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Sex-Specific Differences in Patients With Psoriatic Arthritis: A Systematic Review

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ABSTRACT. ***Objective.*** A systematic review of published literature was conducted to collate evidence on sex-specific differences in clinical characteristics, disease activity, and patient-reported outcomes (PROs) in psoriatic arthritis (PsA), including response to treatment.

Methods. Searches of MEDLINE, Embase, and the Cochrane Database of Systematic Reviews were performed in November 2020 for observational studies of adults with PsA reporting outcomes by sex (published from January 1, 2015, to November 13, 2020). In addition, hand searches of systematic literature reviews and (network) metaanalysis bibliographies were performed. Searches of ClinicalTrials.gov and congress abstracts from the European Alliance of Associations for Rheumatology, the American College of Rheumatology (ACR), and the American Academy of Dermatology (2019-2020) were also carried out. Eligible studies with 100 or more patients prespecified a comparison by sex and reported clinical characteristics and/or disease activity. Data extracted included patient characteristics, study design, baseline clinical characteristics, and disease activity results, including PROs.

Results. Database searching yielded 3283 unique records; 31 publications of 27 unique studies were included. The review found generally higher rates of peripheral disease in women, including higher tender joint counts. There was some evidence of more axial disease in men, plus greater skin disease burden. There were consistently no differences in Dermatology Life Quality Index scores, though across other PROs, women had worse scores, including pain and fatigue. Women had poorer responses to treatment, indicated by outcome measures such as ACR responses and minimal disease activity.

Conclusion. This review indicates that important differences exist between the sexes in PsA. However, the limited evidence for this conclusion underlines the need for additional research in this area.

Key Indexing Terms: gender, patient-reported outcome measures, psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory disease affecting possibly as many as 30% of patients with psoriasis.[1,2] Affecting men and women at equal rates, PsA typically develops in patients aged 30 to 50 years old.[3,4] In addition to pain and swelling of peripheral and often axial joints, other symptoms commonly experienced include psoriatic skin disease, nail disease, dactylitis, and enthesitis.[4,5] Joint damage may be irreversible, resulting in severe functional impairment and detriment to quality of life (QOL).[4,6]

Previous real-world investigations have suggested that sex-specific differences exist for axial spondyloarthritis (axSpA) and rheumatoid arthritis (RA), manifesting as differences in clinical presentation, response to treatment, and patient-reported outcomes (PROs).[7-9] The pathophysiology of PsA and disease

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impact have also been reported to differ by sex.[6] However, in contrast with RA and axSpA, which have a higher prevalence in women and men, respectively, PsA has equal sex prevalence.[3]

Investigating and identifying sex-specific differences in PsA is important for encouraging greater awareness among clinicians when caring for patients, supporting more personalized care, and informing better clinical decision making. To our knowledge, this is the first systematic review with the aim of collating real-world evidence on the sex-specific differences in clinical characteristics, such as joint and skin involvement; disease activity; response to treatment; and PROs in adults with PsA.

METHODS

Study design. MEDLINE, Embase, and the Cochrane Database of Systematic Reviews were systematically searched for literature published from January 1, 2015, to November 13, 2020, for observational studies reporting outcomes separately by sex in adults with PsA. Interventional studies and studies with fewer than 100 included patients were not included. Full eligibility criteria can be found in Supplementary Table S1 (available with the online version of this article).

Search terms included combinations of free-text and MeSH or Emtree terms for PsA, men and women, as well as study design terms using the Scottish Intercollegiate Guidelines Network filter.[10] Full database search terms can be found in Supplementary Tables S2 to S4 (available with the online version of this article). Additional keyword searches of annual proceedings for congresses of interest from 2019 to 2020 were performed; these included the European Alliance of Associations for Rheumatology (EULAR), American College of Rheumatology (ACR), and American Academy of Dermatology annual meetings (Supplementary Table S5, available with the online version of this article).

In addition to the electronic databases and grey literature, the bibliographies of all relevant systematic reviews and (network) metaanalyses identified during the review were hand searched to identify any additional, relevant studies for inclusion. ClinicalTrials.gov was also searched (Supplementary Table S6, available with the online version of this article).

