Sex Differences in Pain Scores and Localization in Inflammatory Arthritis: A Systematic Review and Metaanalysis

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ABSTRACT. ***Objective.*** To systematically identify and examine reports of sex-stratified pain measurements in patients with inflammatory arthritis.

Methods. Data sources included PubMed (1950 to April 2010), Embase (1980 to April 2010), and manual searches of reference lists and conference abstracts. We included cohort studies and randomized trials comparing pain scores, treatment efficacy at reducing pain, or pain localization, between females and males with inflammatory arthritis [rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, and reactive arthritis].

Results. Twenty-six cohorts and 1 randomized trial reported sex-stratified pain scores, and all but 1 cohort identified worse pain scores at enrollment in females. In a metaanalysis of mean visual analog scale (VAS) scores (0 to 10) in 16 RA cohort studies (reporting on 21,612 females and 6871 males), the standardized mean difference in VAS was 0.21 (95% CI 0.16, 0.26). Treatment with disease-modifying therapy results in improvement in mean scores for both sexes; however, female absolute scores remain higher. In 12 spondyloarthropathy cohorts reporting pain localization, females develop more peripheral arthritis during their disease course (68.9% vs 51.2%) but less inflammatory back pain (50.6% vs 66.4%).

Conclusion. We identified important sex differences in pain scores in inflammatory arthritis, with higher pain levels in females. In spondyloarthritis, females develop more peripheral arthritis and have less frequent spinal involvement compared to males. These differences may affect a clinician's perception of disease severity and activity, and thus influence management decisions. (First Release April 15 2012; J Rheumatol 2012;39:1221–30; doi:10.3899/jrheum.111393)

Key Indexing Terms:

RHEUMATOID ARTHRITIS | SPONDYLOARTHROPATHIES | SEX FACTORS
PAIN | PAIN MEASUREMENT | METAANALYSIS

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Articular and axial region pain is frequently the presenting symptom of inflammatory arthritis. Joint inflammation results in peripheral sensitization, mediated by primary afferent neurons under the influence of bradykinins, prostaglandins, and other neuropeptides and cytokines[1]. Central sensitization is also suspected to play a key role in the pain experience in inflammatory arthritis[2]. Uncontrolled pain has a significant effect on a patient's quality of life[3]. Pain also remains an important symptom in the longitudinal assessment of an individual patient's disease activity and treatment efficacy, because it affects the patient's global assessment of their illness, a critical variable in many disease activity indices[4,5].

It has been established that women report more pain than men in chronic musculoskeletal conditions such as persistent neck and back pain[6] and osteoarthritis[7,8]. To date, however, no systematic assessment has been performed of sex differences in pain experience in inflammatory arthritis, despite frequent sex-based analysis in disease prevalence[9], treatment response[10,11], and predictors for achieving disease remission[12,13,14].

To address this deficiency, we conducted a systematic literature review and metaanalysis as part of the 3E Initiative (Evidence, Expertise, Exchange) in Rheumatology, a multinational initiative aimed at promoting evidence-based practice. The 2010 3E Initiative theme was Pain Management in Inflammatory Arthritis [inclusive of rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and reactive arthritis]. The aim of this systematic review was to evaluate whether there are differences in the baseline level of pain, location of pain, and response to treatment between males and females with inflammatory arthritis.

MATERIALS AND METHODS

A systematic review and metaanalysis was performed according to the framework outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to increase standardization and quality in reporting[15].

Data sources and searches. We conducted a systematic literature search of PubMed (1950 to April 2010) and Embase (1980 to April 2010). Pertinent narrative review articles and reference lists of key articles were searched for further relevant publications. Conference abstracts from 2007 to 2010 for annual meetings of the European League Against Rheumatology (EULAR) and American College of Rheumatology were also reviewed. We used the search strategy developed by the 3E Initiative faculty and librarians to identify "inflammatory arthritis" articles (Appendix). We combined the results of the "inflammatory arthritis" search strategy with the results retrieved using a filter developed for sex-specific articles[16] and then subsequently with filters to identify cohort studies and randomized controlled trials (RCT) in PubMed and Embase using the Boolean operator "AND." In consultation with a medical librarian, a "sex-differences" filter using keywords and synonyms in titles and abstracts and Medical Subject Headings terms was created by 1 author (CB) and combined with the "inflammatory arthritis" search.

