Original article

Tender to touch–Prevalence and impact of concomitant fibromyalgia and enthesitis in spondyloarthritis: An ancillary analysis of the ASAS PerSpA study

Gillian E. Fitzgerald [a,b,*], Sinead Maguire [c,d], Clementina Lopez-Medina [e,f], Maxime Dougados [e], Finbar D. O'Shea [c,d], Nigil Haroon [g,h,i,j]

[a] School of Medicine, National University of Ireland Galway, Galway, Ireland
[b] Department of Rheumatology, Galway University Hospitals, Galway, Ireland
[c] School of Medicine, Trinity College Dublin, Dublin, Ireland
[d] Department of Rheumatology, St. James's Hospital, Dublin, Ireland
[e] University of Paris, Department of Rheumatology, Hôpital Cochin, Assistance publique–Hôpitaux de Paris, INSERM (U1153), Clinical epidemiology and biostatistics, PRES Sorbonne Paris-Cité, France
[f] Rheumatology Department, Reina Sofia University Hospital, IMIBIC, University of Cordoba, Cordoba, Spain
[g] Schroeder Arthritis Institute, University Health Network, M5T 0S8 Toronto, Ontario, Canada
[h] Krembil Research Institute, University Health Network, M5T 0S8 Toronto, Ontario, Canada
[i] Division of Rheumatology, Toronto Western Hospital, University Health Network, M5T 2S8 Toronto, Ontario, Canada
[j] Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, M5S 1A8 Toronto, Ontario, Canada

I N F O   A R T I C L E

A B S T R A C T

Objectives. – The primary objective was to evaluate the co-existence of fibromyalgia (FM) & enthesitis in individuals with spondyloarthritis (SpA). Secondary objectives were to identify clinical features associated with the presence of FM in enthesitis and analyse sex-specific differences.

Methods. – This was an ancillary analysis of the Assessment of SpondyloArthritis International Society Peripheral Involvement in SpA (PerSpA) study. Enthesitis was defined as the presence of enthesitis ever. Clinical FM was defined as the rheumatologist's confirmation of the presence of FM. A score of $\geq$ 5/6 on the Fibromyalgia Rapid Screening Test (FiRST) defined a positive screening test for FM.

Results. – Enthesitis ever and FM (EFM) co-existed in 10.3% ($n = 425$) of the cohort using FiRST criteria and 5.3% using clinical diagnosis of FM. More individuals with FM by clinical diagnosis had imaging-confirmed enthesitis ever than by FiRST criteria. More females had EFM than males, defined clinically (76.9% vs 23.1%) or by FiRST criteria (62.6% vs 37.4%). Individuals with EFM had more severe disease across all measures compared to those with enthesitis only, with no significant difference between sexes. EFM was significantly associated with age, female sex, BMI, BASDAI and region.

Conclusion. – FM is an important comorbidity in the setting of enthesitis in SpA. While EFM is more common in females, it is not a rare condition in males. EFM is associated with worse disease severity measures in SpA in both males and females. Recognition of FM in the setting of enthesitis is essential to prevent overtreatment and optimise patient outcomes.

1. Introduction

Spondyloarthritis (SpA) is a chronic inflammatory arthritis predominantly involving the axial spine and sacroiliac joints (SIJs) [1]. The two most common forms of SpA are axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) [2]. Enthesitis is a characteristic feature, affecting up to 56% of patients with axSpA [3] and 30% of patients with PsA [4]. The enthesis is an extra-articular structure, referring to the insertion of tendons and ligaments into bone [5]. The enthesis is a key target of inflammation in SpA, resulting in enthesitis [6], characterised by localised tenderness and stiffness, often without overt clinical evidence of inflammation. Recognising enthesitis in SpA is important for the optimal treatment of SpA. However, identifying enthesitis can be challenging, traditionally diagnosed by assessing tenderness at entheseal sites. A number

* Corresponding author at: Department of Rheumatology, Galway University Hospitals, Galway, Ireland.
Adresse e-mail : Gillian.Fitzgerald@nuigalway.ie (G.E. Fitzgerald).

of reliable clinical instruments have been developed to assist in the assessment of enthesitis [7]. More recently, imaging, especially ultrasound, is increasingly relied upon for confirmation [8].

Diagnosing enthesitis is further complicated by the anatomic overlap between the tender points of FM in the original American College of Rheumatology (ACR) classification criteria for FM [9] and the clinical diagnosis of enthesitis, which presents a diagnostic challenge [10]. Existing literature has demonstrated a high prevalence of FM in SpA, with a co-existing diagnosis in up to 25% of individuals with axSpA and 22% of individuals with PsA, which can inflate patient-reported outcomes and influence response to treatment [11]. However, individuals with primary FM rarely fulfil classification criteria for SpA [12].

There is limited published research examining the co-existence of FM and enthesitis in SpA [13]. Literature on the effect of sex in this setting is even more sparse, although FM is known to be more common in women. As women with axSpA have been recognized to have worse patient reported outcomes compared to men [14], it is important to understand and quantify the interaction between FM and enthesitis in SpA. Lastly, the prevalence of co-existent FM and enthesitis has never been previously evaluated and compared among subtypes of SpA. The ASAS Peripheral involvement in Spondyloarthritis (PerSpA) study aims to characterize peripheral musculoskeletal features in individuals with SpA across the globe [15]. Data from this study allows vital insights into the interaction between enthesitis, FM and sex in patients with SpA.

Therefore, the primary aim of this study was to evaluate the co-existence of FM & enthesitis in individuals with SpA through an ancillary analysis of PerSpA. Secondary aims were to identify clinical features associated with the presence of FM in enthesitis, and analyse sex-specific differences.

2. Methods

2.1. The ASAS PerSpA Study

This is an ancillary analysis of the ASAS PerSpA study, an international multicentre observational study. Full details of this study have been previously published [15]. This cross-sectional study included patients from 24 countries across multiple major geographical regions. Patients were recruited between July 2018 and February 2020. All included patients were at least 18 years old, with a diagnosis of axSpA, peripheral SpA (pSpA) or PsA according to their rheumatologist. Participants with axSpA included both radiographic axSpA (r-axSpA) and non-radiographic axSpA (nr-axSpA). Ethical approval for the study was obtained from local hospital ethics committees in all participating centres. Written informed consent was obtained from all participants.

