Activity Limitations in Patients with Axial Spondyloarthritis

Activity Limitations in Patients with Axial Spondyloarthritis: A Role for Fear of Movement and (Re)injury Beliefs

Thijs W. Swinnen, Johan W.S. Vlaeyen, Wim Dankaerts, René Westhovens, and Kurt de Vlam

ABSTRACT. ***Objective.*** To determine whether fear of movement and (re)injury [FOM/(R)I] beliefs, measured with the Tampa Scale for Kinesiophobia 11-item version (TSK-11), influence activity limitations and mediate the relationship between pain severity and activity limitations in axial spondyloarthritis (axSpA).

Methods. In 173 patients with axSpA, these data were collected: sex, body mass index, disease duration, medication, activity limitations (BASFI; Bath Ankylosing Spondylitis Functional Index), disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); BASDAIinf, items 5 and 6; BASDAIpain, items 2 and 3; C-reactive protein and physician's global assessment], spinal mobility (BASMI; Bath Ankylosing Spondylitis Metrology Index), and FOM/(R)I (TSK-11). Scaling assumptions and reliability of TSK-11 were tested with item-to-total correlations, item variances, and Cronbach's alpha coefficient. Hypothesis testing determined TSK-11's construct validity. Multiple linear regression showed the contribution of TSK-11 to BASFI (enter and backward modeling). Mediation by TSK-11 was analyzed (bias-corrected bootstrapping and Sobel test).

Results. Adequate scale (Cronbach's alpha = 0.80) and item internal consistency (range item-scale correlations 0.41–0.58, except for item 5, r = 0.23), equal item-scale correlations, and item variances were found for TSK-11. Construct validity was confirmed, except for the hypothesized positive relationship between TSK-11 and BASMI. Regression models (enter method, adjusted R^2 range 53–74%) consistently identified TSK-11 as a determinant of BASFI (β range 0.155 to 0.321, $p < 0.05$), although BASMI (β range 0.441 to 0.537) and disease activity (β range 0.243 to 0.571, $p < 0.05$) were the largest determinants. TSK-11 partially mediated the BASDAIpain/BASFI relationship (B = 0.107; Sobel test, p = 0.004; bias-corrected CI 0.046–0.197).

Conclusion. TSK-11 is a promising and valid tool to assess fearful beliefs in relation to activity limitations in axSpA. Future research applying TSK-11 may reveal FOM/(R)I as a novel treatment target in axSpA. (First Release November 15 2017; J Rheumatol 2018;45:357–66; doi:10.3899/jrheum.170318)

Key Indexing Terms:
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Axial spondyloarthritis (axSpA) is a chronic rheumatic disease driven by inflammation and damage (pathological bone formation and/or erosion) dominantly at spinal synovio-entheseal joint regions[1,2]. Clinically, axSpA manifests as sacroiliitis and spinal inflammation at the anterior vertebral bodies and posterior structures[3], but asymmetrical oligoarthritis of large joints and enthesitis are also common peripheral manifestations[4]. Extraskeletal features such as psoriasis, inflammatory bowel disease, or uveitis establish the systemic characteristics of disease. Typical impairments

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include inflammatory back pain, spinal stiffness, and mobility restrictions[5,6,7].

Although the precise etiology of axSpA remains unknown, increased understanding of dysfunctional immunological pathways [e.g., cytokine overexpression of tumor necrosis factor-α, interleukin (IL)-17, IL-22, or IL-23] in axSpA has led to the development of highly effective biological disease-modifying antirheumatic drugs (bDMARD) blocking inflammation and possibly aspects of bone formation[8,9]. Unfortunately, only 50–80% of patients with axSpA can be classified as "responders" to bDMARD, depending on the response criteria used[10]. Biological factors [e.g., high C-reactive protein (CRP) levels, HLA-B27 negativity, or long disease duration] moderately predict nonresponse at best. Thus, a broader bio-psycho-social view is needed to elucidate the mechanisms underlying clinical status and therapy response[11].

A major attempt to shift from a biomedical to a bio-psycho-social framework for the management of axSpA was the development of the World Health Organization's (WHO) International Classification of Functioning, Disability, and Health (ICF) Core Sets for axSpA, endorsed by the Assessment in SpondyloArthritis international Society (ASAS)[7,12]. The WHO/ASAS/ICF Core Set tackles the idea that underlying pathophysiological axSpA disease processes are the sole determinants of functioning[6] and recognize an equally possible influence of personal (e.g., beliefs, habits) and environmental (e.g., workplace exposure) factors, together referred to as context. Indeed, Brionez, *et al*[13] showed that a composite of personal factors such as depression, arthritis helplessness, internality, and coping explained about 24% of the variance in activity limitations in axSpA, in contrast to biological factors, which accounted for only 10% of the variance explained. Similarly, several authors have reported on the association of anxiety and depression (psychological distress) on physical aspects of health-related quality of life in axSpA[14].

Unfortunately, prior research did not provide a theoretical framework explaining how psychological variables exert their influence on activity limitations in axSpA. In the broader field of health psychology, the Fear-Avoidance Model of Pain (FAM; Figure 1A) predicts that if pain (associated with movement) is catastrophically appraised, pain-related fear of movement and (re)injury [FOM/(R)I] emanates and leads to a vicious cycle of avoidance behavior, disuse, disability, and depression, and finally more pain[15]. To date, the value of the FAM model, its predictions and therapeutic approaches, remains unexamined in axSpA, while extensive research in subgroups of nonspecific chronic low back pain exhibiting fearful beliefs resulted in effective model-based interventions such as graded exposure *in vivo*[16,17]. Also, very few studies applied the 17-item Tampa Scale for Kinesiophobia or its shortened 11-item version (TSK-11), the most popular instruments to assess FOM/(R)I beliefs, in arthritis research and none of these involved axSpA[18,19].

