Rheumatology Advances in Practice, 2023, **7(3)**, rkad084
https://doi.org/10.1093/rap/rkad084
Advance access publication 11 October 2023
Systematic Review and Meta-Analysis

British Society for Rheumatology
RHEUMATOLOGY ADVANCES IN PRACTICE
OXFORD

Clinical science

Prevalence and factors associated with fatigue in patients with axial spondyloarthritis: a systematic review and meta-analysis

Haoming Tang [1,‡], Benjamin Sachdev Manjit Singh[2,‡], Warren Fong [3,4,5,*]

[1]Duke-NUS Medical School, Singapore, Singapore
[2]Rheumatology Unit, Department of Medicine, Sarawak General Hospital, Kuching, Sarawak, Malaysia
[3]Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, Singapore
[4]Office of Education, Duke-NUS Medical School, Singapore, Singapore
[5]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

*Correspondence to: Warren Fong, Department of Rheumatology and Immunology, Singapore General Hospital, Academia, Level 4, 20 College Road, Singapore 169856, Singapore. E-mail: gmsfwsw@nus.edu.sg

‡H.T. and B.S.M.S. contributed equally.

Abstract

Objectives: Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease associated with significant morbidity. Fatigue, a widely recognized disease manifestation, has considerable impacts on patients' work productivity, physical function and mental well-being. However, the reported prevalence of fatigue varies across studies, and pooled data are currently lacking. We aimed to characterize the prevalence of fatigue in patients with axSpA and to identify factors associated with fatigue.

Methods: A systematic review and a meta-analysis were conducted to determine the global prevalence of fatigue in patients with axSpA. Databases including CINAHL, Embase, Medline, Cochrane Library, PubMed and Google Scholar were searched from inception until April 2023. Data were extracted, and the quality of studies was assessed. A pooled prevalence of fatigue was determined by using a random-effects model. Meta-analyses were used to determine the observed heterogeneity via subgroup analysis and associations between relevant predictors and the presence of fatigue.

Results: Thirty eligible articles were included in the study, including 7893 patients with axSpA. The pooled prevalence of fatigue in patients with axSpA was 0.56 (95% CI: 0.49, 0.63; $I^2 = 94.6\%$), with significant levels of heterogeneity. Among the factors of heterogeneity explored, the geographical region of the study ($P = 0.0013$) was significant for being a possible source. Poorer quality of life was associated with more fatigue ($P < 0.05$).

Conclusion: More than half of patients with axSpA experience fatigue, with poorer quality of life being associated with more fatigue.

Lay Summary

What does this mean for patients?

We reviewed data from 30 different studies to find out how common fatigue is in patients with axial spondyloarthritis (axSpA). We also looked at factors that are associated with fatigue. The data suggest that fatigue is present in about half of axSpA patients. Patients who had poor quality of life also appeared to have more fatigue. Biological sex, the use of anti-tumour necrosis factors (a type of drug used to treat AxSpA), age, disease duration, functional status, C-reactive protein levels and disease activity levels did not seem to be associated with fatigue levels. Patients might want to consider factors that could improve their quality of life when discussing their levels of fatigue with their treating physician and making shared care decisions.

Keywords: fatigue, axial spondyloarthritis, systematic review, meta-analysis.

Key messages

- Fatigue is significant in patients with axSpA, with a pooled prevalence of 56%.
- The geographical region of the study was a possible source of heterogeneity in pooled fatigue.
- Poorer quality of life was associated with increased fatigue.

Received: 8 August 2023. **Accepted:** 27 September 2023

Introduction

Axial spondyloarthritis (axSpA), comprising AS or radiographic axial spondyloarthritis (r-axSpA) and non-radiographic axial spondyloarthritis (nr-axSpA), is a chronic inflammatory rheumatic disease that often manifests with involvement of the axial skeleton in late adolescence and early adulthood [1, 2]. Commonly seen presentations include SI joint inflammation, spine, entheses, and other associated extra-articular features, such as anterior uveitis, IBD and psoriasis [3–5].

Fatigue is widely recognized as an integral part of the disease manifestation of axSpA, along with pain, stiffness and reduced mobility, and it is defined as a state of reduced muscle capacity and decreased ability to work, accompanied by feelings of weariness, tiredness and lack of energy [2, 6, 7]. For patients with axSpA, fatigue has been highlighted as a substantial burden, highlighting the importance of understanding the impact of fatigue on patients with axSpA [8–11]. It has previously been associated with adverse effects on work productivity, physical function and mental well-being, leading to poorer quality of life and significant morbidity in patients with axSpA [12, 13].

Consequently, epidemiological estimates of fatigue are crucial for understanding the impact on the burden of disease in axSpA. However, existing literature on the characterization of fatigue in axSpA has been variable in the methodology, assessment tools and estimates, and it is difficult to ascertain the prevalence of fatigue in patients with axSpA. There is also a lack of systematic reviews to present an up-to-date and accurate prevalence estimate and risk factors for fatigue in patients with axSpA.

