Frequency of irritable bowel syndrome in spondyloarthritis: a multicentric cross-sectional study and meta-analysis

Jessika Bernard, Thomas Barnetche, Charlotte Amory, Jerome Despres, Maxime Vandersmissen, Justine Landrin, Cecile Gaujoux-Viala, Cédric Lukas, Adeline Ruyssen-Witrand, Marie-Elise Truchetet, et al.

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Frequency of irritable bowel syndrome in spondyloarthritis: a multicentric cross-sectional study and meta-analysis

Jessika Bernard,[1] Thomas Barnetche,[2] Charlotte Amory,[3] Jerome Despres,[4] Maxime Vandersmissen,[5] Justine Landrin,[2] Cecile Gaujoux-Viala,[6,7] Cédric Lukas,[3,7] Adeline Ruyssen-Witrand,[4] Marie-Elise Truchetet ,[2] Pascale Vergne-Salle ,[5] Sylvain Mathieu ,[1] Anne Tournadre [1]

To cite: Bernard J, Barnetche T, Amory C, *et al*. Frequency of irritable bowel syndrome in spondyloarthritis: a multicentric cross-sectional study and meta-analysis. *RMD Open* 2024;**10**:e003836. doi:10.1136/rmdopen-2023-003836

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2023-003836).

Received 21 October 2023
Accepted 19 December 2023

For numbered affiliations see end of article.

Correspondence to
Dr Anne Tournadre; atournadre@chu-clermontferrand.fr

ABSTRACT

Objective To evaluate the prevalence of symptoms and factors associated with irritable bowel syndrome (IBS) in axial spondyloarthritis (ax-SpA).

Methods In a cross-sectional multicentric study, consecutive patients with ax-SpA treated with biologics in five rheumatology departments were asked for IBS Rome IV criteria. Demographic data, lifestyle behaviours and disease characteristics were recorded. Second, a systematic literature review and meta-analysis were performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results Of the 500 patients with ax-SpA included, 124 reported IBS symptoms (25%). Female gender, unemployment, higher Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and worse Bath Ankylosing Spondylitis Functional Index scores, multiple lines of biologics, fibromyalgia, anxiety, depression and lower physical activity were associated with IBS symptoms. In multivariate model, the risk of IBS was associated with anxiety and physical inactivity. From the literature review, the prevalence of IBS in patients with SpA was 15.4% (8.8% to 23.3%). Meta-analysis of the five studies comparing the presence of IBS in patients with SpA (323/7292) and healthy controls (484/35587) showed a significant increase of IBS in patients with SpA (OR=1.59 (1.05 to 2.40)).

Conclusion The prevalence of IBS symptoms was high in the ax-SpA population and should therefore be considered in the presence of gastrointestinal disorders. The presence of IBS symptoms was associated with anxiety and low physical activity in multivariate analysis. Patients with IBS symptoms tended to have more difficult to manage disease characterised by higher activity, worse functional score and multiple lines of treatment in univariate analysis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Gastrointestinal pain, loose stools and/or diarrhoea symptoms are frequent, reported in about 30%–50% of patients with spondyloarthritis (SpA). Gastrointestinal symptoms can be related to inflammatory bowel disease observed in approximatively 9% of patients but also to functional bowel disorders such as irritable bowel syndrome (IBS) much more frequent in the general population. Limited data are available on the prevalence and factors associated with IBS in SpA.

WHAT THIS STUDY ADDS

⇒ IBS symptoms were observed in 25% of patients with ax-SpA in the cross-sectional study, similar to the prevalence found in the meta-analysis (23%) when the diagnosis was defined by the Rome criteria and not by disease code. Results from the meta-analysis showed a significant increase of IBS in patients with SpA as compared with healthy controls. The presence of IBS was primarily associated with anxiety and physical inactivity. Patients with IBS also tend to have more fibromyalgia, unemployment, higher disease activity, worse functional score and multiple lines of treatment which could contribute to difficult to manage disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ IBS symptoms should be screened in the presence of gastrointestinal disorders in patients with ax-SpA. This comorbidity may be considered in the identification of patients with difficult to manage disease.

INTRODUCTION

Axial spondyloarthritis (ax-SpA) is a heterogeneous disease associated with extra-articular manifestations that can impact both disease severity and quality of life. Prevalence of uveitis, psoriasis and inflammatory bowel disease (IBD) in ankylosing spondylitis (AS) was reported in 25.8%, 9.3% and 6.8% of patients, respectively, in a meta-analysis.[1] Gastrointestinal pain, loose stools and/or diarrhoea symptoms are frequent and reported in about 30%–50% of patients with SpA.[2] Gastrointestinal symptoms can be related to subclinical gut inflammation, IBD but also to functional bowel disorders, which

are characterised by chronic abdominal pain, bloating or distension, constipation, diarrhoea.[3] Irritable bowel syndrome (IBS) is a functional bowel disorder in which recurrent abdominal pain is associated with defecation or change in stool consistency or frequency. IBS can be clinically diagnosed based on symptoms and limited testing using the Rome IV criteria in the absence of obvious anatomic or physiological abnormalities identified by routine diagnostic examination.[3] Differential diagnoses include IBD, coeliac disease, lactose and fructose intolerance, microscopic colitis and colorectal cancer. IBS is more frequent than IBD in the general population with a worldwide prevalence of 11% and a relatively higher prevalence in women and young adults.[3] It can be associated with chronic inflammatory conditions such as IBD and coeliac disease and also with multiple comorbidities (eg, fibromyalgia, chronic pain, anxiety and depression) shared with SpA.[4] Gut microbiota and the environmental factors that influence it could explain the link between SpA, gastrointestinal disorders and comorbidities.[5–7] Data regarding the prevalence and factors associated with IBS in SpA are sparse in the literature.

The objectives of this study were to evaluate in a cross-sectional multicentric study the prevalence of IBS symptoms in ax-SpA and to identify associated factors including demographic and ax-SpA characteristics, treatments and adherence, lifestyle behaviours, diet and comorbidities. In addition, a systematic literature review and meta-analysis were performed.

