Improving outcome for people with chronic widespread pain and fibromyalgia

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Abstract

Chronic widespread pain is characteristic of fibromyalgia, a condition which also includes features such as cognitive dysfunction, sleep problems, fatigue and mood disorders. The lack of objective measures of the disorder has proved challenging in terms of diagnostic criteria, and thus timely diagnosis and access to effective management. Although there is a perception that the aetiology of the condition is not known and that there is no effective treatment, this is not the case. Over the past decades understanding of the pathophysiology and aetiology of the condition has improved and management that results in improved symptoms for many patients, has been identified. This thesis addresses important components in relation to improving outcome for patients with chronic widespread pain and fibromyalgia.

The thesis focuses on three areas (over seven published manuscripts): effective management for persons with chronic widespread pain and fibromyalgia; investigating excess mortality in people with chronic widespread pain; Identifying and managing fibromyalgia when it occurs in the context of inflammatory arthritis. It includes seven manuscripts.

The results of the manuscripts show that there is good evidence for the non-pharmacologic therapies of exercise and a cognitive behaviour informed approach to managing people with chronic widespread pain/fibromyalgia, that the excess mortality in such patients could be addressed by focussing on lifestyle factors (diet and exercise). When fibromyalgia occurs in the context of axial spondyloarthritis, such patients do (as a group) respond to biologic therapy but that specific aspects of their conditions (high somatic symptom burden) predict non-response and the likely need for additional (non-pharmacologic approaches) to management.

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Accompanying Material: Publications included in the thesis

Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, Choy E, Kosek E, Amris K, Branco J, Dincer F, Leino-Arjas P, Longley K, McCarthy GM, Makri S, Perrot S, Sarzi-Puttini P, Taylor A, Jones GT. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017;76(2):318-328.

Macfarlane GJ, Barnish MS, Jones GT. Persons with chronic widespread pain experience excess mortality: longitudinal results from UK Biobank and meta-analysis. Ann Rheum Dis. 2017;76(11):1815-1822.

Macfarlane GJ, Barnish MS, Pathan E, Martin KR, Haywood KL, Siebert S, Packham J, Atzeni F, Jones GT. Co-Occurrence and Characteristics of Patients With Axial Spondyloarthritis Who Meet Criteria for Fibromyalgia: Results From a UK National Register. Arthritis Rheumatol. 2017;69(11):2144-2150.

Jones GT, Jones EA, Beasley MJ, **Macfarlane GJ.** Investigating generalizability of results from a randomized controlled trial of the management of chronic widespread pain: the MUSICIAN study. Pain. 2017;158(1):96-102.

Macfarlane GJ, MacDonald RIR, Pathan E, Siebert S, Gaffney K, Choy E, Packham J, Martin KR, Haywood K, Sengupta R, Atzeni F, Jones GT. Influence of co-morbid fibromyalgia on disease activity measures and response to tumour necrosis factor inhibitors in axial spondyloarthritis: results from a UK national register. Rheumatology (Oxford). 2018;57(11):1982-1990.

Macfarlane GJ, Pathan E, Siebert S, Packham J, Gaffney K, Choy E, Sengupta R, Atzeni F, Martin KR, Jones GT, Dean LE. AxSpA patients who also meet criteria for fibromyalgia: identifying distinct patient clusters using data from a UK national register (BSRBR-AS). BMC Rheumatol. 2019;3:19.

Macfarlane GJ, Beasley M, Jones GT, Stannard C. The epidemiology of regular opioid use and its association with mortality: prospective cohort study of 466 486 UK Biobank participants. EClinicalMedicine 2020:100321

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I am indebted to my parents, John and Margaret Macfarlane for making the sacrifices to allow me to undertake two undergraduate degrees at the University of Glasgow which set me on the path to a career in academia, a path chosen which I have never regretted.

I am grateful to my family for their love and support: my wife Tatiana and my children Matthew and Catherine. They all certainly make sure my feet are kept firmly on the ground! The work on this thesis was interrupted by COVID19 but it helped that we were all together again – each working towards a different degree.

I would like to thank all my colleagues who have co-authored papers which have formed part of this thesis. In particular I would like to thank Gareth Jones, with whom I have worked for over twenty years. Academic work is much more enjoyable when undertaken as a team, and I am fortunate with the colleagues I have worked with on the studies presented here as well as more generally

Author's Declaration

I hereby declare that the work described therein has been done by myself or, in the case of joint work, the attached statement as to the extent of collaboration is true and correct.

As head of the Epidemiology group at the University of Aberdeen, I lead a programme of work focussed on the epidemiology and management of rheumatic and musculoskeletal disorders. One of the clinical areas of focus for this work has been on chronic pain. These papers arise from this programme of work.

Each of the manuscripts included in this thesis has a statement in the published article about the contribution of each author. For six of the seven publications, I am the first (lead) author and either solely conceived the idea of the study or took a lead role in this and planned the analyses and oversaw its conduct. I either drafted the full manuscript or in some publications the analyst provided input to drafting the methods and tables. In one manuscript I am the last (senior) author. I was the Chief Investigator of the study from which this analysis arose and the author contribution statement from the manuscript states that I was involved in the conception and design, analysis and interpretation of data. Jones drafted the article but as stated "Macfarlane revised it and prepared it for submission" and I am the corresponding author of this article.

Abbreviations

ACR	American College of Rheumatology
AS	ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis International Society
ASDAS	ankylosing spondylitis disease activity scale
ASQoL	ankylosing spondylitis quality of life index
AxSpA	axial spondyloarthritis
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
BAS-G	Bath ankylosing spondylitis global score
BASMI	Bath ankylosing spondylitis metrology index
BMI	Body Mass Index
BSRBR-AS	British Society for Rheumatology Biologics Register in axial spondyloarthritis
CFS	Chalder fatigue scale
CI	confidence interval
CRP	c-reactive protein
CWP	chronic widespread pain
DMARD	disease modifying anti-rheumatic drug
ESR	Ethrythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FDA	Federal Drug Administration
FM	fibromyalgia
GP	general practitioner
HADs	hospital anxiety and depression scale
IBD	inflammatory bowel disease
IMD	index of multiple deprivation
mNY criteria	modified New York criteria
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NSAID	non steroidal anti-inflammatryu drugs
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RCT	randomised controlled trial
SDS	sleep disturbance score
SOL	shortage occupation list
SSS	symptom severity scale
TNFi	tumour necrosis factor inhibition
WPAI:SHP	work productivity and activity impairment scale: specific health problem
WPI	widespread pain index

Chapter 1 Introduction

Chronic widespread pain (CWP) is the characteristic feature of fibromyalgia, a condition which also includes fatigue, poor quality sleep and cognitive dysfunction. The population prevalence of chronic widespread pain has been estimated, in a meta-analysis and using high quality studies, at 11.8% 95% CI (10.3%-13.3%) (Mansfield et al, 2016) while that of fibromyalgia has been estimated at 1.78% (1.65, 1.92) (Heidari et al, 2017). The prevalence of both increases with age, reaching a peak around the seventh decade and decreasing thereafter (Wolfe et al, 1995). Chronic widespread pain is more common in females than males (as is pain generally). Originally fibromyalgia was considered to occur almost exclusively in females, with early studies suggesting a female:male ratio of around 9:1 (Yunus et al, 2001). However, these early studies were of consulters and based on clinical diagnoses; when considering more recent classification criteria (such as the 2011 "research criteria" (Wolfe et al, 2011)) and use in population studies, the proportion of females is ≤ 60% (Wolfe et al, 2018).

Risk factors for the development of chronic widespread pain and fibromyalgia include physical trauma and psychological stressors (Jones et al, 2011). In adult populations, high levels of psychological distress, poor sleep and aspects of illness attitudes and behaviour are predictive of new onset of chronic widespread pain (Benjamin et al, 2000; Gupta et al, 2007) although the first onset of chronic widespread pain is rare in mid-life. Indeed poor sleep is a predictor of ongoing-CWP (Mundal et al, 2014) while restorative sleep is associated with resolution of symptoms (Davies et al, 2008). It has been demonstrated, in longitudinal studies, that although persons with chronic widespread pain may not have symptoms at each follow-up they remain at high risk for continuing to experience symptoms (Landmark et al, 2019). Further, also in longitudinal studies, it is unusual for a person who has reported chronic widespread pain to be pain-free subsequently and vice-versa (Papageorgiou et al, 2002).

Although it is often claimed that the aetiology of these conditions is "unknown" – we do understand a considerable amount about risk factors for the conditions, effective ways to manage symptoms and indeed the underlying pathophysiology. There is good evidence that they involve altered central nervous system processing leading to central sensitisation and a heightened awareness of sensory inputs (Sluka and Clauw et al, 2016). These inputs may

be from physically traumatic events (such as a motor vehicle accident) but also psychologically traumatic events or adverse experiences (such as death of a spouse). In combination with this, descending "inhibitory" pathways appear to be less effective; indeed many of the pharmacological therapies which are licensed for use (although none are licensed in the United Kingdom or European Union) are targeted at inhibiting the function of the former and enhancing the function of the latter. One aspect on which neurobiology and epidemiology completely agree, and which has informed criteria development, is that chronic widespread pain and fibromyalgia are part of a continuum rather than discrete entities.

The first scientific focus of the thesis will consider the evidence for effective management of fibromyalgia and specifically for pharmacological and non-pharmacological therapies using work undertaken as part of the European League Against Rheumatism (EULAR) revised recommendations for the management of fibromyalgia. The data which inform these recommendations comes exclusively from randomised controlled trials, and the thesis will also include a manuscript considering how generalisable results are from such designs, taking advantage of a trial which had detailed information on eligible non-participants.

The second focus of the thesis will consider observations that persons with chronic widespread pain may be at risk of premature death using data from the largest-ever study with such data available together with all other currently published data, and if so what may be the mechanism for such premature mortality. It will also provide data on the possible role of the use of opioids, which are predominantly used for the treatment of pain, in premature deaths. Although their routine prescription in patients with chronic pain is not supported by the available evidence, including in patients with fibromyalgia, their use generally has become more common and the adverse effects have become more evident including an increased risk of death, particularly from non-disease related causes (Volkow et al, 2018).

Although fibromyalgia is itself common, it seems to occur more commonly than would be expected in people with inflammatory arthritis, with a recent meta-analysis reporting pooled prevalence of 13%, 18% and 21% in axSpA, PsA and RA respectively (Duffield et al, 2018). This may be because they share a common aetiology and/or that aspects of these diseases (e.g. inflammation) act as peripheral nociceptive drivers facilitating central sensitisation. It can be difficult to distinguish the conditions – since for example, widespread pain is a common symptom of inflammatory arthritis. There is concern also that having fibromyalgia may distort inflammatory disease specific markers and people therefore may receive inappropriate therapy for their inflammatory arthritis. This is particularly true for

axial spondyloarthritis where back pain as a result of inflammation in the spine is a key feature, but this symptom (referred to as axial pain) is also a key feature of fibromyalgia and indeed its presence was a requirement to meet the 1990 ACR criteria for fibromyalgia. Therefore, the third focus of the thesis will be fibromyalgia occurring in patients with axial spondyloarthritis. How common does co-morbid fibromyalgia occur in people with axSpA, how can these people be identified, how does this affect disease markers, and does it affect response to biologic therapy?

The publications are produced in Chapter 2 (Manuscripts) and are organised as follows according to the themes discussed above.

Effective management for fibromyalgia

2.1 Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, Choy E, Kosek E, Amris K, Branco J, Dincer F, Leino-Arjas P, Longley K, McCarthy GM, Makri S, Perrot S, Sarzi-Puttini P, Taylor A, Jones GT. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017 Feb;76(2):318-328.

2.2 Jones GT, Jones EA, Beasley MJ, **Macfarlane GJ.** Investigating generalizability of results from a randomized controlled trial of the management of chronic widespread pain: the MUSICIAN study. Pain. 2017;158(1):96-102.

Mortality experience of persons with chronic widespread pain

2.3 Macfarlane GJ, Barnish MS, Jones GT. Persons with chronic widespread pain experience excess mortality: longitudinal results from UK Biobank and meta-analysis. Ann Rheum Dis. 2017;76(11):1815-1822.

2.4 Macfarlane GJ, Beasley M, Jones GT, Stannard C. The epidemiology of regular opioid use and its association with mortality: prospective cohort study of 466 486 UK Biobank participants. eClinicalMedicine 2020 (in press)

Chronic widespread pain and fibromyalgia in the context of inflammatory arthritis (axial spondyloarthritis)

2.5 Macfarlane GJ, Barnish MS, Pathan E, Martin KR, Haywood KL, Siebert S, Packham J, Atzeni F, Jones GT. Co-Occurrence and Characteristics of Patients With Axial Spondyloarthritis Who Meet Criteria for Fibromyalgia: Results From a UK National Register. Arthritis Rheumatol. 2017;69(11):2144-2150.

2.6 Macfarlane GJ, MacDonald RIR, Pathan E, Siebert S, Gaffney K, Choy E, Packham J, Martin KR, Haywood K, Sengupta R, Atzeni F, Jones GT. Influence of co-morbid fibromyalgia on disease activity measures and response to tumour necrosis factor inhibitors in axial spondyloarthritis: results from a UK national register. Rheumatology (Oxford). 2018;57(11):1982-1990.

2.7 Macfarlane GJ, Pathan E, Siebert S, Packham J, Gaffney K, Choy E, Sengupta R, Atzeni F, Martin KR, Jones GT, Dean LE. AxSpA patients who also meet criteria for fibromyalgia: identifying distinct patient clusters using data from a UK national register (BSRBR-AS). BMC Rheumatol. 2019;3:19.

Chapter 3 (Discussion) then considers the results in the context of the wider scientific literature, specifically what the group of papers add to current knowledge and the clinical implications of such.

Chapter 2.1

EULAR revised recommendations for the management of fibromyalgia

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Abstract

Objective: The original EULAR recommendations for managing fibromyalgia assessed evidence up to 2005. The paucity of studies meant that most recommendations were “expert opinion”.

Methods: A multidisciplinary group from 12 countries assessed evidence with a focus on systematic reviews and meta-analyses concerned with pharmacological/non-pharmacological management for fibromyalgia. A review, in May 2015, identified eligible publications and key outcomes assessed were pain, fatigue, sleep and daily functioning. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used for making recommendations.

Results: 2979 titles were identified: from these 275 full papers were selected for review, and 107 reviews (and/or meta-analyses) evaluated as eligible. Based on meta-analyses, the only “strong for” therapy-based recommendation in the guidelines was exercise. Based on expert opinion, a graduated approach, following four main stages is suggested underpinned by shared decision-making with patients. Initial management should involve patient education and focus on non-pharmacological therapies. In case of non-response, further therapies (all of which were evaluated as “weak for” based on meta-analyses) should be tailored to the specific needs of the individual and may involve psychological therapies (for mood disorders and unhelpful coping strategies), pharmacotherapy (for severe pain or sleep disturbance) and/or a multimodal rehabilitation programme (for severe disability)

Conclusion: These recommendations are underpinned by high-quality reviews and meta-analyses. The size of effect for most treatments is relatively modest. We propose research priorities clarifying who will benefit from specific interventions, their effect in combination, and organisation of health care systems to optimise outcome.

Introduction

Fibromyalgia is common with a prevalence of 2% in the general population [1,2]. However, its diagnosis and management remain a challenge for patients and healthcare professionals. It often takes more than 2 years for a diagnosis to be made with an average of 3.7 consultations with different physicians [3]. Referral to specialists and investigations results in high healthcare utilisation, for up to 10 years prior to diagnosis, when compared with persons who do not have fibromyalgia [4]. Although pain is the dominant symptom in fibromyalgia, other symptoms such as fatigue, non-refreshed sleep, mood disturbance and cognitive impairment are common, but not universal, have an important influence on quality of life, and emphasize that it is a heterogeneous and complex condition [5,6].

The original EULAR recommendations for the management of fibromyalgia assessed evidence up to and including 2005 [7]. Given the paucity of information and poor quality of the studies available, it was recommended that the guidelines be revised after a period of 4 years. However, no subsequent revision took place and thus a decade later we revisit the recommendations with the aim of making them more evidence based. In the time since the original recommendations there have been a considerable number of individual trials examining pharmacological and non-pharmacological interventions and, moreover, there have been systematic reviews conducted for nearly all of the commonly used management strategies. Our aim therefore was, using the systematic reviews conducted and taking into account their quality, to make evidence-based recommendations for the use of individual pharmacological and non-pharmacological approaches, and how these could be combined. Further we aimed to identify priority areas for future research.

Methods

Working group membership

The working group included 18 members from 12 European countries: clinicians (representing rheumatology, internal medicine, pain medicine and epidemiology), non-clinical scientists (occupational health, epidemiology), patient representatives, and the allied health professions (nursing).

Eligibility, search strategy and quality assessment

We focused on systematic reviews (with or without meta-analysis) concerned with the management of fibromyalgia. Details of eligibility, review and quality assessment is provided in supplementary text available on-line.

Evaluating evidence

We retained pain as one of the key outcomes of interest, from the original guidelines, but also included fatigue, sleep and daily functioning. The committee considered the following in making a recommendation: number of trials; number of patients; outcomes assessed; quality of reviews and the trials included within the reviews; effect size (and 95% CI); adverse events; cost. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for making recommendations [8]. This is a 4-point scale: strong for/weak for/ weak against/ strong against; or allowing a recommendation "use only for research". The strength of recommendation is based on the balance between desirable and undesirable effects (considering values and preferences), confidence in the magnitude of effects and resource use. A strong recommendation implies that, if presented with the evidence, all or almost all informed persons would make the recommendation for or against the therapy, while a weak recommendation would imply that most people would, although a substantial minority would not [9].

Two sub-groups considered the evidence for pharmacological and non-pharmacological therapies and proposed a recommendation. At a face-to-face meeting, after presentation of the evidence and the preliminary recommendation, discussion resulted in a "final recommendation". In addition to the evidence on efficacy/effectiveness, the committee also took into account safety. All participants then voted on their level of agreement with the recommendation on a scale from 0 "completely disagree" to 10 "completely agree". The percentage of the committee scoring at least 7 was taken to indicate level of agreement.

Results

In total, 2979 titles were identified. From these, 571 abstracts and then 275 full papers were selected for review, and 107 reviews evaluated as eligible for consideration in making recommendations for management (Figure 1).

Information on the reviews informing these recommendations on pharmacological therapy and on non-pharmacological and complementary and alternative medicines/therapies is

collated in Supplementary Tables A and B respectively while information from one review, for each medicine/therapy, selected based on recency and quality is provided in Tables 1 and 2 respectively.

Evaluation of pharmacological medicines

Amitriptyline: Five reviews included up to 13 trials and a maximum of 919 subjects. Hauser et al [10] reported that patients receiving amitriptyline were more likely to achieve 30% pain reduction (RR 1.60, 95% CI (1.15,2.24)), equivalent to a "number needed to treat" (NNT) of 3.54 95% CI (2.74, 5.01). There was a moderate effect on sleep (SMD -0.56, 95% CI -0.78,-0.34)[1] and small effect on fatigue (-0.44; -0.71, -0.16). There was no difference in discontinuation rates compared to patients receiving placebo. Nishishinya et al [11] in their high-quality review concluded that 25mg/day improved pain, sleep and fatigue at 6-8 weeks of treatment but not at 12 weeks while 50 mg/day did not demonstrate efficacy *Amitriptyline Evaluation: Weak for, at low dose (100% agreement)*

Anticonvulsants: Nine reviews of pregabalin included up to 7 studies and a maximum of 3344 patients. A recent Cochrane review [22] reported patients receiving active treatment were more likely to have 30% pain reduction RR 1.37 95% CI (1.22, 1.53) with a "number needed to benefit" (NNTB) over placebo of 9 95% CI (7, 13). There was a very small effect on fatigue (-0.17; -0.25, -0.09) and small effect on sleep (-0.35; -0.43, -0.27) but no effect on disability (-0.01; -0.11, 0.09). A single, moderate quality, study of gabapentin in 150 subjects (e.g. in [101) showed a significant effect on 30% pain reduction (RR 1.65 95% CI 1.10, 2.48), a small effect on sleep (-0.71; -1.08, -0.24) and a large effect on disability (-0.94; -1.32, -0.56). *Anticonvulsant Evaluation*: *Pregabalin - Weak for (94% agreement); Gabapentin – Research only (100% agreement)*

Cyclobenzaprine: A single systematic review of 5 studies involving 312 patients reported that of those taking cyclobenzaprine 85% experienced side effects and only 71% completed the studies. They were more likely to report themselves as "improved" (NNT 4.8 95% CI (3.0, 11.0)). Only two studies reported an "intention-to-treat" (ITT) analysis. Sleep, but not pain, showed a significant, very small, improvement relative to baseline at the longest outcome considered (12 weeks: SMD 0.34) and patients on placebo showed similar improvement (SMD 0.52) [23]. *Cyclobenzaprine Evaluation: Weak for (75% agreement)*

[1] All effect sizes are expressed as SMD with 95% CI unless otherwise stated.

Growth hormone: A single systematic review of 2 studies involving 74 patients reported an effect size on pain of 1.36 (0.01, 1.34)[14]. The improvement in functional deficit was not statistically significant (1.24; −0.36, 2.84). There are concerns on safety (sleep apnœa, carpal tunnel syndrome). The drug is not approved for FM or related disorders in Europe. *Growth hormone Evaluation: Strong against (94% agreement)*

Monoamine Oxidase Inhibitors (MAOIs): Four reviews identified up to 3 studies and 241 patients. Hauser et al [24] reported a moderate effect on pain across the studies (-0.54; -1.02, - 0.07), but the single studies which evaluated fatigue and sleep showed no effect. There were no differences in dropouts or adverse events compared with placebo. There was no comparison between compounds. Life-threatening interactions have been documented. *MAOIs Evaluation: Weak against (81% agreement)*

NSAIDs: A single review [19] identified two small trials with no evidence of improved outcome compared to placebo. One low quality review was not considered *NSAIDs Evaluation*: *Weak against (100% agreement)*

Serotonin-Noradrenalin re-uptake inhibitors (SNRIs): Eight systematic reviews were identified which presented data separately for duloxetine. The largest review of 2249 subjects [30] reported duloxetine, short term (up to 12 wks)and long-term (up to 28 wks), was more effective than placebo at reducing pain (RR > 30% pain RR 1.38, 95% CI 1.22, 1.56) although there was no significant effect at 20-30 mg/day and no difference between doses of 60 and 120 mg/day. NNTB, based on 60mg/day up to 12 weeks, was 6 95% CI (3, 12). A previous review reported small effects on sleep (-0.24; -0.37,-0.12) and disability (-0.33; -0.43,-0.24) but no effect on fatigue [28]. Seven systematic reviews were identified of milnacipran, a recent one of which evaluated 5 trials [28]. Patients taking milnacipran were more likely, at the end of treatment, to have 30% pain reduction (RR 1.38, 95% CI 1.25, 1.51) but there was only a small benefit on fatigue (-0.14; -0.19, -0.08), disability (-0.16; -0.23,-0.10) and no effect on sleep. *Duloxetine and Milnacipran Evaluation: Weak for (100% agreement)*

Selective Serotonin Reuptake Inhibitors (SSRIs): Seven systematic reviews included up to 11 trials and a maximum of 521 subjects. Given that reviews have not focussed on specific drugs or comparisons, drugs within this class were considered together. A recent review, of medium quality included 7 trials and reported a moderate effect on pain (-0.40; -0.73,-0.07), sleep (-0.31; -0.60,-0.02) and no effect on fatigue (-0.17; -0.46, 0.11)[34]. *SSRI Evaluation: Weak against (94% agreement)*

Sodium Oxybate: A single systematic review of 5 studies including 1535 patients reported small effects sizes on pain (0.44; 0.31, 0.58], sleep problems (0.47; 0.28, 0.66) and fatigue [0.48; 0.35, 0.60). EMA and FDA refused the approval for FM because of safety concerns [14]. The drug is only approved for narcolepsy. *Sodium Oxybate evaluation: Strong against (94% agreement)*

Tramadol, a weak opioid with mild SNRI activity, was considered by two reviews. Roskell et al [20] identified a single study of tramadol with paracetamol. Those in the active arm were more likely to have 30% improvement in pain (RR 1.77 95% CI 1.26, 2.48). *Tramadol Evaluation*: *Weak for (100% agreement)*

The literature search did not identify any reviews on corticosteroids, strong opioids, cannabinoids, and anti-psychotics. The committee made a "Strong against" evaluation (100% agreement) regarding the use of strong opioids and corticosteroids in patients with fibromyalgia, on the basis of lack of evidence of efficacy and high risk of side effects/addiction reported in individual trials.

Evaluation of non-pharmacological therapies; complementary and alternative medicines and therapies

Acupuncture: Eight reviews included up to 16 trials and 1081 participants. One high quality review included nine trials, with 395 patients and demonstrated that acupuncture, added to standard therapy resulted in a 30% (21%, 39%) improvement in pain [68]. Electric acupuncture was also associated with improvements in pain (22%; 4%, 41%) and fatigue (11%; 2%, 20%). Some adverse events were reported, but these were commonly mild and transient. There is little understanding of the active component of acupuncture, and the evidence supporting the use of real versus sham acupuncture was less consistent. *Acupuncture evaluation: Weak for (93% agreement)*.

Biofeedback: Two reviews included up to seven trials and 307 participants. Glombiewski et al [90] reviewed seven studies, comprising 321 participants. Treatment sessions varied from 6-22; with control therapy comprising sham biofeedback, attention control, medication, and treatment as usual. Biofeedback was effective in reducing pain intensity (Hedges' g = 0.79; 0.22, 1.36) although all trials were poor quality. There was no evidence of effectiveness in terms of fatigue or sleep and sub-group analysis suggested that any effect was limited to electromyographic (0.86; 0.11, 1.62) rather than electroencephalographic biofeedback (0.71; -0.37, 1.8). *Biofeedback evaluation: weak against (100% agreement)*.

Capsaicin: Two reviews included two trials and 153 participants. The most recent review, a narrative review of two trials, considered data on 153 patients [92]. Both showed some evidence of positive effect in terms of pain relief, although results were not consistent for other outcomes. Capsaicin gel is generally considered safe, although many users report a mild burning sensation when applied to the skin. However, the number of patients and trials was small and were therefore limited in the extent to which they can provide evidence for toxicity. *Capsaicin evaluation: Weak against (86% agreement).*

Chiropractic: Three reviews included up to 13 trials and 102 participants. The most recent review summarised three studies [87]. One study was an open pilot study, one quasi-randomised, and in the third no between-group differences were observed in terms of pain . The studies were poor quality and lacked robust interpretable data. *Chiropractic evaluation: Strong against (93% agreement).*

Cognitive behavioural therapies (CBTs): Five reviews included up to 30 trials and at least 2031 participants. One high quality review included 23 trials, comprising >2000 patients, although the quality of individual trials was reported as generally poor [56]. CBTs were effective in reducing pain (-0.29; -0.49, -0.17) and disability (-0.30; -0.51, -0.08) at the end of treatment, compared to a variety of controls groups, and results were sustained long term. *Behavioural therapy evaluation: Weak for (100% agreement).*

Exercise: 20 reviews included up to 34 trials and at least 2494 participants[2]. The largest, a Cochrane review, considered 47 different exercise interventions [39]. Aerobic exercise was associated with improvements in pain (0.65; -0.09, 1.39) and physical function (0.66; 0.41, 0.92). Busch et al [40] reviewed five trials with 219 participants and concluded that resistance training resulted in a significant improvement in pain (-3.3cm on a 10cm scale; -6.35, -0.26) as well as function, compared to control. There is some consistency with regards to aerobic and strengthening exercises, although insufficient evidence to suggest superiority of one over the other; land and aquatic exercise appear equally effective [54]. *Exercise therapy evaluation: Strong for (100% agreement).*

Hydrotherapy / spa therapy: Four reviews included up to 21 trials and 1306 participants. One high quality review included ten trials, 446 participants, and compared a median of 4hrs hydrotherapy (range 200-300mins) against various comparators [74]. There was a significant improvement in pain (-0.78; -1.42, -0.13) at the end of therapy, maintained in the longer term (median 14 weeks), although the review authors noted that no trials

[2] It is unclear from some of the reviews how many participants were included. The number of participants represents the minimum about which we can be confident.

conducted an ITT analysis. There was consistency with regards to the evidence for hydrotherapy and balneotherapy, although little evidence to suggest superiority of one over the other [75]. *Hydrotherapy evaluation: Weak for (93% agreement).*

Hypnotherapy: One review included four trials, although the number of participants is unclear [89]. Although six trials of hypnotherapy and/or guided imagery were reviewed, only four examined hypnotherapy in isolation. Median treatment duration (where reported) was 360 minutes and hypnotherapy was compared with a variety of control therapies: cognitive intervention, active control (physical therapy / massage / relaxation / autogenic training), and treatment as usual. A meta-analysis is presented on all six trials, and isolated data for hypnotherapy is not presented. Two of the four hypnotherapy trials report some significant benefit in terms of pain, the other two demonstrate null, non-significant results. *Hypnotherapy evaluation: Weak against (86% agreement).*

Massage: Six reviews have been reported and one meta-analysis with nine trials and 404 patients [61] with sessions lasting 25-90 mins, and treatment duration ranging from 1-24 weeks (median five weeks). Comparator treatments, included TENS, standard care, guided relaxation and acupuncture. Methodological problems were noted with all of the studies, only four were at low risk of bias in terms of random allocation, and only two were analysed as ITT. Overall, massage was not associated with a significant improvement in pain (0.37; -0.19, 0.93) and of the two ITT analyses, one favoured massage and one favoured control (both significant). A sub-group analysis revealed some evidence of a positive effect with massage of ≥5 weeks duration, although this was based solely on lower quality trials. *Massage evaluation: Weak against (86% agreement).*

Meditative movement: Six reviews, including up to eight trials and 559 participants focused on qigong, yoga, tai chi, or a combination of these therapies. However, there was insufficient evidence to make individual recommendations. One review included 7 trials, with 362 participants randomised to tai chi, yoga, qigong, or body awareness therapy[78]. Total treatment time ranged from 12-24hrs and was compared to a variety of controls, including treatment as usual and active control groups (aerobics, wellness education and stretching). At the end of therapy, improvements were seen in sleep (-0.61; -0.95, -0.27) and fatigue (-0.66; -0.99, -0.34) some of which were maintained in the longer term. *Meditative movement evaluation: Weak for (71% agreement).*

Mindfulness / mind-body therapy: Six reviews included up to 13 trials and 1209 participants. One recent review, a meta-analysis of 6 trials, with 674 patients [82] provided evidence that mindfulness-based stress reduction resulted in improvements in pain (-0.23; -0.46, -

0.01) immediately post-treatment, when compared to usual care, and when compared to active control interventions (-0.44; -0.73, -0.16). However, these effects were not robust against bias. *Mindfulness / mind-body therapy evaluation*: *Weak for (73% agreement)*.

Multi-component therapy: Two reviews including up to 27 trials and 2407 participants examined the additional benefit of combining therapies, compared to individual therapy. Häuser et al [58] conducted a review of management involving both educational or psychological therapies and exercise. In a meta-analysis of nine trials and 1119 patients, multi-component therapy was effective in reducing pain (-0.37; -0.62, -0.13), and fatigue, immediately post-treatment, compared to waiting-list, relaxation, treatment as usual, and education. . However effects were short-lived. *Multi-component therapy evaluation: Weak for (93% agreement)*.

S-Adenosyl methionine (SAMe): Two reviews each included one trial with, in combination, 74 participants. De Silva et al [91] reported that, after the end of treatment, significant improvements were observed in pain and fatigue compared to placebo. Sim and Adams [50] reviewed a trial comparing SAMe with transcutaneous electrical nerve stimulation (TENS) but data on the main trial comparison is omitted. Side-effects are usually mild and infrequent. However, the number of patients and trials were small and therefore cannot provide a robust assessment of toxicity and safety. *SAMe evaluation: Weak against (93% agreement)*.

Other complementary and alternative therapies: Three reviews of guided imagery included up to six trials and 357 participants. The highest quality, including only one trial, provided some evidence that guided imagery may be effective in reducing pain (-1.52; -2.17, -0.87)[88]. Two reviews of homeopathy, including four trials and 163 participants [95,96]. Both contained a review including only four randomised trials, each of which showed some benefit of homeopathy, on some outcomes. However, none of the individual trials were without serious flaws. *Other complementary and alternative therapies (guided imagery, homeopathy): strong against (93% agreement)*.

Reviews were identified that examined electrothermal and phototherapeutic therapy [97]; phytothermotherapy [98]; music therapy, journaling/story-telling [102], and static magnet therapy [99], although each was insufficient to allow a recommendation. Marlow et al [100] examined the effectiveness of transcranial magnetic and/or direct current stimulation. Eight trials included 244 participants, although not all were analysed by ITT, and appropriate group comparisons were not presented for all studies. Overall, there was little evidence to support either therapy, and several studies reported an unacceptably high rate of adverse events and/or discontinuation due to headache.

EULAR Revised Recommendations:

In terms of overall principles we recommend, based on unanimous expert opinion, that optimal management requires prompt diagnosis, and providing the patient with information (including written material) about the condition. There should be a comprehensive assessment of pain, function, and the psychosocial context. Management should take the form of a graduated approach with the aim of improving health-related quality of life. It should focus firstly on non-pharmacological modalities. This is based on availability, cost, safety issues and patient preference. We have used the evaluation of individual therapies (above) to make ten specific recommendations, all based on evidence from systematic reviews and all but one from meta-analysis. The recommendations are given in Table 3 and a flow chart of how these therapies may be used in management is shown in Figure 2.

We were unanimous in providing a "strong for" recommendation for the use of exercise, particularly given its effect on pain, physical function and well-being, availability, relatively low cost and lack of safety concerns. The available evidence did not allow us to distinguish between the benefits of aerobic or strengthening. We gave "weak for" recommendations in relation to meditative movement therapies (which improved sleep, fatigue and quality of life) or mindfulness-based stress reduction (which improved pain and quality of life); the physical therapies acupuncture or hydrotherapy for which there was evidence that they improved pain/fatigue and pain/quality of life respectively. The effects seen in pragmatic trials of such therapies, will include specific and non-specific effects and it is not possible to disentangle these. There were some non-pharmacological therapies we did not recommend because of lack of effectiveness and/or low study quality: biofeedback, capsaicin, hypnotherapy, massage, SAMe and other complementary and alternative therapies. We provided a "strong against" evaluation for chiropractic based on safety concerns.

In case of lack of effect of the above therapeutic approaches, we recommend individualized treatment according to patient need. Psychological therapies ("weak for") should be considered for those with mood disorder or unhelpful coping strategies: CBT was effective at producing modest, long-term reductions in pain, disability and improving mood. Pharmacological therapies (all "weak for") should be considered for those with severe pain (duloxetine, pregabalin, tramadol) or sleep disturbance (amitriptyline, cyclobenzaprine, pregabalin). Multimodal rehabilitation ("weak for") programs should be considered for those with severe disability – in comparison to individual therapies those which were multi-modal improved a range of short-term outcomes. We did not recommend several pharmacological

therapies including NSAIDs, MAOIs, SSRIs, because of lack of efficacy and specifically gave a "strong against" evaluation to growth hormone, sodium oxybate, strong opioids and corticosteroids based on lack of efficacy and high risk of side effects.

Discussion

The previous EULAR recommendations provided an important milestone in the management of fibromyalgia. There were nine recommendations, but only three were supported by strong evidence from the scientific literature; most were based on expert opinion. Since that time there have been a considerable number of trials published addressing issues in the management of fibromyalgia. The availability of systematic reviews and meta-analysis of RCTs for all the most common approaches to management allowed us to concentrate on these.

Comparison with 2007 EULAR Recommendations

Despite the very large increase in the amount of trial data and summarised in meta-analyses, there are no major changes to the approach of managing patients with fibromyalgia, although we provide new evidence in support for some additional non-pharmacological therapies. In addition, all the recommendations are now firmly evidence-based. We now recommend that non-pharmacological therapy should be first-line therapy and then if there is a lack of effect that there should be individualised therapy according to patient need, which may include pharmacological therapy.

