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REVIEW

Patient-Reported Outcome Measures in Takayasu Arteritis: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: We conducted a systematic review of patient-reported outcome measures (PROMs) regarding quality of life, disability, mood abnormalities (anxiety, depression), fatigue, illness perceptions and fibromyalgia in Takayasu arteritis (TAK). Wherever available, comparisons with healthy controls, disease controls or longitudinal changes in PROMs were noted.

Methods: MEDLINE, EMBASE, Scopus, Web of Science and Pubmed Central databases, major recent international rheumatology conference abstracts, clinical trial databases and the Cochrane library were searched for relevant articles. Wherever possible, outcome measures across studies were pooled using the restricted maximum likelihood model. Inter-group differences were pooled and compared using standardized mean differences (SMD) with 95% confidence intervals (95% CI). Heterogeneity was assessed using the I^2 statistic. Quality of randomized controlled trials was assessed using the Cochrane risk of bias tool. For cross-sectional and cohort studies, the Joana Briggs Institute checklist and Newcastle–Ottawa scale were used, respectively. GRADE methodology was used to determine the certainty of evidence for outcomes.

Results: Twenty-one studies (all but one observational) involving 1311 patients with TAK and 308 healthy controls were identified. Ten studies (559 TAK patients, 182 healthy controls were synthesized in a meta-analysis. Patients with TAK had worse quality of life (pooled SMD − 6.66, 95% CI − 10.08 to − 3.23 for individual domains; − 0.64, 95% CI − 1.19 to − 0.09 for pooled physical and mental component scores of 36-item Short Form Survey), depression (SMD 0.26, 95% 0.05–0.47) and anxiety (SMD 0.34, 95% CI − 0.06 to 0.75)

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scores and higher disability (SMD 0.64, 95% CI 0.43–0.84) than healthy controls. Patients with active TAK had worse quality of life, depression and work impairment when compared with those with inactive disease. Included studies were of moderate to high quality. Certainty of evidence for individual outcomes was low to very low.

Conclusion: Literature on PROMs in TAK, albeit sparse, appears to indicate worse scores in patients with TAK compared to healthy individuals. These results, however, require cautious interpretation. Development of a TAK-specific PROM is an important focus of the research agenda.

Keywords: Takayasu arteritis; Patient-reported outcome measures; Quality of life; Depression; Anxiety; Fibromyalgia

Key Summary Points

Published literature on patient-reported outcome measures (PROMs) in patients with Takayasu arteritis (TAK) is sparse.

Available evidence appears to suggest that patients with TAK have greater disability and depression than healthy individuals and that active TAK is associated with worse quality of life, disability, depression and anxiety.

However, the comparison of PROMs from patients with TAK and healthy controls and from those with active and those with inactive disease is based on small numbers of studies with considerable statistical heterogeneity in some of the pooled estimates (therefore, requiring cautious interpretation).

Research gaps in this area include the assessment of longitudinal changes in PROMs in patients with TAK, changes following therapy and relationship of PROMs with disease activity.

There is a need to develop a validated disease-specific PROM for patients with TAK.

DIGITAL FEATURES

This article is published with digital features, including a slide deck, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.15067938.

INTRODUCTION

The importance of comorbidities in rheumatic diseases, including vasculitis, is increasingly being recognized [1, 2]. The Outcome Measures in Rheumatology (OMERACT) group has proposed core outcome measures in different diseases, including large vessel vasculitis (LVV) [3]. Takayasu arteritis (TAK) is a subtype of LVV commonly affecting young females [4]. Patient-reported outcome measures (PROMs) relate to the patient's perceptions of living with disease [5]. PROMs are a well recognized assessment tool for the more common rheumatic diseases, such as rheumatoid arthritis (RA) and spondyloarthritis [6], but the development of PROMs for vasculitides is an evolving area [3, 7, 8]. Collaborative efforts have successfully developed and validated a PROM for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) [9]. In the absence of a similarly validated tool, various generic PROMs have been used in TAK, such as the 36-item Short Form Survey (SF-36) [10], the Health Assessment Questionnaire (HAQ) [11, 12] and the Hospital Anxiety and Depression Scale (HADS) [13].

The aim of this systematic review was to assess the degree of impairment of quality of life (QOL), disability, mood abnormalities, fatigue, illness perceptions and fibromyalgia in patients with TAK reported using different PROMs. Further, we systematically evaluated differences between PROMs in patients with TAK compared with healthy controls or other disease conditions, and their relationship with disease activity.

METHODS

This systematic review was conducted according to guidance provided by the Cochrane

collaboration [14] and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Electronic Supplementary Material [ESM] Table S1) [15], its amendment regarding literature searches (PRISMA-S) (ESM Table S2) [16] and the meta-analysis of observational studies in epidemiology guidelines (ESM Table S3) [17]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Study Selection

Studies reporting PROMs in TAK (both adult-onset [18–21] and childhood-onset [22] forms) reporting original data on any PROM were included. Due to the paucity of randomized controlled trials (RCTs) in TAK [23], both RCTs and observational studies (with or without control group) were included. Review articles, case reports, editorials and letters to editors were excluded.

Literature Searches

MEDLINE (via OVID), EMBASE (via OVID), Pubmed Central (via Pubmed), Web of Science and Scopus were searched on 12 April 2021 without any date or language restrictions (search strategy presented in ESM Table S4). Identified articles were downloaded to Endnote X9.3 and duplicates were removed. Titles and abstracts were screened to identify relevant full-text articles, noting reasons for exclusion. Conference abstracts of major international Rheumatology conferences from 2018 to 2020 (American College of Rheumatology [ACR], European Alliance of Associations for Rheumatology [EULAR], Asia–Pacific League of Nations for Rheumatology), Cochrane database of controlled clinical trials (CENTRAL) and clinicaltrials.gov were hand searched for completed but unpublished studies of TAK reporting PROMs. Searches were analyzed in duplicate by two investigators (DPM, PP); any disagreements were resolved by mutual discussion. Additional studies were included based on prior knowledge or screening reference lists of previous reviews [24]. The search results are shown in ESM Fig. S1.

Quality Analysis of Included Studies

Cochrane Risk of Bias 2 tool [25] for RCTs, the Newcastle–Ottawa scale for cohort studies [26] and the Joanna Briggs Institute checklist for cross-sectional studies [27] were used. The study quality of conference abstracts was not assessed. Publication bias was evaluated if at least ten studies assessed a particular outcome [28, 29].

Data Extraction

Data were extracted to pre-designed paper proformas independently by two investigators (DPM, UR). Means and standard deviations (SD) were imputed from medians with interquartile range or medians with range using published methods [30, 31].

Data Analysis

Data were pooled using the STATA version16.1 I/C software package (StataCorp LLC, College Station, TX, USA), using the restricted maximum likelihood model (REML) to estimate 95% confidence intervals (95% CI). Differences between groups for a particular PROM were pooled after computing the standardized mean difference (SMD) using Hedges' g. Effect sizes were rated as small, medium or large based on SMD cut-offs of 0.2, 0.5 and 0.8, respectively [32]. The random effects model was used a priori due to the expected heterogeneity owing to the small sample sizes [33] of the TAK studies and diverse PROMs assessed. Statistical heterogeneity was assessed using I^2 statistic; values > 50% denoted significant heterogeneity [14]. In such cases, individual studies were excluded to assess whether this exclusion ameliorated the observed heterogeneity. Results were summarized descriptively wherever appropriate. Subgroup analyses were pre-planned for adult and childhood-onset TAK [34, 35]. Studies using version 2 of SF-36 were excluded to evaluate the impact of the version of SF-36 in a secondary

analysis. Sensitivity analyses were based on study design (cross-sectional or cohort).