2.2. Data collected

All data was collected during a face-to-face interview and review of medical records in a single clinical visit conducted by a trained investigator:

- demographics included date of birth, sex, smoking status, weight, height, socio-educational level;
- disease-specific information included SpA characteristics, family history, date of diagnosis, date of symptom onset, treatment history;
- presence of enthesitis was established by a 'yes' answer to 'Do you consider that this patient has ever suffered from at least one episode of Spondyloarthritis-related enthesitis?'. The locations of first and subsequent sites of enthesitis were collected. Confirmation of enthesitis by imaging was not required. Data regarding

previous imaging to confirm enthesitis was collected. Data regarding specific treatment for enthesitis was also collected. The presence of enthesitis on examination was assessed during data collection by applying pressure with the dominant thumb until the nail blanches: 0 represented no pain, 1 mild tenderness, 2 moderate tenderness and 3 wince/withdraw;
- the presence of clinical FM was established by a positive response to the following question: 'Do you consider that your patient is concomitantly suffering from FM?'

2.3. Outcome measures

The following validated clinical metrics were collected:

- Patient Global Assessment (PGA): measured on a scale of 0–10;
- Bath Ankylosing Disease Activity Index (BASDAI): measured on a scale of 0-10; higher scores reflect more active disease [16];
- Ankylosing Spondylitis Disease Activity Score–C-reactive protein (ASDAS-CRP): scores greater than 2.1 reflect active disease [17,18];
- Bath Ankylosing Spondylitis Functional Index (BASFI): assess function on a scale of 0–10; higher scores indicate worse function [19];
- Fibromyalgia Rapid Screening Test (FiRST): self-questionnaire containing six questions; score of ≥ 5/6 indicates positive screening test [20];
- Assessment of SpondyloArthritis Society-Health Index (ASAS-HI): assesses health in SpA on a scale of 0–17 [21].

2.4. Statistical analysis

Baseline descriptives of the SpA cohort are presented as mean with SD, median with 25th and 75th percentiles or frequencies with percentages, as appropriate. The prevalence of those with enthesitis ever, a clinical diagnosis of FM and FM by FiRST criteria was calculated.

The cohort was subsequently divided into SpA only, enthesitis only (EO) and co-existing enthesitis (defined as enthesitis ever) and FM (EFM). The demographics, clinical characteristics, and severity of disease of the three groups were compared using Analysis of Variance (ANOVA) with Tukey's method for post hoc analysis for continuous variables and Chi^2 tests for categorical variables. The Bonferroni correction was applied to control for multiple comparisons. We additionally performed a sex-stratified analysis, using independent 2-tailed T-tests or Mann-Whitney tests for continuous variables and Chi^2 tests for categorical variables.

Logistic regression was performed. Separate models were developed with EFM as the dependent variable using (1) FM by FiRST criteria and (2) clinical diagnosis of FM. Variables with P-value < 0.1 in univariable analysis were retained for each model. Age, sex and exposure to biologics were considered clinically relevant variables and controlled for in every model. Odds ratios (OR) with confidence intervals (CI), adjusted for the presence of all variables in the model, are presented.

Sensitivity analysis was additionally performed using the variable 'enthesitis present on exam' in place of 'enthesitis ever'. A P-value of < 0.05 was considered statistically significant. IBM SPSS Statistics Version 26 was used for statistical analysis.

3. Results

3.1. Description of SpA cohort

In total, 4465 individuals participated in the PerSpA study, of whom 61% ($n = 2724$) were male and average age was 44.5 (SD

Table 1
Baseline clinical and demographic characteristics of the SpA cohort, stratified by sex.

	SpA cohort	Males	Females	Missing
n	4465 (100.0)	2724 (61.0)	1741 (39.0)	0
Age (years)	44.5 (14.0)	43.4 (14.2)	46.2 (13.4)***	0
Delay to dx (years)	3.0 (0.7, 9.2)	2.9 (0.7, 9.0)	3.0 (0.6, 10.0)	47
Disease duration (years)	11.4 (5.5, 20.2)	11.8 (5.7, 11.8)	10.8 (5.1, 19.4)***	41
BMI (kg/m^2)	26.3 (5.4)	26.0 (4.8)	26.8 (6.2)***	16
Smoker ever	1900 (42.6)	1330 (48.9)	570 (32.7)***	4
University education	1815 (40.7)	1171 (43.0)	644 (37.0)***	4
Disease diagnosis				
AS	2137 (47.9)	1566 (57.5)	571 (32.8)***	0
nr-AxSpA	582 (13.0)	292 (10.7)	290 (16.7)***	0
PsA	1033 (23.1)	501 (18.4)	532 (30.6)***	0
PSpA	433 (9.7)	203 (7.5)	230 (13.2)***	0
Classification criteria				
ASAS criteria axSpA	2910 (65.2)	1953 (71.7)	957 (55.0)***	0
Imaging Arm	2716 (60.8)	1852 (68.0)	864 (49.6)***	0
Clinical Arm	1651 (37.0)	1184 (43.5)	467 (26.8)***	0
ASAS criteria pSpA	555 (12.4)	250 (9.2)	305 (17.5)***	0
CASPAR criteria	1043 (23.4)	508 (18.6)	535 (30.7)***	0
HLA-B27 positive	2066 (66.2)	1457 (73.1)	609 (54.0)***	1345
HLA-B15 positive	39 (6.6)	24 (7.0)	15 (6.0)	3872
SpA features				
Axial	3428 (76.8)	2243 (82.3)	1185 (68.1)***	0
AAU	738 (16.5)	482 (17.7)	256 (14.7)**	0
PsO	1212 (27.1)	615 (22.6)	597 (34.3)***	1
IBD	275 (6.2)	150 (5.5)	125 (7.2)*	0
Root disease	1503 (33.7)	975 (35.8)	528 (30.3)***	0
Peripheral arthritis	2541 (56.9)	1404 (51.5)	1137 (65.3)***	0
Dactylitis	685 (15.3)	359 (13.2)	326 (18.7)***	0
Enthesitis	1984 (44.4)	1149 (42.2)	835 (48.0)***	0
Enthesitis confirmed on imaging[a]	767 (38.7)	396 (34.5)	371 (44.4)***	2
SPARCC score	0.7 (1.8)	0.5 (1.4)	1.0 (2.2)***	14
Treatment history				
bDMARD use	2647 (59.3)	1644 (60.4)	1003 (57.6)	0
csDMARD use	2987 (66.9)	1710 (62.8)	1277 (73.3)***	0
Outcome scores				
BASDAI (0–10)	3.9 (2.4)	3.5 (2.3)	4.5 (2.5)***	11
BASFI (0–10)	3.0 (2.7)	2.7 (2.6)	3.4 (2.7)***	7
ASAS-HI (0–17)	6.6 (4.6)	5.9 (4.5)	7.7 (4.5)***	4
ASDAS-CRP[b]	2.5 (1.1)	2.4 (1.1)	2.7 (1.1)***	63
PGA (0–10)	4.4 (2.7)	4.1 (2.7)	4.9 (2.7)***	29

