessment of treatment response [8, 9]. We have previously shown that patients with axSpA and FM report higher levels of axSpA disease activity, depression, anxiety, fatigue and work interference compared with patients with axSpA alone [10]. The presence of FM also contributes negatively to the quality of life of these patients [11]. However, FM in axSpA may not be a permanent state, and studies have reported that ∼50% 'recover' following the start of TNF inhibitor (TNFi) treatment [8, 9].

The identification of predictors for longitudinal FM development has been identified as a research priority in a recent systematic review and meta-analyses [7] and the change in the FM state is of particular interest. This article examines the longitudinal factors associated with FM development and recovery in patients with axSpA.

Methods

The British Society of Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS) is a prospective cohort study that recruited biologic therapy–naïve patients fulfilling the ASAS criteria for axSpA [8]. Participants were recruited from 83 secondary care rheumatology centres across the UK between December 2012 and December 2017 and the full protocol has been published previously [12]. Visits were scheduled at 3 and 6 months for participants commencing TNFi therapy and then yearly for the whole cohort. At each visit the presence of extraspinal manifestations, history of 14 prespecified common comorbidities and BASMI score were recorded and blood samples were analysed for inflammatory markers (CRP and ESR). In addition, the following patient-reported questionnaires were mailed to participants at the time of each visit: BASDAI, BASFI, Hospital Anxiety and Depression Scale (HADS; score 0–21) [10], (Chalder Fatigue Scale (score 0–11) [11] and the Jenkins Sleep Evaluation Questionnaire (score 0–20) [12].

The 2010 ACR Fibromyalgia Preliminary Diagnostic Criteria introduced the possibility of diagnosing FM using a self-reported questionnaire, in contrast to the 1990 classification criteria for FM (FM 1990) that required pain in ≥11 of 18 tender points upon digital palpation [5, 13]. The 2011 version of the Fibromyalgia Survey Diagnostic Criteria (FSDC), a modification of the 2010 criteria that has been validated for use in epidemiological surveys, was included in the BSBR-AS postal questionnaires from August 2015(14). The FSDC includes a Symptom Severity Scale (SSS) and a Widespread Pain Index (WPI). The SSS is the sum of self-reported fatigue, cognitive symptoms, waking unrefreshed (each scored on a 0–3 scale) and the presence of headache, abdominal pain and depression [graded as present (1) or absent (0)] [5, 14]. The WPI is scored as the number of areas where the patient has experienced pain during the past week, graded 0 (best) to 19 (worst). The diagnostic criteria are met if the SSS is ≥5 and the WPI is ≥7 or the SSS is ≥9 and the WPI is 3–6 [5]. The 2016 update of the FSDC clarified that a diagnosis of FM may be made in participants with concurrent rheumatic disease [15]. It also added a stipulation that the pain should be present in at least four of five regions and that the self-reported version is not valid for making a clinical diagnosis in individuals but is valid for research purposes.

In this study we refer to 'FM development' as the change in individuals from not fulfilling to fulfilling the 2016 FSDC and, conversely, 'FM recovery' is the change from fulfilling to not fulfilling the 2016 FSDC. We included participants who had participated at more than one visit with a minimum 10 month interval between consecutive visits. In order for the visit to be eligible, the patient should have completed the FSDC within 4 months of a clinical visit. The FSDC score was the main outcome variable of interest.

Statistics

We identified factors associated with FM development and recovery in participants with axSpA. Baseline demographics were compared between participants who did and did not develop FM and between those who did and did not recover from FM using bivariable analyses with Bonferroni corrections. The chi-squared test, Mann–Whitney *U* test and independent-samples Student's *t*-test were used as appropriate.

Separate logistical regression models were constructed to identify factors associated with FM development and recovery. Demographic and FM- and axSpA-related features were tested consecutively in univariable models that were adjusted for age and gender. Variables that were related to the outcome with a *P*-value ≤0.1 were then included in the multivariable model and a backwards regression was performed until all variables were significantly associated with the outcome at $P < 0.05$. Age and gender were forced into all models. Separate multivariable models were constructed for FM- and axSpA-related variables.

