Original Article

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Running Head - Pain Definitions in Fibromyalgia

Full title - **The impact of moving from a widespread to multi-site pain definition on other fibromyalgia symptoms**

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ABSTRACT:

Objectives: The current study investigated whether associations between pain and the additional symptoms associated with fibromyalgia are different in persons with chronic widespread (CWP) compared to multi-site pain (MSP), with or without joint areas.

Patients/Methods: Six studies were utilized: 1958 British birth cohort, EpiFunD, Kid LBP, MUSICIAN, SHAMA and WHEST (females) studies. MSP was defined as the presence of pain in ≥8/≥10 body sites (adults/children) indicated on 4-view body manikins; conducted firstly to include joints (+joints) and secondly without (-joints).

The relationship between pain and fatigue, sleep disturbance, somatic symptoms and mood impairment, were assessed using logistic regression. Results are presented as odds ratios (OR), with 95% confidence intervals (CI).

Results: There were 34,818 participants across the study populations (adults: mean age range 42-56yrs, % male 43-51 (excluding WHEST), CWP prevalence 12-17%). Amongst those reporting MSP, the proportion reporting CWP ranged between 62-76%.

Amongst those reporting the symptoms associated with fibromyalgia, there was an increased likelihood of reporting pain, the magnitude of which were similar regardless of definition used. For example, within WHEST; reporting moderate/severe fatigue (Chalder fatigue scale 4-11) was associated with over a 5-fold increase in likelihood of reporting pain [CWP OR 5.2, 95%CI 3.9-6.9; MSP+joints 6.5, 5.0-8.6; MSP-joints 6.5, 4.7-9.0].

Discussion: This large-scale study demonstrates that, regardless of pain definition used, the magnitude of association between pain and other associated symptoms of fibromyalgia are similar. This supports the continued collection of both when classifying fibromyalgia but highlights that pain may not require to follow the definition outlined within the 1990ACR criteria.

Significance and Innovations –

- We have developed a description of multi-site pain which gives a similar prevalence to chronic widespread – defined as the presence of ≥8 pain sites,
- The magnitude of association between pain and the symptoms associated with fibromyalgia are similar regardless if joint areas were included in the definition of multisite pain or not,
- The continued collection of information on both pain and associated symptoms when classifying fibromyalgia remains important, however the definition of pain may not necessarily require to follow those outlined by the 1990 ACR criteria for fibromyalgia.

INTRODUCTION

The understanding and classification of pain syndromes, such as fibromyalgia, have been evolving. Since its early beginnings, as fibrositis, interest in fibromyalgia has steadily increased especially with regard to strategies used for the classification of affected individuals, which remain controversial.

The initial, American College of Rheumatology (ACR) endorsed, 1990 classification criteria for fibromyalgia required the presence of contralateral (left side, right side, above waist and below waist) and axial body pain in addition to pain on palpation in at least 11 (of 18) specified anatomical points [1]. Although these criteria resulted in many clinical and epidemiological studies, which improved the understanding of the aetiology and outcome of fibromyalgia, there were issues with operationalisation in the clinical setting, partly due to the inconsistency in examination for tender points [2]. These pain-centred criteria also failed to consider other common, non-pain, fibromyalgia symptoms such as fatigue. Generally, the agreement between the ACR 1990 classification criteria and clinical fibromyalgia diagnosis is around 75% [3].

In response to these limitations, the proposed 2010 preliminary diagnostic criteria (and the 2011 modification for research) moved fibromyalgia from a pain-focussed, to a symptom-focussed condition [4, 5]. In doing so, the pain aspect of the criteria moved from requiring this to be 'widespread', to being 'multi-site' and the previously required tender point examination was removed. In addition to the presence of chronic multi-site pain (lasting ≥3 months), the proposed diagnostic criteria also required the presence of additional symptoms associated with fibromyalgia; fatigue, waking unrefreshed, somatic and cognitive symptoms. The 2010 diagnostic criteria have provoked considerable debate, have been criticized as being difficult to operationalise [6], and alternative criteria have also been proposed [7]. It is also important to note that all three proposed

criteria for fibromyalgia (1990, preliminary 2010 and 2011 modification) were developed in populations of rheumatic disease patients.

In this context the current analysis was undertaken, as part of the ACTTION initiative (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks): developing a new taxonomy for pain conditions. Specifically informing the development of a taxonomy for fibromyalgia, the aims of the current analysis were to a) assess and compare the descriptive epidemiology of pain reporting in the general population, using 'widespread' and 'multi-site' pain definitions (with and without the inclusion of joints), b) assess the relationship between these pain definitions and the other associated symptoms of fibromyalgia, and due to the predominance of fibromyalgia in females, c) determine whether there is any sexual dimorphism in the reporting of these symptoms.

PATIENTS AND METHODS

Study populations:

Six existing studies (five with general population and one with school-based sampling frame), were used for the current post-hoc analysis. In all studies participants were asked if they had experienced, during the previous month, aches or pains lasting for at least one day. Positive responders were consequently invited to mark the specific areas in which this pain had occurred on four-view blank body manikins (which were thereafter coded with a maximum of 35 marked sites (Figure 1)). They were also asked whether the pain had lasted at least three months (indicating chronic pain). Manikin coding was conducted within each study by trained research staff. This procedure has previously shown high interrater reliability in the classification of widespread pain [8].