Record screening followed the most stringent process, as recommended by the Cochrane Collaboration. Each title and abstract were reviewed against the eligibility criteria by 2 independent reviewers. Where the applicability of the inclusion criteria was unclear, the article was included here to ensure that all potentially relevant studies were captured. The results of the 2 reviewers were compared, and any disagreements resolved by discussion, until a consensus was met. If necessary, a third independent reviewer arbitrated the final decision. The same process was followed for full-text publications included at the abstract stage. If the applicability of the inclusion criteria was unclear at the abstract stage, the publication was included so that the full text could be reviewed. This was to ensure only clearly relevant papers were included in the systematic literature review (SLR).

Data extraction. Data extraction was performed in line with guidelines from the York University Centre for Reviews and Dissemination.[11] Data were extracted by a single individual for each included study. When the initial extraction was complete, a second individual independently verified the extracted information, checking that no relevant information had been missed. Any discrepancies or missing information identified by the second individual were discussed by both until a consensus was reached on the information to present in the extraction grid. If necessary, a third individual arbitrated the final decision.

The data extracted included patient characteristics and characteristics of the included studies, such as study design, population size, interventions under investigation, outcomes stratified by sex, and inclusion and exclusion criteria.

Because of the wide heterogeneity of study designs included in the review, the quality of all included studies was assessed using an abbreviated version of the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields developed by Kmet et al.[12] Quality assessment was conducted by one individual, with decisions verified by a second independent reviewer. If necessary, a third individual arbitrated the final decision.

Statement of ethics and consent. This SLR is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

A total of 4245 records were retrieved by the electronic database searches. After deduplication, 3283 unique records were suitable for review. After title and abstract review, 1362 records were selected for full-text review. Of these, 29 fulfilled the eligibility criteria for inclusion in the review. Following supplementary searches of congresses, ClinicalTrials.gov, and systematic review bibliographies, 2 additional records fulfilling the eligibility criteria were identified. In total, 31 publications of 27 unique studies were included in the review (Supplementary Figure S1, available with the online version of this article).

Of the included studies, 11 were prospective cohort or observational studies,[13-23] including 1 post hoc analysis of a prospective observational study.[15] In total, 5 included studies were retrospective observational studies,[24-28] and 9 were cross-sectional studies.[29-37] Only 1 study was reported as a qualitative research study[38] and, finally, 1 study was reported as a population-based cohort study.[39] Population size varied greatly across the included studies, from 108 patients[14] to 8677 patients[25] (Supplementary Table S7, available with the online version of this article).

Quality assessment. Identified studies showed a general low to moderate risk of bias, with all conclusions sufficiently supported by the results. However, the studies tended not to report on methods for controlling bias, and in some studies, the sources of information were not appropriate or not accurately described (Supplementary Table S8, available with the online version of this article).

Patient characteristics. Patient characteristics for the 27 included studies are presented in the Table. In total, 9 studies reported fairly complete patient characteristics data, 7 reported limited data, and 11 reported no patient characteristics or only patient numbers by sex.

Where reported, there were usually more women than men (15/23 studies). The average ages of men and women were similar within all of the included studies (statistically significant result in 3 studies, nonsignificant or *P* value not reported [NR] in 24 studies). Patients' mean ages across the studies ranged from 41.9 to 58.3 years. In 6 studies, patients initiated a biologic disease-modifying antirheumatic drug (bDMARD) as part of their inclusion.[13,14,17,18,22,23] In total, 7 further studies reported current or prior bDMARD exposure, by sex. One study reported significantly greater current or prior bDMARD exposure in women,[29] and 1 study reported significantly greater current bDMARD exposure in men, but no significant difference for overall exposure.[33] In total, 3 studies reported nonsignificant differences,[19,30,34] and 1 study did not give a *P* value.[16]

Table. Patient characteristics.