Random effect maximum likelihood linear regression models, accounting for repeated measures, were

Table 1 Baseline demographics

Variables		*n*	Values
Age, years, median (IQR)		801	51.4 (39.9– 62.2)
Male, *n* (%)		801	554 (67.7)
Symptom duration, years, median (IQR)		772	9.0 (3–22)
Education, *n* (%)		752	
Primary			222 (29.5)
Secondary			82 (10.9)
Apprenticeship			223 (29.6)
Further education (college)			150 (20.0)
University degree			75 (10.0)
HLA-B27 positive, *n* (%)		598	482 (80.6)
Criteria fulfilled, *n* (%)	mNY	801	534 (66.7)
	ASAS imaging		225 (28.1)
	ASAS clinical		42 (5.2)
BMI, kg/m^2, mean (S.E.)		519	26.7 (24.0–30.5)
Met 2016 FSDC, *n* (%)		801	115 (14.4)
BASDAI score, median (IQR)		796	4.1 (2.1–6.0)
Comorbidities present, *n* (%)		801	213 (26.6)

constructed for participants who had three consecutive visits, to identify factors associated with SSS and WPI levels. In addition, we examined longitudinal change in the SSS and WPI over time.

Several sensitivity analyses were performed, including stratification. The main multivariable analyses for FM development were stratified for participants who did and did not start on TNFi during the observation period and for participants who did and did not fulfil the mNY criteria for AS. Additionally, we repeated the main analyses using the 2011 FSDC to diagnose FM.

Results

A total of 2687 participants who were starting on a first TNFi or who were continuing a conventional synthetic DMARD (csDMARD) were included in the BSRBR-AS study and 1285 had at least one follow-up visit. A total of 801 participants (29.8% of the total number of participants in the BSRBR-AS) were eligible for inclusion with a minimum of two completed visits at a $\geq$10 month interval; of these, 138 participants had three visits (Supplementary Fig. S1, available at *Rheumatology* online). The median age at baseline was 51.4 years [interquartile range (IQR) 39.9–62.2], the median symptom duration was 9 years (IQR 3–22) and 67.7% were male (554/801). HLA-B27 was available in 598 patients and 482 (80.6%) were positive. Of eligible participants, 534 (66.7%) fulfilled the mNY criteria for AS, 225 (28.1%) met the ASAS imaging criteria but not the mNY criteria and 42 (5.2%) met only the ASAS clinical criteria for axSpA. The median number of months between the first and second visit was 12.5 (IQR 11.8–14.7) and 24.4 (IQR 23.7–25.7) between baseline and the third visit. Baseline demographics are presented in Table 1.

The median baseline SSS was 5 (IQR 3–7) and 90% of participants had an SSS $\leq$9 at all visits. The median WPI was 4 (IQR 2–6) and 70% of the participants had a WPI $\leq$7 at baseline and all visits.

Fig. 1 shows an illustration of the changing states of FM between baseline and the 1 year follow-up. A total of 686 participants did not fulfil the FM criteria at baseline; of these, 45 (6.6%) fulfilled the criteria at the first follow-up visit (Table 1). In bivariable analyses, participants who developed FM had higher baseline BASDAI and BASFI scores and more FM-related symptoms compared with participants who did not develop FM.

A total of 115 participants fulfilled the FM criteria at baseline; of these, 77 (70%) did not fulfil the criteria at the follow-up (Table 2). Patients who recovered from FM had lower baseline BASFI scores compared with patients with permanent FM (Table 2).

Baseline variables associated with longitudinal FM development in participants without FM at baseline

In multivariable logistic regression models (Table 3), the axSpA features associated with FM development were the absence of HLA-B27 and high baseline BASDAI scores, while high WPI and HADs anxiety scores were the FM-related variables that were significantly associated with FM development. In the final multivariable models, baseline BASDAI [OR 1.27 (95% CI 1.08, 1.49)] and WPI [OR 1.14 (95% CI 1.02, 1.28)] scores remained significantly associated with the outcome.

