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Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

# Effect of depressive symptoms on treatment response in patients with axSpA: data from the RABBIT-SpA register

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**To cite:** Reich A, Weiß A, Lindner L, *et al*. Effect of depressive symptoms on treatment response in patients with axSpA: data from the RABBIT-SpA register. *RMD Open* 2025;**11**:e005422. doi:10.1136/rmdopen-2025-005422

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/rmdopen-2025-005422).

Received 3 January 2025
Accepted 6 April 2025



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## ABSTRACT

**Objectives** This analysis aimed to evaluate the effect of depressive symptoms on treatment outcomes in patients with axial spondyloarthritis (axSpA), focusing on low disease activity (LDA) and inactive disease (ID) at 3 and 6 months after the start of a new systemic therapy.

**Methods** This analysis used data from the longitudinal, observational RABBIT-SpA register. Depressive symptoms were assessed using the WHO-5 Well-Being Index, with scores below 29 indicating moderate-to-severe symptoms. The treatment outcomes LDA and ID, based on the Axial Spondyloarthritis Disease Activity Score with C-reactive protein, were evaluated after 3 and 6 months. Logistic regression models adjusted for confounding variables, selected via a directed acyclic graph, were used to assess the relationship between baseline depressive symptoms and treatment outcomes. Multiple imputation was used to handle missing data.

**Results** A total of 1755 patients with axSpA were included in the analysis. Moderate-to-severe depressive symptoms were present in 29% of patients at baseline. Fewer patients with moderate-to-severe depressive symptoms reached LDA or ID at 3 months and 6 months compared with those with no or mild symptoms. Logistic regression analysis showed that depressive symptoms were associated with lower odds of reaching LDA or ID at both time points.

**Conclusion** Depressive symptoms have a significant and independent negative effect on treatment response in patients with axSpA, particularly in achieving LDA and ID. These findings highlight the importance of routine mental health screening and treatment of depressive symptoms in axSpA management to optimise disease outcomes.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Depressive symptoms are common among patients with axial spondyloarthritis (axSpA).
⇒ There is only limited evidence that depression can negatively impact disease outcomes.

### WHAT THIS STUDY ADDS

⇒ Patients with moderate-to-severe depressive symptoms had higher disease activity, worse physical functioning and reached inactive disease or low disease less often.
⇒ After adjusting for confounding variables, depressive symptoms at the start of a new systemic therapy had an independent negative effect on treatment outcomes.
⇒ These results emphasise that depressive symptoms negatively affect therapy response in patients with axSpA.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ By highlighting the impact of depressive symptoms on disease outcomes, this study underscores the need for routine mental health screening in rheumatology practice, which could influence both clinical guidelines and future research on the holistic management of axSpA.

## INTRODUCTION

Depressive symptoms are a relevant concern in patients with chronic rheumatic diseases like axial spondyloarthritis (axSpA). A recent systematic review indicates that, depending on the instrument and cut-offs used, 11–64% of patients with axSpA experience depressive symptoms, with the authors computing a pooled prevalence of 'at least moderate symptoms' of 15%.[1] In our register, we found a prevalence of moderate-to-severe depressive symptoms of 29% in patients with axSpA.[2] Depressive symptoms have been shown to be associated with higher disease activity and functional impairment, pain perception and reduced quality of life.[1–4]

There are several potential mechanisms through which depressive symptoms can negatively influence clinical outcomes. These include poor medication adherence[5] and

amplified pain perception through central sensitisation.[6 7] There is growing evidence that depression and inflammation are linked through shared immunological pathways.[8 9]

Studies on the effect of depressive symptoms on treatment outcomes in rheumatic diseases, especially in axSpA, are still scarce. Michelsen *et al*[10] found that baseline depression or anxiety negatively predicted remission in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) from the Scandinavian registries. Wong *et al*[11] found a reduced probability of achieving sustained minimal disease activity in patients with PsA with depression/anxiety from the University of Toronto PsA Clinic. An analysis from the British Society for Rheumatology Biologics Register in patients with RA (BSRBR-RA) showed that depressive symptoms at treatment initiation were associated with lower odds of achieving good treatment response according to European Alliance of Associations for Rheumatology (EULAR) guidelines.[12] In an analysis of patients with axSpA at initiation of tumour necrosis factor-alpha inhibitor (TNFi) treatment from their register for ankylosing spondylitis (BSRBR-AS), the authors found that patients with moderate-to-severe symptoms of depression had significantly poorer responses compared with those without depressive symptoms.[13]

The aims of this analysis were to assess the effect of depressive symptoms at the start of a new systemic therapy on reaching inactive disease (ID) or low disease activity (LDA) after 3 and 6 months, respectively.