Analysis of the Certainty of Evidence

Certainty of evidence for pooled outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiler [36].

RESULTS

Summary of Included Studies

Twenty-one studies (1311 patients with TAK, 308 healthy controls) were identified [37–57], all but one [52] were observational. Ten studies (559 patients with TAK, 182 healthy controls) were synthesized in meta-analysis [37, 39–42, 45, 51, 53, 55, 56], all of whom reported patients with prevalent disease (rather than newly diagnosed disease) on a variety of treatments (ESM Table S5). Most subjects included in the studies were female. Thirteen studies included healthy or disease controls. Eight studies reported longitudinal changes in PROMs. Twelve studies were multicentric. Various PROMs were used for QOL (SF-36, original and version 2 [10], EuroQol 5 dimensions [EQ-5D] [58]], mood disorders (HADS-anxiety [HADS-A], HADS-depression [HADS-D] [13]), fatigue (Multidimensional fatigue inventory [MFI-20] [59]), disability (HAQ, International Physical Activity Questionnaire—Short Form [IPAQ-SF] [60], Walking Impairment Questionnaire (WIQ) [61], Work Productivity and Activity Impairment Questionnaire (WPAI) [62]], perceptions about illness (Illness Perception Questionnaire [IPQ-R] [63], Brief Illness Perception Questionnaire [BIPQ] [64], Nottingham Health Profile [NHP] [65]) and fibromyalgia [66]. Characteristics of included studies are summarized in Table 1. Figure 1 presents the geographical distribution of identified studies. Pre-planned subgroup analyses based on childhood or adult-onset TAK were not feasible since only one study exclusively focused on childhood-onset TAK [55].

Quality Assessment of Included Studies

The RCT of tocilizumab in TAK [52] had some concern about the risk of bias due to unclear allocation concealment and unavailability of a pre-published statistical analysis plan. Most cross-sectional studies were of high quality. Some were downgraded due to lack of adjustment for potential confounders and concerns about the appropriate statistical analysis (ESM Table S6). Most cohort studies were of moderate quality (Newcastle–Ottawa scale scores ranged from 4 to 7) and were downgraded for the lack of appropriate control group or selection of control groups unadjusted for confounders (ESM Table S7). Assessment of publication bias was not feasible.

Patient-Reported Outcome Measures

Quality of Life Assessment

36-Item Short Form Survey The SF-36 assesses QOL in eight domains, four physical (physical function, physical role limitation, bodily pain and general health) and four mental (social functioning, emotional role limitation, mental health and vitality). Each domain is measured with a score ranging from 0 to 100. In addition, summary scores are provided for the physical component score and the mental component score, respectively (each with their four domains). Higher scores indicate better QOL [10].

Fifteen studies evaluated SF-36 in TAK [37–40, 42–46, 50–53, 55, 56], nine studies compared TAK patients with healthy controls [38–40, 42, 46, 50, 52, 55, 56] and three studies compared TAK patients with disease controls [38, 39, 53]. Five studies each reported longitudinal changes in SF-36 in TAK [39, 40, 43, 45, 52] and the relationship with disease activity [38, 42, 43, 46, 53]. Nine studies used version 1 of SF-36 [37–40, 42, 46, 51, 55, 56] and two used version 2 of SF-36 [52, 53] (the version used could not be determined for four studies [43–45, 50]).

Individual SF-36 Domains Pooling data from five studies [37, 39, 45, 51, 56] (three cross-

Table 1 Characteristics of included studies

First author of study (reference No)	Number of patients	Gender (male:female)	Age (years)	Duration of disease (years)	QOL outcomes assessed	Included comparison with control	Longitudinal changes in QOL	Relationship of QOL with disease activity	Single/ Multicenter
Abularrage 2008 [37]	158 TAK	14:144	42.2 ± 1.1[a]	11.7[b]	SF-36	Yes (DC)	No	No	Multi
Akar 2008 [38]	51 TAK, 75 HC	10:41 TAK, 22:53 HC	38.4 ± 13.5 [a]TAK, 38.8 + 10.9[a] HC	7.6 ± 7.5[a]	SF-36, NHP	Yes (HC, DC)	No	Yes	Multi
Quartuccio 2012 [39]	10 TAK	NA	NA	NA[d]	SF-36, EQ-5D	Yes (HC, DC)	Yes	No	Multi
Alibaz-Oner 2013 [40]	55 TAK, 40 HC	6: 49 TAK, 9: 31 HC	42.3 ± 12.4[a] TAK, 41 ± 10.8[a] HC	4.7 ± 6.5	SF-36, HADS, HAQ, FM	Yes (HC)	Yes	No	Single
Grayson 2013 [41]	57 TAK	3:54	49.4 + 34.1[a]	9.5 ± 14.8[a]	IPQ-R, MFI-20	Yes (DC)	No	No	Multi
Yilmaz 2013 [42]	165 TAK, 109 HC	12: 153 TAK, 10:99 HC	41.3 + 12.1[a] TAK, 40.4 ± 10.3[a] HC	8.7 + 7.7[a]	SF-36, HADS, HAQ	Yes (HC)	No	Yes	Multi
Sreih 2016 [43]	207 TAK	6: 201	38.7 + 12.9[a]	NA	SF-36	No	Yes	Yes	Multi
Gunsay 2017 [44]	68 TAK	8:60	42.9[b]	NA	SF-36	No	No	No	Multi
Oliveira 2017 [45]	6 TAK	0:6	35.3 + 6.6[a]	11.3 + 5.9[a]	SF-36, HAQ	No	Yes	No	Single

Table 1 continued

First author of study (reference No)	Number of patients	Gender (male:female)	Age (years)	Duration of disease (years)	QOL outcomes assessed	Included comparison with control	Longitudinal changes in QOL	Relationship of QOL with disease activity	Single/ Multicenter
Omma 2017 [46]	165 TAK, 51 HC	19:146 TAK, 6:45 HC	32.5 + 11.7[a] TAK, 38.2 ± 7.9[a] HC	6 ± 5.4[a]	SF-36	Yes (HC)	No	Yes	Multi
Chen 2018 [47]	14 TAK	NA	NA	NA	EQ-5D	No	Yes	No	Single
Sreih 2018 [48]	31 TAK	NA	NA	NA	Qualitative study	No	No	No	Multi
Campochiaro 2020 [49]	23 TAK	2:21	43.8 + 14.4[a]	8.0 ± 5.1[a]	HAQ	No	Yes	No	Single
Garen 2020 [50]	33 TAK	0:33 TAK	32[c] TAK	8.9[c]	SF-36	Yes (HC)	No	No	Single
Luna-Vargas 2020 [51]	15 TAK	0:15	38.7 ± 11.1[a]	10 ± 8.8[a]	SF-36, HAQ, MFI	No	No	No	Single
Nakaoka 2020 [52]	36 TAK	5:31 TAK	30.9 ± 15.5[a] TAK	5.0 ± 6.0[a]	SF-36	Yes (HC)	Yes	No	Multi
Rimland 2020 [53]	56 TAK	11:45	33.4 ± 15.9[a]	7.4 ± 10.1[a]	SF-36, BIPQ, MFI	Yes (DC)	No	Yes	Single
Schwartz 2020 [54]	47 TAK	7:40	34 ± 14[a]	NA	BIPQ	Yes (DC)	Yes	No	Single
Astley 2021 [55]	17 TAK, 17 HC	6:11 TAK, 6:11 HC	18.4 ± 3.4[a] TAK, 18.5 + 3.5[b] HC	9.5 + 4.2[a]	SF-36	Yes (HC)	No	No	Multi