Study selection. One author (CB) screened all the titles and abstracts retrieved from the search strategies to identify those that were potentially pertinent to the research question and required full-text review. No language restrictions were placed in the search strategy but only English articles are included in our analysis. Predefined inclusion criteria were (1) Population: adults with inflammatory arthritis (including RA, AS, PsA, and reactive arthritis); (2) Comparison: females versus males; (3) Outcomes: pain score (by any metric), change in pain score with nonbiologic therapy, or pain localization; and (4) Design: RCT and observational cohorts. To avoid a conflict of interest with the funding source, we did not include publications where patients were treated with biologic therapies. However, if a small proportion of patients in a large cohort had unspecified biologic therapy, or if pain scores were obtained as baseline information prior to initiating a biologic therapy, they were included in our analysis.

Data extraction and quality assessment. We recorded the patient demographics, disease activity measures, and treatments received to analyze the homogeneity of the study populations. Sex-stratified pain scores and pain localization were directly extracted from the publication or provided by the corresponding authors upon request if additional information was needed for analysis. Information necessary to assess study quality in accord with a checklist proposed by Egger, *et al* for observational cohorts was also extracted[17].

Data synthesis and analysis. After reviewing the results of the systematic review and assessing study quality, we determined that it was feasible to proceed with 3 analyses, as follows.

(1) A metaanalysis of cohort studies reporting sex-stratified pain scores: cross-sectional studies in RA meeting inclusion criteria were included in a metaanalysis to calculate the standardized mean difference (SMD) in pain measured by visual analog scale (VAS) or the Bodily Pain component of the Medical Outcomes Study Short Form-36 questionnaire (SF-36BP). To do this, we used the "metan" command in Stata IC version 10.0 (StataCorp, College Station, TX, USA) and the DerSimonian and Laird random-effects model because of heterogeneity in the study populations. Egger's test and visual analysis of the funnel plot were used to assess for the possibility of publication bias.

(2) Calculation of the sex-stratified absolute and percentage improvement in mean VAS with treatment in longitudinal RA cohort studies: we summarized the change in pain VAS from baseline to 4 followup times (6 months, 1 year, 2 years, 5 years) for all studies meeting the inclusion criteria.

(3) Localization of pain in spondyloarthritis (SpA): we summarized the total proportion of females and males with SpA reporting either (i) inflammatory back pain or (ii) peripheral arthritis pain at both disease onset and throughout the disease course.

RESULTS

A total of 9949 publications were identified with our search strategy, and an additional 11 abstracts were identified from conference proceedings. One hundred three papers were selected for full-text review (Figure 1). Based on the prespecified inclusion criteria, we identified 24 RA cohorts, 1 PsA cohort, 1 inflammatory polyarthritis cohort, and 1 AS cohort where sex-stratified pain scores were reported (Table 1). Twelve cohorts of AS and PsA patients reported sex-stratified pain localization (Table 2). Of note, we identified only 1 RCT that reported a sex-stratified pain score, and we did not identify any sex-stratified pain reports in reactive arthritis. As well, 1 study reported both mean VAS and mean SF-36BP scores and it appears twice in Table 1[18].

Study quality. Publications included in this systematic review and metaanalysis were assessed according to components suggested by Egger, *et al*[17]. In studies reporting a pain score, 18 of 25 had adequate information on study participation, all but 1 were specific in how the pain score was obtained, and 23 of 25 presented the actual pain score without adjusting for disease activity variables. In studies assessing pain response longitudinally, only 2 of 6 reported their attrition rate. For reports with sex-stratified pain location, 8 of 12 provided adequate information on study participation, 6 of 9 described attrition over the followup period, and only 5 of 12 sufficiently described their method of case ascertainment; however, analysis was appropriate in all studies.

Cohort studies reporting sex-stratified pain scores. As summarized in Table 1, the majority of the cross-sectional studies were RA cohorts that reported a mean VAS or SF-36BP score. There was a significant difference in inception pain reports between women and men with RA, with higher pain levels reported by women in all studies except 1 where men reported more pain[19]. The SMD for pain score measured by VAS was 0.21 (95% CI 0.16, 0.26; $p < 0.001$; Figure 2A). The SMD for the SF-36BP score was not significantly different between women and men, with a value of –0.14 (95% CI –0.49, 0.20; $p = 0.41$); however, this calculation considers only 3 studies, including the 1 study where men had higher pain levels[19] (Figure 2B). There was heterogeneity in these cohort studies ($I^2 = 60.1\%$, $p = 0.001$, for VAS and $I^2 = 80.5\%$,