## METHODS

### Data source

RABBIT-SpA is a longitudinal, observational cohort study focusing on patients with axSpA and PsA. The primary aim of the study is to assess the long-term effectiveness and safety of biological and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs). The study includes patients from practices and clinics across Germany, who are enrolled at the initiation of a new systemic therapy. The control group comprises patients receiving conventional synthetic DMARDs (csDMARDs) or non-steroidal anti-inflammatory drugs (NSAIDs). For this analysis, all patients were included regardless of whether they received bDMARDs, tsDMARDs, or were part of the control group receiving csDMARDs or NSAIDs.

Both physician and patient case report forms (CRFs) are completed at baseline, at 3 and 6 months post-baseline and every 6 months thereafter, with a maximum follow-up period of 10 years per patient. Further details of the study design and methodology are available in previous publications.[2 14 15]

### Patient and public involvement

The German Rheumatology Research Center (DRFZ) collaborates closely with the Deutsche Rheuma-Liga, a German patient organisation for individuals affected by rheumatic and musculoskeletal disorders, which has a representative on the DRFZ's scientific advisory board. The research question addressed in this analysis is highly relevant to clinical practice, as mental health remains an often overlooked aspect in clinical research.

### Patient recruitment

Patient recruitment was performed by individual study centres and all patients provided written, informed consent.

This analysis includes all patients with axSpA enrolled from the start of the study in May 2017 until the database closure on 1 March 2024. Patients were included if they had a baseline physician's CRF, regardless of whether they had completed a 6-month follow-up visit. However, patients without a 6-month follow-up, who had not yet reached the beginning of the 6-month follow-up window (the 6-month questionnaire is available from 21 to 42 weeks after study enrolment, the 3-month questionnaire from 9 to 20 weeks) by the time of data analysis were excluded.

### Outcome and exposure

The WHO-5 Well-Being Index (WHO-5) measures depressive symptoms. It is frequently used as a depression screening tool and has been shown to be highly valuable in both clinical practice and research.[16]

It consists of five items (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'.), each measured on a scale from 0 (never) to 5 (all of the time). The scores are summed up and multiplied by 4, resulting in a WHO-5 percentage score from 0 to 100. Patients were separated into two groups using established cut-offs[17–19]: a score below 29 points indicating moderate-to-severe depressive symptoms and a score of 29 or above for mild depressive symptoms or well-being. Patients are asked to complete the WHO-5 once a year, so no additional measurement was available during the time frame analysed in this study.

Disease activity was measured with the Axial Spondyloarthritis Disease Activity Score with C-reactive protein (ASDAS-CRP), the recommended disease activity measure for patients with axSpA. LDA and ID, defined as ASDAS-CRP below 2.1 and 1.3, respectively, were chosen as response criteria.[20]

Functional impairment was measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). Comorbidity data were collected from the physician's CRF, with a checklist of relevant comorbidities, like cardiovascular diseases, renal diseases, malignancies and depression. Engagement in sports was collected in the patient CRF with the question 'How often do you engage in sport?' with possible answers 'more than 4 hours a week', '2 to 4 hours a week', '1 to 2 hours a week', 'less than one hour a week' and 'do not engage in sport'. This variable was dichotomised into 'at least 1 to 2 hours a week' versus