Comparison with other recommendations

There are three recent guidelines on the management of FM from Canada, Israel and Germany which have been compared with respect to their recommendations [103]. These guidelines and our EULAR recommendations are in agreement on the principles of approach to management, the need for tailored therapy to the individual and the first-line role of non-pharmacological therapies. There are differences between our guidelines and previous, which can partly be explained by us using more recently available evidence. There are differences in the strength of recommendations relating to pharmacological therapies: anticonvulsants and SNRIs were strongly recommended by the Canadian and Israeli guidelines while the German and these EULAR guidelines provide a weak recommendation. There are also differences in relation to individual non-pharmacological therapies across

guidelines in terms of whether they were assessed. For example meditative movement is strongly recommended by the German guidelines, but recommended only for a minority of patients in Israel, while these EULAR guidelines provide a “weak for” recommendation.

The committee recommend that an update is conducted after 5 years in order to determine whether for those therapies with relatively little current evidence, further trials have been conducted and secondly whether any new therapies have emerged for the management of fibromyalgia

Research priorities

In the course of discussion we identified important questions in terms of guiding management where there was either insufficient (or often no) evidence base to guide decisions i.e. “research gaps”. We discussed their relatively priority taking into account their potential to guide management, the likelihood that such studies could be conducted and were likely to be funded. We identified five such priority questions:

- Which type of exercise is most effective: strength and/or aerobic training?
- Is combined pharmacological and non-pharmacological approaches to management more effective than single modality management?
- Are there characteristics of patients with fibromyalgia which predict response to specific therapies?
- How should fibromyalgia be managed when it occurs as a co-morbidity to inflammatory arthritis?
- What aspects of a healthcare system optimise outcome for patients (who is best for the management of FM patients?)

Some of these questions are best answered by randomised controlled trials. Given, however the expense of such studies and that they can take almost 10 years from identifying the questions to be answered to results being obtained, alternatives including registers and observational studies should be considered. These can be complemented by qualitative studies to determine the needs of patients.

Dissemination

These recommendations will be disseminated, by the international working group, through national rheumatology societies. This will include scientific meetings, newsletters, continuing education programmes. We will produce a summary of the recommendations suitable for dissemination through EULAR-affiliated patient groups and through national patient societies. We will investigate assessing agreement with the recommendations in the target population.

Summary

In summary, these revised EULAR recommendations newly incorporate a decade of evidence in relation to the pharmacological and non-pharmacological management of fibromyalgia. They allow EULAR to move from recommendations which are predominantly based on expert opinion to ones which are firmly based on scientific evidence from high-quality reviews and meta-analyses. Despite this evidence, however, the size of effect for many treatments is relatively modest .We propose focussing on the research priorities we outline to address issues clarifying to whom certain interventions may best be delivered, their effect in combination, matching patients to therapies and the organisation of health care systems to optimise outcome.

Acknowledgements and Author Contribution

GJM, FA, PS-P, EC and GTJ were applicants on the grant. EF and LD undertook the literature search and together with FA identified eligible reviews. EF, LD, FA and CK evaluated the quality of each of the eligible reviews. GTJ led the evaluation of non-pharmacological therapies and FA and CK led the evaluation of pharmacological therapies. GJM drafted the manuscript with input from GTJ, WH, EC, CK and EK. All authors (with the exception of FA and EF) participated in a two-day project meeting, and all authors made important intellectual contributions to the manuscript.

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was head of the steering committee of the German guidelines on fibromyalgia and is a member of the medical board of the German Fibromyalgia Association. GJM has received personal fees from Pfizer (research activities). EK reports personal fees from Lundbeck, Orion and research funding from Eli Lilly. GMM reports personal fees from Pfizer, A Menarini, Hospiri and BMS, and has received research funding from AbbVie and Pfizer. PS-P reports personal fees from Abbott, Roche, Pfizer, UCB, MSD and has received research funding from Pfizer, UCB, Roche.

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Figure 1 Identifying eligible reviews

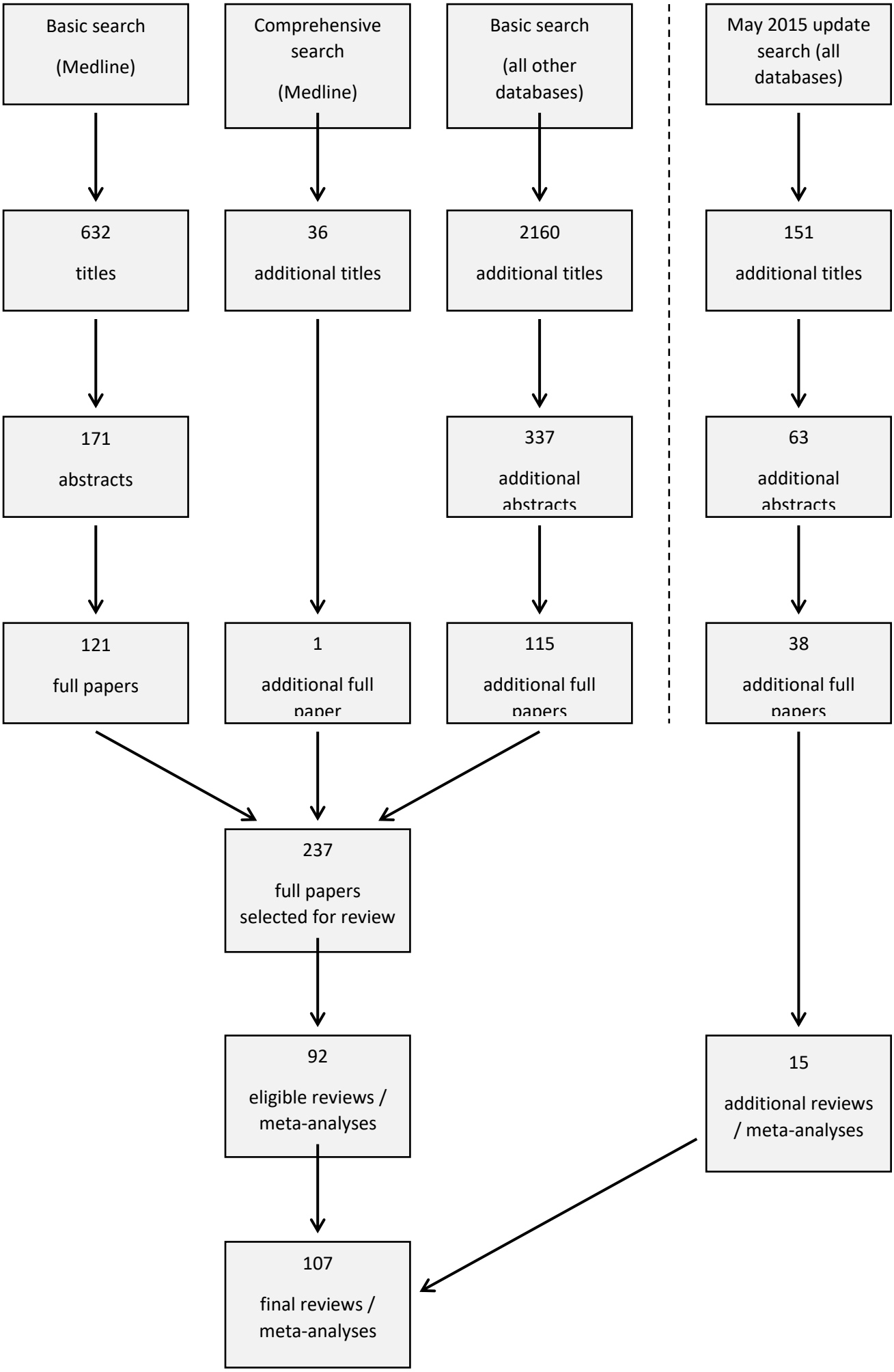
Basic search (Medline)
Comprehensive search (Medline)
Basic search (all other databases)
May 2015 update search (all databases)
632 titles
36 additional titles
2160 additional titles
151 additional titles
171 abstracts
337 additional abstracts
63 additional abstracts
121 full papers
1 additional full paper
115 additional full papers
38 additional full papers
237 full papers selected for review
92 eligible reviews / meta-analyses
15 additional reviews / meta-analyses
107 final reviews / meta-analyses

Figure 2 Management recommendations as flowchart

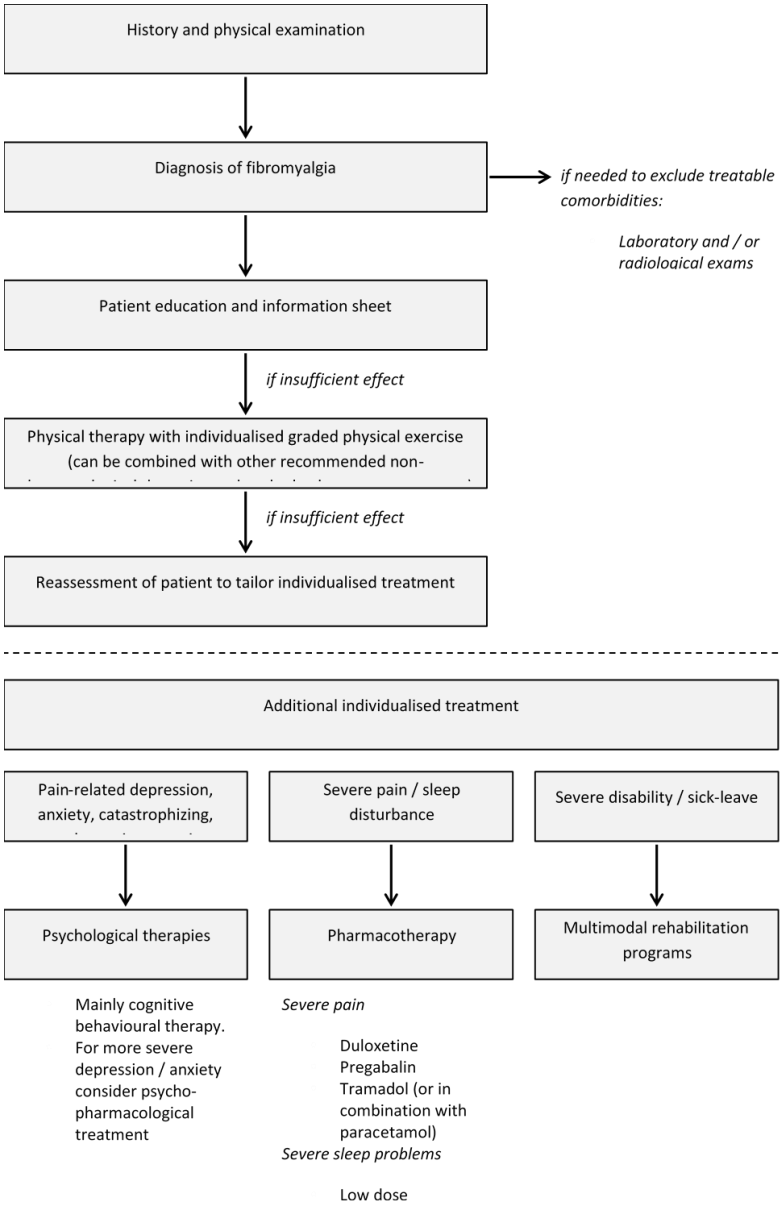
History and physical examination
Diagnosis of fibromyalgia
if needed to exclude treatable comorbidities:
Laboratory and / or radioloaical exams
Patient education and information sheet
if insufficient effect
Physical therapy with individualised graded physical exercise (can be combined with other recommended non-
if insufficient effect
Reassessment of patient to tailor individualised treatment
Additional individualised treatment
Pain-related depression, anxiety, catastrophizing,
Severe pain / sleep disturbance
Severe disability / sick-leave
Psychological therapies
Pharmacotherapy
Multimodal rehabilitation programs
Mainly cognitive behavioural therapy. For more severe depression / anxiety consider psycho-pharmacological treatment
Severe pain
Duloxetine
Pregabalin
Tramadol (or in combination with paracetamol)
Severe sleep problems
Low dose

Table 1: Overview of results from selected systematic reviews of placebo-controlled pharmacological trials

Treatment (Review Reference)	N trials (N participants) Review quality	Dosages; durations of treatment	Overall Trial quality[3]	Safety and comments
Amitriptyline [10]	10 (767) AMSTAR=6	10-50mg/day; 8-24 weeks	Low	There was no analysis of safety but no difference in discontinuation rates compared to patients on placebo was reported
Anti-convulsants - Pregabalin [22]	5 (3256) AMSTAR=10	three studies with fixed doses of 300, 450, 600 mg/day; one with fixed doses of 150, 300 or 450 mg/day; one flexible dosing study of 300 or 450 mg/day; 8-14 weeks	High	Increased likelihood of withdrawal due to adverse events RR 1.68, 95% CI (1.36, 2.07); NNH 12 95% CI (9, 17). No difference in likelihood of serious adverse events.
Cyclobenzaprine [23]	5 (312) AMSTAR=7	10-40mg; 2-24 weeks	Moderate	There was no analysis of adverse outcomes in the trials reviewed although dropout across trials was large (Cyclobenzaprine 29%, placebo 43%) Only 2 studies conducted ITT

[3] According to the method of quality evaluation used in the review

Growth Hormone [14]	2 (74) AMSTAR=5	0.0125 mg/kg/d; adjusted to maintain IGF-1 level of 250 ng/mL after first month, 0.0125 mg/kg/d; 9 months-1 year	NE[4]	Safety concerns include sleep apnoea and carpal tunnel syndrome.
Monoamine oxidase inhibitors [24]	3 (241) AMSTAR=9	Pirlindole 150 mg/d, Moclobemide 150-300 mg/d; 4 - 12 weeks	Low	MAOIs are known to cause potentially fatal hypertensive crises, serotonin syndrome and psychosis when they interact with foods containing tyramine and medications (many of which are commonly used in the treatment of FM), including SSRIs, tricyclic antidepressants and tramadol. The clinical trials had restrictions on concomitant medications.
NSAIDs [19]	2 (242) AMSTAR=7	ibuprofen 600mg QDS, tenoxicam 20mg/d; 6-8 weeks	Low	The adverse event profile, although not considered in this review, is well established for this class of drugs.
Serotonin Norepinephrine Reuptake inhibitors (SNRIs) – Duloxetine [29]	6 (2249) AMSTAR=10	20-120 mg/d; 12-28 weeks	Moderate	Dropout rates due to side effects across studies higher than with placebo. No difference in serious adverse events.
Serotonin Norepinephrine	5 (4118) AMSTAR=10	100 or 200 mg/day; 12-27 weeks	High	Dropout rates due to side effects across studies were double compared to placebo but

[4] Not Evaluated

Reuptake inhibitors (SNRIs) – Milnacipran [28]				there was no difference in serious adverse events
Selective Serotonin Reuptake Inhibitors (SSRIs)[34]	7 (322) AMSTAR=8	20-40 mg/d citalopram, 20-80mg/day fluoxetine, 20-60 mg/day paroxetine; 6-16 weeks	Moderate to High	Acceptability and tolerability were similar to placebo NNTH 40 95% CI (19,66).Although several studies excluded patients with depression/anxiety, Hauser et al [24] showed a small effect of SSRIs in improving depressed mood (SMD -0.37, 95% CI (-0,66, -0.07).
Sodium Oxybate [14]	5 (1535) AMSTAR=5	4.5-6g/day; 8-14 weeks	NE	There is the potential for abuse and central nervous system effects associated with abuse such as seizure, respiratory depression, and decreased levels of consciousness
Tramadol [20]	1 (313) AMSTAR=3	37.5mg Tramadol/325mg paracetamol 4x/d; 3 months;	High	No significant difference in discontinuation due to adverse events (RR 1.62, 95% CI (0.94, 2.80)). A high-quality review (AMSTAR score 7) identified a single study, which amongst persons who tolerated and benefitted from Tramadol, demonstrated a lower discontinuation rate, in a double-blind phase, compared to placebo [19].

Table 2: Overview of results from selected systematic reviews of non-pharmacological; complementary and alternative medicine and therapy trials

Treatment (Review Reference)	N Trials (N Participants[5]) Review Quality	Dosages; durations of treatment	Overall Trial quality[6]	Safety and comments
Acupuncture [68]	9 (395) AMSTAR=11	Treatment sessions ranged from 3 to 13wks (median = 4), with needle retention ranging from 20-30mins. Only one study provided journal references for the acupuncture point selection, and the description of the type of needle stimulation / manipulation was clear in only three studies	Moderate	One in six people who had acupuncture, and one in three controls, reported adverse events. Such events were minor and lasted less than one day. No serious adverse events were reported in any trials.
Biofeedback [90]	7 (321) AMSTAR=8	Electro-myographic (EMG) biofeedback. Individual sessions varied between 45 and 180mins, and the number of sessions varied between 6 and 16.	Poor	Only two[7] trials reported adverse event data. 4% of patients in one trial receiving EMG biofeedback reported stress. And 74% of patients in another, receiving EEG biofeedback reported a variety of side

[5] Total number of persons randomised

[6] According to the method of quality evaluation used in the review

[7] Elsewhere in the review, it reports that three studies reported on adverse events. However, in the table where this data is presented, it is only clear for two. However, in a third trial, there were no dropouts due to side effects.

		Electro-encephalographic (EEG) biofeedback. 20-22 sessions of (where reported) 30min duration.		effects, including: headache, fatigue, and sleep problems.
Capsaicin [92]	2 (153) AMSTAR=5	Topical application of *Capsicum annuum L.* cream, either: 0.025%capsaicin for 4wks,or 0.075% for 12wks.	Not reported	Patients reported moderate, transient, burning or stinging
Chiropractic [87]	3 (102) AMSTAR=4	Little detail is given for any trials, but treatment elements included massage, stretching, spinal manipulation, education, and resistance training.	Low	Around 50% of patients experience mild to moderate transient adverse effects after spinal manipulation.[8]
Cognitive behavioural therapy [55]	23 (2031) AMSTAR=11	Median duration of therapy = 10wks, with a median number of 10 sessions, and median total hours = 18hrs. All bar two studies delivered therapy face-to-face. Median follow-up (where this was performed 17/23 studies) = 6 months.	Low	The assessment of safety in most studies was insufficient. Two studies reported dropout, due to worsening of co-morbid mental disorders. However, CBT is generally considered safe.
Exercise [39]	34 (2276) AMSTAR=9	Exercise programmes lasting 2.5 to 24wks. Aerobic exercise for >=20mins, once a day (or twice for >=10mins), 2 to	Moderate	Although patients may initially notice a deterioration in symptoms, exercise is

[8] This data was not contained in this review. The initial recommendation for chiropractic was Weak Against. However, after discussion, this was downgraded to Strong against, due to potential safety concerns.

		3 days a week. Strength training with >=8 repetitions per exercise, 2 to 3 times a week.		generally considered safe, especially when practised under supervision.
Hydrotherapy / spa therapy[74]	10 (446) AMSTAR=9	Wide variation in precise treatment strategy between trials. Most consisted of water or mud baths at body temperature 36-37°C), or slightly above (40-45°C), with a median treatment time of 240mins (range 200-300), over several weeks.	Low	Three studies reported no side effects of treatment; one reported slight flashes in 10% of the patients. The remaining trials did not explicitly mention safety.
Hypnotherapy [89]	4 (152) AMSTAR=11	Some variation between trials ranging (where reported) from 300 to 420mins, delivered over 10 to 26wks.	Good	Adverse events were not reported in any of the trials.
Massage [61]	9 (404) AMSTAR=7	Massage therapy time lasted 25-90mins, with between 1 and 20 massage sessions in total	Low to moderate	No adverse events were reported in any of the trials
Meditative movement [78]	7 (362) AMSTAR=9	Wide variation in treatments between trials, and included yoga, tai chi, qigong, or body awareness therapy. Median (range) duration of treatment = 16 (6-24) hrs, over 4-12wks.	Moderate	Although no serious adverse events were reported, six participants (3.1%) withdrew from the trials because of adverse events (increase of pain; muscle inflammation; chlorine hypersensitivity). The review authors concluded that the acceptance and safety of all

				types of meditative movement therapies were high.
Mindfulness / mind-body therapy [82]	6 (674) AMSTAR=9	Some variation between trials. Single 2-3.5hr session per week, for 8-10wks. Four out of six programmes also included daily home practice (30-45mins) plus a single all-day retreat.	Low	Safety was assessed and reported in none of the trials
Multi-component therapy [58]	9 (1119) AMSTAR=9	Enormous variation in treatment strategies between trials. Most included different combinations of exercise (land and/or water based); education; relaxation; and/or some other specific therapeutic component (e.g. Tai Chi; or massage)	Moderate	No adverse events were reported in any of the trials
S-Adenosyl methionine (SAMe) [91]	1 (44) AMSTAR=6	400mg tablet, twice a day, for 6wks	Moderate	Mild adverse effects such as stomach upset and dizziness were reported.
Other: Guided imagery [89]	1 (48) AMSTAR=9	Audiotape-led, individual, guided imagery: 30 min daily for 6wks recommended. Median of 44 exercises (range 37-136)	Good	Adverse events were not reported.
Other: Homeopathy [96]	4 (163) AMSTAR=7	Variation between trials. Two studied individualised homeopathic treatment,	Low to moderate	No information was provided on safety.

		consisting of an initial consultation (and treatment), plus follow-up interviews every 4-8wks. Two studied *Arnica montana*, *Bryoniaalba* or *Rhus toxicodendron* (potency 6c) daily for between 1 and 3 months.		

Table 3: Recommendations

Recommendation	Level of evidence	Grade	Strength of recommendation	Agreement[9]
Overarching Principles:				
Optimal management requires prompt diagnosis. Full understanding of fibromyalgia requires comprehensive assessment of pain, function, and psychosocial context. It should be recognised as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features. In general, the management of FM should take the form of a graduated approach	IV	D		100%
Management of fibromyalgia should aim at improving health-related quality of life balancing benefit and risk of treatment which often requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment modalities tailored according to: pain intensity, function, associated features (such as depression), fatigue, sleep disturbance and patient preferences and comorbidities; by shared decision making with the patient. Initial management should focus on non-pharmacological therapies	IV	D		100%
Specific Recommendations				
Non-Pharmacological Management				
Aerobic and strengthening exercise	Ia	A	Strong for	100%

[9] % of working group scoring at least 7 on 0-10 numerical rating scale assessing agreemen

Cognitive Behavioural Therapies	Ia	A	Weak for	100%
Multicomponent therapies	Ia	A	Weak for	93%
Defined physical therapies: Acupuncture or hydrotherapy	Ia	A	Weak for	93%
Meditative movement therapies (qigong, yoga, tai chi) and Mindfulness Based Stress Reduction	Ia	A	Weak for	71-73%
Pharmacological Management				
Amitryptiline (at low dose)	Ia	A	Weak for	100%
Duloxetine or Milnacipran	Ia	A	Weak for	100%
Tramadol	Ib	A	Weak for	100%
Pregabalin	Ia	A	Weak for	94%
Cyclobenzaprine	Ia	A	Weak for	75%

Chapter 2.2

Investigating generalisability of results from a randomised controlled trial of the management of chronic widespread pain (CWP): the MUSICIAN study

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Abstract

The generalisability of randomised controlled trials will be compromised if markers of treatment outcome also affect trial recruitment. In a large trial of chronic widespread pain (CWP), we aimed to determine the extent to which randomised participants represented eligible patients, and whether factors predicting randomisation also influenced trial outcome. Adults from eight UK general practices were surveyed to determine eligibility for a trial of two interventions (exercise, and cognitive behavioural therapy (CBT)). Amongst those eligible, logistic regression identified factors associated with randomisation. The main trial analysis was recomputed, weighting for the inverse of the likelihood of randomisation, and the numbers needed to treat (NNT) were calculated for each treatment. 884 persons were identified as eligible for the trial, of whom 442 (50%) were randomised. Several factors were associated with the likelihood of randomisation: higher Body Mass Index (BMI) (odds ratio: 1.99; 0.85-4.61); more severe/disabling pain (1.90; 1.21-2.97); having a treatment preference (2.11; 1.48-3.00); and expressing positivity about interventions offered (exercise: 2.66; 1.95-3.62; CBT: 3.20; 2.15-4.76). Adjusting for this selection bias decreased the treatment effect associated with exercise and CBT but increased that observed for combined therapy. All were associated with changes in NNT. This has important implications for the interpretation of pain trials generally.

Introduction

Randomised controlled trials (RCTs) remain the gold standard for assessing the efficacy and effectiveness of interventions. However, typically, they are conducted with highly selected patient populations and the results then generalised to wider patient populations. The appropriateness of this generalisation is based, at least in part, on the extent to which the randomised patients resemble the entire eligible patient population, and the belief that the biological effect will be the same in other populations. A concern with the external validity of trials (including those concerned with pain) has led to renewed interest in "Real World Evidence" (i.e. observational data) as perhaps providing more appropriate evidence on treatment effectiveness in settings in which they may be typically applied.

These assumptions may not hold true. It is known that certain population groups are, generally, more willing to be randomised than others – these include the less well educated [6,12] and those with more severe symptoms [2,6] – and the generalisability of trial results may be compromised if certain patient characteristics that are associated with trial recruitment are also markers of the trial treatment outcome. However, the extent to which this is the case for individual trials is often impossible to gauge, as trial recruitment frequently occurs in such a way that detailed information on eligible but non-randomised patients is not available.

Recent reviews and meta-analyses have shown that eligible individuals may be less likely to enter a trial if they have strong treatment preferences [11,16]. In addition, treatment preference may be associated with prognostic indicators in trial participants, such as anxiety [15], and symptom severity [2,11]. There is also evidence that, among trial participants, treatment effect differs according to *a priori* treatment preferences [11,16].

We conducted an RCT of the management of chronic widespread pain in primary care – the MUSICIAN study (Managing Unexplained Symptoms In primary Care: Involving traditional and Accessible New approaches [13]. The trial was a factorial 2*2 design and interventions were (a) prescribed exercise delivered by trained fitness instructors, and including access to a fitness facility; (b) cognitive behavioural therapy (CBT) delivered over the telephone by trained therapists; (c) both of the above; or (d) usual care. We found that both exercise and CBT were associated with important and statistically significant improvements in patient global assessment

in both the medium and long-term, although no additional benefit was gained from receiving both treatments [1,13]. Trial patients were identified using a large population-based survey. This gave rise to a unique opportunity to gather detailed information from a large pool of eligible individuals; to characterise those who did and those who did not consent to randomisation; and to determine the influence of treatment preference on the likelihood that an eligible individual would be randomised.

Thus, using data from the MUSICIAN study, the aims of the current study were, firstly, to examine factors that may affect the generalisability of trial results and secondly, to examine the extent to which external validity may be compromised, by determining whether factors predicting randomisation also influenced trial outcome.

Methods

The MUSICIAN study was a 2x2 factorial RCT investigating the management of chronic widespread pain (registration number: ISRCTN67013851), the methods and main results (including CONSORT statement) of which have been described elsewhere [1,13,14]. In brief, potential trial participants were identified by means of a large-scale postal questionnaire survey, mailed to all 45,994 individuals aged 25 years and older registered with eight general practitioners in the city of Aberdeen, Scotland, and North Cheshire, England. As over 95% of UK residents are registered at a GP practice, and these practices were located in areas of varying levels of socioeconomic status, this was considered to be suitably representative of the general population. Questionnaire respondents were potentially eligible to be randomised if they reported:

(a) Pain consistent with the American College of Rheumatology definition of chronic widespread pain in their 1990 classification criteria for fibromyalgia [21];
(b) Pain of some impact, defined as a score of ≥1 on the Chronic Pain Grade [20]; and
(c) Pain for which they had consulted their general practitioner at least once, within the previous twelve months.

In addition, trial inclusion criteria required patients to consent to be contacted again, and to have:

(d) No health condition identified as requiring an alternative treatment;
(e) Access to a land-line telephone; and
(f) No contra-indications to exercise. (Note: pain alone was not considered a contra-indication.)

The questionnaire provided brief information about the exercise and CBT treatments offered in the trial (although, at this stage, participants did not know that they might be invited to take part in a trial). It also elicited information about participants' familiarity with these treatments; how positive they would be about receiving the treatments (using a 0-10 visual analogue scale); and how effective they believed they would be, were they to receive them (on a five point Likert scale from 'much improved', to 'much worse'). Treatment preference was assessed by a single question asking participants which of the available treatments they would opt for, were they to have been given a choice.

Survey respondents who were potentially eligible for the RCT were then mailed information about the trial itself, after which they were contacted by a research nurse to confirm eligibility and arrange an initial assessment appointment in a local clinical research facility. At this appointment, participants completed an additional questionnaire which contained measures of psychological distress (General Health Questionnaire (GHQ) [9]); sleep problems (Sleep Problems Scale [10]); fatigue (Chalder Fatigue Scale [4]); and fear of movement (Tampa Scale for Kinesiophobia [18]); and, if eligibility was confirmed and consent was obtained, randomisation took place.

The primary outcome for the trial was a seven-point, patient global impression change score, assessed by self-completion questionnaire, at six and nine months post-randomisation. Patients were asked to rate how they felt their health had changed since the period prior to entering the trial, ranging from 1 ('very much worse') to 7 ('very much better'). Questionnaire non-respondents were asked the same question verbally, by telephone interview.

Analysis

Firstly, amongst individuals surveyed, responders and non-responders were compared and among survey respondents eligible for randomisation, differences were examined between those individuals who were / were not subsequently randomised. This was done using x^2 tests and non-parametric tests for trend [5] and the magnitude of any differences characterised using logistic regression. Thus, differences are expressed as odds ratios with 95% confidence intervals (95%CI). Secondly, a forward stepwise regression model was constructed, to identify which variables independently predicted randomisation. If not already dichotomous, these variables were then dichotomized and N*2 categories were created, where N represented the number of factors in the multivariable regression model. The primary trial analysis (presented elsewhere [13]) was then recomputed, weighting for the inverse of the likelihood of randomisation, for every given

combination of N*2 categories. Finally, the number needed to treat (NNT) was calculated for each of the treatments, based on the weighted odds ratios.

Statistical analysis was conducted using STATA 11.1 from STATACORP, Texas. NNTs were calculated in Microsoft Excel, using published formula [3].

Results

Of 45,994 individuals invited to participate in the survey, useable questionnaire responses were received from 15,313 (33%). Women were significantly more likely to respond than men (37% versus 29%; chi^2=328.1, p<0.001) and there was a significant increase in response rate with age (21% among those aged 25-40yrs, increasing to 45% in those >60yrs; non-parametric test for trend p<0.001). Of the 15,313 responders, 1844 (12%) reported chronic widespread pain of whom 884 (48%) were eligible to take part in the trial and 442 (50%) were eventually randomised. Of the 442 responders not randomised, 94 were subsequently found to be ineligible, and one died before they attended the screening visit. Thus, there were 347 participants who met all trial inclusion criteria, but were not randomised. The flow of participants from initial survey invitation to subsequent randomisation is shown in Figure 1.

The median age of eligible participants was 57yrs (inter-quartile range: 46-66yrs), and 68% were female. Two-thirds (67%) rated their health as 'good', or better; 28% had a body mass index >30kgm^{-2}; and 51% were ex- or current smokers. Of the eligible survey participants, those aged 41-60yrs were significantly more likely to be randomised than younger respondents (odds ratio: 1.54; 95%CI: 1.02-2.33). However, this effect was not linear and there was no further increase in the likelihood of randomisation among those aged >60yrs (1.31; 0.87-1.98). Also, there was no difference in the likelihood of randomisation between men and women (odds ratio for women: 1.23; 0.91-1.66).

A significant trend existed, such that participants with higher BMI (p=0.03) and higher Chronic Pain Grade (signifying more severe and / or disabling pain) (p=0.002) were more likely to be randomised than other individuals (Table 1). Similarly, participants with a treatment preference were twice as likely to be randomised as those without (2.11; 1.48-3.00), and this effect existed irrespective of whether the preference was for exercise, CBT, or both (Table 2). Positivity about receiving either exercise (2.66; 1.95-3.62) or CBT (3.20; 2.15-4.76) was associated with an increase in the

likelihood of randomisation, although no such effect was observed with participant expectations of outcome, for either treatment (Table 2).

Five factors were found to be independently associated with randomisation: age, positivity about exercise, positivity about CBT, more severe/disabling Chronic Pain Grade, and taking regular exercise. Weighting the analysis by the inverse of the likelihood of randomisation (essentially, simulating the effect of all eligible non-participants actually being randomised) resulted in slight difference in the treatment effect estimates at both six and nine months. For the single therapies, at six months, the weighted model resulted in an 11% decrease in the magnitude of treatment effect for CBT (from an odds ratio of 6.45; 2.42-17.2 to 5.72; 1.92-17.0) and a 25% decrease in the treatment effect associated with exercise (from 7.28; 2.79-19.0 to 5.49; 1.89-16.0). In contrast, the weighted model gave a 16% increase in the estimate of treatment effect of the combined therapy (Table 3). The same pattern was true at nine months, although the magnitude of the changes in effect estimates was less (5% decrease, 11% decrease and 19% increase, respectively). For CBT, the weighted model produced no change in the number needed to treat. However, for exercise, there was an increase in the NNT from 4 to 5, for improvement at six months, and from 7 to 8 for improvement at nine months. For the combined therapy, NNT fell from 5 to 4 for improvement at nine months.

Discussion

In the context of a large randomised controlled trial examining the effectiveness of exercise therapy and CBT for chronic widespread musculoskeletal pain, we have shown that individuals who were randomised were different, in a number of ways, from the entire eligible patient population that was originally identified. Randomised individuals had a higher BMI, and more severe and / or disabling pain. They were also more likely to have a treatment preference, for either or both of available trial treatments, and be more positive about receiving either of the treatments available in the trial. We have demonstrated that this selection bias resulted in a change in treatment effect estimation, and in the associated NNT, although the changes noted were modest.

The design of the MUSICIAN study and, specifically, the opportunity to collect a large amount of data on individuals who were eligible to participate in the trial, but who were not ultimately randomised, allowed an assessment of potential selection bias which is rare in trials. This notwithstanding, there are a number of methodological issues to discuss, in interpreting these findings. The first issue is the timing of data collection. All predictors of randomisation were

collected by population survey typically 1-2 weeks prior to randomisation. Although this has the advantage that participants completed these questions naïve to their eligibility for the trial, it may be that participants report different treatment preferences, positivity and expectations in what they believe to be a hypothetical situation, than they would if actually faced with the possibility of receiving either therapy. Secondly, only one-third of the survey questionnaires were returned. Population survey questionnaire response rates are falling over time [8] and participation rates of 33% are not uncommon. The current study aimed to determine whether trial participants were different from eligible nut non-randomised participants. By definition, individuals who failed to complete the initial survey questionnaire were not eligible for the trial. This study looked at how refusal to participate after the identification of eligible patients affected representativeness; a separate source of selection bias (not under examination in the current study) comes from not being able to identify eligible patients in the first place. Although the prevalence of chronic widespread pain in the current study was very similar to other large population studies [13], we know that responders / non-responders differ with respect to age and gender. The differences were 24% and 8.0% respectively, with older individuals and women significantly more likely to respond than other individuals, and among all respondents, these individuals were also significantly more likely to be randomised. This illustrates further that trial participants are different from the wider eligible patient population and would suggest that, if anything, we have underestimated these differences.

Our findings concur with other studies which have shown that trial participants differ from the wider eligible population in a number of ways. That participants with severe and / or disabling pain were more likely to be randomised is perhaps no surprise. These individuals may be more willing than other participants to try novel or hard-to-access treatments. It is also plausible that those with a higher BMI may have been more willing to enter the trial, in order to benefit (potentially) from the exercise therapy. What is particularly pertinent, however, is not why randomised / non-randomised participants are different, but the fact they are different with respect to a number of important prognostic markers.

Our findings also show that eligible individuals with a preference for one or both of the investigative treatments in the MUSICIAN trial were more likely to be randomised than those no preference. This is likely to be at least partially explained by the nature of the interventions offered in the MUSICIAN trial. In the UK, neither prescribed exercise (including free gym membership for six months, and complimentary access to a fitness instructor) nor CBT are routinely available for chronic widespread pain in primary care. Previous trials have reported that a strong treatment preference was a key reason for refusing randomisation [7,11,17,19] and this

also has important implications for the generalisability of findings. A recent meta-analysis of eleven musculoskeletal trials found that, among participants, treatment preference was an important determinant of outcome [16].

