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The prevalence and impact of comorbid fibromyalgia in inflammatory arthritis

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A B S T R A C T

Fibromyalgia (FM) is one of the most common conditions that rheumatologists encounter. It is characterised by chronic widespread pain, fatigue, sleep disturbances and impaired cognition. The prevalence of comorbid FM among populations with rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) are considerably higher than among the general population, with pooled prevalence estimates of 18–24% in RA, 14–16% in axSpA and 18% in PsA. Prevalence estimates should be interpreted with care as the criteria for FM have not been validated for use in patients with inflammatory arthritis. Comorbid FM appears to affect assessment of disease severity in these conditions, particularly patient-reported outcome measures, and may influence response to treatment. There is a need for better identification, classification and management of FM in the context of inflammatory rheumatic diseases.

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Introduction

Fibromyalgia (FM) is a common condition characterised by chronic widespread pain, fatigue, sleep disturbances and impaired cognition [1]. The prevalence of FM in the general population ranges from 2

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to 4% [2], making it one of the most common conditions that rheumatologists will encounter. Its prevalence is similar across different countries and cultures, with no evidence that it is more common in industrialised countries [3]. The prevalence of FM increases with age [4] and is more common in females, with female-to-male ratios ranging from 2:1 to 30:1 depending on the criteria used [1].

The key concept in FM pathophysiology is pain centralisation: the central nervous system augments and amplifies pain, such that an individual feels more pain than would be expected given the degree of nociceptive stimuli. This activation of pain-processing areas in the brain can be observed using functional magnetic resonance imaging [5,6].

There are two main groups of FM. Many individuals have no identifiable ongoing nociceptive input that could account for pain. In most cases, these individuals with 'primary' FM initially develop regional pain conditions that become widespread over time [1]. As FM shares many symptoms with rheumatic diseases, such as pain and fatigue, these individuals frequently present a diagnostic challenge to the rheumatologist.

Centralised pain can also occur alongside, or as a consequence of, a disease that has identifiable ongoing nociceptive input, such as from inflammatory arthritides. Chronic inflammation may mediate transition from peripheral to central pain resulting in symptoms of FM. In animal models, proinflammatory cytokines such as tumour necrosis factor and interleukin-6 have been implicated in aberrant central pain processing and widespread pain sensitivity [7]. This review will predominantly focus on individuals with comorbid FM, which in many cases will be this 'secondary' FM.

Comorbid FM has profound implications for the management of inflammatory arthritides. Non-inflammatory pain may lead to unnecessary escalation of potentially toxic anti-rheumatic treatment. Alternatively, as interventions to reduce peripheral nociceptive stimuli may not alter the long-term course of fibromyalgia [8], comorbid FM may blunt the patient-reported response, leading to treatment discontinuation.

In this review, we begin with a brief overview of diagnostic and classification criteria for FM, and then focus the discussion on the prevalence and impact of comorbid FM in common chronic inflammatory arthritides (Box 1 summarises methods of the systematic review and meta-analysis).

Diagnostic and classification criteria for fibromyalgia

The understanding of FM has improved with formalisation of its definition, but as understanding advances, there has been a need to revise its diagnostic/classification criteria. Such evolving disease definitions can present a challenge for both clinicians and researchers. Knowing the FM criteria is essential for understanding its interplay with rheumatic diseases.

The first approved and widely adopted criterion for FM was the 1990 American College of Rheumatology (ACR) classification criteria [10]. These included a combination of chronic widespread pain and tender point examination (Box 2). Although designed for classification, the 1990 criteria became widely used by rheumatologists for diagnosis. It was later recognised that FM was mostly diagnosed in primary care, where tender point examinations were often omitted or incorrectly performed [11–13]. The focus on tender point examination also gave an erroneous impression that FM is a peripheral musculoskeletal disease.

Box 1

Summary of methods for systematic review and meta-analysis

The prevalence of FM and its associations with disease outcome measures in inflammatory arthritides were collated through systematic literature review. We updated a prior systematic review and meta-analysis [9] using the original protocol (PROSPERO registration CRD42017076504). In brief, we searched PubMed, MEDLINE, Web of Science, PsycINFO, Scopus and the Cochrane Library, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Meta-analysis was performed using random-effects models in MetaXL v5.3 (www.epigear.com). Heterogeneity of estimates was presented using the I^2 statistic.

Box 2

Evolution of fibromyalgia criteria

ACR 1990 classification criteria.

1. History of chronic widespread pain for ≥3 months
2. Exhibit ≥11/16 tender points

ACR 2010/2011 diagnostic criteria.

1. WPI ≥7 and SSS ≥5, or WPI 3–6 and SSS ≥9
2. Symptoms present at similar levels for ≥3 months
3. Does not have disorder that would otherwise (sufficiently) explain the pain

ACR 2016 diagnostic and classification criteria.