METHODS

Cross-sectional study

Population

This was a cross-sectional, multicentric, observational study in which consecutive patients fulfilling the Assessment of Spondyloarthritis International Society diagnosis criteria for ax-SpA[8 9] were included between June 2021 and June 2022. All patients were treated by biologics. This study was conducted at the rheumatology departments of 5 French university hospitals (Bordeaux, Clermont-Ferrand, Limoges, Montpellier and Toulouse).

Clinical assessment

Patients completed an anonymous self-questionnaire assessing IBS symptoms as defined by the ROME IV criteria.[3] The updated Rome IV criteria for the diagnosis of IBS require that patients had recurrent abdominal pain on average at least 1 day per week during the previous 3 months and with symptom onset at least 6 months before diagnosis, which was associated with two or more of the following: related to defecation (may be increased or unchanged by defecation), associated with a change in stool frequency, associated with a change in stool form or appearance. In addition, the self-questionnaire included demographic data, lifestyle behaviours (age, sex, tobacco and alcohol use, educational level and occupation, physical activity level, sedentary time, sleep, and diet), the Girerd questionnaire for treatment adherence,[10 11] the Fibromyalgia Rapid Screening Tool (FIRST),[12] and the Hospital Anxiety and Depression Scale.[13] Patients were not included if there were more than three missing data entries per self-questionnaire.

A medical questionnaire was completed by rheumatologists including disease duration, HLA-B27 status, X-ray or MRI sacroiliitis, extra-articular manifestations (psoriasis, IBD, uveitis), disease activity score based on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[14] functional index based on the Bath Ankylosing Spondylitis Functional Index (BASFI),[15] C reactive protein (CRP) levels, current treatments (non-steroidal anti-inflammatory drugs (NSAIDs); biologics: TNF, IL17, or IL12/23 inhibitors), and comorbidities including Charlson Comorbidity Index and body mass index. The Charlson Comorbidity Index is calculated as follows[16]: 1 point for history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease and diabetes without end-organ damage; two points for hemiplegia, moderate-to-severe renal disease, diabetes with end-organ damage, tumour without metastases, leukaemia, lymphoma, and myeloma; three points for moderate or severe liver disease; and six points for metastatic solid tumour or AIDS; one point is added to the score for every decade >40 years of age.

Statistical analysis

Categorical data are presented as the number of patients and associated percentages, and continuous data as mean±SD or median (25th; 75th percentiles), according to the statistical distribution. Comparisons were made by the χ^2 test or the Fisher's exact test for categorical variables, and by the Student's t test or the Mann-Whitney test for continuous variables. For the percentage of patients with IBS, the χ^2 test was used for comparisons between groups and logistic or linear regressions were used to test the association with different parameters. Adjusted ORs were estimated using multivariate logistic regression model including the variables statistically significant within the univariate analysis. Statistical analyses were performed with Stata software (V.13.1; StataCorp). All tests were two-sided, with an alpha level set at 5%.

Systematic literature review and meta-analysis

Literature search

The PubMed, Cochrane Library and Embase databases were searched for randomised control trials of interest published up to 24 May 2023. Our analysis included all observational studies that monitored IBS in patients with SpA or case/control studies that considered characteristics of patients with SpA with or without IBS. The following search terms were used: "irritable bowel syndrome" AND (ankylosing OR psoriatic OR spondylitis). Our search only included articles published in English or French. We also performed a manual search of references. Additionally,

we collected data from the electronic abstract databases of the annual scientific meetings of the European Alliance of Associations for Rheumatology and American College of Rheumatology from 2002 to 2022 using the term “irritable bowel syndrome”.

Trial selection

Two investigators (SM and AT) selected potentially relevant articles after reading the title, keywords, abstract and then the full text. The other authors monitored the different steps of this selection to confirm included and excluded studies and to ensure that no studies of interest were missed. Uncertainties regarding article selection were resolved by consensus after discussion with other investigators. Articles were excluded if the full-text article was unavailable or in cases of insufficient or unclear data in the abstract, if it was a meta-analysis or a review, and if the data were not suitable for statistical analysis (ie, no information on number of patients or percentages). The studied population comprised patients with SpA, that is, AS, psoriatic arthritis and other spondyloarthropathies. No comparator was necessary in this research. The outcomes were the number and percentage of patients with SpA with IBS. We distinguished the studies that used the Rome criteria to classify patients with SpA as having IBS and those using codes.

Data extraction

One investigator (SM) extracted all data using a standardised data abstraction form. The type of included study (abstract or full-text article) was recorded. For all included studies, the number of patients with IBS and the total number of patients with SpA were obtained. Discrepancies in data extraction were resolved by consensus after discussion with other investigators.

Quality of assessment

The two forms of Newcastle-Ottawa Scale were used, one for case control studies and one for cross-sectional studies, to check the quality of articles.[17]

Statistical analysis

Continuous variables were expressed as weighted mean±SD. Prevalence of IBS was calculated by meta-analysis of proportions (inverse variance method) and 100 patient-years of exposure. The Mantel-Haenszel procedure was used to determine the OR of IBS in patients with SpA versus controls. This method provided a common OR estimate and 95% CI. For patient characteristics (continuous variables), differences between patients with SpA with IBS and those without IBS were expressed by standardised mean difference using inverse of variance method: moderate=0.2–0.8, large>0.8. Statistical heterogeneity between results was assessed using I^2, which is the most common metric for measuring the magnitude of between-study heterogeneity and is easily interpretable. I^2 values range between 0% and 100% and are typically considered low for <25%, modest for 25%–50%, and high for >50%. This statistical method generally assumes heterogeneity when the p value of the I^2 test is <0.05. Random effects models were used if heterogeneity was observed; otherwise, a fixed effect model was used. Finally, to check the robustness of the results, sensitivity analyses were performed according to funnel plots. Statistical analysis was conducted using Review Manager software (V.5.0) produced by the Cochrane Collaboration.