We have also shown that the factors that influence whether a potential participant is likely to be randomised into a trial also influence trial outcome. Re-computing the main trial analysis, to adjust for the fact that the randomised participants are different from the total eligible patient population, gave intriguing findings. For the single therapies, our weighted model resulted in a decrease in treatment effect, suggesting that any selection bias (in the original analysis) acted to overestimate treatment effects. Whereas, for combined therapy, the opposite was true, suggesting that any selection bias led to an underestimate of the effect of treatment. In the context of the current trial, where the treatment effect sizes were large (OR_{range}: 6.45 to 7.28 at six months, and 3.41 to 5.57 at nine months) an over- or under-estimate of the magnitude observed in the current study makes little difference to the overall conclusions of the trial. However, many trials have smaller effect sizes and, while it is impossible to predict what the results would be, over- / under-estimates of between 10 and 24% may have important implications in interpretation of trial findings. As in the current study, even minor changes in effect size, may result in changes in NNT, and this may have potentially important implications for estimates of the cost-effectiveness of treatments. In the original MUSICIAN trial for the primary outcome [13] exercise was not cost effective, and the cost effectiveness of CBT was marginal. In this context, even minor errors in estimation of effect measures are important.

In summary, the status of randomised controlled trials as the gold standard method for determining the effectiveness of healthcare interventions is based upon their inherent internal validity and the ability to control potential confounding variables, but they are commonly conducted on highly selected patient groups. Their real world value, therefore, depends on the assumption that these patient groups adequately represent the entire eligible patient population, yet rarely is information available to test this assumption. Capitalising on a unique opportunity to collect data on a wider eligible population we have shown, firstly, that trial participants differ not only in terms of clinical variables, but also in terms of treatment preference; and, secondly, that the factors associated with trial participation also influence trial outcome. This has important implications for trials generally and emphasises that, where possible, collecting information on eligible but non-randomised patients allows a better estimate of treatment effectiveness.

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The MUSICIAN study team are: Professor Gary J Macfarlane (chief investigator), Professor Phil Hannaford, Dr Philip Keeley, Professor Karina Lovell, Dr John McBeth, Dr Paul McNamee, Professor Deborah Symmons and Dr Steve Woby (investigators), Marcus Beasley (research assistant), Chrysa Gkazinou (trial manager), Dr Elizabeth Jones (researcher), Dr Gordon Prescott (statistician) and Dr Graham Scotland (health economist).

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GTJ, EAJ, MB and GJM were involved in (a) the conception and design, or analysis and interpretation of data; (b) drafting the article or revising it critically for important intellectual content. None of the authors report a conflict of interest with respect to the contents of this manuscript.

Author Disclosures

None of the authors declare any relevant interests or conflicts

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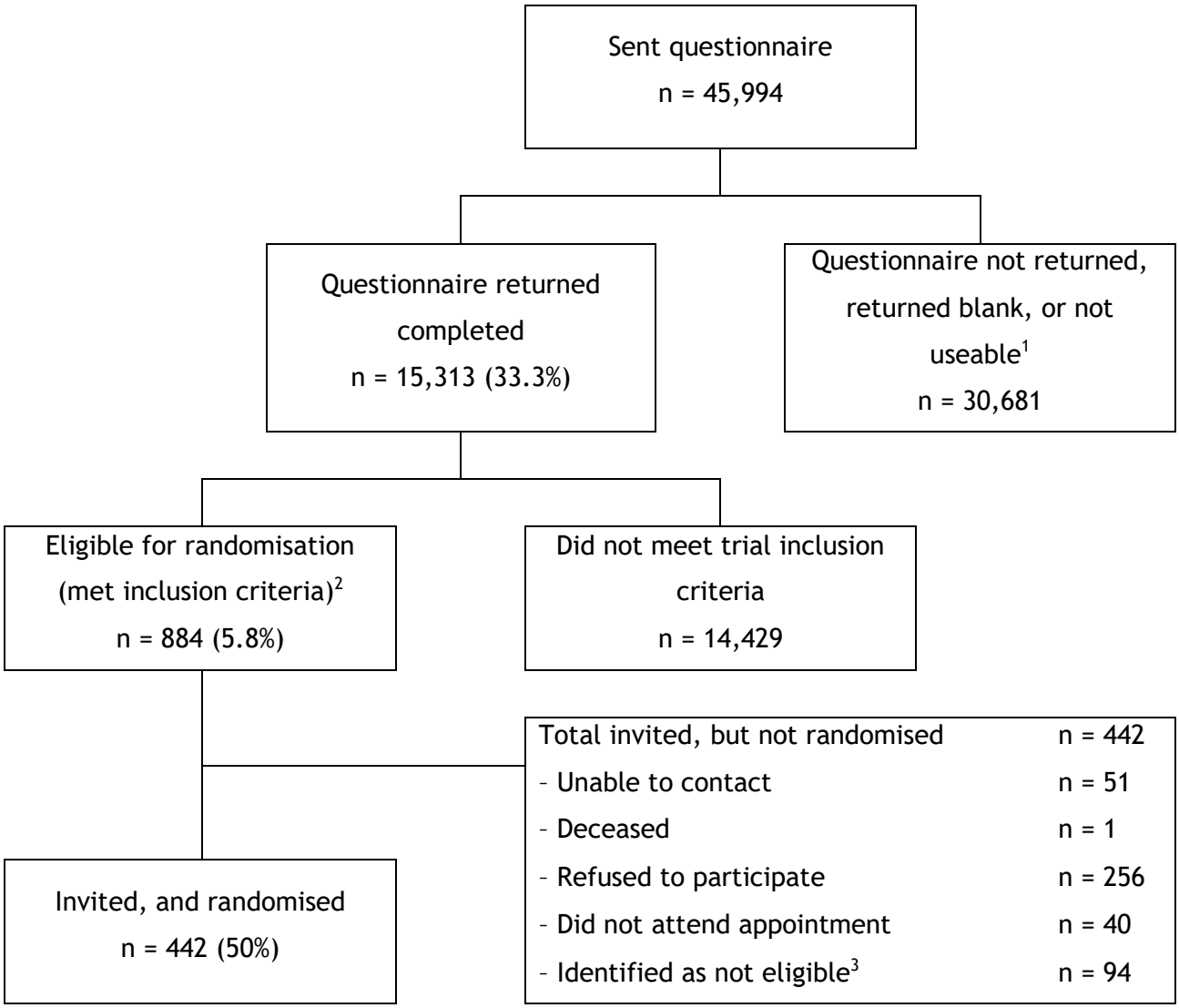
Figures and Tables

Figure 1: Flow of participants in the study



1 Includes one (eligible) person who returned a questionnaire but died before being invited.

2 Includes six people marked as not eligible, but invited due to error, one of whom was subsequently randomised.

3 Identified as ineligible either on the invitation phone call, or at the screening appointment.

Table 1: Differences in demographics and health, between eligible survey participants who were / were not randomised

		Randomised		Odds ratio (95%CI)	
		Yes	No	Crude	Age adjusted
Age (years)	25-40	61	64	1.00	-
	41-60	197	134	1.54 (1.02-2.33)	-
	>60	184	147	1.31 (0.87-1.98)	-
Gender	Male	135	120	1.00	1.00
	Female	307	225	1.21 (0.90-1.64)	1.23 (0.91-1.66)
Self-rated health	Excellent	7	10	1.00	1.00
	Very good	76	63	1.72 (0.62-4.79)	1.70 (0.61-5.47)
	Good	210	158	1.90 (0.71-5.10)	1.84 (0.68-4.96)
	Fair	127	96	1.89 (0.69-5.15)	1.82 (0.66-4.98)
	Poor	20	16	1.79 (0.55-5.74)	1.71 (0.53-5.54)
BMI (kgm^{-2})	≤20	15	15	1.00	1.00
	20.1-25.0	133	119	1.13 (0.53-2.40)	1.10 (0.51-2.36)
	25.1-30.0	157	128	1.23 (0.58-2.60)	1.16 (0.54-2.49)
	30.1-35.0	74	53	1.40 (0.63-3.10)	1.30 (0.58-2.91)
	>35.0	62	31	2.00 (0.87-4.61)	1.99 (0.85-4.61)
Smoking status	Never	219	161	1.00	1.00
	Ex-smoker	154	111	1.02 (0.74-1.40)	1.02 (0.74-1.40)
	Current smoker	63	67	0.69 (0.46-1.03)	0.70 (0.47-1.05)
Regular exercise[1]	None	84	82	1.00	1.00
	1-2 times per week	177	113	1.53 (1.04-2.25)	1.55 (1.05-2.28)
	3-4 times per week	100	75	1.30 (0.85-1.99)	1.33 (0.86-2.04)
	≥5 times per week	79	72	1.07 (0.69-1.66)	1.08 (0.69-1.69)
Chronic Pain Grade[2]	I	86	100	1.00	1.00
	II	152	117	1.51 (1.04-2.20)	1.53 (1.05-2.23)
	III	85	53	1.86 (1.19-2.92)	1.90 (1.21-2.99)
	IV	86	53	1.89 (1.21-2.95)	1.90 (1.21-2.97)

1 Number of times per week doing 30minutes of moderate physical activity or walking that increased the heart rate or increased breathing.
2 Due to trial eligibility criteria, there were no participants with a Chronic Pain Grade = 0.

Table 2: Differences in treatment preference and expectation, between eligible survey participants who were / were not randomised

		Randomised		Odds ratio (95%CI)	
		Yes	No	Crude	Age adjusted
Treatment preference	No[1]	68	95	1.00	1.00
	Yes	362	245	2.06 (1.45-2.93)	2.11 (1.48-3.00)
Treatment preference	None[1]	68	95	1.00	1.00
	Exercise	170	151	1.57 (1.07-2.30)	1.60 (1.09-2.34)
	CBT	27	16	2.36 (1.18-4.71)	2.38 (1.18-4.76)
	Both treatments	165	78	2.96 (1.96-4.46)	2.10 (2.04-4.70)
Expectations of exercise[2]	Improve	347	236	1.00	1.00
	No change	58	64	1.62 (1.10-2.40)	1.67 (1.12-2.48)
	Worsen	21	17	1.36 (0.66-2.83)	1.34 (0.64-2.79)
Expectations of CBT[2]	Improve	228	129	1.00	1.00
	No change	175	168	1.70 (1.25-2.30)	1.74 (1.28-2.37)
	Worsen	3	5	0.58 (0.14-2.45)	0.55 (0.13-2.33)
Positivity re: exercise[3,4]	Low	113	159	1.00	1.00
	Moderate / High	325	182	2.51 (1.86-3.40)	2.66 (1.95-3.62)
Positivity re: CBT[3]	Low	125	154	1.00	1.00
	Moderate	165	116	1.75 (1.25-2.45)	1.85 (1.31-2.60)
	High	141	60	2.90 (1.97-4.25)	3.20 (2.15-4.76)

1 Includes participants with no preference, and those who responded 'don't know'.
2 The imagined effect of six months of treatment, on participants' chronic pain.
3 How positive participants would be about receiving the treatment, one a 0-10 scale; divided into tertiles for analysis.
4 Due to the skewed distribution of positivity regarding exercise, the moderate and high tertiles form one category.

Table 3: The influence of factors associated with randomisation, on trial outcome

Treatment group	Improvement[1] at 6 months post randomisation Odds ratio (95%CI) [NNT]		Improvement[1] at 9 months post randomisation Odds ratio (95%CI) [NNT]	
	Original findings[2]	Weighted model	Original findings[2]	Weighted model
Treatment as usual	1.00	1.00	1.00	1.00
CBT	6.45 (2.42-17.2) [NNT=4]	5.72 (1.92-17.0) [NNT= 4]	5.57 (2.34-13.3) [NNT=5]	5.31 (2.06-13.7) [NNT= 5]
Exercise	7.28 (2.79-19.0) [NNT=4]	5.49 (1.89-16.0) [NNT= 5]	3.41 (1.42-8.15) [NNT=7]	3.02 (1.18-7.76) [NNT= 8]
CBT + Exercise	6.76 (2.56-17.8) [NNT=4]	7.86 (2.69-23.0) [NNT= 4]	5.18 (2.19-12.3) [NNT=5]	6.19 (2.41-15.9) [NNT= 4]

1 'Much better' or 'very much better' on patient global change score on how patients felt their health had changed since entering the trial, from 1 ('very much worse') to 7 ('very much better').

2 Effect estimates and NNTs differ slightly from those in the original manuscript[7] because we have excluded individuals with missing values for variables used in the weighting calculation.

Chapter 2.3

Persons with chronic widespread pain experience excess mortality: longitudinal results from UK Biobank and meta-analysis

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Abstract

Objective: It is uncertain whether persons with chronic widespread pain (CWP) experience premature mortality. Using the largest study conducted, we determine whether such a relationship exists, estimate its magnitude and establish what factors mediate any relationship.

Methods: UK Biobank, a cohort study of 0.5 million people aged 40-69 years, recruited throughout Great Britain 2006-10. Participants reporting "pain all over the body" for >3 months were compared with persons without chronic pain.. Information on death (with cause) was available until mid-2015. We incorporated these results in a meta-analysis with other published reports to calculate a pooled estimate of excess risk..

Results: 7130 participants reported CWP and they experienced excess mortality (Mortality Risk Ratio 2.43, 95% Confidence Interval 2.17, 2.72). Specific causes of death in excess were cancer ($1.73_{\text{adjusted age and sex}}$; 1.46, 2.05); cardiovascular ($3.24_{\text{adjusted age and sex}}$; 2.55, 4.11); respiratory ($5.66_{\text{adjusted age and sex}}$; 4.00, 8.03); and other disease-related causes ($4.04_{\text{adjusted age and sex}}$; 3.05, 5.34). Excess risk was substantially reduced after adjustment for low levels of physical activity, high body mass index (BMI), poor quality diet and smoking. In meta-analysis, all studies showed significant excess all-cause (combined estimate 1.59 (1.05, 2.42)). cardiovascular and cancer mortality.

Conclusions: Evidence is now clear that persons with CWP experience excess mortality. UK Biobank results considerably reduce uncertainty around the magnitude of excess risk, and are consistent with the excess being explained by adverse lifestyle factors, which could be targeted in the management of such patients.

Introduction

Persons with CWP, the characteristic symptom of fibromyalgia, have been reported to experience premature mortality. The original observation, in a UK study, found 30% excess mortality was explained primarily by increased cancer incidence and reduced survival [1,2]. A subsequent UK study, confirmed the 30% excess mortality, primarily from increased cancer and cardiovascular deaths [3].

Studies to identify the mediators of such a relationship have focussed on low levels of physical activity, since the specific cancers contributing to excess mortality (female breast, prostate and colon) have been linked to low physical activity [4,5]. It has been hypothesised that CWP may lead to low levels of physical activity and this was confirmed by a longitudinal study [6]. Further studies have suggested additional lifestyle mediators of excess mortality: overweight has been shown to predict CWP onset and persistence [7,8]; persons with CWP have been reported as more likely to smoke and women with CWP have been shown to have poorer quality diet [9].

However not all studies conducted have found an excess mortality amongst persons with CWP. Meta-analyses have reported considerable heterogeneity which has been attributed to differences in study populations, follow-up time, pain phenotype, methods of analysis and use of confounding factors [10,11]. Currently there is considerable uncertainty as to whether there is an excess mortality risk. It is important to determine whether an excess risk exists and if so to quantify it, since there remains the potential, as part of managing patients with CWP or fibromyalgia, to modify the mediators of any excess risk.

We therefore now report on the largest study to examine the relationship between chronic widespread pain and mortality experience, and with considerably more detailed information on potential mediators of any excess risk. Further we include these results in a meta-analysis, with other published reports, to evaluate the coherence of evidence.

Methods

UK Biobank

Detailed methods used by UK Biobank have been published previously [12] and we provide only summary details of relevance to the current analysis. The study aimed to recruit around half a million persons aged 40-69 years who were registered with a general practitioner

within the NHS. Approximately 9.2 million invitations were issued, between 2006-10, to people living within 25 miles of one of 22 assessment centres throughout Great Britain.

At the assessment centre, participants completed questionnaires including items on lifestyle and environment. Information on pain was collected by means of a touch screen questionnaire. Participants were asked "In the last month have you experienced any of the following that interfered with your usual activities?" If they answered positively, they were then provided with a list which included individual regional pain sites, or alternatively they could choose the response "pain all over the body". Subjects who reported "pain all over the body" were not offered the option of choosing any further regional sites. Respondents were asked whether the reported pain had lasted at least three months and those with "pain all over the body" which had lasted three months were defined as having chronic widespread pain (CWP). Participants were identified on the Office for National Statistics (ONS) records. ONS collects information on cause of death from civil registration records. For registered deaths, the underlying cause of death is derived from the sequence of conditions leading directly to the death and is recorded on the death certificate. The current analysis uses data on vital status up to August 2015.

The determinants or exposures which we considered in terms of mediating any relationship between CWP and mortality were focussed on factors potentially modifiable as part of the management of CWP:

- age (in five-year groups) and sex,
- body mass index (BMI), derived from measured height and weight, categorised according to standard cut-offs of the World Health Organisation.
- physical activity: minutes of walking per week ("In a typical week, on how many days did you walk for at least 10mins at a time" and "How many minutes did you usually spend walking on a typical day?"); minutes of moderate activity per week ("In a typical week, on how many days did you do 10mins or more of moderate physical activities like carrying light loads, cycling at a normal pace (do not include walking)" and "How many minutes did you usually spend doing moderate activities on a typical day ?"); minutes of vigorous activity per week (as before but vigorous defined as "activities that make you sweat or breathe had such as fast cycling, aerobics, heavy lifting". These were categorised as nil and then by quartiles.
- Diet: Participants were asked (i) "On average how many heaped tablespoons of cooked vegetables would you eat per day? (Do not include potatoes.)" (ii) "On average how many heaped tablespoons of salad or raw vegetables would you eat per day? (Include lettuce and tomato in sandwiches)" (iii) "About how many pieces of

fresh fruit would you eat per day?" (iv) "About how many pieces of dried fruit would you eat per day?" Total daily "portions" of cooked vegetables, raw vegetables, salad consumption were calculated and re-coded as quintiles. Frequency of alcohol consumption was determined with response categories: Never; Daily or almost daily; Three or four times a week; Once or twice a week; One to three times a month; Special occasions only. The latter two categories were combined into "Less frequently than once or twice per week"

- Smoking status; a history of smoking was recorded which allowed us to classify respondents as current , never (or very rare) or ex-smokers, the latter group being divided into ex-regular and ex-occasional smokers.

UK Biobank Analysis

We used Poisson regression models, with robust estimation of standard errors to model the relationship between CWP and all-cause mortality, adjusted for age-group and sex. We tested and confirmed that the mediating variables were not collinear. We compared persons with CWP to persons who did not report any chronic pain. We additionally examined specific major causes of death as outcomes including cardiovascular disease, respiratory disease and cancer. We report the MRiR including all deaths in the follow-up period, but exclude deaths in the first two years of follow-up from all subsequent analyses, since CWP may be a manifestation of an existing illness. Starting with a basic model containing CWP, age-group and sex, we added, individually, lifestyle factors or markers which could possibly mediate any observed relationship. We then added all such potential mediators to a final model. Associations are expressed as Mortality Risk Ratios (MRiR) with 95% Confidence Intervals (CI).

Meta-analysis

We used (in a modified way) and updated a search conducted by Smith et al [10] which identified studies examining the relationship between chronic pain and/or widespread pain and mortality. Although their review focussed generally on chronic pain, our update focussed only on studies examining widespread pain or chronic widespread pain. A second difference is that although previous meta-analyses extracted effect measures which were maximally adjusted for potential confounding factors we have extracted data that is (as close as possible) only adjusted for age and sex. The difference is that we are answering the question "Do persons with CWP experience excess mortality (in comparison to those without chronic pain)" whereas using fully-adjusted effect measures is answering the

question of whether the report of pain (per se) is associated with excess mortality. Thus the data on effect on measures extracted from studies which they identified as eligible, may be different.

We re-ran the published search strategy (in Appendix S1 of the original meta-analysis) from January 2014 (in order to ensure that articles published close to the time of the previous search were not missed) to January 2017.

Studies were eligible for the current meta-analysis provided that they:

- Were observational studies
- Sampled from a population sampling frame (or an approximation to such)
- Identified persons with widespread pain (WP) or chronic widespread pain (including fibromyalgia) and a comparison group of persons without such pain. The definition of widespread pain should involve recognised criteria or the reporting of pain all over the body.
- Provided either a Mortality Rate Ratio (MRtR) or Mortality Risk Ratio (MRiR) quantifying the relationship between WP or CWP and mortality
- Were published as a manuscript in English in a peer-reviewed journal

Identified abstracts were screened by two authors and any disagreement resolved by discussion. We also checked studies included in the meta-analysis by Smith et al [10] to determine that they met the above eligibility criteria. Meta-analysis was conducted using a random effects model, to reflect known differences in studies including geographical location, phenotypes and follow-up. The effect measures extracted from the eligible studies (MRrR or MRiR) were as closely as possible only adjusted for age and sex. In the meta-analysis, conducted using RevMan software, MRR has been used to signify the combined estimates using MRtR and MRiR. Sources of heterogeneity in effect measures were explored, specifically in relation to the geographical area in which the study was conducted and prevalence estimate.

Results

UK Biobank

From 502,627 UK Biobank participants, 2193 (0.4%) did not answer the pain questions and are therefore excluded from this analysis. Amongst the remaining 500,434 persons, 7130 reported CWP (prevalence 1.4%) while 281,718 reported that they did not have any chronic

pain. These two sub-cohorts are the study population for the current analysis and their characteristics are shown in Table 1. The CWP and the "no chronic pain" groups had the same median age (58 years). Persons with CWP were less likely to be male (36.3% v. 50%); were more likely to be heavier than normal weight (80.4% v. 63.5%), be a current smoker (18.6% v. 9.3%) and not to drink any alcohol (22.7% v. 6.7%). They also undertook physical activity less often, In total there were 12,799 deaths in the study population within the period of observation: 7486 (58%) classified as being due to cancer, 2691 (21%) cardiovascular disease, 728 (6%) respiratory disease, 436 (3%) due to external causes, and 1458 (11%) were classified as 'other'.

After adjusting for age and sex, participants with CWP had a more than two fold risk of dying in the follow-up period (MRiR 2.56, 95% CI (2.32,2.82)), an excess which remained largely unchanged when deaths occurring in the first two years of follow-up were excluded (2.43; 2.17, 2.72). Deaths occurring in the first two years are excluded from all further analyses. Specific causes of death in excess were cancer (1.73 $_{\text{adjusted age and sex}}$; 1.46, 2.05); cardiovascular (3.24 $_{\text{adjusted age and sex}}$; 2.55, 4.11); respiratory (5.66 $_{\text{adjusted age and sex}}$; 4.00, 8.03); and other disease-related causes (4.04 $_{\text{adjusted age and sex}}$; 3.05, 5.34), while the excess of deaths from external causes was not statistically significant (1.55 $_{\text{adjusted age and sex}}$; 0.68, 3.49).

We then examined to what extent the factors which were identified as being associated with pain status, also predicted death in the period of follow-up (Table 2). Age-adjusted risk of death was lower in women (MRiR 0.58 (0.56, 0.60). Age and gender adjusted risk was higher in obese participants (35-39 kgm^{-2} v. normal weight 5.54 (5.08, 6.03), ≥40kgm^{-2} 9.02 (8.23, 9.89) those who reported no walking (v. 1-100 mins/week: 4.15 (3.77, 4.57) or no moderate physical activity (v. 1-60 mins/week: 2.95 (2.74, 3.19). Risk of death was also higher in smokers (current smokers 2.54 (2.39, 2.70), ex-smokers 1.44 (1.36, 1.52)), and persons who reported never drinking alcohol (v. daily drinkers 6.18 (5.68, 6.73).

Finally, we tested to what extent adjusting the risk models for these measured lifestyle variables attenuated the relationship between CWP and excess mortality (Table 3). Such attenuation would be consistent with the effects being mediated through such variable(s). When we did this, each class of variable (physical activity, BMI, smoking, diet including alcohol) when added to the model containing only pain status (CWP/no chronic pain), age-group and sex resulted in a small attenuation of effect from a MRiR of 2.4 to MiRRs in the range 2.0 to 2.2. However, when all such potentially mediating variables were entered in to the model the MiRR reduced to 1.47 (1.24, 1.73). In cause-of-death specific models with

potential mediating variables there remained an excess risk of cardiovascular 1.99 (1.41, 2.80), respiratory 1.91 (1.08, 3.36) and "other disease" deaths 2.14 (1.42, 3.21) but the there was no longer an excess risk of cancer death 1.06 (0.82, 1.38) and external deaths 1.01 (0.30, 3.40).

Meta-analysis

Our search identified 3171 unique publications, of which 15 proceeded to abstract screening and one to full-text screening and subsequent inclusion [12]. Of the five studies included in the meta-analysis of Smith et al [10], one did not meet eligibility criteria for the current meta-analysis [13], since the pain phenotype did not include any measure of "widespreadness". Instead the phenotype examined was multiple joint pain. Thus a total of six studies (including the current analysis) were eligible for the current meta-analysis [1,3,12,14,15]. Characteristics of studies identified as eligible are given in Table 4. One study presented data only to one decimal place and thus in the meta-analysis was identified as having a non-symmetrical log-transformed confidence interval [3]. We therefore contacted the first author of the publication and they provided more precise data (for analyses only adjusted for age and sex). Eligible studies included 580, 020 participants from three European countries (Norway, Sweden and the United Kingdom). There was significant heterogeneity between studies: I^2 = 98% for all-cause mortality, 95% for cardiovascular, 96% for respiratory and 91% for cancer (all $p<0.001$). All studies showed significant excess of all-cause mortality and the combined estimate of this was 57% (MRR 1.57; 1.06, 2.33). For cardiovascular mortality, three out of five studies showed a significant association and the combined estimate of this was 63% (1.63; 0.98, 2.70). For respiratory mortality, only one out of three studies showed a significant excess mortality and there was considerable uncertainty around the pooled estimate of excess risk (1.70; 0.45, 6.45). For cancer, three out of five studies showed significant excess mortality and the pooled estimate was 51% (1.51; 1.06, 2.13) (Figure 1).

We investigated the source of heterogeneity with respect to the relationship between CWP and all-cause mortality. When restricted by geographical area, the meta-analysis showed that considerable heterogeneity was present in studies conducted in Great Britain (I^2=90%)(MRR 1.60; 1.06,2.42) but not in in studies conducted in Scandinavia (I^2=0%) (MRR 1.06; 1.02,1.10). Similarly when analysis was restricted to those studies with prevalence of CWP in the 10-20% mid-range i.e. excluding those with the extreme prevalence estimates, there was no evidence of heterogeneity (I^2=0%)(MRR 1.30, 1.07-1.58).

Discussion

Using data from UK Biobank, involving over half a million study participants, we have demonstrated that persons with CWP have an important excess of risk of dying in the medium and long-term. This excess risk was evident across all disease and non-disease categories. The meta-analysis of this relationship, shows that all six studies conducted find excess mortality, and estimates the excess risk across all studies at 59%, although there is significant heterogeneity. Similar excesses of cancer and cardiovascular mortality are observed. In UK Biobank, adjustment for lifestyle factors substantially reduced the excess risk and this observation is consistent with them mediating the relationship between CWP and mortality

Methodological issues

The main strengths of UK Biobank in addressing this question include that it uses a sampling frame which is considered to have almost complete population coverage[10]. Although the participation rate was low (5.5%), we have previously published an analysis which demonstrates that the prevalence of regional pains in UK Biobank is very similar to more traditional pain epidemiological studies with higher participation, and that the study reproduces known relationships with aetiological factors. The large sample has allowed us to examine specific causes of death, to exclude deaths within two years of the assessment (since widespread pain may be a manifestation of a disease linked to death e.g. metastatic cancer) and consider the role of mediating factors.

The phenotype used in studies which have examined the relationship with mortality has varied considerably. They have included WP according to the definition within the American College of Rheumatology (ACR) criteria (1990) for fibromyalgia [1,3], and modifications of the ACR 1990 FM criteria in terms of pain timing and distribution [12,15] or bespoke definitions to capture "widespreadness" [14]. The comparison populations also differ: persons who are free of pain [1,3,14], free of chronic pain [15] or who simply do not meet the phenotype [12] are variously used. Some studies had an additional criterion that WP required to be chronic, although studies of widespread pain have shown that the vast majority of persons with WP report chronic symptoms (81% in UK Biobank). These have resulted in prevalence proportions within population-based studies of between 1.4-23.1% and suggest important differences in the symptomatic populations studied. Interestingly the study with the highest prevalence [12] reported a markedly lower excess risk of mortality.

[10] http://www.adls.ac.uk/department-of-health/gp-patient-register-dataset/?detail

UK Biobank has used the most stringent definition, which has resulted in a prevalence similar to that of fibromyalgia [16], and across all-cause and disease-specific mortality reports some of the highest excess mortality. This is consistent with the hypothesis that the greatest excess mortality is amongst those with the more severe symptoms. Sensitivity analyses confirmed that heterogeneity in risk estimates was indeed partly explained by differences in prevalence, as well by geographical area.

We have approached the analysis in a different way to some previous studies on this topic. We adjusted for the confounding factors of age and sex. Given that the question we are asking is "Do patients with CWP experience prematurely mortality?" we believed that no further adjustment should be made. However when excess mortality is observed it is of relevance to examine mediators – since these can become targets for intervention. Previous studies have identified lack of physical activity and poor quality diet as the variables which may explain a relationship. UK Biobank has a rich source of data to allow the assessment of these potential mediators. They nevertheless represent markers of these lifestyle factors rather than comprehensive assessments. Despite this, adjustment for these lifestyle markers almost completely explained cancer and "non-disease" excess mortality and explained 56% , 80% and 62% of the excess mortality for cardiovascular, respiratory and "other-disease", respectively.

Comparison with other studies and coherence of evidence

UK Biobank has provided results which are generally consistent with previously conducted studies. For cardiovascular mortality it has provided the largest estimate for excess mortality. It is the first study to suggest a relationship between CWP and excess mortality from respiratory disease.

The meta-analysis of Smith et al [10] conducted on this topic chose to extract the most fully-adjusted model available in included studies which means that this examines a subtly different question of whether pain directly increases mortality risk (independent of any lifestyle, psychosocial or clinical factors)[11]. We believe that the most clinically relevant question for clinicians managing patients with WP/CWP or fibromyalgia is what factors can be modified which could reduce any excess mortality which such patients experience. We also excluded one study included in the previous meta-analysis. The study of Macfarlane et al [13] was not eligible for this analysis as it examined the mortality consequences of multi-

[11] We note that the data included in the Smith et al [10] meta-analysis for the study of McBeth et al [3], do not correspond to the data in the original manuscript.

joint pain (at least 4 joints). There was no requirement for pain to be widespread. All included studies had some requirement for the pain to be widespread or for the participant to endorse that the pain was all over their body. Even if the study of Macfarlane et al [13], which did not find any excess mortality MRiR (0.86; 0.74,1.01), had been included in the meta-analysis, the combined estimate would still have suggested an important excess. Exclusion of a phenotype that excludes a measure of "widespreadness" is supported by a proposed modification to the 2011 research criteria for fibromyalgia which requires that multi-site pain is also widespread across the body [17]. The meta-analysis of Åsberg et al [18] concluded that "pooled data gave no evidence for a higher mortality rate among individuals with chronic widespread musculoskeletal complaints". This put emphasis on a pooled unadjusted MRR of 1.69 which was not statistically significant, and a markedly reduced excess (MRR 1.13) after full adjustment. The inclusion of UK Biobank, considering age- and sex- adjusted risks, has provided a similar pooled estimate of excess risk (MRR 1.59) and is now statistically significant.

We conclude that the evidence is now clear that persons with CWP experience excess mortality. UK Biobank results considerably reduce uncertainty around the magnitude excess risk, demonstrate that the risk is unlikely to be due to the experience of pain per se, but is substantially explained by lifestyle factors associated with having pain (poor diet, low levels of physical activity, smoking, high BMI). These provide important targets for intervention in managing patients with CWP. Optimal management of fibromyalgia should include exercise, but this is often not provided in a structured and supported way to facilitate long-term behaviour change. Few patients with CWP or fibromyalgia receive specific supported care in improving diet or stopping smoking. The data from this study shows that changing the habits of persons with CWP to be similar to persons without CWP could reduce mortality by around 35%. Such approaches should have high priority in the routine care of such patients.

Acknowledgements and Author Contribution

This manuscript uses the UK Biobank resource (Application 1144). We acknowledge the authors of a previous meta-analysis on this topic (Diane Smith, Ross Wilkie, Olalekan Uthman, Joanne L. Jordan, John McBeth) whose published search strategy we used as the basis for our meta-analysis, albeit that our meta-analysis had a more restricted focus and the criteria for determining eligibility and the data we extracted from eligible studies was not identical and resulted in selection of a different group of studies. We thank John McBeth (University of Manchester) for providing additional data relating to one of the studies, to

allow it be included in the meta-analysis. GJM had the idea for the study and together with GTJ designed the analysis plan for UK Biobank. GTJ undertook the UK Biobank analysis. MSB conducted the updated systematic review and all authors participated in undertaking the meta-analysis. GJM drafted the manuscript but all authors made an important intellectual contribution to the text.

Author Disclosures

None of the authors report a conflict of interest.