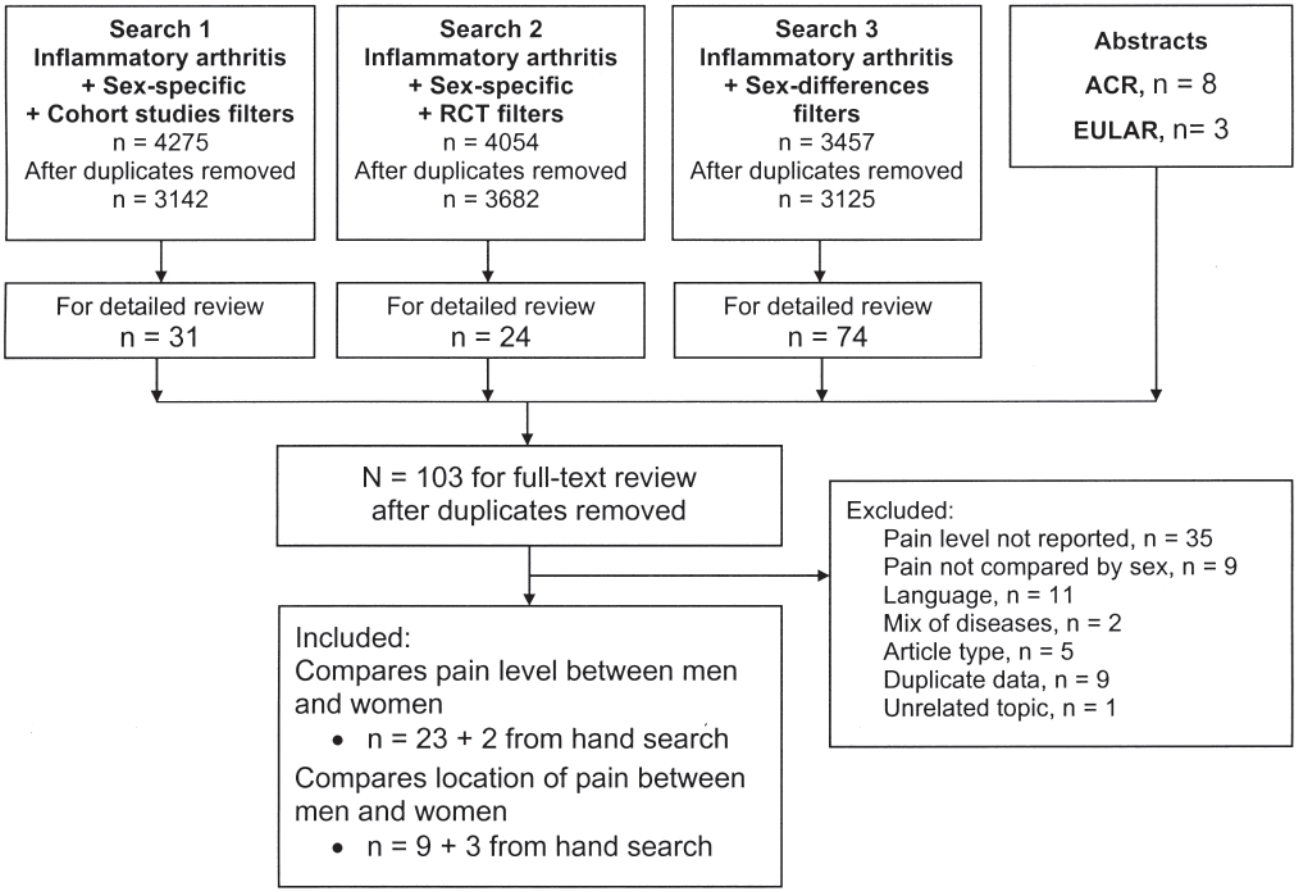

Figure 1. The process of the metaanalysis. RCT: randomized controlled trials; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism.

p = 0.006, for SF-36BP studies), and Egger's test did not suggest publication bias (p = 0.113).

We did explore whether disease duration could have an effect on the observed differences between pain scores. The SMD between sexes for patients with early disease (< 1 year) was 0.30 (95% CI 0.15, 0.45), and for patients with established disease 0.20 (95% CI 0.14, 0.25). Therefore the chronicity of symptoms did not appear to play a role in explaining the observed sex differences in pain scores.