Baseline factors associated with longitudinal FM recovery in participants without FM at baseline

In multivariable logistic regression models (Table 4) the baseline axSpA-related features that were associated with FM recovery were low BASFI score and starting on a TNFi, whereas the FM-related variables that were most strongly associated with FM recovery were low WPI and Jenkins Sleep Evaluation scores. In the final multivariable logistic regression model, baseline BASFI

Fig. 1 The changing states of FM between the baseline visit and 1 year follow-up visit. FM: 2016 FSDC

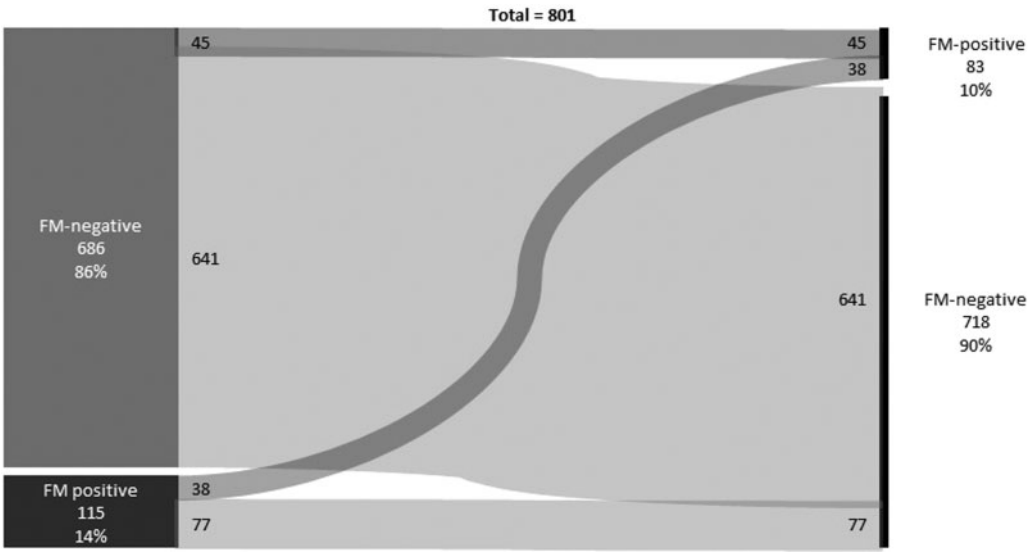

Table 2 Bivariable comparison between changing states of FM

Variables	Participants who did not fulfil the FSDC at baseline ($n = 686$)				Participants who fulfilled the FSDC at baseline ($n = 115$)			
	n	No FM ($n = 641$)	Developed FM ($n = 45$)	*P*-value	*n*	Recovered from FM ($n = 77$)	Permanent FM ($n = 38$)	*P*-value
Age, years, mean (S.E.)	686	51.04 (0.55)	51.39 (2.31)	0.87	115	49.80 (1.90)	52.27 (2.37)	0.46
Female, *n* (%)	686	195 (30.42)	20 (44.44)	0.05	115	29 (37.66)	15 (39.47)	0.85
Duration, years, mean (S.E.)	686	13.92 (0.52)	11.91 (2.08)	0.10	86	11.39 (1.30)	10.29 (1.91)	0.63
Education, mean (S.E.)	643	2.74 (0.06)	2.73 (0.21)	0.96	109	2.54 (0.14)	2.23 (0.21)	0.22
BMI, kg/m^2, mean (S.E.)	448	27.10 (0.23)	27.87 (1.28)	0.80	54	27.44 (0.94)	29.28 (1.51)	0.29
Comorbidities, *n*(%)	686	155 (24.18)	12 (26.67)	0.71	115	33 (42.86)	13 (34.21)	0.37
SpA-related features								
HLA-B27 positive, *n* (%)	525	411 (83.7)	22 (64.71)	0.005	73	35 (76.09)	14 (51.85)	0.03
Sacroiliitis CXR, *n* (%)	571	456 (84.76)	26 (78.79)	0.36	95	51 (76.69)	26 (83.87)	0.63
Sacroiliitis MRI, *n* (%)	457	327 (76.76)	29 (93.55)	0.03	80	45 (88.24)	25 (86.21)	0.79
Uveitis, *n*(%)	672	112 (17.83)	6 (13.64)	0.48	115	20 (25.97)	5 (13.16)	0.12
CRP, mg/dl, mean (S.E.)	499	2.11 (0.29)	0.98 (0.21)	0.81	87	1.77 (0.61)	1.91 (0.74)	0.68
ESR, mean (S.E.)	333	14.49 (0.92)	13.18 (1.99)	0.55	52	11.77 (2.65)	18.76 (3.94)	0.07
BASDAI, mean (S.E.)	681	3.71 (0.09)	5.47 (0.30)	<0.001*	115	6.14 (0.18)	6.87 (0.36)	0.04
BASMI, mean (S.E.)	461	3.56 (0.09)	3.81 (0.38)	0.54	69	4.58 (0.24)	4.80 (0.55)	0.54
BASFI, mean (S.E.)	684	3.64 (0.10)	4.97 (0.40)	0.001*	115	6.01 (0.23)	7.42 (0.39)	0.001*
ASDAS-CRP, mean (S.E.)	443	1.07 (0.06)	1.71 (0.20)	0.01	73	1.83 (1.11)	2.45 (0.29)	0.05
Started on TNFi, *n* (%)	686	127 (19.81)	15 (33.33)	0.03	115	43 (55.84)	12 (31.58)	0.01
Months on TNFi, mean (S.E.)	151	11.30 (0.46)	9.53 (0.93)	0.18	46	11.23 (0.90)	9.48 (1.57)	0.33