Therefore, the aims of the present study were to summarize and pool the previously published statistics for the prevalence of fatigue among patients with axSpA, and to synthesize and present the reported predictors of fatigue that have been published in the literature to inform future discourse.

Methods

The study was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) [14]. A systematic review with meta-analysis and meta-regression was performed to obtain estimates of the prevalence of fatigue in patients with axSpA.

Search strategy

Six online databases were searched from inception until April 2023: CINAHL, Cochrane, EMBASE, MEDLINE, PubMed and Google Scholar. Keyword combinations and subject-specific searches relating to axSpA were used (Supplementary Data S1, available at *Rheumatology Advances in Practice* online). Two authors (H.T. and B.S.M.S.) independently reviewed reference lists of included studies and existing reviews to identify additional relevant publications.

Study selection

After removing the duplicates, two authors (H.T. and B.S.M.S.) independently screened all titles and abstracts of the searched studies. For inclusion, the studies have to meet the following criteria: (i) the study was published in a peer-reviewed journal, including both observational and experimental studies available; (ii) the study population included only patients with axSpA or incorporated an identifiable and analysed subgroup of patients with axSpA; (iii) the study assessed fatigue as a primary or secondary outcome; and (iv) the study was published in English. Abstracts without full manuscripts, case reports, conference papers, opinion or discussion papers and repeated papers on the same cohort were excluded. Any disagreements arising during the independent review were discussed, and a consensus was eventually achieved. If both reviewers agreed that the abstract satisfied the inclusion criteria, the article proceeded to a full-text review.

The same two authors independently conducted the full-text review with the following exclusion criteria: (i) the study did not report the statistics needed to calculate prevalence (e.g. the numerator and/or denominator, or the percentage, needed for calculation of fatigue); (ii) the study was conducted strictly on inpatients (i.e. probably leading to an over-estimate of fatigue); (iii) the study was conducted as a medication trial and therefore not representative of the broader patient population with axSpA; and (iv) the study selectively recruited a set of patients with axSpA without a comparator group. Any disagreements present in the review process were resolved by consensus among the authors.

Data extraction

H.T. and B.S.M.S. independently conducted data extraction for the following study characteristics in each selected article: author's name, study design, year of publication, country of study, sample size, age, biological sex breakdown, disease subtype, disease duration, disease activity, medication status, the definition of fatigue, whether fatigue was the primary objective of the study, any measurement tool for used for quantifying fatigue and the reported prevalence of fatigue, the classification criteria used for axSpA, and HLA-B27 positivity. The primary outcome of interest in the study was the prevalence of fatigue, according to the disease subtype of axSpA. In the included studies, the secondary objective was to extract measures of the effect of potential predictors of fatigue available. Discrepancies between the two authors were resolved by discussion among the authors with consensus.

Methodological quality assessment

The methodological quality assessment was examined independently by two reviewers using the Joanna Briggs Critical Appraisal Tools, widely used to evaluate the quality of various qualitative and quantitative study designs available [15]. This quality assessment tool was chosen specifically because of its widest applicable range for the purpose of this systematic review and meta-analysis, including randomized controlled trials, case–control studies, cross-sectional studies and cohort studies, compared with other quality assessment tools, which are more dedicated to specific study designs [16]. For each question, four options are available: 'yes', 'no', 'unclear' or 'not applicable'. One point was assigned to the study for each answer 'yes', and no point was assigned for the answers 'no', 'unclear' and 'not applicable'. All studies were eventually included for analysis.

Statistical analysis

All analyses were performed by H.T. using RStudio statistical software, v.2022.12.0. We calculated the prevalence and 95% CI to estimate the prevalence of fatigue in patients with axSpA. A random-effects model was used for the pooled

estimate of fatigue because significant between-study heterogeneity was expected. In all the studies, the overall axSpA estimate was used (r-axSpA/AS and nr-axSpA combined) when it was reported. If the study reported more than one estimate for fatigue in the same sample population, the patient-reported outcome measures were selected based on the following rankings: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [17], Fatigue Severity Scale [18, 19], Short Form 36-item Health Survey (SF-36) [20], question on fatigue level in BASDAI 10 cm visual analogue scale [21], based on their comprehensiveness and reliability [7, 22]. Cochran's Q test and I^2 were used, with the latter assessing the percentage of variation across studies. Subgroup analysis was performed to determine potential causes of between-study heterogeneity, if there was the presence of statistical heterogeneity, as evidenced by an $I^2 > 75\%$ or Cochran's Q statistic P-value < 0.1 [23].

Variables reported in individual studies as potential risk factors for fatigue and the statistical relationships between them and the presence of fatigue were extracted and analysed. The most commonly chosen variables from the selected studies that were reported using the same definition were the sex of the patients, age of the patients, disease duration, CRP concentration (CRP), use of anti-TNF-α medications, quality of life using Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) [24], disease activity using the BASDAI, and functional health status using the BASFI [25]. The measure of effect of the variables was extracted and analysed with a meta-analysis using a random-effects model if the number of studies available using the same measurement scale and definition for its presence was equal or more than two. To report on the predictors of fatigue in patients with axSpA, the odds ratios (OR) or beta coefficient (β) and the associated 95% CIs or P-values were extracted from the studies included. Pooling of estimates of the predictors was done if the number of studies using the same measurement scale and definition criteria were equal to or more than two. Publication bias was assessed by using the Egger test, with a P-value of <0.05 indicative of statistically significant publication bias [26].