The Epidemiology of Functional Disorders (EpiFund) is a prospective cohort study, consisting of a random sample of 25-65 year-olds from three areas of the UK [9]. Data from the initial recruitment survey, collected by means of self-complete postal questionnaire, was used for the current analysis. Information was collected on sleep problems (Estimation of sleep problem scale [10]), mood symptoms (Hospital anxiety & depression scales [11]) and the presence of somatic symptoms (Somatic symptom scale [12]).

The Kid Low Back Pain (Kid LBP) study is a prospective cohort study conducted across secondary schools in Cheshire and North Derbyshire, UK [13]. School children, aged between 11 and 14 years were eligible for the study. Data from the initial self-complete questionnaire was used for the current analysis.

The Managing Unexplained Symptoms (Chronic Widespread Pain) in Primary Care: Involving Traditional and Accessible New Approaches (MUSICIAN) study is a 2x2 factorial randomised controlled trial, undertaken to investigate the management of chronic widespread pain (CWP) [14].

GP practices across Aberdeen City and the North Cheshire County of the UK were used as a sampling frame, from which randomly selected individuals aged 25 years or above were sent a self-complete screening questionnaire by post, data from which is used in the current analysis.

The Study of Health and its Management (SHAMA) is a cross-sectional study of individuals, residing in the Grampian region of the UK, aged 25 years or over [15] who self-completed a questionnaire sent by post. The questionnaire included a measurement of quality of life (Short form 36 [16]).

The National Child Development (1958 British birth cohort) study included all children born in Great Britain over a period of time in March 1958. Subjects have been followed up over the course of their lifetime [17]. In 2003 (when the cohort was 45 years old), participants self-completed a questionnaire which included a measure of psychological distress (General health questionnaire [18]).

The Women's Health Study (WHEST) is a cross-sectional study of females, aged 25 years or above, resident in the Grampian region of the UK who were sent a self-complete questionnaire by post. This questionnaire included measures of fatigue (Chalder fatigue scale [19]), sleep disturbance (Estimation of sleep problem scale [10]), somatic symptom reporting (Somatic symptom scale [12]) and depression (Patient health questionnaire–9 [20]).

Consent was obtained from potential participants within each original study as per their individual governance arrangements. All data used within the current study were fully anonymised.

Classification of pain:

Participants were classified as having widespread pain (contralateral pain and pain in the axial skeleton) and chronic widespread pain (widespread pain lasting ≥3 months), regional pain (pain which was not widespread) or no pain [1].

The cumulative distribution of the number of painful body sites was examined within each of the six study populations and was used to determine definitions of multi-site pain (MSP) which produced the closest prevalence to that of chronic widespread pain (according to the ACR 1990 definition). As an example; if X% of the study population reported CWP (ACR 1990); we chose the number of sites whose cumulative distribution was closest to 100-X% as the definition of 'MSP'. This process was conducted twice, once to include all body locations, hereafter defined as 'MSP (+joints)', and secondly with the exclusion of all 10 joint areas, hereafter defined as 'MSP (-joints)'.

Statistical analysis

The characteristics of each of the populations, and the subgroups fulfilling the CWP, MSP +joints, and MSP -joints definitions, were examined using simple descriptive statistics: reported as proportions for categorical variables and population mean (standard deviation) for continuous factors.

The relationship between the additional symptoms associated with fibromyalgia and the reporting of each of these pain definitions, were assessed using multiple binary logistic regression models. Fatigue was assessed using the Chalder fatigue scale, categorised by standard cut-offs into: none (score 0), mild (scores 1-3) and moderate/severe (scores 4-11) [19] or the short form 36 vitality score. Due to the skewed distribution of the data a pragmatic approach was chosen to categorise the short form vitality into three tertiles; highest tertile (scores 81-100), mid tertile (scores 58-80) and poorest tertile (scores 0-57) [16]. All analyses were thereafter conducted comparing the

poorest tertile to the middle and highest combined in order to maximise patient N while also retaining a clinically meaningful group. Sleep problems were assessed using the Estimation of sleep problem scale, categorised by standard cut-offs as no sleep problems (scores 0 -11) or sleep problems (scores 12- 20) [10] and the presence of any somatic symptoms by the Somatic symptom scale [12]. Lastly, emotional/mental health was assessed by four different instruments. The General health questionnaire (GHQ) was subdivided into tertiles (highest tertile (score 0), mid tertile (scores 1-2) and poorest tertile (scores 3-12) [18]). The Patient health questionnaire was subdivided into mild, moderate, moderately/severe and severe according to standard instrument cut-offs [21]. The Short form 36 mental health score was divided into tertiles due to skewed distribution (highest tertile (score 0-79) mid tertile (scores 80-86) and poorest tertile (scores 87-100) [16]) and analysis conducted on the poorest vs. the moderate and high groups. Lastly the Hospital anxiety and depression scales (HADS) were group into: no, borderline and clinical anxiety/depression according to standard instrument cut-offs [11].

Additionally, to assess potential sexual dimorphism; of those reporting MSP +joints, differences in the reporting of the additional symptoms associated with fibromyalgia were assessed, stratified by gender. For all logistic regression models, results are presented as odds ratios (OR) and 95% confidence intervals (CI).

All statistical analysis was undertaken using STATA (StataCorp LP version 13).

