Comorbidity burden in axial spondyloarthritis: a cluster analysis.

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Abstract

Objectives. To examine how comorbidities cluster in axial spondyloarthritis (axSpA) and whether these clusters are associated with quality of life, global health and other outcome measures.

Methods. We conducted a cross-sectional study of consecutive patients meeting ASAS criteria for axSpA in Liverpool, UK. Outcome measures included quality of life (EQ5D), global health and disease activity (BASDAI). We used hierarchical cluster analysis to group patients according to 38 pre-specified comorbidities. In multivariable linear models, the associations between distinct comorbidity clusters and each outcome measure were compared, using axSpA patients with no comorbidities as the reference group. Analyses were adjusted for age, gender, symptom duration, BMI, deprivation, NSAID-use and smoking.

Results. We studied 419 patients (69% male, mean age 46 years). 255 patients (61%) had at least one comorbidity, among whom the median number was 1 (range 1 to 6). Common comorbidities were hypertension (19%) and depression (16%). Of 15 clusters identified, the most prevalent clusters were 1) hypertension-coronary heart disease and 2) depression-anxiety. Compared to patients with no comorbidities, the fibromyalgia-irritable bowel syndrome cluster was associated with an adverse patient-reported outcome measures; these patients reported 1.5-unit poorer global health (95%CI 0.01, 2.9), reduced quality of life (0.25-unit lower EQ5D; 95%CI -0.37, -0.12) and 1.8-unit higher BASDAI (95% CI 0.4, 3.3). Similar effect estimates were found for patient in the depression-anxiety cluster.

Conclusion. Comorbidity is common among axSpA patients. The two most common comorbidities were hypertension and depression. Patients in the depression-anxiety and fibromyalgia-IBS clusters reported poorer health and increased axSpA severity.

Keywords: axial spondyloarthritis, ankylosing spondylitis, comorbidity, multimorbidity, depression, fibromyalgia, cluster analysis.

Key messages:

1. Comorbidity is common among axial spondyloarthritis patients.

2. The most common comorbidity-clusters were those dominated by hypertension-coronary artery disease and depression-anxiety.

3. The depression-anxiety and fibromyalgia-irritable bowel syndrome clusters were associated with poorer patient-reported outcome measures.

Introduction

As life expectancy increases in many countries, healthcare professionals are seeing a growing number of patients living with multiple coexisting conditions. Healthcare delivery and clinical research have traditionally focused on individual diseases, but the paradigm is shifting towards holistic care, aligning healthcare services more closely with patient-needs [1–3]. Although the terms are often used interchangeably, “comorbidity” refers to coexisting morbidities in addition to an index disease, whereas “multimorbidity” is a more patient-centred concept that refers to the combination of any two chronic conditions [1].

Comorbidity is common among patients with chronic rheumatic diseases due to shared risk factors and sequelae of systemic inflammation. In rheumatoid arthritis (RA), increasing morbidity burden is associated with poorer quality of life, function and treatment response [4–6]. Comorbidity profiles are likely to differ in axSpA patients given their different demographic, younger age of onset and lower levels of systemic inflammation, but detailed descriptions are lacking.

Comorbidities have commonly been studied using count-based indices [7,8] that assign importance to individual conditions according to their impact on mortality [9,10]. However, health-related quality of life and global health are equally important outcomes in chronic diseases; these measures are well-aligned with the model of patient-centred care. Count-based approaches also do not account for relationships between morbidities, for instance between hypertension and cardiovascular disease. Cluster analysis is a statistical technique that allows assessment of which comorbidities commonly co-occur, and facilitates identification of patient-groups with specific clusters of disease most associated with poor quality of life, who may benefit from additional intervention.

The aim of this cross-sectional study was to 1) describe axSpA patients according to clusters of comorbidities and 2) assess whether these clusters are associated with quality of life, global health and other disease-specific outcome measures.

Methods

Study population

We conducted a cross-sectional study of consecutive axSpA patients attending a tertiary referral service in Liverpool, UK, between 2010 and 2017. Patients were included if they fulfilled the Assessment of Spondyloarthritis international Society (ASAS) criteria for axSpA [11]. The time at which all variables of interest were collected - the baseline - was defined as each patient's first clinical assessment at this referral centre, which was not necessarily the time of diagnosis. Data were retrospectively collected through review of medical records, including: age, gender, symptom duration, meeting modified New York criteria for ankylosing spondylitis (AS) [12], HLA-B27 status, peripheral joint involvement, uveitis, psoriasis, inflammatory bowel disease (IBD), body mass index (BMI), smoking status and medications. Socioeconomic status was measured

using a post-code-derived index of multiple deprivation; decile 1 relates to the top 10% most deprived areas and decile 10 the most affluent [13].