Study Author, Year	Patients, n	Sex, Male, n (%)	Age, yrs[a]			Disease Duration, yrs[a]			BMI[a,b]			Smoking Status[a]		
			Male	Female	*P*	Male	Female	*P*	Male	Female	*P*	Male	Female	*P*
Benavent, 2019[13]	109	55 (51)	55.8 (12.2)	58.3 (16.7)	0.2	17.3 (7.3)	18.1 (10.9)	0.6	27.7 (3.8)	26.7 (5.9)	0.3	NR	NR	NR
Benavent, 2019[14]	108	55 (50.9)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Braaten, 2019[29]	253	115 (45.4)	47.0 (12.3)	51.4 (14.1)	0.01	5.6 (8.8)	5.2 (10.2)	0.44	NR	NR	NR	NR	NR	NR
Colombo, 2015[15]	225	121 (53.8)	48.9 (12.8)	50.8 (12.5)	0.2499	NR	NR	NR	NR	NR	NR	NR	NR	NR
Duruoz, 2019[28]	1134	408 (36)	46.0 (12.2)	47.4 (12.1)	NR	5 (0-42)[c]	4 (0-44)[c]	NR	27.7 (3.7)	29.3 (5.5)	NR	NR	NR	NR
García, 2019[16]	347	151 (43.5)	50.5 (22-78)[d]	48.5 (22.3-81.1)[d]	NR	6.9 (1.2-10.0)[e]	6.5 (1.8-8.7)[e]	NR	NR	NR	NR	NR	NR	NR
Gorlier, 2018[36]	451	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gossec, 2019[30]	2270	1223 (53.9)	48.8 (12.8)	48.3 (13.7)	0.42	4.95 (5.79)	4.87 (6.15)	0.42	NR	NR	NR	NR	NR	NR
Grivas, 2020[31]	135	52 (38.5)	56.6 (50-65.7)[f]	55.1 (46.8-63)[f]	0.419	2.8[g]	2.4[g]	0.605	30.1 (26.8-33.3)[d]	27.9 (24.9-35)[d]	0.181	27.5 (0-46)[h]	15 (5-30)[h]	0.002
Hagberg, 2016[24]	8493	4248 (50)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hagberg, 2016[25]	8677	4325 (49.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Haque, 2016[32]	262	158 (60.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Haugeberg, 2020[34]	137	68 (49.6)	51.8 (10.4)	52.8 (10.4)	0.56	8.6 (7.3)	9.0 (6.3)	0.70	28.5 (3.9)	28.2 (4.8)	0.67	9 (13.2)[i]	15 (21.7)[i]	0.19
Haugeberg, 2020[33]	131	66 (50.4)	51.4 (10.2)	52.5 (10.2)	0.55	8.4 (7.0)	8.8 (6.1)	0.73	28.6 (3.9)	27.9 (4.9)	0.36	9 (13.6)[i]	12 (18.5)[i]	0.45
Højgaard, 2018[17]	1750	815 (46.6)	46.9 (11.4)	48.8 (12.6)	< 0.01	4 (1-10)[d]	3 (1-8)[d]	< 0.01	28.1 (5.1)	27.5 (6.1)	0.18	155/591 (26)[i]	233/733 (32)[i]	0.03
Kalyoncu, 2017[27]	1081	379 (35.1)	44.4 (12.5)	48.3 (12.8)	< 0.001	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kenar, 2018[35]	117	39 (33.3)	46 (25-73)[c]	49 (24-70)[c]	0.28	6 (1-44)[c]	6 (1-44)[c]	0.80	26.8 (21.0-33.9)[d]	27.8 (18.9-41.0)[d]	0.52	20.5[j]	25.6[j]	0.15
Kristensen, 2018[39]	1473	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Landgren, 2020[38]	692	332 (48.0)	54.8 (10.8)	56.4 (11.9)	0.066	NR	NR	NR	27.5 (4.1)	28.0 (6.1)	0.194	25 (7.5)[i]	49 (13.6)[i]	0.008
Lindström, 2016[37]	1310	552 (42.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nas, 2017[19]	187	72 (38.5)	43.8 (13.6)	41.9 (11.6)	0.309	7.5 (6.8)	10.2 (9.1)	0.023	25.9 (3.8)	28.5 (7.0)	0.001	34 (47.2)[i]	26 (22.8)[i]	0.001
Nas, 2021[20]	373	150 (40.2)	45.9 (12.2)	47.4 (12.0)	0.25	5 (0-42)[d]	4 (0-41)[d]	0.206	28.1 (4.1)	30.0 (5.7)	< 0.001	NR	NR	NR
Ng, 2018[26]	163	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nurmohamed, 2020[18]	929	417 (44.5)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Passia, 2020[21]	567	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Vieira-Sousa, 2019[22]	750	373 (49.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zavada, 2020[23]	493	262 (53.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	100 (43.3)[i]	132 (63.2)[i]	0.168

[a] Values reported as mean (SD) unless otherwise indicated. [b] BMI is calculated as weight in kilograms divided by height in meters squared. [c] Values are median (range). [d] Values are mean (range). [e] Values are mean (IQR). [f] Values are median (IQR). [g] Values are mean. [h] Values are pack-years (range). [i] Values are n (%). [j] Values are %. NR: not reported.