FM-related features								
SSS, mean (S.E.)	614	4.45 (0.11)	6.30 (0.42)	<0.001*	96	7.85 (0.24)	8.83 (0.33)	0.02
WPI, mean (S.E.)	686	3.74 (0.11)	5.91 (0.44)	<0.001*	115	9.13(0.30)	10.66 (0.55)	0.01
Anxiety, mean (S.E.)	581	5.94 (0.17)	8.31 (0.64)	<0.001*	86	9.39 (0.50)	10.34 (0.91)	0.32
Chalder fatigue scale, mean (S.E.)	548	2.81 (0.13)	4.49 (0.56)	0.003	115	5.78 (0.39)	6.89 (0.61)	0.08
Jenkins Sleep Evaluation, mean (S.E.)	544	8.51 (0.23)	10.91 (0.82)	0.01	115	12.71 (0.62)	15.44 (0.81)	0.005

Comparison between participants who do not develop FM and those who develop FM and between those who recover from FM and those who still have FM after 1 year of observation using the 2016 FSDC. *Significant after Bonferroni correction. All groups are mutually exclusive. Duration: years since the first visit to a rheumatologist; CXR: conventional radiography;

TABLE 3 Baseline predictors of developing FM in participants without FM at baseline

Variables	*n*	Adjusted univariable, OR (95% CI)	Multivariable model (*n* = 681), FM variables, OR (95% CI)	Multivariable model (*n* = 521), baseline SpA variables, OR (95% CI)	Multivariable model (*n* = 681), FM and SpA variables, OR (95% CI)
Age (years)	686	1.01 (0.98, 1.03)	1.01 (0.99, 1.03)	1.00 (0.98, 1.03)	1.00 (0.98, 1.03)
Female	686	1.89 (1.01, 3.53)**	2.61(1.27, 5.35)**	1.91 (0.91, 4.00)*	2.04 (0.99, 4.21)*
Years since first contact	686	0.98 (0.95, 1.01)			
Education	643	0.98 (0.77, 1.23)			
Number of comorbidities	448	1.11 (0.55, 2.22)			
BMI (kg/m^2)	686	1.02 (0.94, 1.10)			
SpA-related features					
HLA-B27 positive	525	0.37 (0.18, 0.80)**		0.44 (0.20, 0.98)**	
Sacroiliitis present on CXR	571	0.73 (0.29, 1.80)			
Sacroiliitis present on MRI	457	3.85 (0.89, 16.60)*			
History of uveitis	672	0.71 (0.29, 1.71)			
CRP (mg/dl)	499	0.91 (0.76, 1.08)			
ESR	333	0.99 (0.96, 1.02)			
BASDAI	681	1.39 (1.21, 1.60)***		1.43 (1.22, 1.68)***	1.27 (1.08, 1.49)**
BASMI	461	1.05 (0.83, 1.33)			
BASFI	684	1.22 (1.08, 1.38)**			
ASDAS-CRP	443	1.47 (1.11, 1.95)**			
Started on TNFi	686	1.95 (0.92, 4.15)*			
Months on TNFi	151	0.87(0.751, 1.01)*			
FM-related features					
SSS	614	1.28 (1.13, 1.45)***			
WPI	686	1.24 (1.13, 1.36)***	1.22 (1.11, 1.35)***		1.14 (1.02, 1.28)**
HADS anxiety	581	1.12 (1.05, 1.20)**	1.10 (1.02, 1.18)**		
Chalder Fatigue Scale	548	1.14 (1.05, 1.24)**			
Jenkins Sleep Evaluation baseline	544	1.07 (1.01, 1.13)**			
ROC/sensitivity/specificity	614		0.75/64.4/75.6	0.78/67.7/78.0	0.75/55.6/75.6

