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EXTENDED REPORT

Determinants of psychological well-being in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data

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Handling editor Josef S Smolen

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Received 1 November 2017
Revised 16 February 2018
Accepted 18 February 2018
Published Online First 10 March 2018

ABSTRACT

Objectives The aim of this study was to assess the psychological well-being and to analyse factors associated with depressive symptoms in axial spondyloarthritis (axSpA).

Methods A stratified random sample of subjects with a diagnosis of axSpA (International Classification of Diseases, Tenth Revision, German Modification M45) was drawn from health insurance data in Germany. These persons received a postal questionnaire on disease-related, psychological and lifestyle factors as well as socioeconomic status. Additional information to verify the axSpA diagnosis was also collected. The psychological well-being was assessed by means of the 5-item WHO Well-Being Index (WHO-5), which is considered a screening tool for depression. The following established cut-offs on the WHO-5 were applied: >50: good well-being, no depressive symptoms; 29–50: mild depressive symptoms; ≤28: moderate-to-severe depressive symptoms. Information on comorbidities, drug prescriptions and non-pharmacological treatment was retrieved from claims data and linked to the questionnaire data.

Results A total of 1736 persons with a confirmed axSpA diagnosis were included. Using the cut-offs on the WHO-5, 533 persons (31%) were found to have moderate-to-severe depressive symptoms, 479 (28%) had mild depressive symptoms and 724 (42%) had a good well-being. Multivariable logistic regression revealed that higher disease activity, higher level of functional impairment, lower income, self-reported stress and lack of exercise, and younger age represent factors associated with moderate-to-severe depressive symptoms.

Conclusions The prevalence of depressive symptoms in axSpA subjects is high and associated with disease-related parameters, socioeconomic status and lifestyle factors. These findings highlight the need for the careful evaluation of depressive symptoms as a part of the management strategy for axSpA.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease characterised by predominant involvement of the spine and/or sacroiliac joints. AxSpA comprises non-radiographic axSpA (nr-axSpA, without definite radiographic sacroiliitis) and radiographic axSpA (also known as ankylosing spondylitis (AS), characterised by the presence of radiographic sacroiliitis according to the modified New York criteria).[1] The leading symptom of axSpA is chronic back pain with onset in early adulthood, usually before age 45. In addition to back pain, peripheral articular (arthritis, enthesitis, daktylitis) and extra-articular manifestations (EAMs), such as uveitis, psoriasis and inflammatory bowel disease (IBD), contribute to the total burden of axSpA.[2]

Psychological distress, including depressive symptoms, is frequently reported in persons with axSpA.[3 4] Furthermore, a recent study showed that AS subjects have an increased risk of developing depressive disorders following their diagnosis.[5]

The objective of this study was to assess the psychological well-being and to identify factors associated with depressive symptoms in a large nationwide group of persons with axSpA by taking advantage of the linkage of claims data and self-reported patient outcomes from a survey within the Linking Patient-Reported Outcomes with CLAIms data for health services research in Rheumatology network.[6]

METHODS

Patients and study design

Data for this study were obtained from a nationwide statutory health insurance fund (BARMER) with 6.6 million members aged 18–79 years in 2014 who were continuously insured in 2013 and 2014. Among those, 21 892 had an outpatient claim with an axSpA diagnosis (International Classification of Diseases, Tenth Revision, German Modification (ICD-10-GM) code M45) in at least two quarters of the year 2014. Out of the 21 892 axSpA subjects, a stratified random sample of 5000 persons (500 within each stratum) was drawn, with stratification based on age group (18–39, 40–49, 50–59, 60–69 and 70–79 years) and sex. The sample size was determined so that mean effect sizes of 0.25 could be detected with a power of 80%, even if subgroups from certain age/sex strata were compared. A questionnaire was sent out in autumn 2015, gathering information on rheumatological care ('Are you currently being treated by a rheumatologist?'), confirmation of axSpA diagnosis ('How is the disease called by your physician?'), disease-related, psychological and lifestyle factors, as well as socioeconomic status. Persons who had not answered within 4 weeks received a reminder.

To cite: Redeker I, Hoffmann F, Callhoff J, *et al*. *Ann Rheum Dis* 2018;**77**:1017–1024.