RESULTS

Characteristics of study populations

The total number of participants was 34,818 and from each study varied from 1,440 (Kid LBP) to 14,680 (MUSICIAN). Excluding WHEST, which contained only females, the proportion of male participants ranged between 43% and 51% (Table 1). The mean age range within the adult cohorts was narrow; 42 - 56 years, while children in the Kid LBP study had a mean age of 12 years. The prevalence of CWP within the adult studies varied between 12 and 17% and was lower within the only child population (7%) (Table 1).

Multi-site pain definition:

Although the prevalence of CWP differed between the adult study populations, the number of corresponding sites defining both MSP +joints and MSP -joints definitions was consistent across all; namely eight sites and above (Table 2). Only within the child population, the corresponding MSP (+ and - joints) definitions were different; at least 10 sites.

There was substantial overlap between CWP and MSP groups (Table 2). Within the adult populations, of persons satisfying the definition of MSP +joints, between 62 and 72% also fulfilled the CWP definition. Amongst those meeting the MSP -joints definition, between 68 and 79% also met the definition of CWP. Amongst the child population, those also fulfilling the CWP definition were substantially lower (39% and 42% respectively). There was consistency in the mean age and gender proportions across the adult population groups (Table 3). For example, within the EpiFunD study, the mean age in both CWP and MSP +joints groups was 48 years (standard deviation (sd) 11) and in the MSP -joints groups was 47yrs (sd11). The proportion male in the same study was 36%, 35% and 30%, for CWP, MSP +joints, and MSP -joints groups, respectively.

Relationship between pain and the additional symptoms associated with fibromyalgia

The populations meeting the CWP, MSP +joints and MSP -joints criteria, were characterised by their reporting of fatigue, sleep problems, somatic symptoms and mental/emotional health.

Fatigue

Fatigue was assessed within two studies (SHAMA and WHEST). Those who reported fatigue were more likely to report pain, regardless of pain definition used (Table 4). The magnitude of this association was greater with multi-site pain definitions. For example, within the WHEST study; compared to no fatigue, reporting moderate/severe fatigue was associated with a 5-fold increase in the odds of CWP (OR 5.2, 95% confidence interval 3.9-6.9) and a 6.5-fold increase in the odds of MSP (MSP +joints 6.5, 5.0-8.6; MSP -joints 6.5, 4.7-9.0) (Table 4).

Sleep Problems

Sleep problems were assessed within two studies (WHEST and EpiFunD). Those who reported sleep problems had a 4-fold increased odds of reporting pain (Table 4) and this was consistent across pain definition. For example, within the EpiFunD study: CWP 4.1, 3.6-4.8, MSP +joints 4.1, 3.6-4.8, MSP -joints 4.2, 3.5-5.0 (Table 4).

Somatic Symptoms

Somatic symptoms were assessed within two studies (WHEST and EpiFunD). The reporting of any somatic symptom was associated with an increased odds of reporting pain. The magnitude of this association was similar across all pain definitions for each individual symptom. For example, within the EpiFund study, reporting breathing difficulties was associated with around a 2.5-fold increase in the odds of reporting pain: CWP 2.5, 2.1-2.8, MSP +joints 2.6, 2.3-2.98, MSP -joints 2.7, 2.3-3.3 (Table 4). The only notable difference in pain reporting was demonstrated within the somatic

symptom of digit pain, in which the odds of pain reporting was larger for MSP +joints compared to the other pain groups: CWP 4.2, 3.7-4.9, MSP +joints 5.2, 4.5-5.9, MSP -joints 4.6, 3.9-5.5 (Table 4).

Mental and Emotional Health

Mental/emotional health was assessed within four studies (1958 British birth cohort, WHEST, SHAMA and EpiFunD). Generally, reporting impaired mental health was associated with an increased odds of reporting pain (Table 4). The magnitude of this association increased as the severity of mental health problems worsened but was consistent across pain definitions. As an example, within the EpiFunD study and using the HADS scale; reporting borderline depression was associated with at least a 2.5-fold increase in the odds of pain (CWP 2.5, 2.1-3.1, MSP +joints 2.5, 2.0-2.99, MSP -joints 2.9, 2.3-3.7) while reporting clinical depression was associated with over a 4-fold increase in this (CWP 4.5, 3.6-5.5, MSP +joints 4.2, 3.4-5.2, MSP -joints 4.7, 3.7-6.0) (Table 4).

Relationship between pain and the additional symptoms associated with fibromyalgia, stratified by gender

With the aim of assessing potential sexual dimorphism, stratification was used to assess gender differences in the association between pain reporting (MSP +joints) and other additional symptoms associated with fibromyalgia.