Four of the cohort studies did not report a mean VAS or SF-36BP score and therefore could not be included in the metaanalysis. We included a narrative summary of these studies for completeness. In Affleck, *et al*[20], daily joint pain was measured by the Rapid Assessment of Disease Activity in Rheumatology score[21], with women reporting a higher score, 15.95 (SD 9.59) versus 10.30 (SD 7.49). Iikuni, *et al* presented median VAS scores, with women reporting higher scores (mean difference 4.49, 95% CI 2.49, 6.49)[22]. In a study by Odegard, *et al* examining the longitudinal disease course of RA, considering pain, depression, and anxiety, female sex was an independent predictor for the longitudinal course of pain over 10 years, along with anxiety, erythrocyte sedimentation rate (ESR), and grip strength, after adjustment for age, rheumatoid factor positivity, and disease duration[23]. In an abstract from the EULAR 2009 meeting, Rodrigues, *et al* compared predictors for pain using 3 measures (VAS, SF-36BP, and Regional Pain Scale) and found that men had less bodily pain in both univariate and multivariate analyses[24].

We also did not include 3 cohort studies in the metaanalysis because they were in different types of inflammatory arthritis, thus the results could not be combined. In 1 cohort of patients with inflammatory polyarthritis, women had a slightly higher mean VAS score (43.9, SD 28.1, vs 42.5, SD 27.8)[25]. In the second cohort, women with AS had higher mean scores measured by VAS and the McGill Pain Questionnaire (32.0 vs 30.0, and 7.5 vs 6.9, respectively)[26]. The third cohort, described by Wallenius, *et al*, reported mean VAS and SF-36BP in patients with PsA, again demonstrating worse scores in women: 49.1 (SD 21.0) versus 45.7 (SD 22.2), and 33.6 (SD 18.0) versus 34.9 (SD 16.9)[27].

Sex-stratified changes in pain with treatment in longitudinal RA cohort studies. Four cohorts reported mean VAS pain scores over multiple assessments[13,28,29] (Table 3). Overall, women start with higher mean VAS scores than men, and both

Table 1. Inflammatory arthritis cohort studies reporting sex-stratified pain scores.

Study		Type of Arthritis	Women; Men, n	Female HAQ Score	Male HAQ Score	Female DAS28 Score	Male DAS28 Score	Pain Measure
Furst 2010[14]	USA (CORRONA)	RA	4166; 1438	0.38 (mHAQ)	0.32	NR	NR	VAS (mean)
Sokka 2009[41]	Various (QUEST-RA)	RA	4755; 1249	1.09	0.76	4.30	3.76	VAS (mean)
Wallenius 2009[18]	Norway	RA	372; 102	0.67 (mHAQ)	0.59	4.7	4.2	VAS (mean)
Wallenius 2009[18]	Norway	RA	372; 102	0.67 (mHAQ)	0.59	4.7	4.2	SF-36 BP (mean)
Wallenius 2009[27]	Norway	PsA	102; 169					VAS, SF-36 BP (mean)
Castrejon 2009[28]	Leiden	RA	160; 57	1.18	0.99	NR	NR	VAS (mean)
Castrejon 2009[28]	Madrid	RA	150; 45	1.17	0.75	4.71	3.76	VAS (mean)
Jawaheer 2009[42]	USA (RADIUS-1)	RA	3327; 1032	1.36	1.08	NR	NR	VAS (mean)
Jawaheer 2009[42]	USA (RADIUS-2)	RA	3357; 1066	1.42	1.11	NR	NR	VAS (mean)
Jawaheer 2009[43]	Denmark (DANBIO)	RA	1852; 656	1.4 (HAQ-DI)	1.0 (HAQ-DI)	5.1 (CRP)	5.1 (CRP)	VAS (mean)
West 2009[19]	Sweden	RA	34; 17	NR	NR	NR	NR	SF-36 BP (mean)
Iikuni 2009[22]	Japan (IORRA)	RA	4027; 796	NR	NR	NR	NR	VAS (median)
Rodrigues 2009[24]	Portugal	RA		NR	NR	NR	NR	VAS, SF-36 BP (coefficient)
Ursum 2008[44]	Netherlands	RA	466; 214	1.30	1.09	5.32	4.98	VAS (mean)
Jawaheer 2008[29]	USA (Western Consortium of Practicing Rheumatologists)	RA	223; 68	1.27	0.91	NR	NR	VAS (mean)
Kristensen 2008[45]	Sweden (SSATG)	RA	1212; 353	1.42	1.12	5.62	5.36	VAS (mean)
Forslind 2007[13]	Sweden (BARFOT)	RA	446; 252	1.11	0.83	5.37	5.09	VAS (mean)
Leeb 2007[46]	Austria	RA	432; 125	NR	NR	3.66	3.01	VAS (mean)
Uhlig 2007[47]	Norway (ORAR)	RA	812; 212	NR	NR	NR	NR	SF-36 BP (mean)
Odegard 2007[23]	Norway (EURIDISS)	RA	NR	NR	NR	NR	NR	VAS, AIMS (coefficient)
Hakkinen 2006[48]	Finland	RA	100; 35	NR	NR	NR	NR	VAS (mean)
Hallert 2003[11]	Sweden (TIRA)	RA	196; 88	NR	NR	NR	NR	VAS (change in mean)
Ramjeet 2005[25]	England	IP	76; 36	0.97	0.78	NR	NR	VAS (mean)
Affleck 1999[20]	USA	RA	58; 18	NR	NR	NR	NR	RADAS (mean)
Katz 1996[49]	USA	RA	531; 157	1.30	0.88	NR	NR	Verbal scale 0-100 (mean)
Barlow 1993[26]	England	AS	48; 129	NR	NR	NR	NR	VAS (mean)
Thompson 1991[50]	England	RA	63; 22	1.7	1.1	NR	NR	VAS (mean)