1. WPI ≥7 and SSS ≥5, or WPI 3–6 and SSS ≥9
2. Generalized pain, defined as pain in at least 4 of 5 regions
3. Symptoms present at similar levels for ≥3 months
4. A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses.

Widespread pain index (WPI) includes 19 sites: right/left shoulder girdle; right/left upper arm; right/left lower arm; right/left hip and buttock; right/left upper leg; right/left lower leg; right/left jaw; chest; abdomen; neck; upper back; lower back.

Symptom severity score (SSS) gives up to 3 points for each of: 1) fatigue, 2) waking unrefreshed, 3) cognitive symptoms (brain fog), 4) somatic symptoms in general (replaced by headache, pain/cramps in lower abdomen or depression in the 2011 modification).

The ACR published an updated diagnostic criterion that no longer necessitated tender point examinations [14]. The 2010 criteria instead included the widespread pain index (WPI) and symptom severity score (SSS) (Box 2). It was further modified in 2011 for use in surveys, with specific caution that it should not be used for diagnosis [15]. The 2011 modified research criteria substituted the physician's estimate of somatic symptoms with three self-reported symptoms (Box 2). The 2010 and 2011 criteria both recognised the spectrum of symptom severity, or 'fibromyalgianess', using a sum of the WPI and SSS.

In clinical practice, many consider FM a diagnosis of exclusion, which rules out the concept of secondary FM. However, the original 1990 criteria stated that 'a diagnosis of fibromyalgia remains a valid construct irrespective of other diagnoses.' Ambiguity may have arisen from the 2010/2011 criteria, which requires that 'the patient does not have a disorder that would otherwise ('sufficiently', added in 2011 criteria) explain the pain', but the authors did not intend for a difference from the 1990 criteria [16]. A revised version (for both diagnosis and classification) was, therefore, published in 2016 partly to clarify this [16]. It also aimed to reduce misclassification of patients who had regional pain, since the WPI does not consider the spatial distribution of pain.

In the following sections, we will discuss comorbid FM in some common inflammatory arthritides. Readers should remain mindful that none of these criteria for FM has been validated for use in patients with any type of inflammatory arthritis.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, auto-immune, systemic inflammatory disease with a prevalence of approximately 1% [17]. Women are more likely to develop RA than men: the cumulative

lifetime risk of developing RA is approximately 3.6% in female adults and 1.7% in males [18]. Synovial joints are the primary sites of disease and, if inadequately controlled, many patients go on to develop irreversible joint destruction and consequent disability.

There are no diagnostic criteria for RA, but the ACR/EULAR 2010 classification criteria [19] are often used to inform diagnosis. Compared to classification criteria for axial spondyloarthritis (discussed later), components of the RA criteria are more objective serology, acute phase reactants, swollen joints and symptom duration. It seems less likely that FM would influence RA diagnosis. However, the odds of FM in rheumatoid factor negative RA have been reported to be twice that of those who were positive (OR 2.1); the effect size was still larger in seronegative patients for anti-citrullinated protein antibody (ACPA) than in seropositive ones (OR 3.0) [20]. When the authors examined the chronology of diagnoses, many patients were diagnosed with FM prior to RA in the seronegative group. They hypothesised that clinicians may be less likely to diagnose RA, or more likely to attribute the prodrome of RA to FM, in seronegative patients. Alternatively, FM may be the underlying diagnosis in some seronegative cases. In another study examining the incidence of secondary FM among an early inflammatory arthritis cohort, ACPA-negative patients were twice as likely to develop FM than seropositive patients (HR 0.48) [21]. The authors suggested that ACPA-positive patients may be treated more aggressively and achieve disease control earlier, or that physicians may be more likely to attribute pain to FM in ACPA-negative individuals [21]. Although the role of FM in RA diagnosis is contested [22], its impact on the monitoring and management of RA is much more established.

The treat-to-target strategy is widely recommended for the management of RA. This approach is based on tight monitoring of disease activity and change of management if a treatment target is not reached [23], similar to treatment paradigms for diabetes or hypertension. Randomised trials in RA found that treating to target substantially improved disease activity, radiographic progression, physical function and quality of life at no additional cost [24]. However, treating to a clinical target, as opposed to a serological biomarker, has limitations. Comorbid FM may affect more subjective aspects of these clinical indices, such as tender joint count and patient global scores, thus influencing treatment decisions. In the following sections, we will summarise evidence for the prevalence of FM in RA and its impact on disease outcomes.