Data are *n* (%), mean (standard deviation), or median (25th, 75th percentile). AAU: acute anterior uveitis; AS: ankylosing spondylitis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C reactive protein; ASAS: Assessment of Spondyloarthritis international society; ASAS-HI: Assessment of Spondyloarthritis international society Health Index; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; bDMARDs: biologic Disease Modifying Antirheumatic Drugs; BMI: body mass index; CASPAR: classification criteria for psoriatic arthritis; csDMARDS: conventional synthetic Disease Modifying Antirheumatic Drugs; dx: diagnosis; HLA: human leukocyte antigen; IBD: inflammatory bowel disease; nr-axSpA: non-radiographic axial spondyloarthritis; PGA: Patient global assessment; PsA: psoriatic arthritis; pSpA: peripheral spondyloarthritis; PsO: psoriasis; SpA: spondyloarthritis; SPARCC: spondyloarthritis research consortium of Canada.

[a] Out of *n* = 1984 with history of enthesitis.

[b] < 1.3 inactive disease, 1.3–2.1 moderate disease activity, > 3.5 very high disease activity.

* Males versus females: $P < 0.05$.

** Males versus females: $P < 0.01$.

*** Males versus females: $P < 0.001$.

14.0) years. AxSpA was the most common diagnosis (47.9% AS, 13% nr-axSpA). Table 1 outlines the baseline demographic and clinical characteristics of the cohort, stratified by sex.

### 3.2. Description of cohort with Enthesitis

Of the whole cohort, 44.4% (*n* = 1984) had at least one episode of enthesitis ever. The prevalence was highest in pSpA (57.3%), followed by nr-axSpA (48.3%), PsA (45.8%), and AS (38.9%). A history of enthesitis ever was more prevalent in females than males (48.0% vs 42.2%, *P* < 0.01). Investigations were used to confirm an episode of enthesitis in 38.7% (*n* = 767) of cases and specific treatment for enthesitis was required in 68.9% (*n* = 1366) of patients (Table S1). Enthesitis was present on exam in 34.8% (*n* = 1552) of the cohort. The feet were most commonly involved — 24.9% (*n* = 1111) reported achilles involvement and 17.6% (*n* = 768) reported plantar fascial involvement (Fig. 1). Most individuals experienced enthesitis intermittently (54.9%), 18.5% had a single episode and 26.7% experienced continuous enthesitis.

3.3. Description of cohort with Fibromyalgia (FM)

A clinical diagnosis of FM was present in 9% (*n* = 400) of the SpA cohort. The prevalence of FM as per the FiRST questionnaire was 17.4% (*n* = 775). Only 28.1% (*n* = 218) of those with FM by FiRST had a clinical diagnosis of FM. Of those with a clinical diagnosis of FM, the majority (77.8%, *n* = 311) were female. When the FiRST questionnaire was applied, 58.6% were women.

Those with FM according to the FiRST questionnaire had a significantly (*p* < 0.01) longer delay to diagnosis compared to those without (7.4 vs 6.1 years) but had a similar age of SpA disease onset (31.1 vs 30.2 years). Significantly more were current smokers (23.5% vs 19.3%) and less had achieved university education (29.3% vs 42.8%).
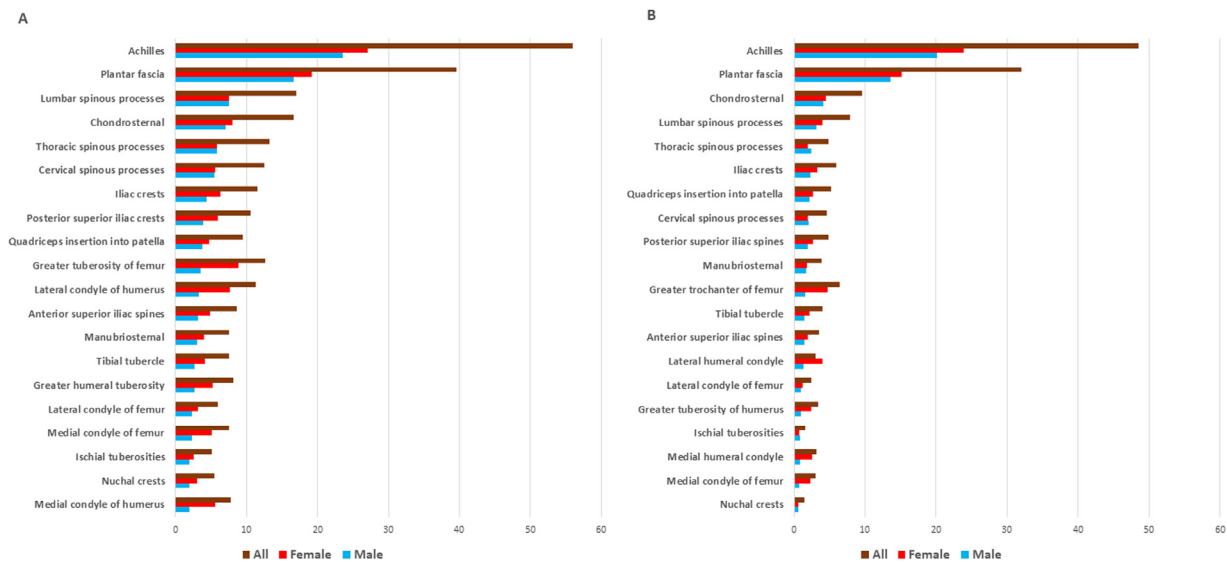
Fig. 1. Prevalence of enthesitis at each entheseal site, stratified by sex (A) in the lifetime of the SpA diagnosis (B) as the initial presentation of enthesitis.

Disease severity scores were significantly higher in those with FM than those without, regardless of whether the FiRST questionnaire (BASDAI: 6.3 vs 3.4; BASFI: 5.3 vs 2.5; ASAS-HI: 11.2 vs 5.6; ASDAS-CRP: 3.4 vs 2.4) or clinical diagnosis was used (BASDAI: 5.9 VS 3.7; BASFI: 4.8 VS 2.8; ASAS-HI 10.3 vs 6.2; ASDAS-CRP 3.2 vs 2.5).