AIMS: Arthritis Impact Measurement Scale; AS: ankylosing spondylitis; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; HAQ-DI: Health Assessment Questionnaire-Disability Index; IP: inflammatory polyarthritis; mHAQ: modified Health Assessment Questionnaire; NR: not reported; PsA: psoriatic arthritis; RA: rheumatoid arthritis; RADAS: Rheumatoid Arthritis Disease Activity Score; SF-36 BP: Bodily Pain component of the Medical Outcomes Study Short Form-36; VAS: visual analog scale.

groups improve over time. At any timepoint, however, the mean VAS score is higher for women. In 1 other longitudinal study, Hallert, *et al* reported the mean change in VAS score for women and men over different followup time periods[11]. Both groups had significant improvements in pain initially, but over 24 months women reported increasing pain in addition to decreasing lower limb function. As well, in the study by West, *et al*, men initially had a worse SF-36BP score, but improved to a greater degree over 72 months of followup[19].

Sex-stratified localization of pain in SpA. The only reports of pain localization were in SpA (AS and PsA; Table 2). These studies were heterogeneous in case ascertainment determination; however, all publications reported findings in patients with well-established disease (minimum mean disease dura-

Table 2. Sex-stratified pain localization in spondyloarthritis.

Study	Disease	Female (%)	Male (%)
Inflammatory back pain at onset			
Gran 1985[51]	AS	26/44 (59)	55/82 (67)
Mathew 1989[52]	AS	8/10 (80)	34/72 (47)
Jimenez-Balderas 1993[53]	AS	15/41 (37)	21/41 (51)
Kidd 1988[54]	AS	18/35 (51)	43/70 (61)
Gladman 1992[55]	PsA	56/82 (68)	77/112 (69)
Queiro 2001[56]	PsA	3/37 (8)	16/63 (25)
Total		126/249 (51)	246/440 (56)
Inflammatory back pain during disease course			
Kidd 1988[54]	AS	27/35 (77)	61/70 (87)
Braunstein 1982[57]	AS	11/32 (34)	22/31 (71)
Eustace 1993[58]	AS	7/19 (37)	44/64 (69)
Queiro 2001[56]	PsA	16/37 (43)	31/63 (49)
Boyer 2000[59]	AS	23/43 (54)	20/40 (50)
Total		84/166 (51)	178/268 (66)
Peripheral arthritis at onset			
Maldonado-Cocco 1985[60]	AS	5/18 (28)	9/34 (27)
Eustace 1993[58]	AS	8/19 (42)	11/64 (17)
Gran 1985[51]	AS	2/44 (5)	10/82 (12)
Jimenez-Balderas 1993[53]	AS	20/41 (49)	26/41 (63)
Resnick 1976[61]	AS	9/18 (50)	18/80 (23)
Queiro 2001[56]	PsA	9/37 (24)	7/63 (11)
Total		53/177 (30)	81/364 (22)
Peripheral arthritis during disease course			
Gran 1985[51]	AS	13/44 (29)	24/82 (29)
Jimenez-Balderas 1993[53]	AS	32/41 (78)	30/41 (73)
Resnick 1976[61]	AS	15/18 (83)	33/80 (41)
Kidd 1988[54]	AS	34/35 (97)	47/70 (67)
Marks 1983[62]	AS	10/25 (40)	4/25 (16)
Braunstein 1982[57]	AS	29/32 (91)	17/31 (55)
Boyer 2000[59]	AS	31/43 (72)	34/40 (85)
Total		164/238 (69)	189/369 (51)