Therefore, our cross-sectional study aimed to (1) establish the psychometric properties of the TSK-11 scale in axSpA, that is, item-to-total correlation, internal consistency, and divergent construct validity; (2) determine the univariate and multivariate contribution of FOM/(R)I to activity limitations relative to disease activity and spinal mobility, the key "biological" outcome measures in axSpA; and (3) study the mediating role of FOM/(R)I in the relationship between pain and activity limitations, as predicted by the FOM in axSpA (Figure 1A and 1B).

MATERIALS AND METHODS

Participants. This observational cross-sectional study randomly included 190 subjects with a diagnosis of axSpA according to the ASAS classification criteria[20], verified by an ASAS expert rheumatologist (KDV) between November 2009 and November 2012. The 5–7 research slots/week available at our outpatient spondyloarthritis clinic were taken by the first patients who signed the informed consent. Exclusion criteria were (1) not being able to autonomously fill in self-reported outcome measures, (2) not being able to understand and speak Dutch, and (3) having other inflammatory or systemic rheumatic conditions. The study protocol and its final reports fulfilled the STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) statement[21] and was approved by the Medical Ethics Committee of the University Hospitals Leuven (ML 5236).

Anthropometrics and demographics. Age (yrs), sex (male = 1/female = 2), body mass index (BMI; kg/m^2), disease duration (yrs), and the use of medication [biologicals, yes = 1/no = 2; nonsteroidal antiinflammatory drugs (NSAID), yes = 1/no = 2; DMARD, yes = 1/no = 2; corticoids, yes = 1/no = 2] were assessed during a structured interview and a clinical examination, and were also verified by referring to the patient's medical record.

Activity limitations. Patient-reported activity limitations were assessed with the ASAS-endorsed and widely accepted Bath Ankylosing Spondylitis Functional Index (BASFI) questionnaire[22]. Respondents were requested to rate their perceived difficulty in executing daily activities on a 11-point numerical rating scale (NRS; 0 = easy, 10 = impossible)[23]. A total score was calculated by dividing the sum of all items by 10, producing a score between 0 (best) and 10 (worst). The psychometric properties of the BASFI in axSpA were well established[24].

Spinal mobility. The Bath Ankylosing Spondylitis Metrology Index (BASMI) guided the spinal mobility measurement and included 5 clinical tests: cervical rotation [measured with a goniometer (accuracy 2°, Ortec Orthopedics) and a tape measure (accuracy 1 mm)], lumbar flexion, lumbar side flexion, tragus to wall distance, and intermalleolar distance. For cervical rotation, lumbar side flexion, and tragus to wall distance, the mean of the left and right measurements was taken and all scores were converted according to the BASMI 10 scoring system[24]. The psychometric properties of the BASMI in axSpA are well established[24,25,26].

Disease activity, pain, and inflammation. Four different measures identified disease activity and inflammation. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) demonstrated patient-reported disease activity. The BASDAI questionnaire consisted of 6 items evaluating the severity of fatigue, peripheral and axial pain, localized tenderness, and morning stiffness during the last week. Each item was rated on an 11-point NRS (0 = none, 10 = very severe), with additional anchor words to determine the duration of stiffness (0/1/> 2 h) for item 6. The total score was calculated by dividing the sum of all items by 5 after averaging item 5 and 6 (stiffness evaluation), producing a score between 0 and 10. The psychometric properties of the BASDAI in axSpA are well established[24]. Patient-reported inflammation was evaluated with the average of BASDAI's stiffness items 5 and 6