3.4. Comparison of SpA versus enthesitis with fibromyalgia versus enthesitis only cohorts

In total, 10.3% ($n = 425$) of the SpA cohort had both enthesitis ever and FM as per the FiRST questionnaire and 5.3% ($n = 238$) had enthesitis ever and a pre-existing diagnosis of FM. Differences in demographic and clinical characteristics between the three groups are outlined in Table 2.

Individuals with a clinical diagnosis of FM were more likely to have undergone investigation to confirm the diagnosis of enthesitis, but there was no difference between those with FM by FiRST criteria (Table S1). Individuals were less likely to have been treated specifically for enthesitis if they had a clinical diagnosis of FM (Table S1).

3.5. Association of EFM and disease outcomes

Compared to the SpA cohort, individuals with enthesitis ever and FM by FiRST criteria had significantly ($P < 0.001$) worse average patient global scores (6.6 vs 4.2), BASDAI (6.4 vs 3.6), BASFI (5.3 vs 2.8), ASDAS-CRP (3.5 vs 2.4) and ASAS-HI score (11.4 vs 6.0). Comparison of the enthesitis ever and FM cohort with the enthesitis only cohort revealed similar findings (patient global scores: 6.6 vs 4.1, $P < 0.01$; BASDAI: 6.4 vs 3.6, $P < 0.01$; BASFI: 5.3 vs 2.7, $P < 0.01$; ASDAS-CRP: 3.5 vs 2.5, $P < 0.01$; ASAS-HI: 11.5 vs 6.3, $P < 0.01$). There were no differences between the enthesitis ever and SpA groups. Tender joint count (TJC) (7.0 vs 2.4), swollen joint count (SJC) (1.5 vs 0.8) and enthesitis number (5.9 vs 3.8) were all significantly ($P < 0.01$) higher in the EFM group also.

3.6. Sex-specific differences

More females than males had enthesitis ever and a clinical diagnosis of FM (4.1% vs 1.2%, $P < 0.01$), or enthesitis ever and FM by FiRST criteria (6.0% vs 3.6%, $P < 0.01$) (Table 3). Confirmation of an episode of enthesitis by imaging was similar between sexes in those with a diagnosis of FM by FiRST (39.8% vs 35.8%, $P =$ non-significant(NS)). Non-significantly more women with a clinical diagnosis of FM had imaging to confirm the diagnosis of enthesitis (47.5% vs 37.0%, $P =$ NS). Females had a higher enthesitis score than men during data collection (9.0 vs 6.6, $P = 0.03$).

Females with enthesitis ever and FM were more likely than men to have been treated with csDMARDs (84.2% vs 72.3%, $P < 0.01$) and there was no difference in biologic use (57.9% vs 56.0%, $P =$ NS; Table 3). More women than men had ever been prescribed muscle relaxants (11.7% vs 7.5%, $P < 0.01$) and antidepressants (18% vs 9.4%, $P < 0.01$) but there were equally low levels of opioid use in both sexes (8.6% vs 8.8%, $P =$ NS).

There was no difference in the disease severity between men and women in the enthesitis ever and FM cohort, with similar BASDAI, BASFI, ASAS-HI and ASDAS-CRP scores in both groups.

3.7. Multivariable analysis of characteristics associated with presence of enthesitis ever and FM (EFM)

Table 4 outlines models with EFM as the dependent variable using (1) FM by FiRST criteria and (2) clinical diagnosis of FM. Female sex and BASDAI were significantly associated with EFM in both models. Age and delay to diagnosis were additionally associated with EFM using FiRST criteria, whereas BMI was significantly associated with EFM using a clinical diagnosis of FM. Regional differences were seen in both models. When a composite variable of EFM using FM defined by FiRST criteria OR clinical diagnosis, the results were similar (Table S2).

3.8. Sensitivity analysis

Subsequent analysis was performed using the definition of enthesitis present on examination (EOE), in place of enthesitis ever. Comparison of three cohorts (SpA versus EOE versus EOE plus FM) is presented in Table S3. Regression analysis revealed similar predictors for EOE plus clinical diagnosis of FM as presented in Table 4 when enthesitis ever was used (Table S4). Smoking additionally increased the risk and university studies protected against the risk of EOE plus FM by FiRST.

Table 2

Comparison of clinical and demographic characteristics of SpA only versus history of Enthesitis only (EO) versus history of Enthesitis & Fibromyalgia (EFM) groups.