Claims data

Age, sex, EAMs (including uveitis, psoriasis and IBD), comorbidities and pharmacological and non-pharmacological treatment were retrieved from claims data from 2015. Comorbidities and EAMs were identified via ICD-10-GM codes and drug prescriptions via the anatomical therapeutic chemical classification, where at least one outpatient claim had to be documented. Non-steroidal anti-inflammatory drugs (NSAIDs), opioids, non-opioid analgesics, biological disease-modifying antirheumatic drugs (bDMARDs), glucocorticoids and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) comprised axSpA-related treatment. Non-pharmacological treatment was represented by physiotherapy, including manual therapy, exercise therapy and therapist massages.

Questionnaire data

The psychological well-being/presence of depressive symptoms was assessed using the 5-item WHO Well-Being Index (WHO-5). It is a short, generic global index based on five positively phrased items measuring the subjective psychological well-being of the respondents over the past 2 weeks.[7] The five items are: (1) 'I have felt cheerful and in good spirits', (2) 'I have felt calm and relaxed', (3) 'I have felt active and vigorous', (4) 'I woke up feeling fresh and rested' and (5) 'My daily life has been filled with things that interest me'. They are scored by using 6-point Likert scales (0–5) for each item.[8] The total of the five scales generates the 0–25 WHO-5 raw score, with higher scores indicating better well-being. The raw score is translated to the 0–100 WHO-5 (percentage) score by multiplying by 4. A cut-off score of ≤28 on the WHO-5 was used to denote the possible presence of moderate-to-severe depressive symptoms. Scores of 29–50 on the WHO-5 indicate mild depressive symptoms, whereas scores of >50 suggest good well-being/no depressive symptoms. The screening performance of the WHO-5 has been validated in previous studies.[8–10] A cut-off score of ≤28 on the WHO-5 was tested against the Structured Clinical Interview for the Diagnostic and Statistical Manual (DSM)-IV as the criterion standard for the presence of 'major depressive disorder', with a sensitivity of 94% and a specificity of 78%.[11]

To validate the diagnosis of axSpA obtained via claims data, persons were asked to confirm the presence of the diagnosis of axSpA/AS. Further, persons were asked about the occurrence (ever) of EAMs. Information about the diagnosing and treating physician, age of symptom onset, age of diagnosis, HLA-B27 status, disease activity and functional status were also collected via questionnaire. The activity of axSpA was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[12] and the functional status by means of the Bath Ankylosing Spondylitis Functional Index (BASFI).[13] Socioeconomic status was determined using household income and type of work arrangement. Lifestyle factors comprised the characteristics body mass index (BMI), lack of exercise, smoking tobacco and perception of suffering from stress.

Statistical analysis

The total number of persons returning the questionnaires who gave their consent for linking questionnaire data to claims data was weighted according to the sex and age group distribution of the source population. Weighted subgroup analyses were performed on those who confirmed their axSpA diagnosis. Descriptive statistics (mean, SE of the mean (SEM) and percentages) were used to describe differences between the groups of persons screened as having no, mild or moderate-to-severe depressive symptoms. The SEM was used instead of SD due to the stratified nature of the study sample. Significant differences were assessed using one-way analyses of variance for continuous variables and using Rao-Scott χ^2 tests otherwise. Tests resulting in p values <0.05 were considered statistically significant.

Stepwise multivariable logistic regression analysis was used to determine factors associated with moderate-to-severe depressive symptoms in persons with axSpA, adjusting for the main demographic (age and sex), disease-related (information on rheumatological care, HLA-B27 status, disease activity and functional status, presence of IBD, uveitis and psoriasis, pharmacological treatment with NSAIDs, opioids, non-opioid analgesics, bDMARDs, csDMARDs and glucocorticoids, non-pharmacological treatment with physiotherapy), lifestyle (BMI, lack of exercise, smoking tobacco and perception of suffering from stress) and socioeconomic (household income, full-time employment) characteristics. A significance level of 0.03 was required to allow a variable into the model, and a significance level of 0.05 was required for a variable to stay in the model. Age and sex were always included in the model. Adjusted ORs were calculated with a 95% CI.