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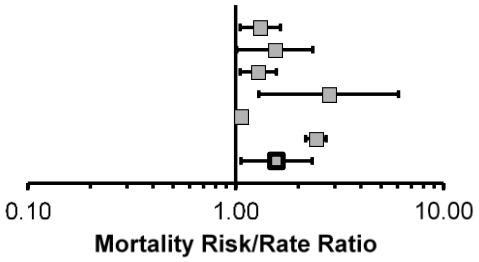
Figures

Figure 1: Forest plots of pain and all-cause and disease specific mortality

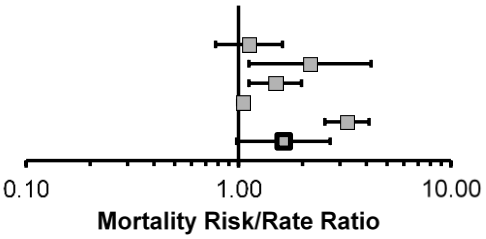
a) All-cause mortality

Study	MRR	Lower CI	Upper CI	Weight
Macfarlane et al, 2001	1.31	1.05	1.64	18%
Andersson, 2009	1.54	1.01	2.35	16%
McBeth et al, 2009	1.28	1.05	1.57	18%
Nitter and Forseth, 2012	2.80	1.29	6.07	11%
Åsberg et al, 2016	1.06	1.02	1.10	19%
Macfarlane et al, 2017	2.43	2.17	2.72	19%
Pooled	**1.57**	**1.06**	**2.33**	



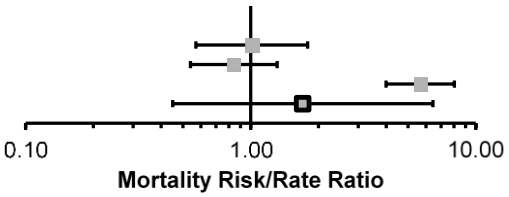
b) Cardiovascular mortality

Study	MRR	Lower CI	Upper CI	Weight
Macfarlane et al, 2001	1.12	0.78	1.61	20%
Andersson, 2009	2.17	1.12	4.21	16%
McBeth et al, 2009	1.49	1.12	1.98	21%
Åsberg et al, 2016	1.05	0.99	1.11	22%
Macfarlane et al, 2017	3.24	2.55	4.11	21%
Pooled	**1.63**	**0.98**	**2.70**	



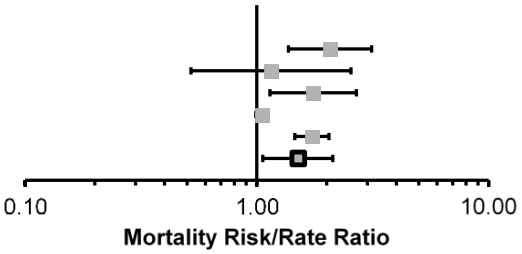
c) Respiratory mortality

Study	MRR	Lower CI	Upper CI	Weight
Macfarlane et al, 2001	1.01	0.57	1.79	33%
McBeth et al, 2009	0.84	0.54	1.31	33%
Macfarlane et al, 2017	5.66	3.99	8.02	34%
Pooled	**1.70**	**0.45**	**6.45**	



d) Cancer mortality

Study	MRR	Lower CI	Upper CI	Weight
Macfarlane et al, 2001	2.07	1.37	3.13	19%
Andersson, 2009	1.15	0.52	2.55	11%
McBeth et al, 2009	1.75	1.14	2.69	19%
Åsberg et al, 2016	1.05	0.99	1.11	26%
Macfarlane et al, 2017	1.73	1.46	2.05	25%
Pooled	**1.51**	**1.06**	**2.13**	



Tables

Table 1: Characteristics of persons with CWP and no chronic pain in UK Biobank study

Characteristic	CWP (n= 7,130)	No chronic pain (n=281,718)
Died during follow-up (n, %)	405 (5.7%)	6,493 (2.3%)
Died in first two years of follow-up (n,%)	95 (1.3%)	1,224 (0.4%)
Age (median years, IQR)	58 (50, 63)	58 (52, 63)
Sex (% male)	2,586 (36.3%)	135,186 (50.0%)
Body Mass Index (kgm^{-2})		
- underweight (< 18.5)	44 (0.6%)	1,609 (0.6%)
- normal (18.5-24.9)	1,354 (19.0%)	101,010 (35.9%)
- overweight (25.0-29.9)	2,572 (36.1%)	121,141 (43.0%)
- obese (30.0-34.9)	1,761 (24.7%)	43,088 (15.3%)
- obese (35.0-39.9)	799 (11.2%)	10,364 (3.7%)
- obese (≥ 40.0)	600 (8.4%)	4,506 (1.6%)
Physical Activity (mean mins/week; sd):		
- walking	350 (579)	363 (511)
- moderate activity	276 (543)	270 (444)
- vigorous activity	72 (275)	93 (192)
Physical Activity (climbing stairs per day)		
- None	1,223 (18.5%)	22,451 (8.1%)
- 1-5 times	2,158 (32.6%)	53,163 (19.1%)
- 6-10 times	1,795 (27.1%)	103,353 (37.2%)
- 11-15 times	720 (10.9%)	53,779 (19.4%)
- 16-20 times	378 (5.7%)	25,048 (9.0%)
- >20 times	346 (5.2%)	20,071 (7.2%)
Smoking status (n,%)		
- current smoker	1,316 (18.6%)	26,241 (9.3%)
- ex-regular smoker	1,779 (25.1%)	61,161 (21.8%)
- ex-occasional smoker	627 (8.9%)	32,581 (11.6%)
- never or v. rarely	3,360 (47.4%)	160,839 (57.3%)
Diet: fruit and vegetable consumption (median portions/day, IQR)	8 (5, 11)	7 (5, 10)
Alcohol consumption (n, %)		
- daily or almost daily	767 (10.8%)	60,829 (21.6%)
- 3-4 times/week	842 (11.8%)	69,667 (24.7%)
- 1-2 times/week	1,485 (20.9%)	74,096 (26.3%)
- < 1 time/week	2,407 (33.8%)	58,139 (20.7%)
- Never	1,616 (22.7%)	18,789 (6.7%)

Table 2: Relationship between demographic and lifestyle factors and risk of death

Characteristic	Status at end of follow-up		Restricted model: Mortality Risk Ratio (95% CI)[12]	Multivariable model: Mortality Risk Ratio (95% CI)[13]
	Alive (n)	Dead (n)[14]		
Pain status				
- CWP	6,725	310	2.43 (2.17, 2.72)	1.47 (1.24, 1.73)
- no chronic pain	275,225	5,269	Reference	Reference
Age group (years)				
- <45	31,373	189	Reference	Reference
- 45-49	38,228	353	1.60 (1.37, 1.87)	1.60 (1.25, 2.07)
- 50-54	43,174	590	2.50 (2.17, 2.89)	2.46 (1.95, 3.11)
- 55-59	51,083	1,021	3.80 (3.32, 4.36)	3.61 (2.90, 4.51)
- 60-64	67,884	2,078	5.61 (4.92, 6.39)	5.59 (4.51, 6.92)
- >64	50,538	2,667	9.09 (7.98, 10.4)	8.91 (7.20, 11.0)
Sex				
- Male	133,453	4,319	Reference	Reference
- Female	148,497	2,579	0.58 (0.56, 0.60)	0.59 (0.55, 0.63)
Body Mass Index (kgm^{-2})				
- underweight (< 18.5)	1,569	84	1.86 (1.40, 2.50)	2.73 (2.07, 3.60)
- normal (18.5-24.9)	100,295	2,069	Reference	Reference
- overweight (25.0-29.9)	120,888	2,825	1.70 (1.59, 1.82)	0.93 (0.86, 1.01)
- obese (30.0-34.9)	43,579	1,270	3.20 (2.98, 3.43)	1.11 (1.01, 1.22)
- obese (35.0-39.9)	10,784	379	5.54 (5.08, 6.03)	1.35 (1.16, 1.58)
- obese (≥ 40.0)	4,835	271	9.02 (8.23, 9.89)	1.94 (1.59, 2.36)
Physical Activity: walking (mins/week)				
- 0	5,150	225	4.15 (3.77, 4.57)	1.19 (0.99, 1.43)
- 1-100	63,711	1,547	Reference	Reference
- 101-210	74,315	1,778	0.73 (0.68, 0.79)	0.98 (0.90, 1.07)
- 211-420	58,945	1,312	0.64 (0.59, 0.69)	0.92 (0.83, 1.01)
- >420	46,710	1,017	0.85 (0.79, 0.92)	0.89 (0.79, 0.99)
Physical activity: moderate (mins/week)				
- 0	32,562	1,127	2.95 (2.74, 3.19)	1.14 (1.02, 1.27)
- 1-60	60,247	1,221	Reference	Reference
- 61-150	51,037	1,086	0.91 (0.83, 0.99)	0.99 (0.90, 1.10)
- 151-360	51,640	1,086	0.87 (0.79, 0.95)	0.98 (0.88, 1.10)
- >360	49,171	1,229	1.30 (1.20, 1.42)	1.09 (0.97, 1.22)

[12] Adjusted for age and/or sex as applicable and excluding first two years of follow-up

[13] All variables entered in to the statistical model and mutually adjusted

[14] Deaths within two years of the baseline assessment are excluded

Physical activity: vigorous (mins/week)				
- 0	94,509	3,068	Reference	Reference
- 1-40	45,581	915	0.37 (0.34, 0.40)	0.77 (0.69, 0.85)
- 41-90	40,814	729	0.30 (0.28, 0.33)	0.78 (0.70, 0.87)
- 91-180	39,355	678	0.27 (0.24, 0.30)	0.76 (0.68, 0.85)
- >180	33,648	645	0.43 (0.39, 0.47)	0.79 (0.70, 0.89)
Physical activity: stairs (times/day)				
- 0	22,789	885	1.29 (1.20, 1.38)	1.02 (0.91, 1.14)
- 1-5	53,707	1,614	Reference	Reference
- 6-10	102,928	2,220	0.43 (0.41, 0.46)	0.83 (0.76, 0.91)
- 11-15	53,420	1,079	0.33 (0.30,0.36)	0.86 (0.77, 0.95)
- 16-20	24,986	440	0.37 (0.33, 0.41)	0.69 (0.60, 0.80)
- >20	20,011	406	0.42 (0.38, 0.47)	0.92 (0.80, 1.07)
Smoking status				
- current smoker	26,309	1,248	2.54 (2.39, 2.70)	2.31 (2.10, 2.54)
- ex-regular smoker	60,770	2,170	1.44 (1.36, 1.52)	1.55 (1.43, 1.67)
- ex-occasional smoker	32,532	676	0.92 (0.85, 1.003)	1.09 (0.97, 1.22)
- never or v. rarely	161,432	2,767	Reference	Reference
Alcohol consumption				
- daily or almost daily	59,954	1,642	Reference	Reference
- 3-4 times/week	69,132	1,377	0.96 (0.87, 1.06)	0.92 (0.84, 1.02)
- 1-2 times/week	73,949	1,632	1.57 (1.44, 1.72)	0.97 (0.88, 1.07)
- <1 time/week	59,073	1,473	3.08 (2.84, 3.34)	1.08 (0.98, 1.20)
- Never	19,639	766	6.18 (5.68, 6.73)	1.49 (1.32, 1.69))
Diet: fruit and vegetable consumption				
- Lowest consumption	62,641	1,802	Reference	Reference
- Quintile 2	58,079	1,363	0.74 (0.69, 0.80)	0.90 (0.82, 0.98)
- Quintile 3	25,448	569	0.78 (0.71, 0.86)	0.88 (0.78, 0.99)
- Quintile 4	50,750	1,156	0.75 (0.69, 0.80)	0.88 (0.80, 0.97)
- Highest consumption	40,733	881	1.01 (0.94, 1.09)	0.86 (0.77, 0.95)

Table 3: Relationship between pain status and risk of death, adjusting for potential mediating variables

Variables added to basic model[15]	**Participants[16] included in model (N)**	**MRR[17] (95% CI): CWP v. no chronic pain**	**MRR (95% CI) CWP v. no chronic pain (participants with full data)[18]**
No additional variables	287,529	2.43 (2.17, 2.72)	2.23 (1.90, 2.62)
+ Body Mass Index category[19]	287,529	2.13 (1.90, 2.39)	1.98 (1.68, 2.33)
+ Physical activity: walking	253,579	2.09 (1.82, 2.40)	2.08 (1.76, 2.44)
+ Physical activity: moderate	249,309	2.23 (1.96, 2.54)	2.06 (1.75, 2.42)
+ Physical activity: vigorous	258,755	2.22 (1.97, 2.51)	2.01 (1.71, 2.36)
+ Physical activity: stairs	283,221	2.12 (1.88, 2.38)	2.07 (1.76, 2.43)
+ Smoking	286,590	2.16 (1.94, 2.42)	2.01 (1.71, 2.37)
+ Diet: alcohol consumption	287,320	2.21 (1.97, 2.47)	2.05 (1.74, 2.41)
+ Diet: fruit and vegetables	242,346	2.30 (2.02, 2.60)	2.21 (1.88, 2.60)
Full multivariable model[20]	193,676	1.47 (1.24, 1.73)	1.47 (1.24, 1.73)

[15] Pain status (chronic widespread pain v. no chronic pain), age and sex are entered in all models
[16] Deaths occurring within two years of the baseline assessment are excluded
[17] Mortality Risk Ratio
[18] Restricted to 193,676 participants with data on all variables included in the full model
[19] Each line represents the basic model with the addition of the single variable stated
[20] All additional variables entered into model: age, sex, body mass index, physical activity (walking, moderate and vigorous activities, climbing stairs), diet (fruit and vegetable, alcohol consumption), smoking status

Table 4: Studies eligible for meta-analysis of chronic widespread pain and mortality

Study (Location)	Sampling Frame	Pain phenotype	Pain phenotype prevalence	Deaths (n)/ Study (n)	Follow-up (years)
Andersson, 2009 (Sweden)	Random sample in 2 municipalities	>4 pain locations representing both the upper and lower body and including axial pain	9.4%	189/1609	14
Åsberg et al, 2016 (Norway)	All inhabitants of one county	CWP modified[21] definition in ACR 1990 criteria of FM	23.1%	12521/65026	14
Macfarlane et al, 2001 (UK)	Persons registered with GP in 2 areas	Widespread pain according to definition in ACR 1990 criteria of FM	15.3%	654/6569	8
Macfarlane et al, 2017[22] (UK)	Persons aged 40-69 registered with GP in 22 areas	"Pain all over the body" lasting ≥3 months	1.4%	12799/288848	7
McBeth et al, 2009 (UK)	Age- and sex-stratified sample from 3 GPs in one region	Widespread pain definition in ACR 1990 criteria of FM	16.9%	1017/4344	8
Nitter and Forseth, 2013 (Norway)	Women born 1940-69 in one town	Pain in muscles and joints and back, or pain in whole body, lasting ≥3 months	12.9%	89/2038	18

[21] There was no requirement to have pain on both sides of the body
[22] Current analysis

Chapter 2.4

The epidemiology of regular opioid use and its association with mortality: prospective cohort study of 466 486 UK Biobank participants

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Abstract

Background: Opioids have, at most, small benefits for non-cancer pain in the medium and long-term but there is good evidence that they cause harm. The current study describes the characteristics and clinical status of people taking regular opioids in Great Britain and determines whether use is associated with mortality risk.

Methods; An analysis of participants in UK Biobank, a prospective population-based study. At recruitment (2006-10) participants reported medicines which they regularly used in addition to lifestyle and health-related factors. Information was available on deaths until October 2016.

Findings: There were 466 486 participants (54% women) aged 40-69 years and without a prior history of cancer of whom 5.5% were regularly using opioids. Use increased with age-group, was more common in females (6.3% v. 4.6%) and 87% of persons using them reported chronic pain. The highest rates of use (~1 in 9) were in people with low household income, who left school <16 years and lived in areas with high deprivation. Amongst 15032 people who could not work because of ill-health, 1 in 3 were regularly taking opioids. Regular users reported insomnia (88.7%), a recent major recent life event (57.3%) and were much more likely than non-users to rate their health as poor (RR 5.5, 99% CI (4.9, 6.1)). Those taking weak (4.2% of participants) or strong (1.4%) opioids were more likely to die during follow-up (6.9% and 9.1% respectively v. 3.3% in non-users) an excess which remained after adjustment for demographic, socio-economic, health and lifestyle factors (MRR 1.18 99% CI (1.06, 1.32) and 1.20 99% CI (1.01, 1.43)) respectively.

Interpretation: Regular use of opioids is common in Great Britain, particularly in groups of low socio-economic status. Most users still report chronic pain, poor health generally and are at increased risk of premature death although it is not established that this relationship is causal.

Introduction

Chronic pain is an important public health problem – around 2 in 10 of the general population sample reported persistent and intense pain in one pan-European study (1) while a meta-analysis of epidemiological studies conducted world-wide found that 3 in 10 persons had chronic pain (2). The aetiology of chronic pain is multifactorial and complex, with onset of pain often in early adulthood. Long-term prospective studies demonstrate an increased risk related to adverse social environment in early life, as well as physically and emotionally traumatic events (3-6). A review of factors which predict an episode of pain becoming chronic, and causing long-term disability, found the strongest evidence in relation to clinical factors (disabling, persistent and multi-site pain), older age, and mood (7). A consequence of chronic pain is an increased risk of death (8). Data from UK Biobank has shown, specifically, that persons with chronic widespread pain (CWP) have a markedly increased risk of dying during follow-up (mortality risk ratio (MRR) 2.43, 99%CI 2.17 to 2.72), an excess risk that was partly explained by low levels of physical activity, high body mass index, poor quality diet and tobacco smoking (9).

In managing chronic pain, although there will be differences in relation to specific diagnoses, both non-pharmacologic and pharmacologic approaches are generally important. Supported self-management is a cornerstone of common pain conditions from early in the course of symptoms through to long-term management. Non-pharmacologic approaches include physical activity, physical, behavioural and relaxation therapies and for conditions such as low back pain, pain and fibromyalgia, these will be the primary approaches to management (10,11). A wide range of analgesics have been used in the management of chronic pain – however a key recommendation from guidelines of management is regular review and stopping medications which are not effective (12).

The World Health Organisation (WHO) analgesic ladder has provided a framework for the use of analgesics in patients with cancer pain (13). The approach recommends that analgesics used should initially be non-opioids, and then opioids, with the expectation that the strength and dose of opioids would increase as cancer progressed. Success in the use of this approach in cancer patients at the end-of-life has led to the same approach being used for patients with chronic non-cancer pain. The idea that increasing pain intensity necessitates stronger medicines in higher doses may hold well for cancer pain where disease burden is progressing. Using this approach more generally, for non-cancer pain, has had the consequence of a dramatic increase in the use of prescription opioids, most obviously in the

United States (14). It has also made evident the negative consequences of such widespread use. Reported pain intensity in chronic non-cancer pain has little to do with tissue damage and escalation of potent medicines is not justified (15). There is good evidence of an increased risk for serious harm (Including overdose, opioid misuse, fractures, myocardial infarction, and markers of sexual dysfunction) At most they are likely to have only small benefits (in terms of pain, function and quality of life) in the medium and long-term (16) - indeed a recent meta-analysis assessed their benefits as similar to non-opioid analgesics in the management of non-cancer chronic pain, although the evidence came primarily from low quality studies (16,17).

The purpose of this analysis is therefore to describe the epidemiology of opioid use in Great Britain, the health and quality of life of people using them and to examine whether their use is associated with excess mortality.

Methods

This study report adheres to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (18).

UK Biobank recruited around half a million persons aged 40-69 years who were registered with a general practitioner within the National Health Service (NHS) (see reference 19 for detailed methods). Approximately 9.2 million invitations were issued, between 2006-10, to people living within 25 miles of one of 22 assessment centres across Great Britain. At the assessment centre, participants responded to questions, including on demography, social, health and lifestyle factors, by using a touchscreen. Indices of multiple deprivation (at the small area level) were used for England, Scotland and Wales to determine the quintile of deprivation of their residential area (within the country of residence).

Pain and medications

In terms of pain, participants were asked “In the last month have you experienced any of the following that interfered with your usual activities?” If they answered positively, they were then provided with a list which included seven individual regional pain sites, or alternatively they could choose the response “pain all over the body”. Respondents were asked whether the reported pain had lasted at least three months and those who reported this for at least one site (or pain all over the body) were categorised as having “chronic pain”. Participants were asked if they were taking regular prescription medication and if

so, in a nurse-led interview, were then asked what these were. Information was collected on regular treatments. It did not include short-term medications (such as a course of antibiotics) or prescribed medication that had not been taken. Interviewers chose the generic or trade name of the treatment from a list. Information on dose and formulation was not collected. For this analysis, the full list of treatments was searched for generic or trade names of opioids, including drugs listed in sub-paragraphs 4.7.1 (Non-Opioid Analgesics and Compound Preparations) and 4.7.2 (Opioid Analgesics) of the British National Formulary (BNF: https://www.bnf.org/products/bnf-online). Those that were not commonly prescribed for pain or did not appear in the BNF sub-paragraphs 4.7.1 and 4.7.2 were not coded as opioids. Treatments that contained an opioid listed in sub-paragraph 4.7.1 were classed as 'Combination' opioids. Other opioids were classed according to their chemical class (i.e. Codeine, Dihydrocodeine, etc.). Participants who took any opioid in the Tramadol, Morphine, Buprenorphine, Oxycodone, Fentanyl, or Hydromorphine categories were classed as taking a strong opioid.

Vital status and causes of death

For the purposes of collecting information on vital status, participants were identified on the Office for National Statistics (ONS) records. ONS collects information on cause of death from civil registration records. For registered deaths, the underlying cause of death is derived from the sequence of conditions leading directly to the death and is recorded on the death certificate. The analysis uses the UK Biobank dataset provided to us in April 2019, which contains death information up to 31 October 2016.

Statistical Analysis

Descriptive analyses are reported for the use of prescription opioids by demography and social factors and in relation to pain status. In all analyses, persons who reported a previous diagnosis of cancer (other than non-melanoma skin cancer) were removed, as opioids may have been prescribed because of cancer pain in such persons. Relationships with use are described using modified Poisson regression with robust error variances (20) and are expressed as crude risk ratios (RR) and adjusted for (as indicated in specific models) age, gender, ethnicity, region, primary employment status, university degree, deprivation, income and pain status, namely, the number of body sites in which pain was reported or pain all over the body and whether pain had lasted more than three months (i.e. chronic pain).

In examining the relationship between opioid use and subsequent mortality, the proportion of persons who died during follow-up according to their regular use of opioids at the time of recruitment, is described. Poisson regression models, with robust estimation of standard errors were used to quantify the relationship expressed as Mortality Risk Ratios (MRR) with adjustment for pain status, socio-economic factors, and lifestyle factors shown previously to be potential mediators of the relationship between chronic pain and mortality.

Role of the funding source

There were no external sources of funding for the conduct of this analysis.

Results

There were 466486 persons who were recruited to UK Biobank who did not report a prior diagnosis of cancer (other than non-melanoma skin cancer) and these were eligible for the current analysis. Of these, 25864 reported regular use of opioid medication, which represents 5.5% of participants. There were striking associations with socio-demographic factors and use of such medications (see Table 1). Use increased with age-group and was more common in females than males (6.3% v. 4.6% adjusted for demographic, employment status, education level and economic factors RR 1.43(1.39-1.48)). There was little variation by ethnic group except that use of opioids was uncommon amongst persons of Chinese origin (1.7% adjusted RR 0.45 99% CI (0.27-0.74) in comparison to persons identifying as “white”). There were marked differences between areas of residence, from 2.8% in South-East England to 7.6% in the North-East of England (adjusted RR 1.75 99% CI (1.61-1.91)). The highest rates of reported use were found in persons with low household income (11.1% in those reporting annual household income of £18000), those who left school before 16 years (10.6%) and who lived in areas with the highest levels of deprivation (9.2%). Amongst the 15032 people who reported that they could not work because of ill-health 33.7% were regularly taking opioids. A total of 6419 persons (1.3%) reported regular use of strong opioids. Use of strong opioids also showed a strong relationship with area of residence, high levels of deprivation, low income and not working due to ill-health (supplementary table).

The most common opioid reported was combined preparations, and thereafter codeine and dihydrocodeine. The most common strong opioids were tramadol then morphine and buprenorphine (Table 2). Of persons reporting taking regular opioids, 23731 (5.1%) reported using a single opioid, 1976 (0.4%) were taking two opioids and 157 (0.03%) were taking 3 or more.

The vast majority (87.3%) of persons regularly taking opioids reported chronic pain: the likelihood of taking opioids increased with greater number of reported pain sites from 3.8% in those reporting one site up to 30.7% in those who reported 7 sites or "pain all over the body" RR (16.66 99% CI (15.42-17.99)) adjusted for age, gender, demographic factors, socio-economic factors and primary employment (Table 3). When the relationship was examined by the reporting of pain at individual sites, with adjustment as above plus total number of pain sites reported, all individual pain sites, with the exception of facial pain, were associated with an excess risk of regular opioid use (data not shown). The associations shown in Table 1 were not explained when adjusted for pain status (chronic pain and number of pain sites) although some were attenuated, most noticeably female gender (RR 1.23 95% CI (1.19-1.26)) and amongst those living in areas with the highest level of deprivation (RR 1.50 95% CI (1.42-1.58)).

The relationship of opioid use with health, lifestyle factors and life events is detailed in Table 4. After adjustment for potential confounding factors, persons rating their health as "poor" were considerably more likely to regularly take opioids compared to those rating their health as "excellent" (RR 5.44 99% CI (4.89-6.05) as were those reporting only minimal physical activity. Those reporting poor quality sleep (both less and more than the average of 7-8 hours, as well as usually suffering from insomnia (RR 1.56 99% CI (1.48-1.64)) and poorer mental health (i.e. reported having consulted a GP for "anxiety, nerves or depression" (RR 1.29 99% CI (1.25-1.34)) were also more likely to report regular opioid use. There was a "dose-risk" relationship between the number of adverse events in last two years and likelihood of using opioids such that those reporting at least four such events were over 50% more likely to be taking opioids regularly (RR 1.55 99% CI (1.36-1.76)).

The relationship between opioid consumption and mortality

16432 persons died during follow-up. Of participants who at recruitment were not regularly taking opioids, 3.3% died during follow-up (428 per 100 000 person-years (py)); in comparison 6.9% of those taking weak opioids (892 per 100 000 py) and 9.1% of those taking strong opioids died (1194 per 100 000py) (age and sex adjusted Mortality Risk Ratio (MRR) 1.86, 99% CI (1.73, 2.00) and 2.59 99% CI (2.34, 2.88) respectively) (Table 5). Chronic pain was also related to excess mortality; for example, of persons who at recruitment reported "pain all over their body" or pain at all seven regional sites 6.8% died during follow-up in comparison to 3.2% of persons with no pain (MRR 2.29, 99% CI 2.06, 2.56). In addition lifestyle factors (physical activity, BMI, diet (including alcohol consumption and cigarette

smoking), socio-economic factors (years of education, income and level of deprivation of area of residence) and morbidities were also importantly linked with risk of mortality. When adjustment was made for all these factors, there remained an association between regular opioid use at recruitment and risk of death over the following 6-10 years (MRR weak opioids 1.18 99% CI (1.06, 1.33)), strong opioids (MRR 1.20 99% CI (1.01, 1.43)). Of the deaths which occurred amongst persons using regular opioids 39% were cancer deaths (in comparison to 53% in non-opioid users) , 28% were cardiovascular (v. 23%), 11% were respiratory (v. 6%), 18% were other diseases (v. 13%) and 3% were from external causes (v. 4%).

Discussion

Regular use of opioids in UK Biobank participants was very strongly related to socio-economic factors: around 1 in 10 people with the lowest level of incomes, those living areas with the highest levels of deprivation and who left education at a young age, reported regular opioid use, while this rose to 1 in 3 of persons reporting that they were unable to work due to ill-health. After adjusting for pain status and socio-economic factors, regularly taking opioids was associated with poorer physical and mental health and quality of life (such as sleep quality) and was associated with increased risk of death, even after additionally taking into account lifestyle factors and other morbidities. The increased risk of death was not primarily as a result of non-disease deaths.

UK Biobank is a very large study, but the proportion of people invited who agreed to take part was low (just over 5%). There is evidence that those taking part are healthier than the general population: specifically they are less likely to be obese, to smoke, and to drink alcohol on a daily basis and they have fewer self-reported health conditions. Rates of all-cause mortality have been shown at age 70-74 years to be 46% and 56% lower in men and women, respectively than the wider population (21). The valid assessment, however, of an exposure outcome relationship does not rely on a population being representative of the underlying population aged 40-69 years who were eligible to take part. Thus our estimate of the use of opioids in Great Britain, although high, is likely to be an underestimate. We have previously compared the prevalence of chronic pain in UK Biobank with other epidemiological studies which measured chronic pain, and shown, for example, that the estimates of prevalence of chronic pain and regional pain using UK Biobank were within 2% of the National Child Development Study (22). The second methodological issue in examining factors associated with the use of opioids is the strong relationship with their use in chronic pain. We do not think that regular opioid use is a cause of chronic pain and so we

have adjusted for the presence of chronic pain and the number of pain sites. However, we do not have a measure of the severity of chronic pain and therefore there may be residual confounding e.g. if more severe pain was linked to greater interference with sleep and a greater likelihood of opioid use. There is also limited information on opioids in this study. We are not aware of the dose of opioids or for how long they have been used at the time of recruitment, nor of changes over follow-up; neither is information available on non-prescription ("over the counter") opioid use. Thus, for example, we cannot examine whether the relationship with poor physical and mental health, for example, is related to dose.

The factors associated with regular opioid use in this study (after adjustment for pain status) namely depression, anxiety and insomnia are recognised adverse effects of opioid use (23). The results do not necessarily mean that opioids themselves are leading to an increased risk of death. There could be unmeasured confounders of the relationship – if so, these factors need to be relatively common, be related to opioid use and be risk factors for premature death. Specifically, there could be confounding by indication, namely that persons are receiving opioids for unmeasured aspects of their clinical condition which are themselves related to an increased risk of death. Such a scenario may explain some or all of the association observed. The association of opioid use and misuse with premature death is well-documented, although that typically has been related to non-disease related deaths (e.g.24). Non-disease related deaths were relatively uncommon in this analysis and not responsible for the excess mortality. Long term opioid use has been shown to relate to an increased risk of death by a number of potential mechanisms including the very common finding of disruption of nocturnal respiratory control leading to both respiratory and cardiovascular morbidity (25,26). Studies of opioids and cancer have primarily focussed on the use of opioids during cancer surgery and subsequent survival. Two studies have reported a higher recurrence rate of breast and prostate cancers (27,28) although the only study of opioid use after surgery found no increased risk of recurrence in breast cancer patients (29). A recent study of approximately 90 000 persons, using electronic records within UK general practice, has however linked the initial prescription of tramadol, in patients over 50 years with osteoarthritis, to higher mortality rates over the subsequent year (hazard ratio 1.71 95% CI (1.41,2.07) v. patients receiving nonsteroidal anti-inflammatory drugs) (30).

We have previously published data from Scotland, using record linkage, which demonstrated a sizeable increase in the prescriptions for opioids across the ten-year period from 2003 (31). This study showed that 18% of the population in Scotland had been prescribed an opioid

in the past year, much higher than the proportion reported in the current study (6.5% persons from Scotland reported regular opioid use). There are likely to be at least three reasons for the discrepancy: the current study is based on "regular use of medication" while the previous study was based on a record of at least one prescription; the selection effects in participating; and that we have excluded persons with a cancer diagnosis in this analysis. The large variations in regular use of opioids across GB in this study, replicate a recent study from England (32) which found that high prescribing was related to deprivation, large primary care list size and rurality. A further study, from one area of Scotland, which analysed prescribing of analgesics between 1995-2010 also found that persons living in deprived areas (as well as those receiving large numbers of non- analgesic drugs) were most likely to be prescribed a strong opioid (33).

It is no surprise that users of opioids are likely to report chronic pain: we assume this is the reason for opioid use. However the data show high levels of continuing poor health among those using opioids including inability to work, poor physical and mental health, quality of life and poor sleep These findings accord with previous findings from a large epidemiological study in Denmark which noted that "*opioid treatment of long-term/chronic non-cancer pain does not seem to fulfil any of the key outcome opioid treatment goals*". (34)

Much evidence on the so-called "opioid epidemic" has come from the United States where the Center for Disease Control (CDC) has developed a guideline to improve the way opioids are prescribed to "ensure patients have access to safer, more effective chronic pain treatment while reducing the number of people who misuse or overdose from these drugs" (35) and the Scottish Intercollegiate Guidelines Network (SIGN) have recently revised their guideline on managing chronic pain in order to update recommendations on opioids (12) . The latter suggest early review of patients newly prescribed opioid medication and at least annual review thereafter. This manuscript has demonstrated high levels of regular opioid use amongst people in the United Kingdom, particularly those in lower socio-economic groups. Amongst users, chronic pain is still common, and a large proportion report poor physical and mental health, while the majority report sleep problems. This study adds to current evidence in showing that regular users also experience an increased risk of death (but not primarily as a result of non-disease deaths). It emphasises the need to take into account such potential harms and lack of benefit of regular opioid use in considering the long-term management of patients with pain.

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This work did not receive any external sources of funding. Data was supplied by UK Biobank under the terms of application reference number 1144CS and GJM had the idea for the study which was planned by all authors. MB and GTJ undertook the analysis. GJM led the drafting of the manuscript to which all authors contributed and all critically reviewed drafts and revisions. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. GJM, GTJ and MB had access to all the data in the study and all authors made the decision to submit.

Author Disclosures

The authors have no relevant interests to declare.

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Tables

Table 1 – Regular use of any opioid analgesics by social and demographic factors

		Opioid Use No: n (%)	Opioid Use Yes: n (%)	Adjusted RR[23][24] (99% CI)
Age (years)	*40-45*	48522 (96.6)	1705 (3.4)	1 [Ref]
	45-49	61043 (96.1)	2462 (3.9)	1.08 (1.00-1.17)
	50-54	68858 (95.4)	3357 (4.7)	1.15 (1.07-1.24)
	55-59	79942 (94.4)	4739 (5.6)	1.16 (1.08-1.24)
	60-64	103711 (93.7)	7020 (6.3)	1.17 (1.08-1.26)
	65-70	78546 (92.3)	6581 (7.7)	1.31 (1.20-1.42)
Gender	*Male*	206841 (95.4)	10057 (4.6)	1 [Ref]
	Female	233781 (93.7)	15807 (6.3)	1.43 (1.39-1.48)
Ethnicity	*White*	413507 (94.4)	24380 (5.6)	1 [Ref]
	Mixed	2632 (94.4)	155 (5.6)	1.07 (0.88-1.30)
	Asian or Asian British	9135 (95.3)	452 (4.7)	1.01 (0.89-1.13)
	Black or Black British	7275 (94.2)	448 (5.8)	1.17 (1.04-1.31)
	Chinese	1485 (98.3)	25 (1.7)	0.45 (0.27-0.74)
	Other ethnicity	4111 (94.3)	246 (5.7)	1.19 (1.01-1.39)
	Not known	2477 (94.0)	158 (6.0)	1.12 (0.92-1.37)
Area of residence	*South East England*	39283 (92.2)	1149 (2.8)	1 [Ref]
	London	61745 (96.9)	1975 (3.1)	0.83 (0.76-0.91)
	South West England	38136 (95.5)	1803 (4.5)	1.38 (1.25-1.51)
	East Midlands	29809 (94.8)	1634 (5.2)	1.30 (1.18-1.43)
	Yorkshire and Humberside	65101 (94.1)	4056 (5.9)	1.46 (1.34-1.58)
	West Midlands	39129 (93.9)	2564 (6.1)	1.43 (1.31-1.57)
	Scotland	31321 (93.5)	2178 (6.5)	1.55 (1.42-1.70)
	North West England	68346 (93.2)	4973 (6.8)	1.51 (1.39-1.64)
	Wales	17784 (92.7)	1407 (7.3)	1.81 (1.64-2.00)
	North East England	49968 (92.4)	4125 (7.6)	1.68 (1.55-1.83)
Age completed full time education (years)	*<16*	84320 (89.4)	10033 (10.6)	1.24 (1.19-1.29)
	16	92270 (93.9)	6041 (6.1)	1 [Ref]
	17	33972 (95.1)	1741 (4.9)	0.90 (0.84-0.96)
	18	35749 (96.1)	1440 (3.9)	0.81 (0.75-0.87)
	>18	38710 (96.0)	1619 (4.0)	0.80 (0.75-0.86)
	Not known	155601 (96.9)	4990 (3.1)	0.71 (0.68-0.75)
Deprivation	*Lowest quintile*	90127 (96.4)	3353 (3.6)	1 [Ref]
	2	88996 (95.8)	3899 (4.2)	1.10 (1.04-1.16)
	3	88556 (95.1)	4563 (4.9)	1.22 (1.16-1.29)
	4	87765 (94.2)	5420 (5.8)	1.41 (1.34-1.49)
	Highest quintile	84634 (90.8)	8597 (9.2)	1.75 (1.65-1.84)
	Not known	544 (94.4)	32 (95.6)	1.45 (0.93-2.25)
Average Household Income (£)	*Less than 18000*	78618 (88.9)	9820 (11.1)	1 [Ref]
	18000 to 30999	94514 (94.7)	5322 (5.3)	0.81 (0.78-0.85)
	31000 to 51999	100399 (96.7)	3447 (3.3)	0.69 (0.66-0.73)
	52000 to 100000	80166 (98.0)	1616 (2.0)	0.53 (0.49-0.57)

[23] Risk Ratio

[24] Adjusted for age, gender, ethnicity, region, age completed education, primary employment status, deprivation, and income

	>100000	21481 (98.9)	240 (1.1)	0.34 (0.29-0.40)
	Not known	65444 (92.4)	5419 (7.6)	0.89 (0.85-0.93)
Primary Employment	*Employed*	264171 (97.1)	7952 (2.9)	1 [Ref]
	Retired	138296 (92.4)	11346 (7.6)	1.76 (1.67-1.85)
	Looking after home	12331 (94.9)	666 (5.1)	1.43 (1.29-1.58)
	Not working due to health	9963 (66.3)	5069 (33.7)	6.62 (6.30-6.94)
	Unemployed	7475 (95.1)	383 (4.9)	1.23 (1.07-1.40)
	Unpaid work	2053 (95.5)	97 (4.5)	1.33 (1.03-1.72)
	Student	1241 (96.2)	49 (3.8)	1.11 (0.77-1.60)
	Not known	5092 (94.4)	302 (5.6)	1.53 (1.31-1.78)

Table 2 Specific opioids reported by participants as being taking regularly?