	Enthesitis & FM by FiRST			Enthesitis & Clinical dx FM		
	SpA only	EO	EFM	SpA only	EO	EFM
n	2285	1417	425	2480	1745	238
Male	1426 (62.4)	907 (64.0)	159 (37.4)[a]	1574 (63.5)	1093 (62.6)	55 (23.1)[a,b]
Age (years)	45.0 (14.4)	43.8 (13.9)	44.8 (11.9)	44.7 (14.0)	43.9 (13.7)	46.1 (11.4)
Age at dx (years)	36.9 (13.8)	35.9 (13.6)	37.9 (12.1)	36.7 (13.7)	36.1 (13.4)	39.1 (11.6)[a,b]
Delay to dx (years)	6.4 (8.8)	5.9 (8.1)	7.7 (9.5)	6.4 (8.8)	6.3 (8.5)	6.5 (8.7)
BMI (kg/m^2)	26.4 (5.3)	25.9 (5.4)	28.0 (6.3)	26.3 (5.3)	26.1 (5.3)	29.2 (6.3)[a,b]
Smoker ever	1034 (45.3)	528 (37.3)[a]	186 (43.9)[b]	1126 (45.4)	683 (39.2)[a]	90 (37.8)
University education	911 (39.9)	614 (43.4)	133 (31.3)[a,b]	1015 (41.0)	729 (41.8)	71 (30.0)[a,b]
Regions						
Europe & North America	1010 (44.2)	420 (29.6)[a]	154 (36.2)[a,b]	1054 (42.5)	535 (30.7)[a]	87 (36.6)
Middle East & North Africa	691 (30.2)	356 (25.1)[a]	113 (26.6)	748 (30.2)	407 (23.3)[a]	120 (50.4)[a,b]
Asia	421 (18.4)	371 (26.2)[a]	64 (15.1)	510 (20.6)	453 (26.0)[a]	12 (5.0)[a]
Latin America	163 (7.1)	270 (19.1)[a]	94 (22.1)[a]	168 (6.8)	350 (20.1)[a]	19 (8.0)[b]
Disease diagnosis						
AS	1181 (51.7)	609 (43.0)[a]	156 (36.7)[a]	1304 (52.6)	743 (42.6)[a]	88 (37.0)[a]
Nr-AxSpA	272 (11.9)	200 (14.1)	64 (15.1)	301 (12.1)	241 (13.8)	40 (16.8)
PsA	536 (23.5)	304 (21.5)	142 (33.4)[a,b]	560 (22.6)	400 (22.9)	73 (30.7)[a,b]
pSpA	170 (7.4)	175 (12.4)[a]	46 (10.8)	185 (7.5)	220 (12.6)[a]	28 (11.8)
Classification criteria						
ASAS criteria axSpA	1453 (63.6)	924 (65.2)	268 (63.1)	1604 (64.7)	1146 (65.7)	159 (66.8)
ASAS criteria axSpA–Imaging Arm	1363 (59.6)	856 (60.4)	244 (57.4)	1509 (60.8)	1054 (60.4)	152 (63.9)
ASAS criteria axSpA–Clinical Arm	827 (36.2)	536 (37.8)	129 (30.4)[b]	923 (37.2)	668 (38.3)	59 (24.8)[a,b]
ASAS criteria pSpA	256 (11.2)	200 (14.1)[a]	81 (19.1)[a,b]	266 (10.7)	246 (14.1)	43 (18.1)
CASPAR criteria	495 (21.7)	345 (24.3)	145 (34.1)[a,b]	521 (21.0)	444 (25.4)[a]	78 (32.8)[a,b]
HLA-B27 positive[c]	1068 (65.8)	664 (68.2)	147 (52.1)[a,b]	1189 (67.3)	809 (66.9)	67 (47.2)[a,b]
HLA-B15 positive[d]	21 (6.2)	10 (5.9)	6 (12.8)	22 (6.1)	15 (7.4)	2 (6.3)
SpA features						
Axial	1741 (76.2)	1096 (77.3)	317 (74.6)	1900 (76.6)	1344 (77.0)	182 (76.5)[a]
AAU	370 (16.2)	235 (16.6)	65 (15.3)	419 (16.9)	289 (16.6)	30 (12.6)
PsO	616 (27.0)	371 (26.2)	157 (36.9)[a,b]	643 (25.9)	489 (28.0)	79 (33.3)
IBD	153 (6.7)	87 (6.1)	26 (6.1)	157 (6.3)	105 (6.0)	12 (5.0)
Root disease	592 (25.9)	589 (41.6)[a]	191 (44.9)[a]	674 (27.2)	750 (43.0)[a]	78 (32.8)[b]
Peripheral arthritis	1091 (47.7)	964 (68.0)[a]	333 (78.4)[a,b]	1165 (47.0)	1213 (69.5)[a]	162 (68.1)[a]
Dactylitis	268 (11.7)	271 (19.1)[a]	109 (25.6)[a,b]	282 (11.4)	361 (20.7)[a]	42 (17.6)[a]
Treatment history						
bDMARD use	1354 (59.3)	866 (61.1)	243 (57.2)	1448 (58.4)	1043 (59.8)[a]	155 (65.1)[a]
csDMARD use	1368 (59.9)	1069 (75.4)[a]	339 (79.8)[a]	1475 (59.5)	1320 (75.6)	190 (79.8)
Disease severity						
BASDAI (0–10)	3.6 (2.4)	3.6 (2.2)	6.4 (2.0)[a,b]	3.6 (2.4)	4.0 (2.5)[a]	5.8 (2.0)[a,b]
BASFI (0–10)	2.8 (2.6)	2.7 (2.4)	5.3 (2.7)[a,b]	2.8 (2.6)	3.0 (2.7)[a]	4.8 (2.5)[a,b]
ASAS-HI (0–17)	6.0 (4.4)	6.3 (4.2)	11.4 (3.4)[a,b]	5.9 (4.4)	7.0 (4.6)[a]	10.4 (3.7)[a,b]
ASDAS-CRP	2.4 (1.1)	2.5 (1.1)	3.5 (1.0)[a,b]	2.4 (1.1)	2.6 (1.2)[a]	3.2 (0.9)[a,b]
PGA (0–10)	4.2 (2.7)	4.1 (2.6)	6.6 (2.2)[a,b]	4.1 (2.7)	4.5 (2.7)[a]	5.9 (2.2)[a,b]

AAU: acute anterior uveitis; AS: ankylosing spondylitis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C reactive protein; ASAS: Assessment of Spondyloarthritis international society; ASAS-HI: Assessment of Spondyloarthritis international society Health Index; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; bDMARDs: biologic Disease Modifying Antirheumatic Drugs; BMI: body mass index; CASPAR: classification criteria for psoriatic arthritis; csDMARDS: conventional synthetic Disease Modifying Antirheumatic Drugs; dx: diagnosis; HLA: human leukocyte antigen; EO: enthesitis only; EFM: enthesitis with fibromyalgia; IBD: inflammatory bowel disease; nr-axSpA: non-radiographic axial spondyloarthritis; PGA: Patient global assessment; PsA: psoriatic arthritis; PsO: psoriasis; pSpA: peripheral spondyloarthritis; SpA: spondyloarthritis.

[a] Significant difference ($P < 0.05$) compared to SpA only.

[b] Significant difference ($P < 0.05$) compared to enthesitis only.

[c] Data available for $n = 2879$ for FiRST data and $n = 3118$ for physician-diagnosed data.

[d] Data available for $n = 557$ for FiRST data and $n = 592$ for physician-diagnosed data.

4. Discussion

To our knowledge, this multinational observational study is the largest to date to characterise the prevalence of FM in an SpA cohort with enthesitis. A history of enthesitis and a clinical diagnosis of FM co-existed in 5% of the SpA cohort, rising to 10% when individuals were screened for FM during data collection using the FiRST questionnaire, a sensitive and specific tool for detecting FM [20].

Enthesitis was most prevalent in pSpA (57%), followed by nr-axSpA (48%) and PsA (46%), and the prevalence was lowest in AS (38.9%). A meta-analysis previously estimated the prevalence of enthesitis in AS and nr-axSpA at 29% and 35% respectively [22]. In PsA, enthesitis is estimated to occur in 60-80% of individuals [23] and in pSpA the estimate is 41–48% [24]. The prevalence of enthesitis in our study is therefore somewhat higher than would be expected for axSpA and pSpA, but lower for PsA.