Table 1 continued

First author of study (reference No)	Number of patients	Gender (male:female)	Age (years)	Duration of disease (years)	QOL outcomes assessed	Included comparison with control	Longitudinal changes in QOL	Relationship of QOL with disease activity	Single/ Multicenter
dos Santos 2021 [56]	20 TAK, 16 HC	0:20 TAK, 0:16 HC	41.9 ± 6.2[a] TAK	15.2 ± 7.8[a]	SF-36, HAQ, IPAQ-SF, WIQ	Yes (HC)	No	No	Multi
Erdal 2021 [57]	77 TAK	7:70	44 ± 9.3[a]	7 ± 3.7[a]	IPQ-R, HADS, WPAI	No	No	Yes	Single

BIPQ Brief Illness Perception Questionnaire, *DC* Disease controls, *EQ-5D* EuroQol 5 dimensions, *FM* Fibromyalgia, *HADS* Hospital Anxiety and Depression Scale, *HAQ* Health Assessment Questionnaire, *HC* healthy controls, *IPAQ-SF* International Physical Activity Questionnaire – Short Form, *IPQ-R* Illness Perception Questionnaire, *MFI* Multidimensional fatigue inventory, *NA* Not available, *NHP* Nottingham Health Profile, *QOL* quality of life, SF-36 36 item Short Form Survey, *TAK* Takayasu arteritis, *WIQ* Walking Impairment Questionnaire, *WPAI* Work Productivity and Activity Impairment Questionnaire

[a] Mean (standard deviation [SD])

[b] Mean

[c] Median

[d] Mean disease duration (± SD) for entire cohort of 15 patients at baseline was 3.2 ± 2.5 years (not separately mentioned for the ten patients for whom SF-36 and EQ-5D were reported)

sectional, two cohort; 209 patients with TAK), mean (95% CI) SF-36 component scores were obtained in different domains: physical function (58.88, 95% CI 48.66–69.10), physical role limitation (53.39, 95% CI 40.85–66.34), bodily pain (57.83, 95% CI 46.05–69.6), general health (50.57, 95% CI 38.76–62.39), social functioning (69.28, 95% CI 57.40–81.15), emotional role limitation (67.22, 95% CI 55.94–78.51), mental health (66.97, 95% CI 59.10–74.83) and vitality (53.67, 95% CI 41.15–66.19) (Fig. 2); all showed considerable heterogeneity. Excluding the study of Quartuccio et al. [39], the I^2 for the domain of emotional role limitation but not for other domains was reduced to < 50%. Excluding the study of Luna–Vargas [51] reduced I^2 to < 50% for the domains of physical function, emotional role limitation and mental health but not for other domains. Thus, no single study adequately explained the heterogeneity. Sensitivity analyses reduced I^2 < 50% for emotional role limitation, mental health, physical role limitation, social functioning and vitality domains for the cohort studies but not for cross-sectional studies.

Comparisons between TAK patients and healthy controls were pooled from two studies (one each cross-sectional or cohort studies, 30 patients with TAK) [39, 56]. Large effect sizes denoted worse scores in all domains for patients with TAK, with considerable heterogeneity [32]; however, the differences were not statistically significant (Fig. 3a).

Longitudinal changes were pooled from two studies (both cohort, 16 patients with TAK) [39, 45], before and after infliximab [39] or before and after exercise therapy [45]. Effect sizes were small to medium for all domains [32], but not statistically significant, with little observed heterogeneity in domains other than bodily pain (Fig. 3b).

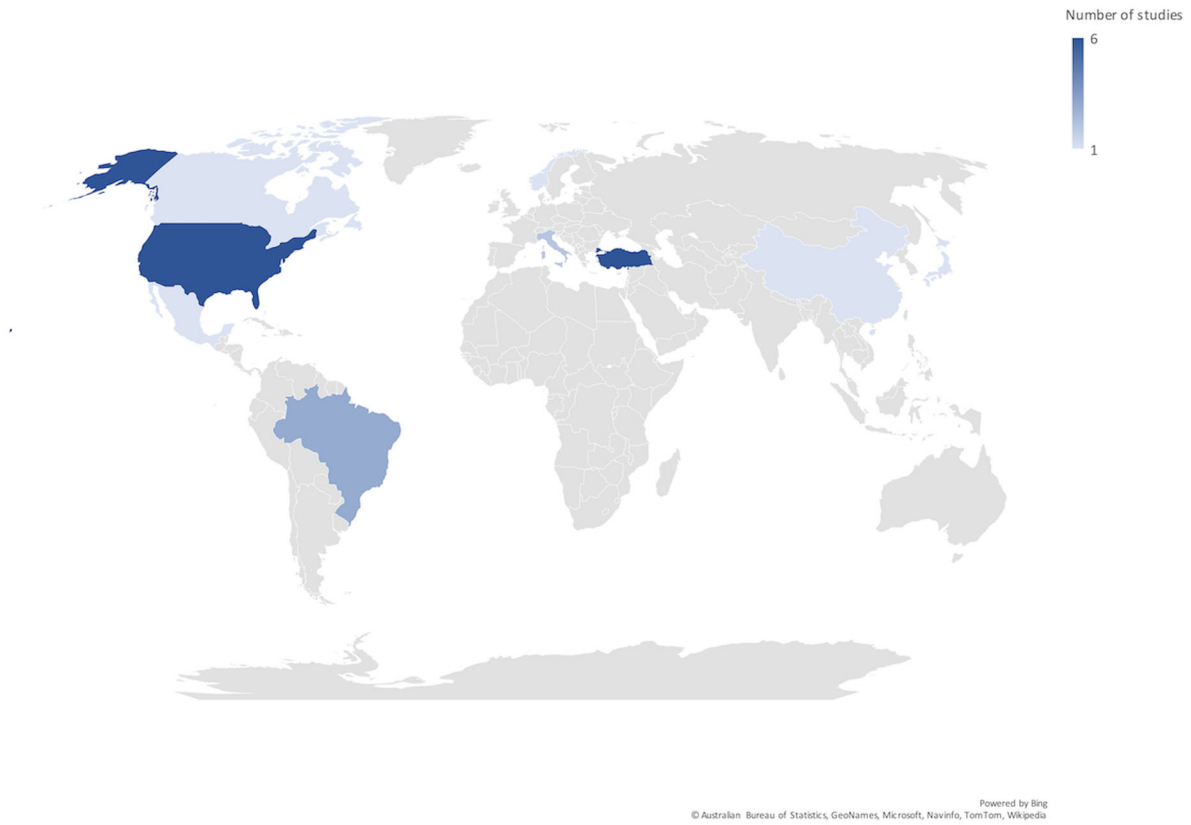
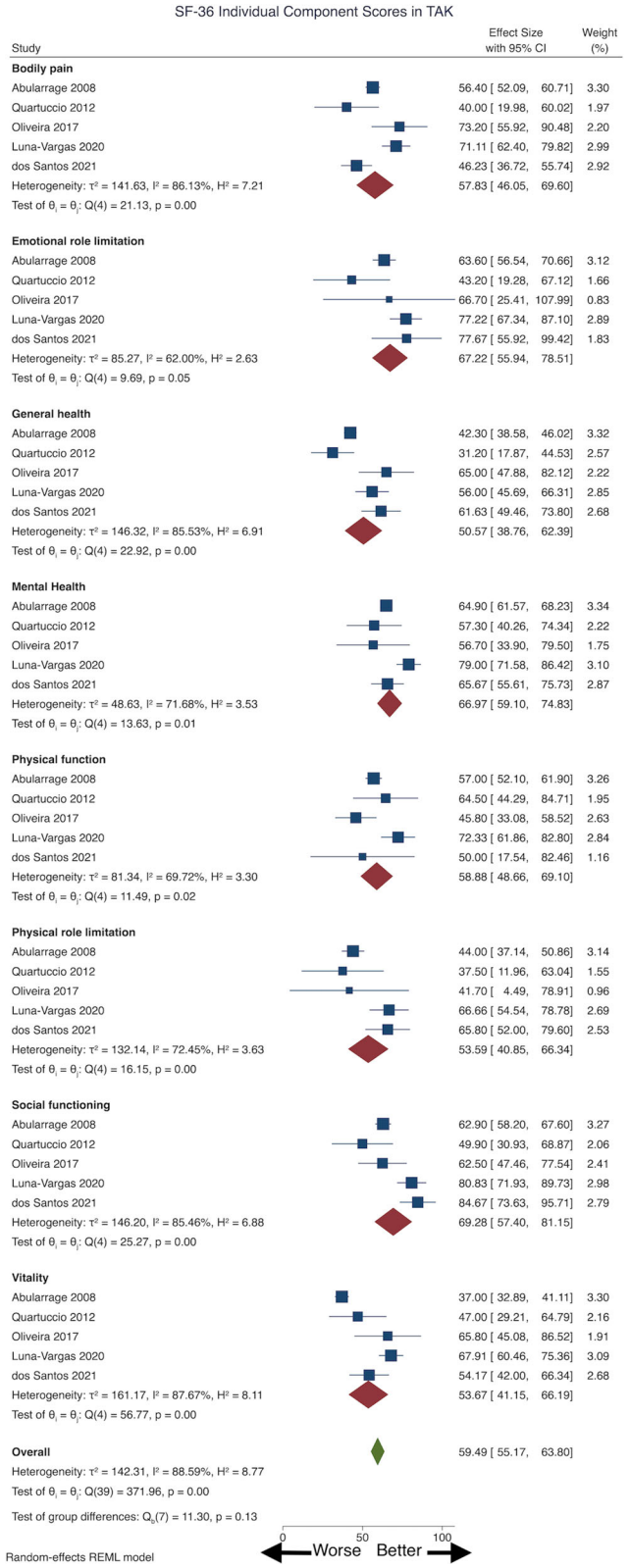