**Table 1** Patient characteristics by baseline depressive symptoms (imputed data)

| | Moderate/severe n=517 (29%) | None/mild n=1238 (71%) | Total n=1755 |
|---|---|---|---|
| Female, n (%) | 247 (48) | 530 (43) | 777 (44) |
| Age (years), mean±SD | 44.3±12.6 | 44±13.4 | 44.1±13.2 |
| Symptom duration (years), mean±SD | 11.6±10.6 | 11.5±11 | 11.5±10.9 |
| HLA-B27 positive, n (%) | 366 (71) | 930 (75) | 1296 (74) |
| Comorbidities, three or more, n (%) | 109 (21) | 203 (16) | 311 (18) |
| Depression*, n (%) | 60 (12) | 61 (5) | 121 (7) |
| Fibromyalgia*, n (%) | 16 (3) | 22 (2) | 37 (2) |
| Obesity (BMI≥30), n (%) | 149 (29) | 278 (22) | 427 (24) |
| Current smoker, n (%) | 237 (46) | 452 (37) | 689 (39) |
| Currently employed, n (%) | 396 (77) | 1006 (81) | 1402 (80) |
| School, ≥10 years, n (%) | 392 (76) | 1047 (85) | 1438 (82) |
| Sports, ≥1 hour/week, n (%) | 216 (42) | 698 (56) | 914 (52) |
| CRP, mg/L, mean±SD | 11.7±17.9 | 9.5±15.4 | 10.2±16.2 |
| ASDAS-CRP, mean±SD | 3.3±0.9 | 2.6±1 | 2.8±1 |
| Arthritic joint count (0–44), mean±SD | 1.5±3.7 | 1.1±2.8 | 1.2±3.1 |
| Enthesitis, number of sites (0–16), mean±SD | 0.6±1.5 | 0.5±1.4 | 0.5±1.5 |
| BASDAI, mean±SD | 6±1.6 | 4.1±1.9 | 4.7±2 |
| BASFI, mean±SD | 5.3±2.2 | 3.1±2.2 | 3.8±2.4 |
| Patient global, mean±SD | 7.1±1.9 | 5.2±2.3 | 5.7±2.4 |
| Patient back pain, mean±SD | 7.2±1.9 | 5.1±2.5 | 5.7±2.5 |
| Patient periph. pain/swelling, mean±SD | 5±2.8 | 3.4±2.7 | 3.9±2.8 |
| Patient duration morning stiffness, mean±SD | 4.5±2.7 | 3±2.4 | 3.5±2.6 |
| Naive to b/tsDMARD therapy, n (%) | 328 (63) | 874 (71) | 1202 (68) |
| Inclusion therapy: NSAID, n (%) | 58 (11) | 139 (11) | 197 (11) |
| Inclusion therapy: csDMARD, n (%) | 30 (6) | 89 (7) | 119 (7) |
| Inclusion therapy: bDMARD, n (%) | 421 (81) | 988 (80) | 1409 (80) |
| Inclusion therapy: tsDMARD, n (%) | 8 (2) | 22 (2) | 30 (2) |

Due to multiple imputation, counts may not sum exactly to the total N.
*Depression and fibromyalgia as reported by the treating rheumatologist, these may be subject to under-reporting.
ASDAS-CRP, Axial Spondyloarthritis Disease Activity Score with CRP; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; b/cs/tsDMARD, biological/conventional synthetic/targeted synthetic disease modifying antirheumatic drug; BMI, body mass index; CRP, C-reactive protein; HLA-B27, human leucocyte antigen B27; NSAID, non-steroidal anti-inflammatory drug.

'less than one hour per week or no sport'. Body mass index (BMI) was calculated from patients' height and weight and dichotomised as obesity (≥30 kg/m$^2$). Dichotomised variables are used in table 1 but for the logistic regression, continuous or categorical variables were used as observed, as recommended in the literature.[21]

All baseline variables including WHO-5 were collected at the same time, within a 2-week window before or after treatment initiation to ensure an accurate reflection of disease activity prior to the new treatment taking effect.

## Statistical analysis

### Multiple imputation

We used multiple imputation to reduce bias by creating multiple plausible data sets using chained equations, reflecting the uncertainty around missing values. We used the Multivariate Imputation by Chained Equations package in R to impute the variables in our model 10 times, using predictive mean matching as a robust method for continuous, binary and categorical variables.[22] All variables used in the directed acyclic graph (DAG) were used for the imputation model; auxiliary variables were used to improve the accuracy and plausibility of the imputed values: current employment, depression as a documented comorbidity, fibromyalgia as a documented comorbidity, fulfilment of Assessment of SpondyloArthritis international Society diagnostic criteria (all at start of therapy), disease activity (physician) and disease activity (patient) at start of treatment and after 3 and 6 months. All missing

data was imputed, including outcome data for the 227 patients who did not complete a 6-month follow-up and the main exposure for the 204 patients who did not have a WHO-5 score at baseline.