Where reported (12 studies), disease duration between the sexes was similar. The largest difference was observed in Nas et al,[19] where the mean disease duration was 7.5 (SD 6.8) years for men and 10.2 (SD 9.1) years for women ($P = 0.023$). BMI, which was reported in 10 studies, was also similar between the sexes. All average BMI values, whether mean or median, leaned toward the overweight or obese categories (Table).

The included studies revealed that, where recorded, greater proportions of women smoked tobacco than men (6/8 studies; Table). However, in the 1 study that reported pack-years,[31] lifetime exposure to tobacco smoking was greater for men (Table).

Clinical and disease characteristics. In total, 17 studies reported on clinical characteristics at baseline in patients with PsA (Figure 1 and Supplementary Table S9, available with the online version of this article).

Peripheral arthritis was generally observed to be more prevalent in women, and 3 of the 4 studies assessing this reported significantly more peripheral arthritis in women at baseline, compared with men. One study showed no significant difference by sex. This greater presence of peripheral arthritis in women, reported generally, was further supported by studies that specifically reported tender joint count (TJC). In total, 8 out of 14 studies concluded that women had a significantly greater mean or median TJC than men, whereas 1 study reported a significantly greater mean TJC in men. Five studies did not report a significant difference by sex. Unlike the results for TJC, results were mixed with regard to swollen joint count (SJC), as 3 out of 14 studies reported a significantly higher mean or median SJC in women, whereas the remaining 11 studies did not report significant differences by sex.

When considering axial disease (Supplementary Table S9, available with the online version of this article), 3 out of 8 studies reported significantly greater prevalence in men compared with women, and a further 2 studies reported that men had a numerically greater prevalence, although this was not statistically significant.

In total, 3 out of 4 studies demonstrated that women had significantly worse Maastricht Ankylosing Spondylitis Enthesitis (MASES) scores than men. When considering all 10 studies that reported enthesitis, by simple count of men and women, and considering either the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) enthesitis domain or MASES scores, 3 reported a numerically greater occurrence of enthesitis or worse scores for men. In Nas et al,[19] although results were not statistically significant, women scored slightly worse in the MASES measure of enthesitis.

In contrast, results for skin disease (ie, plaque psoriasis), measured by the body surface area (BSA) score or the Psoriasis Area and Severity Index (PASI), indicated a tendency for worse skin disease in men than women. Out of 12 studies, 5 reported significantly worse scores for men; these were 5 of the 7 studies that specifically reported PASI scores. In the remaining 2 studies, scores for men were numerically higher but without a statistically significant difference.

No significant differences were observed in current dactylitis by sex (0/6 studies). However, considering the presence of nail disease, the 3 studies reporting on this showed a numerically greater occurrence in men. In 1 study, this was statistically significant (Supplementary Table S9, available with the online version of this article).

Comorbidities reported at baseline included measures such as the Charlson Comorbidity Index, the Fibromyalgia Rapid Screening Tool (FIRST) score, and counts of patients with specific comorbidities (eg, cardiovascular disease, diabetes, and