Opioid drug/preparation[25]	**N**	**%**
Weak Opioids		
Combined[26]	17065	3.7
Codeine	2304	0.5
Dihydrocodeine	1617	0.4
Meptazinol	67	0.0
Pethidine	24	0.0
Dextropropoxyphene	1	0.0
Strong Opioids		
Tramadol	5346	1.2
Morphine	508	0.1
Buprenorphine	349	0.1
Oxycodone	220	0.0
Fentanyl	233	0.0
Hydromorphone	7	0.0

[26] Combined = preparations listed in the BNF Sub-paragraph 'Non-Opioid Analgesics and Compound Prep', e.g. co-codamol, co-codaprin, etc.

Table 3 – Regular use of opioid analgesics in relation to pain reporting

		Opioid Use No, n (%)	**Opioid Use Yes, n (%)**	**Adjusted RR[27] [28] (99% CI)**
Chronic pain	*No*	259318 (98.8)	3271 (1.2)	1 [Reference]
	Yes	179367 (88.9)	22460 (11.1)	6.69 (6.38-7.02)
Number of pain sites	*0*	181619 (99.0)	1797 (1.0)	1 [Reference}
	1	123042 (96.2)	4925 (3.8)	3.72 (3.47-4.00)
	2	71910 (92.9)	5468 (7.1)	6.27 (5.85-6.72)
	3	35369 (87.1)	5225 (12.9)	10.14 (9.46-10.87)
	4	14521 (81.0)	3396 (19.0)	13.32 (12.38-14.33)
	5	5044 (74.3)	1748 (25.7)	15.84 (14.59-17.20)
	6	1387 (69.7)	604 (30.3)	17.60 (15.81-19.60)
	7 or all over	5793 (69.3)	2568 (30.7)	16.66 (15.42-17.99)

Table 4 Regular use of any opioid analgesic in relation to health status

[27] Risk Ratio

[28] Adjusted for age, gender, ethnicity, region, primary employment, age completed education, deprivation, and income

		Opioid Use No, n (%)	Opioid Use Yes, n (%)	Adjusted RR[29]
Hours of sleep	*4 or less*	4010 (77.5)	1163 (22.5)	1.55 (1.45-1.67)
	5 or 6	101161 (92.7)	8024 (7.4)	1.23 (1.19-1.27)
	7 or 8	300512 (95.9)	12923 (4.1)	1 [Reference]
	9 or 10	30068 (91.5)	2794 (8.5)	1.21 (1.16-1.28)
	11 or more	1492 (77.7)	428 (22.3)	1.41 (1.27-1.57)
Insomnia	*Never/rarely*	110911 (97.4)	2926 (2.6)	1 [Reference]
	Sometimes	212122 (95.5)	10105 (4.5)	1.21 (1.15-1.27)
	Usually	116227 (90.1)	12749 (9.9)	1.56 (1.48-1.64)
Overall activity	*Minimal*	84354 (91.9)	7407 (8.1)	1 [Reference]
	Low	74214 (95.7)	3368 (4.3)	0.74 (0.70-0.77)
	Adequate	120525 (95.3)	5929 (4.7)	0.74 (0.71-0.77)
	High	125585 (96.3)	4803 (3.7)	0.67 (0.64-0.70)
Overall health rating	*Excellent*	77541 (99.1)	732 (0.9)	1 [Reference]
	Good	261428 (96.9)	8327 (3.1)	1.98 (1.80-2.19)
	Fair	84888 (88.9)	10598 (11.1)	3.92 (3.54-4.33)
	Poor	13908 (70.2)	5908 (29.8)	5.44 (4.89-6.05)
Seen doctor for anxiety/ nerves/depression	*No*	293787 (96.1)	11907 (3.9)	1 [Reference]
	Yes	142478 (91.3)	13598 (8.7)	1.29 (1.25-1.34)
Adverse events in last 2 years (illness, injury, assault, bereavement, divorce, financial difficulty)	*0*	245686 (95.8)	10801 (4.2)	1 [Reference]
	1	139738 (93.8)	9301 (6.2)	1.16 (1.12-1.20)
	2	39180 (91.4)	3693 (8.6)	1.26 (1.20-1.31)
	3	7710 (87.0)	1147 (13.0)	1.37 (1.27-1.47)
	4 or more	1201 (80.3)	295 (19.7)	1.55 (1.36-1.76)

[29] Adjusted for age, gender, ethnicity, region, primary employment, age completed education, deprivation, income, any chronic pain, and number of pain sites

Table 5 Predictors of death during follow-up period

Recruitment characteristic		**Death during follow-up**		**MRR[30] (99% CI)**	**MRR[31] (99% CI)**
		No: N (%)	*Yes: N (%)*		
Regular Opioid use	*None*	426534 (96.7%)	14513 (3.3%)	1 [Reference]	1 [Reference]
	Weak	18136 (93.1%)	1336 (6.9%)	1.86 (1.73, 2.00)	1.18 (1.06, 1.33)
	Strong	5853 (90.9%)	583 (9.1%)	2.59 (2.34, 2.88)	1.20 (1.01, 1.43)
Chronic Pain	*No*	254379 (96.8%)	8417 (3.2%)	1 [Reference]	1 [Reference]
	Yes	194172 (96.1%)	7900 (3.9%)	1.22 (1.17, 1.27)	0.85 (0.78, 0.93)
Number of pain sites	*0*	179617 (96.8%)	6004 (3.2%)	1 [Reference]	1 [Reference]
	1	123741 (96.6%)	4334 (3.4%)	1.06 (1.01, 1.11)	1.07 (0.97, 1.17)
	2	74684 (96.4%)	2794 (3.6%)	1.17 (1.11, 1.24)	1.05 (0.94, 1.17)
	3	38990 (95.9%)	1665 (4.1%)	1.36 (1.27, 1.46)	1.09 (0.96, 1.25)
	4	17245 (96.1%)	700 (3.9%)	1.35 (1.23, 1.50)	0.94 (0.79, 1.12)
	5	6517 (95.8%)	286 (4.2%)	1.58 (1.35, 1.83)	0.85 (0.66, 1.09)
	6	1913 (96.0%)	80 (4.0%)	1.65 (1.25, 2.19)	1.07 (0.73, 1.56)
	7 or all over	7803 (93.2%)	567 (6.8%)	2.29 (2.06, 2.56)	1.19 (0.98, 1.45)
Age Category (years)	*40-45*	49892 (99.2%)	396 (0.8%)	1 [Reference]	1 [Reference]
	45-49	62760 (98.7%)	796 (1.3%)	1.61 (1.37, 1.88)	1.71 (1.33, 2.20)
	50-54	70924 (98.1%)	1361 (1.9%)	2.43 (2.10, 2.81)	2.33 (1.84, 2.95)
	55-59	82301 (97.1%)	2464 (2.9%)	3.73 (3.25, 4.28)	3.41 (2.72, 4.28)
	60-64	105927 (95.6%)	4905 (4.4%)	5.63 (4.92, 6.43)	4.64 (3.72, 5.80)
	65-69	78706 (92.4%)	6508 (7.6%)	9.50 (8.32, 10.85)	6.89 (5.51, 8.62)
Gender	*Male*	206662 (95.2%)	10364 (4.8%)	1 [Reference]	1 [Reference]
	Female	243848 (97.6%)	6066 (2.4%)	0.53 (0.51, 0.55)	0.51 (0.48, 0.55)
Body Mass Index (kgm^{-2})	*Underweight (< 18.5)*	2208 (93.0%)	166 (7.0%)	2.83 (2.34, 3.43)	1.76 (1.31, 2.38)
	Normal (18.5-24.9)	146451 (97.1%)	4308 (2.9%)	1 [Reference]	1 [Reference]

[30] Mortality Risk Ratio adjusted for age and gender

[31] Fully adjusted mortality risk ratio – i.e. adjusted for all factors in table

	Overweight (25.0-29.9)	190832 (96.6%)	6674 (3.4%)	0.96 (0.91, 1.01)	0.87 (0.81, 0.94)
	Obese (30.0-34.9)	77950 (95.9%)	3302 (4.1%)	1.17 (1.10, 1.24)	0.94 (0.86, 1.02)
	Obese (35.0-39.9)	22033 (95.2%)	1116 (4.8%)	1.55 (1.42, 1.68)	1.05 (0.93, 1.20)
	Obese (≥40)	11036 (92.7%)	864 (7.3%)	2.56 (2.34, 2.81)	1.45 (1.24, 1.69)
Physical Activity (walking: mins/week)	0	9251 (93.7%)	622 (6.3%)	1.90 (1.71, 2.11)	1.22 (1.05, 1.40)
	1-100	101757 (96.6%)	3594 (3.4%)	1 [Reference]	1 [Reference]
	101-210	115233 (96.7%)	3939 (3.3%)	0.91 (0.86, 0.96)	0.97 (0.89, 1.05)
	211-420	90340 (96.8%)	2983 (3.2%)	0.87 (0.82, 0.93)	0.92 (0.84, 1.01)
	>420	75450 (96.8%)	2502 (3.2%)	0.90 (0.84, 0.96)	0.87 (0.79, 0.96)
Moderate Physical Activity (mins/week)	0	54253 (95.3%)	2691 (4.7%)	1.58 (1.47, 1.69)	1.11 (1.005, 1.23)
	1-60	93837 (97.1%)	2787 (2.9%)	1 [Reference]	1 [Reference]
	61-150	79046 (97.0%)	2446 (3.0%)	0.98 (0.91, 1.05)	0.98 (0.89, 1.09)
	151-360	79792 (96.9%)	2564 (3.1%)	0.95 (0.88, 1.01)	1.01 (0.91, 1.11)
	>360	79205 (96.5%)	2908 (3.5%)	0.99 (0.93, 1.06)	1.06 (0.95, 1.17)
Vigorous Physical Activity (mins/week)	0	158097 (95.6%)	7323 (4.4%)	1 [Reference]	1 [Reference]
	1-40	71056 (91.2%)	2053 (2.8%)	0.65 (0.61, 0.69)	0.87 (0.79, 0.95)
	41-90	62605 (97.4%)	1689 (2.6%)	0.64 (0.60, 0.69)	0.88 (0.79, 0.97)
	91-180	57870 (97.5%)	1536 (2.5%)	0.63 (0.59, 0.68)	0.85 (0.76, 0.95)
	>180	51434 (97.2%)	1486 (2.8%)	0.65 (0.60, 0.69)	0.84 (0.75, 0.93)
Physical activity (stairs times/day)	0	38711 (94.1%)	2425 (5.9%)	1.12 (1.05, 1.20)	1.02 (0.93, 1.11)
	1-5	89429 (95.7%)	3984 (4.3%)	1 [Reference]	1 [Reference]
	6-10	161615 (96.9%)	5114 (3.1%)	0.71 (0.67, 0.75)	0.85 (0.79, 0.92)
	11-15	82692 (97.3%)	2301 (2.7%)	0.63 (0.59, 0.68)	0.82 (0.75, 0.91)
	16-20	38451 (97.3%)	1058 (2.7%)	0.63 (0.57, 0.68)	0.80 (0.70, 0.92)
	>20	31363 (97.3%)	876 (2.7%)	0.68 (0.62, 0.75)	0.81 (0.69, 0.94)
Diet (Fruit and Vegetable Consumption)	*Lowest consumption*	101510 (95.9%)	4393 (4.1%)	1 [Reference]	1 [Reference]
	Quintile 2	91076 (96.7%)	3119 (3.3%)	0.77 (0.73, 0.82)	0.91 (0.84, 0.99)
	Quintile 3	40106 (96.8%)	1343 (3.2%)	0.75 (0.69, 0.81)	0.92 (0.82, 1.02)
	Quintile 4	80665 (96.8%)	2641 (3.2%)	0.73 (0.68, 0.77)	0.91 (0.83, 0.99)
	Highest Consumption	64907 (96.7%)	2205 (3.3%)	0.75 (0.70, 0.80)	0.90 (0.82, 0.99)
	(almost) daily	90705 (95.9%)	3843 (4.1%)	1 [Reference]	1 [Reference]

Alcohol Consumption	*3-4 times/week*	104889 (97.1%)	3127 (2.9%)	0.82 (0.78, 0.88)	0.90 (0.82, 0.98)
	1-2 times/week	116686 (96.9%)	3715 (3.1%)	0.94 (0.89, 0.99)	0.91 (0.83, 0.99)
	<1 time/week	101408 (96.5%)	3698 (3.5%)	1.15 (1.08, 1.22)	0.95 (0.86, 1.04)
	Never	35463 (94.7%)	1966 (5.3%)	1.59 (1.48, 1.70)	1.23 (1.10, 1.37)
Cigarette Smoking	*Current smoker*	45818 (92.8%)	3546 (7.2%)	3.12 (2.96, 3.29)	2.44 (2.24, 2.65)
	Ex-regular	101104 (95.1%)	5253 (4.9%)	1.59 (1.51, 1.66)	1.46 (1.35, 1.57)
	Ex-occasional	51343 (97.1%)	1536 (2.9%)	1.09 (1.02, 1.17)	1.14 (1.02, 1.27)
	Never	249750 (97.7%)	5942 (2.3%)	1 [Reference]	1 [Reference]
Morbidity[32]	*0*	120558 (98.0%)	2416 (2.0%)	1 [Reference]	1 [Reference]
	1	122894 (97.4%)	3285 (2.6%)	1.15 (1.07, 1.23)	1.07 (0.97, 1.19)
	2	88310 (96.4%)	3299 (3.6%)	1.40 (1.31, 1.50)	1.22 (1.10, 1.36)
	3	54451 (95.2%)	2743 (4.8%)	1.72 (1.60, 1.85)	1.47 (1.32, 1.64)
	4	30396 (94.4%)	1819 (5.4%)	1.93 (1.78, 2.09)	1.51 (1.34, 1.71)
	5	16020 (93.2%)	1169 (6.8%)	2.27 (2.08, 2.49)	1.65 (1.43, 1.90)
	6	8481 (82.6%)	680 (7.4%)	2.49 (2.23, 2.78)	1.70 (1.43, 2.01)
	7	4437 (91.3%)	421 (8.7%)	2.91 (2.56, 3.32)	1.83 (1.49, 2.25)
	8	2257 (90.6%)	233 (9.4%)	3.15 (2.67, 3.73)	2.22 (1.74, 2.84)
	9	1259 (89.9%)	142 (10.1%)	3.63 (2.94, 4.48)	2.59 (1.92, 3.49)
	>=10	1147 (86.6%)	223 (13.4%)	4.77 (4.04, 5.63)	2.95 (2.27, 3.82)
Age completed full time education	*<16*	88210 (93.8%)	5824 (6.2%)	1 [Reference]	1 [Reference]
	16	95204 (96.8%)	3202 (3.3%)	0.78 (0.74, 0.83)	0.93 (0.86, 0.999)
	17	34717 (97.1%)	1030 (2.9%)	0.69 (0.63, 0.75)	0.88 (0.78, 0.98)
	18	36264 (97.4%)	953 (2.6%)	0.67 (0.62, 0.74)	0.95 (0.84, 1.06)
	>18	39102 (96.9%)	1264 (3.1%)	0.70 (0.65, 0.76)	1.02 (0.92, 1.13)
Average household income	*Less than 18000*	83059 (93.8%)	5480 (6.2%)	1 [Reference]	1 [Reference]
	18000 to 30999	96144 (96.2%)	3788 (3.8%)	0.66 (0.62, 0.69)	0.85 (0.79, 0.92)
	31000 to 51999	101608 (97.8%)	2339 (2.3%)	0.47 (0.44, 0.51)	0.68 (0.61, 0.75)
	52000 to 100000	80513 (98.4%)	1334 (1.6%)	0.39 (0.36, 0.43)	0.61 (0.53, 0.70)
	>100000	21443 (98.7%)	293 (1.4%)	0.33 (0.29, 0.39)	0.51 (0.37, 0.71)
	Do not know	18475 (94.8%)	1011 (5.2%)	1.02 (0.94, 1.11)	1.03 (0.89, 1.19)

[32] Self-reported illness (non-cancer) at baseline

	Prefer not to answer	44092 (96.2%)	1752 (3.8%)	0.69 (0.64, 0.74)	0.79 (0.70, 0.88)
Deprivation	*Lowest quintile*	90849 (97.1%)	2727 (2.9%)	1 [Reference]	1 [Reference]
	2	90161 (97.0%)	2826 (3.0%)	1.04 (0.97, 1.12)	0.93 (0.84, 1.03)
	3	90242 (96.8%)	2962 (3.2%)	1.12 (1.05, 1.20)	1.00 (0.91, 1.11)
	4	89972 (96.5%)	3302 (3.5%)	1.32 (1.24, 1.41)	1.08 (0.98, 1.19)
	Highest quintile	88726 (95.1%)	4596 (4.9%)	1.92 (1.81, 2.04)	1.22 (1.11, 1.35)
Seen doctor for anxiety/ nerves/depression	*No*	295416 (96.6%)	10519 (3.4%)	1 [Reference]	1 [Reference]
	Yes	150588 (96.4%)	5695 (3.6%)	1.26 (1.21, 1.31)	0.98 (0.92, 1.04)

Chapter 2.5

The co-occurrence and characteristics of patients with axial spondyloarthritis who meet criteria for fibromyalgia: results from a UK national register (BSRBR-AS)

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Abstract

Objective: To estimate the proportion of patients with axial spondyloarthritis (axSpA) who meet criteria for fibromyalgia (FM) and to characterise such patients.

Methods: The British Society for Rheumatology Biologics Register of Ankylosing Spondylitis (BSRBR-AS) recruits two cohorts of patients who meet ASAS criteria for axSpA across 83 centres in the United Kingdom. Patients are either newly starting (biologic cohort) or naïve (non-biologic cohort) to biologic therapy and are followed prospectively. At recruitment and follow-up, clinical information and measurements are recorded, while patients complete the 2011 research criteria for FM, assessments of disease activity and impact.

Results: 1504 patients (68% male) were eligible for the current analysis of whom 311 (20.7%) met criteria for FM. Prevalence was similar among those who fulfilled modified New York (mNY) criteria (19.7%), and ASAS imaging but not mNY criteria (25.2%), but lower among those who only fulfilled ASAS clinical criteria (9.5%). Patients who met FM criteria reported significantly worse disease activity, function, global severity scores, quality of life and were more likely to have moderate/severe levels of mood disorder and clinically important fatigue. They reported work impairment around half the time. Meeting FM criteria was not related to elevated C-reactive protein, or most extra-spinal manifestations, but was associated with a higher likelihood of having received biologic therapy.

Conclusion: Developing management approaches that address the significant unmet needs of the 1 in 5 axSpA patients who meet criteria for FM should be a research priority.

Introduction

Fibromyalgia (FM) may be more common in patients with axial spondyloarthritis (axSpA) than in the *general* population. In comparison to a population prevalence of 2-4% based on American College of Rheumatology (ACR) 1990 criteria (1), studies in ankylosing spondylitis (AS) patients from Turkey (prevalence 12.6%; n=119), Italy (prevalence 12.7%; n=211) and Brazil (prevalence 15%; n=71) have all reported similar excess prevalence (2-4). This is consistent with the observation of a high prevalence of FM in inflammatory rheumatic diseases generally (5). However, distinguishing axSpA and FM is problematic, given that the ACR 1990 criteria require the report of axial skeleton pain, which is the key clinical feature of axSpA, while enthesitis may result in multi-site pain which is the cardinal feature of FM, and included in all established or proposed sets of FM criteria (6-8). A pooled analysis of data from clinical trials treating AS patients with etanercept, sulfasalzine or placebo has shown higher disease burden and poorer response to treatment in women. They identified the possibility that this may be due to concomitant FM, and proposed this as a priority for future research (9,10).

FM may distort responses to some of the key patient reported measures used in axSpA such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI). In the previously-mentioned study from Turkey: comparing those patients with and without FM, there was no difference in C-reactive protein (CRP) or Erythrocyte Sedimentation Rate (ESR) but those with FM had higher BASDAI scores (3). In July 2013, the US Food and Drug Administration (FDA) met to consider whether patients who had non-radiographic axSpA, based on criteria of the Assessment of SpondyloArthritis international Society (ASAS) (11), should be eligible for new therapies. The FDA committee recognized the unmet need for effective pharmacologic therapy for patients who either only had positive MRI changes, or were HLA-B27 positive with other characteristic SpA features. They were, however, concerned about the possibility, especially in those without MRI changes, that patients with highly prevalent conditions such as mechanical back pain or FM might be incorrectly diagnosed with inflammatory spondylitis and be inappropriately treated with expensive and potentially toxic biologic therapies. This highlights the need to understand better, the characteristics of patients who have overlapping axSpA and FM, to assess and distinguish the two conditions, and develop treatment strategies that can effectively work in parallel. As an initial step in such endeavours the current study, within a national axSpA register aimed to a) determine the

prevalence of FM amongst patients who meet ASAS criteria for axSpA and b) to identify clinical and patient-reported measures which distinguish axSpA patients with co-morbid FM.

Patients and Methods

The British Society for Rheumatology Biologics Register of Ankylosing Spondylitis (BSRBR-AS) is a prospective cohort study which has recruited patients who meet ASAS defined axSpA from 83 secondary care centres in the United Kingdom with the first centres recruiting from December 2012. Patients meeting only the ASAS clinical criteria have been eligible to be recruited since November 2014. All patients are naïve to anti-TNF biologic therapy at the time of recruitment but may either be starting such therapy (Adalimumab, Etanercept or Certulizumab Pegol) or continuing on current therapy. The study protocol has previously been published (12) but in brief patients starting biologic therapy have clinical and patient reported information collected at recruitment, 3, 6 and 12 months. Those not on biologics, have information collected at recruitment and annually thereafter, but may transfer to the follow-up schedule of patients on biologic therapy if they commence such therapy at a later date. From September 2015, the patient-reported data included the 2011 FM research criteria (8). Satisfying the criteria depended on the presence of widespread pain and somatic symptoms.

Patients on the register were included in the current analysis if they had completed the 2011 FM research criteria either at recruitment or follow-up. We used data from the first completion of the items which contribute to this criteria. Information on clinical status at recruitment allowed us to determine whether patients were known to meet an imaging criteria for axSpA (modified New York (mNY) criteria (13) or ASAS imaging criteria (11)) or not (ASAS clinical criteria). Data collected from or measured on each patient included:

- Bath Indices of disease activity (BASDAI), function (BASFI), metrology index (BASMI) and global assessment (BAS-G) (14), each scored to provide a scale from 0 (best) to 10 (worst).
- Extra-spinal manifestations including uveitis, psoriasis, inflammatory bowel disease, swollen and tender forty-four joint count, as per ASAS recommendations (15)

Quality of life was measured by:

- the 18-item Ankylosing Spondylitis Quality of Life (ASQoL) scale (14), providing a score from 0 (good quality of life (QoL)) to 18 (poor QoL)

- EQ-5D, a five-item generic scale with score from 0 (equivalent to death) to 1 (best possible health (although scores less than 0 (worse than death) are also possible) (16)

Other patient reported measures collected were:

- A sleep disturbance score (SDS) consisting of four items with each scored from 0-5 (total score 0-20) with higher scores indicating worse problems (17).
- Chalder fatigue scale (CFS) an eleven item scale measuring the extent and severity of fatigue. Each item was scored as 0 or 1 providing a total score 0-11 with higher scores indicating worse fatigue. A score of 4 or more is taken to indicate significant fatigue (18).
- Hospital Anxiety and Depression Scale (HADS) (19) provides a measure of emotional distress, anxiety disorders and depression in somatic, psychiatric and primary care patients and in the general population. It has been shown to have a two-factor structure corresponding to the anxiety and depression subscales (20). Each subscale has seven items scored 0-3 providing a total score for each of anxiety and depression between 0-21 with higher scores indicating higher levels of anxiety or depression. Scale scores are categorised as 0-7 (normal), 8-10 (mild), 11-14 (moderate), 15-21 (severe).
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI: SHP), a validated instrument to measure impairments in work, including both absenteeism and presenteeism (21).

Height and weight (for the calculation of Body Mass Index (BMI)), and C-reactive protein (CRP) were measured. We constructed a co-morbidity index based on the number reported by the clinician (from myocardial infarction, angina, congestive cardiac failure, stroke, hypertension, diabetes, asthma, chronic bronchitis or emphysema, peptic ulcer, liver disease, renal disease, tuberculosis, demyelination, depression or cancer).

An area-level deprivation score was calculated (the index of multiple deprivation (IMD)) using comparable official government individual indices from the relevant countries within the UK. These were the English (EIMD), Scottish (SIMD) and Welsh (WIMD) Index of Multiple Deprivation respectively, and were all based on lower-level census areas, which represent neighbourhoods. All indices include income, employment, health, education, housing and crime/community safety. SIMD and WIMD include access to services, while in EIMD this is combined with the housing domain. Additionally, EIMD adds living environment and WIMD adds physical environment. IMD was categorised into quintiles and standardised to be presented as representing most deprived as 1 and least deprived as 5, following SIMD practice.

We compared axSpA patients, according to whether they met 2011 FM research criteria, across the range of clinical and patient reported measures listed above, using t-tests (continuous outcomes), two-sample proportion tests (binary outcomes), chi-square test (categorical non-ordered outcomes) and non-parametric tests for trend (ordinal outcomes) or comparing distributions (Mann Whitney U test) as appropriate. 95% Confidence intervals (CI) are given for effect estimates. This analysis used data from the January 2017 version of the study database.

Results

Amongst 2449 participants on the BSRBR-AS, 1504 (68% male) were eligible for the current analysis: 553 (35.4%) were in the biologic-exposed cohort. The study population is described in Table 1: they had a median age of 51.2 years, reported a median time since symptom onset of 19 years, 82.2% of those who had been tested were HLA B-27 positive and approximately 1 in 6 were current smokers. Most participants (69.2%) met the mNY criteria for AS, an additional 26.5% fulfilled ASAS imaging criteria but not mNY, and 4.3% fulfilled only ASAS clinical criteria. 311 (20.7%) met 2011 research criteria for FM. The proportion meeting FM criteria in each of these groups was 19.7%, 25.2% and 9.5% respectively (p=0.006). The proportion meeting FM criteria was higher in females (26.1% v. 18.2%, p<0.001) but there was no difference by age-group (p=0.56). HLA-B27 positive patients (17.0%) were less likely than negative (32.1%) or untested (21.7%) patients to meet FM criteria (p<0.001). Prevalence did vary by level of deprivation: those in the most deprived quintile had a prevalence of 38.0%, those in the least deprived had a prevalence of 13.8% and in the intermediate quintiles prevalence varied between 17.5%-20.3% (p< 0.001).

AxSpA Disease Indices

Persons who met 2011 FM research criteria had markedly worse indices of disease (Table 2). They had significantly worse disease activity, function, metrology and global status. C-reactive protein measurement was available on 1034 participants. There was no significant difference, between those who did and did not meet FM criteria, in the proportion of participants having a CRP which exceeded 1 mg/dl (39.3% v. 38.7% p=0.86), nor was there any difference in the overall distribution (Mann Whitney U test (p=0.82)) nor within either the biologic (p=0.53) or non-biologic (p=0.76) cohorts.

Patient reported measures

Quality of Life was significantly worse in those who met FM research criteria whether measured by a disease specific or generic measure (Table 3). Patients meeting FM criteria scored significantly more highly on the HADS anxiety and depression subscales. Of those who met FM criteria, 39.9% were classified as having moderate/severe depression in comparison to 7.0% in those who did not ($p<0.001$). The comparable figures for anxiety were 55.3% and 17.9% respectively ($p<0.001$) They also scored more highly for sleep disturbance and levels of fatigue with 79.2% exceeding the cut-off for clinically important fatigue in the FM group in comparison to 34.2% in the non-FM group($p < 0.001$).

Clinical status and therapy

Patients who satisfied FM research criteria had higher BMI (28.7 v. 27.6 kgm^{-2} difference 1.2; 0.3,2.0), and a greater swollen (mean 0.47 v. 0.21 difference 0.26; 0.03, 0.49) and tender (mean 1.3 v. 0.5; difference 0.8; 0.4, 1.2) joint count. They were also more likely to report at least one co-morbidity (36.9% v. 19.9%, $p<0.001$). In contrast, there was only a small and not statistically significant excess in proportion of persons reporting extra-spinal manifestations amongst patients positive for FM criteria (uveitis 19.0% v. 18.0%; psoriasis 9.2% v. 6.4%; inflammatory bowel disease 8.5% v. 7.0%). Persons meeting FM research criteria were more likely to be on biologic therapy (50.5% vs 31.5%).

Work-related factors

Patients meeting criteria for FM had a significantly greater percentage of work time missed (15.1% v. 2.5%; difference 12.7%; 9.7%, 15.4%) and reported that when present, their work was impaired around half their working time (50.8% v. 22.8%; difference 28.1%; 23.8%, 32.3.

Discussion

This national study, the largest to have been conducted on the co-occurrence of axSpA and FM has demonstrated that around 1 in 5 patients with axSpA meet current research criteria for FM. The proportion was not higher in those meeting only ASAS clinical criteria. Patients who meet FM criteria have considerably worse disease indices, have a significantly greater number of physical and psychological co-morbidities, markedly poorer quality of life (as measured by generic and disease-specific scales) and they report a much greater impact on work than those who do not fulfil the FM criteria. In contrast there are no differences in measured inflammation nor in most extra-spinal disease manifestations. Patients meeting FM criteria were more likely to have been started on biologic therapy.

This multi-centre study involves a relatively unselected secondary care patient population – recruitment takes place across specialist and non-specialist centres and this analysis involves data from patients naïve to anti-TNF biologic therapy, those newly starting and those previously started (although all patients on recruitment to the register are naïve to biologic therapy). Therefore the results are likely to represent the prevalence of persons who meet FM criteria in a typical secondary care axSpA population. The key methodological issue in the current study is that the 2011 FM research criteria used in this study have not specifically been validated for use in patients with axSpA. Indeed neither these nor any other criteria set (nor screening instrument) for FM have been validated for use in patients with any type of inflammatory arthritis. The 2010 preliminary diagnostic criteria (for clinician completion) and the 2011 research criteria (for patient completion) both require that the following is fulfilled "The patient does not have a disorder that would otherwise explain the pain" (7,8). However this is challenging for the clinician to determine and almost impossible for the patient to assess, and it is noteworthy that most studies which have implemented the 2010 or 2011 FM research criteria have ignored this specific requirement, as we have done in the current study. Irrespective of this, applying these criteria are identifying patients with significant unmet need.

In a study by Almódovar et al (22), conducted in Spain, AS patients with an elevated BASDAI/Bath Ankylosing Spondylitis Radiological Index (BASRI) or BASFI/BASRI ratio, had a high probability of having a FM diagnosis. In the same study, there was also some evidence that patients with AS and FM (in comparison to those with AS only) responded less well to management strategies such as NSAID therapy. Because of the distortion of the patient reported measures which influence management decisions (such as BASDAI, which includes items on both pain and fatigue), it has been hypothesised that some patients with AS and FM may inappropriately receive biologic therapy. This is consistent with data from the current study: patients meeting FM were more likely to receive biologic therapy but also more likely to stop or switch such therapy. Nevertheless, although patients who met FM research criteria did not demonstrate any differences in most extra-spinal manifestation of disease, they did have a greater number of swollen and tender joints which might imply greater disease activity. The only other study, of which we are aware, which has used similar FM criteria (the 2010 preliminary diagnostic criteria for FM which are the clinician version of the 2011 research criteria) studied 91 patients with axSpA in clinics in Germany and reported that 34.1% met the 2010 FM criteria (23). In contrast, a much lower proportion (14.3%) met the 1990 ACR FM classification criteria. A study by Bello et al (24) used the self-administered Fibromyalgia Rapid Screening tool (FiRST) (25) to screen 196 patients with a

clinical diagnosis of spondyloarthritis, attending a single tertiary care university hospital in France. They reported a FM prevalence of 21%. There was no difference in the prevalence of FM in patients satisfying the imaging or clinical ASAS criteria. Patients with co-existing FM also had higher BASDAI, spinal pain and BASFI scores. There was no statistically significant difference in the proportion of patients with or without FM receiving anti-TNF therapy, however patients with FM who received anti-TNF therapy were, much less likely to be on the same therapy two years later (28.1% v. 41.7%, p=0.01).

The European League Against Rheumatism (EULAR) has recently revised its recommendations for the management of FM and all specific recommendations are now based on either systematic review or meta-analysis (26). However, the working group noted that there were no trials informing how to treat FM when it occurred together with an inflammatory arthritis: this was therefore made a priority recommendation for future research. There are effective therapies for FM (albeit that most have modest effect sizes) including non-pharmacological and pharmacological approaches. Indeed there is consensus, reflected in recommendations produced at national and international level that non-pharmacological therapies, principally cognitive behaviour therapy and exercise should constitute first-line therapy (27). Whether such therapies are as effective in managing FM as a co-morbidity, alongside best care for an inflammatory condition, and improve long-term outcome remains to be determined.

Even in the absence of validated criteria for FM in inflammatory arthritis patients, the 2011 FM research criteria identify a group of axSpA patients who have markedly worse patient reported disease activity measures, high levels of co-morbidity and with clinically important differences in measures of quality of life. They are also less likely to remain on initial-prescribed biologic therapy. For example the ASQoL scores of patients who satisfy FM criteria (13.1) indicate worse quality of life than the patient acceptable clinical state (8.0) (28) and in relation to centile charts for BASDAI, patients who meet criteria for FM have a mean score between the 75th and 90th centile (29). Almost 4 out of 5 of patients with axSpA who meet FM criteria have significant fatigue, and although there is some circularity in the observations (for example, fatigue is a single item in the 2011 FM research criteria) it is emphasising that the items of the FM criteria when taken together are identifying a group with very significant unmet needs. This is particularly true in relation to work with, amongst patients meeting criteria for FM, 17% of work time missed and impaired performance during more than half of their working time.

In summary this study has shown that an important proportion of axSpA patients meet current research criteria for FM, but the proportion is no greater in those meeting only ASAS clinical criteria. They have markedly worse disease indices and this may therefore represent an unmet and unrecognised need amongst axSpA patients. A recent large-scale survey of a patient group, the National Ankylosing Spondylitis Society in the United Kingdom, identified "developing a greater understanding of the impact of dealing with other conditions associated with AS" as one of their top ten research priorities (30). Future research should validate the use of FM research criteria sets in patients with inflammatory arthritis (including axSpA) and investigate effective management strategies for patients in whom these rheumatic conditions co-occur.

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Author Declaration

None of the authors declare any conflict of interest with respect to this manuscript.

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Tables

Table 1 Characteristics of study population

Characteristic		
Age (years)	Median (IQR)	51.2 (40.1-63.1)
Gender	N; % male	1025, 68.2%
Time since symptom onset (years)	Median (IQR)	19 (9-33)
HLA-B27 status	N; % positive	765; 82.2% of those tested
	N; % negative	165; 17.8% of those tested
	N	511
CRP in mg/dL	Median (IQR)	0.55 (0.10-2.00)
Smoking status	N; % current	247; 16.7%
	N; % former	578; 39.2%
	N; % never	651; 44.1%
Diagnostic criteria	N; % fulfilling mNY[33] criteria	1026; 69.2%
	N; % fulfilling ASAS[34] imaging but not mNY criteria	393; 26.5%
	N; % fulfilling ASAS clinical criteria only	63; 4.3%

[33] modified New York

[34] Assessment of SpondyloArthropathy international Society

Table 2: AxSpA disease indices according to 2011 research criteria for FM

Bath Disease Indices	**2011 research criteria for fibromyalgia**					
	FM positive		**FM negative**			
	Mean Score	95% CI	Mean Score	95% CI	Difference	95% CI
Disease Activity (BASDAI)	6.7	6.5, 6.9	3.6	3.5, 3.8	3.1	2.8, 3.3
Function (BASFI)	6.6	6.4, 6.9	3.7	3.6, 3.9	2.9	2.6, 3.3
Metrology (BASMI)	4.2	4.0, 4.5	3.6	3.5, 3.8	0.6	0.3, 0.9
Global (BAS-G)	6.9	6.7, 7.2	3.7	3.6, 3.8	3.2	2.9, 3.6

Table 3: A comparison of axSpA patient reported measures according to 2011 research criteria for FM status

Patient Reported Measures	2011 research criteria for fibromyalgia					
	FM positive		FM negative			
	Mean Score	95% CI	Mean Score	95% CI	Difference	95% CI
Quality of Life (ASQoL)	13.1	12.7, 13.6	6.1	5.8, 6.4	7.1	6.4, 7.7
Quality of Life (EQ-5D)	0.45	0.42, 0.48	0.76	0.74, 0.77	-0.31	-0.33,-0.28
Depression (HADS-depression)	9.4	8.9, 9.8	4.6	4.4, 4.8	4.8	4.3, 5.2
Anxiety (HADS anxiety)	11.0	10.5, 11.5	6.4	6.2,6.6	4.7	4.1, 5.2
Sleep (SDS)	13.4	12.7, 14.0	8.1	7.8, 8.4	5.3	4.5, 6.0
Fatigue (CFS)	6.8	6.4, 7.2	2.8	2.6, 3.0	4.0	3.5, 4.4

Chapter 2.6

Influence of co-morbid fibromyalgia on disease activity measures and response to TNF inhibitors in axial spondyloarthritis: results from a UK national register

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Abstract

Objective: To quantify the extent to which co-morbid fibromyalgia (FM) is associated with higher disease activity, worse quality of life and poorer response to TNF inhibition (TNFi) in patients with axSpa.