All results are based on the multiply imputed data, combined using Rubin's rules.[23]

### Logistic regression

We used dagitty.net[24] to create a DAG and derive an adjustment set of variables to identify and control for confounders, aiming to minimise bias in the estimation of the causal relationship between the exposure and outcome. Potential confounders were identified by integrating clinical expertise with evidence from peer-reviewed literature. We also applied the principles of causality and temporality to construct the DAG, ensuring that the directionality of relationships reflected the correct temporal order of events. The effect of interest to us was the direct effect of depressive symptoms on treatment response, not mediated through the type of therapy initiated. The adjustment set consisted of: ASDAS-CRP at baseline, age, sex, arthritic joint count, enthesitis, number of sites, BMI, human leucocyte antigen B27 (HLA-B27) positive (yes/no), number of comorbidities, engagement in sports, type of therapy initiated and symptom duration.

We fitted separate regression models for each imputed data set,[25] adjusting for those variables and combined estimates according to Rubin's rules. Adjusted odds ratios (OR) are given with 95% confidence intervals (95% CI).

Baseline characteristics of patients with moderate/severe depressive symptoms and patients with no or mild depressive symptoms are shown as means (±SD) or counts and percentages.

Calculations were carried out with R, V.4.4.1.[26]

## RESULTS

The data set contained 1850 patients, 95 of whom did not have enough follow-up time for a 6-month follow-up and were therefore excluded. The remaining 1755 patients were eligible for this analysis. A patient selection flowchart is provided in figure 1.

Moderate or severe depressive symptoms were present in 517 (29%) of patients. Patients with moderate or severe depressive symptoms were more often obese, current smokers or not engaging in sports than those with no or mild symptoms. They also had higher ASDAS-CRP, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and BASFI scores and more comorbidities. Table 1 presents descriptive baseline characteristics based on imputed data. The original data and the multiply imputed data, along with the percentage of missing data for each variable, are shown in online supplemental table S1.

Patients with moderate or severe depressive symptoms achieved LDA less frequently than those with no or mild depressive symptoms; only 41% reached LDA after 3 months compared with 62% of those with no or mild symptoms. Similarly, after 6 months, 44% of patients with moderate or severe symptoms reached LDA, compared with 65% of those with no or mild symptoms. The difference was also observed in achieving ID, with 20% versus 32% at 3 months and 19% versus 35% at 6 months, respectively (figure 2).

Mean ASDAS-CRP scores and its individual components (CRP, patient global assessment, the BASDAI questions on back pain, peripheral pain/swelling and duration of morning stiffness) across baseline, 3 months and 6 months, stratified by the severity of baseline depressive symptoms, are shown in figure 3. Across all measures, a clear pattern of improvement was observed from baseline to 3 months, with further improvement observed by 6 months. This trend is consistent in both groups, patients with no or mild depressive symptoms and those with moderate or severe depressive symptoms. However, patients with moderate or severe depressive symptoms started with higher mean baseline scores and, despite improvements, maintained higher scores at both 3 and 6 months compared with those with no or mild symptoms.