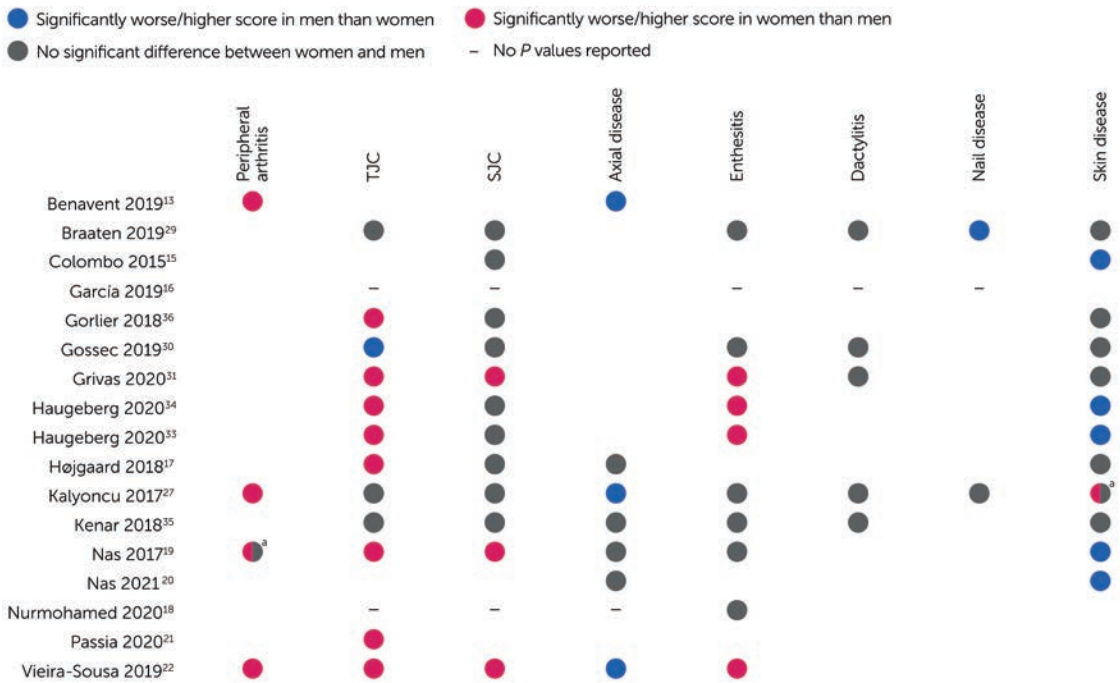

Figure 1. Summary of clinical characteristics. [a] Study reported *P* values for > 1 comparison and the result was different between comparisons. SJC: swollen joint count; TJC: tender joint count.

depression; Supplementary Table S10, available with the online version of this article). Many of the outcomes were reported in only 1 study. In total, 4 studies reported the total number of comorbidities by sex; in 3 out of 4 studies with relevant results, there were greater numbers of comorbid or concomitant diseases in women than men. However, when looking at diabetes mellitus specifically and while there were no statistically significant differences in prevalence between the sexes, there were numerically greater proportions of men with the condition (4/6 results). Liver disease was reported in 2 studies,[17,31] with 1 statistically significant result leading toward greater prevalence in men. Where reported, fibromyalgia was significantly worse in women than men, as measured by the FIRST score (2/2 studies; Supplementary Table S10, available with the online version of this article).

Clinical characteristics reported after treatment were also collated (Supplementary Table S11, available with the online version of this article); these included TJC and SJC, painful joint count, enthesitis, dactylitis, nail disease, and C-reactive protein (CRP). Limited evidence was identified, and no consistent differences were observed by sex. Only 1 study reported statistically significant outcomes: Colombo et al[15] demonstrated that women had significantly higher painful joint counts at month 6 and significantly higher SJCs at month 12 following treatment with immunosuppressive therapies. In Zavada et al,[23] men showed a greater reduction in CRP levels (mg/L) from baseline at month 12; however, this result was not adjusted for differences at baseline.

Disease activity thresholds and scores with treatment. In total, 4 studies reported changes in the achievement of specific disease activity thresholds over time when on treatment, by sex (Supplementary Table S12, available with the online version of this article).

The majority (3/4) of studies reported responses with tumor necrosis factor inhibitor (TNFi) treatment; one study looked at unspecified biologic therapy. The outcomes reported included ACR20, ACR50, ACR70, low disease activity, improvement of ≥ 1.2 in the delta Disease Activity Score in 28 joints (DAS28), Disease Activity in Psoriatic Arthritis remission, good EULAR response, minimal disease activity (MDA), minimal joint activity, and Psoriatic Arthritis Response Criteria response. Most outcomes were reported by only 1 study; however, good EULAR response featured in 2 studies, and MDA featured in 3 studies.

In addition to these thresholds of response, some studies reported absolute disease activity scores after time on treatment. This included the Ankylosing Spondylitis Disease Activity Score, the BASDAI, the DAS28, the patient global assessment of disease activity, and the physician global assessment of disease activity. Only 1 study reported on each of these absolute disease activity scores (Supplementary Table S12, available with the online version of this article).

Aside from disease activity thresholds at single timepoints, 4 of these studies reported changes in disease activity on treatment over multiple timepoints (Supplementary Table S12, available with the online version of this article). Evidence of higher response rates in men remained consistent over time and across all reported outcomes. Of the studies that reported good EULAR response, higher response rates among men—with TNFi treatment—were seen at both month 3 and month 6. The identified evidence also found that men had higher rates of MDA and ACR20/50/70 response than women, following TNFi treatment. Similar to good EULAR response, these results remained consistent between months 3 and 6. In 1 study reporting MDA at month 12, there was similarly a greater response rate in men than women.

In terms of absolute disease activity scores, women overall had higher disease activity than men across most outcomes at the timepoints studied (Supplementary Table S12, available with the online version of this article).