Prevalence of comorbid fibromyalgia in RA

The reported prevalence of fibromyalgia in established RA varies considerably from 5 to 52%. In the updated meta-analysis, consisting of 26 cross-sectional studies in total [9,22,25,26], the pooled prevalence of FM was 20% (95%CI 16 to 25%). Heterogeneity was high between studies ($I^2 = 93\%$) and was not improved when stratifying prevalence estimates by FM criteria (Fig. 1). There was a clear trend that smaller studies reported higher prevalence, but restricting to larger studies did not improve heterogeneity significantly. Prevalence of FM defined using the 2010/2011 criteria was higher than using the 1990 criteria (24 vs 18%). This is consistent with studies in the general population, where the 2011 survey criteria gave higher population estimates of FM than both the 2010 and 1990 criteria [4].

Fibromyalgia and disease outcomes measures in RA

Studies included in the updated meta-analysis were examined to see whether comorbid FM was associated with disease activity in RA. In contrast to the heterogenous prevalence estimates, there was good consistency across studies reporting the impact of comorbid FM upon DAS28. Of 18 studies, all but one reported higher DAS28 scores in patients with comorbid FM. When results from these studies were combined, patients with comorbid FM had significantly higher pooled DAS28 than those with RA alone (DAS28 mean difference 1.30, 95% CI 1.17 to 1.44; $I^2 = 37\%$). Put in context, a difference of 1.3 can change ACR disease activity category from remission (<2.6) to moderate disease (3.2 to 5.1) [27]. Like DAS28, the simplified disease activity index (SDAI) and the clinical disease activity index (CDAI) were also higher in the presence of comorbid FM [9].

When studies reported components of the DAS28, patients with comorbid FM had significantly higher tender joint counts and, in most cases, higher patient global scores than those without. This was in contrast to comparisons using objective DAS28 components: swollen joint counts were higher in

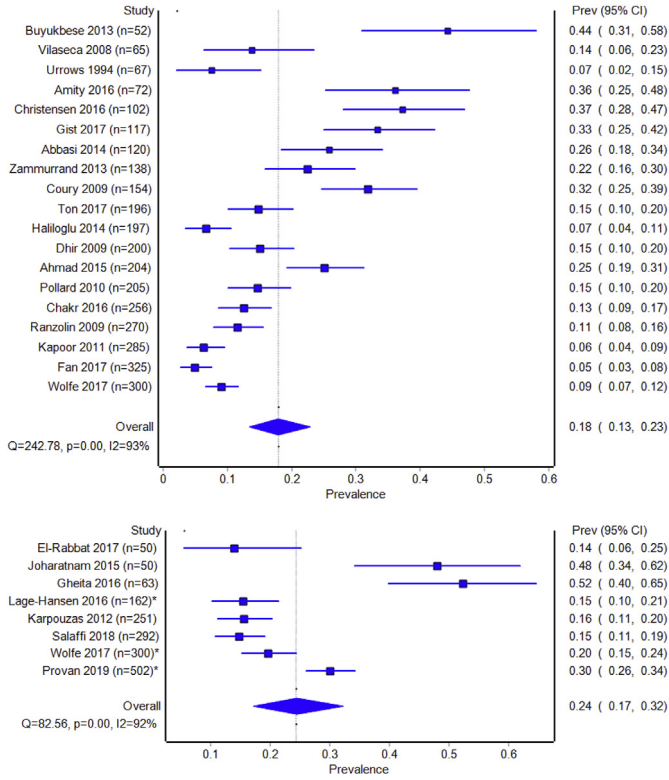

Fig. 1. Prevalence of comorbid fibromyalgia among patients with rheumatoid arthritis. Fibromyalgia was defined using the ACR 1990 criteria in the top panel and the 2010/11 criteria in the bottom panel (*indicates 2011 criteria).

those with comorbid FM in only 3 out of 15 studies; the remaining studies showed no significant differences. ESR was also not statistically different between the comparison groups in any of the studies in which it was reported. There have been concerns about the weight that subjective DAS28 components are given. For example, tender joint count (weight=0.56) has twice the weight of swollen joint count (0.28); in two patients with the same number of swollen/tender joints and ESR, the one reporting 100 on the patient global visual analogue score (VAS) will have a DAS28 score 1.4 units higher than the other reporting 0. In clinical practice, healthcare professionals should be mindful of comorbid FM when assessing disease activity, particularly when making treatment decisions. Musculoskeletal ultrasound may be useful in distinguishing between inflammation and high disease activity due to concomitant FM. Data from our centre have shown that ultrasound is effective in preventing unnecessary treatment-escalation to biologics, with an overall cost saving [28].

In addition to RA-specific disease activity scores, patients with comorbid FM also reported more severe disease using generic outcome measures. In a large study of 11,866 patients, those with comorbid FM had greater functional limitation (Health Assessment Questionnaire (HAQ) 1.8 vs 1.0), pain (VAS 7.6 vs 3.4) and poorer quality of life (using the 36-Item Short Form Survey and EuroQoL) [29]. These findings were consistently replicated in other RA cohorts [30,31].