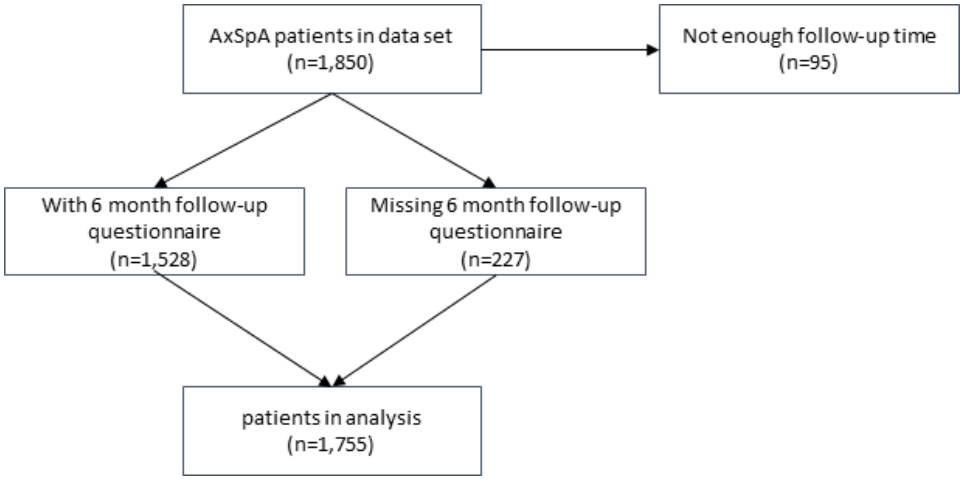


**Figure 1** Patient selection chart. AxSpA, axial spondyloarthritis.

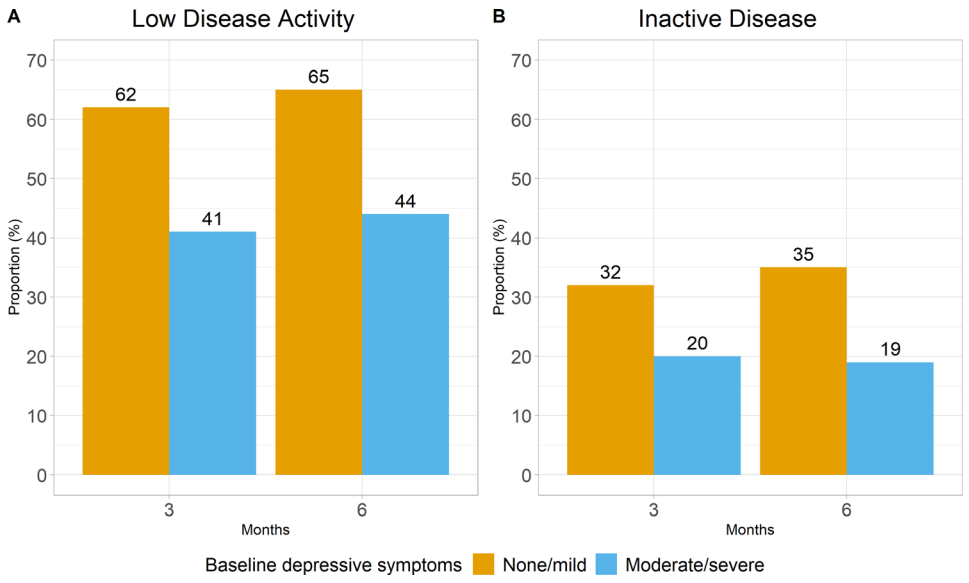


**Figure 2** Patients reaching low disease activity or inactive disease based on ASDAS-CRP by baseline depressive symptoms. ASDAS-CRP, Axial Spondyloarthritis Disease Activity Score with C-reactive protein.

Figure 4 displays the logistic regression results for the effect of the severity of depressive symptoms on the likelihood of achieving LDA or ID at 3 and 6 months. At 3 months, a higher WHO-5 score was significantly associated with higher odds of reaching LDA (OR=1.15, 95% CI: 1.07 to 1.23 per 10 points on the WHO-5 score) and ID (OR=1.08, 95% CI: 1.01 to 1.16). Similarly, at 6 months, a higher WHO-5 score was significantly associated with higher odds of achieving both LDA (OR=1.20, 95% CI: 1.13 to 1.27) and ID (OR=1.11, 95% CI: 1.05 to 1.19).

## DISCUSSION

In our analysis, patients with moderate or severe depressive symptoms at treatment initiation reached LDA or ID less frequently than those with no or mild symptoms.