Methods: A prospective study recruiting across 83 centres in the United Kingdom. Clinical information and patient reported measures were available, including 2011 criteria for FM. Multivariable linear regression was used to model the effect of meeting the FM criteria on disease activity, quality of life and response to TNFi.

Results: 1757 participants were eligible for analyses of whom 22.1% met criteria for FM. Those with comorbid FM criteria had higher disease activity (BASDAI average difference FM+ve - FM-ve 1.04; 95% CI 0.75, 1.33) and worse quality of life (ASQoL difference 1.42; 95% CI 0.88, 1.96) after adjusting for demographic, clinical and lifestyle factors. Amongst 291 participants who commenced biologic therapy, BASDAI scores in those with co-morbid FM were 2.0 higher at baseline but reduced to 1.1 higher at 12 months. There was no significant difference in likelihood of meeting ASAS20 criteria at 12 months. Less improvement in disease activity and quality of life over three months of TNFi therapy was most strongly related to high scores on the FM criteria symptom severity (SSS) component.

Conclusion: Fulfilling criteria for FM has a modest impact on assessment of axSpa disease activity and quality of life, and does not significantly influence response to biologic therapy. Those with high SSS on FM assessment, may benefit from additional specific management for FM.

Introduction

The issue of fibromyalgia (FM) as a co-morbidity to axial Spondyloarthritis (axSpa) is of considerable recent interest. In July 2013, the US Food and Drug Administration met to consider Tumour Necrosis Factor inhibitors (TNFi) in patients with non-radiographic axSpa based on the International Association for Ankylosing Spondylitis (ASAS) classification criteria.[1] The FDA Arthritis Advisory Committee recognised the unmet need for effective pharmacologic therapy for patients who had positive MRI rather than radiographic changes, or based on positive HLA-B27 plus other characteristic SpA features, but who did not fulfil the modified New York (mNY) criteria for AS.[2] However, they were concerned about the specificity of the ASAS criteria[3] and the possibility that patients with highly prevalent conditions such as mechanical back pain or FM might be incorrectly diagnosed with non-radiographic axSpa and be inappropriately treated with TNFi medications. This highlights the need to understand better the characteristics of axSpa patients who have co-morbid FM, in order to assess and distinguish the two conditions (including when they co-exist), and to develop treatment strategies that can effectively work in parallel.

This led to research which sought to understand how often axSpa and FM co-occur. Notwithstanding the fact that research criteria for FM have not been validated in the context of inflammatory rheumatic conditions, studies have sought to understand how often people with axSpa met one or more of the criteria for FM. These demonstrated that co-occurrence was common. We have shown that 21% of 1504 persons within the British Society for Rheumatology Biologics Register of axial spondyloarthritis (BSRBR-AS) met 2011 criteria for FM (also known as the modified 2010 criteria and as "research criteria").[4] In a smaller study of 200 patients meeting ASAS criteria for axSpa, Baraliakos et al[5] found that 24% met the above research criteria, while 14% met the previous 1990 American College of Rheumatology (ACR) criteria. This is consistent with the observation of high prevalence of FM in inflammatory rheumatic diseases generally.[6] However, identifying co-morbid FM in people with axSpa is challenging. The ACR 1990 criteria for FM require the report of axial skeleton pain, which is one of the key clinical features of axSpa. These criteria, as well as the 2011 criteria, require multi-site pain which is also reported by axSpa patients due to inflammatory enthesitis/synovitis.[7,8]

The key issue is distinguishing and providing appropriate management for both conditions when they occur together. A pooled analysis of data from clinical trials treating axSpa patients with etanercept, sulphasalazine or placebo showed a higher disease burden and

poorer response to treatment in women and identified the possibility that this may be due to concomitant FM.[9,10] We currently do not know how patients with co-morbid FM respond to TNFi therapy in comparison to those without. However, several standard disease indices (such as the Bath Ankylosing Spondylitis Disease Index (BASDAI), as well as wider measures of disease impact (such as the Ankylosing Spondylitis Quality of Life Index (ASQoL)) are based entirely on patient report and may be inflated due to co-morbid FM. This could lead to inappropriate management since guidelines include BASDAI score as one determinant for use of TNFi therapy.[11-13]

The purpose of this analysis is therefore two-fold. Amongst people with axSpa:

- to quantify the extent to which meeting criteria for FM is associated with higher measures of disease activity and impact (Aim 1).
- to determine whether meeting research criteria for FM is associated with poorer response on first use of TNFi therapy (Aim 2).

Methods

The BSRBR-AS is a prospective cohort study which has recruited patients who have a physician diagnosis of axSpa and meet the Assessment of SpondyloArthritis international Society (ASAS) defined criteria from 83 secondary care centres in the United Kingdom. Recruitment started in December 2012, initially for people meeting the ASAS imaging criteria for axSpa. Patients meeting only ASAS clinical criteria were subsequently eligible to be recruited in November 2014. All participants are naïve to TNFi therapy at the time of recruitment but may either be starting such therapy or continuing on current non-TNFi therapy. The study protocol has previously been published[14] but, in brief, participants starting TNFi therapy have clinical and patient reported information collected at the start of therapy, 3, 6 and 12 months later. Those not on TNFi therapy have information collected at recruitment and annually thereafter, but may transfer to the follow-up schedule of participants on TNFi therapy if they commenced such therapy during the course of the study. Eligible TNFi therapies were adalimumab, etanercept and certolizumab pegol. From September 2015, the patient-reported data included the 2011 FM criteria.

Data collected from or measured on each participant at recruitment and each follow-up point included:

- BASDAI, Bath Ankylosing Spondylitis Functional (BASFI) and metrology (BASMI) Indices.[15-17]

- The 18-item ASQoL scale, providing a score from 0 (good quality of life (QoL)) to 18 (poor QoL).[18]
- 2011 FM criteria[8]: There are two components to the criteria; the Widespread Pain Index (WPI) and the Symptom Severity Scale (SSS). The WPI records in how many of 19 body areas the respondent reports pain in the past week (score 0-19). For the SSS, respondents indicate the severity of fatigue, waking unrefreshed and cognitive symptoms "brain fog" over the past week (scored 0-3 each). The criteria also include 3 items on whether depression, headaches, pain or cramps in the lower abdomen have occurred in the past 6 month (score 1 each if present), giving a maximum total score of 12.
- Hospital Anxiety and Depression Scale (HADS) provides a measure of emotional distress, anxiety disorders and depression. There are two subscales, for anxiety and depression each with scores ranging from 0-21, higher scores indicating more severe problems.[19]
- Cigarette smoking : current, ex-smoker, never smoker

C-reactive protein (CRP) was measured at recruitment but was only measured subsequently if clinically indicated. A measure of socio-economic status, the Index of Multiple Deprivation (IMD), was derived from the postcode of residence of participants and categorised into quintiles with references to their country of residence.[20,21]

Analysis

Aim 1: participants were included if they had completed the FM criteria either at recruitment or follow-up. Data from the first completion of the items which contribute to this criteria were used (and are referred to as "baseline"). The effect of FM status on baseline BASDAI and ASQoL was firstly determined. Thereafter, multivariate linear regression analyses were used to evaluate the influence of FM status on a) baseline disease activity (BASDAI) adjusted for BASMI and CRP (both measured within 3 months of the self-report data), BASFI, age group, gender, IMD, disease management (on TNFi) and smoking status, and b) baseline ASQoL adjusted for BASDAI, BASFI, BASMI, age group, gender, IMD, disease management and smoking status. As the availability of CRP restricted numbers available for analysis and it was shown not to be related to BASDAI, it was only included in an additional (sensitivity analysis) model predicting ASQoL. Both the BASDAI and ASQoL analyses were first conducted with a dichotomous FM status variable and then using the WPI and SSS components of the criteria instead.

Aim 2: participants were included in this analysis if they had completed FM research criteria within the six months before, or one month after, commencing TNFi therapy for the first time. They were also required to have completed at least one follow-up questionnaire 3, 6 and/or 12 months later. Two-sample t-tests were used to compare differences in BASDAI and ASQoL between patients meeting FM criteria (called "FM+ve") and those who did not ("FM-ve") at baseline, 3 months, 6 months and 12 months, as well as ASAS20 and ASAS40 responses at each of these follow-up points. In predicting the contribution of FM status on change in BASDAI after 3 months, adjustment was made for baseline BASDAI, BASFI, age group, IMD, gender and smoking status, while in the analysis predicting ASQoL change after 3 months, adjustment was made additionally for baseline ASQoL. Analysis was again conducted first with dichotomous FM criteria status and then with the WPI and SSS components of the criteria. Inclusion of clinically-measured variables reduced the sample size available to the analysis but a sensitivity analysis with CRP and BASMI was included to investigate their effects. We separately included baseline HADS to determine if this mediated the relationship between FM status and treatment response.

All analyses were conducted using Stata14 SE-64 for statistical analysis and the June 2017 study dataset.

Results

A total of 1757 participants (67% male) completed the research criteria for FM on at least one occasion and were eligible for the current analyses. Their median age was 50.8 years, with a median time since symptom onset of 27 years, and 80.2% of those who had been tested were HLA B27 positive. Most participants (66.8%) met the mNY criteria for AS, an additional 28.4% fulfilled ASAS imaging criteria but not mNY, and 4.8% fulfilled only ASAS clinical criteria for axSpa.

Influence of FM status on disease activity and quality of life (Aim 1).

Those who were FM+ve at baseline (n=388; 22.1%) had higher BASDAI scores than those FM-ve (6.7 v. 3.6; Difference 3.1, 95% CI (2.8,3.3)). Higher BASDAI score was independently predicted by being FM+ve (1.04 higher average scores) in a multivariable linear regression model (which included participants who had a CRP within 3 months of the self-reported information, n=1093) (Table 1). Additional predictors were higher BASFI (0.67 average increase in BASDAI per unit increase in BASFI), lower BASMI (0.14/unit), younger age group, and not being on a TNFi (0.34 higher average score). BASDAI was not significantly related to

CRP, gender, smoking or IMD. When the individual component scores of the FM criteria were entered in the model (instead of the dichotomous FM variable), BASDAI was related both to the WPI score (0.11 average increase in BASDAI for every additional area of pain reported) and the SSS (0.20 average increase/unit).

Those who were FM+ve at baseline had poorer quality of life scores than those FM-ve (13.1 v. 6.1; difference 7.0 95% CI (6.5,7.6)). Poorer quality of life at baseline was predicted, on multivariable analysis, by being FM+ve (1.42 higher average ASQoL) in addition to higher BASDAI score (0.85 increase in ASQoL per unit increase in BASDAI), higher BASFI (1.00/unit), lower BASMI (0.13/unit), female gender (0.74 higher average ASQoL score), and being a current smoker (0.94 higher average score) (Table 2). Quality of life increased with older age group but was not related to TNFi management or IMD. When the FM component scores were entered, poorer quality was life was strongly related to SSS (0.50 increase in ASQoL/unit) with a 0.09 in increase in ASQoL per unit increase in WPI. As a sensitivity analysis, when the CRP was included in Model 2 it was not related to quality of life (co-efficient 0.00 95% CI (-0.02,0.02)).

Response to TNFi therapy according to FM status (Aim 2)

There were a total of 291 participants who commenced TNFi therapy and had completed FM criteria within the required timescale. Of these 139, 123 and 74 had reached the follow-up and completed a questionnaire 3, 6 and 12 months later, respectively. At the time of commencing TNFi therapy, participants who were FM+ve had significantly higher BASDAI scores (7.2 v. 5.2; difference 2.0 95% CI (1.5,2.4)). They continued to have higher scores throughout follow-up, although the magnitude of the difference reduced over time: 3 months (5.7 v. 3.7; 1.9 (1.0,2.8)), 6 months (4.8 v. 3.2; 1.6 (0.7,2.6)) and 12 months (4.1 v. 3.1; 1.1 (-0.0,2.2)). Quality of life was poorer amongst those FM+ve (14.0 v. 9.4; difference 4.6 95% CI (3.5,5.7)) and remained so: 3 months (10.5 v. 7.0; 3.5 (1.5,5.5)), 6 months (10.2 v. 5.6; 4.6 (2.5,6.6)) and 12 months (9.0 v. 5.4; 3.6 (0.9,6.3)) (Figure 1). It is noteable in FM+ve patients that BASDAI continues to reduce throughout the 12 month follow-up period. Throughout follow-up those originally FM+ve were less likely to meet ASAS20 response criteria at all time-points. The differences reduced through follow-up and none were statistically significant: 3 months (36% v. 46%; -10% (-28%,8%)), 6 months (56% v. 61%; -5% (-24%,14%)) and 12 months (60% v. 63%; -4% (-30%,23%)). Similar sized differences in response were observed for ASAS40: 3 months (24% v. 34%; -11% (-28%,7%)), 6 months (39% v. 44%; -5% (-24%,14%)), and 12 months (32% v. 42%; -11% (-37%,16%)). The proportion of participants who were FM+ve at baseline, who continued to meet criteria at follow-up was 36.2% at 3

months, 40.5% at 6 months and 40% at 12 months. The decrease in the proportion of patients fulfilling the FM over time is due to improvements in both WPI and SSS. WPI improved by 1.5, 1.8 and 1.4 over 3, 6 and 12 months respectively and SSS improved by 0.8, 1.2 and 0.8. These represent very similar improvements as a percentage of the relevant maximum scale score (e.g. 8% and 7% at 3 months for WPI and SSS respectively).

A multivariable model predicting change in BASDAI ($BASDAI_{baseline}$ – $BASDAI_{3\ months}$) demonstrated that those FM+ve at baseline had 0.58 less improvement in BASDAI than those FM-ve but this was not statistically significant (Table 3). Larger improvements were related to higher baseline BASDAI (every unit increase in BASDAI associated with an average 0.72 greater improvement in BASDAI) and lower baseline BASFI (0.38 less improvement/unit increase). However, when the effect of the individual components of FM criteria were considered, higher scores on SSS were significantly associated with poorer response (0.32 lower average improvement per unit increase in SSS). When CRP or BASMI was added to Model 2 (as a sensitivity analysis, since their inclusion restricted numbers available for analysis), they were not associated with improvement in BASDAI (0.00 95% CI (-0.02,0.03) and 0.21 (-0.06,0.48) respectively) and neither was HADS (Anxiety) (severe anxiety 0.18 95% CI (-1.36,1.72) per unit increase in score) or HADS (Depression) (severe depression -0.51 95% CI (-2.45,1.42) per unit increase in score) when put into the model together.

A corresponding analysis was run with quality of life as the outcome ($ASQOL_{baseline}$ – $ASQOL_{3\ months}$). High scores on the SSS of the FM criteria were predictive of lower improvement in quality of life, as were poorer quality of life and worse disease activity on commencing treatment (Table 4). When CRP or BASMI was added to Model 2 (again as a sensitivity analysis), they were not associated with improvement in ASQoL (0.11 95% CI (-0.47,0.69) and -0.01 (-0.07,0.06), respectively) and neither was HADS (Anxiety) (severe anxiety -0.79 95% CI (-4.13,2.55)) or HADS (Depression) (severe depression -3.29 95% CI (-7.48,0.91)).

Discussion

Patients with axSpa who were FM+ve had only modestly higher disease activity and worse quality of life, after adjustment for disease indices, demographic and socioeconomic factors. Poor quality of life was more strongly determined by a high score on the SSS of FM criteria, indicating a high burden of somatic symptoms. Persons who were FM+ve had higher BASDAI scores on commencement of TNFi therapy and throughout the 12 month follow-up,

although the difference in magnitude reduced over the period of treatment. There was no significant difference in likelihood of meeting ASAS20 or ASAS40 response criteria according to FM status. While FM status was not significantly related to response to therapy, as assessed by BASDAI or ASQoL, high somatic symptom burden was associated with worse response. Approximately 2 in 5 of persons who met FM criteria at commencement of therapy, continued to do so at each follow-up over the year.

The BSRBR-AS is a national register involving non-specialist and specialist centres and thus the patients recruited are likely to represent the spectrum encountered in routine clinical practice. The study protocol dictated that participants were followed-up clinically and by questionnaire at 3, 6 and 12 months. This schedule was chosen to fit in with routine clinical practice. If the routine follow-up did not occur (or sufficient time had not passed for the follow-up to be due) or the participant did not return their questionnaire, then they could not fully participate in all the analyses presented. Therefore, for the 12 month follow-up in particular, the numbers analysed are considerably lower than those recruited. However, it is of note that the patterns of response are very similar across follow-up and therefore this is unlikely to have impacted on the interpretation of results. Specifically we examined whether BASDAI or ASQoL were importantly or statistically significantly related to likelihood of follow-up and confirmed they were not. Similarly, we opted not to use the ASDAS as an outcome measure because of the necessity that the clinic visit (for the CRP) and the questionnaire (for self-reported measures) occur sufficiently close in time. CRP was shown not to be related to BASDAI (at baseline) or as a predictor of response to therapy and did not play an important part in the analyses. While the patient-reported measures could be performed without a clinic visit, the BASMI required that a clinical visit had occurred. However, the BASMI was shown not to be importantly related to disease activity or a predictor of response.

In interpreting the results of this study it is important to consider that although we were able to determine if participants met research criteria, this is not the same as a clinical diagnosis of FM. Distinguishing, for example, multi-site pain of axSpa from the axial and widespread pain of FM is extremely challenging. As previously noted, the criteria for FM have not been validated in people with inflammatory arthritis and indeed the 2010[22] and 2011 research criteria[8] (but not the most recent 2016 criteria[23]) have sought to exclude persons from meeting FM criteria if they have symptoms which could be explained by inflammatory conditions.

This is one of the first studies to examine these issues in relation to co-morbid FM in people with axSpa. We and others have previously reported that disease indices are substantially elevated in patients who meet FM criteria.[4,24] This study provides new information that when the comparison of FM+ve and FM–ve patients takes account of clinical, demographic and lifestyle differences between the groups, the effect on disease indices is much less pronounced. Using the FM rapid screening tool (FIRST) Bello et al[24] found that those who scored highly on the tool were more likely to discontinue TNFi therapy and that this was a predictor of discontinuation of first therapy (together with peripheral involvement) on multivariable analysis. Molto et al[25] found that response to therapy was lower in those who scored highly on FIRST, for most endpoints, but not CRP. This study confirms this but has looked at longer term outcome (12 months compared to 3 months) and using internationally accepted criteria has identified one specific FM component (SSS), rather than meeting FM criteria generally, which identifies persons most likely to have a poor response.

The clinical implications from this study are that as meeting criteria for FM *per se* only had a modest effect on BASDAI (i.e. 1 point) or ASQoL (1.5 points), there should not be undue concern that FM distorts disease indices. Being FM+ve also did not predict poor or non-response to TNFi therapy amongst axSpa patients. Indeed with TNFi therapy and reduction in BASDAI, 3 out of 5 people with co-morbid FM will no longer meet criteria for FM. Specifically, the widespread distribution of pain was not a key determinant of response, instead it was a high somatic symptom burden captured by the SSS of the FM criteria which was a strong predictor. As an example, assuming a patient had a SSS of 12 and a WPI of 2 then their predicted improvement on BASDAI would be 4 less than a patient scoring zero on both scales whereas a patient with a SSS of 2 and WPI of 14 would have an improvement only 2 less than a patient scoring zero on both scales. Specifically we did not find that mood was an independent predictor of response. For patients with high SSS, treatments employing a cognitive behaviour approach, which have been shown to be effective for FM[26] may be indicated, and studies to test the feasibility of such an approach are underway.

In summary, meeting criteria for FM, in this study, only had a modest impact on assessment of disease activity by BASDAI, and did not influence the response to TNFi therapy. A high score on the symptom severity scale (SSS), representing a high somatic symptom burden, was a bigger influence on quality of life, assessed by ASQoL, and did identify persons who had significantly poorer response to TNFi therapy. It may be useful for rheumatologists to identify patients with high SSS who are commencing TNFi therapy and to consider additional non-pharmacological therapies to target such symptoms and potentially improve outcome.

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Tables and Figures

Table 1: Predictors of Bath AS Disease Index (BASDAI) score at baseline

	Model 1 (n=705)		Model 2 (n=626)	
Baseline Variable	**Coefficient**	**95% Confidence Interval**	**Coefficient**	**95% Confidence Interval**
Constant	2.54	(1.97, 3.12)	1.33	(0.73, 1.93)
BASMI	-0.14	(-0.22, -0.07)	-0.08	(-0.15, -0.00)
BASFI	0.67	(0.62, 0.73)	0.51	(0.45, 0.57)
CRP (mg/dL)	-0.00	(-0.01, 0.01)	-0.00	(-0.01, 0.01)
Age (years)				
- *< 30*	0		0	
- *30-39*	-0.26	(-0.75, 0.22)	-0.16	(-0.62, 0.30)
- *40-49*	-0.41	(-0.89, 0.07)	-0.15	(-0.61, 0.30)
- *50-59*	-0.50	(-0.98, -0.01)	-0.28	(-0.75, 0.18)
- *60-69*	-0.86	(-1.40, -0.33)	-0.47	(-0.98, 0.04)
- *≥ 70*	-1.03	(-1.62, -0.45)	-0.58	(-1.15, 0.00)
Gender				
- *Male*	0		0	
- *Female*	0.20	(-0.04, 0.43)	0.06	(-0.17, 0.30)
Deprivation (quintiles)				
1 (highest deprivation)	0		0	
2	-0.16	(-0.57, 0.24)	-0.12	(-0.51, 0.28)
3	-0.33	(-0.73, 0.06)	-0.31	(-0.70, 0.09)
4	-0.11	(-0.49, 0.27)	-0.10	(-0.48, 0.28)
5	-0.33	(-0.73, 0.06)	-0.25	(-0.64, 0.15)
Management				
- *Biologic*	-0.34	(-0.58, -0.09)	-0.30	(-0.53, -0.06)
Smoking status				
- *Never*	0		0	
- *Ex*	0.04	(-0.21, 0.28)	-0.01	(-0.24, 0.23)
- *Current*	0.01	(-0.31, 0.33)	-0.01	(-0.32, 0.31)
Fibromyalgia	1.04	(0.75, 1.33)	Not entered	
Fibromyalgia	Not entered			
- *WPI*			0.11	(0.08, 0.15)
- *SSS*			0.20	(0.15, 0.25)

Model fit: 1) R-squared 0.6454 2) R squared 0.7055

Table 2 Predictors of AS Quality of Life (ASQoL) score at baseline

	Model 1 (n=886)		Model 2 (n=796)	
Baseline Variable	**Coefficient**	**95% Confidence Interval**	**Coefficient**	**95% Confidence Interval**
Constant	0.88	(-0.17, 1.93)	-0.88	(-1.94, 0.18)
BASDAI	0.85	(0.72, 0.99)	0.54	(0.39, 0.68)
BASFI	1.00	(0.87, 1.13)	0.91	(0.78, 1.04)
BASMI	-0.13	(-0.26, -0.00)	-0.10	(-0.23, 0.03)
Age (years)				
- *<30*	0		0	
- *30-39*	-0.34	(-1.18, 0.50)	-0.05	(-0.85, 0.76)
- *40-49*	-1.10	(-1.93,-0.28)	-0.64	(-1.43, 0.15)
- *50-59*	-1.55	(-2.40,-0.71)	-1.07	(-1.88, -0.25)
- *60-69*	-1.71	(-2.63,-0.79)	-0.76	(-1.66, 0.13)
- *≥ 70*	-2.20	(-3.21,-1.19)	-1.31	(-2.31, -0.31)
Gender				
- *Male*	0		0	
- *Female*	0.74	(0.33, 1.16)	0.58	(0.16, 0.99)
Index of Multiple Deprivation (quintiles)				
1 (highest deprivation)	0		0	
2	-0.14	(-0.85, 0.57)	0.03	(-0.68, 0.74)
3	-0.14	(-0.84, 0.55)	0.11	(-0.60, 0.82)
4	-0.24	(-0.90, 0.42)	-0.09	(-0.76, 0.58)
5	-0.34	(-1.02, 0.34)	-0.15	(-0.84, 0.55)
Management				
- *Biologic therapy*	0.11	(-0.33, 0.56)	-0.01	(-0.45, 0.43)
Smoking status				
- *Never*	0		0	
- *Ex smoker*	0.05	(-0.37, 0.47)	0.05	(-0.36, 0.46)
- *Current*	0.94	(0.38, 1.49)	0.97	(0.42, 1.52)
Fibromyalgia	1.42	(0.88, 1.96)	Not entered	
Fibromyalgia	Not entered			
- *WPI*			0.09	(0.02, 0.16)
- *SSS*			0.50	(0.41, 0.59)

Model fit: 1) R-squared 0.7467 2) R squared 0.7821

Table 3 Predicting response to biologic therapy: improvements in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

	Model 1 (n=135)		Model 2 (n=121)	
Baseline Variable	**Coefficient**	**95% Confidence Interval**	**Coefficient**	**95% Confidence Interval**
Constant	-0.99	(-2.72, 0.75)	-0.28	(-2.03, 1.48)
BASDAI	0.72	(0.49, 0.95)	0.84	(0.60, 1.08)
BASFI	-0.38	(-0.60, -0.17)	-0.17	(-0.41, 0.07)
Age (years)				
- *<30*	0		0	
- *30-39*	0.75	(-0.56, 2.07)	0.82	(-0.46, 2.10)
- *40-49*	0.58	(-0.73, 1.89)	0.29	(-0.98, 1.56)
- *50-59*	0.31	(-1.11, 1.73)	0.26	(-1.14, 1.66)
- *60-69*	0.41	(-1.03, 1.86)	0.13	(-1.35, 1.62)
- *≥ 70*	-1.03	(-3.25, 1.19)	-0.89	(-3.22, 1.43)
Index of Multiple Deprivation (quintiles)				
1 (highest deprivation)	0		0	
2	0.58	(-0.71, 1.87)	0.66	(-0.68, 2.00)
3	-0.20	(-1.43, 1.03)	-0.50	(-1.79, 0.80)
4	0.91	(-0.28, 2.11)	0.71	(-0.52, 1.94)
5	0.55	(-0.67, 1.78)	0.19	(-1.12, 1.49)
Gender				
- *Male*	0		0	
- *Female*	-0.61	(-1.38, 0.17)	-0.10	(-0.91, 0.70)
Smoking status				
- *Never*	0		0	
- *Ex Smoker*	0.13	(-0.72, 0.98)	0.21	(-0.64, 1.06)
- *Current*	0.19	(-0.76, 1.13)	0.59	(-0.40, 1.57)
Fibromyalgia criteria met	-0.58	(-1.40, 0.23)	Not Applicable	
Fibromyalgia	Not applicable			
- *WPI*			-0.10	(-0.24, 0.03)
- *SSS*			-0.32	(-0.53, -0.12)

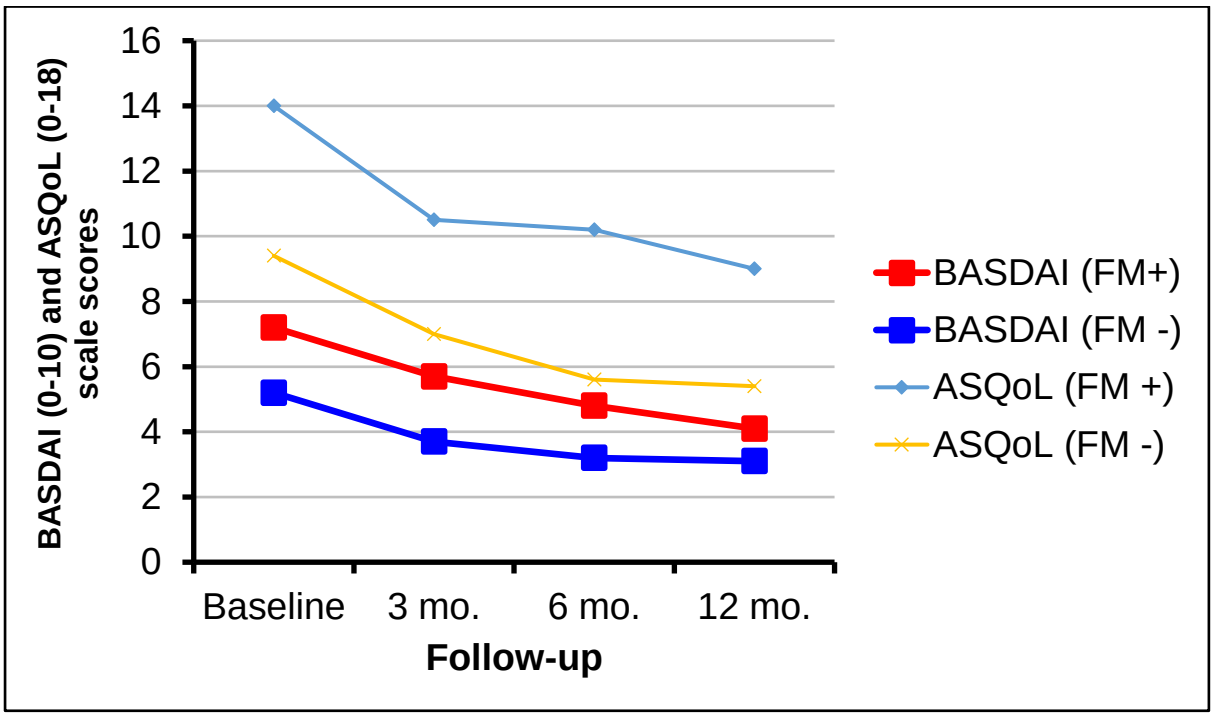
Model fit: 1) R-squared 0.3261 2) R-squared 0.4079

Table 4 Predicting response to biologic therapy: improvements in quality of life (Ankylosing Spondylitis Quality of Life Score (ASQoL)

	Model 1 (n=133)		**Model 2 (n=119)**	
Variable	**Coefficient**	**95% Confidence Interval**	**Coefficient**	**95% Confidence Interval**
Constant	-0.93	(-4.72, 2.86)	-0.15	(-3.96, 3.66)
ASQOL	0.30	(0.01, 0.59)	0.52	(0.20, 0.84)
BASDAI	0.36	(-0.17, 0.89)	0.52	(-0.03, 1.06)
BASFI	-0.50	(-1.06, 0.06)	-0.23	(-0.82, 0.35)
Age (years)				
- *30-39*	2.37	(-0.46, 5.21)	2.31	(-0.46, 5.08)
- *40-49*	2.16	(-0.71, 5.03)	1.75	(-1.03, 4.53)
- *50-59*	0.93	(-2.20, 4.07)	1.01	(-2.07, 4.09)
- *60-69*	0.90	(-2.30, 4.10)	0.49	(-2.74, 3.72)
- *≥ 70*	0.82	(-3.99, 5.62)	1.60	(-3.42, 6.63)
Index of Multiple Deprivation (quintiles)				
1 (highest deprivation)	0		0	
2	-1.27	(-4.05, 1.51)	-0.45	(-3.35, 2.46)
3	-1.28	(-3.97, 1.42)	-1.01	(-3.85, 1.83)
4	0.77	(-1.80, 3.35)	0.95	(-1.71, 3.61)
5	-0.40	(-3.04, 2.24)	-0.61	(-3.42, 2.20)
Gender				
- *Female*	-0.67	(-2.37, 1.04)	0.17	(-1.60, 1.94)
Smoking status				
- *Never*	0		0	
- *Ex*	1.31	(-0.55, 3.17)	1.33	(-0.51, 3.18)
- *Current*	0.43	(-1.72, 2.57)	0.72	(-1.48, 2.92)
Fibromyalgia criteria met	-0.51	(-2.29, 1.26)	Not applicable	
Fibromyalgia	Not applicable			
- *WPI*			-0.19	(-0.49, 0.10)
- *SSS*			-0.74	(-1.22, -0.25)

Model fit: 1) R-squared 0.1830 2) R-squared 0.2896

Figure 1: Disease activity and quality of life after commencement of biologic therapy[35]



BASDAI (n)	286	138	121	73
ASQOL (n)	282	139	122	74

[35] BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASQoL: Ankylosing Spondylitis Quality of Life Score

Chapter 2.7

AxSpA patients who also meet criteria for fibromyalgia: identifying distinct patient clusters using data from a UK national register (BSRBR-AS)

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Abstract

Background: Around 1 in 8 patients with axial spondyloarthritis (axSpA) also meet criteria for fibromyalgia and such patients have considerable unmet need. Identifying effective therapy is important but to what extent fibromyalgia-like symptoms relate to axSpA disease severity has not been established. The aim of the current analysis was to determine whether distinct clusters of axSpA patients exist and if so to determine a) whether they differ in terms of prevalence of fibromyalgia and b) the features of patients in clusters with high prevalence.

Methods: The British Society for Rheumatology Biologics Register (BSRBR-AS) recruited axSpA patients from 83 centres 2012-2017. Clinical data, and information from patients was collected (including research criteria for fibromyalgia). Cluster analysis was undertaken using split samples for development and validation both in the whole population and the sub-group which met fibromyalgia criteria.

Results: 1338 participants were included of whom 23% met research criteria for fibromyalgia. Four clusters were identified. Two exhibited very high disease activity, one which was primarily axial (n=347) and a smaller cluster (n=32) with axial and peripheral disease, and in both groups more than half of members met criteria for fibromyalgia. The remaining two clusters (n=437, n=462) had overall less severe disease however the one which showed greater disease activity and poorer quality of life had a higher proportion meeting fibromyalgia criteria (16% v. 4%). Within those meeting fibromyalgia criteria there were three clusters. The two main groups were defined by level of symptom severity with a smaller third cluster noted to have high average swollen and tender joint counts and high levels of comorbidity.

Conclusions: The major feature defining clusters with a high proportion of persons meeting criteria for fibromyalgia is high axSpA disease activity although clusters with features of fibromyalgia in the absence of high disease activity also show moderately high prevalence. Management may be most successful with pharmacologic therapy to target inflammation but enhanced by the concurrent use of non-pharmacologic therapy in such patients.

Background

Fibromyalgia is common as a co-morbidity in inflammatory arthritis. A recent meta-analysis estimated the prevalence as 21% (95% CI 17, 25) in rheumatoid arthritis (RA) across twenty five studies, 13% (95% CI 7, 19) in axial spondyloarthritis (axSpA) across eight studies and 18% (95% CI 13, 23) in psoriatic arthritis across six studies (1). There has been specific interest in the co-occurrence of fibromyalgia and axSpA for two reasons. The first is a result of a United States Food and Drug Administration Arthritis Advisory Committee meeting in 2013 which considered the case for expanding the use of Tumour Necrosis Factor inhibition (TNFi) therapy from ankylosing spondylitis to non-radiographic axSpA. The application was not approved partly because of concerns about the inappropriate use of such therapy for conditions such as back pain and fibromyalgia in the presence of minor magnetic resonance imaging (MRI) changes or positive HLA-B27 results (2). The second reason is around understanding the mechanisms of development of fibromyalgia. One hypothesis is that peripheral nociception, if sustained such as in axSpA, could in the context of an individual susceptible to its development, lead to central sensitisation and the development of fibromyalgia . An alternative possibility is that high levels of disease activity, and consequent pain, poor function and impact on quality of life including work, lead to emotional distress which itself has been shown to increase the risk of fibromyalgia. (3)

The British Society for Rheumatology Biologics Register (BSRBR-AS) of patients with axSpA is by far the largest study to have examined fibromyalgia as a comorbidity in this condition. In analysis of 1504 patients, it reported that 20.7% met the 2011 research criteria for fibromyalgia (4, 5). Those with co-morbid fibromyalgia had high levels of unmet need; this included substantially worse disease activity scores , function, global status (all measured using Bath indices) and quality of life (4), findings which have been consistent across studies (6, 7). If persons with poorly controlled disease are more likely to fulfill criteria for fibromyalgia through the process of central sensitisation, then management should focus on reducing disease activity associated with axSpA. Alternatively if the co-morbid fibromyalgia-like symptoms are unrelated to disease activity and arise through distinct mechanisms, then management should focus on the fibromyalgia (in addition to any management necessary for axSpA).