Results

Searching framework

The search process was summarized by the PRISMA flowchart (Fig. 1). A total of 4613 articles were initially identified via the primary literature investigation, and no additional articles were identified from the references of these articles. Nine hundred and sixty articles were excluded as duplicates, and 3653 articles proceeded to the abstract review stage. Based on the initial inclusion criteria, 3453 articles were excluded, and the remaining 200 articles proceeded to full-text review. A total of 30 studies were included in the final review, with a total of 7893 patients.

Characteristics of incorporated studies

Detailed individual study characteristics are available in Supplementary Tables S1 and S2, available at *Rheumatology Advances in Practice* online. The majority of studies had a cross-sectional design ($n = 22$), and most of the studies were conducted in Asia ($n = 12$) and America ($n = 10$). The prevalence of fatigue in axSpA or its subtypes (i.e. r-axSpA/AS or nr-axSpA) was either reported directly or was able to be calculated based on the available data in all of the studies included.

Study quality assessment

Using the Joanna Briggs Institute Critical Appraisal tools, five cohort studies [2, 27–30], one case–control study [31] and two cross-sectional studies failed to identify any specific confounding factors while conducting the analysis [32, 33]. Otherwise, most of the studies were of sufficient quality to be included in the final analysis. The mean score percentage was 85% (95% CI: 79, 91), with 26 studies achieving a score of >70%, demonstrating high quality (Supplementary Tables S3–S5, available at *Rheumatology Advances in Practice* online).

Assessment of fatigue

The majority of studies ($n = 26$) incorporated a specific measurement scale for fatigue. Some of the commonly used tools in the studies included FACIT-F, the Fatigue Severity Scale [18], SF-36, 0–100 mm visual analogue scale [34], BASDAI 10 cm/100 mm visual analogue scale and Chalder Fatigue Scale [35]. Other forms of reporting fatigue include the Patient Health Questionnaire (PHQ-15) [36], Evaluation of AS Quality of Life (EASi-QoL) [37] and self-report without the use of a measurement tool. The definition of the criteria meeting fatigue varied across all the included studies, mostly divided into two categories, namely 'any' presence of fatigue or 'moderate to severe' fatigue present.

The pooled prevalence of fatigue in patients with axSpA was 0.56 (95% CI: 0.49, 0.63; $I^2 = 94.6\%$; $Q = 536$; $P < 0.01$; Fig. 2). Substantial heterogeneity was observed across the studies, and consequently, stratified subgroup analyses were conducted to explore sources of heterogeneity. Among the variables incorporated were the percentage of male patients in the sample, the sample size of the study, disease duration of patients with axSpA, whether fatigue was the primary objective of the study, the definition of fatigue meeting the criteria set in the study, the subtype of axSpA reported, the type of study design, the geographical region where the study was conducted and whether a specific fatigue measurement scale was employed. Ultimately, only the geographical region where the study was conducted was concluded to be significant ($P = 0.0014$). Heterogeneity among all other groups, including between patients with r-axSpA and nr-axSpA, was not significant, with results displayed in Table 1. No publication bias was found by the Egger test ($P = 0.1369$).

Determination of the predictors of fatigue

Among all the variables examined by the meta-analysis, worse quality of life measured by ASQoL scores (i.e. increased scores indicating worse quality of life) had significant associations with the presence of fatigue in patients with axSpA (OR: 1.22; 95% CI: 1.07, 1.39; $P < 0.05$). The other variables explored were not significant in their associations with the presence of fatigue, with the results displayed in Table 2.

Discussion

This systematic review and meta-analysis provided an estimate of the prevalence of fatigue in axSpA and identified factors associated with the presence of fatigue using a