Logistic regression models. Interaction term between HLA-B27 and started on TNFi near significant at 0.05. *$P < 0.1$, **$P < 0.05$, ***$P < 0.001$. CXR: conventional radiography; ROC: receiver operating characteristics curve.

score [OR 0.68 (95% CI 0.53, 0.86)], starting on TNFi [OR 4.23 (95% CI 1.63, 11.00)] and WPI score [OR 0.84 (95% CI 0.72, 0.97)] were significantly associated with FM recovery (Table 4).

Longitudinal mixed models

A total of 138 participants had three visits with at least 10 month intervals. A total of 128 (92.8%) participants did not have FM at baseline, but 4 of these fulfilled the diagnostic criteria at the third visit. Of the 10 (7.2%) participants who had FM at baseline, 5 did not meet the diagnostic criteria at the third visit.

In longitudinal mixed models that examined factors associated with the components of the FSDC over time, BASDAI and BASFI scores were both significantly associated with SSS and WPI, while the BASMI score was significantly associated with WPI (Table 5). Over the 24 month period, the median change in SSS was 0 (IQR −1–2) and the median change in WPI was 0 (IQR −2–2). There was no evidence of a longitudinal trend in change in either the SSS [β-coefficient for time in months −0.00 (95% CI −0.02–0.01)] or the WPI [0.01 (95% CI −0.01–0.03)] (Table 5).

Sensitivity analyses

Stratification

Baseline WPI was the only variable significantly associated with developing FM in multivariable models that were restricted to participants who started a TNFi (Supplementary Table S1, available at *Rheumatology* online). Baseline BASDAI was the only variable significantly associated with developing FM in multivariable analyses that were restricted to participants who did not start a TNFi (Supplementary Table S1, available at *Rheumatology* online). The baseline variables associated with FM development were very similar in multivariable models that were stratified across in participants who did and did not fulfil the mNY criteria (Supplementary Table S2, available at *Rheumatology* online).

Alternative diagnostic criteria for FM

The analyses for this article were repeated using the 2011 FSDC and the results are presented in