Patient-reported outcomes. In total, 17 studies reported PROs separately by sex at baseline, including a wide range of outcomes and PRO instruments that measured symptom burden, functional status, and health-related quality of life (HRQOL; Figure 2 and Supplementary Table S13, available with the online version of this article). The overall picture across studies and across all PRO measures was that scores in women were significantly worse than in men, with few exceptions.

For 8 out of 13 study outcomes that included self-reported pain at baseline, women had significantly worse pain than men. Across the 9 studies that recorded it, women also reported significantly higher levels of fatigue compared with men. Women also scored significantly worse on the Health Assessment Questionnaire (HAQ)—the gold-standard tool for measuring functional status in RA—which has been validated for use in PsA.[40] Higher scores on the HAQ indicate increased difficulty with activities of daily living. All 12 studies that reported HAQ, HAQ–Disability Index, or HAQ for the Spondyloarthropathies results demonstrated significantly worse scores for women. Though 1 study found a nonsignificant difference[19] when results were adjusted for various baseline characteristics, women still had numerically worse scores.

While other outcomes, such as the EuroQol 5-Dimension (EQ-5D), the 12-item Psoriatic Arthritis Impact of Disease (PsAID-12), sleep disturbances, depression, the Modified HAQ, the 15-dimensional instrument, a global health visual analog scale, and several domains from the 36-item Short Form Health Survey (eg, role limitation and social functioning), were less frequently reported, it was predominantly women who had worse scores. The Dermatology Life Quality Index (DLQI), a validated measure assessing dermatology-specific HRQOL, was the only measure where there were consistently no differences in scores between women and men (Figure 2 and Supplementary Table S13, available with the online version of this article).

PROs—pain, fatigue, HAQ scores, and EQ-5D scores—reported by sex after treatment were also collated. Limited evidence was identified, and no consistent differences were observed by sex (Supplementary Table S11, available with the online version of this article).