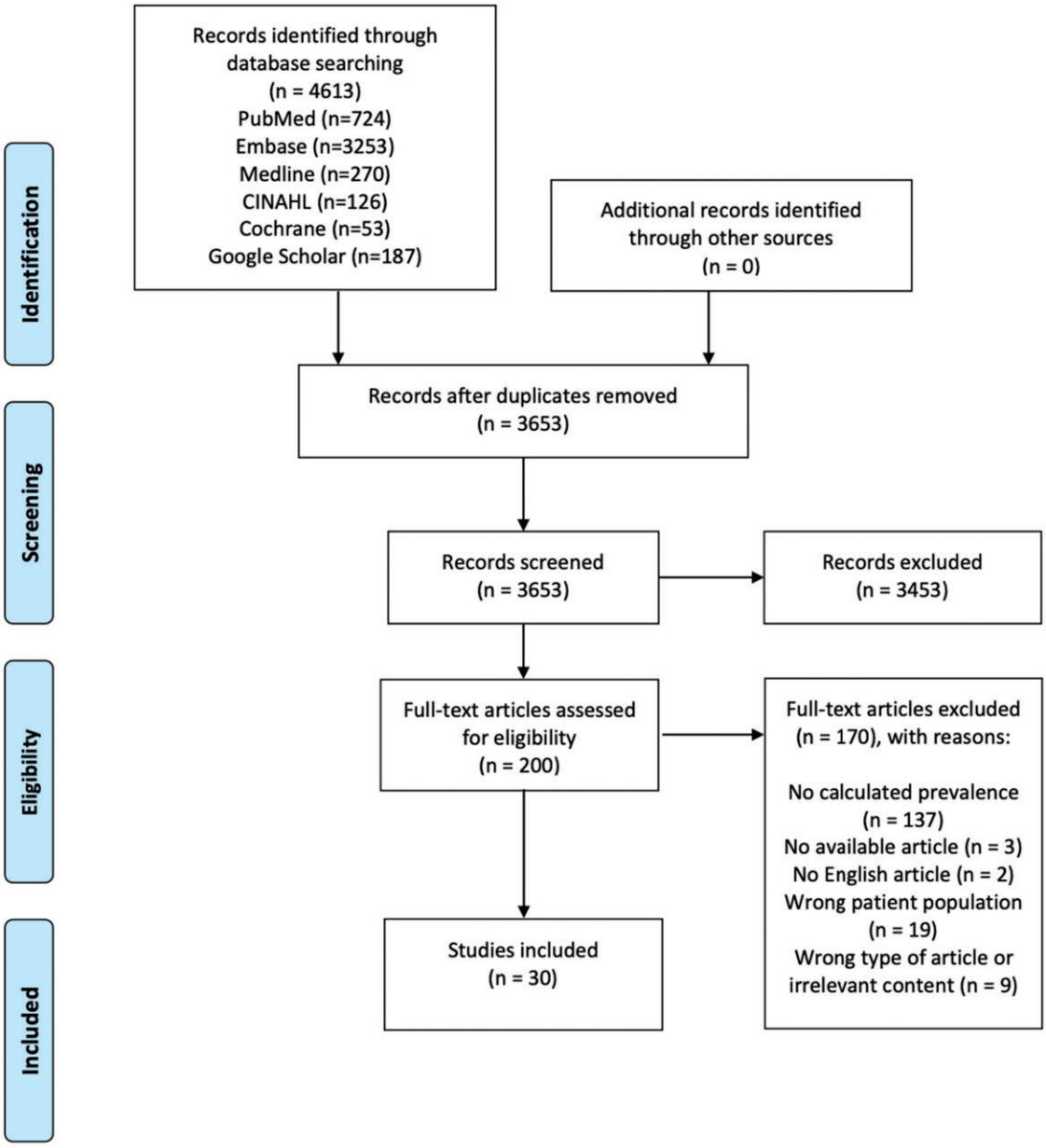

Figure 1. Flowchart of included studies

meta-analytical approach, with an overview of how fatigue was quantified in various studies involving patients with axSpA. The prevalence of fatigue in axSpA was comparable to that of RA and PsA in a study comparing the mean fatigue scores for these three types of inflammatory arthritis [38].

We found that although fatigue had been investigated in patients with axSpA, the measurement tools and the cut-off values often differed, resulting in different values derived and rendering it challenging to draw meaningful conclusions from the statistics, potentially leading to the large heterogeneity across the studies in meta-analysis [39]. For most of the studies included, the BASDAI fatigue scale and the Fatigue Severity Scale [18] were the principal measurement tools used to delve into the severity of fatigue. However, the cut-off values often differed across studies, and the definition of fatigue, whether it was 'any fatigue' or 'moderate to severe fatigue', could be incongruent with the scores obtained from the various scales. However, in the subgroup analysis, we failed to demonstrate whether the variable definition of fatigue had any conclusive effect on the heterogeneity of fatigue observed. In addition, compared with non-fatigue measurement tools or self-report without the use of a measurement tool, the fatigue measurement tools used in studies also did not explain the heterogeneity noted across the studies. The characterization of fatigue remains a crucial but unresolved area in the management of patients with axSpA. A standardized definition of the presence of fatigue and a novel scale that is reliable and comprehensive enough to capture various aspects of fatigue to be used in patients with axSpA in future research pursuits is much needed and remains to be developed [40]. This is not only important for an accurate assessment of fatigue in the clinical setting, but also to assist clinicians with therapeutic management of patients with fatigue.