Table 4 Predictors of recovery from FM in participants with FM at baseline

Variables	*n*	Adjusted univariable, OR (95% CI)	Multivariable model (*n* = 115), FM variables, OR (95% CI)	Multivariable model (*n* = 115), baseline SpA variables, OR (95% CI)	Multivariable model (*n* = 115), FM and SpA variables, OR (95% CI)
Age (years)	115	1.00 (0.97, 1.02)	1.00 (0.97, 1.02)	1.03 (0.99, 1.06)	1.02 (0.99, 1.06)
Female	115	0.90 (0.40, 2.04)	1.29 (0.53, 3.13)	1.03 (0.42, 2.52)	1.20 (0.48, 3.03)
Years since first contact	86	1.02 (0.97, 1.06)			
Education	109	1.27 (0.89, 1.80)			
Number of comorbidities	54	1.49(0.65, 3.40)			
BMI (kg/m^2)	115	0.93 (0.86, 1.01)*			
SpA-related features					
HLA-B27 positive	73	3.14 (1.11, 8.88)**			
Sacroiliitis present on CXR	95	0.64 (0.12, 2.13)			
Sacroiliitis present on MRI	80	1.18 (0.30, 4.62)			
History of uveitis	115	2.51 (0.83, 7.60)			
CRP (mg/dl)	87	0.99 (0.89, 1.10)			
ESR	52	0.98 (0.95, 1.02)			
BASDAI	115	0.79 (0.63, 1.00)**			
BASMI	69	0.88 (0.65, 1.19)			
BASFI	115	0.70 (0.56, 0.88)**		0.66 (0.53, 0.84)**	0.68 (0.53, 0.86)**
ASDAS-CRP	73	0.63 (0.39, 1.01)*			
Started on TNFi	115	2.78 (1.21, 6.38)**		3.86 (1.54, 9.71)**	4.23 (1.63, 11.00)**
Months on TNFi	46	1.08 (0.96, 1.21)			
FM-related features					
SSS	96	0.76 (0.61, 0.96)**			
WPI	115	0.84 (0.73, 0.96)**	0.84 (0.73, 0.97)		0.84 (0.72, 0.97)**
HADS anxiety	86	0.96 (0.88, 1.04)			
Chalder Fatigue Scale	115	0.91(0.81, 1.02)			
Jenkins Sleep Evaluation baseline	115	0.90 (0.83, 0.98)**	0.90 (0.83, 0.98)		
ROC/sensitivity/specificity	96		0.68/50.7/68.4	0.76/45.4/79.0	0.78/62.3/73.7

Logistic regression models. *$P < 0.1$, **$P < 0.05$. CXR: conventional radiography; ROC: receiver operating characteristics curve.

Table 5 Longitudinal mixed model examining the change in the SSS and WPI over time in 138 patients

Variable	SSS, β (95% CI)	WPI, β (95% CI)
BASDAI	0.60 (0.44, 0.62)**	0.78 (0.65, 0.90)**
BASFI	0.53 (0.44, 0.62)**	0.60 (0.45, 0.69)**
BASMI	0.15 (−0.02, 0.32)*	0.51 (0.29, 0.73)**
Time	−0.00 (−0.02, 0.01)	0.01 (−0.01, 0.03)

Mixed models. All models are univariable and include variables at all time points stratified for individuals and adjusted for time. A 1 unit increase in BASDAI is associated with an increase in the SSS of ∼0.6 points. *$P < 0.1$, **$P < 0.001$.

Supplementary Tables S3–S5, available at *Rheumatology* online. There are no important differences between the 2016 and 2011 FSDC models.

Discussion

In patients with axSpA, baseline levels of axSpA disease activity and widespread pain both contribute to FM development and recovery. Starting on a TNFi is associated with recovering from FM. The coexistence of FM in patients with axSpA has previously been found to be associated with high levels of axSpA disease activity in cross-sectional studies [16, 17]. The current study adds to this body of knowledge by providing evidence that while high levels of axSpA disease activity are associated with future FM development, low levels of axSpA disease activity are associated with recovery from FM.

The strength of this study is the large multicentre design, longitudinal follow-up and comprehensive data collection. There are several weaknesses that should be considered. We have included a relatively low proportion of the total number of patients in the BSRBR-AS. This was mainly due to the fact that the FSDC was only recorded from 2015 and that only about half of the patients in the register came for a follow-up visit within the time frame stipulated. The relationship between starting a TNFi, clinical data and the self-reported

questionnaires may have been weakened by the time gap between the visit and the return of the questionnaire, which was a maximum of 4 months in this study. Despite the logistical issues, we have to acknowledge that the chief challenge of the article concerns the use of the FSDC to signify the presence or absence and development of or recovery from FM. The FSDC have not been validated in axSpA populations, but the 2016 FSDC may be used in populations with other conditions, including musculoskeletal disorders [15]. For a clinical diagnosis of FM in individual patients it is important to also gather medical and social information.