Comorbidity

We selected comorbidities according to previous work conducted in the UK population; this study included 40 chronic diseases based on recommendations for measurement of multiple chronic diseases, and on diseases considered important by the National Health Service [3]. Extra-articular manifestations of axSpA (uveitis, psoriasis and IBD) were considered as disease features rather than separate comorbidities, given that they share pathogenesis with, aid diagnosis of, and influence treatment for, axSpA [14,15]. We also excluded inflammatory polyarthropathy/connective tissue disease, changed "painful conditions" to fibromyalgia, and added osteoporosis because of its importance in chronic rheumatic musculoskeletal diseases [6]. Two clinicians independently reviewed clinical notes, medications, and correspondence from primary and secondary care physicians to determine the presence or absence of these 38 conditions for every patient. Some conditions (e.g. asthma and epilepsy) were only counted if currently treated, while other conditions were assumed to be present if indicative medications were used, for example diabetes mellitus (insulin or oral hypoglycaemics) and hypertension (antihypertensives without kidney or heart disease). A list of definitions used for each condition is provided in Supplementary Table 1.

Outcome measures

Primary outcome measures of interest were quality of life and global health. Quality of life was measured using the 3-level version of EuroQol (EQ5D-3L); this index assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) to generate a score anchored at 1 for 'best health state', and 0 for 'worst health state equalling death' [16]. Global health was assessed using the question "how would you describe your general state of health

today?" on a visual analogue scale (VAS), with 0 being best and 10 being worst. Other variables included ESR, CRP, fatigue ("How would you describe the level of fatigue/tiredness you have experienced?" VAS with 0 being no fatigue and 10 being worst ever experienced), and axSpA-specific outcome measures such as the Bath AS Disease Activity Index (BASDAI), spinal pain VAS and Bath AS Functional Index (BASFI).

Statistical analysis

Patient and disease characteristics were compared according to whether patients had isolated axSpA, or axSpA with at least one comorbidity. We then used agglomerative hierarchical cluster analysis to classify individuals into groups based on comorbidities; this is a commonly used method suited to binary variables [17,18]. The algorithm starts with individual patients and successively clusters them until the final group contains all patients. We used the Jaccard similarity coefficient as a measure of distance between binary variables, and average linkage, to define the average distance between data points in separate clusters [19]. All prevalent conditions in this cohort were included in the cluster analysis. The optimum number of clusters was determined by the pseudo-F statistic [20].

Patient characteristics of each comorbidity cluster were described. We then compared each cluster to patients with isolated axSpA (i.e. no comorbidity) using multivariable linear models for each outcome measure as the dependent variable, and cluster as a dummy independent variable. Small clusters (less than 5 patients) were combined into one cluster for regression modelling. All models were adjusted for age, gender, symptom duration, smoking status, BMI, social deprivation and current NSAID-use. ESR and CRP were log-transformed prior to regression. We did not correct for multiple comparisons, since the outcome variables were not independent.

Primary analyses were performed with no imputation for missing data; we additionally performed sensitivity analyses using multiple imputation by chained equations [21]. We also repeated the cluster analysis only using comorbidities that were prevalent in at least two patients to test the stability of cluster formation. Statistical analyses were performed using Stata version 13.

Results

The study included 421 patients with established axSpA. Sufficient clinical data were available for 419 patients. The cohort was predominantly male (69%) with a mean age of 45.5 years (SD±14.3). 82% fulfilled the modified New York criteria for AS. HLA-B27 was available in 269 and of these 59% were positive. Two patients were prescribed TNF inhibitors and 17% were currently using NSAIDs at baseline.

At least one comorbidity was seen in 255 (61%) axSpA patients, among whom the median number of conditions was 1 (range 1 to 6; histogram shown in supplementary figure 1). Compared to those with isolated axSpA, patients with comorbidity were older (48.9 vs 40.4 years, P<0.001) and reported impaired quality of life (P<0.001), global health (P=0.005), fatigue (P=0.021), BASDAI (P=0.011), spinal pain (P=0.029) and BASFI (P<0.001), but did not have significantly different ESR or CRP levels (table 1). The most common comorbidities were hypertension (19%), depression (16%) and dyspepsia (11%) (prevalence of each comorbidity is shown in supplementary table 2).

<u>Cluster analysis</u>

No patients had dementia, hearing loss, bronchiectasis or anorexia. The diagram from cluster analysis of the remaining 34 conditions is shown in figure 1. The pseudo-F statistic identified 15 as the optimum number of clusters (dotted horizontal line in figure 1), labelled in numerical order from left to right. Clustering generally occurred at low levels of similarity.