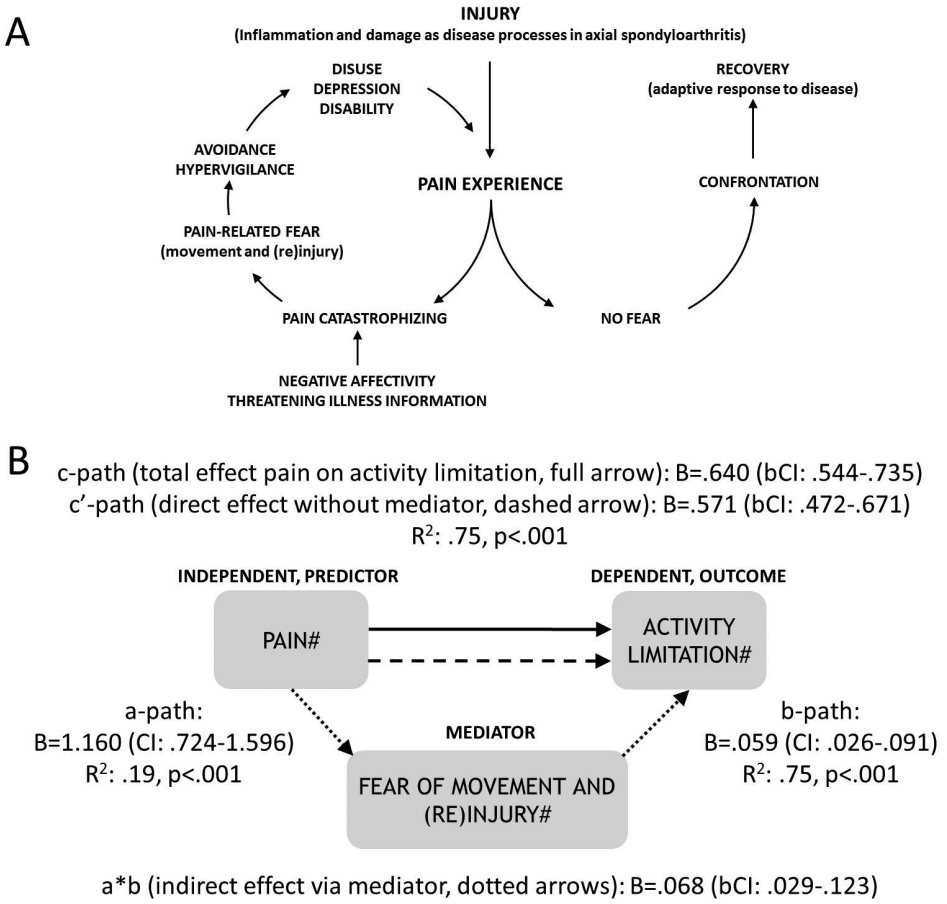

Figure 1. Illustration of the fear avoidance model of pain (A) and mediating role of fear of movement and (re)injury (B) in the relationship between pain and activity limitations in axial spondyloarthritis (n = 173). # Mediating effect ($a \times b = c - c'$) of fear of movement and (re)injury (Tampa Scale for Kinesiophobia 11-item version) in the relationship between pain (average items 2 and 3 of BASDAI) and activity limitations (BASFI) showing unstandardized B weights with 5000 samples bias-corrected bootstrap 95% CI and explained variance (R^2) for each path ($p < 0.05$). BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index.

(BASDAIinf), as recommended by the ASAS group[24]. Physician global disease activity (PGDA) assessed during the routine rheumatology visit at inclusion represented physician-reported disease activity. PGDA was evaluated using a reliable and valid 11-point NRS scale (0 = none, 10 = very severe)[24]. CRP (mg/l) served as the laboratory-based disease activity marker[24]. Pain severity (BASDAIpain) was assessed by the average of BASDAI item 2 (overall level of AS neck, back, or hip pain) and item 3 (overall level of pain in joints other than neck, back, or hips) on an 11-point NRS[24].

Evaluating FOM/(R)I. The Dutch TSK-11 evaluated the patient's FOM/(R)I beliefs using 4-point Likert scales with scoring alternatives ranging from "strongly disagree" to "strongly agree." The psychometric properties of TSK-11 (Supplementary Table 1, available with the online version of this article) are well established across different non-axSpA populations[27,28,29].

Data reduction and statistical analysis. Descriptive data were presented as mean, median, percentile 25 and 75, minimum, and maximum values. Normal distribution of all variables was evaluated with the Shapiro-Wilk test ($p < 0.05$) and deviated for CRP and PGDA, which were LOG_{10} transformed to obtain adequate normality of data.

To test the 4 basic scaling assumptions for Likert scales such as TSK-11[27,30,31], homogeneity was assessed by Cronbach's alpha coefficient with values between 0.70 and 0.90, indicating adequate scale internal consistency[32], and corrected item-to-total correlations with values above 0.20 as acceptable and above 0.40 as good item internal consistency[30]. Also, the latter correlations and item variances presented as SD should be roughly equal across items to confirm the equality of item-scale correlations and equality of item variances assumptions. To test the convergent and divergent construct validity of TSK-11, bivariate Pearson product-moment correlations were calculated among TSK-11 and measures of activity limitations, spinal mobility, and spinal pain (significant, positive and moderate > 0.40, but < 0.80 correlations expected), and with BMI (positive), disease duration (negative), and age [positive, (non)significant, weak < 0.40 correlations expected].

Multiple linear regression (enter method) was applied to model BASFI from demographic and anthropometric factors (sex, age, BMI), disease-related characteristics (use of biologicals, NSAID, disease duration, disease activity and inflammation, spinal mobility), and TSK-11. We built BASFI models for disease activity (BASDAI or PGDA and CRP combined), inflammation (BASDAIinf), and spinal pain (BASDAIpain) separately. Adjusted R^2 showed each model's explanatory power. Standardized β

weights allowed for direct comparison of each variable's contribution to the model. Commonality analysis provided unique and common variance estimates for each determinant and their combinations[33]. Further, a backward elimination procedure with a probability of F to remove a determinant of ≤ 0.1 was used to model the BASFI from an optimal set of determinants. To avoid co-linearity, the variance inflation factor (VIF) was set at < 3 for all analyses. To evaluate the basic tenet of the FAM in axSpA (Figure 1B), the mediating effect of TSK-11 [FOM/(R)I as mediator] in the relationship between BASDAIpain (independent as pain experience) and BASFI (dependent as disability outcome) was determined through the PROCESS macro version 2.13 for SPSS using bias-corrected bootstrap 95% CI with 5000 samples, and the Sobel test ($p < 0.05$)[34]. All remaining variables from previous models were entered as covariates. All analyses were performed with SPSS 20.0 (IBM Statistics).

RESULTS

Demographic data. Of all 190 patients invited, 4 refused to participate because of a lack of time. The number of cases with missing data was 2 (1.1%) for the BASMI; 3 (1.6%) for the TSK-11; 7 (3.8%) for the BASFI; 6 (3.2%) for the BASDAI, BASDAIpain, and BASDAIinf; 26 for PGDA (14.0%); and 31 for CRP (16.7%). Full data across outcome measures were available for 173 patients (6.9% data loss) for analyses without PGDA and CRP. For models including PGDA or CRP, data for 133 subjects were available (28.4% data loss). No statistically significant differences were found between the subsamples ($p > 0.05$). Full demographic data were shown in Table 1 and reflected a typical outpatient axSpA sample[23].