The impact of fibromyalgia on treatment response in RA

In a longitudinal study of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) in RA, FM symptom severity (WPI + SSS) was one of the strongest independent predictors of not being in SDAI remission (SDAI≤3.3) at 6 months [32]. Another study of 156 patients with RA

found that the presence of FM was independently predictive of functional impairment over 2 years (using the Multi-Dimensional Health Assessment Questionnaire, MDHAQ). This increase in functional impairment in patients with RA and FM was estimated to be 4- to 7-fold higher than those without FM from other studies [33]. This study also showed that FM symptom severity was independently predictive of MDHAQ: every 1-point increase in this scale was predictive of a 0.013 greater increase in MDHAQ over 2 years.

Axial spondyloarthritis

Axial spondyloarthritis (axSpA) is another common rheumatic condition with prevalence between 0.3 and 1.4% [34]. It is a chronic inflammatory disease predominantly affecting the spine, but also the entheses and peripheral joints. axSpA can be classified into radiographic (also known as ankylosing spondylitis, AS) or non-radiographic axSpA (nr-axSpA) depending on whether sacroiliac joint damages are evident on plain-film radiographs [35] (see Box 3 for classification criteria). Both have similar disease features, comorbidities and symptom burden, but patients with AS tend to be older, more frequently male and have higher inflammatory markers than their nr-axSpA counterparts [36–38]. These observations led many to consider both AS and nr-axSpA to be part of the same disease spectrum, although not all patients with nr-axSpA progress to AS [39].

Distinguishing nr-axSpA from FM is challenging. All versions of the FM criteria include axial skeletal pain, which is the principal clinical feature of axSpA. Widespread pain and tenderness - key features of FM that are included in all established criteria - can also be caused by enthesitis, which can be present in up to 33% of patients with axSpA depending on the screening methods used [40] (we defer more detailed discussion of enthesitis for the section on psoriatic arthritis). When the United States (US) Food and Drug Administration (FDA) met in 2013 to consider TNF inhibitors (TNFi) for patients with nr-axSpA, they raised concerns that patients with highly prevalent conditions such as FM might be incorrectly diagnosed with nr-axSpA and inappropriately treated, particularly because (mis)classification may be made with physiological MRI changes [41] or indeed no imaging at all (i.e. the ASAS clinical arm [35]). This was one reason that biologic treatment remained unlicensed for nr-axSpA in the US until March 2019.

These concerns were not shared to the same extent in Europe, where TNFi are licensed for nr-axSpA. Rates of such misclassification may be low; in a study of 40 patients who fulfilled the 2010 criteria for FM and had HLA-B27 tested, only two patients would have fulfilled the ASAS criteria for axSpA [42]. Furthermore, the prevalence of comorbid FM was lower in the clinical arm than in the imaging arm (10 vs 23%) among those with nr-axSpA, which was replicated in a UK cohort (10 vs 25%) [43]. Whether the FDA's concerns were warranted, FM has unique implications for the management of axSpA. In the following sections, we will summarise current evidence on the prevalence of FM and its associations and effects on disease outcome measures in axSpA.

Box 3

ASAS criteria for axial spondyloarthritis

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

- Sacroiliitis on imaging* plus ≥1 SpA feature** (imaging arm) or
- HLA-B27 plus ≥2 SpA features** (clinical arm)

*active inflammation on MRI highly suggestive of sacroiliitis associated with SpA; or definite radiographic sacroiliitis (grade ≥2 bilaterally or grade ≥3 unilaterally).

**including: inflammatory back pain; arthritis (synovitis); heel enthesitis; anterior uveitis; dactylitis; psoriasis; inflammatory bowel disease; good response to NSAIDs; HLA-B27; elevated CRP (above upper limit of normal); and family history (of AS, reactive arthritis, psoriasis, uveitis, or inflammatory bowel disease).

Prevalence of comorbid fibromyalgia in axSpA

As axSpA is a more recent concept, many historical studies have been of AS cohorts. Among 10 studies of AS [9,42], the prevalence of comorbid FM ranged from 4 to 25%. The pooled prevalence was 14% (95% CI 8 to 20%). There were high levels of heterogeneity between studies ($I^2 = 92\%$). Like RA, larger studies tended to report lower prevalence (Fig. 2). There were only three studies of nr-axSpA cohorts, where the prevalence of FM ranged from 10 to 18% with a pooled estimate of 15% (95% CI 11 to 20%; $I^2 = 0\%$). Four papers studied axSpA cohorts (i.e., both AS and nr-axSpA); prevalence of FM to range from 14 to 21%, with a pooled prevalence of 16% (95%CI 12 to 21%; $I^2 = 76\%$) [9,42]. There were not enough studies to stratify the meta-analysis by FM criteria. When Baraliakos et al. applied two FM criteria to the same cohort [42], the prevalence of comorbid FM using the 2010 criteria was significantly higher than the 1990 criteria (24 vs 14%), similar to results from RA studies.