Fig. 1 Geographical distribution of studies assessing patient-reported outcome measures in Takayasu arteritis. Figure generated using the map chart function of Microsoft Excel for Mac v 16.48


SF-36 Individual Component Scores in TAK
Study
Effect Size with 95% CI
Weight (%)
Bodily pain
Abularrage 2008 56.40 [52.09, 60.71] 3.30
Quartuccio 2012 40.00 [19.98, 60.02] 1.97
Oliveira 2017 73.20 [55.92, 90.48] 2.20
Luna-Vargas 2020 71.11 [62.40, 79.82] 2.99
dos Santos 2021 46.23 [36.72, 55.74] 2.92
Heterogeneity: τ² = 141.63, I² = 86.13%, H² = 7.21 57.83 [46.05, 69.60]
Test of θi = θj: Q(4) = 21.13, p = 0.00
Emotional role limitation
Abularrage 2008 63.60 [56.54, 70.66] 3.12
Quartuccio 2012 43.20 [19.28, 67.12] 1.66
Oliveira 2017 66.70 [25.41, 107.99] 0.83
Luna-Vargas 2020 77.22 [67.34, 87.10] 2.89
dos Santos 2021 77.67 [55.92, 99.42] 1.83
Heterogeneity: τ² = 85.27, I² = 62.00%, H² = 2.63 67.22 [55.94, 78.51]
Test of θi = θj: Q(4) = 9.69, p = 0.05
General health
Abularrage 2008 42.30 [38.58, 46.02] 3.32
Quartuccio 2012 31.20 [17.87, 44.53] 2.57
Oliveira 2017 65.00 [47.88, 82.12] 2.22
Luna-Vargas 2020 56.00 [45.69, 66.31] 2.85
dos Santos 2021 61.63 [49.46, 73.80] 2.68
Heterogeneity: τ² = 146.32, I² = 85.53%, H² = 6.91 50.57 [38.76, 62.39]
Test of θi = θj: Q(4) = 22.92, p = 0.00
Mental Health
Abularrage 2008 64.90 [61.57, 68.23] 3.34
Quartuccio 2012 57.30 [40.26, 74.34] 2.22
Oliveira 2017 56.70 [33.90, 79.50] 1.75
Luna-Vargas 2020 79.00 [71.58, 86.42] 3.10
dos Santos 2021 65.67 [55.61, 75.73] 2.87
Heterogeneity: τ² = 48.63, I² = 71.68%, H² = 3.53 66.97 [59.10, 74.83]
Test of θi = θj: Q(4) = 13.63, p = 0.01
Physical function
Abularrage 2008 57.00 [52.10, 61.90] 3.26
Quartuccio 2012 64.50 [44.29, 84.71] 1.95
Oliveira 2017 45.80 [33.08, 58.52] 2.63
Luna-Vargas 2020 72.33 [61.86, 82.80] 2.84
dos Santos 2021 50.00 [17.54, 82.46] 1.16
Heterogeneity: τ² = 81.34, I² = 69.72%, H² = 3.30 58.88 [48.66, 69.10]
Test of θi = θj: Q(4) = 11.49, p = 0.02
Physical role limitation
Abularrage 2008 44.00 [37.14, 50.86] 3.14
Quartuccio 2012 37.50 [11.96, 63.04] 1.55
Oliveira 2017 41.70 [4.49, 78.91] 0.96
Luna-Vargas 2020 66.66 [54.54, 78.78] 2.69
dos Santos 2021 65.80 [52.00, 79.60] 2.53
Heterogeneity: τ² = 132.14, I² = 72.45%, H² = 3.63 53.59 [40.85, 66.34]
Test of θi = θj: Q(4) = 16.15, p = 0.00
Social functioning
Abularrage 2008 62.90 [58.20, 67.60] 3.27
Quartuccio 2012 49.90 [30.93, 68.87] 2.06
Oliveira 2017 62.50 [47.46, 77.54] 2.41
Luna-Vargas 2020 80.83 [71.93, 89.73] 2.98
dos Santos 2021 84.67 [73.63, 95.71] 2.79
Heterogeneity: τ² = 146.20, I² = 85.46%, H² = 6.88 69.28 [57.40, 81.15]
Test of θi = θj: Q(4) = 25.27, p = 0.00
Vitality
Abularrage 2008 37.00 [32.89, 41.11] 3.30
Quartuccio 2012 47.00 [29.21, 64.79] 2.16
Oliveira 2017 65.80 [45.08, 86.52] 1.91
Luna-Vargas 2020 67.91 [60.46, 75.36] 3.09
dos Santos 2021 54.17 [42.00, 66.34] 2.68
Heterogeneity: τ² = 161.17, I² = 87.67%, H² = 8.11 53.67 [41.15, 66.19]
Test of θi = θj: Q(4) = 56.77, p = 0.00
Overall 59.49 [55.17, 63.80]
Heterogeneity: τ² = 142.31, I² = 88.59%, H² = 8.77
Test of θi = θj: Q(39) = 371.96, p = 0.00
Test of group differences: Qb(7) = 11.30, p = 0.13
Random-effects REML model
0
50
100
Worse
Better