Psychometric properties of TSK-11. An adequate Cronbach's alpha value of 0.80 was found for the TSK-11 scale. Item-to-total correlation coefficients (Table 2) showed overall values between 0.41 and 0.58, except for item TSK-5 ("People aren't taking my medical condition seriously enough"), with an acceptable value of 0.23. Omitting this item only marginally improved Cronbach's alpha for the TSK-11 scale, so the full scale was included in further analyses (no differences with or without this item included were found for all analyses). Item-to-total correlations were equal across items, as were item variances (Table 2). In sum, scaling assumptions of TSK-11 were confirmed.

Construct validity was confirmed as hypothesized, except for spinal mobility, which correlated positively but weakly ($r = 0.11$, $p = 0.025$) with TSK-11. Positive and moderate associations with TSK-11 were found for activity limitations ($r = 0.45$, $p < 0.001$), and pain ($r = 0.41$, $p < 0.001$), while weak associations ($p > 0.05$) were found with BMI ($r = 0.04$, $p = 0.585$, positive), disease duration ($r = –0.02$, $p = 0.773$, negative), and age ($r = 0.12$, $p = 0.118$, positive). In sum, construct validity was confirmed.

Bivariate and multivariate determinants of activity limitations. Bivariate correlation coefficients revealed TSK-11, BASMI, BASDAI, BASDAIinf, BASDAIpain, PGDA, and age as possible determinants of BASFI (Table 3). All hierarchical regression models consistently identified TSK-11 as an important determinant of BASFI (Table 4) with β varying

Table 1. Descriptives for all demographic, anthropometric, and disease-related outcomes in patients with axial spondyloarthritis (n = 173).

Variables	Mean	SD	P25	Median	P75	Min	Max
Age, yrs	42.74	12.26	31.77	42.70	52.55	19.40	73.81
Disease duration, yrs	13.27	11.13	3.89	10.83	21.20	0.01	53.93
Height, cm	171.43	9.47	164.35	172.30	177.70	146.80	193.10
Weight, kg	76.69	15.18	65.55	75.70	86.40	43.60	120.00
BMI, kg/m^2	26.02	4.40	22.55	25.52	28.98	16.55	40.79
BASDAI total (0–10)	3.85	2.17	2.10	3.70	5.40	0.00	9.80
BASDAI inf (0–10)	3.63	2.74	1.50	3.00	6.00	0.00	10.00
BASDAI pain (0–10)	3.91	2.18	2.25	3.75	5.50	0.00	9.75
BASFI (0–10)	3.66	2.36	1.80	3.40	5.60	0.00	9.80
TSK-11 (11–44)	24.83	6.22	20.00	25.00	30.00	11.00	38.00
BASMI (0–10)	3.06	1.78	1.80	2.80	3.90	0.00	8.40
Cervical rotation, cm	60.54	19.55	50.00	65.00	75.00	4.00	95.00
Tragus-to-wall, cm	13.65	4.54	10.60	11.75	15.30	8.20	31.35
Lateral flexion, cm	12.33	5.53	8.20	12.50	16.50	1.05	24.45
Intermalleolar distance, cm	98.88	22.41	88.65	102.50	113.60	11.00	140.20
Hip internal rotation, cm	44.45	12.75	36.95	44.60	52.10	9.60	97.20
Modified Schober, cm	5.27	2.13	4.10	5.50	6.55	0.40	14.20
Frequencies (%)							
Sex, male/female	109/64 (63/37)						
NSAID, yes/no	89/84 (51/49)						
Biologicals, yes/no	69/104 (40/60)						
Corticosteroids, yes/no	13/160 (8/92)						
DMARD, yes/no	72/101 (42/58)						

Height and weight were measured with a stadiometer (Holtain Ltd.) and digital scale (SECA) respectively. P: percentile; Min: minimum; Max: maximum; BMI: body mass index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASDAI inf: average of stiffness items 5 and 6 of BASDAI; BASDAI pain: spinal pain item of BASDAI; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Disease Metrology Index; TSK-11: Tampa Scale for Kinesiophobia 11-item version; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs.

Table 2. Item-to-total correlations, item variances, and Cronbach's alpha coefficients for the TSK-11 scale and its items in patients with axial spondyloarthritis (n = 173).

Variables	Item-to-total Correlation*	SD for Each Item**	Cronbach's Alpha if Item Deleted
TSK-1	0.55	1.00	0.77
TSK-2	0.53	1.00	0.77
TSK-3	0.58	0.96	0.77
TSK-5	0.23	1.06	0.80
TSK-6	0.45	0.92	0.78
TSK-7	0.45	0.94	0.78
TSK-10	0.42	1.05	0.78
TSK-11	0.47	1.01	0.78
TSK-13	0.42	0.96	0.78
TSK-15	0.52	0.99	0.77
TSK-17	0.41	0.86	0.79

* Correlation of > 0.20 (acceptable) and > 0.40 (good) between 1 TSK-11 item and the full TSK-11 scale with this item deleted reflects item internal consistency assumption. ** Roughly equal SD across items reflects item variance assumption. TSK-11: Tampa Scale for Kinesiophobia 11-item version.