DISCUSSION

The results of this SLR support the existence of sex-specific

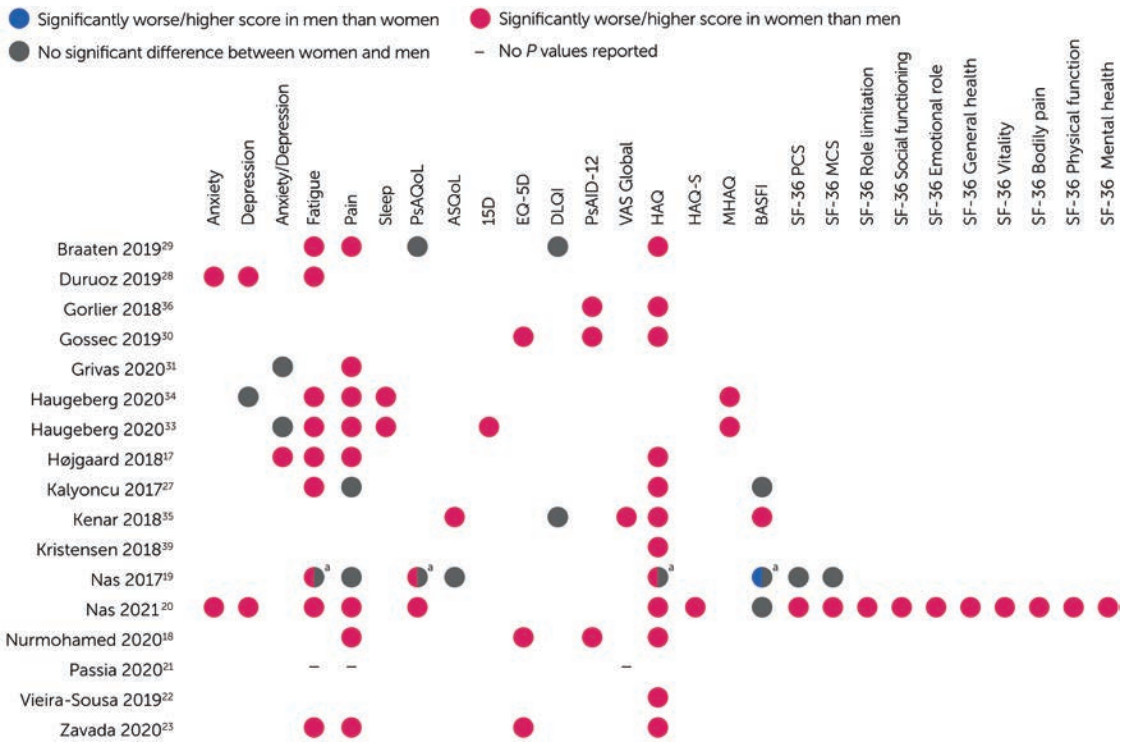

Figure 2. Summary of patient-reported outcomes. [a] Study reported *P* values for the comparison of results with (left hand side of the circle) and without (right hand side of the circle) adjustment for age, BMI, smoking and disease progression. 15D: 15-dimensional instrument; ASQoL: Ankylosing Spondylitis Quality of Life; BASFI: Bath Ankylosing Spondylitis Functional Index; DLQI: Dermatology Life Quality Index; EQ-5D: EuroQoL-5 Dimensions; HAQ: Health Assessment Questionnaire; HAQ-S: Health Assessment Questionnaire for the Spondyloarthropathies; MCS: mental component summary; MHAQ: Modified Health Assessment Questionnaire; PCS: physical component summary; PsAID-12: 12-item Psoriatic Arthritis Impact of Disease; PsAQoL: Psoriatic Arthritis Quality of Life; SF-36: 36-item Short Form Health Survey; VAS: visual analog scale.

differences in PsA. Further research in the form of large-scale observational studies, qualitative patient interviews, and analyses of particular outcomes adjusted for comorbidities or clinical characteristics would be valuable to confirm and further elaborate on these findings, as well as investigation of the mechanisms for these differences. Nonetheless, this systematic review of published literature about real-world populations may be the first of its kind to capture this breadth of PsA disease aspects compared by sex.

Several studies identified in this review found sex-specific differences in clinical characteristics, with a significantly greater presence of peripheral arthritis in women. This result aligns with previous investigations that suggest peripheral disease is more prevalent in women.[3] However, the evidence for this from our included studies was principally from higher TJCs rather than SJCs, and peripheral arthritis stemming from joint inflammation would be expected to encompass both. Therefore, the question remains of whether these observations in women are more linked to differences in inflammation or pain perception. Differences are unlikely to be related to treatment durations, which were shown to be similar between the sexes.

In line with the majority of other available literature, this review found some evidence to support findings that axial disease, which is typically associated with greater detriment to QOL, is more prevalent in men.[3,4] Axial disease was recorded in our findings if it was described as present or was indicated with Bath Ankylosing Spondylitis Metrology Index scores. However, alternative evidence suggests that there is no difference in axial disease prevalence between men and women with PsA. Most notably, analysis of the US Corrona PsA/Spondyloarthritis Registry found no significant differences in the proportions of men and women with axial involvement.[41]

Differences in the prevalence of axial PsA disease by sex may be analogous to what is seen for axSpA. For example, there is a significant male predominance in ankylosing spondylitis, whose diagnostic criteria (ie, modified New York criteria) include radiographic changes in the sacroiliac joints. By contrast, there are approximately equal numbers of men and women with nonradiographic axSpA.[42] It is possible that these differences by sex also exist in PsA, depending on the presence of axial radiographic changes. However, it was not possible to discern from the included studies whether patients with axial disease had radiographic changes. Additionally, sex differences in axial PsA disease are not known to relate to disease severity or prognosis.

Many studies identified in this review found no difference between sexes in the presence or severity of particular clinical characteristics, but these results should be considered in the context of evidence suggesting that the instruments used in this field are not sensitive to sex-specific differences.[43] For example, men and women in this review had similar SJCs, but the same

number of swollen joints may be associated with more pain and functional deterioration for members of one sex, which would not be captured.[43] We considered study sample sizes, regarding outcomes where the picture was more mixed between significant and nonsignificant or opposing results. For the presence of peripheral arthritis at baseline, as well as the TJC, worse outcomes in women are a consistent result across a range of study sample sizes. For the skin domain, the significant results came from smaller studies, but it is notable that where there was a significant result, it tended to be in men.