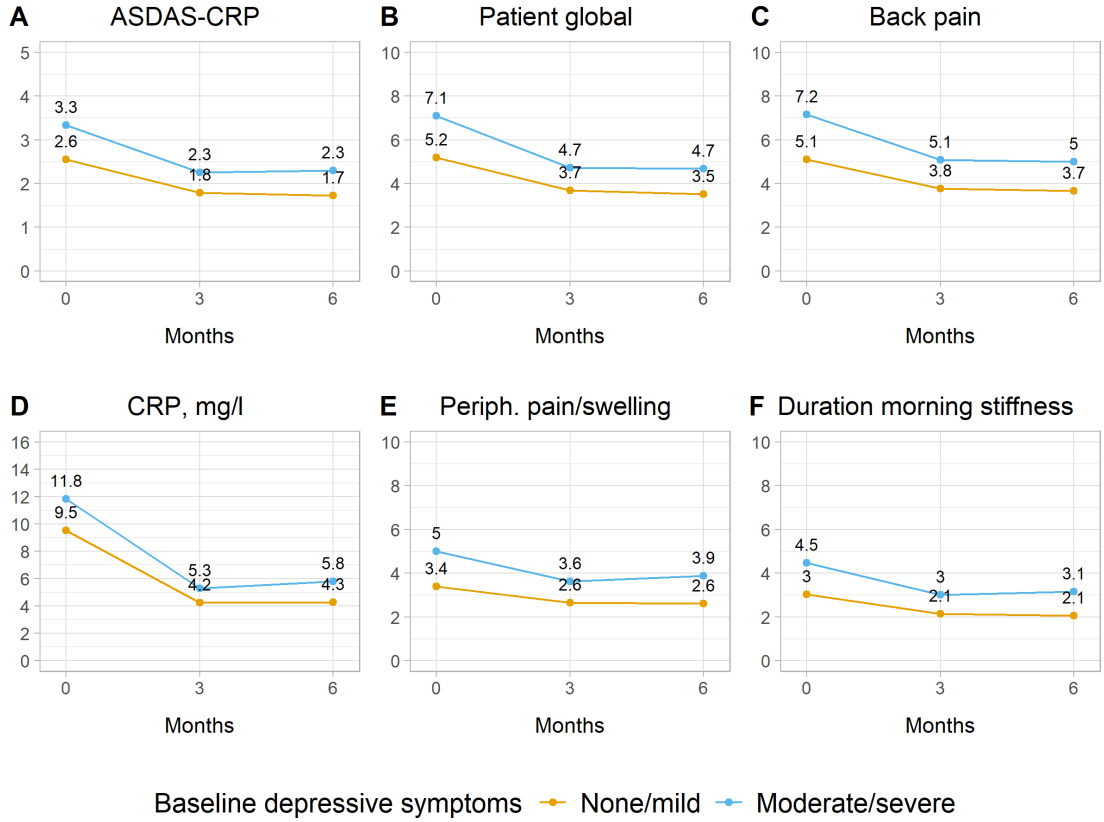


**Figure 3** Mean value of ASDAS-CRP and its component values by baseline depressive symptoms. ASDAS-CRP, Axial Spondyloarthritis Disease Activity Score with C-reactive protein.

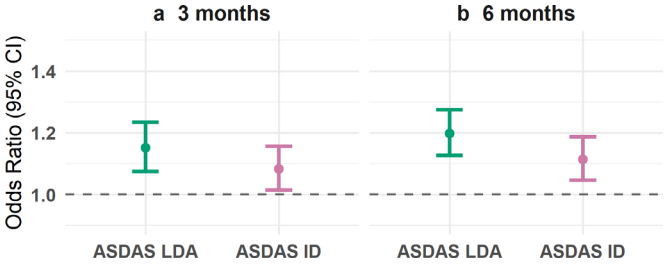


**Figure 4** ORs with 95% CIs for the effect of WHO-5 Well-being index on reaching low disease activity or inactive disease (per 10 points). ASDAS, Axial Spondyloarthritis Disease Activity Score; ID, inactive disease; LDA, low disease activity.

After adjusting for potential confounders, including baseline ASDAS-CRP, depressive symptoms had an independent, negative effect on treatment response.