from 0.165 (n = 177, BASDAIpain as spinal pain, adjusted R^2 = 0.74; p = 0.001) to 0.321 (n = 133, PGDA/CRP as disease activity, adjusted R^2 = 0.53, p < 0.001; Table 3). Largest contributions were consistently found for BASMI with β ranging from 0.441 (n = 133, BASDAI as disease activity, adjusted R^2 = 0.70; p < 0.001) to 0.537 (n = 177, BASDAIinf as inflammation, adjusted R^2 = 0.67; p < 0.001) and for definitions of disease activity, spinal pain, and inflammation varying from 0.243 (n = 133, PGDA as disease activity, adjusted R^2 = 0.53; p < 0.001) to 0.571 (n = 177, BASDAIpain as spinal pain, adjusted R^2 = 0.74; p < 0.001). Explanatory power was grossly comparable across models, with slightly lower values when PGDA and CRP were used to measure disease activity (adjusted R^2 = 0.53; p < 0.001). Unique variance explained was somewhat lower for TSK-11 (R^2 = 0.02 to 0.10) than for definitions of disease activity/pain/inflammation (R^2 = 0.13 to 0.23) and BASMI (R^2 = 0.11–0.16), but its contribution to common variance was more similar (TSK-11 R^2 = 0.12–0.19, disease activity/pain/inflammation R^2 = 0.04–0.30, BASMI R^2 = 0.17–0.25; Supplementary Tables 2 and 3, available with the online version of this article). Regression models with backward elimination yielded comparable results, with BASMI, disease activity (BASDAI, BASDAIinf), spinal pain (BASDAIpain), and TSK-11 as key determinants of BASFI (p < 0.001; Figure 2).

FOM/(R)I beliefs as mediator. The total effect (c-path) of BASDAIpain (independent outcome, pain experience in the FAM model; Figure 1B, n = 173) on BASFI (dependent outcome, disability in the FAM model) was B = 0.640 [bootstrap CI (bCI) 0.544–0.735, R^2 = 0.75; p < 0.001], with a direct effect of B = 0.571 (c′-path; bCI 0.472–0.671; R^2 = 0.73; p < 0.001). BASDAIpain predicted TSK-11 (a-path; B = 1.160, bCI 0.724–1.596; R^2 = 0.19; p < 0.001) and TSK-11 predicted BASFI (b-path; B = 0.059, bCI 0.026–0.091). The indirect effect of BASDAIpain by mediator TSK-11 on BASFI was significant (a × b = c – c′; B = 0.068, bCI 0.029–0.123), corresponding to a partially mediated effect (ratio c′ path/c-path: 0.068/0.640) of 11% (B = 0.107, bCI 0.046–0.197; Sobel test, p = 0.004).

Table 3. Bivariate correlations# for all continuous modeled variables in patients with axial spondyloarthritis (n = 173§).

Variables	1	2	3	4	5	6	7	8	9	10	11
1. Activity limitation (BASFI, 0–10))	—	0.45**	0.61**	0.71**	0.55**	0.71**	0.19*	0.32**	0.13	0.17	0.30**
2. Fear of movement/(re)injury (TSK-11, 0–44)	0.45**	—	0.17*	0.40**	0.29**	0.41**	–0.02	0.12	0.04	0.06	0.13
3. Spinal mobility (BASMI, 0–10)	0.61**	0.17*	—	0.20**	0.14	0.21**	0.46**	0.57**	0.15	0.14	–0.00
4. Patient-reported disease activity (BASDAI, 0–10)	0.71**	0.40**	0.20**	—	0.83**	0.98**	–0.03	0.07	0.05	0.09	0.45**
5. Patient-reported inflammation (BASDAIinf, 0–10)	0.55**	0.29**	0.14	0.83**	—	0.72**	–0.00	0.00	0.06	0.11	0.43**
6. Patient-reported pain (BASDAI pain, 0–10)	0.71**	0.41**	0.21**	0.98**	0.72**	—	–0.04	0.09	0.05	0.08	0.42**
7. Disease duration, yrs	0.19*	–0.02	0.46**	–0.03	–0.00	–0.040	—	0.58**	–0.03	–0.06	–0.08
8. Age, yrs	0.32**	0.12	0.57**	0.07	0.00	0.09	0.58**	—	0.17*	–0.03	–0.08
9. Anthropometrics, BMI, kg/m^2	0.13	0.04	0.15	0.05	0.06	0.09	–0.03	0.18*	—	–0.00	–0.00
10. Inflammation, CRP, mg/l)§	0.17	0.06	0.14	0.09	0.11	0.08	–0.06	–0.03	–0.00	—	0.23**
11. PGDA, 0–10§	0.30**	0.13	–0.00	0.45**	0.43**	0.42**	–0.08	–0.08	–0.00	0.23**	—

** p < 0.01. * p < 0.05. # Pearson product-moment correlation coefficients. § For analyses including CRP or PGDA, n = 133. CRP: C-reactive protein; PGDA: physician global disease activity; BASFI: Bath Ankylosing Spondylitis Functional Index; TSK-11: Tampa Scale for Kinesiophobia 11-item version; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BMI: body mass index.

Table 4. Multivariate models showing the effect of fear of movement and (re)injury beliefs (TSK-11) on activity limitations (BASFI) in patients with axial spondyloarthritis.