The primary mode of diagnosis of enthesitis remains clinical, by assessing tenderness at entheseal locations. There is considerable overlap between the clinical diagnosis of enthesitis and the tender points of FM as described in the original classification of FM [9]. Imaging (MRI, ultrasound, plain radiography) can confirm a diagnosis of enthesitis [6]. Ultrasound studies distinguished patients with FM from those with SpA in inflammatory bowel disease (IBD) [25] and demonstrated that entheseal abnormalities occur less frequently in FM than PsA [13]. In our study, imaging was used in less than half of cases of clinical enthesitis to confirm the diagnosis and was more likely to be used in women than in men. Individuals in whom FM was recognised by their physician were significantly more likely to have undergone imaging to confirm a previous diagnosis of enthesitis; however, at 45% it was still less than half of the cohort. In contrast, only 38% of the cohort with FM on screening had previously had the diagnosis of enthesitis confirmed by

Table 3

Sex differences in the Enthesitis ever & Fibromyalgia (EFM) cohort using (1) FM by FiRST questionnaire and (2) clinical diagnosis of FM.

	Enthesitis & FM by FiRST		Enthesitis & Clinical dx FM	
	Women	Men	Women	Men
n	266 (6.0)	159 (3.6)***	183 (4.1)	55 (1.2)***
Symptom onset age	31.3 (13.2)	28.6 (11.0)*	34.4 (12.5)	27.2 (11.1)***
Age at diagnosis	39.6 (11.5)	35.2 (12.6)***	40.5 (11.1)	34.5 (11.8)***
Delay to diagnosis	8.2 (9.9)	6.9 (8.8)	6.3 (8.6)	7.2 (9.0)
Enthesitis confirmed on imaging	106 (39.8)	57 (35.8)	87 (47.5)	20 (37.0)
Enthesitis score at enrolment	9.0 (10.9)	6.6 (11.5)*	9.5 (10.2)	7.5 (9.0)
Body Mass Index	28.8 (6.7)	26.6 (5.3)***	29.9 (6.6)	26.9 (4.9)***
Diagnosis				
nr-axSpA	50 (18.8)	14 (8.8)***	37 (20.2)	3 (5.5)**
pSpA	35 (13.2)	11 (6.9)***	24 (13.1)	4 (7.3)**
AS	70 (26.3)	86 (54.1)***	55 (30.1)	33 (60.0)**
PsA	98 (36.8)	44 (27.7)***	61 (33.3)	12 (21.8)**
Treatment				
csDMARDs	224 (84.2)	115 (72.3)**	32 (17.5)	16 (29.1)
bDMARDs	154 (57.9)	89 (56.0)	65 (35.5)	18 (32.7)
Muscle relaxants	31 (11.7)	12 (7.5)**	23 (12.6)	6 (10.9)
Anti-depressants	48 (18.0)	15 (9.4)**	51 (27.9)	13 (23.6)
Opioids	23 (8.6)	14 (8.8)	11 (20.0)	21 (11.5)
Disease severity measures				
BASDAI	6.5 (1.9)	6.2 (2.1)	5.9 (1.9)	5.4 (2.2)
BASFI	5.3 (2.6)	5.4 (2.8)	4.8 (2.5)	4.8 (2.7)
ASAS-HI	11.5 (3.5)	11.3 (3.4)	10.6 (3.7)	9.8 (3.8)
ASDAS-CRP	3.4 (0.9)	3.5 (1.1)	3.2 (0.9)	3.2 (1.0)

AS: Ankylosing Spondylitis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C reactive protein; ASAS-HI: Assessment of Spondyloarthritis international society Health Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; bDMARDs: biologic Disease Modifying Antirheumatic Drugs; csDMARDS: conventional synthetic Disease Modifying Antirheumatic Drugs; dx: diagnosis; EFM: enthesitis with fibromyalgia; FiRST: Fibromyalgia Rapid Screen Tool; FM: fibromyalgia; nr-axSpA: non radiographic axial Spondyloarthritis; PsA: psoriatic arthritis; pSpA: peripheral spondyloarthritis.

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

Table 4

Logistic regression assessing association between clinical and demographic variables, and the presence of FM in individuals with history of enthesitis ever (EFM) as the dependent variable using (1) Model 1: FM by FiRST criteria; (2) Model 2: Clinical diagnosis of FM.

	Model 1: EFM using FM by FiRST criteria		Model 2: EFM using clinical diagnosis of FM	
Dependent variable	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
n		2845		1346
Determinants	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age	1.00 (1.00 to 1.01)	0.98 (0.97 to 0.99)**	1.01 (1.00 to 1.02)	1.00 (0.98 to 1.02)
Delay to diagnosis	1.02 (1.01 to 1.03)***	1.02 (1.01 to 1.04)*	1.00 (0.99 to 1.02)	
Females	2.85 (2.32 to 3.51)***	2.56 (1.92 to 3.42)***	5.70 (4.19 to 7.75)***	4.03 (2.60 to 6.24)***
HLA-B27 positive	0.54 (0.43 to 0.70)***	0.87 (0.63 to 1.20)	0.44 (0.31 to 0.61)***	0.68 (0.44 to 1.05)
BMI	1.05 (1.04 to 1.07)***	1.01 (0.99 to 1.04)	1.09 (1.06 to 1.11)***	1.04 (1.01 to 1.08)*
Smoker ever	1.07 (0.87 to 1.31)		0.81 (0.62 to 1.06)	
University studies	0.65 (0.52 to 0.81)***	0.88 (0.65 to 1.17)	0.61 (0.46 to 0.81)***	0.91 (0.60 to 1.38)
BASDAI	1.67 (1.59 to 1.76)***	1.63 (1.53 to 1.74)***	1.41 (1.33 to 1.49)***	1.29 (1.18 to 1.41)***
Regions[a]				
Europe & North America	0.50 (0.38 to 0.66)***	0.54 (0.37 to 0.79)**	1.49 (0.90 to 2.48)	
Asia	0.37 (0.27 to 0.52)***	0.67 (0.42 to 1.07)	0.34 (0.16 to 0.71)**	0.87 (0.36 to 2.12)
Middle East & North Africa	0.50 (0.37 to 0.67)***	0.52 (0.34 to 0.81)**	2.83 (1.73 to 4.65)***	5.31 (2.75 to 10.24)***
Diagnosis[b]				
pSpA	1.37 (0.98 to 1.92)		1.40 (0.92 to 2.13)	
PsA	1.74 (1.39 to 2.18)***	1.34 (0.91 to 1.98)	1.54 (1.14 to 2.07)**	0.68 (0.39 to 1.18)
Biologics ever	0.89 (0.73 to 1.09)	1.24 (0.93 to 1.66)	1.30 (0.99 to 1.71)	1.16 (0.76 to 1.76)
Enthesitis confirmed on imaging	1.01 (0.81 to 1.26)		1.35 (1.03 to 1.78)*	1.39 (0.94 to 2.05)*

Age & exposure to biologics included in all models, as clinically relevant variables. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BMI: body mass index; CI: confidence interval; EFM: enthesitis with fibromyalgia; FM: fibromyalgia; HLA: Human leucocyte antigen; OR: odds ratio; P: P-value; pSA: psoriatic arthritis; pSpA: peripheral spondyloarthritis.