RESULTS

Cross-sectional study

Study population

Five hundred patients were included in the study (mean age 49.5±13.8 years, 47% women (n=234), mean disease duration 14.7±11 years, and mean BASDAI 3.6±2.1). Radiographic and MRI sacroiliitis were observed in 51% (n=256/416) and 56% (n=277/362) of patients, respectively. HLA-B27 status was positive in 71% of patients (n=355/452). Psoriasis was reported in 118 patients (23.6%). IBD was observed in 53 patients (11%) and among them 41 had Crohn’s disease (77%), 12 had ulcerative colitis (23%) and 7 patients were considered to have active IBD by a rheumatologist (15%). The proportion of females was higher (63%; p=0.017) in patients with IBD, whereas HLA-B27 was less prevalent (54%; p=0.016). Current smoking and alcohol use were reported by 36% (n=180) and 9% (n=46) of patients with ax-SpA, respectively. The median Charlson Comorbidity Index was 0.3±0.7. Fibromyalgia was found in 21% (n=107), anxiety in 26% (n=128) and depression in 11% (n=55). Current treatment with NSAIDs was reported in 25% (n=126) of patients with ax-Spa, 86% (n=429) received TNF inhibitors, 13% (n=66) IL17 inhibitors and 1% (n=5) IL12/IL23 inhibitors. More than half of patients had previously been treated by at least one biologic drug. Patients with IBD received less IL17 and IL12/IL23 inhibitors (p=0.01) and NSAIDs (p<0.001). Good adherence (Girerd score=0) was reported by 49% of patients. Patients reported following a medical diet in 26 cases (5%) and a non-medical diet in 47 cases (9%). Most common non-medical diets were lactose-free (22 patients), gluten-free (11 patients), vegetarian (6 patients), and low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) in 4 patients; other dietary restrictions were noted in 4 patients.

IBS prevalence and associated factors

IBS criteria were present in 124 patients (25%). Female gender (60%; p=0.001), unemployment (27%; p=0.013), higher disease activity (BASDAI; p<0.001), worse functional score (BASFI; p<0.001), multiple lines of biologics (p=0.002), fibromyalgia (34%; p<0.001), anxiety (41%; p<0.001), depression (16%; p=0.037) and lower physical activity (p=0.001) were associated with IBS (table 1). In multivariate model, anxiety (OR=2 (1.21 to 3.32), p=0.007) and physical activity (OR=0.45 (0.23 to 0.88),

Table 1 Irritable bowel syndrome (IBS) prevalence and associated factors

	IBS (n=124)	No IBS (n=376)	P value
Age (years)	49.4±14.0	49.5±13.7	0.96
Female	74/124 (59.6)	160/376 (42.8)	0.001
BMI, kg/m^2	25.9±5.2	26.3±5.5	0.56
Education (university level)	160 (43)	50 (40)	0.23
Occupational activity			
Unemployed	34 (27)	52 (14)	0.013
Retired	21 (17)	76 (20)	
Workers	4 (3)	23 (6)	
Employee	38 (30)	127 (34)	
Manager	14 (11)	69 (18)	
Artisan	11 (9)	23 (6)	
Farmer	2 (1)	4 (1)	
Smokers	33 (27)	102 (27)	0.59
Alcohol use (>2 glasses/day)	13 (10)	33 (9)	0.09
Disease duration, years	14.5±10.9	14.8±11.1	0.76
X-ray sacroiliitis	62 (50)	192 (51)	0.91
MRI sacroiliitis	70 (57)	205 (55)	0.24
Presence of HLA-B27	85 (70)	269 (72)	0.73
Psoriasis history	35 (28)	82 (22)	0.15
Uveitis history	26 (21)	67 (18)	0.45
IBD history	11 (8.8)	42 (11.2)	0.46
BASDAI (0–10)	4.5±2.0	3.3±2.1	<0.001
BASFI (0–10)	3.5±2.4	2.2±2.2	<0.001
CRP, mg/L	3.4±6.6	3.3±4.7	0.95
Current use of NSAIDs	33 (26)	91 (24)	0.61
Current use of TNF inhibitors	101 (81)	326 (87)	0.11
Current use of IL17 inhibitors	21 (17)	45 (12)	0.16
Current use of IL12/23 inhibitors	2 (1.6)	3 (0.8)	0.60
Number of previous biologics			0.002
0	41 (33)	199 (53)	
1	34 (27)	79 (21)	
2 or 3	39 (31)	80 (20)	
≥4	10 (8)	16 (4)	
Adherence (Girerd score)			0.85
High	64 (51)	181 (48.4)	
Medium	55 (44.3)	179 (47.8)	
Low	5 (4)	14 (3.7)	
Comorbidities (Charlson Index)	0.4±1.0	0.2±0.4	0.20
Fibromyalgia (FIRST)	43 (34)	64 (17)	<0.001
Anxiety (HADS A>10)	52 (41)	76 (20)	<0.001
Depression (HADS D>10)	20 (16)	35 (9)	0.037
Physically active (moderate physical activity>150 min/week)	12 (9.7)	88 (23.5)	0.001

Continued

Table 1 Continued

	IBS (n=124)	No IBS (n=376)	P value
Sedentary behaviour (sitting time >7 hours/day for the last 7 days)	24 (20)	85 (23)	0.42
Sleeping (hours/day)	6.9±1.8	7.0±1.8	0.48
Diet	26 (21)	58 (15.5)	0.16
Medical diet	8 (7.1)	18 (5.3)	0.44
Non-medical diet	14 (11.8)	33 (8.8)	0.32

Data are presented as number of patients (percentages) or mean±SD.
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; CRP, C reactive protein; FIRST, Fibromyalgia Rapid Screening Tool; HADS, Hospital Anxiety and Depression Scale; IBD, irritable bowel disease; NSAID, nonsteroidal anti-inflammatory drug.

p=0.02) were associated with the risk of IBS (figure 1). A significant interaction between fibromyalgia and anxiety was observed. No difference was noted regarding diet or adherence between patients with or without IBS. The prevalence of IBS was not significantly different between patients with or without IBD (respectively, 11/53 (21%) vs 113/447 (25%)). In contrast to IBS (n=124), there was no observed differences for comorbidities and physical activity in patients with IBD (n=53).

Systematic literature review and meta-analysis

Literature search

The initial search identified a total of 406 citations (figure 2). Of these, nine eligible studies were included.