Determinants	Model Patient-reported Inflammation, n = 133				Model Patient-reported Inflammation, n = 173			
	β	B (95% CI)	p	Adj R^2	β	B (95% CI)	p	Adj R^2
BASMI	0.473	0.639 (0.451–0.827)	**< 0.001**		0.537	0.713 (0.559–0.867)	**< 0.001**	
BASDAIinf	0.427	0.355 (0.263–0.447)	**< 0.001**		0.388	0.333 (0.253–0.414)	**< 0.001**	
TSK-11	0.243	0.095 (0.052–0.138)	**< 0.001**		0.237	0.090 (0.055–0.125)	**< 0.001**	
Age	0.082	0.016 (–0.012 to 0.043)	0.264		0.027	0.005 (–0.018 to 0.029)	0.665	
Disease duration	–0.066	–0.014 (–0.042 to 0.013)	0.313		–0.059	–0.012 (–0.036 to 0.011)	0.304	
Sex, M/F:1/2	0.127	0.626 (0.096–1.155)	**0.021**		0.159	0.777 (0.341–1.212)	**0.001**	
BMI	0	0 (–0.058 to 0.058)	0.998		0.034	0.018 (–0.030 to 0.067)	0.456	
Biologicals, Y/N:1/2	–0.078	–0.366 (–0.905 to 0.062)	0.181		–0.073	–0.348 (–0.795 to 0.098)	0.125	
NSAID, Y/N:1/2	–0.099	–0.468 (–0.999 to 0.062)	0.083	**0.64**	–0.114	–0.539 (–0.966 to –0.111)	**0.014**	**0.67**
Determinants	Model Patient-reported Pain, n = 133				Model Patient-reported Pain, n = 173			
BASMI	0.446	0.602 (0.427–0.777)	**< 0.001**		0.472	0.628 (0.489–0.767)	**< 0.001**	
BASDAIpain	0.534	0.575 (0.455–0.696)	**< 0.001**		0.529	0.571 (0.472–0.671)	**< 0.001**	
TSK-11	0.178	0.069 (0.028–0.110)	**0.001**		0.155	0.059 (0.026–0.091)	**0.001**	
Age, yrs	–0.009	–0.002 (–0.027 to 0.024)	0.889		–0.032	–0.006 (–0.027 to 0.015)	0.556	
Disease duration, yrs	0.005	0.001 (–0.025 to 0.027)	0.933		0.011	0.002 (–0.019 to 0.024)	0.823	
Sex, M/F:1/2	0.028	0.140 (–0.358 to 0.638)	0.579		0.055	0.270 (–0.130 to 0.671)	0.185	
BMI	0.030	0.016 (–0.038 to 0.070)	0.551		0.042	0.022 (–0.021 to 0.066)	0.311	
Biologicals, Y/N:1/2	–0.072	–0.341 (–0.837 to 0.155)	0.176		–0.070	–0.339 (–0.736 to 0.059)	0.094	
NSAID, Y/N:1/2	–0.026	–0.122 (–0.624 to 0.379)	0.630	**0.69**	–0.052	–0.243 (–0.632 to 0.146)	0.219	**0.74**
Determinants	Model Patient-reported Disease Activity, n = 133				Model Patient-reported Disease Activity, n = 173			
BASMI	0.441	0.596 (0.424–0.767)	**< 0.001**		0.475	0.632 (0.494–0.769)	**< 0.001**	
BASDAI	0.537	0.576 (0.460–0.692)	< 0.002		0.527	0.572 (0.475–0.670)	**< 0.001**	
TSK-11	0.177	0.069 (0.029–0.109)	**0.001**		0.156	0.059 (0.027–0.091)	**< 0.001**	
Age, yrs	0.018	0.003 (–0.022 to 0.028)	0.789		–0.013	–0.002 (–0.023 to 0.018)	0.814	
Disease duration, yrs	–0.010	–0.002 (–0.027 to 0.023)	0.871		–0.004	–0.001 (–0.022 to 0.020)	0.936	
Sex, M/F:1/2	0.049	0.241 (–0.0245 to 0.727)	0.328		0.073	0.357 (–0.035 to 0.749)	0.074	
BMI	0.022	0.012 (–0.041 to 0.065)	0.659		0.891	0.019 (–0.023 to 0.062)	0.374	
Biologicals, Y/N:1/2	–0.078	–0.368 (–0.856 to 0.120)	0.138		–0.073	–0.352 (–0.744 to 0.041)	0.079	
NSAID, Y/N:1/2	–0.034	–0.161 (–0.652 to 0.329)	0.516	**0.70**	–0.057	–0.266 (–0.649 to 0.117)	0.172	**0.74**
Determinants	Model Physician-reported Disease Activity and CRP, n = 133							
BASMI	0.536	0.724 (0.507–0.941)	**< 0.001**					
TSK-11	0.321	0.125 (0.077–0.173)	**< 0.001**					
CRP	0.019	0.076 (–0.432 to 0.584)	0.768					
PGDA	0.243	0.929 (0.455–1.403)	**< 0.001**					
Age, yrs	0.040	0.008 (–0.024 to 0.039)	0.633					
Disease duration, yrs	–0.048	–0.010 (–0.042 to 0.021)	0.523					
Sex, M/F:1/2	0.105	0.514 (–0.093 to 1.121)	0.096					
BMI	0.015	0.008 (–0.059 to 0.075)	0.814					
Biologicals, Y/N:1/2	–0.028	–0.134 (–0.749 to 0.481)	0.668					
NSAID, Y/N:1/2	–0.135	–0.633 (–1.237 to –0.030)	**0.040**	**0.53**				

Significant results in bold ($p < 0.05$). β: standardized beta coefficient; B (95% CI): beta coefficient with 95% CI; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASDAIinf: average item 5, 6 of BASDAI; BASDAIpain: average item 2, 3 of BASDAI; BASFI: Bath Ankylosing Spondylitis Functional Index; TSK-11: Tampa Scale for Kinesiophobia 11-item version; CRP: C-reactive protein; PGDA: physician global disease activity; BMI: body mass index; NSAID: nonsteroidal antiinflammatory drug; BASMI: Bath Ankylosing Spondylitis Metrology Index.

DISCUSSION

To our knowledge, our current study was the first to investigate the role of FOM/(R)I in patients with axSpA and to establish key psychometric qualities of the TSK-11 in axSpA, that is, its scaling assumptions and divergent construct validity.