[a] Compared to reference category: Latin America.
[b] Compared to reference category: axSpA.

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

imaging, which was not different to the cohort with a history of enthesitis only.

The FiRST questionnaire has a sensitivity of 90.5% and specificity of 85.7% in the general population in detecting FM [20] and good agreement with a rheumatologist's clinical diagnosis of FM in an inflammatory arthritis population [26]. When systematic screening was applied in our study, 17% fulfilled the criteria for FM, much higher than the 9% with a clinical diagnosis, suggesting FM is under-recognised in individuals with SpA. As the FiRST questionnaire takes under three minutes to perform, it is a convenient tool that could be introduced in clinical practice to screen for the presence of FM. Furthermore, considering the significant clinical overlap between FM and enthesitis, more liberal use of imaging to confirm the diagnosis of enthesitis may be beneficial, particularly in those who screen positive for FM using FiRST.

Across all disease severity measures, individuals with EFM had significantly worse disease compared to those with enthesitis alone, and this did not differ whether enthesitis ever or enthesitis on exam was used. Interestingly, despite the higher disease severity scores in the EFM group, there was no difference in the overall use of csDMARDs or biologics. There is conflicting evidence in the literature as to the effect of FM on achieving remission in SpA [27]. Previously, the presence of FM in individuals with SpA has amplified the disease severity measures [11,28], however ASDAS is less often affected, as it is a composite measure incorporating CRP [29]. In our study, ASDAS-CRP was significantly higher in individuals with concomitant FM compared to those with enthesitis alone. The disease severity assessment measures used in our study play a crucial role in the treatment algorithms of SpA[30]. Therefore, the presence of FM in those with enthesitis may lead to unnecessary escalation of treatment for SpA, particularly if it is unrecognised. In addition, our findings suggest the need for holistic management strategies that will improve the quality of life in individuals with comorbid FM and enthesitis.

When the 2009 ASAS classification criteria for axSpA were released [31], there was concern amongst the rheumatology community that the presence of FM would lead to the overdiagnosis of nr-axSpA using the clinical arm of the criteria. Many studies have since demonstrated this not to be the case [10,32]. This study adds further reassurance to the wider rheumatology community that the presence of FM does not lead to over-classification of nr-axSpA via the clinical arm of the criteria.

Women represented 78% of all individuals in our study with an existing diagnosis of FM, which is in-keeping with the literature [33]. However, when the cohort was screened for FM using the FiRST questionnaire, the male to female ratio of FM was more balanced (59% vs 41%). Only 23% of those with enthesitis ever and a clinical diagnosis of FM were men; however in those with both enthesitis ever and FM by FiRST criteria, the proportion of men increased to 37%. Women with enthesitis ever and comorbid FM were older at symptom onset and older at diagnosis of SpA than men, but there was no difference in the delay to diagnosis between both sexes. There was also no sex effect in the pattern of enthesitis ever experienced in those with FM. Women were more likely to have been prescribed muscle relaxants and antidepressants than men. There was an equal level of opioid use in those with enthesitis ever and comorbid FM.

Our study demonstrates that FM and enthesitis commonly coexist in women with SpA. However, it is not rare in men when screened. Physician bias is known to play a part in diagnosing FM, with a higher burden of proof required to assign a diagnosis of FM to men than women [34]. Physicians are also more likely to attribute a non-medical cause to symptoms reported by women than men [35]. The FiRST criteria may detect more FM in men with rheumatic disease than a rheumatologist's clinical opinion [26]. Despite this, FM continues to be perceived as a female-dominated disease, with

80–90% of FM diagnosed in women [36,37]. When studies recruit using unbiased selection criteria for FM, women only represent 58% of cases with FM [38]. However, existing literature investigating FM is dominated by women, therefore there is a paucity of data regarding men with FM [38,39]. In our study, women had more severe disease than men. A large study exploring gender differences in PsA similarly found more severe disease in women [40]. In addition, the authors demonstrated that FM was more prevalent in women, but it did not lower the odds of achieving disease remission, in contrast to enthesitis. That study did not specifically investigate the co-existence of FM and enthesitis. Recognition of comorbid FM in both sexes can avoid inappropriate escalation of disease-modifying treatment and under-treatment of chronic pain.

A limitation of our study is the way in which FM was defined, although this is not a unique challenge, as FM is a clinical diagnosis. The FiRST criteria have excellent discriminative ability in diagnosing FM [20], but have not been validated as classification criteria, nor have they been validated for use specifically in a SpA population with enthesitis. There is some overlap between the questions asked in the FiRST questionnaire, and the pain experienced by those with enthesitis. Therefore, further research is required to determine whether the FiRST questionnaire performs well in detecting FM in those with enthesitis, ideally using imaging to confirm the presence of enthesitis. However, it is important that this research is carried out in both sexes, and not limited to a female-only population. Our definition of clinical FM was purely subjective, and this may have resulted in an under-diagnosis of clinical FM and partially explain the discrepancy seen between patients diagnosed with FM clinically and by FiRST criteria. However, both of these definitions reflect clinical practice, thus making our results applicable to a clinical setting. Finally, the cross-sectional nature of the data allows us only to draw correlations, and limits our ability to infer causation. However, the multinational participation combined with a large number of enrolled individuals are notable strengths of the data used in this study.

In summary, FM is an important comorbidity in the management of enthesitis in SpA. FM occurs more often in females with enthesitis, but is not a rare finding in males. The presence of FM inflates disease severity measures in individuals with enthesitis, with no sex effect demonstrated. It remains unknown whether the presence of FM in individuals with enthesitis leads to over-treatment of SpA. Further sex-stratified studies are required to validate the FiRST questionnaire in individuals with enthesitis, further delineate the role of imaging in coexistent FM and enthesitis and develop holistic management strategies.