◀**Fig. 2** Pooled 36-Item Short Form Survey (*SF-36*) individual component scores in patients with Takayasu arteritis (*TAK*). *CI* Confidence interval, *REML* restricted maximum likelihood model

Physical and Mental Component Summary SF-36 Scores Pooled from four studies (two each cross-sectional or cohort, 153 patients with TAK) [40, 51, 53, 55], the physical component scale score was 56.67 (95% CI 44.64–68.69) and mental component scale score was 60.71 (95% CI 43.69–77.73), with considerable heterogeneity (Fig. 4a) that was not explained by any single study. Sensitivity analyses by study design ameliorated heterogeneity for both the physical component and mental component scales for cross-sectional studies, but only for the mental component scale for cohort studies. Excluding the study using SF-36 version 2 [53] in a secondary analysis, the pooled physical component scale score was 58.80 (95% CI 42.50–75.10) and mental component scale score was 65.48 (95% CI 44.97–86.00).

Comparison with healthy controls were pooled from two studies (72 patients with TAK, 57 healthy controls, one each cross-sectional and cohort) [40, 55]. Effect size was large for the physical component score and small for the mental component scores [32], both favoring worse scores for TAK (statistically significant for physical component score alone). The pooled physical component score had considerable heterogeneity (Fig. 4b). Alibaz-Oner et al. [40] reported no significant changes in the SF-36 physical or mental component scores of 30 patients with TAK over 6 months. Quartuccio et al. [39] reported significant increase in normalized physical component scores (36.9 ± 10.9 before, 44.3 ± 7 after) and non-significant increase in normalized mental component scores (40 + 15 before, 47.7 + 14 after) following infliximab therapy.

Descriptive Results Akar et al. [38] reported worse SF-36 scores in 51 patients with TAK when compared with 75 healthy controls across all domains; however, the scores were comparable with those for RA or AS. Bodily pain (but not other domains) scored significantly worse for patients with TAK with active disease than for those with inactive disease [38]. Rimland et al. [53] reported similar SF-36 summary physical and mental component scores in 56 patients with TAK or giant cell arteritis (GCA). Yilmaz et al. [42] reported worse SF-36 scores in all domains for 165 patients with TAK compared with 109 healthy controls; with the exception of the domain for mental health, all domains were significantly worse for 71 patients with active TAK compared with 94 patients with inactive TAK. Sreih et al. [43] assessed 207 patients with TAK longitudinally (881 visits with clinical remission, 196 visits with relapse). The physical component score (43.3 ± 10.1 vs. 39 ± 10) but not the mental component scores (46.5 ± 12.3 vs. 47 ± 11) of SF-36 (normalized to North American population) were significantly worse with active disease. Adjusted odds of relapse in the following two visits increased with increment in the physical component score by 1 unit at any visit (odds ratio [OR] 1.07, 95% CI 1.02–1.13) [43]. Gunsay et al. [44] reported that better mental component scores were associated with lesser vascular damage in TAK. Omma et al. [46] reported significantly worse SF-36 scores in all domains except emotional role limitation and summary mental component scores in 165 patients with TAK when compared with 51 healthy controls. Those with resistant TAK (35% of the cohort) had worse scores in all SF-36 domains (except physical function and emotional role limitation) and worse summary physical and mental component scores compared with the rest [46]. Garen et al. [50] reported worse SF-36 scores in six domains in 33 patients with TAK compared with Norwegian standards. Better pain and fatigue were associated with higher mental health scores [50]. Nakaoka et al. [52] assessed SF-36 scores in a RCT of tocilizumab (36 patients with TAK; parallel group, placebo-controlled until 24 weeks, then open-label extension until 96 weeks on tocilizumab). Patients with TAK had worse baseline SF-36 domain scores than the Japanese standard population. There was significant improvement in summary mental component scores of SF-36 from week 12 and in the summary physical component

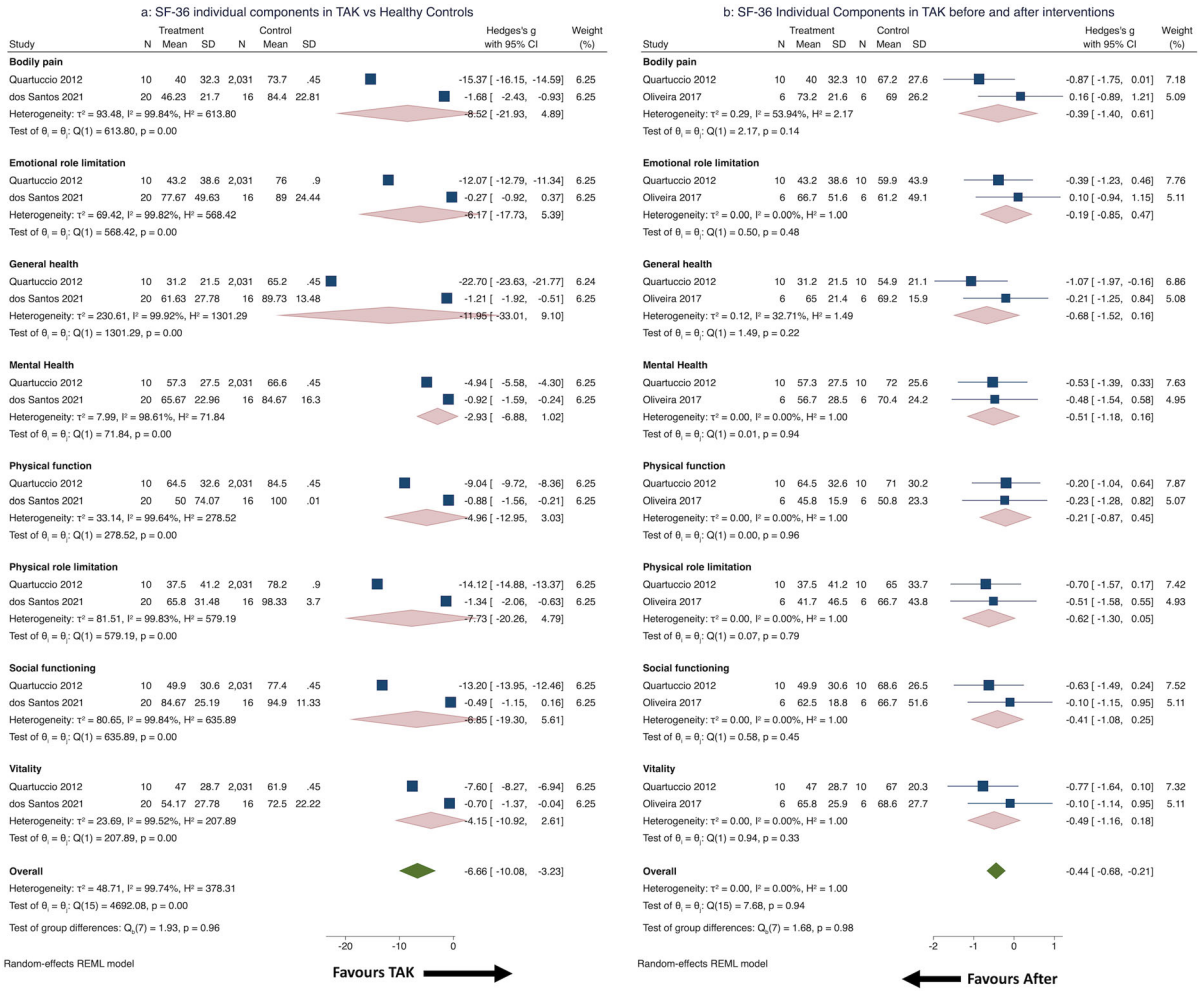


Fig. 3 SF-36 individual component scores in TAK: comparison with healthy controls and longitudinal changes. **a** SF-36 individual component scores in patients with TAK compared with healthy controls, **b** SF-36 individual component scores in patients with TAK before and after therapeutic interventions

score by week 24 compared with baseline scores (sustained until week 96) with tocilizumab [52].