In the field of rheumatology, few studies have tapped into the FOM/(R)I or related constructs, especially in axSpA. First, Mielenz, *et al*[19] applied item-response theory modeling to establish the reliability and fit of the original 17-item Tampa Scale for Kinesiophobia in patients with self-reported arthritis taking part in an exercise intervention. Similar to previous work on the structural validity of TSK-11[27,28,35], they confirmed the misfit of all inversely stated items in the original 17-item version and reduced the number of items to 11. Nevertheless, we preferred the TSK-11 version of Woby, *et al*[27], removing the inversed items 4, 8, 12, and 16, as well as items 9 and 14, given its extensive structural validation

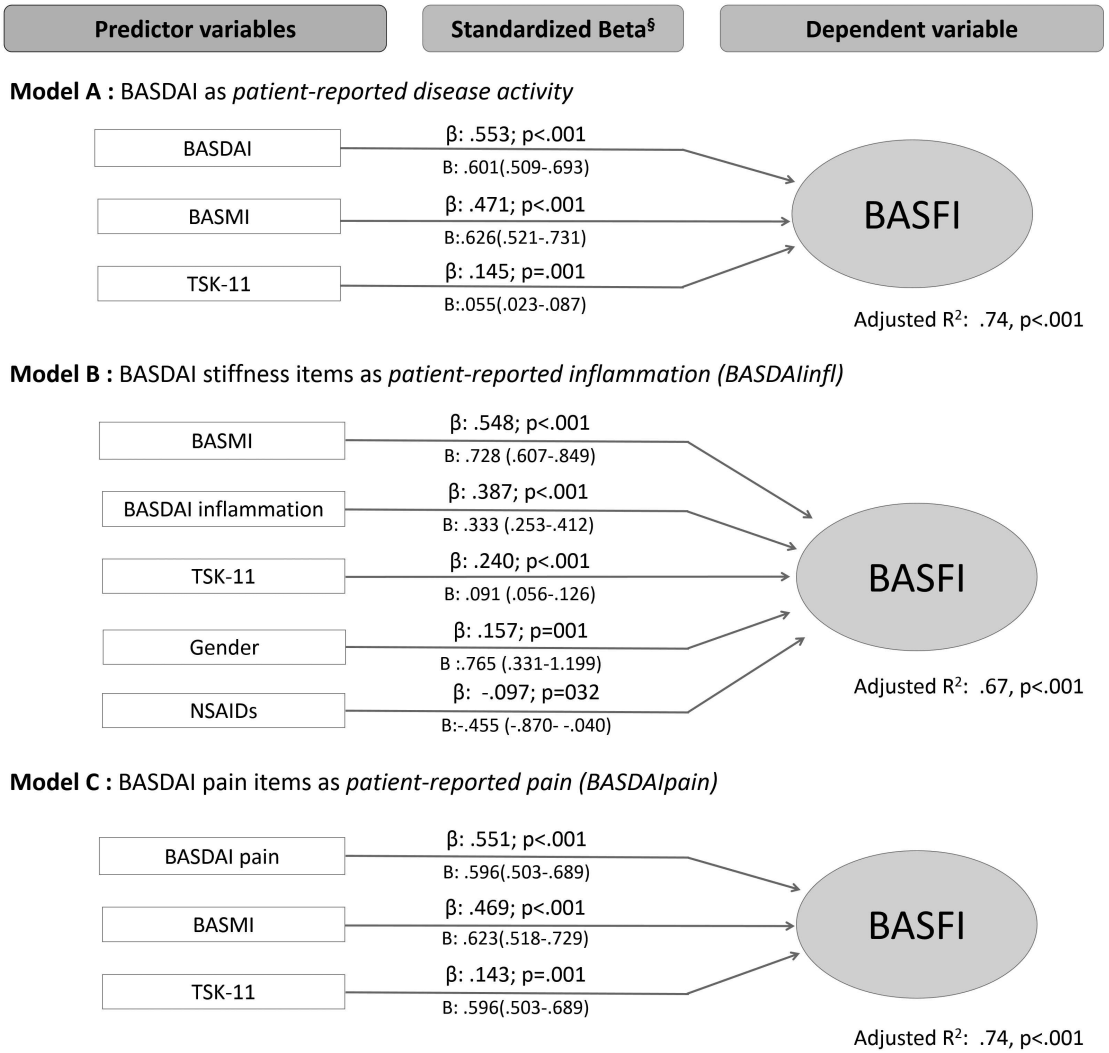

Figure 2. Multiple linear regression modeling (backward elimination) of activity limitations (BASFI) in patients with axial spondyloarthritis (n = 173). # Multiple linear regression using backward elimination with a probability of F to remove a predictor of ≤ 0.1. § Apart from standardized β regression coefficients β also unweighted regressions coefficients B and their corresponding 95% CI are given, variance inflation factors between 1.018 and 1.162; squared variance explained is given as R^2. BASFI: Bath Ankylosing Spondylitis Functional Index (activity limitations); BASMI: Bath Ankylosing Spondylitis Metrology Index 10 percentile version (spinal mobility); BASDAI: Bath Ankylosing Spondylitis Disease Activity Index full scale (disease activity), average items 2–3 (pain), average items 5-6 (inflammation); TSK-11: Tampa Scale for Kinesiophobia 11-item version; NSAID: nonsteroidal antiinflammatory drugs.

across diagnoses[29,35]. The strikingly similar internal consistency (Cronbach's alpha 0.79 vs 0.80 in our study), and comparable item-to-total correlations in general and for possible problem items 5 (0.340 vs 0.229), 13 (0.430 vs 0.415), and 6 (0.340 vs 0.446) justified this choice[27]. Although TSK-11 showed satisfactory scaling assumptions and construct validity in this study, future research by our group on its test-retest reliability and structural validity is needed and under way.