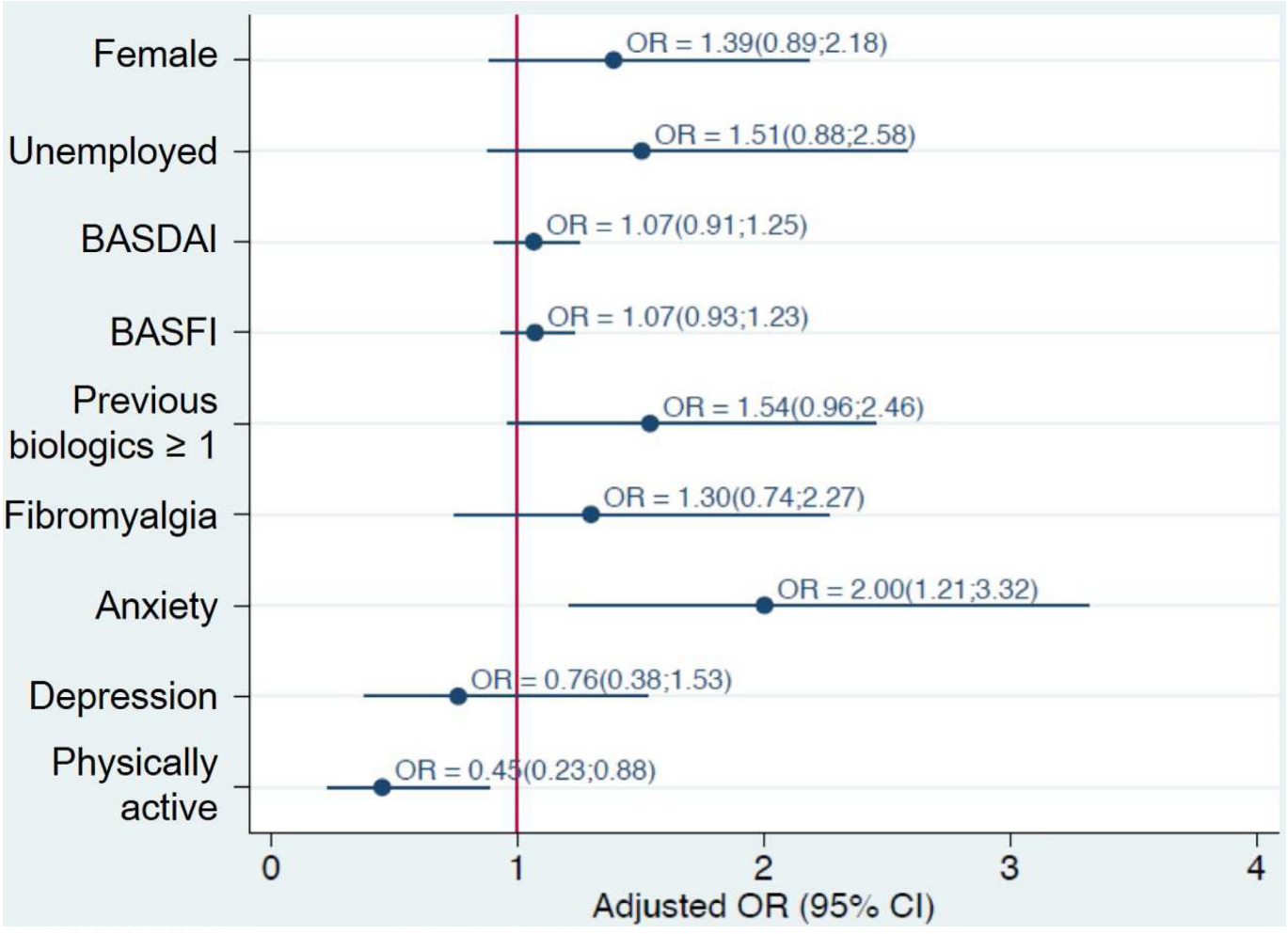

Figure 1 Forest plot showing the risk for irritable bowel syndrome (ORs) in multiple regression model. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.