We and others have previously shown that depressive symptoms are common in axSpA. In our cohort, almost every third patient had moderate-to-severe depressive symptoms. These are associated with higher disease activity, functional impairment, pain and reduced quality of life. Recent research[27] suggests several mechanisms underlying the link between axSpA and depression. Several mechanisms may contribute to this relationship. Chronic inflammation (interleukin-6, interleukin-17, TNF-α) plays a key role in both axSpA and depression, affecting neuroinflammatory pathways and neurotransmitter systems such as serotonin, dopamine and glutamate. Psychological and physical burdens, including pain, fatigue, work disability and financial stress, further exacerbate depressive symptoms. Genetic predisposition (eg, HLA-B27) and gut microbiome alterations may also contribute to immune dysregulation and hypothalamic–pituitary–adrenal axis dysfunction, linking depression and axSpA. Evidence suggests that anti-inflammatory treatments such as TNF-α inhibitors can improve both axSpA symptoms and depressive symptoms, highlighting their shared inflammatory pathways.[27] However, the effect of depressive symptoms on reaching remission in axSpA and other inflammatory arthritides is not well studied. We have identified only one publication on the effect on treatment response in axSpA. In the analysis of the BSRBR-AS register, Zhao *et al* found that symptoms of depression and anxiety at the start of TNFi treatment are associated with poorer outcomes at 6 months. Patients with moderate-to-severe symptoms of depression had significantly poorer responses, with differences of approximately 2.2 units in BASDAI and 0.8 units in ASDAS-CRP after 6 months, compared with those without depressive symptoms.[13] Our analysis of the German registry confirms these findings.

Our results are also in line with earlier ones on patients with RA and PsA,[10 12] which all found that depressive symptoms at the start of a new therapy were associated with lower rates of remission and poorer response. Michelsen *et al* reported that baseline depression or anxiety was a significant predictor of poorer remission outcomes at 3 and 6 months in patients with RA and PsA. Depressive symptoms were associated with patients' and physicians' global assessments, tender joint count and joint pain in RA but not with swollen joints or CRP/erythrocyte sedimentation rate.[10]

Analyses from the BSRBR-RA register showed that in patients with RA, depressive symptoms at treatment initiation were associated with 20–40% lower odds of achieving a good treatment response according to EULAR guidelines.[12] Similarly, our analysis found higher odds of reaching LDA and ID with a higher WHO-5 score, adjusted for meaningful confounding variables.

The analysis by Wong *et al*[11] showed similar results to our analysis but with a larger effect size in patients with PsA. The presence of depression/anxiety was associated with lower odds of reaching sustained (two or more consecutive visits) minimal disease activity (ORs of 0.3, 0.34 and 0.47, with three different definitions of depression/anxiety), but in their analysis, the authors did not adjust for baseline disease activity.

## Strengths and limitations

The strengths of our analysis are the large sample size, the prospective, standardised way of collecting real-world data as well as the careful monitoring of data to ensure a high quality of data.

One limitation is the lack of a formal diagnosis of depression; however, the WHO-5 has been shown to be a suitable screening tool. We deliberately decided not to use documented comorbid depression, as an earlier analysis showed a low proportion of documented depression, even in the group of patients with severe depressive symptoms, indicating under-reporting of comorbid depression[2] in our data. While our main exposure was likely *missing at random* (ie, the probability of missingness depends on observed variables) and not *missing completely at random* (ie, unrelated to both observed and unobserved data), we addressed this by imputing missing values instead of excluding patients with missing WHO-5, in order to reduce the risk of selection bias.

We aimed to estimate the effect of depressive symptoms on treatment response using a causal inference approach. Under the assumptions that the DAG (online supplemental figure S1 and table S2) and subsequent statistical model were correctly specified and that no unmeasured confounding is present, our estimates can be interpreted causally. Any misspecification, such as omitted variables or incorrect assumptions about causal pathways, could bias the estimates. Despite controlling for potential confounders, residual confounding due to unmeasured or inadequately measured variables cannot be ruled out completely, which might limit the robustness and generalisability of our findings.

Our research question focused on how depressive symptoms affect the effectiveness of antirheumatic treatment for the underlying rheumatic condition, so the current analysis does not take into account changes in depressive symptoms over time or the fact that the causal

effect between depressive symptoms and disease activity is likely bidirectional.