Reporting fatigue was associated with an increased odds of reporting pain regardless of gender (Table 5). Amongst females, compared to those reporting moderate/high vitality (SF-36 vt score 58-100): those reporting poor vitality (score 0-57) had a 5-fold increase in the odds of also reporting MSP +joints (5.1, 3.3-7.7). Within males, the odds of pain reporting in the presence of poor vitality was 4.4, 2.7-7.1. Those who reported sleep problems demonstrated an increased odds of reporting MSP +joints, and the magnitude of this association was similar across both males and females: 4.4, 3.5-5.6 (males), 3.8, 3.2-4.6 (females) (Table 5). Additionally, those reporting somatic symptoms

were more likely to report MSP +joints (Table 5) and the magnitude of this was similar across gender. For example, reporting breathing difficulties was associated with around a 2.5-fold increase in the odds of pain in both males (2.4, 1.9-3.1) and females (2.6, 2.2-3.1). Lastly, those who reported impaired mental health were more likely to report MSP +joints regardless of gender (Table 5). For example, reporting borderline depression (compared to no depression) was associated with over a doubling in the odds of pain (males: 2.9, 2.1-4.1, females: 2.3, 1.8-2.9) and reporting clinical depression was associated with over a quadrupling in the odds of this (males: 5.0, 3.6-6.7, females: 4.2, 3.2-5.5).

In addition to the raw comparison of the relationship between pain and the additional associated symptoms of fibromyalgia by gender, potential differences were further assessed using interaction terms. These additional models (data not shown) confirmed that there were no statistically significant interactions between gender and fatigue, sleep problems, somatic symptoms or mental/emotional health (p values all >0.05).

DISCUSSION

The aims of this study were to assess and compare the descriptive epidemiology of pain area reporting using widespread and multi-site definitions and to determine if the relationship between these definitions and the other symptoms associated with fibromyalgia differ. We have demonstrated that there is little difference - the magnitude of association was similar between fatigue, sleep disturbance, the reporting of somatic symptoms or cognitive problem and CWP or MSP (with or without consideration of joint pain). Additionally, there is no indication of systematic differences in the magnitude of these associations by gender.

There are a number of methodological considerations in interpreting the current findings. Firstly, one of the primary aims of the study was to assess the relationship between alternative pain area definitions (CWP/MSP) and the additional associated symptoms of fibromyalgia. The MSP definition was formulated in such a way as to identify a population which gave a similar prevalence to that of CWP. Due to this, one may expect that a) both groups would include many of the same individuals and b) therefore the study would have only modest power to detect potential differences. The overlap observed was between 60 and 76%, leaving a substantial number of unique individuals within each group. Additionally, the characteristics of those within the groups differed – pain chronicity being the most apparent. By definition, 100% of the CWP group experienced chronic pain (pain ≥ 3 months duration), however within the MSP groups this dropped to as low as 77% (adult population). The similarities shown between groups are therefore not solely due to the overlap of patients, although this will have contributed.

The relationship between pain and the other associated symptoms of FM was assessed through bivariate analysis using studies which contained both a measure of pain (which allowed the classification of CWP and MSP) and at least one of the associated symptoms FM features.

Unfortunately no single study contained all predictors, therefore a fully adjusted model could not be created. Although the aim here was to deduce how these features individually predicted pain; future studies assessing whether these relationships remain when controlling for the other symptoms would be valuable.

Additionally, although the magnitude of association between these symptoms and pain were broadly similar across pain definition, there were differences noted across the study and measure used. Although there was little overlap in the instruments across studies, both WHEST and EpiFunD collected identical sleep disturbance and somatic symptom measures. The results from these studies exhibited small differences in the magnitude of association with pain; differences which may largely be due to the study populations themselves. While EpiFunD is a general population survey, WHEST only recruited females, and as females are generally more likely to report symptoms such as insomnia and sleep disturbance [22], these differences are perhaps not surprising. Conversely, multiple instruments were used to measure both fatigue and emotional/mental health. Although differences in the magnitude of association with pain can partly be attributed to the fact that different instruments, although broadly measure similar concepts, are not identical and may be expected to be capturing slightly different aspects. It should be noted that although there were differences in OR across measures, all multiple level outcomes demonstrated similar dose-relationship trends – e.g. the worse the mental/emotional category the greater the likelihood of reporting pain.

Within the current study four-view body manikins were used to assess pain areas rather than those presented within the published fibromyalgia criteria [1, 4, 5]. As the 2011 modification, for use within epidemiological and clinical studies, is a relatively recent development, none of the population studies used within the current analysis included this. Pain areas were assessed, through the pain manikins present across all six studies. It is interesting to note that despite the use of a

different pain area definition, ultimately the number of pain sites needed (≥ 8) to define MSP within the adult studies was very similar and is consistent to those proposed within other studies [23].

This large scale post hoc study, encompassing over 34,000 individuals across multiple studies, is the first to assess the association between different pain area definitions and the relationship with the other symptoms associated with fibromyalgia and demonstrated similar magnitudes of association regardless of the definition used. In the absence of 'gold standard' criteria for fibromyalgia, we have shown that there may be multiple ways in which the core feature of this syndrome, namely pain, could be defined - a concept which has been demonstrated in other conditions, such as within the classification of shoulder pain [24]. Although CWP has been the underpinning concept of the ACR 1990 classification of fibromyalgia, its prevalence differs considerably based on the specific definition used [25]. In line with previous studies which sought to compare associations of widespread and multi-site pain with known risk factors, the current study supports classification of pain simply by number of sites [26, 27].

The original ACR 1990 classification criteria included a definition of pain distribution which is widespread and included joint areas [1], however the more recent 2010/2011 modifications have gone on to classify multi-site pain without considering many of the original joint areas [4, 5]. Within the current study we aimed to determine if the re-inclusion of joints within a MSP definition would result in differences in the relationship with the additional features of fibromyalgia. The results presented have shown, in fact, that there is little difference in the relationship between pain and the other features regardless as to whether joint areas were included or not. Excluding these areas from classification criteria may omit a large proportion of individuals who exhibit pain in multiple sites but due to the specific location of these do not meet the current widespread definition [4, 5]. Future classification criteria for fibromyalgia may consider the re-inclusion of joint areas within the definition of pain..