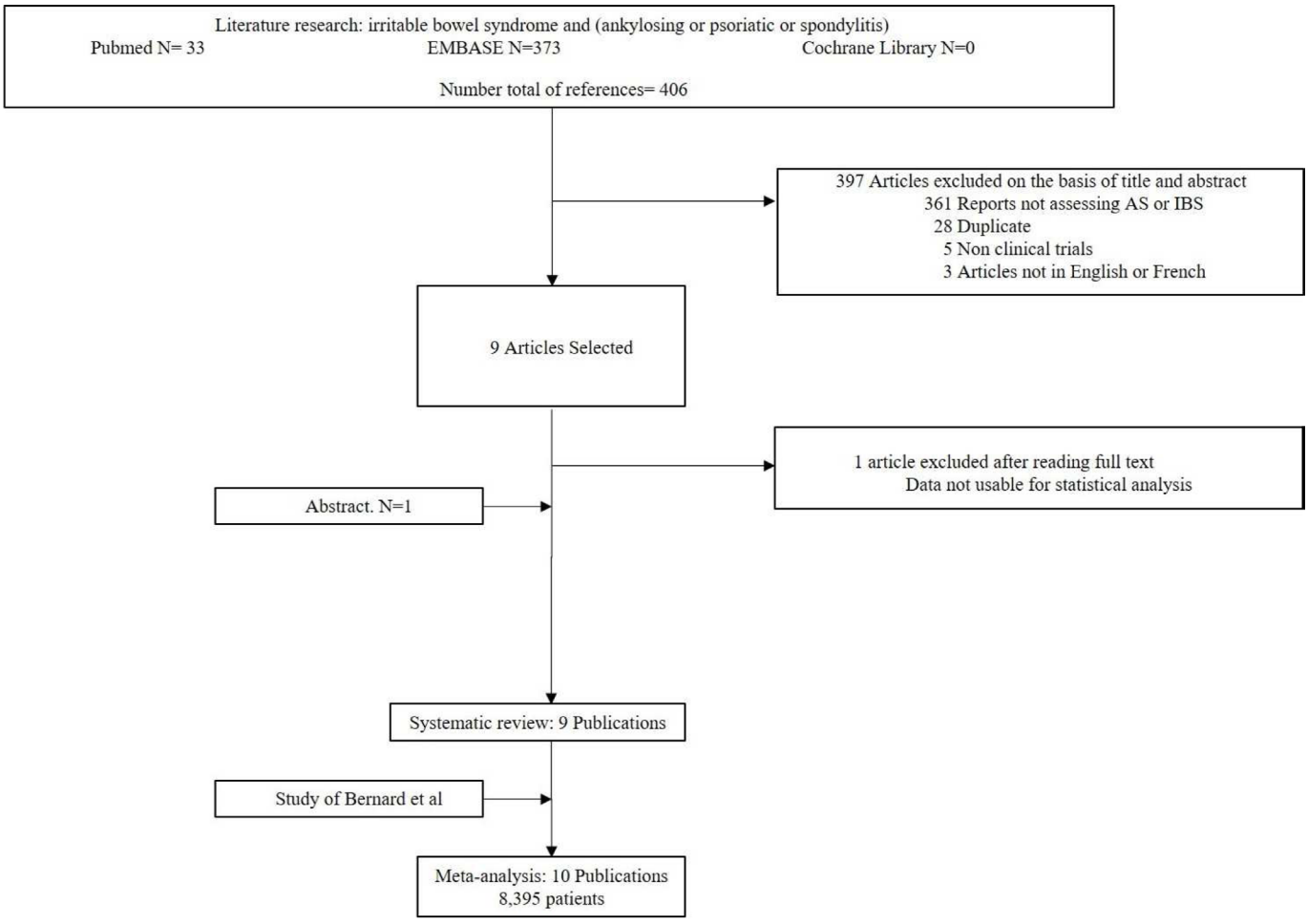

Figure 2 Flow chart of research article selection. AS, ankylosing spondylitis; IBS, irritable bowel syndrome;

One reference was added from congress/conference abstract databases[18] and we found the corresponding article published in 2022.[19] One reference was excluded from the meta-analysis because data were not usable for statistical analysis. Ten references were included for the meta-analysis: nine from the literature search along with the study of Bernard *et al* previously described. Characteristics of the 10 included studies are presented in table 2.

Table 2 Characteristics of the included publications

Authors	Number of participants		Type of study	Outcome measures for meta-analysis
	SpA	Controls		
Feng *et al* 2022[37]	3516	3516*	Cohort	IBS
Wallman *et al* 2019[38]	182	50	Case/control	IBS, BASDAI, BASFI
Wang *et al* 2022[39]	153	56	Case/control	IBS
Williamson *et al* 2004[40]	103	0	Cross-sectional	IBS
Zhao *et al* 2019[41]	255	0	Cross-sectional	IBS
Zohar *et al* 2016[42]	3161	31 610	Case/control	IBS
Sagard *et al* 2022[19]	132	0	Cross-sectional	IBS
Solmaz *et al* 2015[43]	113	0	Cross-sectional	IBS
Ozgocmen *et al* 2010[44]	280	355	Case/control	IBS
Bernard *et al*	500	5000	Cross-sectional	IBS, BASDAI, BASFI

*Propensity score matched patients.
BASDAI, Bath Ankolysing Spondylitis Activity Index; BASFI, Bath Ankolysing Spondylitis Functional Index; IBS, irritable bowel syndrome; SpA, spondyloarthropathies.

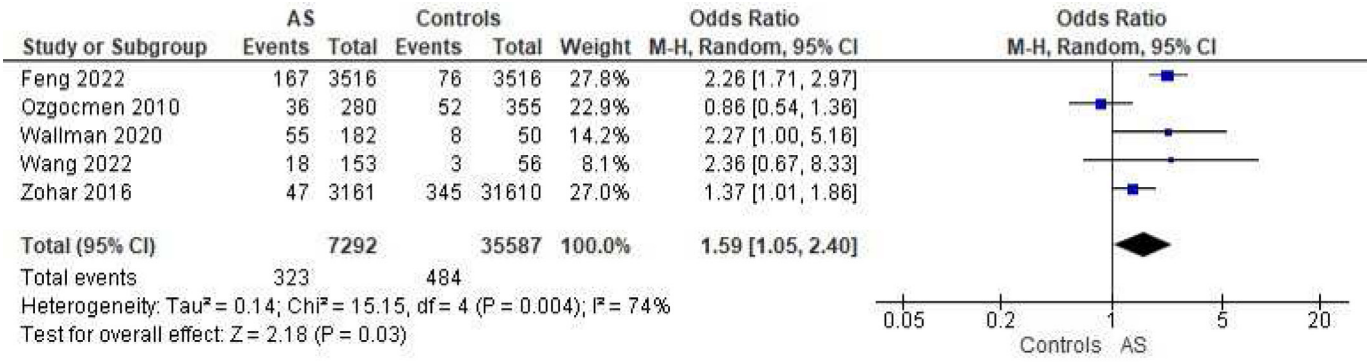

Figure 3 Comparison of irritable bowel syndrome risk occurrence in ankylosing spondylitis (AS) and controls.

Study characteristics

Of the 10 publications, 5 were cross-sectional, 4 were case/control studies and 1 was an observational cohort study. Ten studies assessed the prevalence of IBS in SpA studies. Of these, 5 reported the presence of IBS in both patients and controls. Two studies analysed disease activity scores (BASDAI, BASFI) in patients with SpA with or without IBS. The methodological quality of these included studies was quite good (online supplemental figures 1 and 2).

Occurrence of IBS

In the 10 included studies, 558 patients with IBS were reported within the SpA patient population (n=8395); the prevalence was 15.4% (8.8% to 23.3%). This prevalence was different when the diagnosis of IBS was obtained by disease code using the International Classification of Diseases (ICD) (n=3) or by Rome III or IV (n=6) classification questionnaire: respectively 3.7% (1.3% to 7.3%) and 23.1% (16.3% to 30.7%). Five studies provided the number of patients with IBS in the control group (n=35 587) and this totalled 484 IBS cases (5.8% (95% CI (2.9% to 9.7%))). Meta-analysis of the five studies comparing the prevalence of IBS in patients with SpA (323/7292) and healthy controls (484/35587) showed a significant increase of IBS in patients with SpA compared with controls: (OR=1.59 (1.05to 2.40)) (figure 3). Sensitivity analysis found a significant, even greater increase of IBS in patients with SpA (OR=1.87 (1.32 to 2.640)) according to the funnel plot when the study by Ozgocmen was excluded. Heterogeneity that was significant in analysis of the five studies (I^2=74%; p=0.004) was no more significant when the study of Ozgocmen was removed (I^2=51%; p=0.10).