In the subgroup analysis, the geographical area where the study was conducted was a factor that partly explained the heterogeneity. Most of the studies were conducted in Asia or

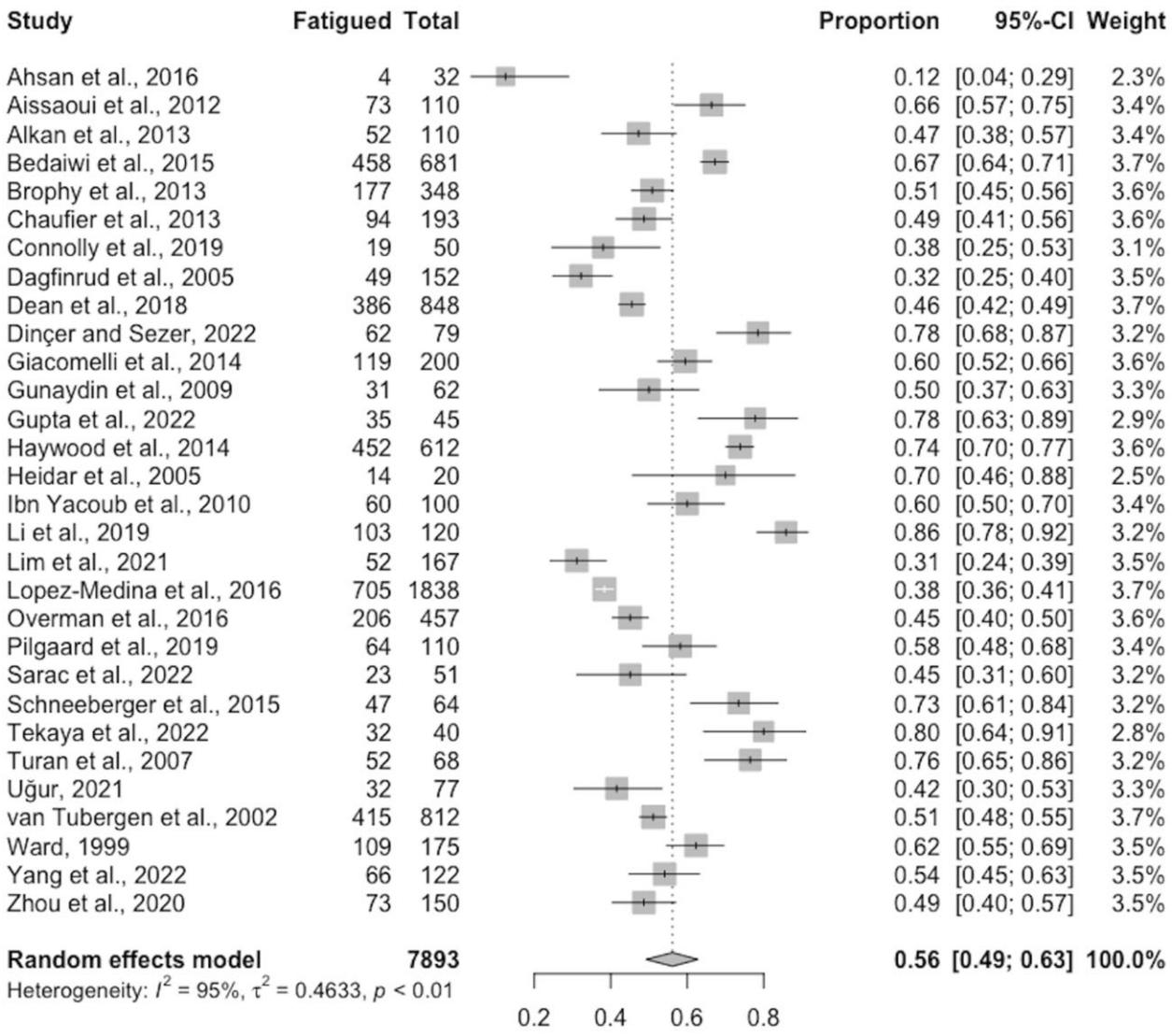

Figure 2. Pooled prevalence of fatigue in patients with axial spondyloarthritis

America, with relatively few reporting on fatigue prevalence in Europe and Africa. The reasons for the discrepancies in fatigue across the different regions are currently unclear. Although fatigue levels were not previously investigated from the angle of geographical differences, it was previously found that African Americans with AS, compared with their White and Hispanic counterparts, experienced greater discomfort, greater functional impairment and higher levels of inflammatory markers with elevated disease activity. Possible explanations offered were genetic factors (e.g. differences in HLA-B27 positivity), inequalities in socioeconomic status and differences in the level of education received [41–43]. Although these findings carried implications for the discrepancies in fatigue levels found across various regions, future multinational studies using a standardized measurement tool for fatigue characterization would provide more definitive conclusions for the observed heterogeneities. The variable reporting across the world currently could potentially limit our understanding of how significant geographical areas could differ in their fatigue prevalence. The two subtypes of axSpA, r-axSpA, and nr-axSpA, were explored in subgroup analysis, but the number of studies available and patients included for nr-axSpA was small compared with patients having r-axSpA, hence the results might not be representative [44, 45]. Therefore, future investigations in areas of under-reporting, such as specifically to characterize the prevalence of fatigue in patients with axSpA in Europe and Africa and reasons behind the current discrepancies in fatigue observed in these regions, and separately, to delve into the level of fatigue in patients with nr-axSpA in comparison to that of patients with r-axSpA, should be conducted to clarify the conclusions drawn in this study.