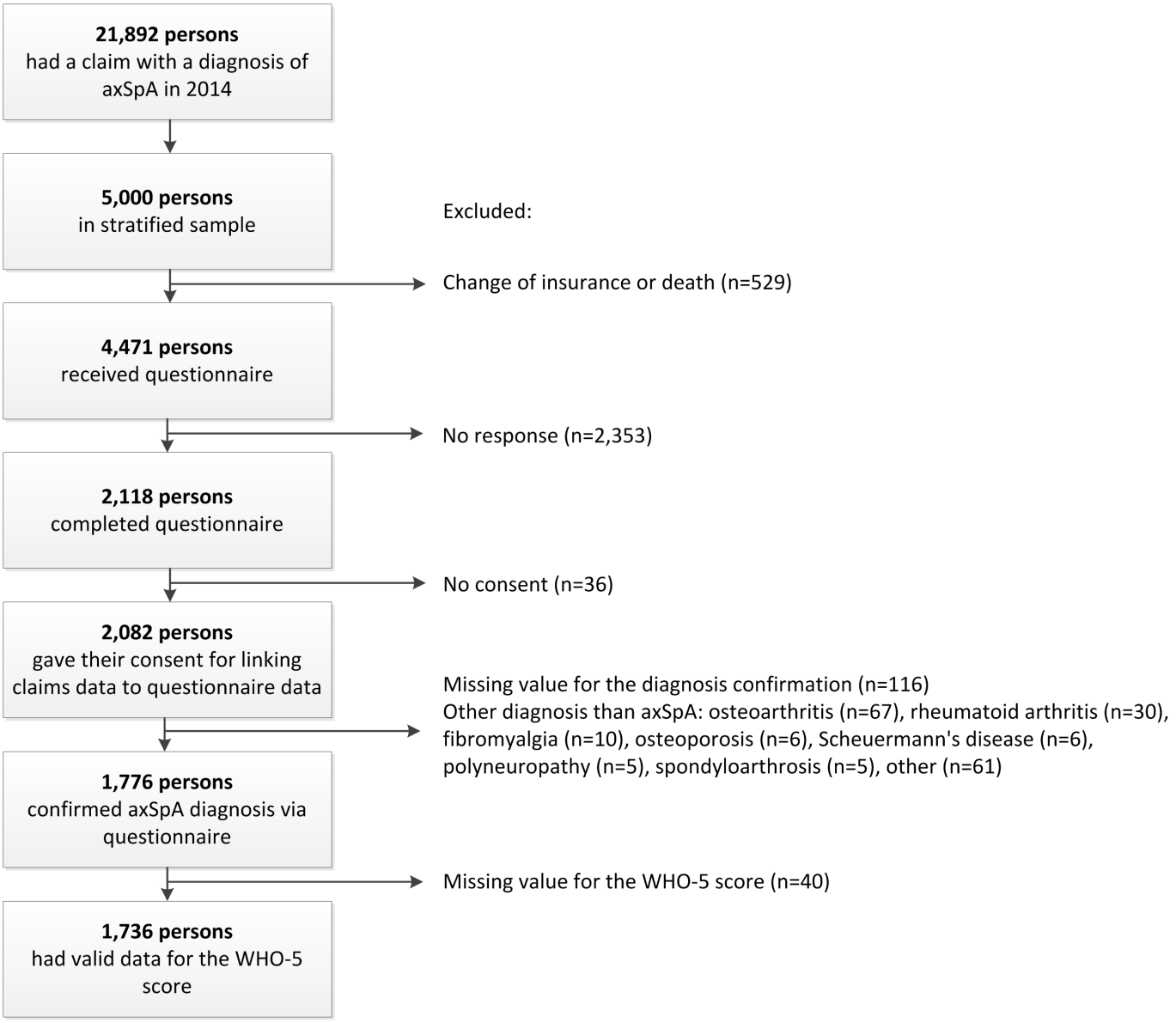
Data analyses were performed with SAS V.9.4 using procedures for complex survey designs (SURVEYMEANS, SURVEYFREQ and SURVEYLOGISTIC), which incorporated the stratified design into the analyses.

RESULTS

A total of 4471 persons (original sample of 5000 persons minus those who had changed their insurance or died) received the questionnaire (figure 1). Of those, a total of 2118 persons responded (47%) and 2082 gave their consent for linking questionnaire data to claims data of whom 1776 persons confirmed their axSpA diagnosis via questionnaire (85%). The remaining 15% reported diagnoses other than axSpA and were excluded from the analysis, including 5.6% who did not report their diagnosis. A total of 1736 persons had valid data for the WHO-5 score and were therefore included in the analysis. The main demographic, disease-related, lifestyle and socioeconomic characteristics are presented in table 1. All variables obtained from questionnaire data had a maximum of 4% of missing values, except for the variables household income (6% missing values) and HLA-B27 status (31% missing values).