Comparison of SpA with or without IBS

Only two studies included BASDAI and BASFI disease activity scores in patients with SpA with (n=179) or without (n=501) IBS and a higher weighted mean BASDAI (4.4±2.1 vs 3.1±2.1; p<0.001) and BASFI (3.3±2.3 vs 2.1±1.9; p<0.001) were observed in patients with IBS.

DISCUSSION

Chronic gastrointestinal symptoms are frequent in patients with SpA affecting more than half of patients[2] contrasting with the low frequency of IBD. There was a high prevalence (25%) of IBS symptoms in our sample of 500 ax-SpA patients as well as 15% in the meta-analysis of more than 8000 patients with SpA. Results from the meta-analysis showed a significant increase of IBS in patients with SpA as compared with controls. In the cross-sectional analysis, prevalence of IBS was higher compared with the frequency reported in the general population (11%)[3] and relative to the meta-analysis. However, the diagnosis of IBS increased to 23% in the meta-analysis when defined by the Rome criteria and not by the ICD disease code which may underestimate the prevalence of the disease. The high proportion of IBS symptoms in our cross-sectional study might also be linked to the patient characteristics, including only ax-SpA treated by biologics and care provided by university hospitals, which corresponds to more severe patients with worse prognostic factors. Consistently, the frequency of IBD (11%) and psoriasis (23%) in this sample of patients with ax-SpA was higher than in the general ax-SpA population.[1] In our study, the prevalence of IBS did not seem to be more frequent when IBD was associated with SpA. These results are in contrast with the literature. In patients with remission IBD, IBS symptoms were found in 60% of patients suffering from Crohn's disease and in 39% of patients with ulcerative colitis.[20]

The presence of IBS symptoms was correlated with disease activity both in the cross-sectional study and meta-analysis. Microscopic gut inflammation associated with SpA disease activity or treatment side effects could contribute to dysbiosis and chronic gastrointestinal disorders.[5] However, in our cross-sectional study, CRP levels were similar in patients with or without IBS symptoms and IBS symptoms were not associated with NSAID use. In addition, more than 80% of patients reporting IBS symptoms were treated with TNF inhibitors which should have been effective on gut inflammation, suggesting other contributors to the link between IBS, SpA and disease activity. Comorbid conditions such as fibromyalgia, anxiety and depression, frequent both in SpA and

IBS, can modify all patient-reported outcomes and make assessment of disease activity and management more difficult. In a meta-analysis that included over 5000 patients, the prevalence of fibromyalgia in SpA was reported to be 16%.[21] The FIRST self-questionnaire was useful for detection of fibromyalgia in patients with rheumatic diseases.[22] In our study, fibromyalgia was 2 times more frequent in patients with IBS symptoms (34 %) as compared with patients without IBS (17%) with a significant interaction with anxiety. Fibromyalgia and IBS are known to be closely linked: fibromyalgia occurs in 30%–70% of patients with IBS, and IBS occurs in 28%–59% of patients with fibromyalgia.[23]

When gastrointestinal symptoms are present, IBS diagnosis should be considered after ruling out other gut differential diagnoses, particularly gut inflammation and IBD, based on alarm signals such as bloody stools, weight loss, family history of colorectal cancer or IBD, abnormal examination, nocturnal symptoms, iron deficiency, anaemia and inflammation on blood or stool testing.[3 24 25] When diagnostic criteria for IBS are fulfilled and alarm features absent, diagnostic tests should be limited. Only individuals with alarm features require a colonoscopy to exclude organic disease. In patients with IBD symptoms according Rome IV criteria and who had alarm features, the diagnostic for an organic disease after a colonoscopy was relatively low, reported to be 12% (IBD, colon cancer, microscopic colitis).[25] A faecal calprotectin assay would be helpful when evaluating a patient with SpA with gastrointestinal symptoms. A recent study reported that evaluation of faecal calprotectin levels was useful in the identification of microscopic inflammation and could be of benefit in the more judicious indication of ileocolonoscopy.[26 27] Wang *et al* reported higher levels of faecal calprotectin in 210 patients with IBD compared with patients with IBS.[28] Thus, a negative faecal calprotectin test in a patient with SpA with gastrointestinal symptoms could reasonably permit to exclude IBD but a positive faecal calprotectin test should be interpreted with caution.[29]

Diet was not a significant factor associated with IBS in our study. However, only 9% of our patients declared that they were following a non-medical diet, mostly lactose-free and gluten-free diets. This proportion can be underestimated because of the cross-sectional nature of our study and since assessment of diet was performed by self-questionnaire. It should not be excluded that some patients adhered to a non-medical diet in the past and have lapsed. Others may have decided not to disclose this information to the physician because their effectiveness is not scientifically proven. By contrast, in the literature, up to 90% of patients with IBS modify their diet in order to improve their symptoms although clear dietary recommendations have not been established.[4 30] Emerging evidence supports low FODMAP and gluten-free diets as well as quality of diet.[4 31 32] Conversely, the Mediterranean diet could increase IBS symptoms. In SpA, low intakes of omega-3 and fibre as well as consumption of ultraprocessed foods were associated with higher SpA activity.[7] A recent meta-analysis found no proof of specialised diet as an effective non-pharmacological treatment for patients with SpA.[33] However, randomised trials on diet in SpA are lacking and future studies could bring new conclusions.[34] In the meantime, the French Society of Rheumatology has recently issued dietary recommendations for patients with rheumatic diseases.[35]

In addition to dietary recommendations, physical activity could have a beneficial impact on IBS symptoms[30] and chronic rheumatic diseases.[33] In our study, patients with IBS symptoms were less physically active than patients without IBS, with a similar sedentary behaviour, supporting the promotion of physical activity in patients with SpA.[36]