Two studies directly compared FM prevalence between AS and nr-axSpA. Baraliakos et al. reported that 29% of patients with AS and 19% of patients with nr-axSpA met the 2010 FM criteria; this was used by the authors to dismiss concerns about misclassification of FM in nr-axSpA [42]. However, Macfarlane et al. found FM in 20% of patients with AS and 23% of patients with nr-axSpA using the 2011 FM criteria [43]. This latter study is consistent with results of our meta-analyses showing very similar prevalence estimates for AS and nr-axSpA. It should be noted that most studies did not distinguish between prevalent (i.e., existing) and incident (i.e., new) cases of axSpA. Baraliakos et al. reported that comorbid FM was more common in patients with prevalent AS (41%) than those with prevalent nr-axSpA (22%), but there were no statistically or clinically meaningful differences of FM in patients with incident AS (12%) and those with incident nr-axSpA (16%) [42]. Although this study did not describe each group's disease duration in detail, these results suggest that FM is more likely to develop following diagnosis of AS than nr-axSpA.

Fibromyalgia and disease outcomes measures in axSpA

Several measures of disease severity in axSpA are self-assessed, which may be influenced by additional symptom burden from comorbid FM. For instance, the Bath AS Disease Activity Index (BASDAI) gives equal weight to fatigue/tiredness and discomfort from areas tender to touch/pressure (key symptoms of FM) as to questions on morning stiffness.

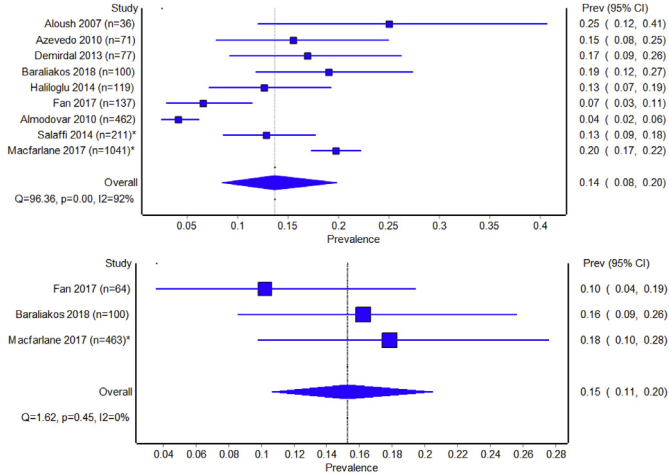

Fig. 2. Prevalence of comorbid fibromyalgia among patients with ankylosing spondylitis (top panel) and non-radiographic axial spondyloarthritis (bottom). *Salaffi used the 2010 criteria; Macfarlane 2011 criteria.

In a prior meta-analysis, patients with AS and concomitant FM were consistently found to have higher disease activity scores than those with AS alone (BASDAI mean difference 2.2, 95%CI 1.9 to 2.6) [9]. Despite the heterogenenous disease definitions and prevalence estimates as described above, there was surprising consistency in the reported BASDAI difference (I^2 = 0%). To put these results in perspective, a difference of 2 units in BASDAI is considered a response to TNFi therapy, and could be the difference between starting or stopping biologics [44,45]. Partly to address concerns about the influence of non-inflammatory symptoms on BASDAI, the Assessment of Spondyloarthritis international Society (ASAS) developed the AS Disease Activity Score (ASDAS) with the aim of improving objectivity. ASDAS does not include assessment of fatigue but does include acute phase reactants. As with RA, there were no statistically significant differences for ESR or CRP levels in patients with and without comorbid FM [9]. Accordingly, ASDAS proved to be more robust to comorbid FM than BASDAI [46].

Other outcome measures were also worse in axSpA patients with comorbid FM. One study reported 3-unit higher functional impairment measured using BASFI in those with FM than without. Quality of life was poorer when assessed using both the AS quality of life questionnaire and EuroQol. Patients with comorbid FM also reported poorer sleep, greater fatigue and more anxiety and depression on the Hospital Anxiety and Depression Scale [43]. Patients meeting FM criteria reported significantly greater proportion of work time missed (15 vs 2.5% missed). When they were at work, productivity was reported to be impaired in 51% of FM vs 23% without. In this study, swollen joint count (0.5 vs 0.2) and BASMI (4.2 vs 3.6) were also higher in those meeting the 2011 FM criteria, but these differences were less marked than patient-reported outcomes [43]. When we clustered patients with axSpA according to their comorbidities, patients with comorbid FM reported more severe disease activity, functional impairment, fatigue, pain and poorer quality of life than any other comorbidities [47].