The current study also aimed to determine, amongst those fulfilling the new definition of MSP, whether there were gender differences in the reporting of the other features of fibromyalgia. Although fibromyalgia is more common in females (particularly when 1990 or clinical diagnoses are used [6]), the current study did not provide evidence of differences in the relationship between pain and these features. This is consistent with previous studies which have shown that there is little difference by gender in the reporting of symptoms such as anxiety/depression [28, 29, 30] and somatic symptoms [29] amongst those reporting pain.

Lastly, in addition to including several independent adult populations, the current study also included a study in schoolchildren (Kid LBP study). Within the juvenile population, the prevalence of CWP was lower than within adults, however regional pain was more common. This may be explained, in part, by the developmental stage of the study participants and indicates that standard 'adult' definitions of pain may not be suitable for child populations. Furthermore, the classification of widespread and multi-site pain may need to be made differently in this group. This is supported by previous studies which indicated differences in the reporting of FM symptoms in young adults [31]. Specifically that the additional features of FM (notably sleep quality and depressive symptoms) demonstrated stronger association with symptom severity than for widespread pain.

To our knowledge, this is the largest study (utilizing information on over 34,000 individuals across multiple studies) to have assessed the association between pain areas and the other associated symptoms of fibromyalgia in the context of alternative pain definitions. We have demonstrated similar magnitudes of association with chronic widespread and multi-site pain (whether or not joint areas are included). Although the results presented here should be further validated within other populations outside the United Kingdom, researchers and clinicians alike should be advised that the continued collection of information on the additional associated symptoms of fibromyalgia, in

conjunction to pain, remain important when classifying fibromyalgia but that this pain definition may not necessarily require to follow those outlined by the 1990 ACR criteria for fibromyalgia.

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Contribution statement

LA, LJC, GJM and RB jointly conceived of the idea of the study. AAA, MB, EF and GTJ provided substantial contributions regarding the acquisition of data. LED conducted the analysis, under the supervision of GJM. LED produced the first draft of the paper. All authors provided critical comments to the interpretation of the results presented, revisions to the final manuscript and gave approval for submission. Dan Buskila (BGU University of the Negev) contributed to discussions in an ACTTION meeting held July 2014 from which this manuscript arose.

Conflicts of interest

The authors declare no relevant conflicts of interest.

REFERENCES

(1) Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis Rheum* 1990;**33**:160-172.

(2) Fitzcharles MA, Boulos P. Inaccuracy in the diagnosis of fibromyalgia syndrome: analysis of referrals. *Rheumatology (Oxford)* 2003;**42**:263-267.

(3) Katz RS, Wolfe F, Michaud K. Fibromyalgia diagnosis: a comparison of clinical, survey, and American College of Rheumatology criteria. *Arthritis Rheum* 2006;**54**:169-176.

(4) Wolfe F, Clauw DJ, Fitzcharles M, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* 2010;**62**:600-610.

(5) Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J Rheumatol* 2011;**38**:1113-1122.

(6) Jones GT, Atzeni F, Beasley M, Flüß E, Sarzi-Puttini P, Macfarlane GJ. The prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. *Arthritis Rheumatol* 2015;**67**:568-575.

(7) Bennett RM, Friend R, Marcus D, Bernstein C, Han BK, Yachoui R, et al. Criteria for the diagnosis of fibromyalgia: validation of the modified 2010 preliminary American College of Rheumatology criteria and the development of alternative criteria. *Arthritis Care Res* 2014;**66**:1364-1373. (8) Lacey, R. J., Lewis, M., Jordan, K., Jinks, C., & Sim, J. Interrater reliability of scoring of pain drawings in a self-report health survey. *Spine* 2005;**30**:E455-E458.

(9) McBeth J, Nicholl BI, Cordingley L, Davies KA, Macfarlane GJ. Chronic widespread pain predicts physical inactivity: results from the prospective EPIFUND study. *Eur J Pain* 2010;**14**:972-979.

(10) Jenkins CD, Stanton B, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. *J Clin Epidemiol* 1988;**41**:313-321.

(11) Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361-370.

(12) Ohtmer E, DeSouza C. A screening test for somatization disorder. *Am J Psychiatry* 1985;**142**:1146-1149.

(13) Watson KD, Papageorgiou AC, Jones GT, Taylor S, Symmons DPM, Silman AJ, et al. Low back pain in schoolchildren: occurrence and characteristics. *PAIN®* 2002;**97**:87-92.

(14) Macfarlane GJ, Beasley M, Jones EA, Prescott GJ, Docking R, Keeley P, et al. The prevalence and management of low back pain across adulthood: Results from a population-based cross-sectional study (the MUSICIAN study). *PAIN®* 2012;**153**:27-32.

(15) Flüß E, Bond CM, Jones GT, Macfarlane GJ. The re-evaluation of the measurement of pain in population-based epidemiological studies: The SHAMA study. *Br J Pain* 2015;**9**:131-141

(16) Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992;**305**:160-164.