There are some limitations of this study. The cross-sectional study is not representative of the general SpA population as all patients were classified as ax-SpA and treated with biologics. Nor does this design permit the follow-up of patients with SpA, especially for diet and physical activity. In addition, some data were self-reported, particularly for the Rome IV criteria of IBS, fibromyalgia, physical activity and sedentary lifestyle, sleep, diet and food. We cannot exclude that some answers did not exactly reflect true patient behaviours and lifestyle. For IBS, other limitations include the lack of information about exclusion criteria for organic diseases or colonoscopy even if many publications recommend limited testing rather than exclusion strategy for IBS diagnosis.[24] Strengths of the study include its multicentric design, the number of patients and their consecutive inclusion, the quality of questionnaires with less than three missing data points, use of the updated Rome IV criteria for IBS, and the investigation of associated factors. A limitation of meta-analyses is related to publication bias. We cannot exclude that some investigations were not published because of unsatisfactory results or insufficient patient populations. However, we searched relevant abstracts in European and American conferences and trial registries, such as the International Prospective Register of Systematic Reviews, and found no other references. The number of included studies assessing IBS prevalence in patients with SpA was low and insufficient to draw strong conclusions, but our meta-analysis included more than 8000 patients which is substantial. Finally, the significant level of heterogeneity in figure 2 seemed to be linked to the study of Ozgocmen as there was no longer heterogeneity in meta-analysis when this study was removed. However, informations were insufficient in the EULAR abstract to detect the specificities of this study that could explain differences compared with the others studies.

CONCLUSIONS

The proportion of IBS symptoms is high in patients with SpA. The diagnosis must be considered in patients with gastrointestinal symptoms, especially in patients with anxiety and low physical activity. Patients with IBS also

tend to have more fibromyalgia, unemployment, higher disease activity, worse functional score and multiple lines of treatment, which could contribute to making the disease more difficult to manage.

Author affiliations
[1]Rheumatology, Clermont-Ferrand University Hospital, Rheumatology Department, UNH-UMR 1019, INRAe and University Clermont Auvergne, Clermont-Ferrand, France
[2]Rheumatology, Bordeaux University Hospital FHU ACRONIM, Bordeaux, France
[3]Rheumatology, University Hospital Lapeyronie, Montpellier, France
[4]Rheumatology, Toulouse University Hospital, Rheumatology Centre, Centre d'Investigation Clinique de Toulouse CIC1436, Inserm, Team PEPSS « Pharmacologie En Population cohorteS et biobanqueS » University of Toulouse 3, Toulouse, France
[5]Rheumatology, Limoges University Hospital, team CAPtuR, UMR Inserm 1308, University of Limoges, France, Limoges, France
[6]Rheumatology, Nîmes University Hospital, Nîmes, France
[7]UA11 Institut Desbrest d'Épidémiologie et de Santé Publique, University of Montpellier, INSERM, Montpellier, France

Acknowledgements The authors thank the patients who participated in this study, and the clinical research associates (Cathy Chen Wa, Angélique Fan). Acknowledgement of prior presentation: EULAR 2023 (Ann Rheum Dis 2023; 82, no Suppl 1 : 1710 11).

Contributors JB, TB, CA, JD, MV, CL, AR-W, M-ET, PV-S and AT contributed to the study conceptualisation. JB, CA, JD, MV, JL and CG-V contributed to investigation and data collection. JB, TB, CG-V, CL, AR-W, M-ET, PV-S, SM and AT contributed to the study by analysing data, drafting the article and revising it critically for important intellectual content, by giving a final approval of the version of the article to be published. All the coauthors of this manuscript have revised critically the manuscript and agree with its content. AT is responsible for the overall content as the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by CPP Sud Est II ID-RCB 2021-A00028-33. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Marie-Elise Truchetet http://orcid.org/0000-0001-8045-0180
Pascale Vergne-Salle http://orcid.org/0000-0003-0037-8540
Sylvain Mathieu http://orcid.org/0000-0003-2017-3227
Anne Tournadre http://orcid.org/0000-0002-5025-0214

REFERENCES

1 Stolwijk C, van Tubergen A, Castillo-Ortiz JD, *et al*. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:65–73.
2 Sundström B, Wållberg-Jonsson S, Johansson G. Diet, disease activity, and gastrointestinal symptoms in patients with ankylosing spondylitis. *Clin Rheumatol* 2011;30:71–6.
3 Mearin F, Lacy BE, Chang L, *et al*. Bowel disorders. *Gastroenterology* 2016;150:1393–407.
4 Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA* 2015;313:949–58.
5 Van Praet L, Van den Bosch FE, Jacques P, *et al*. Microscopic gut inflammation in axial spondyloarthritis: a multiparametric predictive model. *Ann Rheum Dis* 2013;72:414–7.
6 Breban M. Gut Microbiota and inflammatory joint diseases. *Joint Bone Spine* 2016;83:645–9.
7 Vergne-Salle P, Salle L, Fressinaud-Marie AC, *et al*. Diet and disease activity in patients with axial spondyloarthritis: spondyloarthritis and nutrition study (SANUT). *Nutrients* 2022;14:4730.
8 Rudwaleit M, Landewe R, van der Heijde D, *et al*. The development of assessment of spondyloarthritis International society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Annals of the Rheumatic Diseases* 2009;68:770–6.
9 Rudwaleit M, van der Heijde D, Landewé R, *et al*. The development of assessment of spondyloarthritis International society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777–83.
10 Girerd X, Hanon O, Anagnostopoulos K, *et al*. Assessment of antihypertensive compliance using a self-administered questionnaire: development and use in a hypertension clinic. *Presse Med* 2001;30:1044–8.
11 Monchablon C, Gondé H, Pouplin S, *et al*. Assessment of adherence to disease-modifying anti-rheumatic drugs in rheumatoid arthritis. *Clin Rheumatol* 2020;39:207–16.
12 Perrot S, Bouhassira D, Fermanian J. CEDR (Cercle D'Etude de la Douleur en Rhumatologie). development and validation of the fibromyalgia rapid screening tool (first). *Pain* 2010;150:250–6.
13 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
14 Garrett S, Jenkinson T, Kennedy LG, *et al*. A new approach to defining disease status in ankylosing spondylitis: the bath ankylosing spondylitis disease activity index. *J Rheumatol* 1994;21:2286–91.
15 Calin A, Garrett S, Whitelock H, *et al*. A new approach to defining functional ability in ankylosing spondylitis: the development of the bath ankylosing spondylitis functional index. *J Rheumatol* 1994;21:2281–5.
16 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
17 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
18 Sagard J, Olofsson T, Mogard E, *et al*. Pos0237 gut dysbiosis linked to worse disease status in axial spondyloarthritis. *Ann Rheum Dis* 2021;80:339.
19 Sagard J, Olofsson T, Mogard E, *et al*. Gut dysbiosis associated with worse disease activity and physical function in axial spondyloarthritis. *Arthritis Res Ther* 2022;24:42.
20 Keohane J, O'Mahony C, O'Mahony L, *et al*. Irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease: a real association or reflection of occult inflammation *Am J Gastroenterol* 2010;105:1789–94.
21 Jones GT, Mallawaarachchi B, Shim J, *et al*. The prevalence of fibromyalgia in axial spondyloarthritis. *Rheumatol Int* 2020;40:1581–91.
22 Fan A, Pereira B, Tournadre A, *et al*. Frequency of concomitant fibromyalgia in rheumatic diseases: monocentric study of 691 patients. *Semin Arthritis Rheum* 2017;47:129–32.
23 Valencia C, Fatima H, Nwankwo I, *et al*. A correlation between the pathogenic processes of fibromyalgia and irritable bowel syndrome in the middle-aged population: a systematic review. *Cureus* 2022;14:e29923.
24 Begtrup LM, Engsbro AL, Kjeldsen J, *et al*. A positive diagnostic strategy is noninferior to a strategy of exclusion for patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2013;11:956–62.
25 Asghar Z, Thoufeeq M, Kurien M, *et al*. Diagnostic yield of colonoscopy in patients with symptoms compatible with Rome IV functional bowel disorders. *Clin Gastroenterol Hepatol* 2022;20:334–41.