The meta-analysis of predictors demonstrated that a worse quality of life was associated with the presence of fatigue in axSpA, a relationship that was in line with previous studies conducted on the same topic [45, 46]. It was noticed that many included studies did not report on factors associated with fatigue, and when they did report such statistics, the statistics were reported with various scales, which limited their usefulness in interpretations. Some of the commonly reported potential factors associated with fatigue and quality of life included psychological co-morbidities, such as depression and anxiety, severity of pain, and physical activity, but they were not studied in the present meta-analysis owing to the poor consistency in reporting in the current literature [31, 47–50].

Table 1. Subgroup analysis

Variables for analysis of heterogeneity	Number of studies	Pooled estimates (95% CI)	I^2 (%)	*P*-value for heterogeneity
Sample size				
≤100	12	0.60 (0.44–0.73)	86.5	0.4721
>100	18	0.54 (0.46–0.62)	96.1	
Male (%)				
51–70	8	0.50 (0.31–0.70)	95.9	0.1404
71–80	11	0.56 (0.46–0.67)	87.2	
81–100	6	0.70 (0.52–0.83)	86.7	
Disease duration, years				
4–10	7	0.56 (0.37–0.74)	92.5	0.9484
11–15	4	0.60 (0.40–0.77)	95.6	
16–24	4	0.58 (0.19–0.89)	94.0	
Fatigue as the primary objective of the study				
Yes	23	0.56 (0.48–0.63)	95.3	0.9546
No	7	0.56 (0.34–0.77)	91.5	
Fatigue definition				
Any fatigue	11	0.59 (0.42–0.73)	94.0	0.5968
Moderate to severe fatigue	19	0.54 (0.47–0.61)	93.5	
axSpA subtype				
r-axSpA	30	0.56 (0.49–0.62)	94.2	0.3568
nr-axSpA	3	0.42 (0.06–0.90)	91.6	
Region of the study				
Asia	12	0.55 (0.40–0.70)	91.9	0.0013
Africa	4	0.67 (0.53–0.79)	41.0	
Europe	3	0.66 (0.57–0.75)	31.5	
America	10	0.50 (0.41–0.59)	96.4	
Fatigue scale utilization				
Yes	26	0.57 (0.50–0.63)	95.0	0.7493
No	4	0.51 (0.11–0.90)	88.0	

axSpA: axial spondyloarthritis; nr-axSpA: non-radiographic axial spondyloarthritis; r-axSpA: radiographic axial spondyloarthritis.

Table 2. Determination of predictors of fatigue

Predictors	Number of studies	Pooled odds ratio	CI	β	*P*-value	I^2 (%)	*Q*
Biological sex (reference female)	4	1.01	0.64–1.58	0.0077	>0.05	75.5	9.2, $P < 0.05$
Anti-TNF use	2	0.94	0.72–1.23	−0.0582	>0.05	0	0.6, $P = 0.46$
Age, years	4	1.00	0.97–1.03	0.0007	>0.05	55.0	5.5, $P = 0.13$
Disease duration, years	5	1.01	0.99–1.02	0.0052	>0.05	22.5	3.14, $P = 0.53$
Quality of life	2	1.22	1.07–1.39	0.1983	<0.05	37.5	1.60, $P = 0.21$
CRP level	2	1.02	0.80–1.30	0.0209	>0.05	19.3	1.24, $P = 0.27$
Disease activity	5	1.56	0.98–2.46	0.4430	>0.05	99.8	553.43, $P < 0.0001$
Functional health	5	1.17	0.98–1.40	0.1583	>0.05	97.4	299.85, $P < 0.0001$

This omission could potentially lead to an incomplete picture of the risk factors associated with fatigue being explored in the present study. Nevertheless, from the available data, we were able to identify quality of life as being associated with worsening fatigue, whereas biological sex, use of anti-TNFs, age, disease duration, functional status, CRP levels and disease activity were not associated with fatigue levels.

Strengths and limitations

This study was one of the first in the literature to review systematically the prevalence statistics on fatigue in patients with axSpA and to look for associated risk factors for its presence in various countries, with a large sample of the population included. In addition, each subgroup of axSpA was identified, and the difference in the presence of fatigue between r-axSpA and nr-axSpA was explored in the current literature.

There are several limitations to this systematic review and meta-analysis. The fatigue scales used in the study and definitions of fatigue across the collected studies were variable, which contributed to heterogeneity in the values of the prevalence of fatigue derived. In addition, some of the stratified subgroup analyses and meta-analyses of predictor variables contained few studies (e.g. nr-axSpA), and the results might not provide the best representation of fatigue in the overall population in those specific subgroups. Furthermore, we could not include potential confounding factors, such as anxiety, depression, sleep disturbances and pain, for analysis owing to the variable reporting of such factors, usage of different scales and inconsistent cut-off values. Future studies are recommended to use validated measurement scales and unified definitions of fatigue to gain a better understanding of the impact on patients with axSpA and to allow more accurate statistics using pooled data.