AS: ankylosing spondylitis; PsA: psoriatic arthritis.

tion 10 years). In general, although the groups were similar at disease presentation, women were found to have peripheral arthritis more frequently than men during their disease course (68.9% vs 51.2%), and men more frequently had inflammatory back pain (66.4% vs 50.6%).

Randomized controlled trials reporting sex-stratified pain scores. We found only 1 RCT reporting sex-stratified pain levels, a 2-week study in patients with RA comparing diclofenac and ibuprofen therapy[30]. Patients recorded pain on an ordinal scale, but the authors erred in summarizing the outcome as a mean change in pain scores rather than the proportion of patients improving by each increment of the scale. However, in the diclofenac arm, women had a higher mean pain score at baseline, 2.29 versus 2.00 on a 0 to 3 scale, but improved to a greater degree with treatment (mean final value 1.29 vs 1.57).

DISCUSSION

We have confirmed that women with inflammatory arthritis report significantly more pain than men, with worse pain scores persisting throughout the disease course. In SpA, disease presentation and course will be different between sexes, women having more peripheral arthritis and men having more inflammatory back pain.

Higher pain levels in women have been reported for other chronic musculoskeletal conditions. In a recent review on outcomes of total knee arthroplasty for osteoarthritis, women were found to have worse pain prior to surgery, and 36% more women than men had moderate to severe pain 2 years after their surgery despite adjustment for preoperative pain level and age[31]. Women undergoing anterior cruciate ligament repair report worse pain scores preoperatively, an effect that persisted even 2 years after the repair was performed[32]. In patients seeking operative treatment for rotator cuff pathology, women experienced greater clinical pain and enhanced sensitivity to pressure pain[33]. Relative to men, women with chronic back, hip, or knee pain had worse pain intensity, reported more functional impairments related to pain, and had more disability days[34].

Current research publications evaluating sex differences in pain focus on understanding the contributions of biologic and psychosocial variables in pain[35,36,37]. Proposed biologic explanations include identified differences between sexes in