Disclosure of interest

The authors declare that they have no competing interest.

Steering Committee members, Clininfo and the pharma companies supporting this initiative.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2022.105420.

Références

[1] Dougados M, Baeten D. Spondyloarthritis. Lancet 2011;377:2127–37.

[2] Garg N, van den Bosch F, Deodhar A. The concept of spondyloarthritis: where are we now? Best Pract Res Clin Rheumatol 2014;28:663–72.

[3] Nadon V, Moltó A, Etcheto A, et al. Clinical peripheral enthesitis in the DESIR prospective longitudinal axial spondyloarthritis cohort. Clin Exp Rheumatol 2019;37:561–5.

[4] Pittam B, Gupta S, Harrison NL, et al. Prevalence of extra-articular manifestations in psoriatic arthritis: a systematic review and meta-analysis. Rheumatology 2020;59:2199–206.

[5] Ball J. Enthesopathy of rheumatoid and ankylosing spondylitis. Ann Rheum Dis 1971;30:213–23.

[6] Schett G, Lories RJ, D'Agostino MA, et al. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol 2017;13:731–41.

[7] Gladman DD, Inman RD, Cook RJ, et al. International spondyloarthritis interobserver reliability exercise—The INSPIRE study: II. Assessment of peripheral joints, enthesitis, and dactylitis. J Rheumatol 2007;34:1740–5.

[8] Kaeley GS, Eder L, Aydin SZ, et al. Enthesitis: a hallmark of psoriatic arthritis. Semin Arthritis Rheum 2018;48:35–43.

[9] Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160–72.

[10] Roussou E, Ciurtin C. Clinical overlap between fibromyalgia tender points and enthesitis sites in patients with spondyloarthritis who present with inflammatory back pain. Clin Exp Rheumatol 2012;30:24–30.

[11] Mease PJ. Fibromyalgia, a missed comorbidity in spondyloarthritis: prevalence and impact on assessment and treatment. Curr Opin Rheumatol 2017;29:304–10.

[12] Alunno A, Carubbi F, Stones S, et al. The impact of fibromyalgia in spondyloarthritis: from classification criteria to outcome measures. Front Med 2018;5:290.

[13] Fiorenza A, Bonitta G, Gerratana E, et al. Assessment of enthesis in patients with psoriatic arthritis and fibromyalgia using clinical examination and ultrasound. Clin Exp Rheumatol 2020;38:31–9.

[14] Rusman T, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender differences in axial spondyloarthritis: women are not so lucky. Curr Rheumatol Rep 2018;20:35.

[15] López-Medina C, Molto A, Sieper J, et al. Prevalence and distribution of peripheral musculoskeletal manifestations in spondyloarthritis including psoriatic arthritis: results of the worldwide, cross-sectional ASAS-PerSpA study. RMD Open 2021;7.

[16] Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.

[17] Lukas C, Landewe R, Sieper J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18–24.

[18] van der Heijde D, Lie E, Kvien TK, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:1811–8.

[19] Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281–5.

[20] Perrot S, Bouhassira D, Fermanian J. Development and validation of the fibromyalgia rapid screening tool (FiRST). Pain 2010;150:250–6.

[21] Kiltz U, van der Heijde D, Boonen A, et al. Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. Ann Rheum Dis 2015;74:830–5.

[22] de Winter JJ, van Mens LJ, van der Heijde D, et al. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. Arthritis Res Ther 2016;18:196.

[23] Coates LC, Helliwell PS. Psoriatic arthritis: state of the art review. Clin Med 2017;17:65–70.

[24] Carron P, De Craemer AS, Van den Bosch F. Peripheral spondyloarthritis: a neglected entity-state of the art. RMD Open 2020;6.

[25] Atzeni F, Sciortino D, Nucera V, et al. Study of entheses in patients with spondyloarthritis and inflammatory bowel disease with and without fibromyalgia: the importance of ultrasonography. Joint Bone Spine 2020;87:507–8.

[26] Fan A, Tournadre A, Pereira B, et al. Performance of Fibromyalgia Rapid Screening Tool (FiRST) to detect fibromyalgia syndrome in rheumatic diseases. Rheumatology 2016;55:1746–50.

[27] Coskun Benlidayi I. Fibromyalgia interferes with disease activity and biological therapy response in inflammatory rheumatic diseases. Rheumatol Int 2020;40:849–58.

[28] Duffield SJ, Miller N, Zhao S, et al. Concomitant fibromyalgia complicating chronic inflammatory arthritis: a systematic review and meta-analysis. Rheumatology 2018;57:1453–60.

[29] Salaffi F, De Angelis R, Carotti M, et al. Fibromyalgia in patients with axial spondyloarthritis: epidemiological profile and effect on measures of disease activity. Rheumatol Int 2014;34:1103–10.

[30] van der Heijde D, Ramiro S, Landewe R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978–91.

[31] Rudwaleit M, Landewe R, van der Heijde D, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis 2009;68:770–6.

[32] Baraliakos X, Regel A, Kiltz U, et al. Patients with fibromyalgia rarely fulfil classification criteria for axial spondyloarthritis. Rheumatology 2018;57:1541–7.

[33] Queiroz LP. Worldwide epidemiology of fibromyalgia. Curr Pain Headache Rep 2013;17:356.

[34] Katz JD, Mamyrova G, Guzhva O, et al. Gender bias in diagnosing fibromyalgia. Gender Med 2010;7:19–27.

[35] Barsky AJ, Peekna HM, Borus JF. Somatic symptom reporting in women and men. J Gen Intern Med 2001;16:266–75.

[36] Yunus MB. The role of gender in fibromyalgia syndrome. Curr Rheumatol Rep 2001;3:128–34.

[37] Ben-Ami Shor D, Weitzman D, Dahan S, et al. Adherence and persistence with drug therapy among fibromyalgia patients: data from a Large Health Maintenance Organization. J Rheumatol 2017;44:1499–506.

[38] Wolfe F, Walitt B, Perrot S, et al. Fibromyalgia diagnosis and biased assessment: sex, prevalence and bias. PLoS One 2018;13:e0203755.

[39] Di Franco M, Iannuccelli C, Bazzichi L, et al. Misdiagnosis in fibromyalgia: a multicentre study. Clin Exp Rheumatol 2011;29:S104–8.

[40] Duruöz MT, Gezer HH, Nas K, et al. Gender-related differences in disease activity and clinical features in patients with peripheral psoriatic arthritis: a multicenter study. Joint Bone Spine 2021;88:105177.