EuroQol 5-Dimensions The EQ-5D score assesses QOL across five dimensions, rated across three or five levels, with a visual analog score estimate of overall health ranging from 0 to 100 (higher scores indicating better health) [58]. Two studies reported EQ-5D in patients with TAK. Quartuccio et al. [39] reported significant improvement in EQ-5D scores (derived from SF-36 scores) following infliximab therapy in ten patients with TAK (before 0.57 ± 0.2, after 0.73 ± 0.2). Chen et al. [47] reported improvement in EQ-5D scores in 14 patients with TAK following vascular bypass surgery (before $58.93 + 14.4$, after $87.14 + 1.25$).

Disability

Health Assessment Questionnaire The HAQ disability index score is used to measure disability in different disease settings, with scores ranging from 0 to 3 in relation to 12 tasks of daily living. The summary scores are divided by 12 to provide a final score out of 3. Higher scores indicate worse disability [11]. HAQ scores of ≥ 1 indicate significant disability [12]. HAQ scores ≥ 1 indicate significant disability [12].

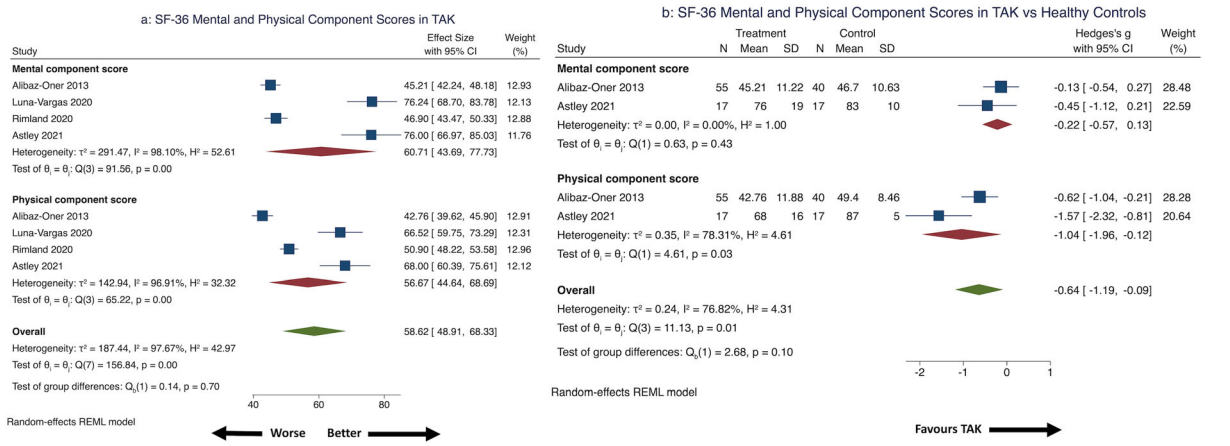


Fig. 4 SF-36 physical and mental component summary scores in patients with TAK. **a** SF-36 summary mental and physical component scores in patients with TAK, **b** SF-36 summary mental and physical component scores in patients with TAK compared with healthy controls

Six studies evaluated HAQ in TAK [40, 42, 45, 49, 51, 56]. Pooled HAQ in 261 patients with TAK (two cohort, three cross-sectional studies) [40, 42, 45, 51, 56] was 0.46 (95% CI 0.37–0.55) with little heterogeneity (Fig. 5a). Three studies (one cohort, two cross-sectional studies) [40, 42, 56] comparing HAQ in 240 patients with TAK with 163 healthy controls identified significantly worse HAQ score in the TAK arm (SMD 0.64, 95% CI 0.43–0.84) (Fig. 5b) with medium effect size [32]. Three studies evaluated longitudinal changes in HAQ. Alibaz-Oner et al. [40] reported similar HAQ for 30 patients with TAK over 6 months. Oliveira et al. [45] reported similar HAQ for six patients with TAK before and after 12 weeks of exercise therapy. Campochiaro et al. [49] reported similar HAQ values at baseline, 6 months and 12 months in 23 patients with TAK after being treated with infliximab biosimilar. This study provided HAQ scores in the range of 3.35 to 3.84 [49]; this was possibly because the authors might have used the original HAQ instead of the HAQ disability index (which provides scores between 0 and 3).

International Physical Activity Questionnaire—Short Form The IPAQ-SF enables assessment of physical activity through seven questions with a subsequent calculation of metabolic equivalents (METs) consumed during such physical activity [60]. dos Santos et al. [56] reported lower physical activity in 20 patients with TAK (mean ± SD: 481.6 ± 379 METs consumed during physical activity per week) compared to 16 healthy controls (1662.7 ± 827.4 METs per week).

Walking Impairment Questionnaire The WIQ allows self-reporting of walking disability in three domains, namely walking distance, speed of walking and climbing of stairs, on a scale of 0 to 100. Lower scores indicate greater impairment [61]. dos Santos et al. [56] reported worse WIQ scores in 20 patients with TAK (mean ± SD: 64.6 ± 44.5) compared to 16 healthy controls (96.3 ± 8.2).

Work Productivity and Activity Impairment The WPAI scale assesses work productivity in four domains, with higher scores indicating worse work impairment status [62]. Erdal et al. [57] reported worse scores in the domain of daily activity impairment in individuals with active TAK when compared with those with inactive disease. Both disease activity and depression (measured using HADS-D) mediated the effect on this domain of the WPAI.

Mood Abnormalities

Hospital Anxiety and Depression Score The HADS assesses the likelihood of anxiety (through the HADS-A questionnaire) and depression (via the HADS-D questionnaire) in respondents. Each questionnaire comprises seven questions, rated between 0 and 3, for a total score of 21 each. Scores of eight or above indicate a greater probability of anxiety (for the HADS-A) or depression (for the HADS-D) [13].

Three studies reported HADS in TAK [40, 42, 57]. Two studies provided comparisons with healthy controls [40, 42]. Data were pooled from two studies (one each cross-sectional and cohort; 220 patients with TAK) [40, 42]. Pooled HADS-A was 7.46 (95% CI 5.67–9.26) and pooled HADS-D was 6.05 (95% CI 4.38–7.73) with significant heterogeneity (Fig. 5c). Comparing 220 patients with TAK with 149 healthy controls revealed significantly higher HADS-D (SMD 0.26, 95% CI 0.05–0.47 without heterogeneity) but not HADS-A (SMD 0.34, 95% CI − 0.06 to 0.75 with considerable heterogeneity) in TAK (Fig. 5d) with a small effect size [32]. Erdal et al. reported higher HADS-A [mean (SD) 10.5 (5.25) versus 6.5 (4)] and HADS-D [8 (4.75) versus 5 (3.25)] in 26 active TAK compared to 50 with inactive TAK [57].