Conclusions

There is substantial fatigue in more than half of the patients with axSpA. The significant heterogeneity derived from the analysis could be contributed to by the geographical region of

the study. The meta-analysis of possible factors associated with fatigue identified poor quality of life to be associated with the presence of increased fatigue; however, the major limiting factor to analysis was the variability of scales and definitions used by studies, ultimately highlighting the need for standardization in the definition of fatigue and fatigue scales used to facilitate further meaningful future research.

Supplementary materials

Supplementary data are available at *Rheumatology Advances in Practice* online.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

Funding

This study is funded by Reverie Rheumatology Research Fund (SPERO programme, 03/FY2020/EX/13-A56). The funder has not taken part in the study design, data collection and analysis, the decision to publish, or the preparation of the manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Acknowledgements

We acknowledge biostatistician Dr Seyed Ehsan Saffari from Centre for Quantitative Medicine (CQM) at Duke-NUS Medical School, National University of Singapore, for his kind biostatistical advice on the conduct of the meta-analysis.

References

1. Strand V, Deodhar A, Alten R *et al.* Pain and fatigue in patients with ankylosing spondylitis treated with tumor necrosis factor inhibitors: multinational real-world findings. J Clin Rheumatol 2021;27:e446–55.
2. Bedaiwi M, Sari I, Thavaneswaran A *et al.* Fatigue in ankylosing spondylitis and nonradiographic axial spondyloarthritis: analysis from a longitudinal observation cohort. J Rheumatol 2015;42:2354–60.
3. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. Ann Rheum Dis 2015;74:65–73.
4. Lim WZ, Fong W, Kwan YH, Leung YY. Exploring the prevalence and factors associated with fatigue in axial spondyloarthritis in an Asian cohort in Singapore. Front Med (Lausanne) 2021;8:603941.
5. Walsh JA, Magrey M. Clinical manifestations and diagnosis of axial spondyloarthritis. J Clin Rheumatol 2021;27:e547–60.
6. Missaoui B, Revel M. Fatigue and ankylosing spondylitis. Ann Readapt Med Phys 2006;49:305–8.
7. Pearson NA, Packham JC, Tutton E, Parsons H, Haywood KL. Assessing fatigue in adults with axial spondyloarthritis: a systematic review of the quality and acceptability of patient-reported outcome measures. Rheumatol Adv Pract 2018;2:rky017.
8. Mercieca C, Ryan S, Borg A. AB1414-HPR patients' experiences of fatigue in axial-spondyloarthritis. Ann Rheum Dis 2019;78:2170.
9. Haywood KL, Packham JC, Jordan KP. Assessing fatigue in ankylosing spondylitis: the importance of frequency and severity. Rheumatology (Oxford) 2014;53:552–6.
10. Pearson NA, Packham JC, Parsons H, Haywood KL. Quality and acceptability of patient-reported outcome measures used to assess fatigue in axial spondyloarthritis (axSpA): a systematic review (protocol). Syst Rev 2018;7:116.
11. Pearson NA, Tutton E, Martindale J *et al.* Qualitative interview study exploring the patient experience of living with axial spondyloarthritis and fatigue: difficult, demanding and draining. BMJ Open 2022;12:e053958.
12. Espahbodi S, Bassett P, Cavill C *et al.* Fatigue contributes to work productivity impairment in patients with axial spondyloarthritis: a cross-sectional UK study. Clin Exp Rheumatol 2017;35:571–8.
13. Liu V, Fong W, Kwan YH, Leung YY. Residual disease burden in patients with axial spondyloarthritis and psoriatic arthritis despite low disease activity states in a multiethnic Asian population. J Rheumatol 2021;48:677–84.
14. Page MJ, McKenzie JE, Bossuyt PM *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
15. Moola S, Munn Z, Sears K *et al.* Conducting systematic reviews of association (etiology): the Joanna Briggs Institute's approach. Int J Evid Based Healthc 2015;13:163–9.
16. Ma L-L, Wang Y-Y, Yang Z-H *et al.* Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? Mil Med Res 2020;7:7.
17. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: properties, applications, and interpretation. Health Qual Life Outcomes 2003;1:79.
18. Mogard E, Olofsson T, Bergman S *et al.* Chronic pain and assessment of pain sensitivity in patients with axial spondyloarthritis: results from the SPARTAKUS cohort. J Rheumatol 2021;48:1672–9.
19. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121–3.
20. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.
21. Garrett S, Jenkinson T, Kennedy LG *et al.* A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
22. van Tubergen A, Coenen J, Landewé R *et al.* Assessment of fatigue in patients with ankylosing spondylitis: a psychometric analysis. Arthritis Rheum 2002;47:8–16.
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
24. Doward LC, Spoorenberg A, Cook SA *et al.* Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis 2003;62:20–6.
25. Calin A, Garrett S, Whitelock H *et al.* A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281–5.
26. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
27. Ahsan T, Erum U, Jabeen R, Khowaja D. Ankylosing spondylitis: a rheumatology clinic experience. Pak J Med Sci 2016;32:365–8.
28. Connolly D, Fitzpatrick C, O'Shea F. Disease activity, occupational participation, and quality of life for individuals with and without severe fatigue in ankylosing spondylitis. Occup Therapy Int 2019;2019:3027280.
29. Ward MM. Health-related quality of life in ankylosing spondylitis: a survey of 175 patients. Arthritis Care Res 1999;12:247–55.
30. Heidar H, Ahmad MA, Othman M, Azab A, Badre NM. Assessment of fatigue in ankylosing spondylitis patients: clinical and self-reported features. Egyptian Rheumatol Rehabil 2005;32:575–85.
31. Schneeberger EE, Marengo MF, Dal Pra F, Maldonado Cocco JA, Citera G. Fatigue assessment and its impact in the quality of life of