Among the 1736 persons with confirmed axSpA, 724 (42%) had a WHO-5 score of >50, suggesting good well-being, 479 (28%) had a WHO-5 score of 29–50, indicating mild depressive symptoms, and 533 (31%) had a WHO-5 score ≤28, denoting the possible presence of moderate-to-severe depressive symptoms. Table 1 also gives an overview of the patients' characteristics in each of the three groups according to the WHO-5. Persons considered as having a good well-being were more often men and aged ≥60 than persons screened as having mild or moderate-to-severe depressive symptoms. Persons with a low score on the WHO-5 were more often provided with rheumatological care compared with persons with a medium or high score on the WHO-5. Statistically significant differences between the three WHO-5 groups were observed in disease activity and functional status: BASDAI and BASFI scores were poorest among persons with moderate-to-severe depressive symptoms and best in persons with good well-being.

The prevalence/self reported occurrence of psoriasis and IBD was higher in persons with moderate-to-severe depressive symptoms as compared with persons with good well-being or mild depressive symptoms, even though differences in the prevalence



AxSpA, Axial Spondyloarthritis; WHO-5, 5-item WHO Well-Being Index.

Figure 1 Flow chart of the study population.

of psoriasis according to the claims data did not reach the level of statistical significance (table 1). At the same time, the prevalence/self reported occurrence of uveitis was similar across the subgroups.

Statistically significant differences between the three WHO-5 groups were also observed in household income, full-time employment, self-reported lack of exercise, perception of suffering from stress, tobacco smoking and BMI. Persons with moderate-to-severe depressive symptoms less often had a high household income and full-time employment than persons with good well-being. More than half of persons with a low WHO-5 score reported a perception of suffering from stress compared with one-fourth of persons with a high WHO-5 score. Self-reported lack of exercise and tobacco smoking were also more often reported among persons with a low WHO-5 score than among persons with a high WHO-5. BMI scores were higher among persons with moderate-to-severe depressive symptoms compared with persons with good well-being.

No statistically significant differences between persons with a low, medium or high WHO-5 score were found with respect to treatment with bDMARDs and csDMARDS. However, persons with moderate-to-severe depressive symptoms more often received NSAIDs, analgesics and glucocorticoids compared with persons considered as having a good well-being. Furthermore, significant differences between the WHO-5 groups were found in treatment with proton pump inhibitors (table 3). However, in persons with no NSAIDs use, the differences between the WHO-5 groups in treatment with proton pump inhibitors were no longer significant. More patients with moderate-to-severe depressive symptoms received pharmacological treatment for SpA in general compared with patients with good well-being. Physiotherapy was more often prescribed for persons with a low WHO-5 score than for persons with a medium or high WHO-5 score.

Most frequent comorbidities (prevalence of ≥10% in at least one WHO-5 group) and their treatments are shown in table 2

Table 1 Main demographic, disease-related, lifestyle and socioeconomic characteristics of patients with axSpA