Fatigue

Multidisciplinary Fatigue Inventory The MFI-20 assesses fatigue using 20 questions scored from 0 to 5, averaged to provide a score from 20, with higher scores indicating worse fatigue [59]. Three studies assessed MFI-20 in TAK [41, 51, 53]. Pooled MFI-20 score in 113 patients with TAK (one each cross-sectional and cohort study) [41, 53] was 15.52 (95% CI 14.48–16.56) denoting significant fatigue (MFI-20 > 13) [41] with considerable heterogeneity (Fig. 5e). Grayson et al. [41] reported similar MFI-20 scores in patients with TAK when compared with those with AAV, GCA, IgA vasculitis, polyarteritis nodosa and primary central nervous system angiitis. Rimland et al. [53] reported similar MFI-20 scores in patients with TAK and GCA. Luna-Vargas et al. [51] reported the association of earlier disease duration with worse general fatigue domain scores of MFI-20 in 15 patients with TAK.

Perceptions of Illness

Illness Perception Questionnaire and Brief Illness Perception Questionnaire The IPQ-R and its modification the BIPQ help assess the perceptions of patients towards their disease. The IPQ-R assesses patient perceptions in eight dimensions, namely identity, consequences of disease, timeline (acute/chronic), timeline (cyclical), personal control, treatment control, emotional representations and illness coherence [63]. The BIPQ was developed as a modification of the IPQ-R to assess perceptions about illness in eight domains, four of which are in common with the IPQ-R (identity, consequences of disease, personal control, treatment control) and four others (timeline, concern, understanding and emotional response), each with a single question rated from 0 to 10. A further question assesses perceptions regarding the cause of illness in an open-ended manner [64].

Grayson et al. [41] reported IPQ-R scores in 692 subjects with vasculitis (57 with TAK). They noted worse perceptions of illness with respect to the dimensions of identity, timeline (acute/chronic) and illness consequences in TAK patients. Worse perceptions of illness were pervasive across different forms of vasculitis. When compared with patients with other chronic diseases (diabetes melllitus, hypertension, osteoarthritis and systemic sclerosis), those with vasculitis had worse scores on the dimensions of consequences and emotional representations. Younger age (OR 1.04, 95% CI 1.02–1.06), depression (OR 4.94, 95% CI 2.9–8.41) and active disease (OR 2.05, 95% CI 1.27–3.29) were associated with worse disease perception [41]. Erdal et al. [57] reported a significant association of scores on the consequences domain of IPQ-R with active disease in 77 patients with TAK. They also identified depression (measured using HADS-D score) as a likely mediator of worse disease perceptions in the consequences domain amongst patients with active TAK [57].

Two cohort studies assessed BIPQ in 103 patients with TAK [53, 54]. Rimland et al. [53] reported mean BIPQ score of 42.6 ± 11.26 (imputed mean with SD) and Schwartz et al. [54] reported BIPQ of 38.4 ± 14.5 (mean with SD) in patients with TAK. Rimland et al. reported

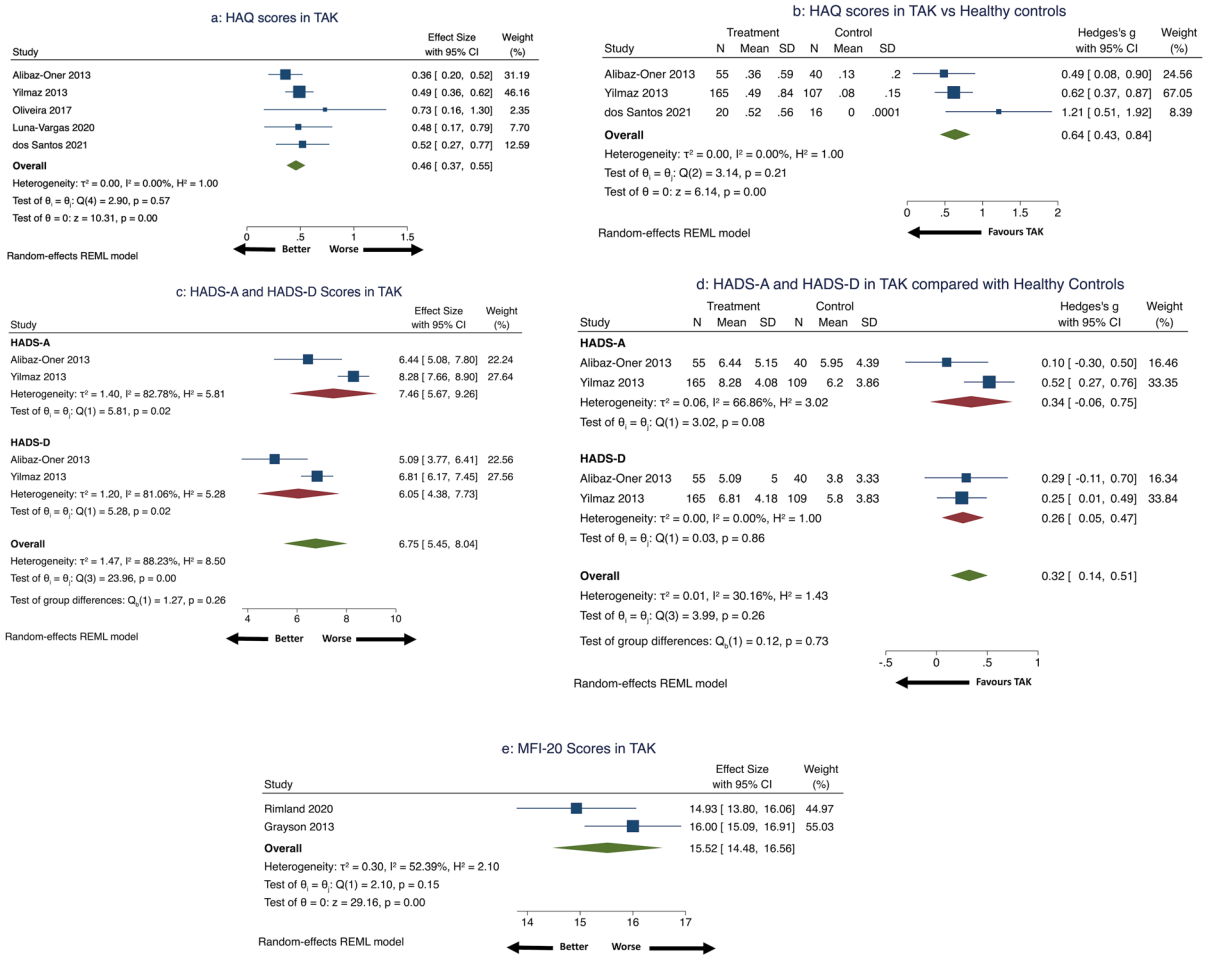


Fig. 5 HAQ, HADS and MFI-20 scores in patients with TAK. **a** Health Assessment Questionnaire (*HAQ*) scores in patients with TAK, **b** Health Assessment Questionnaire (*HAQ*) scores in patients with TAK compared with healthy controls, **c** Hospital Anxiety and Depression Scale (*HADS-A* and *HADS-D*, respectively) scores in patients with TAK, **d** Hospital Anxiety and Depression Scale (*HADS*) scores in patients with TAK compared with healthy controls, **e** Multidisciplinary Fatigue Inventory (*MFI-20*) scores in patients with TAK

similar BIPQ scores in patients with TAK and GCA [53]. Schwartz et al. compared BIPQ scores in different systemic vasculitides. Scores for TAK were highest for the timeline domain and lowest for the domains of personal control and identity. BIPQ scores for TAK were similar to GCA or AAV but worse than those for relapsing polychondritis [54].