patients with ankylosing spondylitis. Clin Rheumatol 2015;34: 497–501.
32. Gupta P, Kharbanda R, Abbasi M, Raj R, Gupta L. Individuals with reactive arthritis suffer from poor health-related quality of life akin to individuals with ankylosing spondylitis: a multigroup study. Indian J Rheumatol 2022;17:110–7.
33. Ibn Yacoub Y, Amine B, Laatiris A, Abouqal R, Hajjaj-Hassouni N. Assessment of fatigue in Moroccan patients with ankylosing spondylitis. Clin Rheumatol 2010;29:1295–9.
34. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res 1991;36:291–8.
35. Chalder T, Berelowitz G, Pawlikowska T *et al.* Development of a fatigue scale. J Psychosom Res 1993;37:147–53.
36. Kroenke K, Spitzer RL, Williams JB. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med 2002;64:258–66.
37. Haywood KL, Garratt AM, Jordan KP, Healey EL, Packham JC. Evaluation of ankylosing spondylitis quality of life (EASi-QoL): reliability and validity of a new patient-reported outcome measure. J Rheumatol 2010;37:2100–9.
38. Pilgaard T, Hagelund L, Stallknecht SE, Jensen HH, Esbensen BA. Severity of fatigue in people with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis – results of a cross-sectional study. PLoS ONE 2019;14:e0218831.
39. Dagfinrud H, Vollestad NK, Loge JH, Kvien TK, Mengshoel AM. Fatigue in patients with ankylosing spondylitis: a comparison with the general population and associations with clinical and self-reported measures. Arthritis Rheum 2005;53:5–11.
40. Pearson NA, Tutton E, Martindale J *et al.* Development of the Warwick Axial Spondyloarthritis faTigue and Energy questionnaire (WASTEd)—a new patient-reported outcome measure. Rheumatol Adv Pract 2022;6:rkac027.
41. Polina P, Sofia R, Anna M *et al.* Individual-level and country-level socioeconomic determinants of disease outcomes in SpA: multinational, cross-sectional study (ASAS-COMOSPA). Ann Rheum Dis 2019;78:486.
42. Jamalyaria F, Ward MM, Assassi S *et al.* Ethnicity and disease severity in ankylosing spondylitis a cross-sectional analysis of three ethnic groups. Clin Rheumatol 2017;36:2359–64.
43. Dilpreet Kaur S, Marina NM. Racial differences in clinical features and comorbidities in ankylosing spondylitis in the United States. J Rheumatol 2020;47:835.
44. Hunter T, Sandoval D, Booth N, Holdsworth E, Deodhar A. Comparing symptoms, treatment patterns, and quality of life of ankylosing spondylitis and non-radiographic axial spondyloarthritis patients in the USA: findings from a patient and rheumatologist survey. Clin Rheumatol 2021;40:3161–7.
45. Clementina L-M, Sofia R, van der Heijde D *et al.* Characteristics and burden of disease in patients with radiographic and non-radiographic axial spondyloarthritis: a comparison by systematic literature review and meta-analysis. RMD Open 2019;5:e001108.
46. Macfarlane GM, Rotariu O, Jones GT, Pathan E, Dean LE. Determining factors related to poor quality of life in patients with axial spondyloarthritis: results from the British Society for Rheumatology Biologics Register (BSRBR-AS). Ann Rheum Dis 2020;79:202.
47. Brophy S, Davies H, Dennis MS *et al.* Fatigue in ankylosing spondylitis: treatment should focus on pain management. Semin Arthritis Rheum 2013;42:361–7.
48. Uğur S. Evaluation of severe fatigue and related factors in ankylosing spondylitis: a cross-sectional study. Turkish J Health Sport 2021;2:49–53.
49. Lopez-Medina C, Schiotis RE, Font-Ugalde P *et al.*; REGISPONSER Working Group. Assessment of fatigue in spondyloarthritis and its association with disease activity. J Rheumatol 2016;43:751–7.
50. Chaufier K, Paternotte S, Burki V *et al.* Fatigue in spondyloarthritis: a marker of disease activity. A cross-sectional study of 266 patients. Clin Exp Rheumatol 2013;31:864–70.