The impact of fibromyalgia on treatment response in axSpA

In an analysis of 291 patients with axSpA, those meeting the 2011 FM criteria had higher BASDAI upon commencement of TNFi, but demonstrated comparable BASDAI response over the 12 month follow-up [48]. There was also no difference in the likelihood of achieving ASAS20 or ASAS40 response criteria at 12 months. These findings were replicated by another group using the 1990 FM criteria: the presence of comorbid FM was not independently predictive of BASDAI50/2 (50% or 2-unit reduction in BASDAI), ASAS20 or ASAS40 responses at 12 weeks [49].

While the presence of FM did not predict treatment response, high SSS (but not WPI) was a strong predictor [48]. This study also found that, with improved disease control using TNFi, three of the five participants with FM at baseline no longer met the 2011 FM criteria through follow-up.

The evidence so far would suggest that comorbid FM in axSpA does not significantly reduce treatment response. However, it is worth highlighting that, unlike RA, an absolute remission target is rarely used in axSpA in clinical practice. There is no validated definition for remission using BASDAI, whereas ASDAS remission (<1.3) and ASAS partial remission are predominantly used in clinical trials [50,51]. Binary response variables may not be suitable outside of trial contexts as, even if all patients responded by an identical degree, the group with higher baseline disease activity (e.g. those with comorbid FM) will have fewer individuals achieving binary response (e.g. ASDAS remission) [52]. One study did find that SpA patients (82% met the ASAS axSpA criteria) with comorbid FM had 70% higher risk of discontinuing their first TNFi than those who did not (FM prevalence 21%) [53]. This study used the Fibromyalgia Rapid Screening Tool (FiRST) [54], which has good specificity (80%) when validated against the ACR 1990 criteria, but a poor positive predictive value of 27% [55].

Psoriatic arthritis

Psoriatic arthritis (PsA) is a common inflammatory arthritis that is associated with psoriasis. PsA affects 0.3–1% of the general population, but its prevalence can be up to 30% among those with psoriasis [56]. The incidence of PsA among psoriasis populations was estimated to be 2.7% per year, predicted by severe psoriasis, nail involvement and uveitis [57]. Its clinical presentation is heterogeneous, involving varying numbers and distribution of peripheral joints as well as the axial skeleton.

There are also a wide range of clinical features, including enthesitis, dactylitis, nail disease, uveitis and osteitis.

PsA emerged as a distinct disease entity relatively recently, in the 1960s, with the classification criteria by Moll and Wright [58], which has since been superseded by the Classification of Psoriasis Arthritis (CASPAR) criteria in 2006 [59]. Nevertheless, classification and diagnosis remain difficult due to its varied clinical features. Among those with known psoriasis, the key diagnostic challenge is to identify whether the patient has inflammatory disease or whether musculoskeletal pain is due to another process. The diagnosis of psoriatic arthritis is often difficult, particularly in the early stages of the disease. There is particular diagnostic uncertainty for the minority of patients that develop arthritis before skin disease [60].

In PsA, shared risk factors and associated comorbidities contribute to the challenge of diagnosing comorbid FM. Both psoriasis and psoriatic arthritis are associated with obesity and depression [61–63] that are, in turn, intimately associated with FM. Similarly to FM, the presence of depression is known to influence the reporting of pain [64], whereas more severe disease increases the risk of developing depression. Obesity and chronic pain also exist in a causal vicious cycle; higher body weight results in greater mechanical stress which, as we will discuss, may have a pathological role in PsA.

Enthesitis

The issue of enthesitis vs FM warrants dedicated discussion. Enthesitis is common feature (prevalence of 35% in patients with PsA) characterised by inflammation of the connective tissue between tendon or ligament and bone [65]. Entheses are sites where force is transmitted and thus undergo high mechanical stress, which, together with abnormal immune response to micro damage, are hypothesised to be a trigger for abnormal immune response [66]. This process may also explain other disease features in the spondyloarthritides: there is evidence that enthesitis precedes clinical joint involvement [67] and that dactylitis [68] and psoriatic nail disease [69] also represent enthesitis.

Distinguishing enthesitis from FM is extremely challenging. Ligaments and tendons are poorly vascularised. Enthesitis is therefore characterised by pain and tenderness, but often without visible signs of inflammation. Furthermore, these localised sites of inflammation are not associated with high systemic levels of acute phase markers and some sites, such as the spine, are not easily accessible. Ultrasound has proven useful in detecting subclinical inflammation, for instance in the synovium. However, with age and high mechanical stress (from being overweight), degenerative changes are often present without inflammatory disease [70]; this may explain high prevalence of ultrasound enthesopathy in FM [71].

Like RA, the treat-to-target approach has been recommended in PsA. In one study, the odds of achieving an ACR20 response at 48 weeks were nearly twice as high as that in the tight control group than in the standard care group (OR 1.91) [72]. Their target was minimal disease activity [73], which is defined by fulfilling 5 out of 7 criteria, including components potentially influenced by FM: tender joint count, pain VAS, patient global VAS and tender entheseal points. Escalating treatment in the presence of non-inflammatory symptoms, such as from FM, may lead to toxicity. This is an important consideration in PsA management, as tight control was not superior for radiological damage, was associated with more adverse events and only provided modestly improved quality of life.