Nottingham Health Profile The NHP assesses the distress of patients in six domains (energy levels, emotional reactions, physical mobility, pain, social isolation and sleep). Higher scores indicate greater distress [65]. Akar et al. [38] reported higher scores in the energy level, physical mobility and pain domains of the NHP for patients with TAK when compared with healthy controls. When compared with patients with RA or AS, those with TAK had comparable NHP scores in most domains other than pain, which was better than the scores for RA [38].

Fibromyalgia

The 2010 ACR diagnostic criteria define fibromyalgia using the WPI and the Symptom Severity Scale (SSS) as persistent pain in patients for at least 3 months without any suitable alternative explanation. The WPI assesses pain in

Table 2 Summary of findings from the systematic review on patient-reported outcome measures in patients with TAK

PROM	Comparison with healthy controls	Changes over time	Comparison between patients with active and inactive disease
Quality of life			
SF-36	Worse in TAK*	Stable or better with time Improvement following exercise therapy or infliximab	Worse in active TAK*
EQ-5D	–	Improve following infliximab or vascular bypass surgery	–
Disability			
HAQ	Worse in TAK*	Stable over time/following exercise therapy/following infliximab	–
IPAQ-SF	Lesser physical activity in TAK*	–	–
WIQ	Worse in TAK*	–	–
WPAI	–	–	Greater work impairment in those with active disease*
Mood			
Anxiety (HADS-A)	Worse in TAK	–	Worse in active TAK*
Depression (HADS-D)	Worse in TAK*	–	Worse in active TAK*
Fatigue			
MFI-20	–	–	–
Perceptions of illness			
IPQ-R	–	–	–
BIPQ	–	–	–
NHP	Worse in TAK*	–	–
Fibromyalgia			
Diagnostic criteria for fibromyalgia	Similar prevalence in TAK and HC	–	Active TAK associated with greater risk of prevalent fibromyalgia*

PROM Patient-reported outcome measure
*Significant difference at the 5% level between comparisons

19 areas of the body, and the SSS assesses the severity of four symptoms, namely fatigue, waking unrefreshed, cognitive symptoms and somatic symptoms, each on a scale of 0–3, with higher scores indicating greater severity. In an individual with duration of symptoms for at least 3 months without a suitable alternative explanation, fibromyalgia can be diagnosed with an WPI score of at least 7 and an SSS score of at least 5, or an WPI score between 3 and 6 and an SSS score of at least 9 [66]. Alibaz-Oner et al. [40] reported fibromyalgia in seven of 55 patients with TAK using the 2010 ACR criteria and in three of 55 patients with TAK using the 1990 ACR criteria, with similar prevalence to the general population. Active TAK was associated with a significantly greater risk of prevalent fibromyalgia than inactive TAK (risk ratio 9.71, 95% CI 1.26–75.15) [40].

Developing a PROM Specific to TAK

A qualitative study by OMERACT reported aspects prioritized by patients with TAK after in-depth interviews with 31 patients from Turkey and the USA. Eleven domains were common between patients from both countries, including impact on various situations at home or work, coping behavior, anxiety, depression, disability in daily activities due to reduced functional capacity, psychological support and social support. These findings might enable the development of a PROM specific to TAK [48].

Certainty of Evidence for Pooled Outcomes

The certainty of evidence for comparisons of QOL, disability, anxiety and depression between TAK and healthy controls ranged from low to very low (ESM Table S8).

DISCUSSION

The present systematic review revealed worse QOL, greater depression and anxiety scores and worse disability in patients with TAK when compared to healthy controls. Fewer studies evaluated changes in PROMs over time or the relationship with disease activity. QOL remained stable or improved with time or following specific treatments in TAK. Disability remained similar over time or after treatment. QOL, depression and work impairment were worse in patients with TAK with active disease when compared with those with inactive disease. Identified studies were of moderate to high quality. Wherever outcomes could be pooled, the certainty of evidence was low to very low. However, it must be emphasized that few studies assessed PROMs in patients with TAK in comparison with healthy controls, or assessed longitudinal changes. Many of the pooled outcomes were heterogenous and, therefore, should be cautiously interpreted. The findings of the systematic review along with the identified knowledge gaps about PROMs in TAK are summarized in Table 2.

Previous systematic reviews have reported impaired QOL in other inflammatory rheumatic diseases, such as RA [67], AS [68], systemic lupus erythematosus (SLE) [69] and systemic sclerosis (SSc) [70]. While active disease associates with worse QOL in AS [68], this is less clear for other rheumatic diseases. Longer duration of RA is associated with better SF-36 scores [67], possibly reflecting better adjustment to disease with time or better control of active disease. Patients with RA have worse HAQ scores which improve following control of disease activity and worsen with longer disease duration [71]. Depression is more prevalent in patients with RA [72], AS [73, 74] and SSc [75] and is associated with worse pain in RA. Risk of developing incident RA is higher in those with depression [76]. Up to one half of patients with SLE [77, 78] and SSc experience work disability [79]. Work disability in the setting of RA [80], AS [81] and SSc [79] is multifactorial, related to disease and socio-behavioral aspects. The current systematic review is the first to highlight worse PROMs in patients with TAK, akin to other systemic vasculitides [53, 54]. Factors determining PROMs in TAK require further exploration via qualitative research.

The present systematic review has a number of limitations. Relatively fewer studies (many with small sample sizes) have evaluated PROMs in TAK. However, this is a limitation of TAK

studies in general and must be viewed in the context of the rarity of the disease. Paucity of identified studies did not permit assessment of publication bias. Pooled outcomes had considerable statistical heterogeneity, possibly due to the small sample size of individual studies [33]; this heterogeneity was partially explained by excluding findings from individual studies. Searching across multiple databases and sources of information to identify relevant studies and reasonable study quality were strengths of our systematic review.

This systematic review has identified research gaps about PROMs in TAK. Hardly any studies assessed PROMs in TAK from Asia, where the disease is relatively more common [4]. Few studies have reported longitudinal changes in PROMs in TAK, changes following treatment or PROMs in childhood-onset TAK. Previous reviews (and this one) have identified the paucity of studies assessing the impact of pharmacotherapy on QOL in LVV [82]. The development of a specific PROM for TAK is underway; however, this effort represents perspectives from patients with TAK from restricted geographic locations (Turkey and USA) [48]. Such a PROM shall require validation across different populations. There might even be a need to develop a specific PROM for TAK from different geographic regions, taking into consideration socio-cultural diversities across the world. While studies have used the generic HAQ disability index (also validated in TAK [42]), this tool had originally been designed for patients with arthritides such as RA and osteoarthritis [83]. Inclusion of clinical features, such as limb claudication, neck pain and breathlessness due to heart failure, might enhance the representativeness of the HAQ in TAK.

CONCLUSIONS

To conclude, the present systematic review uncovers reasonable evidence for worse disability and depression in patients with TAK compared with healthy controls. Patients with active TAK have worse QOL, mood and disability than those with inactive TAK. There exists an unmet need to longitudinally assess changes in PROMs in TAK (particularly following therapy) and to develop and validate a TAK-specific PROM.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. All the analyses performed for this systematic review have been reported in the main text or in the

supplementary files. The datasets generated during and/or analyzed during the current study are available from the corresponding author (Durga Prasanna Misra, durgapmisra@gmail.com) on reasonable request.

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