(17) Atherton K, Fuller E, Shepherd P, Strachan DP, Power C. Loss and representativeness in a biomedical survey at age 45 years: 1958 British birth cohort. *J Epidemiol Community Health* 2008;**62**:216-223.

(18) Goldberg DP. The detection of psychiatric illness by questionnaire: a technique for the identification and assessment of non-psychotic psychiatric illness. London, New York: Oxford University Press; 1972.

(19) Chalder T. Development of a fatigue scale. *J Psychosom Res* 1993;**37**:147-153.

(20) Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. *Qual Life Res* 2009;**18**:873-880.

(21) Kroenke K, Spitzer RL, Williams JB. The Phq-9. *J Gen Intern Med* 2001;**16**:606-613.

(22) Ohayon, M. Epidemiological study on insomnia in the general population. *Sleep* 1996;**19**:S7-15.

(23) Wolfe F. Pain extent and diagnosis: development and validation of the regional pain scale in 12,799 patients with rheumatic disease. *J Rheumatol* 2003;**30**:369-378.

(24) Pope DP, Croft PR, Pritchard CM, Silman AJ. Prevalence of shoulder pain in the community: the influence of case definition. *Ann Rheum Dis* 1997;**56**:308-312.

(25) Butler S, Landmark T, Glette M, Borchgrevink P, Woodhouse A. Chronic widespread pain-the need for a standard definition. *PAIN®* 2016;**157**:541-543.

(26) Beasley M, Macfarlane GJ. Chronic widespread pain versus multi-site pain: does the distribution matter? *Arthritis Rheumatol* 2014;**66**:S908-S909.

(27) Coggon D, Ntani G, Palmer KT, Felli VE, Harari R, Barrero LH, et al. Patterns of multisite pain and associations with risk factors. *PAIN®* 2013;**154**:1769-1777.

(28) Yunus MB. The role of gender in fibromyalgia syndrome. *Curr Rheumatol Rep* 2001;**3**:128-134.

(29) Häuser, W, Kühn-Becker, H, von Wilmoswky, H, Settan, M, Brähler, E, Petzke, F. (2011). Demographic and clinical features of patients with fibromyalgia syndrome of different settings: a gender comparison. *Gender medicine* 2018:**2**:116-125.

(30) Hooten, W. M., Townsend, C. O., & Decker, P. A. Gender differences among patients with fibromyalgia undergoing multidisciplinary pain rehabilitation. *Pain medicine* 2007;**8**:624-632.

(31) Lourenço S, Costa L, Rodrigues AM, Carnide F, Lucas R. Gender and psychosocial context as determinants of fibromyalgia symptoms (fibromyalgia research criteria) in young adults from the general population. *Rheumatology (Oxford)* 2015 May 14:kev110.

Figure 1 - 4-View Body Manikins with scoring

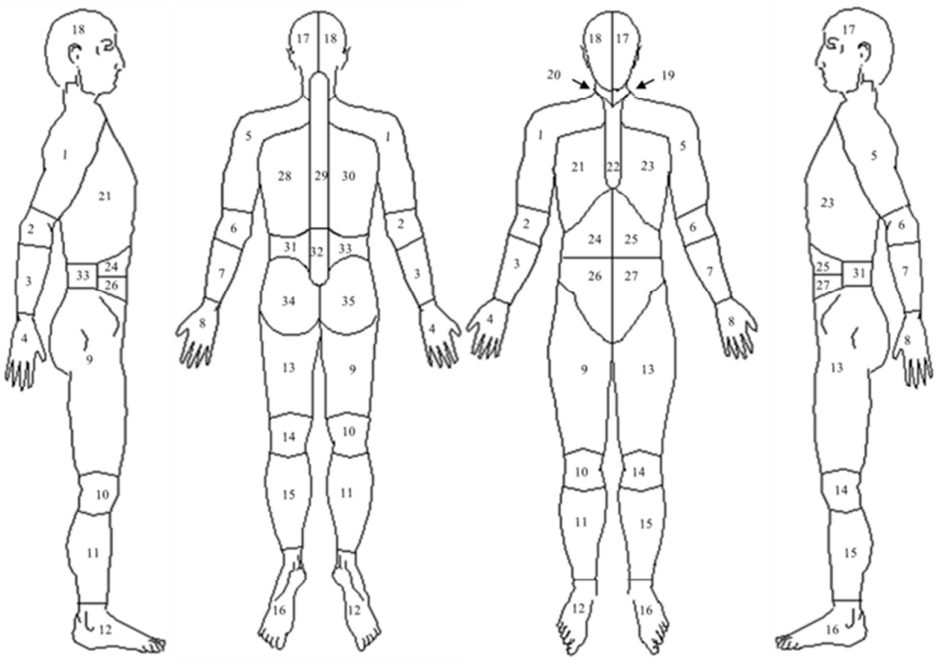

Table 1 - Characteristics of those in the included studies, who answered pain question

	SHAMA	WHEST	EpiFund	MUSICIAN	Kid LBP	1958 BBC
N.	1,579	2,303	6,244	14,680	1,440	8,572
% male	45%	0%	43%	43%	46%	51%
Age (mean, SD) years	55 (15)	53 (15)	46 (11)	56 (16)	12 (0.9)	42 (-)
Type of pain (n (%))						
No	782 (50)	1,028 (45)	2,343 (38)	5,424 (37)	390 (27)	4,019 (47)
Regional	570 (36)	884 (38)	2,709 (43)	6,601 (45)	863 (60)	3,318 (39)
Widespread	30 (2)	54 (2)	129 (2)	239 (2)	109 (8)	179 (2)
Chronic Widespread	197 (12)	337 (15)	1,603 (17)	2,416 (16)	78 (7)	1,056 (12)