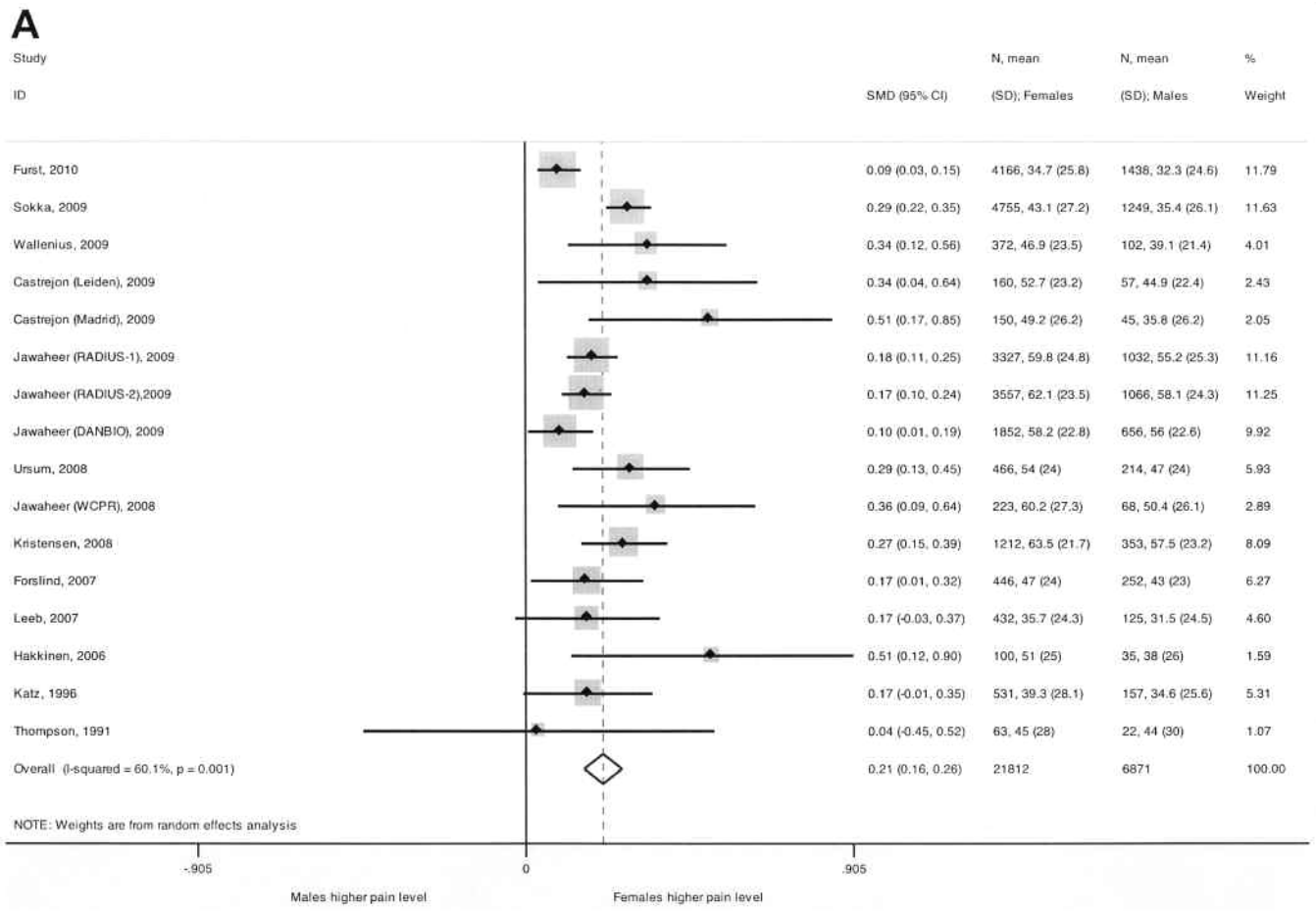

Figure 2. Forest plots of standardized mean differences in pain scores between women and men in rheumatoid arthritis cohort studies: (A) measured by visual analog scale; (B) measured by the Medical Outcomes Study Short Form-36 questionnaire Bodily Pain scale.

Table 3. Longitudinal studies reporting sex-stratified mean visual analog scale scores*.

Followup Time	Author (Cohort)	Cohort Size (Females; Males)	Baseline Score (Females; Males)	Followup Score (Females; Males)	% Improvement Females	% Improvement Males
6 months	Jawaheer (WCPR)[29]	223; 68	60; 50	37; 30	39	41
1 year	Castrejon (Madrid)[28]	150; 45	49; 36	34; 22	31	39
	Jawaheer (WCPR)[29]	223; 68	60; 50	35; 30	42	40
2 years	Jawaheer (WCPR)[29]	223; 68	60; 50	36; 25	41	51
	Castrejon (Madrid)[28]	150; 45	49; 36	31; 27	37	25
	Forslind[13]	446; 252	47; 43	30; 25	36	42
5 years	Castrejon (Madrid)[28]	150; 45	49; 36	26; 27	47	25
	Castrejon (Leiden)[28]	160; 57	53; 45	30; 27	44	39
	Forslind[13]	446; 252	47; 43	32; 26	32	40

* Values rounded for table readability. WCPR: Western Consortium of Practicing Rheumatologists.

gonadal hormones, nervous system anatomy, and neurochemistry[38]. Psychological explanations include the imposition of societal gender roles and differences in coping mechanisms, and an increased frequency of comorbid conditions of anxiety and depression in women, as well as an experiential mechanism related to the sex-specific experience of childbirth[38]. Another potential explanation relates to the influence of sex on access to healthcare professionals, and thereafter diagnosis, ongoing assessment, and management[6]. A recent literature review summarizes laboratory evidence of differences in pain perception between men and women[39,40].

Given these considerations, we need to understand whether observed differences between sexes for reporting pain are true reflections of increased underlying pain burden in females. There may be differences in pain perception, and therefore self-reported pain in inflammatory arthritis. Physicians must consider whether our pain measurement metrics should be different between sexes. We should also pursue investigation of how sex differences in pain affect our initial impression of a patient's symptoms and our longitudinal assessment of disease activity and resulting management. Researchers should include sex-stratification in their analysis, and adjust for confounding factors such as patient age and disease activity measures where appropriate. Although the majority of patients with RA are female, with the inverse being true for SpA, it is important to consider the implications of sex differences in classifying disease treatment response or remission, as fewer women may meet criteria if their global score is significantly affected by higher pain levels in addition to higher expected values for inflammatory markers such as the ESR.