	Total	Depressive symptoms			
	n=1736	No n=724 (42%)	Mild n=479 (28%)	Moderate/severe n=533 (31%)	P value
Sex, female	46.3	41.0	50.6	49.7	**0.0008**
Age, years	55.8±0.1	57.4±0.4	54.1±0.5	55.1±0.4	**<0.0001**
Symptom duration	25.2±0.3	26.6±0.5	23.9±0.6	24.3±0.6	**0.0013**
Duration since diagnosis	19.4±0.3	21.3±0.5	17.9±0.6	18±0.6	**<0.0001**
In rheumatological care	46.1	39.5	47.2	54.0	**<0.0001**
HLA-B27 positive	86.0	87.4	83.5	86.6	0.2816
BASDAI, 0–10	4.5±0	3.3±0.1	4.8±0.1	5.8±0.1	**<0.0001**
BASFI, 0–10	4.1±0.1	2.9±0.1	4.2±0.1	5.6±0.1	**<0.0001**
IBD (claims data)	5.5	4.9	3.9	7.8	**0.0164**
IBD (ever, self-reported)	8.8	6.9	6.2	13.9	**<0.0001**
Uveitis (claims data)	13.7	14.4	14.9	11.8	0.2969
Uveitis (ever, self-reported)	27.3	28.7	28	24.9	0.3181
Psoriasis (claims data)	9.5	8.3	9.7	11.1	0.2789
Psoriasis (ever, self-reported)	15.1	12.1	16.8	17.7	**0.0152**
Body mass index, kg/m²	27±0.1	26.8±0.2	27±0.2	27.4±0.2	0.0872
Lack of exercise	24.4	19.0	25.3	30.8	**<0.0001**
Suffering from stress	39.9	25.5	47.8	52.6	**<0.0001**
Full-time employment	31.7	32.2	35.6	27.4	**0.0187**
Household income, €					
<1500	25.9	20.1	26.7	33.1	**< 0.0001**
1500–3200	56.0	55.0	58.3	55.2	
>3200	18.1	24.9	15.0	11.7	
Smoking, current	18.9	14.8	20.0	23.4	**0.0006**
Pharmacological treatment					
NSAIDs	59.7	50.9	63.4	68.6	**<0.0001**
Non-opioid analgesics	22.6	18.2	20.6	30.3	**<0.0001**
Opioids	16	9.4	16.5	24.4	**<0.0001**
bDMARDs*	17.1	15.5	19.1	17.5	0.2520
csDMARDs†	11.7	10.6	10.5	14.4	0.0818
Glucocorticoids	18.3	15.6	17.5	22.8	**0.0046**
No pharmacological treatment	22.1	30.3	21.2	11.8	**<0.0001**
Physiotherapy	49.7	45.6	48.1	56.6	**0.0006**

Values are presented as mean±SE of the mean for continuous characteristics and as percentages otherwise. P values were assessed using analyses of variance for continuous characteristics and Rao-Scott χ^2 tests otherwise.
P values <0.05 are shown in bold.
*bDMARDs: 17.0% tumour necrosis factor blocker, 0.07% secukinumab, 0.06% tocilizumab, 0.06% ustekinumab, 0.05% abatacept.
†csDMARDs: 5.7% sulfasalazine, 5.6% methotrexate, 0.9% leflunomide, 0.6% azathioprine, 0.2% ciclosporin.
AxSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs.

and table 3, respectively. Remarkably, the prevalence of mental and neurological disorders was higher in patients with depressive symptoms according to WHO-5 compared with patients with good well-being. They also most frequently received antidepressants, anxiolytics, hypnotics and sedatives. In addition, the prevalence of fibromyalgia increased with increasing level of depressive symptoms.

Univariable logistic regression models showed that BASDAI, BASFI, sex, household income, perception of suffering from stress and self-reported lack of exercise were associated with a low WHO-5 score, whereas age was not associated (table 4). Stepwise multivariable logistic regression analysis revealed that higher BASDAI and BASFI, perception of suffering from stress, self-reported lack of exercise, as well as lower income level and younger age were factors associated with moderate-to-severe depressive symptoms while controlling for the other variables (table 4). Here, we additionally entered sex in the final model since it is a biologically meaningful parameter but was not selected by the stepwise procedure. However, sex was not associated with moderate-to-severe depressive symptoms while controlling for the other variables (table 4).

DISCUSSION

The objective of this nationwide population-based study was to assess the psychological well-being and its associated factors in axSpA subjects to raise the awareness of such factors on the patient level and to manage adequate axSpA therapy on the healthcare level. In a number of studies evaluated in a recent review, the WHO-5 demonstrated an adequate validity. This review showed that the WHO-5 is a highly useful tool that can be applied in clinical practice.[14]

Table 2 The most frequent comorbidities* according to the claims data from 2015 in patients with axSpA