Table 2 - New multi-site definitions and comparisons with CWP definition

	SHAMA		WHEST		EpiFund		MUSICIAN		Kid LBP		1958 BBC	
MSP definition	**+ joints**	**- joints**	**+ joints**	**- joints**	**+ joints**	**- joints**	**+ joints**	**- joints**	**+ joints**	**- joints**	**+ joints**	**- joints**
No of sites for definition	≥8	≥8	≥8	≥8	≥8	≥8	≥8	≥8	≥10	≥10	≥8	≥8
N. of those fulfilling MSP	219	136	397	235	1,061	568	2,715	1,623	84	26	1,110	633
% who also had CWP*	62%	68%	66%	75%	72%	75%	68%	79%	39%	42%	66%	74%

*Chronic Widespread Pain defined according to the ACR 1990 criteria

Table 3 - Characteristics of pain populations

	SHAMA			WHEST			EpiFund			MUSICIAN			KidsLBP			1958birth		
	CWP	MSP + joints	MSP - joints	CWP	MSP + joints	MSP - joints	CWP	MSP + joints	MSP - joints	CWP	MSP + joints	MSP - joints	CWP	MSP + joints	MSP - joints	CWP	MSP + joints	MSP - joints
% male	37%	37%	35%	-	-	-	36%	35%	30%	36%	37%	36%	45%	46%	58%	47%	47%	48%
Mean age (SD)	56 (12)	54 (14)	53 (14)	54 (15)	53 (15)	45 (13)	48 (11)	48 (11)	47 (11)	57 (15)	57 (15)	56 (16)	13 (1)	13 (1)	13 (1)	-	-	-
Pain chronicity (>3 months)	100%	89%	88%	100%	77%	95%	100%	93%	93%	100%	93%	92%	100%	45%	42%	100%	89%	89%

Table 4 – Relationship between MSP/CWP and symptoms associated with fibromyalgia

Measure [population]	CWP			MSP + joints			MSP - joints		
	N.*	OR	95% CI	N.*	OR	95% CI	N.*	OR	95% CI
Fatigue									
SF-36 Vitality (vs. Med/High tertile – score 58-100) [SHAMA]									
Poor (score 0-57)	1579	5.3	3.8-7.5[b]	1579	4.9	3.5-6.7[b]	1579	5.1	3.4-7.6[b]
Chalder Fatigue Scale (vs. absent) [WHEST]									
Mild (score 1-3)	2178	2.9	2.1-3.9[b]	2178	3.0	2.2-4.0[b]	2178	3.0	2.1-4.3[b]
Mod/Severe (score 4-11)		5.2	3.9-6.9[b]		6.5	5.0-8.6[b]		6.5	4.7-9.0[b]
Sleep Problems									
Estimation of sleep problems (vs. no) [WHEST]									
Yes	2258	3.6	2.9-4.7[b]	2258	3.8	3.0-4.7[b]	2258	4.3	3.3-5.7[b]
Estimation of sleep problems (vs. no) [EpiFunD]									
Yes	6039	4.1	3.6-4.8[b]	6027	4.1	3.6-4.8[b]	6039	4.2	3.5-5.0
Somatic Symptoms Present									
Somatic Symptom Scale (yes vs no) [WHEST]									
Breathing difficulties	2291	2.7	2.1-3.4[b]	2291	3.1	2.5-3.9[b]	1195	2.0	1.5-2.6[b]
Menstrual cramps	2276	2.4	1.9-3.1[b]	2276	2.3	1.8-2.8[b]	1187	2.1	1.6-2.8[b]
Lost voice	2290	1.3	1.0-1.8	2290	1.6	1.2-2.1[b]	1195	1.1	0.8-1.7
Difficulty swallowing	2298	2.9	2.2-3.7[b]	2298	3.0	2.3-3.8[b]	1200	1.9	1.4-2.6[b]
Memory loss	2293	2.9	2.2-4.0[b]	2293	3.4	2.5-4.5[b]	1194	2.6	1.8-3.6[b]
Frequently vomit	2294	2.4	1.6-3.6[b]	2294	2.5	1.7-3.7[b]	1197	1.9	1.2-3.0[a]
Digit pain	2289	4.8	3.7-6.2[b]	2289	5.7	4.4-7.2[b]	1192	2.3	1.7-3.1[b]
Somatic Symptom Scale (yes vs no) [EpiFund]									
Breathing difficulties	6196	2.5	2.1-2.8[b]	6210	2.6	2.3-3.0[b]	6210	2.7	2.3-3.3[b]
Menstrual cramps	3426	1.7	1.4-2.0[b]	3432	1.7	1.4-2.0[b]	3432	1.8	1.5-2.3[b]
Lost voice	6214	1.5	1.3-1.8[b]	6228	1.4	1.2-1.7[b]	6228	1.5	1.2-1.8[a]
Difficulty swallowing	5326	2.7	2.3-3.2[b]	5338	2.7	2.3-3.2[b]	5338	2.6	2.1-3.2[b]
Memory loss	6208	2.5	2.1-3.0[b]	6221	2.4	2.0-2.9[b]	6221	2.4	1.9-3.0[b]
Frequently vomit	6185	2.8	2.2-3.7[b]	6198	2.8	2.1-3.7[b]	6198	3.4	2.5-4.7[b]
Digit pain	6187	4.2	3.7-4.9[b]	6201	5.2	4.5-5.9[b]	6201	4.6	3.9-5.5[b]
Emotional/Mental Health									
General Health Questionnaire (vs. top tertile – score 0) [1958 British birth cohort]									
Mid (score 1-2)	8283	1.5	1.3-1.8[b]	8283	1.3	1.1-1.5[a]	8283	1.3	1.1-1.7[b]
Poor (score 3-12)		2.3	1.9-2.7[b]		2.2	1.9-2.6[b]		2.5	2.1-3.1[b]
Patient Health Questionnaire - 9 (vs. no depression) [WHEST]									
Mild depr.	2215	3.4	2.6-4.5[b]	2215	3.3	2.5-4.5[b]	1145	2.1	1.5-3.1[b]
Moderate depr.		7.1	5.0-10.1[b]		5.7	3.9-8.2[b]		4.1	2.7-6.4[b]
Moderately severe depr.		10.5	6.4-17.3[b]		10.5	6.4-17.4[b]		7.9	4.3-14.3[b]
Severe depr.		11.2	6.0-21.1[b]		9.1	4.8-17.3[b]		7.9	3.6-17.2[b]
SF-36 Mental Health (vs. Med/High tertile – score 80-100) [SHAMA]									
Poor (score 0-79)	1578	2.9	2.1-3.9[b]	1578	3.3	2.4-4.5[b]	1578	3.2	2.2-4.7[b]
Hospital Anxiety and Depression Scale (vs. none (score 0-7)) [EpiFund]									
Anx. Borderline (score 8-10)	6161	1.9	1.6-2.3[b]	6148	1.8	1.5-2.1[b]	6161	2.1	1.7-2.7[b]
Present (score 11-21)		3.2	2.7-3.7[b]		3.2	2.7-3.8[b]		3.3	2.7-3.7[b]
Depr. Borderline (score 8-10)	6169	2.5	2.1-3.1[b]	6155	2.5	2.0-3.0[b]	6169	2.9	2.3-3.7[b]
Present (score 11-21)		4.5	3.6-5.5[b]		4.2	3.4-5.2[b]		4.7	3.7-6.0[b]