26 Campos JF, Resende GG, Ferrari M de L. Fecal calprotectin as a biomarker of microscopic bowel inflammation in patients with spondyloarthritis. *Int J Rheum Dis* 2023;26:175–6.
27 Klingberg E, Strid H, Ståhl A, *et al*. A longitudinal study of fecal calprotectin and the development of inflammatory bowel disease in ankylosing spondylitis. *Arthritis Res Ther* 2017;19:21.
28 Wang S, Wang Z, Shi H, *et al*. Faecal calprotectin concentrations in gastrointestinal diseases. *J Int Med Res* 2013;41:1357–61.
29 Freeman K, Taylor-Phillips S, Willis BH, *et al*. Test accuracy of faecal calprotectin for inflammatory bowel disease in UK primary care: a retrospective cohort study of the IMRD-UK data. *BMJ Open* 2021;11:e044177.
30 Radziszewska M, Smarkusz-Zarzecka J, Ostrowska L. Physical activity and supplementation in irritable bowel syndrome. *Nutrients* 2023;15:3662.
31 Dale HF, Lorentzen SCS, Mellin-Olsen T, *et al*. Diet-microbiota interaction in irritable bowel syndrome: looking beyond the low-FODMAP approach. *Scand J Gastroenterol* 2023;58:1366–77.
32 Altobelli E, Del Negro V, Angeletti PM, *et al*. Low-FODMAP diet improves irritable bowel syndrome symptoms: a meta-analysis. *Nutrients* 2017;9:940.
33 Gwinnutt JM, Wieczorek M, Rodríguez-Carrio J, *et al*. Effects of physical exercise and body weight on disease-specific outcomes of people with rheumatic and musculoskeletal diseases (RMDs): systematic reviews and meta-analyses informing the 2021 EULAR recommendations for lifestyle improvements in people with RMDs. *RMD Open* 2022;8:e002167.
34 Couderc M, Pereira B, Schaeverbeke T, *et al*. Glutenspa trial: protocol for a randomised double-blind placebo-controlled trial of the impact of a gluten-free diet on quality of life in patients with axial spondyloarthritis. *BMJ Open* 2020;10:e038715.
35 Daien C, Czernichow S, Letarouilly J-G, *et al*. Dietary recommendations of the French society for rheumatology for patients with chronic inflammatory rheumatic diseases. *Joint Bone Spine* 2022;89:105319.
36 Rausch Osthoff A-K, Niedermann K, Braun J, *et al*. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. *Ann Rheum Dis* 2018;77:1251–60.
37 Feng H-Y, Chan C-H, Chu Y-C, *et al*. Patients with ankylosing spondylitis have high risk of irritable bowel syndrome: a long-term nationwide population-based cohort study. *Postgrad Med* 2022;134:290–6.
38 Wallman JK, Mogard E, Marsal J, *et al*. Irritable bowel syndrome symptoms in axial spondyloarthritis more common than among healthy controls: is it an overlooked Comorbidity *Ann Rheum Dis* 2020;79:159–61.
39 Wang L, Song C, Wang Y, *et al*. Symptoms compatible with Rome IV functional bowel disorder in patients with ankylosing spondylitis. *Mod Rheumatol* 2023;33:823–9.
40 Williamson L, Dockerty JL, Dalbeth N, *et al*. Gastrointestinal disease and psoriatic arthritis. *J Rheumatol* 2004;31:1469–70.
41 Zhao SS, Radner H, Siebert S, *et al*. Comorbidity burden in axial spondyloarthritis: a cluster analysis. *Rheumatology (Oxford)* 2019;58:1746–54.
42 Zohar A, Cohen AD, Bitterman H, *et al*. Gastrointestinal comorbidities in patients with psoriatic arthritis. *Clin Rheumatol* 2016;35:2679–84.
43 Solmaz D, Avci O, Yildirim O, *et al*. FRI0206 prevalence of irritable bowel syndrome in patients with ankylosing spondylitis. *Ann Rheum Dis* 2015;74:499.
44 Ozgocmen S, Kaya A, Senel K, *et al*. Prevalence of gastrointestinal symptoms in patients with rheumatic diseases with particular reference to reflux type symptoms. *Ann Rheum Dis* 2010;69 Suppl 3:717. Available: https://scientific.sparx-ip.net/archiveeular/index.cfm