In this analysis, using BSRBR-AS, we aimed to establish if distinct clusters of patients with axSpA exist, and if so to a) ascertain whether such clusters exhibit important differences in

the prevalence of fibromyalgia and b) determine features of the clusters which exhibit a high prevalence of fibromyalgia.

Methods

BSRBR-AS is a prospective cohort study which recruited biologic-therapy naïve patients from across Great Britain fulfilling Assessment of SpondyloaArthritis international Society (ASAS) criteria for axSpA (8). Recruitment for the study took place between December 2012 and December 2017 across 83 secondary care rheumatology centres. Initially only those fulfilling the imaging ASAS criteria were eligible for inclusion, however from November 2014 those meeting the clinical arm were also eligible. The full protocol has been published previously (9). Patients were recruited to one of two sub-cohorts: those about to commence a biologic therapy (adalimumab, etanercept or certolizumab pegol) and those continuing on non-biologic therapy. The biologic cohort was followed up at 3 months and 6 months, and both cohorts were followed-up at 12 months and yearly thereafter up to a maximum of 5 years. If a patient in the non-biologic cohort commenced biologic therapy they switched sub-cohort and started a new follow-up schedule.

Clinical data collected during recruitment and follow-up appointments included: the presence of extra-spinal manifestations (history of uveitis, psoriasis, inflammatory bowel disease (IBD), peripheral joint involvement, dactylitis and enthesitis), history of comorbidities and physician-assessed swollen and tender joint count (40 and 44 joints respectively), and Bath metrology index (BASMI). In addition to clinical data, patient reported questionnaires were mailed at the same time and included validated instruments assessing, among others: Bath indices of disease activity (BASDAI), function (BASFI), global assessment (BAS-G), mental health (Hospital Anxiety and Depression Scale (HADs) (anxiety and depression subscales each scored 0-21) (10)), fatigue (Chalder fatigue scale, scored 0-11 (11)) and sleep disturbance (Jenkins Sleep Evaluation Questionnaire, scored 0-20 (12)). From August 2015, the patient reported questionnaire included the 2011 modification of the 2010 ACR criteria for fibromyalgia (5). As the aim of the current analysis was to identify discrete clusters within the axSpA population, in which the prevalence of fibromyalgia would be calculated; only participants who had completed a questionnaire after August 2015 were eligible for inclusion and amongst those who had, the first completion of the fibromyalgia research criteria was used as the time-point for data included in the current analysis.

Cluster analysis classifies individuals into groups (clusters) which optimise homogeneity within groups and heterogeneity between groups, based on a selection of pre-defined characteristics (clustering variables). The groups formed are highly dependent on the variables offered for clustering, therefore, the choice of these is ideally underpinned by empirical evidence. As the number of clusters is not known prior to analysis, a common approach is to determine the optimal clustering solution in one sample and to validate in a second sample. The choice of variables for the current analysis was determined through simple descriptive statistics (t-tests) in which those factors associated with fibromyalgia at $p \leq 0.05$ were considered important. To mitigate the effects of any differences in measurement scale used across clustering variables, and to adjust for non-normal distribution; each variable was standardised through z-score transformation. Prior to analysis, the eligible BSRBR-AS population was split into two equal-sized samples in which the optimal clustering solution was developed (Sample A) and then validated (Sample B). A three-stage approach was chosen:

Stage 1 - An agglomerative hierarchical cluster analysis was applied to Sample A using the Euclidean distance measure and weighted-average linkage method. The optimal number of cluster solutions was determined through consultation of the dendrogram and agglomeration schedule.

Stage 2 - The optimal solution from stage 1 was validated in Sample B using K-means clustering. The characteristics of each cluster was assessed and compared against those identified by the hierarchical analysis. Where the clustering solutions appeared identical, or near-identical, the solution was considered validated.

Stage 3 - Once the optimal solution was determined and validated (stages 1 & 2) the K-means clustering was conducted once more within Samples A and B combined to identify the final groupings of all participants. These clusters were examined in terms of both the clustering variables used (mean and standard deviations of non-transformed values) and the prevalence of fibromyalgia (or more specifically meeting research criteria for fibromyalgia).

On completion of the clustering procedure, the final clusters were examined to explore differences in both clinician and patient-reported factors. Demographic characteristics included: age, age at symptom onset, gender, smoking and alcohol use, while clinical factors included: classification criteria met, treatments prescribed and spinal mobility (BASMI: scored 0 (least) - 10 (most) severe (13)). Patient reported measures of health, from questionnaires, included the BASDAI, BASFI and BAS-G: all scored 0 (least) - 10 (most) severe (14-16)) and spinal pain (scored 0 (least) - 10 (most) severe). Quality of life was assessed

by the Ankylosing Spondylitis Quality of Life Index (ASQoL: scored 0 (good) to 18 (poor) (17)) and the short form 12 (scored 0 (poor) to 100 (best) (18)). Participants were asked to report co-morbidities including: myocardial infarction, unstable angina, congestive heart failure, stroke, hypertension, diabetes, asthma, chronic bronchitis/emphysema, peptic ulcer, liver disease, renal disease, tuberculosis, demyelination, depression and cancer. This allowed a co-morbidity "count" to be derived. Lastly, employment status was assessed by the Work Productivity and Activity Impairment scale (WPAI:SHP) to give an indication of work absence (absenteeism), impairment in work-productivity (presenteeism), overall work and non-work activity impairment (all scored as 0-100% (19)). From the information collected, the Ankylosing Spondylitis Disease Activity Scale (ASDAS) was calculated using the measure of CRP (preferentially) or ESR closest to the patient completed questionnaire used, provided it was within 90 days (20). In addition to calculating the proportion of participants within each cluster meeting criteria for fibromyalgia, the sub-scales of the criteria, namely the Widespread Pain Index (WPI, score 0-19) and Symptom Severity Score (SSS, score 0-12) could be calculated. Differences were assessed using chi-square or t-tests as appropriate and results are given as proportions or means (with 95% Confidence Intervals). To determine if similar clusters exist *within* the subgroup of participants meeting research criteria for fibromyalgia, this subgroup was split into two equal-sized samples (C and D) and the entire clustering process described above was repeated.

All analysis was conducted on the August 2017 dataset using STATA (StataCorp LP version 15.0).

Results

In total 1,338 participants were eligible for the current analysis of whom 65% were male, with a median age of 49 years, and median time since symptom onset of 18 years, and 36% had been recruited to the biologic cohort of the study. Of those tested, 79% were HLA-B27 positive. Most participants (64.6%) met the modified New York (mNY) criteria for ankylosing spondylitis, a further 29.7% fulfilled the ASAS imaging criteria for axSpA but not mNY, while 5.7% only met ASAS clinical criteria for axSpA. At the time when first completing research criteria for fibromyalgia, 23% (n=307) were classified positive. Prior to further analysis, the study population was randomly split in two equal sized groups.

Factors significantly associated with meeting fibromyalgia research criteria were identified and were eligible to be used in the cluster analysis. Where an eligible variable was strongly

related to another eligible variable, only the factor with the strongest relationship to fibromyalgia was used for clustering. The final variable group used for clustering was: number of extra-spinal manifestation and co-morbidity count, swollen joint count, tender joint count, anxiety, depression, fatigue and sleep disturbance.

The results of the hierarchical analysis in Sample A indicated the presence of 4 distinct clusters which were validated in Sample B with the K-means analyses. Differences in the clustering factors across each of the 4 clusters for samples A and B combined are detailed in Table 1 and Figure 1. There was one small cluster (Cluster 1) with 32 subjects. It was characterised by high scores or levels across all clustering variables and amongst participants in this cluster there was a very high proportion of participants who met research criteria for fibromyalgia (53%). The remaining clusters were of roughly equal size (varying between 347 and 462 subjects). Cluster 2 was characterised by few extra-spinal manifestations and comorbidities, low number of tender and swollen joints but high levels of anxiety, depression, fatigue and sleep disturbance. This cluster also had a very high proportion meeting research criteria for fibromyalgia (54%). Participants classified in Cluster 3 had few extra-spinal manifestations or comorbidities, a low number of tender and swollen joints low levels of anxiety, depression, fatigue and sleep disturbance. There was a low proportion meeting research criteria for fibromyalgia (4%). Finally Cluster 4 was characterised by few extra-spinal manifestations or comorbidities, a low number of tender and swollen joints, low levels of anxiety, depression and fatigue, but moderate sleep disturbance. There was a moderate proportion meeting research criteria for fibromyalgia (16%).

Examining factors which were not used in the clustering (Table 2), it is notable that the members of Clusters 1 and 2, with more than half meeting criteria for fibromyalgia, had markedly worse axSpA disease activity, function, global status, spinal pain, poorer mental and physical health. Both clusters had mean ASDAS values in the “very high disease activity” range. (i.e. >3.5). Quality of Life and work impact were also worst in Clusters 1 and 2, with intermediate levels in Cluster 4 in comparison to Cluster 3. Clusters 1 and 2 were the most likely to be receiving biologic therapy (31% and 39% respectively) followed by Cluster 4 (24%) and Cluster 3 (14%). There were approximately double the proportion of smokers in Clusters 1 and 2 (25% and 29% respectively) compared to Clusters 3 and 4 (13% and 14%), however in contrast, more had given up alcohol (28% and 28% v. 10% and 14%). Cluster 1 was distinguished by having a much higher proportion of female members (59%) than any other cluster (30-40%).

Participants meeting research criteria for fibromyalgia were split into two samples (C and D). The results of the hierarchical analysis on Sample C indicated that there were three distinct clusters which was validated in the K-means analysis using Sample D. The 3 cluster solution using both Samples C and D combined is shown in Table 3. Cluster 1 was small (n=17) with members scoring very highly on tender and swollen joints, anxiety, depression, fatigue and sleep problems and consequently had high pain and symptom severity scores on the fibromyalgia research criteria. This cluster was predominantly female (77%), in contrast to the other clusters which had 40-48% female members. Cluster 2 was larger (n=157), with average characteristics very similar to Cluster 1 except that almost all members had no swollen or tender joint and had lower levels of co-morbidities and extra-spinal manifestations. Nevertheless the WPI and SSS were very similar between Clusters 1 and 2. In contrast, subjects in Cluster 3 (n=120) scored lower across all domains and consequently had average WPI scores lower by between 1.3-1.5 and SSS lower by between 2.0-2.2.

Examining factors which were not used in the clustering of fibromyalgia patients (Table 4) Clusters 1 and 2 were very similar with respect to almost all the characteristics examined although Cluster 1 had primarily female members and members who were less likely to have recent use of DMARDs. Cluster 3 had better disease activity, although all three fibromyalgia patient clusters had ASDAS scores in the “very high disease activity” range. Cluster 3 also had better function, physical and particularly mental health, quality of life and work parameters.

Discussion

We have found evidence of distinct groups of axSpA patients: those with high disease activity which is either mainly axial or (in a smaller group) both axial and peripheral and in whom more than half of persons meet criteria for fibromyalgia; patients with low disease activity (in whom the prevalence of fibromyalgia is similar to persons without axial spondyloarthritis); and a group of patients with intermediate disease activity but with high levels of sleep disturbance and a raised prevalence of fibromyalgia. Within patients who meet criteria for fibromyalgia, there are two groups with higher axSpA disease activity (one with primarily axial disease and a smaller group with axial and peripheral disease) and this is reflected in higher pain and symptom severity scores of the fibromyalgia research criteria, in comparison to a third group.

The strength of this study was that it used a large national register to which most patients with axial spondyloarthritis were eligible to be enrolled. In examining clusters it used a split sample approach for their development and validation. It found consistent results – there were similar clusters within the total axSpA participant group and the sub-group who met research criteria for fibromyalgia. The clusters within the population group exhibited proportions meeting the research criteria for fibromyalgia which varied from the norm in the general population (~2-5%) ((21) to two groups with a prevalence of more than 50%. There are some methodological issues to be considered in the interpretation. Ideally the cluster structure should be confirmed in an external dataset. Not all patients with axSpA meeting ASAS criteria were eligible to join the register – those patients who had already commenced biologic therapy or had previous experience of biologic therapy were not eligible to be enrolled. The overall proportion of biologic therapy patients recruited was 7% lower than the proportion reporting taking biologic therapy in a recent survey of 1979 members of the National Ankylosing Spondylitis Society – the UK patient support group (36% v. 43%) (22). The relative size of the clusters should be considered indicative, therefore. This is particularly true with respect to patients who meet only the clinical arm of the ASAS criteria. They were only eligible for the registry in the latter 3 years of the 5-year recruitment period. We therefore examined the relative sizes of the clusters if only this latter period was considered. For all patients the distribution (for 1000 nominal patients) changed from 25:274:337:364 across Clusters 1-4 to 25:296:302:377 and for FM patients from 58:534:408 across Clusters 1-3 to 62:541:397. Thus it can be seen that the relatively sizes of the clusters are changed very little when we consider only the period over which patients meeting the clinical criteria of ASAS were eligible.

The second methodological issue is that the patient data used in this study varied with respect to their entry into the study. Some patients who were enrolled later in the recruitment period would have completed the fibromyalgia criteria at baseline or at one of the first follow-ups while for those recruited early it may have been up to 2.5 years before they completed their fibromyalgia assessment. Thus for the biologic therapy group, they will have completed this at various points in their history of such therapy. Finally the 2011 research criteria for fibromyalgia have not specifically been validated in the context of inflammatory arthritis. Indeed the criteria as published exclude persons if their pain could be explained by another condition. However almost all studies which have implemented the 2011 research criteria have dropped this question as it is considered difficult to evaluate and indeed it has been removed from the 2016 revision of the criteria (23). We note however

that in the cluster analysis of all axSpA patients, most of the axSpA patients with high swollen and tender joint count were in Cluster 1, and that cluster has a very high prevalence of fibromyalgia. It is possible that such peripheral involvement may result in high numbers of body regions scored as painful in the fibromyalgia criteria (although the influence on abdominal pain and headache aspects of the criteria is less obvious).

The results of the current study show that inflammation is strongly associated with meeting criteria for fibromyalgia. The clusters with high disease activity all had a high prevalence of fibromyalgia. Basu et al (24) have shown that RA patients who have features of fibromyalgia (what they call "fibromyalgianess"), demonstrate similar neurobiologic features, on imaging, to that observed in fibromyalgia patients. A further study reported that high levels of inflammation in RA were associated, on MRI, with more positive connections between the inferior parietal lobule, medial prefrontal cortex, and multiple brain networks, as well as reduced inferior parietal lobule grey matter, and that these patterns of connectivity were associated with reported fatigue, pain and cognitive dysfunction (25). The authors postulate that such networks may provide a mechanism by which peripheral inflammation results in central changes and features typically associated with fibromyalgia, although to what extent this association is mediated through emotional distress remains to be established. When treated with TNFi therapy, axSpA patients in BSRBR-AS with co-morbid fibromyalgia showed a similar absolute improvement in disease activity and quality of life over 6 months compared to those without co-morbid fibromyalgia, and two-thirds no longer satisfied fibromyalgia criteria suggesting that targeting inflammation is important to reduce fibromyalgia symptoms in patients with active axSpA (26).

An alternative explanation is that having fibromyalgia distorts the measures used to assess axSpA. Indeed, Alluno et al (27) demonstrated that measures thought to be disease specific such as the Bath indices are not axSpA specific. However it is unlikely that this can entirely account for the current observations. Duffield et al (1) in their meta-analysis of chronic inflammatory arthritis reported that across studies included, patients with axSpA and fibromyalgia had BASDAI scores that were around two points higher than those with axSpA alone (mean difference 2.2 95% CI (1.9, 2.6)). The differences observed in BASDAI between clusters in our study greatly exceed such levels. A previous paper from the BSRBR-AS demonstrated that the presence of co-morbid fibromyalgia increased BASDAI scores, on average only by 1.04 (after adjustment for other features of the disease) and increased the the ASQoL score (indicating poorer quality of life) by 1.42 (26).

However around one-third of patients with axSpA and fibromyalgia still have co-morbid fibromyalgia even after TNFi and those least likely to respond have high scores on the fibromyalgia symptom severity scale (26). The retention rate on TNFi at 2 years is also lower for axSpA patients with co-morbid fibromyalgia (28% v. 42%) (6). It seems therefore that even if inflammation is the primary driver of fibromyalgia symptoms, then once developed, therapeutic targeting of inflammatory pathways while important, is not sufficient. Further we have observed in the cluster results of all axSpA, a group of patients with modest disease activity and high levels of sleep disturbance who show a high prevalence of fibromyalgia. Whether additionally using non pharmacologic therapies (such as cognitive behaviour therapies) improves outcomes in such patient groups is not known but evidence in relation to pain (including fibromyalgia) and sleep disorders is promising (28, 29) and is currently being evaluated in ongoing studies of patients with axSpA and fibromyalgia.

Conclusions

In summary, this analysis has demonstrated distinct groups of axSpA patients with very different likelihood of reporting co-morbid fibromyalgia. The major feature defining clusters with a high prevalence of fibromyalgia is high disease activity and taken together with evidence from previous studies in this population, and others, managing the co-morbid fibromyalgia may be most successful with pharmacologic therapy to target inflammation but enhanced by the concurrent use of non-pharmacologic therapy. This hypothesis awaits testing in formal studies. The recording of information on features of fibromyalgia is not routine in most clinics assessing axSpA – and it would be important, if we seek to provide appropriate approaches to management to firstly ensure we are collecting relevant information to identify such disease features.

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approval was obtained from the UK National Research Ethics Service (NRES) Committee North East – County Durham and Tees Valley (Research Ethics Committee (REC) reference 11/NE/0374). All patients provided written informed consent to participate. GJM conceived the idea for the study and devised the analysis plan. LED undertook the analysis and LED and GJM together drafted the manuscript. All authors provided input in to the study plan, and critically reviewed the manuscript. GTJ is responsible for data management on BSRBR-AS.

Author Disclosures

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Tables and Figure

Table 1 – Clustering variables across clusters (total population) and proportion meeting research criteria for fibromyalgia				
	Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**
N	32	347	427	462
Clustering Factors	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**
Extra-spinal manifestation & comorbidity count	3.3 (2.7, 3.9)	1.3 (1.1, 1.4)	0.7 (0.6, 0.8)	1.2 (1.1,1.3)
Swollen joint count	8.1 (5.5, 10.7)	0.1 (0.03, 0.2)	0.05 (0.01, 0.1)	0.1 (0.05, 0.13)
Tender joint count	14.3 (11.2, 17.3)	0.4 (0.2, 0.5)	0.2 (0.1, 0.3)	0.4 (0.3, 0.6)
Anxiety score	10.5 (8.6, 12.5)	12.2 (11.8, 12.5)	3.6 (3.4, 4.0)	4.5 (4.2, 4.7)
Depression score	9.2 (7.6, 10.8)	10.3 (10.0, 10.7)	2.2 (2.0, 0.4)	5.2 (5.0, 5.5)
Fatigue score	7.1 (5.9, 8.3)	8.0 (7.7, 8.3)	0.9 (0.8, 1.1)	3.2 (2.9,3.4)
Sleep disturbance score	14.4 (12.4, 16.5)	14.5 (14.0, 15.0)	3.9 (3.6, 4.2)	11.2 (10.7, 11.6)
FM research criteria (and components)				
Proportion positive (%)	53%	54%	4%	16%
Widespread pain index	7.2 (6.0, 8.5)	7.4 (7.0, 7.8)	2.9 (2.7, 3.2)	5.0 (4.7, 5.3)
Symptom severity score	7.9 (6.9, 8.9)	8.4 (8.2, 8.7)	2.7 (2.5, 2.9)	5.4 (5.2, 5.6)

Table 2 – Differences in clinical and patient reported characteristics (not used in clustering) across clusters (total population)						
		Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**	
		N (%)	**N (%)**	**N (%)**	**N (%)**	**p value**
Categorical variable						
Gender:	male female	13 (40.6) 19 (59.4)	209 (60.2) 138 (39.8)	297 (69.6) 130 (30.4)	298 (64.5) 164 (35.5)	p<0.001
Smoking Status:	never ex current	10 (31.2) 14 (43.8) 8 (25.0)	129 (37.6) 116 (33.8) 98 (28.6)	201 (47.4) 168 (39.6) 55 (13.0)	214 (46.8) 180 (39.4) 63 (13.8)	p<0.001
Alcohol Use:	never ex current	1 (3.1) 9 (28.1) 22 (68.8)	39 (11.4) 94 (27.5) 209 (61.1)	20 (4.7) 41 (9.7) 361 (85.6)	25 (5.5) 63 (13.9) 366 (80.6)	p<0.001
Employed:	no yes	15(46.9) 17 (53.1)	164 (47.3) 183 (52.7)	113 (26.5) 314 (73.5)	160 (34.9)* 299 (65.1)	p<0.001
Job type:	mainly sedentary mainly physical	8 (50.0) 8 (50.0)	81 (45.5) 97 (54.5)	171 (56.1) 134 (43.9)	179 (61.5) 112 (38.5)	p=0.009
Current biologic therapy:	no yes	22 (68.8) 10 (31.2)	211 (61.0) 135 (39.0)	364 (86.3) 58 (13.7)	350 (76.1)* 110 (23.9)	p<0.001
NSAID (last 6m):	no yes	7 (21.9) 25 (78.1)	114 (32.9) 233 (67.1)	136 (31.9) 291 (68.1)	142 (30.7) 320 (69.3)	p=0.611
DMARD use in past 6m:	no yes	21 (65.6) 11 (34.4)	305 (87.9) 42 (12.1)	374 (87.6) 53 (12.4)	401 (86.8) 61 (13.2)	p=0.004
HLA B27 status:	positive negative untested	20 (62.5) 7 (21.9) 5 (15.6)	148 (42.7) 58 (16.7) 141 (40.6)	260 (60.9) 52 (12.2) 115 (26.9)	242 (52.4)* 66 (14.3) 154 (33.3)	p<0.001
		Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**	
Age	years	49.5 (45.2, 53.8)	47.5 (46.0, 48.9)	49.4 (48.1, 50.7)	50.3 (48.9, 51.6)	p=0.062

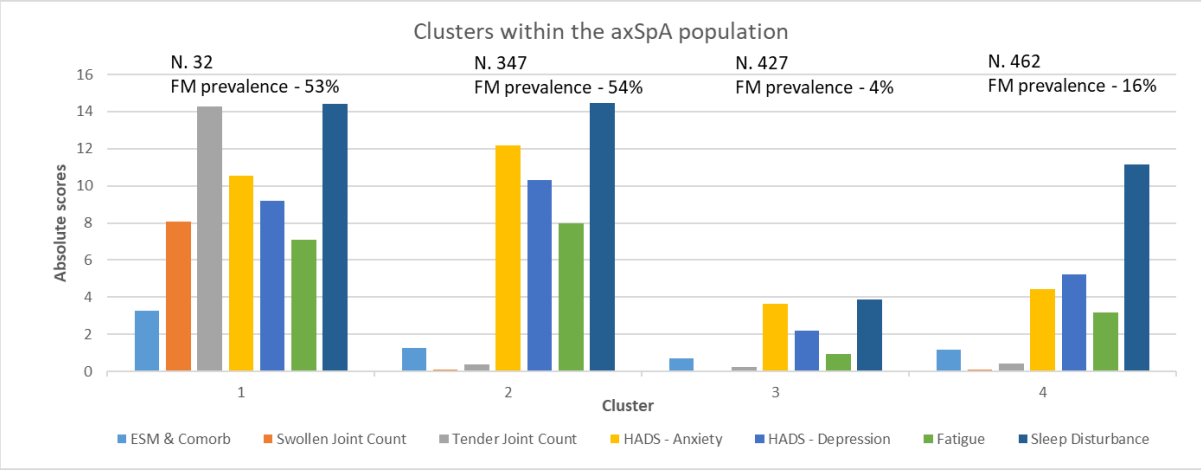
Age at symptom onset	years	31.7 (27.7, 35.7)	30.7 (29.3, 32.0)	28.7 (27.8, 29.8)	29.7 (28.6, 30.8)	p=0.074
Disease Activity	BASDAI: 0 (best) – 10 (worst)	6.7 (5.9, 7.4)	6.7 (6.5, 6.9)	2.5 (2.3, 2.6)	4.5 (4.3, 4.7)*	p<0.001
Disease Activity	ASDAS Score	3.6 (3.2, 4.0)	3.7 (3.6, 3.8)	2.2 (2.1, 2.3)	2.9 (2.7, 3.0)*	p<0.001
Physical Function	BASFI: 0 (best) – 10 (worst)	6.2 (5.4, 6.9)	6.5 (6.3, 6.8)	2.5 (2.3, 2.7)	4.2 (4.0, 4.5)*	p<0.001
Spinal Mobility	BASMI: 0 (best) – 10 (worst)	4.2 (3.6, 4.8)	4.1 (3.8, 4.3)	3.4 (3.2, 3.6)	3.7 (3.4, 3.9)	p<0.001
Patient Global	BASG: 0 (best) – 10 (worst)	6.9 (6.2, 7.5)	7.0 (6.8, 7.2)	2.6 (2.4, 2.8)	4.6 (4.3, 4.8)*	p<0.001
Spinal Pain	VAS: 0 (best) – 10 (worst)	5.1 (4.1, 6.2)	6.3 (6.1, 6.6)	2.2 (2.0, 2.4)	4.0 (3.7, 4.2)*	p<0.001
SF12 Mental Component	100 (best) – 0 (worst)	37.6 (33.0, 42.1)	35.2 (34.3, 36.1)	54.0 (53.3, 54.6)	47.2 (46.3, 48.0)*	p<0.001
SF12 Physical Component	100 (best) – 0 (worst)	32.3 (29.3, 35.3)	32.3 (31.2, 33.4)	46.2 (45.3, 47.1)	39.4 (38.4, 40.5)*	p<0.001
Quality of Life	ASQoL: 0 (best) – 18 (worst))	12.9 (11.3, 14.4)	13.3 (12.9, 13.7)	3.0 (2.7, 3.3)	7.9 (7.5, 8.3)*	p<0.001
Work absence	absenteeism (%)	17.4 (0.1, 34.7)	11.2 (7.7, 14.6)	0.4 (0.1, 0.7)	4.4 (2.6, 6.1)*	p<0.001
Work impairment	presenteeism (%)	48.6 (36.4, 60.7)	52.5 (49.0, 56.1)	15.1 (13.1, 17.0)	28.8 (26.3, 31.4)*	p<0.001
Overall work impairment	(%)	48.8 (35.7, 62.0)	55.1 (51.3, 58.9)	15.4 (13.4, 17.5)	30.4 (27.7, 33.2)*	p<0.001
Other activity impairment	(%)	63.1 (53.8, 72.4)	65.4 (63.1, 67.6)	19.8 (17.9, 21.7)	38.4 (36.1, 40.6)*	p<0.001
* significant difference between cluster 3 & 4 at p<0.05						

Table 3 – Clustering variables across clusters and fibromyalgia criteria sub-scale scores (amongst participants who met criteria for fibromyalgia)			
	Cluster 1	**Cluster 2**	**Cluster 3**
N	17	157	120
Clustering Factors	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**
Extra-spinal manifestation & comorbidity count	3.7 (2.8, 4.6)	1.5 (1.2, 1.7)	1.3 (1.0, 1.5)
Swollen joint count	7.1 (4.2, 10.0)	0.08 (0.002, 0.16)	0.1 (0.01, 0.13)
Tender joint count	15.0 (11.7, 18.3)	0.5 (0.2, 0.8)	0.4 (0.1, 0.7)
Anxiety *(HADs - scored 0-21)*	12.4 (9.8, 15.1)	13.2 (12.6, 13.7)	8.1 (7.5, 8.7)
Depression *(HADs - scored 0-21)*	10.8 (8.7, 12.9)	11.2 (10.7, 11.7)	6.2 (5.7, 6.7)
Fatigue *(Chalder Fatigue - scored 0-11)*	8.9 (7.6, 10.2)	8.5 (8.1, 8.9)	4.6 (4.0, 5.2)
Sleep disturbance *(Jenkins - scored 0-20)*	18.1 (16.6, 19.6)	16.0 (15.4, 16.6)	10.1 (9.1, 11.1)
FM components			
Widespread pain index	9.4 (7.7, 10.0)	9.2 (8.6, 9.8)	7.9 (7.3, 8.4)
Symptom severity score	9.5 (8.6, 10.4)	9.7 (9.4, 10.0)	7.5 (7.2, 7.9)

Table 4 – Differences in clinical and patient reported characteristics (not used in clustering) across clusters (fibromyalgia positive participants)					
		Cluster 1	**Cluster 2**	**Cluster 3**	
		N (%)	**N (%)**	**N (%)**	**p value**
Gender:	male female	4 (23.5) 13 (76.5)	94 (59.9)* 63 (40.1)	63 (52.5) 57 (47.5)	p=0.014
Smoking Status:	never ex current	5 (29.4) 6 (35.3) 6 (35.3)	53 (34.2) 52 (33.5) 50 (32.3)	51 (43.6) 48 (41.0) 18 (15.4)	p=0.027
Alcohol Use:	never ex current	1 (5.9) 7 (41.2) 9 (52.9)	21 (13.5) 50 (32.3) 84 (54.2)	13 (11.1) 21 (18.0) 83 (70.9)	p=0.032
Employed:	no yes	8 (47.1) 9 (52.9)	85 (54.1) 72 (45.9)	47 (39.5) 72 (60.5)	p=0.054
Job type:	mainly sedentary mainly physical	1 (12.5) 7 (87.5)	30 (43.5) 39 (56.5)	39 (55.7) 31 (44.3)	p=0.044
Current biologic therapy:	no yes	13 (76.5) 4 (23.5)	87 (55.4) 70 (44.6)	74 (61.7) 46 (38.3)	p=0.189
NSAID (last 6m):	no yes	3 (17.6) 14 (82.4)	55 (35.0) 102 (65.0)	32 (26.7) 88 (73.3)	p=0.160
DMARD use in past 6m:	no yes	10 (58.8) 7 (41.2)	136 (86.6)* 21 (13.4)	102 (85.0) 18 (15.0)	p=0.011
		Mean 95% CI	**Mean (95% CI)**	**Mean (95% CI)**	
Age	years	49.2 (43.3, 55.0)	47.8 (45.7, 50.0)	50.4 (47.8, 53.0)	p=0.445
Age at symptom onset	years	29.2 (25.6, 33.0)	29.7 (27.7, 31.7)	29.7 (27.5, 31.9)	p=0.873
Disease Activity	BASDAI: 0 (best) – 10 (worst)	7.8 (7.2, 8.5)	7.4 (7.2, 7.6)	6.0 (5.7, 6.2)	p<0.001
Disease Activity	ASDAS	3.8 (3.4, 4.2)	3.9 (3.8, 4.1)	3.3 (3.2, 3.5)	p<0.001
Physical Function	BASFI: 0 (best) – 10 (worst)	7.2 (6.3, 8.1)	7.2 (6.9, 7.5)	5.5 (5.1, 5.9)	p<0.001
Spinal Mobility	BASMI: 0 (best) – 10 (worst)	4.3 (3.4, 5.1)	4.2 (3.8, 4.6)	4.1 (3.6, 4.6)	p=0.934

Patient Global	BASG: 0 (best) – 10 (worst)	7.7 (7.1, 8.3)	7.7 (7.4, 7.9)	6.1 (5.7, 6.5)	p<0.001
Spinal Pain	0 (best) – 10 (worst)	6.2 (4.7, 7.6)	7.1 (6.8, 7.4)	5.6 (5.1, 6.0)	p<0.001
SF12 Mental Component	100 (best) – 0 (worst)	31.4 (26.6, 36.3)	32.5 (31.1, 34.0)	44.2 (42.5, 45.9)	p<0.001
SF12 Physical Component	100 (best) – 0 (worst)	28.9 (25.0, 32.8)	29.9 (28.4, 31.5)	34.3 (32.4, 36.2)	p<0.001
Quality of Life	ASQoL: 0 (best) – 18 (worst)	15.4 (14.2, 16.7)	14.6 (14.1, 15.1)	10.9 (10.2, 11.5)	p<0.001
Work absence	absenteeism: %	7.0 (1.3, 12.7)	14.2 (8.2, 20.1)	9.3 (4.4, 14.1)	p=0.737
Work impairment	presenteeism: %	55.6 (42.4, 68.7)	60.3 (55.1, 65.6)	44.8 (39.8, 49.8)	p<0.001
Overall work impairment	%	56.4 (41.3, 71.6)	63.4 (58.0, 68.9)	48.0 (42.7, 53.3)	p<0.001
Other activity impairment	**%**	75.9 (66.4, 85.4)	72.0 (69.4, 74.7)	54.5 (50.2, 58.8)	p<0.001
* significant difference between cluster 1 & 2 at p<0.05					

Figure 1 - Cluster solutions within whole BSRBR-AS population



Chapter 3 Discussion

The work in this thesis has demonstrated that:

- there is a reasonably good evidence-base on which to make recommendation for the management of fibromyalgia as determined by work undertaken for the revised EULAR management recommendations. In terms of improving pain, sleep, fatigue and daily functioning in people with fibromyalgia, a non-pharmacological approach should be the initial strategy. Exercise is effective. However, it is unknown whether the effectiveness is modified by type of exercise or frequency/duration. Of other therapies, a cognitive behavioural approach was effective across a large number of trials, although the effect sizes were relatively modest. Pharmacological therapies generally showed at best modest benefits and were associated with side effects. It was recommended that pharmacological approaches should only be used to address specific aspects of the condition which weren't sufficiently improved by a non-pharmacological approach. The recommendations from the review gave specific research recommendations which will be discussed later.

- the results of an RCT testing exercise and CBT for chronic widespread pain (which demonstrated benefit of both approaches but no additional benefit of receiving both), were robust to taking account of the characteristics of persons who were identified as eligible but chose not to take part in the trial. The estimated "number needed to treat" changed by no more than 1 for either (or both) of the interventions at short and long-term follow-ups.

- persons with chronic widespread pain are at considerable increased risk of premature mortality (in comparison to persons of similar age and gender without chronic widespread pain). In addition to all-cause mortality the excess is present also for cardiovascular and cancer mortality. This is unlikely to be due to the experience of pain itself but rather consequences of that experience. When the statistical models took account of lifestyle factors (or markers of such) amongst people with chronic widespread pain, the major part of the excess risk was no longer evident, which is consistent with them being on the path between the experience of chronic widespread pain and mortality risk.

- a large part of the excess risk of death in persons with chronic widespread pain, after taking account of lifestyle factors, was further attenuated when adjustment was made for use of opioid medicines. This work showed that there could be a relationship between opioid use and excess mortality although there is considerable uncertainty in this observation which may be explained by unmeasured confounding factors. If there is a risk, however, it is small in magnitude and any excess risk is with disease related, rather than non-disease related, deaths. The major finding from this paper is, even in a study whose participants have been shown to be more healthy than the general population, the widespread use of opioid medication (the vast majority amongst persons with chronic pain). Specific groups (e.g. those living in areas with high levels of deprivation, with low household income and/or who left education at a young age, and those no longer working due to ill-health) were identified who had very high levels of use.