	Total	Depressive symptoms			
	n=1736	No n=724 (42%)	Mild n=479 (28%)	Moderate/severe n=533 (31%)	P value
Cardiovascular diseases					
Hypertensive diseases (I10–I15)	51.5	51.5	49.1	53.6	0.3624
Ischaemic heart diseases (I20–I25)	12.5	13.4	11.1	12.4	0.5153
Diseases of arteries (I70–I79)	9.5	9	8.5	11.1	0.3208
Diseases of veins (I80–I89)	18.4	17.3	17.3	21	0.2059
Mental disorders					
Depressive disorders (F32, F33)	22.2	12.6	22.9	34.6	**<0.0001**
Anxiety disorders (F40, F41)	9.5	6.1	8.4	14.9	**<0.0001**
Reaction to severe stress, and adjustment disorders (F43)	9.8	7.3	7.6	15.3	**<0.0001**
Somatoform disorders (F45)	21.2	14.7	21.2	29.9	**<0.0001**
Neurological disorders					
Nerve, nerve root and plexus disorders (G50–G59)	11.7	9	9.8	17.1	**<0.0001**
Polyneuropathies (G60–G64)	8.4	5.9	7.9	12.2	**0.0006**
Sleep disorders (G47)	9.9	8.5	9.6	12.2	0.1022
Obstructive sleep apnoea (G47.31)	2.9	2.5	3.7	2.7	0.4671
Musculoskeletal disorders (other than axSpA)					
Osteoarthritis (M15–M19)	35.9	34.6	36.2	37.5	0.5771
Spondylosis (M47)	24.2	18.8	24.3	31.4	**<0.0001**
Other soft tissue disorders, not elsewhere classified (M79)	26.4	22.6	24.2	33.5	**<0.0001**
Fibromyalgia (M79.7)	4.5	1.9	4.9	7.7	**<0.0001**
Disorders of bone density (M80–M85)	13.1	14	13.1	12	0.5929
Metabolic and endocrine disorders					
Disorders of thyroid gland (E00–E07)	28.2	28	28.2	28.6	0.9775
Diabetes mellitus (E10–E14)	16.2	16.9	14.2	16.9	0.4036
Type two diabetes mellitus (E11)	14.3	14.2	12.9	15.6	0.5172
Overweight (E65–E68)	14.7	14.4	12.6	17.2	0.1295
Respiratory tract diseases					
Chronic obstructive pulmonary disease (J44)	8.8	9.3	6.3	10.2	0.0790
Asthma bronchiale (J45)	9.9	9.2	9.2	11.5	0.3269
Gastrointestinal diseases					
Diseases of oesophagus, stomach and duodenum (K20–K31)	24.5	23.4	23.4	27	0.2874

Values are presented as percentages. P values were assessed using Rao-Scott χ^2 tests. P values <0.05 are shown in bold.
*With prevalence of ≥10% in at least one WHO-5 group excluding axSpA and EAMs.
AxSpA, axial spondyloarthritis; EAMs, extra-articular manifestations.

Using a cut-off score of ≤28 on the WHO-5, we found that 31% of persons with axSpA had moderate-to-severe depressive symptoms; with the cut-off score of ≤50, an additional 28% with mild depressive symptoms would be added to the previous number, yielding a total of 59% of patients with depressive symptoms/impaired well-being. This is consistent with the results of previous studies. For example, a study conducted by Barlow *et al*[15] reported that about one-third of AS subjects presented a high level of depressive symptoms according to the Centre for Epidemiological Studies-Depression (CES-D) scale.[16] A national study in Sweden showed that the consultation rate for depression was increased by >60% in AS patients compared with the background population seeking care.[17] In a nationwide population-based study of psychiatric disorders among patients with AS in Taiwan, an increased risk of depressive, anxiety and sleep disorders in AS subjects was found compared with general populations.[5] We found a mean WHO-5 score of 44.70 in axSpA subjects, which is considerably below the WHO-5 score of 69.95 reported among the population in Germany aged 41–60 years.[18] However, the prevalence of depressive symptoms according to the WHO-5 among axSpA subjects is similar to 54% among German patients aged 50–64 years with rheumatoid arthritis reported in a recent study.[19] For comparison, Busch *et al*[20] assessed current depressive symptoms with the 9-item Patient Health Questionnaire among the adult population in Germany and reported a prevalence of depressive symptoms of 8.1%.

We found a clear and statistically significant association between patient-reported depressive symptoms derived from the WHO-5 score and both physician-reported mental disorders and the use of antidepressants according to the claims data, confirming the validity of the results. The same was also true for anxiety, adjustment and somatoform disorders (and drugs used for the treatment of mental disorders), as well as fibromyalgia—their prevalence was significantly higher in patients with higher level of depressive symptoms.