Prevalence of comorbid fibromyalgia in PsA

The reported prevalence of concomitant FM in PsA range from 10 to 27% [9]. In proportional meta-analysis, the overall prevalence of FM was 18% (95% CI 13 to 23%; $I^2 = 73\%$). Prevalence estimates were the same when we stratified by FM criteria (Fig. 3), with greater consistency among studies using the 2010 FM criteria ($I^2 = 0\%$).

Fibromyalgia and disease outcomes measures in PsA

There were very few studies of how comorbid FM impacts disease outcomes in PsA. In one small study of 73 patients with PsA, those with FM had over two-fold higher scores across several patient-

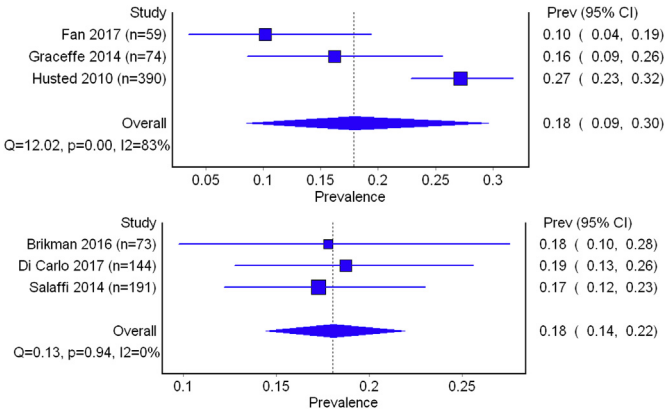

Fig. 3. Prevalence of comorbid fibromyalgia among patients with psoriatic arthritis. Top panel shows studies using the 1990 ACR criteria, bottom panel the 2010 criteria.

reported measures: Disease Activity Index for Psoriatic Arthritis (DAPSA, 28 vs 13), HAQ (1.75 vs 0.25) and BASDAI (7.2 vs 2.9). The Leeds Enthesitis Index was also higher with a median of 3 tender points in the FM group and 0 in the non-FM group, although this is difficult to interpret for the reasons discussed previously. Differences in DAS28 were smaller (3.4 vs 2.5) and absent in more object measures (CRP, Psoriasis Activity and Severity Index, and swollen joint count) [74]. In another study of 74 patients with PsA treated with biologics over 1 year, those without FM were 12 times more likely to achieve remission [75]. This dramatic effect size is unsurprising given their unique definition of remission required the absence of tender joints and enthesitis.

Results from RA, axSpA and PsA studies all highlight the importance of identifying comorbid fibromyalgia. Recognising that apparent high disease activity, based on disease activity scores, may not reflect increased inflammatory burden alone is essential in guiding treatment decisions. Pursuing disease remission targets by treatment escalation may not be the optimum management option when fibromyalgia is present. Patient-centred, rather than disease-centred, care is essential for optimising outcomes. Healthcare professionals should consider whether more holistic care can be provided for patients with inflammatory arthritis and comorbid FM.

Future research

The prevalence of FM in RA, axSpA and PsA are significantly higher than in the general population. However, these results should be interpreted with care as disagreement exists between versions of the ACR FM criteria (especially as to whether FM is a diagnosis of exclusion) and none of the FM criteria have been validated for use in patients with inflammatory arthritis. Future research should validate the use of FM criteria in inflammatory rheumatic diseases. Although likely to be challenging for the reasons outlined in this review, such research would provide a firmer foundation for work on comorbid FM to continue.

The pooled prevalence estimate was higher in RA (18–24%) than PsA (18%) and axSpA (14–16%). This is likely explained by the fact that FM is strongly associated with female gender [76]. FM and mental health problems are also strongly associated, but studies frequently did not account for comorbid mental health problems when assessing the impact of FM on disease activity; therefore, it is difficult to discern what is driving the observed differences. Future studies should examine mental health symptoms alongside FM, particularly because somatic symptoms appear to be the main predictor of longitudinal outcome [48].

Patients with inflammatory arthritis and more severe disease should have greater inflammatory burden and nociceptive stimuli, both of which can increase the risk of central sensitisation. In cross-sectional studies, where there is no direction of causality, those with FM should therefore also have

higher objective inflammatory disease severity. However, objective measures generally show no difference between those with and without comorbid FM. Longitudinal evidence on the predictors of incident secondary FM might be illuminating but there is a paucity of studies. One existing study found that the incidence rate for developing comorbid FM was highest during the first 12 months after diagnosis of early inflammatory arthritis, and that the most significant predictors were self-reported pain severity and poor mental health - not objective markers of inflammation [21]. These findings do not support theories identifying objective inflammation as the driver of central pain sensitisation in comorbid FM, although work by Macfarlane et al. suggested that reducing inflammatory disease activity improves FM symptom severity [48]. Subsequent research should focus on the longitudinal evolution of comorbid FM and its predictors.