The lack of physical signs by which disease activity in FM or axSpA may be assessed [18] is an additional challenge in interpreting the results of this article. We thus have to bear in mind that there might be some cross-contamination of patient-reported outcomes, whereby high axSpA disease activity is registered as a high WPI, while FM disease activity could inflate the BASDAI. Indeed, a previous paper from this cohort found that the average difference in BASDAI score between patients who did and did not have comorbid FM was 1.04 (95% CI 0.88, 1.33) [8]. The BASDAI covers fatigue, morning stiffness and axial and entheseal pain [19], while the BASFI consists of 10 questions that cover everyday physical functioning [20]. In mixed models exploring the relationship between SpA and FM disease activity we found that BASDAI and BASFI scores are highly and significantly associated with both the SSS and WPI. The overlap between the questions covered by the BASDAI, SSS and WPI has previously been noted [7], and the BASFI also contains questions of functions that are impacted by fatigue. A study by Salaffi *et al.* [21] reported that there was not any statistical difference in BASDAI scores between patients who were diagnosed with axSpA and patients with FM alone. The Bath indices are the most commonly used measures of axSpA disease activity and are endorsed as core outcome measures in axSpA by the ASAS [22].

Our study also highlights the limitations of the FM and axSpA diagnostic criteria, as neither the 2016 FSDC nor the ASAS criteria are 'gold standard' instruments with a high level of specificity. A study by Barakliakos *et al.* [25] found that as many as 29% of AS and 19% of non-radiographic SpA patients fulfilled the 2010 FSDC. Indeed, TNFi treatment for patients with non-radiographic axSpA was originally denied by the US Food and Drug Administration due to concern about the specificity of the non-radiographic axSpA criteria [7, 25]. Our model for FM development was therefore stratified according to classification criteria and was confirmed in both patients who did and did not meet the mNY criteria.

The association between baseline high levels of axSpA disease activity and the development of FM may be explained by the causal link between nociceptive stimuli and central sensitization [28]. AxSpA disease activity causes nociceptive pain, and central sensitization is an essential feature of FM. FM might therefore have developed as a long-term consequence of axSpA disease activity. This explanatory path is also supported by our findings that in subgroup analyses, BASDAI scores seem to be more strongly associated with FM development in patients not receiving TNFi and that starting on a TNFi was associated with FM recovery.

For patients and clinicians worried about the development of FM in axSpA, our article implies that the patients with high BASDAI and WPI scores are at the highest risk of fulfilling the FSDC. Conversely, starting a TNFi, together with a lower Ankylosing Spondylitis Disease Activity Score (ASDAS) and WPI score, is associated with recovery from FM. The clinician should keep in mind that an unexpectedly high axSpA disease activity might have captured FM disease activity and that disentangling the two is necessary in order to target the therapy, while also considering the possibility of misdiagnosis. The knowledge that 50% of patients who fulfilled the FSDC at baseline did not fulfil the criteria after ~2 years may give hope to patients suffering from FM, although we have to acknowledge that there was no overall trend of improving SSS or WPI scores in this study.

In summary, the current study shows that in patients with axSpA, high levels of axSpA activity and the presence of widespread pain are associated with the development of FM, while low levels of the same variables are associated with recovery from FM. The presence of comorbid FM should be considered in patients with a history of high SpA disease activity and widespread pain.

Acknowledgements

We are grateful to the staff of the BSRBR-AS register, Claudia Zabke, Elizabeth Ferguson-Jones, Maureen Heddle, Nafeesa Nazlee and Barry Morris, and to the recruiting staff at the clinical centres, details of which are available at:

https://www.abdn.ac.uk/iahs/research/epidemiology/spondyloarthritis.php#panel1011.

The BSRBR-AS is funded by the British Society for Rheumatology, who have received funding for this from Pfizer, AbbVie and UCB. These companies receive advance copies of manuscripts for comments but made none in relation to this manuscript. They have no input in determining the topics for analysis or work involved in undertaking it. SP received a travel grant from the South Eastern Health Authority of Norway.

SP had the idea for the study and with GJM planned the analysis. SP undertook the analysis and drafted the manuscript. The results were discussed by all authors, who also commented on the draft manuscript.

Funding: No specific funding was received from any funding agency in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

Data from the British Society for Rheumatology Biologics Register for Ankylosing Spondylitis are available to external investigators, on reasonable request. For information on how toaccess data, see: http://www.rheumatology.org.uk.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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