Limitations of the studies included in our analysis, and therefore our own results, relate to the fact that crude pain scores were presented in the reports, without adjustment for differences in baseline demographics or other measures of disease activity (e.g., tender and swollen joint counts). We also could not address potential systematic sex differences in healthcare delivery or use between countries, and we had to assume that clinicians treat women and men to similar disease activity targets. We also acknowledge that article selection for full-text review could be completed by 2 reviewers to reduce the risk of relevant articles being missed. That being said, a thorough review of all references in the articles selected for full-text review, and any pertinent reviews on sex differences in pain, did not identify other potentially relevant articles. Exclusion of non-English publications may also potentially affect our conclusions.

Based on our analysis of sex differences in pain in inflammatory arthritis, we recommend that future randomized trials and cohort studies recognize the need to evaluate for differential baseline pain levels and responses to treatment. For instance, RCT could stratify randomization by sex or adjust by sex if there are disproportionate frequencies of women between treatment arms. These differences may be explained by delay in referral resulting in more severe disease phenotype at presentation, more aggressive disease, and psychological or social factors affecting pain interpretation, which require further study specifically in inflammatory arthritis conditions.

APPENDIX. Search strategy and terms.

i) Inflammatory Arthritis

1. rheumatoid arthritis.mp. or exp Arthritis, Rheumatoid/
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.
3. (felty$ adj2 syndrome).tw.
4. (caplan$ adj2 syndrome).tw.
5. (sjogren$ adj2 syndrome).tw.
6. (sicca adj2 syndrome).tw.
7. still$ disease.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Spondylitis, Ankylosing/
10. (ankylos$ or spondyl$).tw.
11. (bekhterev$ or bechterew$).tw.
12. (Marie adj struempell$).tw.
13. 9 or 10 or 11 or 12
14. exp Arthritis, Psoriatic/
15. (psoria$ adj (arthriti$ or arthropath$)).tw.
16. ((arthriti$ or arthropath$) adj psoria$).tw.
17. 14 or 15 or 16
18. exp Spondyloarthropathies/
19. exp Arthritis, Infectious/
20. reactive arthritis.tw.
21. (reiter$ adj (disease or syndrome)).tw.
22. ((sexual$ or chlamydia or yersinia or postyersinia or postdysenteric or salmonella or shigella or b27 or postinfectious or post infectious) adj5

arthrit$).tw.
23. reactive enthesitis.tw.
24. undifferentiated oligoarthritis.tw.
25. 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 8 or 13 or 17 or 25
ii) Cohort Studies
a) BMJ EMBASE Cohort Filter
1. exp cohort analysis/
2. exp longitudinal study/
3. exp prospective study/
4. exp follow up/
5. cohort$.tw.
6. or/1-5
b) BMJ Medline Cohort Filter
1. exp cohort studies/
2. cohort$.tw.
3. controlled clinical trial.pt.
4. epidemiologic methods/
5. limit 4 to yr=1971-1988
6. or/1-3,5
iii) Randomized Controlled Trials
a) BMJ EMBASE RCT Filter
1. (random$ or placebo$).ti,ab.
2. ((single$ or double$ or triple$ or treble$) and (blind$ or mask$)).ti,ab.
3. controlled clinical trial$.ti,ab.
4. RETRACTED ARTICLE/
5. or/1-4
6. (animal$ not human$).sh,hw.
7. 5 not 6
b) Cochrane RCT Filter
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.
11. 9 not 10
iv) Sex-Specific Search
a) Sex-Specific Filter (11)
1. (gender$ or sex$).af.
2. (boys or girls).tw.
3. (women or men).ti.
4. (women adj8 men).ab.
5. (male$1 or female$1).ti.
6. (women or men).ab. /freq=4
7. (male$1 or female$1).ab. /freq=4
8. (female$1 adj8 male$1).ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
b) Barnabe/Lorenzetti Sex-Specific Filter
1. exp Sex Factors/
2. gender difference$.mp.
3. gender effects.mp.
4. sex differences.mp.
5. (sex-based difference$ or sex based difference$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
6. (gender-based difference$ or gender based difference$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
7. (sex-related difference$ or sex related difference$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
8. (gender-related difference$ or gender related difference$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
9. (sex-specific response$ or sex specific response$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
10. (gender-specific response$ or gender specific response$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

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