Furthermore, we found statistically significant differences in the prevalence/self reported occurrence of IBD among the WHO-5 groups which is consistent with a current study focused on IBD and depression.[21] The same applies to psoriasis which is known to be associated with depression, as well as fibromyalgia.[22]

In general, persons with more depressive symptoms tended to have more frequently also other comorbidities not directly related to SpA as indicated in table 2. This indicates that the presence of other chronic disease other than SpA and related EAMs might

Table 3 Treatment of comorbidities according to the claims data from 2015 in patients with axSpA

	Total	Depressive symptoms			
	n=1736	No n=724 (42%)	Mild n=479 (28%)	Moderate/severe n=533 (31%)	P value
Cardiovascular diseases					
Antihypertensive agents (C02, C07, C08, C09)	51	51.1	49.3	52.4	0.6261
Antithrombotic agents (B01A)	15.2	15.1	13.8	16.5	0.5283
Diuretics (C03)	13.3	11.9	14.2	14.5	0.3464
Mental and neurological disorders					
Antidepressants (N06A)	16.9	9.9	18.5	24.9	**<0.0001**
Antiepileptic drugs (N03)	6.4	3.9	5.2	10.7	**<0.0001**
Psycholeptic drugs (N05)	6.2*	4.5	4.6	10	**<0.0001**
Metabolic and endocrine disorders					
Thyroid hormones (H03AA)	19.4	18.3	19.6	20.8	0.5638
Lipid modifying agents (C10)	18.1	19.2	17.9	16.6	0.5117
Insulins and analogues (A10A)	3.8	4.4	4.2	2.6	0.2384
Blood glucose-lowering drugs, excluding insulins (A10B)	8.3	9.3	5.1	10	**0.0152**
Respiratory tract diseases					
Drugs for obstructive airway diseases (R03)	14.4	13.4	11.4	18.4	**0.0050**
Gastrointestinal diseases					
Proton pump inhibitors (A02BC)	42.3	35.9	44.4	49.3	**<0.0001**

Values are presented as percentages. P values were assessed using Rao-Scott χ^2 tests. P values <0.05 are shown in bold.
*Psycholeptic drugs: 1.8 % antipsychotics, 3.1 % anxiolytics, 2.5 % hypnotics and sedatives.
AxSpA, axial spondyloarthritis.

significantly affect well-being. There were statistically significant differences between the WHO-5 groups in the frequency of administrations of oral antidiabetic drugs and drugs for obstructive pulmonary disease (table 3) with the highest use in persons with moderate-to severe depressive symptoms. Given no significant differences in the prevalence of the corresponding diagnoses, this data might indicate a higher severity of diabetes and obstructive pulmonary disease in persons with the worst depressive symptoms.

Previous studies showed that patients with axSpA with depressive symptoms have increased disease activity,[23 24] impaired functional status[25] and work disability.[26–29] In our study, we found that higher disease activity, functional limitations, perception of suffering from stress, self-reported lack of exercise and lower income and younger age were factors associated with the risk of moderate-to-severe depressive symptoms in persons with axSpA while controlling for the other variables.

What is the practical meaning of these findings? First, the practical relevance is related to a high prevalence of depressive symptoms indicating that a substantial proportion of persons with axSpA might suffer from depression requiring intervention that is not recognised by treating physicians. Such an impaired subjective well-being might affect the perception of pain and other axSpA-related symptoms and therefore on the patient-reported outcomes relevant for the therapy. Indeed, in our study, patients with depressive symptoms had higher BASDAI and BASFI scores and more frequently received NSAIDs and analgesics (including opioids) in comparison with the patients considered as having a good psychological well-being. However, higher disease activity and a higher level of functional disability (as indicated by BASDAI and BASFI) might be indicators of a severe disease resulting in the development of depressive symptoms and requiring more intensive therapy. In this case, the reduction of disease activity would also improve psychological well-being.

The same is true for the relationship between behavioural and socioeconomic factors (lack of exercise, perception of stress and low income)—they may be a cause but in some cases also a consequence of depression. However, if the causal role of these factors is true, at least some of them (lack of exercise and perception of stress) are potentially modifiable and should therefore be considered in the patients' management.