OR – Odds Ratio 95% CI – 95% Confidence Interval [a] p<0.05 [b] p<0.001

* Model N.

Table 5 – Relationship between MSP (+ joints) and symptoms associated with fibromyalgia, stratified by gender

Measure [population]		Males			Females		
		N.*	OR	95% CI	N.*	OR	95% CI
Fatigue							
SF-36 Vitality (vs. Med/High tertile – score 58-100) [SHAMA]							
Poor (score 0-57)		705	4.4	2.7-7.1[b]	874	5.1	3.3-7.7[b]
Sleep Problems							
Estimation of sleep problems (vs. no) [EpiFunD]							
Yes		2631	4.4	3.5-5.6[b]	3408	3.8	3.2-4.6[b]
Somatic Symptoms							
Somatic Symptom Scale (yes vs no) [EpiFund]							
Breathing difficulties		2706	2.4	1.9-3.1[b]	3504	2.6	2.2-3.1[b]
Menstrual cramps			-	-	3400	1.7	1.4-2.0[b]
Lost voice		2709	1.2	0.8-1.7	3519	1.3	1.1-1.6[a]
Difficulty swallowing		2360	2.9	2.2-3.9[b]	2975	2.5	2.0-3.1[b]
Memory loss		2704	2.7	2.0-3.6[b]	3517	2.3	1.8-2.9[b]
Frequently vomit		2686	2.8	1.7-4.6[b]	3512	2.7	1.9-3.7[b]
Digit pain		2699	4.8	3.9-6.1[b]	3502	5.2	4.4-6.3[b]
Emotional/Mental Health							
General Health Questionnaire (vs. top tertile – score 0) [1958 British birth cohort]							
Mid (score 1-2)		4046	1.1	0.9-1.4	4237	1.5	1.2-1.9[b]
Poor (score 3-12)			1.9	1.5-2.4[b]		2.5	2.0-3.1[b]
SF-36 Mental Health (vs. Med/High tertile – score 80-100) [SHAMA]							
Poor (score 0-79)		705	3.3	2.0-5.3[b]	873	3.2	2.2-4.7[b]
Hospital Anxiety and Depression Scale (vs. none (score 0-7)) [EpiFund]							
Anxiety	Borderline (score 8-10)	2685	2.3	1.7-3.0[b]	3476	1.6	1.3-2.0[b]
	Present (score 11-21)		3.8	2.9-5.0[b]		2.7	2.2-3.3[b]
Depression	Borderline (score 8-10)	2681	2.9	2.1-4.1[b]	3488	2.3	1.8-2.9[b]
	Present (score 11-21)		5.0	3.6-7.0[b]		4.2	3.2-5.5[b]

OR – Odds Ratio
95% CI – 95% Confidence Interval
[a] p<0.05
[b] p<0.001
* Model N.