Taking together the three manuscripts on fibromyalgia and axial spondyloarthritis, the major findings were that:

- around 1 in 5 of people with axial spondyloarthritis met criteria for fibromyalgia. They reported significantly worse disease activity, function, global severity scores, and quality of life, and were more likely to have moderate or severe levels of mood disorder and clinically important fatigue, but they did not have higher C-reactive protein levels or most extraspinal manifestations. They were more likely to have received biologic therapy. They appeared to have more severe disease but the only measure that was not self-reported did not differ between people with and without fibromyalgia.

- persons who met criteria for fibromyalgia had marginally worse quality of life and disease activity, which could not be explained by features of their axial spondyloarthritis. However the absolute benefit of biologic therapy on disease activity was similar in people with co-morbid fibromyalgia and their likelihood of meeting ASAS20 response criteria was the same as persons without co-morbid fibromyalgia.

- the defining feature of clusters of people with axial spondyloarthritis in whom a high proportion of people met criteria for fibromyalgia was high axSpA disease activity, although clusters which included people with some of the symptoms associated with

fibromyalgia (e.g. sleep disturbance) in the absence of high disease activity also showed moderately high prevalence. This emphasised the likely important role of management specifically targeted at features of fibromyalgia in those not responding to pharmacological therapy, alongside other appropriate management.

The main implications of the work, taken together, is influencing how people with chronic widespread pain or fibromyalgia can be optimally managed. Some of the key issues will be discussed below.

3.1 Optimising outcomes for people with chronic widespread pain/fibromyalgia with approaches which have been shown to be effective

Exercise is effective – however the challenge is how to deliver this. We know from behaviour change studies that simply giving people information is not sufficient. People with chronic pain or fibromyalgia are more likely to be overweight than persons without, may not be used to regular exercise, and indeed may find it difficult to know how to start. Often exercise can initially cause pain to become worse and without appropriate support and knowledge, persons with chronic pain and fibromyalgia may believe that the exercise is causing damage and stop. One of the participants in our trial of CBT and exercise (Beasley et al, 2015) who took part in the qualitative evaluation, made this point (as reported by Bee et al, 2016):

"It wasn't fair to keep going to the gym and making myself – because I was worse, so much worse when I'd been. So I thought, well,.. I'm not going to carry on doing it to make myself worse and suffer."

It also takes considerable commitment in terms of planning and preparation, as emphasised by another participant reported in the same study:

"It wasn't easy and a couple of times, when I had lots on, I didn't go. It seemed to take up a lot more time than you expected, getting there and changing. It did take up quite a lot of time. It needs a lot of planning really, because for me, well, I found it changes your routine."

Nevertheless a meta-analysis of adherence to walking programmes among women with fibromyalgia, found that in quasi-experimental and randomised controlled trials, adherence ranged from 73-87% (Sanz-Baños et al, 2018). Further in long-term follow-up of participants

in our trial of exercise and CBT (Beasley et al, 2015) we identified that 164 out of 196 participants maintained around 5 exercise sessions per week (which were at least moderate intensity) 5 years after the end of the intervention (Martin et al, 2019). Of this group 20 were people who had always maintained very high levels of exercise (around 10 sessions/week).

Most support for exercise probably comes through physiotherapy in secondary care, although this is likely to be an expensive mode of delivery. However it does allow physiotherapists the opportunity to deliver exercise within an overall behavioural (or psychologically-informed) approach to management (as discussed by Denneny et al, 2020) and as implemented in one of our trials of low back pain (Johnson et al, 2007). There are also models of linking with providers of physical activity in the community (such as sports centres); this necessitates the training of personnel and providing appropriate levels of support. The National Institute for Health and Care Excellence (NICE) reviewed exercise referral schemes and have supported their use for persons who are sedentary, have existing health conditions which put them at increased risk of ill-health, provided the schemes meet certain criteria (NICE Public Health Guideline PH54, 2014) – one of which is that they incorporate sets of techniques which aim to change the health behaviours of individuals. There has also been support, within specific clinical guidelines, for structured exercise programmes, including those for low back pain (NICE Guideline NG 59, 2016) and chronic fatigue syndrome (NICE Clinical Guideline 53, 2007).

Despite this, many recommendations or guides for management simply focus on recommendations that exercise is effective without giving any indication of how exercise is best facilitated. Arnold et al (2016) in recommendations for management of fibromyalgia in primary care state "*continuation of the exercise regimen is important, because ongoing exercise has been associated with maintenance of improvements in FM*" and indeed this could be a criticism also of the revised EULAR guidelines. However O'Dwyer et al (2019) in a systematic review of interventions in patients with fibromyalgia, using behaviour techniques to increase physical activity, reported only limited success, although Meade et al (2019) in a systematic review showed with respect to patients with musculoskeletal pain, that trials which included behaviour change techniques were more like to report adherence to the exercise regime.

In terms of thinking of other non-pharmacological therapies such as behavioural therapies, a common criticism is that although it is known that behavioural therapies are somewhat effective for chronic pain conditions, there is very limited access to clinical psychologist services. Indeed in 2019 the Migration Advisory Committee (MAC) considered that there was

a national shortage of psychologists and recommended adding them to the Shortage Occupation List (SOL). In their evidence to the committee the Department of Health and Social Care stated that "there is a need for clinical psychologists to go onto the SOL due to limited increases in supply and significant increases in demand as well as high vacancy rates" (MAC report, 2019). Notwithstanding the necessity for clinical psychologists to be available to deliver care for persons with chronic pain, it should be emphasised that it is not necessary to have such highly skilled persons delivering behavioural therapy to all such patients even where behavioural therapy is identified as appropriate. In the trial which formed the basis of the data in Chapter 2.2 (Beasley et al, 2015) the intervention was delivered by therapists accredited by the British Association for Behaviour and Cognitive Psychotherapies (BABCP). At a minimum this requires a Bachelor of Science degree and a two-year course leading to a postgraduate diploma in cognitive behaviour psychotherapies (CBP). Further there has been a considerable amount of research in terms of internet-based therapies. The potential advantage of such a self-directed approach is that it requires less input by the therapist (usually somewhere between 1-15 mins/week). A meta-analysis of 20 studies involving 1460 participants showed that internet delivered CBT was effective in the treatment of insomnia (Zachariae et al, 2016) while a meta-analysis of 20 studies involving 1418 participants comparing face-to-face and internet delivered CBT for psychiatric and somatic symptoms found that there was no evidence to conclude that they were not equivalent (although encouraged further larger trials) (Carlbring et al, 2018). Further studies have examined the training of members of the care team to deliver behavioural therapy (usually nurses) in terms of making any service sustainable and these have been shown to be effective in terms of chronic pain (e.g. Rutledge et al, 2018) and in related areas such a fatigue (Hewlett et al, 2019). Thus we need to move away from thinking of behaviour therapies just being delivered by clinical psychologists and to reserve such specialist expertise for those patients with the most complex requirements, instead looking at different methods of delivery and delivery by members within existing clinical teams.

A second issue with behavioural therapies is that often patients are unenthusiastic in engaging with them. In trials of CBT both in terms of managing chronic widespread pain and preventing its onset of which I was chief investigator (Beasley et al, 2015; Macfarlane et al, 2016), around one-third of persons allocated to receive CBT did not engage with the treatment. This was, of course, in groups who had agreed to be randomised into a trial where either one of the active arms or the only active arm was CBT and thus the non-engagement rate is likely to be much higher in an unselected sample. Indeed in the qualitative work undertaken alongside one of these trials Bee et al (2016) reported that "*psychological therapy brought with it connotations of social judgement, deviance and*

stigma" but also that the "*experience of psychological therapy often exceeded expectation*". Higgins et al (2018) examined characteristics of people with chronic low back pain who did not agree to be enrolled in a non-inferiority trial of cognitive behaviour therapy comparing face-to-face v. technology enabled delivery at a Veterans Health Affairs (VHA) centre in the United States. In total 54% of 290 persons declined participation and the single factor predicting such was currently taking opioid therapy. It may be that in order to increase engagement with such therapies introductory sessions may be useful in terms of discussing what the therapy is (and what it is not) and perhaps also involving people who have derived benefit from such approaches speaking about their experience. If done within a formal evaluation, outputs of interest would be the proportion of people originally not willing to take part in a behavioural therapy course who did subsequently take part and also whether these people benefit to the same extent as others taking part in such a course. The perception of a therapy such as CBT is important as within the same trial, treatment expectations were shown to influence the likelihood of response (Beasley et al, 2017) while overall in musculoskeletal trials a meta-analysis demonstrated that patients who received their preferred treatment had better outcomes than those who did not (Preference Collaborative Review Group, 2008).

In terms of the role of pharmacological therapies – there are currently no medicines licensed in the UK or the European Union specifically for fibromyalgia, although there are medications used for specific features (such as low-dose short-term amitryptiline which has been shown to improve sleep, pain and fatigue). In contrast there are three drugs licensed in the United States (duloxetine, milnacipran and pregabalin). A "consumer report" carried out in Germany amongst 1661 patients showed that the most common therapies used were self-management, pain prescription and aerobic exercise, while the therapies considered most effective were local and systemic heat therapies, education and rest. Pharmacological therapies featured strongly in approaches which were noted by patients to have had important side effects and included opioid therapies, tramadol, γ-amino butyric acid analogues (gabapentin and pregabalin) and tramadol (Hauser et al, 2012). In a further study using a research registry of patients with rheumatic diseases, it was reported that amongst patients with fibromyalgia taking one of the "new centrally acting drugs" (pregabalin, duloxetine and milnacipran) the median time to drug discontinuation was 2.5 years 95% CI (2, 3.5 years) (Wolfe et al, 2013). In the same study, with data collection in 2010, 13% of patients with fibromyalgia were using strong opioids (medications for which there was a "strong against" recommendation in the EULAR revised recommendations for the management of fibromyalgia on the basis of their lack of efficacy and side effect profile) while 47% were using any type of opioid.

In terms of whether there are new approaches to the pharmacological management of fibromyalgia, a subsequent Cochrane review has examined the evidence in relation to combined pharmacological therapy but concluded on the basis of 16 studies with 1474 participants that "*there are few, large, high-quality trials comparing combination pharmacotherapy with monotherapy for fibromyalgia, consequently limiting evidence to support or refute the use of combination pharmacotherapy for fibromyalgia*" (Thorpe et al, 2018). There has been some interest in the use of cannabinoids for the management of pain in rheumatic and musculoskeletal disorders and specifically fibromyalgia (Sarzi-Puttini et al, 2019). A meta-analysis (with meta-regression by pain type) examined the efficacy of cannabinoids for chronic pain. Thirty-three studies contributed to the meta-analysis and these demonstrated a mean benefit over placebo (in terms of a 0-10 scale pain score) of 0.7. Reductions were evident across mode of delivery and there was no difference in effectiveness for neuropathic and non-neuropathic pain (Wong et al, 2020). These conclusions are similar to another meta-analysis published around the same time and using a broadly similar body of evidence, which in addition reported that while there was no difference in serious adverse events at two weeks follow-up there was an increase in non-serious adverse events (the most common of which was dizziness reported by 31% of participants across studies) (Johal et al, 2020). This review also emphasised that conclusions were restricted at present to short-term follow up (2 weeks of treatment). There was a single trial included in the latter study in relation to fibromyalgia, testing the use of Nabilone, a synthetic cannabinoid (Skrabek et al, 2008). A subsequent Cochrane review on this topic included two studies, both involving nabilone (compared to placebo in one study and amitryptiline in the other) with a total of 72 subjects (Walitt et al, 2018). They concluded that there was "no convincing, unbiased, high quality evidence suggesting that nabilone is of value in treating people with fibromyalgia. The tolerability of nabilone was low in people with fibromyalgia."

Considering the research priorities listed in the revised recommendations for fibromyalgia – how can they be best addressed and what progress has been made? Where relevant we will bring in results in the current thesis in considering specific recommendations.

3.2 Which type of exercise is most effective: strength and/or aerobic training?

Common questions asked in terms of exercise for fibromyalgia are about "What type of exercise is most beneficial?" and also in relation to dose "How much exercise should people

with fibromyalgia undertake?". Specifically in relation to the latter, people with fibromyalgia describe a cycle of "boom and bust" in that they undertake activities and if they do "too much" then that has a negative effect on their health subsequently. Studies have shown that cognitive and physically demanding tasks result in greater reporting of cognitive and physical fatigue in people with fibromyalgia compared to people without (Dailey et al, 2015). For that reason, management often focusses on pacing as described in Jamieson-Lega et al (2013). Therefore the questions are extremely relevant. The ways in which this question could be addressed include a randomised controlled trial, although the likelihood is that the trial would need to be very large. It is likely that both forms of exercise have positive effects and therefore the trial would be seeking to detect the difference in effect between two forms of exercise which may be quite small. Further the trials would need to have their sample sizes inflated because of likely issues with adherence to the type of exercise allocated. Alternatively, one could undertake a network meta-analysis i.e. a meta-analysis which not only compares treatments which have been the subject of direct comparisons in trials but also compares treatments indirectly. For example, if there are trials which have compared treatments A and B, and trials which have compared treatments B and C, a network meta-analysis will allow one also to make estimates of the effectiveness comparing A with C.

I am not aware of any trials examining differences between type of exercise nor a network meta-analysis examining such. Andrade et al (2020) undertook an umbrella review of studies of exercise in patients with fibromyalgia. They focussed on systematic reviews but did not undertake a meta-analysis. They concluded that there were positive effects for aerobic exercise, strength training, aquatic exercises and movement therapies, although the greatest amount (and highest quality) of evidence was for aerobic exercise and strength training. In terms of outcomes they improved, the evidence was strongest in relation to improvement in pain and quality of life.

At present therefore the best advice would be for patients to engage with exercise (ideally different types) but importantly those which they either enjoy or feel they can undertake in the medium term, since as discussed below, engagement with the therapy is a prerequisite to improvement and people are most likely to keep doing types of exercise which they enjoy.

3.3 Is combined pharmacological and non-pharmacological approaches to management more effective than single modality management?

Evaluations (through randomised controlled trials) of management have focussed on either pharmacological approaches (usually funded by pharmaceutical companies) or non-pharmacological approaches (usually funded by government or charitable sources). The literature reviews undertaken as part of the revised EULAR recommendations did not identify any trials set up specifically to either compare pharmacological and non-pharmacological approaches nor to look at the effect of their combination on outcome. If there are no head to head comparisons of such approaches their relative benefit could still be evaluated through a network meta-analysis (as described in Section 3.2). Wang et al (2017) attempted to do this, looking at cognitive behaviour and pharmacological therapies for childhood anxiety disorders - there was a lack of relevant data but from that which was available there were no differences between CBT and any specific medication for the outcomes considered, but there was a large degree of uncertainty.

For fibromyalgia there is a strong rationale for directly comparing benefit. Firstly these therapies have a different place in the management of the conditions, non-pharmacological therapies being first line and long-term, whereas pharmacological approaches are for specific symptoms and are either not intended for use long-term or as discussed previously, data on their use shows they are not being used long-term by most people. The second issue is methodological. When undertaking pharmacological trials of a product, the standard design is that the trial is randomised and placebo- controlled, with both the investigator and the participant unaware of allocation. This is not possible with most non-pharmacological therapies in that it is not possible to blind the participant as to whether they are receiving the therapy or not. Although for some such therapies (such as those involving talking to the patient) it has been argued that there can be attention controls i.e. where the person receives the same amount of person to person interaction but without any of the "active ingredient" of the therapy. For example, in a review of the effectiveness of exercise interventions for people with lower limb osteoarthritis, some of the eligible trials included "active" control interventions such as home visits and providing sham gel (Hurley et al, 2018). In a systematic review and meta-analysis of the effectiveness of cognitive behaviour therapy, Bernardy et al (2018) of 29 studies, just 5 used "attention controls", 6 used an alternative non-pharmacological therapy for comparison , while the remainder either used waiting list controls (n=5) or "treatment as usual" (n=13). For example, the studies of Pilar Martinez et al (2014) and Miro et al (2011) both used a sleep hygiene education programme as a control against which to compare cognitive behaviour therapy for insomnia.

Why is the lack of a "placebo" control potentially problematic? Hróbjartsson and Gotzsche (2001) undertook a meta-analysis examining trials that included both a placebo and a no treatment arm. Their conclusion was "*Although placebos had no significant effects on objective or binary outcomes, they had possible small benefits in studies with continuous subjective outcomes and for the treatment of pain*". From the 27 trials involved with treatment of pain, there was a significant reduction in pain in the placebo compared to the no treatment arm (standardised mean difference -0.27; 95 percent confidence interval, -0.40 to -0.15)) which corresponds to an improvement of 6.5mm on a 0-100mm scale. Even though the most effective non-pharmacological managements (exercise and behaviour therapies) have relatively modest effect sizes, it needs to be acknowledged that at least some of this relates to "non-specific" benefits of the therapy.

So, is there a stronger rationale for looking at combined approaches? Certainly from a management point of view with education and exercise forming first line therapy, there is no reason one would then think of an either/or situation, and if one was later to start pharmacological therapy then exercise should still be continued. Similarly with cognitive behaviour therapy, there is no good reason that this would only be provided in the absence of pharmacological therapy. I am not aware of any trial in chronic pain or fibromyalgia which has examined the effectiveness of behavioural therapy with or without pharmacological therapy. In attention deficit hyperactivity disorder (ADHD), a secondary analysis of an RCT compared a total of 48 participants randomised to CBT and a stimulant(dextroamphetamine) with those randomised to CBT and placebo (Weiss et al, 2012); both groups showed a clear improvement in symptoms but there was no difference between them. A more recent trial for the same condition randomised 88 participants to receive CBT with or without medication (Cherkosova et al, 2020). The combination of CBT and medication was superior for the trial outcomes, although this superiority reduced over time.

There have however, been trials for pain and fibromyalgia using CBT which have examined whether treatment reduces the use of medication. For example in a trial of fibromyalgia and insomnia, participants received CBT for their insomnia and pain and were compared with waitlist controls. While the intervention led to short-term (but not long-term) changes in sleep medication, there was no effect on opioid use for pain (McCrae et al, 2020).

While randomised controlled trials provide "gold standard" evidence for the effectiveness or efficacy of treatments the reality is that not every comparison can feasibly be answered by a trial, either for scientific reasons or just the cost of each trial. Trials generally cost at least £1m and most address a single comparison. Thus other approaches will be required – and the use of disease registries may be able to play a role in evaluation. They allow a

greater range of comparisons to be made and reflect practice in a "real world setting". However the major drawback of this approach is that allocation of treatment is not randomised – and therefore there is the potential for "confounding by indication" whereby the characteristics of patients who receive alternative treatments are different. Patients who receive a specific therapy might appear to have worse outcomes if such a therapy is given to people with severe disease (who would be expected, all other things being equal, to have poorer outcomes). There are statistical techniques which are used to try to take account of this, the most popular of which is using propensity scores. The characteristics of people (which could be sociodemographic, clinical or patient reported factors) are used to predict the probability (propensity) that each person would have received a given treatment. The analysis depends on the fact that these characteristics should not perfectly predict treatment allocation and compares, amongst people with similar propensities, the outcomes for those who did and did not actually receive a given therapy (discussed in Suvarna, 2017). An example, which I led, using such an approach was in determining the role of biologic therapies in improving work outcomes for people with axial spondyloarthritis (Shim et al, 2018).

3.4 Are there characteristics of patients with fibromyalgia which predict response to specific therapies?

In the context of precision medicine (also previously known as personalised medicine) there has recently been great interest in how one can tailor management so that patients receive therapy to which they are likely to respond. This can take account, for example, of genetic factors, lifestyle and environment. While much research activity has focussed on cancer therapy in relation to molecular markers in tumours, the principle applies also to musculoskeletal conditions such as inflammatory arthritis and chronic pain. Can we provide the therapy to which a person is most likely to respond? There has been some discussion of this in relation to fibromyalgia; Hauser et al (2018) discuss "individualized management" and whether this should be based upon the predominant symptoms or based on overall symptom severity. There has long been a recognition that patients with fibromyalgia as a group are heterogeneous. Yim et al (2017) in a cluster analysis of 313 patients from Korea found four sub-groups which were distinguished by different levels of pain and physical, social and psychological function. This seems likely to be a reflection of different levels of severity of the condition rather than necessarily distinct subgroups based on different

manifestations of the condition. Bartley et al (2018) in a study of 256 patients, who completed daily patient diaries for up to 154 days in the United States, identified three patient clusters based on symptom variability; a high and low symptom variability cluster and a low symptom variability cluster but with high anxiety. There have also been studies which have examined patho-physiological processes which may be found in subgroups of patients. For example, small fibre pathology has been shown to be high in fibromyalgia with a meta-analysis (using 222 patients from 8 studies) suggesting a prevalence of 49% (95% CI 38-60%) (Grayston et al 2019), although doubt has been cast on whether these observations are specific to this condition (Clauw, 2015).

In terms of factors predicting response to treatment (or specific treatments), Schmidt-Wilcke et al (2014), found that in an imaging study of 15 patients with fibromyalgia that reduction in pain using Milnacipran was more common amongst patients with low levels of connectivity between pro-inflammatory and anti-inflammatory brain regions (specifically the rostral part of the anterior cingulate cortex (ACC) and Insular cortex (ICC)) while there were other specific patterns which predicted response to placebo. Evaluating a brief (1.5 days) inter-disciplinary treatment programme amongst 139 patients who met ACR Criteria for fibromyalgia, Worrel et al (2001) found that those who were more affected by symptoms were most likely to benefit. In a larger (and later) study from the same centre, predictors were reported to be younger age, more years of education, higher depression score, lower tender point count, and with no history of abuse (Oh et al, 2012). In our trial of telephone-delivered cognitive behaviour therapy and/or exercise therapy we conducted a post-hoc analysis to identify characteristics of people who responded to the individual therapies (Beasley et al, 2015). Those persons with more disabling pain, higher psychological distress and those who exhibited passive coping at the time of recruitment to the trial were more likely to meet response criteria, in comparison to persons without these characteristics. There were no patient characteristics which were predictive of response in the exercise group. Although not significant, it was noteworthy that the odds of response in males (compared to females) was lower in each of the telephone delivered cognitive behaviour therapy, exercise and combined study arms. An analysis of the same trial follow-up data examined the role of treatment expectations and preferences in relation to treatment response. While preference did not predict response at 24 months follow-up (34.8% response in those matched to their preferred treatment v. 30.3% in those not) , if a subject was allocated a treatment which they expected to result in improvement, they were more likely to meet response criteria compared to those allocated a treatment which they didn't think would result in improvement (32.8% v. 19.1%) (Beasley et al, 2017). Of course to benefit from a therapy patients have to engage with it, for medications that simply means taking

the medication as intended but for non-pharmacological therapies it means "engaging" in a wider sense. The previous trial followed participants in the exercise arm over a longer period (after the conclusion of the trial follow-up) and 164 out of 196 were classified as engagers. Predictors of non-engagement 5 years post-treatment were higher body mass index, more disabling chronic pain, poorer self-rated health, physical functioning, more frequent use of passive coping strategies and less frequent use of active coping strategies at the time of recruitment to the trial (Martin et al, 2019).

In summary, currently there is no good evidence of characteristics which predict response to treatment in patients with fibromyalgia neither for pharmacological or non-pharmacological therapies. With respect to non-pharmacological therapies (recommended as the mainstay for management by EULAR), there are several issues which have been identified as important: expectations of improvement with a therapy, engagement with therapy as well as other physical and psychosocial characteristics of patients.

3.5 How should fibromyalgia be managed when it occurs as a co-morbidity to inflammatory arthritis?

Three of the published manuscripts on this thesis have provided results relevant to this question although none are randomised controlled trials. They have quantified the co-occurrence of meeting criteria for fibromyalgia in persons with axial spondyloarthritis (1 in 5). This was higher than the 13% pooled estimate of co-occurrence in ankylosing spondylitis in a meta-analysis by Duffield et al (2018), but closer to their estimates for rheumatoid arthritis (21%) and psoriatic arthritis (18%). The characteristics of people with axSpA who also met criteria for fibromyalgia were consistent with higher disease activity although, in contrast, there was no difference in C-reactive protein nor in extra spinal manifestations. An alternative hypothesis is that meeting criteria for fibromyalgia is associated with a general increase in symptom reporting and this causes an elevation of self-reported axSpA disease markers. Indeed the manuscript of Macfarlane et al (2018) quantified this as approximately one point in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) after socio-demographic, clinical and lifestyle factors were taken into account. The concern is that such patients with fibromyalgia and axSpA may therefore be over-treated with biologics if that is partly determined by BASDAI. However the work in the same study showed that the absolute response to biologic therapy (in terms of disease activity and quality of life) was similar nor was there any difference in the likelihood of meeting the ASAS20

response criteria twelve months after starting therapy. Of particular note in this study was the fact that high somatic symptom burden (as measured by the symptom severity scale of the fibromyalgia criteria) was a predictor of non-response. As was stated within the relevant manuscripts, criteria for fibromyalgia have not been validated in the context of inflammatory arthritis and it is very challenging to separate features of axSpA from fibromyalgia and therefore these aspects, specifically cognitive dysfunction, fatigue and unrefreshed sleep may be particularly important in this respect. In contrast, Molto et al (2018) did find that there was a differential response to biologic therapy in axSpA patients who did and did not meet criteria for fibromyalgia (45 v. 54% response according to BASDAI50).

The conclusions from these papers would dictate that the decision to commence biologic therapy should not be influenced whether someone meets criteria for fibromyalgia – although it is worth noting that if persons have a high score on the fibromyalgia symptom severity scale then there are higher risk of non-response and may benefit from specific management focussed on fibromyalgia symptoms either alongside or post-biologic therapy (if no response). There are no studies available currently to determine which of these two options are best. Further the manuscript which undertook a cluster analysis identifies an additional group (low axSpA disease activity but features of fibromyalgia) which could benefit from management specifically targeted at features of fibromyalgia.

There is therefore a strong case for examining, in inflammatory arthritis, through a randomised controlled trial, the use of therapies for fibromyalgia symptoms, in order to improve outcomes. Issues to be determined would be whether there was a case for conducting such studies across inflammatory arthritis or whether there are key differences between them, what the timing of the intervention would be e.g. close to or soon after the time of diagnosis or at the time of commencing biologic therapy, and what the intervention would be (cognitive behaviour therapy would be one option, but whether it should be wider than that, for example more akin to “coaching”).

3.6 What aspects of a healthcare system optimise outcome for patients with fibromyalgia?

This recommendation arose out of the observation that while there was a reasonable body of evidence around some treatments (pharmacological and non-pharmacological) there was perceived to be a lack of data about how you then organise healthcare systems to deliver

effective treatments. Indeed we were not aware of relevant evidence to inform this part of the recommendations. Because of this "gap" I subsequently led a grant application (which was successful) to Versus Arthritis to address this lack of evidence. The PACFiND study (PAtient-centred Care for Fibromyalgia: New pathway Design) is a five year programme (2019-24), based in the United Kingdom, which is organised around three workpackages:

Workpackage A: Patient experiences of fibromyalgia and the healthcare they receive

This work will undertake an in-depth analysis of the patient journey, focussing on experiences of care and areas of unmet need, and identify current patterns of healthcare use using data linkage to map the patients' digital healthcare journey. The outputs from this will include a) creation of a new Healthtalk online resource: this will provide a web-based set of video resources describing patient experiences of the condition which is free and readily accessible to patients (https://www.healthtalk.org) b) a short film to act as a learning tool for the training of health professionals as well as a basis for the co-design process proposed later in the project (workpackage C) c) a dataset from the data linkage work which can be interrogated to ask specific questions about current use of health services by patients with fibromyalgia. This is being accomplished (the work is currently underway) by undertaking: a survey of a population sample of people with fibromyalgia; interviews with people with fibromyalgia from different healthcare and geographical settings; linking patient clinical records held in primary and secondary care with prescribing records and, where available, with patient self-report.

Workpackage B: Organisation and delivery of care for people with fibromyalgia

This work examines the organisation and delivery of care for people with fibromyalgia through a mapping exercise to identify and describe current provision of care for people with fibromyalgia and a series of geographically diverse case studies across the United Kingdom. We will employ non-participant qualitative observations of practice, analysis of local and national service documents, and qualitative interviews with healthcare professionals and service managers to understand the context and mechanisms influencing current healthcare interventions and outcomes for people with fibromyalgia.

Workpackage C: Developing a new model of care for people with fibromyalgia

This work will identify and develop new models of care for people with fibromyalgia, informed by results from workpackages A and B, adopting a co-design approach to work with patients, their families and care providers as partners alongside healthcare professionals and decision makers. The benefits and costs of existing and proposed models of care will be modelled and patient preferences for key features of a new model will be determined before

assessing and selecting a new model of care in collaboration with all key stakeholders. The project will produce a framework to support implementation and evaluation of the new care model in a range of different healthcare contexts.

Some early work from this programme has already reported (Doebl et al, 2020). This involved systematic reviews around models of care for people with fibromyalgia and patient experiences, preferences and unmet need. The major finding was that there was little evidence to inform the first question although there was evidence of a lack of benefit of ongoing care in secondary care settings. In terms of the second question, there were aspects that may be argued to be common across many long-term conditions such as inconsistent and poorly co-ordinated care. However there was also some aspects likely to be specific to fibromyalgia: patients reported that "fibromyalgia was often not viewed as a real condition, resulting in difficult encounters with healthcare staff, in particular not feeling believed or listened to". Unsurprisingly they also reported significant time taken to receive a diagnosis.

I am not aware of any other major project addressing the same issues at the current time.

3.7 What are the implications for management of the data around pain and mortality, as well as use of opioids

The data are now clear that persons with chronic widespread pain have increased premature mortality and this is not directly related to pain itself but likely a consequence of having it. Thus it becomes an important, but to date neglected, issue in patient management, although this may be changing (Nijs et al, 2020). Key features of the mechanism relating chronic pain to excess mortality are body mass index, exercise and diet. At present none of these feature strongly in management of chronic pain – and changing lifestyle is challenging. For example William et al (2019) evaluated, in a randomised controlled trial, a healthy lifestyle coaching intervention consisting of brief advice and a 6-month telephone delivered programme for people with musculoskeletal pain who were overweight or obese. The intervention did not reduce weight, improve diet or physical activity nor change pain beliefs. In a review of the role of lifestyle factors in managing chronic pain, Dean and Söderlund (2015) identified three important areas in relation to lifestyle interventions: firstly that physical therapies might complement lifestyle behaviour change; secondly that adopting a healthy lifestyle may reduce the need for physical therapies; and thirdly that persons with healthy lifestyle might respond more favourably to physical therapies for chronic pain. Of course the effect on mortality can be added to these benefits. We now need to work towards

incorporating consideration of lifestyle factors in the management of chronic pain and research how to enable people with chronic pain to effect change.

The final paper addressed the issue of opioid use – which clinically is most commonly prescribed for chronic pain. UK Biobank participants are not representative of the general population, and an analysis has shown that they are less likely to be obese, to smoke, to drink alcohol daily, and they have fewer self-reported health conditions (Fry et al, 2017). Specifically on follow-up they have lower cancer incidence and all-cause mortality. So appreciating that the data will be an underestimate of opioid use, the figures are remarkable in that 1 in 20 of participants were regular users rising to 1 in 9 amongst those of low socio-economic status and to 1 in 3 of persons who had stopped work because of their health. The data are not new in showing high rates of use but what the study adds are that it allows us to characterise people with particularly high usage in terms of level of education, socio-economic status and geography. Further it is clear from the data presented in the manuscript that the health of regular users is poor and in particular they still report chronic pain and poor quality of life. While this does not *demonstrate* that opioids are ineffective in the medium term, the data is consistent with such an interpretation and accords with a meta-analysis of their effects which showed only small improvements in pain and function and suggested (based only on low quality studies) that their effect was similar to non-opioid medications (Busse et al, 2018). The result in the manuscript demonstrating a relationship with excess mortality has not demonstrated that this association is causal. What it has done, however, is to identify that people who regularly consume opioids have excess mortality and this is still the case (albeit a small excess) after one controls for a range of health factors.

Mathieson et al (2020) reviewed world-wide data on what proportion of patients with chronic non-cancer pain are prescribed opioids and found that from 42 studies, the pooled estimate was 31%, 95% CI (29%-33%). Strong opioids were more frequently prescribed than weak opioids. Prescribing did not vary by region of the world but was becoming more common with time. Given that opioid use is associated with serious risks (including addiction and overdose) this is now a global priority about how to deal with the so-called "opioid epidemic" firstly by reducing opioid consumption in current users and secondly reducing the use in new patients. Many countries have produced guidelines (e.g. Dowell et al (2016) for the Untied States) but the challenge is that there are not obvious alternatives providing effective and safe relief from chronic pain. A systematic review examining studies focussed on methods to reduce opioid consumption found 67 studies (11 of which were randomised

controlled trials) studying 8 different types of intervention. These included interdisciplinary pain programs, buprenorphine-assisted dose reduction and behavioural therapy programs. Most of the studies (n=51) were rated as poor quality. Among 40 studies examining patient outcomes after dose reduction, improvement was reported in pain severity (8 of 8 fair-quality studies), function (5 of 5 fair-quality studies), and quality of life (3 of 3 fair-quality studies) (Frank et al, 2017). A Cochrane review of randomised controlled trials focussed on reducing (or cessation of) opioid consumption found only 5 trials with a total of 278 participants. The interventions included acupuncture, mindfulness and CBT. The results were described as "mixed" and the authors noted that while there were reductions in opioid consumption with the interventions, such reductions were also often seen in the control interventions (Eccleston et al, 2017).

Further studies are underway to determine how to effectively (and safely) reduce opioid consumption. For example in the United Kingdom a randomised controlled trial (i-WOTCH) has been funded by the National Institute of Health Research (NIHR) (https://warwick.ac.uk/fac/sci/med/research/ctu/trials/iwotch/). Eligible persons are those with chronic (non-malignant) pain who have been regularly using opioids for at least three months. The intervention (which aims to reduce pain interference) is described (abridged) as follows:

"The aim of the active arm intervention group is to empower people so that they are better able to make informed choices jointly with their healthcare provider. The active arm intervention includes a three day group course, relaxation CD, mindfulness CD, educational DVD and a copy of "My Opioid Manager" book. ….. Additionally, participants will be offered two one-to-one tapering support appointments with a specially trained nurse to agree a programme of tapering their opioid dosage, and two follow-up phone calls. The three-day course is delivered … by a trained lay facilitator ….. using Cognitive Behavioural Therapy techniques and grounded in the biopsychosocial approach to health and illness…..The control group participants will receive the relaxation CD and "My Opioid Manager" book only."

Thus as with the management of pain, behavioural approaches underpin methods to reduce reliance on opioid medication. This will be one of the major challenges in pain management over the coming years – reducing the prescribing of opioids to new patients while helping those who have been taking them long-term to come off and to replace that with other forms of management for chronic pain. The main challenge is what the other forms of management will be. Patients can perceive negatively the attempt to reduce or stop

medications which some patients believe are key to reducing pain and allowing them to be able to function. Emphasising the public health issue, newspaper headlines recently have focussed on the scale of the problem *"Thousands prescribed addictive opioids in north and north-east (Press and Journal , May 6th 2019)"* and *Opioid crisis fears as fifth of Scots given powerful painkillers (The Times Scotland, 30th August 2018),* the latter in response to a nationwide record linkage study (Torrance et al, 2018) but also the responses of patients *"Painkillers help me get through 'torture of daily life', says head of chronic pain support group" (Press and Journal, May 7th 2019).*

3.8 Summary

The work in this thesis has summarised the evidence base for managing fibromyalgia, of which chronic widespread pain is a key feature. It has highlighted priority areas for research and how some of these are currently being tackled and how others could be tackled. The discussion has emphasised that this is not always going to be possible through randomised controlled trials. It has provided new evidence around the co-occurrence of fibromyalgia and an inflammatory arthritis and presented data which can influence approaches to management of patients who may have both conditions, in the current absence of definitive management trials (or other study designs providing relevant information). Finally it has provided clear new data around the link between chronic pain and premature mortality which highlights the key role of lifestyle factors and a strong rationale for including a focus on such factors in management. The data on opioid use while not the first such data, do emphasise that this is a public health issue affecting particular socio-economic groups and such descriptive data must help to inform the approach to tacking this epidemic.

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