The number of high-quality PsA studies was limited. Researchers may be discouraged by the difficulty of distinguishing somatic symptom severity from common mental health comorbidities in PsA or distinguishing enthesitis from tender points and widespread pain. Ultrasound imaging has been used in RA to help differentiate synovitis from non-inflammatory causes of raised disease activity [77,78]. Research is needed to examine the efficacy and cost-effectiveness of medical imaging in clinical practice to discriminate fibromyalgia tender points from inflammatory enthesitis and joint disease. Such work would help avoid inappropriate treatment decisions as a result of FM mimicking inflammatory disease activity in axSpA and PsA.

The management of FM has been covered in detail elsewhere [79–82]. The guidelines are all in agreement that non-pharmacological therapy such as exercise should be encouraged in the first instance, and thereafter, management should be tailored to the individual needs of the patient. The European League Against Rheumatism (EULAR) recommends using duloxetine, pregabalin or tramadol (in combination with paracetamol) for severe pain and low-dose amitriptyline, cyclobenzaprine or pregabalin for sleep problems. These agents may be of particular benefit in those with concurrent depression. However, strength of recommendations was weak for all pharmacological options. There is a degree of disagreement between recommendations from different societies. This may be due to paucity of high-quality randomized control trials in FM and reliance on expert consensus, but also because of the varying license-status of available drugs. Despite the high prevalence of comorbid FM described in this review, there have also been no dedicated trials to guide management of FM when it occurs in inflammatory arthritis. Trials in this area are urgently needed to inform management of this prevalent comorbidity.

The EULAR working group has identified several other areas of research needed for the management of FM generally. These include identifying: 1) the most effective form of exercise therapy, 2) the benefit of combined pharmacological and non-pharmacological approaches over single modality management, 3) predictors of response to specific FM therapies, and 4) which healthcare systems and personnel are best for the management of patients with FM [79].

Summary

Comorbid FM is a common and complex disease of great significance for rheumatologists, both in the diagnosis and monitoring of inflammatory rheumatic diseases. This review has emphasised the high prevalence of FM in three common inflammatory arthritides compared to the general population. Comorbid FM also appears to have a considerable impact on measures of disease severity, particularly for patient-reported outcomes. In meta-analysis of RA and axSpA studies, the size of this effect was sufficient to influence assessment of disease activity. Identifying comorbid FM is therefore important and healthcare professionals should consider its presence when making treatment decisions based on disease activity scores. Comorbid FM also appears to be an important predictor of treatment response in RA, although further evidence is needed in axSpA and PsA. Results should be interpreted with care as FM may be considered a diagnosis of exclusion and FM criteria have not been validated for use in patients with inflammatory arthritides. Other research-needs were identified in this review: Predictors of incident FM among patients with inflammatory arthritides are limited. There is need for guidance regarding the management of comorbid FM; such guidance should be based on evidence from clinical trials, which are currently lacking.

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Conflicts of interest

None.

Practice Points

- Rheumatologists should be aware of the likelihood of encountering comorbid FM among patients with RA, axSpA and PsA.
- Comorbid FM is associated with increased disease activity scores in these three inflammatory arthritides, particularly affecting patient-reported outcomes.
- The presence of comorbid FM should be considered where there are discrepancies between subjective and objective measures of disease activity, particularly when there is apparent non-response to treatment.
- The presence of comorbid FM should be identified and considered for additional management. Management should include good control of the underlying inflammatory disease as this may also improve FM symptom severity.

Research agenda

- **Defining comorbid FM:** FM criteria should be validated for use in inflammatory arthritides and other chronic rheumatic diseases. Particularly, there is a need to distinguish FM tender points from inflammatory pathology.
- **Predicting secondary FM:** Longitudinal predictors of incident FM among patients with inflammatory arthritis should be explored, especially detailing the relationship between objective inflammatory markers, patient-reported outcomes and the development of secondary FM.
- **Exploring FM and disease activity in inflammatory arthritis:** Future research should determine whether worse disease activity is primarily due to comorbid FM or comorbid mental health conditions. More research is also needed to explore the impact of comorbid FM in PsA.
- **Development of medical imaging in practice:** There is need to explore the efficacy and cost-effectiveness of medical imaging in clinical practice to discriminate fibromyalgia tender points from inflammatory entheseal or joint disease.
- **Management of comorbid FM:** Clinical trials are needed to inform the management of comorbid FM in rheumatic diseases, and to assess whether treating FM affects treatment response for the underlying inflammatory disorder.

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