Second, Berenbaum, *et al*[36] qualitatively studied patient's attitudes and beliefs regarding their disease in axSpA. Patients reported "too intense physical activity over a longer period" and "physical or tiring professional activity" as factors causing outbreak of disease, while on the other hand "sports activities and exercise" were believed to attenuate such outbreaks. In this context, it is hypothesized that FOM/(R)I does not represent a "phobic" state toward movement in axSpA, but rather reflects the belief that especially strenuous physical activities relate to increased disease activity. This hypothesis is strengthened by prior research from our group using accelerometry-based monitoring of physical activity in axSpA[37]. This study indeed observed an almost complete lack of (very) vigorous, but not moderate physical activities, suggesting that avoidance of intense movements may have occurred. Also, the current study showed the unique and clinically relevant contribution

of FOM/(R)I to experienced activity limitations as measured with BASFI. Together, these data seem in line with the FAM predicting the harm of FOM/(R)I beliefs on disability through avoidance[15] and further corroborate the importance of FOM/(R)I beliefs to explain functioning in axSpA.

Third, Lööf, *et al*[18] revealed that FOM/(R)I was associated with male sex, low income, high pain, low health-related quality of life, and low exercise self-efficacy in patients with rheumatoid arthritis participating in the Physical Activity in Rheumatoid Arthritis 2010 exercise intervention. Our TSK-11 results (median 25 with a range of 11–44) indicated that patients with axSpA also exhibit concerns about movement or (re)injury. TSK-11 was, even on a group level, a consistent determinant of BASFI regardless of the regression modeling approach used[38], the latter being a major strength of our study. At least in an acute stage, pathological tissue inflammation and destruction in the musculoskeletal system (and beyond) likely trigger the defensive capacities of predominantly the immune and pain system and urge the organism to escape/avoid this imminent or actual threat[15,39]. For some patients, these fearful beliefs may emanate from direct respondent and operant learning of the altered relationship between biomechanical loading and pain/disease processes in axSpA[1]. Depending on the motivational context[40], adaptive protective posture and movement behaviors (e.g., limiting the range[41,42], amount[37], or velocity[41] of movement) develop that may lead to disability, as observed in our study. Controlling disease processes will likely result in spontaneous recovery of these adaptive behaviors. In other patients, however, these fearful concerns become incongruent with disease processes, resulting in similar but maladaptive protective posture and movement behaviors and their consequences[43]. Possibly, fear overgeneralization to previously neutral cues (e.g., painful back extension spreads to overall painful spinal movements) or operant reinforcement of fear/avoidance (e.g., through observation of other patients' pain, fearful media stories[44,45], or verbal instruction on the harmfulness of movement by healthcare professionals[45]) may inhibit the extinction of these fearful beliefs. Although our mediation analysis revealed TSK-11 as a partial mediator of pain toward activity limitations, the underlying processes leading to FOM/(R)I and its resolution in axSpA merit further study. Also, the statistical identification and validation of the proposed subgroups and piloting stratified care interventions in axSpA will be the focus of our future research in this area. For now, we can only recommend screening for FOM/(R)I in clinical practice.

There are some limitations to our study that need to be acknowledged. Although sequential relationships cannot be ascertained, the cross-sectional design was appropriate to evaluate psychometric properties, and was able to show a significant association between FOM/(R)I and activity limitations. A longitudinal perspective is needed, however, to extend the pilot mediation analysis toward a full analysis of the FAM predictions over time[46].

Another limitation of our study is that magnetic resonance imaging (MRI) or the Ankylosing Spondylitis Disease Activity Score (ASDAS) and standard radiographs were not included to define, respectively, disease activity and bone formation. To date, there is no gold standard for the assessment of disease activity in axSpA[24]. Although MRI is highly attractive owing to its reliability and objectivity[47], its role is mostly established for diagnostic purposes[24] because issues of validity arise when quantifying the amount of disease activity[48]. The ASDAS, still under development during our study, was not included, but similar associations between BASFI-ASDAS and BASFI-BASDAI were reported[49]. In our study, we were primarily interested in the relative contribution of FOM/(R)I to BASFI compared to different definitions of disease activity and spinal mobility. We observed an increased contribution of TSK-11 (from 29% to 60% in comparison to known major determinants of disease activity and spinal mobility[38]) when using the less patient-reported disease activity outcomes CRP and PGDA. Because of the known relationship between patient-reported disease activity and psychological factors[50] and given that our data confirmed TSK-11 as only a partial mediator between spinal pain and BASFI, we suspected that part of the BASDAI, BASDAIpain, or BASDAIinf effect covaries with TSK-11 despite the absence of collinearity in all models (VIF very low). Increased importance of TSK-11 in the CRP/PGDA model and the common/shared variance between BASDAI or BASDAIpain or BASDAIinf and TSK-11 consistently revealed in the commonality analysis also confirmed this idea. In contrast, spinal mobility showed a quite low correlation and common variance with TSK-11 and a similar proportional contribution in comparison to TSK-11 across models. Thus, we can be confident that spinal mobility indeed mimicked bone formation, which is in line with prior research[25]. Nevertheless, future research should study these effects in models including different imaging outcomes.

Our study established the TSK-11's scaling assumptions and construct validity as essential psychometric properties in axSpA. Also, an important role for FOM/(R)I in explaining activity limitations was confirmed in addition to the major contributions of spinal mobility impairment and disease activity in axSpA. Future research should focus on a better understanding of FOM/(R)I and avoidance behavior in the development and maintenance of disability in patients with axSpA, which likely will lead to novel and more targeted patient-centered multidimensional interventions for patients with this rheumatic disease.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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