Table 4 Factors associated with the presence of symptoms suggestive of depression (WHO-5 score of ≤28): results from univariable and multivariable logistic regression analyses

		OR (95% CI)	
	Reference	Univariable analysis	Multivariable analysis
Sex, female	Male	**1.22 (1.00 to 1.48)**	1.00 (0.77 to 1.29)
Age	Per 10 years	1.00 (0.99 to 1.00)	**0.98 (0.97 to 0.99)**
BASDAI	Per unit	**1.65 (1.56 to 1.75)**	**1.37 (1.27 to 1.49)**
BASFI	Per unit	**1.38 (1.33 to 1.44)**	**1.25 (1.17 to 1.33)**
Lack of exercise	No	**1.62 (1.30 to 2.03)**	**1.50 (1.14 to 1.98)**
Suffering from stress	No	**2.12 (1.73 to 2.60)**	**2.03 (1.55 to 2.64)**
Household income, <€ 1500	>€ 3200	**2.62 (1.88 to 3.66)**	**1.88 (1.27 to 2.78)**
Household income, € 1500–3200	>€ 3200	**1.77 (1.30 to 2.40)**	**1.54 (1.08 to 2.19)**

Odds ratios of variables associated with a WHO-5 score of ≤ 28 are shown in bold .
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; WHO-5, 5-item WHO Well-Being Index.

The high prevalence of depressive symptoms that are potentially not recognised by physicians is also clinically relevant in the context of new drugs currently under investigation for the treatment of axSpA, which might worsen depressive symptoms and/or provoke suicidal behaviour like apremilast, a phosphodiesterase-4 inhibitor,[30] or brodalumab, a monoclonal antibody against interleukin-17 receptor.[31]

We also found an interesting negative association of age with the presence of depressive symptoms. This might indicate that with increasing age, patients with axSpA are able to cope with the disease better, despite increasing non-SpA-related comorbidities (that showed no significant association with depressive symptoms in our analysis), leading to a lower prevalence of depressive symptoms.

Our study has strengths and limitations. The main strength of the present study was the linkage of a large nationwide claims database to questionnaire data in patients with axSpA. Claims data represent a very valid source of data on drug prescriptions, healthcare utilisation and comorbidities, while questionnaire data contained valuable additional information on disease-related, psychological, socioeconomic and lifestyle factors normally not available via claims data. The linkage of the questionnaire data to the claims data allowed for the validation of key variables, such as the diagnosis and the presence of depressive symptoms.

The primary limitation of the present study was its cross-sectional design, which did not allow us to determine the direction of significant associations or to investigate the consequences of depressive symptoms on the long-term outcome of axSpA. A prospective cohort or interventional study design is required to answer the question of a causal relationship. However, such a relationship between depressive symptoms and its associated factors may act in both directions with a substantial individual variation in the strength and direction of the association. Furthermore, claims data are normally collected for administrative rather than for scientific purposes, and the recorded diagnoses must be interpreted with caution. However, we validated the initial diagnosis from the claims data against the self-reported diagnosis obtained from the questionnaire and selected only patients who confirmed the presence of axSpA; as a result, the characteristics of the resulting group in terms of age, sex distribution, prevalence of EAMs and therapy are comparable to those of prospectively recruited axSpA cohorts.[32–34] Finally, we used only a simple screening tool (WHO-5) to assess patients' psychological well-being/depressive symptoms. The WHO-5 has been validated in several studies (usually in non-rheumatological indications) as a sensitive and specific tool for the detection of depression. Nonetheless, the specific validation of the tool with the confirmation of the presence/absence of depression by a specialist has not yet been performed for patients with axSpA.

Conclusion

In summary, we found a high prevalence of depressive symptoms/impaired psychological well-being in patients with axSpA. Higher BASDAI and BASFI, the perception of suffering from stress, lack of exercise, lower income level and younger age are factors associated with moderate-to-severe depressive symptoms in patients with axSpA while controlling for other variables. These findings highlight the need for the careful evaluation of depressive symptoms as a part of the management strategy for axSpA, helping to improve axSpA outcomes.

Acknowledgements The authors would like to thank the participating patients who took the time to complete the survey and the BARMER for providing data for this study.

Contributors All authors have substantially contributed to conducting the underlying research and drafting this manuscript.

Funding This work was supported by the Federal Ministry of Education and Research within the research network PROCLAIR (01EC1405) and by the Leibniz ScienceCampus Chronic Inflammation (www.chronische-entzuendung.org).

Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval The study was approved by the ethics committee of the Charité - Universitätsmedizin Berlin, Berlin, Germany.

Provenance and peer review Not commissioned; externally peer reviewed.

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