Finally, there is a recognised lack of robust objective parameters for evaluating disease activity in axSpA, which often relies on subjective measures. This presents a unique challenge, as disease monitoring relies heavily on patient-reported outcomes (PROs) which are included in the ASDAS-CRP score. While shared decision-making and incorporating the patient's perspective are vital for effective care, particularly in chronic conditions like axSpA, this reliance on PROs can be problematic when comorbid conditions like depression confound these measures. Depression can distort how patients perceive and report their symptoms, leading to elevated disease activity scores that may not reflect the true inflammatory burden. Central sensitisation and catastrophising behaviour are further factors that have been shown to have independent negative associations with disease activity scores like ASDAS-CRP[28 29] and need to be considered when making decisions to change or escalate antirheumatic therapies.

This highlights the need to integrate more objective measures of disease activity in axSpA and carefully consider the role of comorbidities like depression in interpreting PROs and guiding clinical decisions. This should include integrating psychological assessments into the routine care of patients with chronic rheumatic diseases and management of concomitant depression, central sensitisation or catastrophising behaviour along with the rheumatic disease. More research is needed into the contribution of these mechanisms to patient-reported disease activity.

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**Acknowledgements** The authors acknowledge the invaluable contributions of all participating consultant rheumatologists and their patients. In particular, we would like to thank those rheumatologists who enrolled the highest numbers of patients: Professor Dr med Xenofon Baraliakos, Professor Hanns-Martin Lorenz, Matthias Eduard Worsch, Dr med Jacqueline Detert, Dr Ilka Schwarze, Dr Jörg Kaufmann, Dr Martin Feuchtenberger, Professor Herbert Kellner, Professor Dr med Uta Syrbe, Dr Werner Harmuth, Dr Jörg Kaufmann, Dr med Daniel Bestler, Dr Thilo Klopsch, Professor Andreas Krause, Dr Anke Liebhaber, Dr Christina Eisterhues, Dr Thomas Marycz, Dr Christine Baumann, Dr Martin Bohl-Bühler, Dr Katharina Pagel, Dr Tamás Borvendég.

**Contributors** AR, AW and ACR had full access to all data of this study and take responsibility for data integrity and accuracy of the analysis. AR serves as guarantor for this work. Study concept and design: ACR, AW and AR. Acquisition of the data: SZ, CS and JD. Analysis and interpretation of the data: AR, AW and ACR. Drafting the manuscript: AR, AW and ACR. Critical revision of the manuscript for important intellectual content: AR, AW, LL, SZ, CS, JD, DP, AS, XB and ACR. Obtaining funding: ACR and AS. All authors read and approved the manuscript. During the preparation of this work, the authors used ChatGPT for minor language editing. After using this tool, the authors reviewed and edited the content as needed. They take full responsibility for the content of the published article.

**Funding** RABBIT-SpA is supported by a joint, unconditional grant from AbbVie, Amgen, Biocon, Biogen, Celltrion, Hexal, Janssen-Cilag, Lilly, MSD, Novartis, Pfizer and UCB.

**Disclaimer** The principal investigators and their team had full academic freedom in study design and conduct, data analysis and publication of results. These stipulations were delineated in their contract with the sponsors. For the purpose of information, all funding companies received the manuscript 30 days prior to submission. Publication of this article was not contingent on their approval. The data interpretation, drafting, critical revision and approval of the final manuscript were performed solely by the authors.

**Competing interests** XB, invited speaker by AbbVie, Alphasigma, Amgen, BMS, Cesas, Celltrion, Galapagos, Janssen, Lilly, MoonLake, Novartis, Pfizer, Roche, Sandoz, Springer, Stada, Takeda, UCB, Zuellig, consultation for AbbVie, Alphasigma, Amgen, BMS, Cesas, Celltrion, Galapagos, Janssen, Lilly, MoonLake, Novartis, Pfizer, Roche, Sandoz, Springer, Stada, Takeda, UCB, Zuellig, grants from AbbVie, Janssen, Novartis, Celltrion. ACR, invited speaker by Amgen, BMS, Novartis, Pfizer, Roche. All other authors have declared no conflicts of interest in relation to this analysis.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by Ethics committee of the Charité - Universitätsmedizin Berlin (EA1/246/16). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** No data are available. RABBIT-SpA data is not approved to be shared. A preliminary version of these results was presented at EULAR 2024 as a poster, reference number POS0497.



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