In this review, women tended to record worse PRO scores compared with men. This was particularly clear in the case of pain, fatigue, and HAQ scores, suggesting greater disease impact in women. One reason for these observations might be differences in patterns of unpaid work. If women are more likely to take on caring responsibilities and household work, this may make it particularly difficult, for example, to avoid using a specific joint. A further reason might be biological differences between men and women affecting the experience of disease, including the effect of sex hormones on pain perception,[44] though it is unclear what the effect of menopause might be. Further, sex differences in levels of central sensitization to pain might affect patient-reported pain.[3,45] Research is ongoing in this area, and studies of mice have demonstrated the potential protective role of testosterone against arthritis and chronic pain.[46,47]

Interestingly, while higher PASI and BSA scores were observed for men, no differences in DLQI scores were observed between men and women. In an observational study in patients with psoriasis, men had higher PASI scores; however, women gave worse ratings than men with the DLQI.[48] This discrepancy in PASI and DLQI scores might be because women are more likely to adhere to emollient application and thus could be systematically underscored with the physician-administered PASI. Further, because of the possibly greater stigmatization of women with skin conditions, they may report worse scores on PRO measures.[49]

Psychological distress has been demonstrated to lead to heightened symptom burden and decreased treatment adherence.[8] Thus, measuring patients' perceptions of their health with PROs is key to providing more patient-centered and personalized care. PsA-specific PRO instruments, such as the PsA-specific Quality of Life instrument and the PsAID-12, studied separately for each sex would have a greater ability to detect changes in patients' health and assess the aspects of QOL that are most important to men and women. PsA-specific measures may represent a better way to illustrate sex-specific differences in the experience of the disease; however, they were employed only in 6 included studies.[18-20,29,30,36]

Further, it is important to consider that although PROs can capture levels of self-reported physical function, the source of pain or reason for the functional impairment cannot be known in detail. In order to better capture the impact of disease on patients and pursue the most relevant improvements in clinical outcomes, qualitative patient interviews might be a useful way to explore sex-specific differences in PsA. They could also be used to understand how differences in clinical characteristics, such as peripheral or axial disease, might translate into functional differences between the sexes. Patient interviews could also help elucidate whether there are patterns in which aspects of PsA matter most to men and women.

Although few studies reported treatment response, a general trend observed was that men had better treatment responses than women. This effect has been observed across various rheumatic diseases.[3,50] Although it is possible that intrinsic physiological differences affect the way men and women respond to treatment, differences in coping mechanisms between the sexes have also been shown to influence response to treatments.[51] Thus, the differences in response rates are interesting to consider alongside the PRO results in this SLR, which suggest that the impact of PsA on men is smaller than it is on women.

Clinical manifestations and pathophysiology of other rheumatological diseases have been shown to differ by sex.[7] Causes for these differences may relate to the effect of sex hormones, different gene expression, occupational exposures, or differences in pain perception.[3] Although exact mechanisms are currently unclear, it is likely that a complex interplay of biological and social factors are responsible for the sex-specific differences observed in PsA and the wider group of rheumatological diseases. This review highlights that further investigation of the sex-specific differences in PsA is warranted, including the potential mechanisms producing these differences. It is likely that both biological (ie, sex) and sociological (ie, gender) factors contribute to these differences. The differences highlighted are marked and should be considered when designing future research studies, particularly head-to-head comparisons of different treatments. This is also an issue that should be considered by clinicians caring for people with PsA, as it may support more tailored management strategies for all patients with PsA in clinical practice. Such strategies might ultimately include a lower threshold to provide women with adequate pain medication or greater readiness to offer support with the management of skin disease in men.

Strengths of this review include adherence to best practice systematic review methods and the focus on observational studies from a range of geographies. These studies characterize disease in real-world clinical practice, so are expected to be broadly generalizable to the PsA population vs randomized controlled studies. However, the focus on observational studies means that there was variation, in both patient characteristics and the measurement of outcomes, which sometimes used a variety of instruments. This impeded adequate aggregation of some results, and given that many outcomes were reported from single studies, pooling of results was often not possible. Studies with populations of fewer than 100 patients were omitted, as they were less likely to detect differences between the sexes. However, it is still possible that these studies had potentially relevant findings. While included studies had populations of 100 or more patients, certain outcomes within studies had results for fewer than 100 patients.

In conclusion, evidence from this SLR suggests that some clinical characteristics in PsA differ between the sexes, particularly the presence of peripheral arthritis and specifically TJC, which was shown to be greater in women, as well as skin disease

burden, which was shown to be greater in men. Women report worse scores across a range of PROs, whereas there is evidence that men respond better to treatment. Although this review did not find consistent evidence of the differences across all included studies, or for all clinical characteristics, clinician awareness of the potential differences in clinical characteristics and patients' perceptions of their disease may help to improve patient outcomes.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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