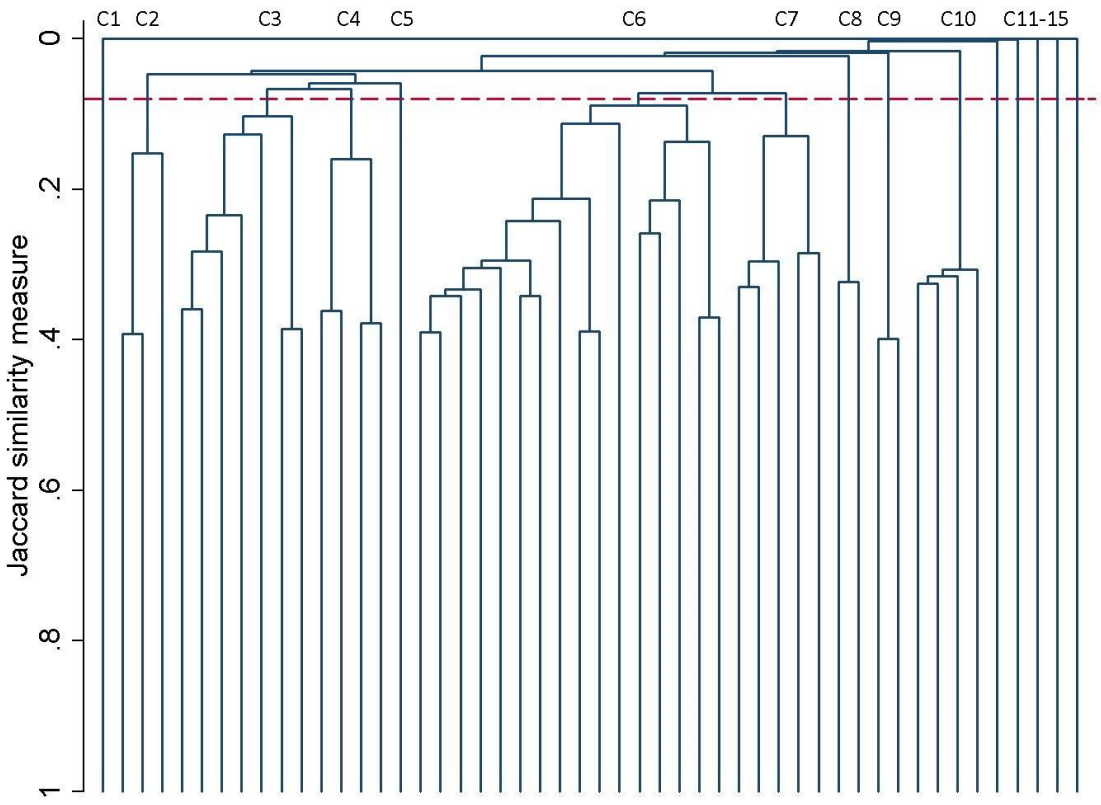

Figure 1. Diagram ("dendrogram") from cluster analysis of 419 patients and 34 comorbidities. Zero on the y-axis indicates no similarity between clusters. From the bottom, clusters progressive joined (at levels of similarity shown at their union) until a single cluster is formed at the top. The pseudo-F statistic determined the optimum number of clusters, indicated by where the dotted horizontal line intersects with the branches. Clusters are labelled 1 to 15 from left to right based on the dominant comorbidity in the cluster (C1: isolated axSpA, C2: dyspepsia, C3: depression-anxiety, C4: fibromyalgia-irritable bowel syndrome, C5: anxiety, C6: hypertension, C7: osteoporosis-alcohol problems, C8: thyroid disorders, C9: other substance misuse, C10: asthma, C11: atrial fibrillation, C12: chronic sinusitis, C13: blind or low vision, C14: multiple sclerosis, C15: learning disability.)

Six clusters were formed at near-zero similarity, indicating relative distinctness. Cluster 1 (C1, n=164) consisted of patients with isolated axSpA with no comorbidities. C11 had two patients with atrial fibrillation, one of whom also had Parkinson's disease. C12 to C15 contained only one patient each with the following conditions: chronic sinusitis, blindness or low vision, multiple sclerosis, and learning disability.

All other clusters were generally dominated by 1 to 2 comorbidities with varying number of other less frequent conditions (table 2). C2 (n=40) was predominantly characterised by patients with concurrent dyspepsia (94%). Clusters 3, 4 and 5 were similar to each other: C3 (n=84) patients most commonly had depression (83%) and anxiety (14%); C4 (n=35) patients frequently had fibromyalgia (72%) and irritable bowel syndrome (IBS, 56%); C5 had only 4 patients, all with anxiety. Clusters 3 and 5 were combined for further analysis since they both include anxiety and would merge in the next clustering (figure 1).

C6, the largest comorbidity cluster (n=88), was predominantly characterised by hypertension (82%) and coronary heart disease (CHD, 24%). C7 (n=38) commonly had osteoporosis (74%) and alcohol problems (47%). CHD and other cardiovascular diseases feature in both groups, explaining their proximity in figure 1.

C8 (thyroid disease), C9 (other psychoactive substance misuse) and C10 (asthma) were largely unrelated to other clusters and each were dominated by a single disease.

The fibromyalgia-IBS cluster and thyroid disorders cluster were predominantly female and least frequently had positive HLA-B27 status or met criteria for AS (table 3). Patients in the hypertension-CHD cluster and alcohol problems-osteoporosis cluster were the oldest and had higher prevalence of uveitis. Current NSAID use was lowest among those in the dyspepsia and other substance misuse clusters. Current smoking was highest among those with other substance misuse and lowest among asthmatics.

Associations between patient-clusters and outcome measures

In multivariable models, we found that patients in the depression-anxiety clusters (C3 and C5), and fibromyalgia-IBS cluster (C4) reported poorer quality of life, global health, fatigue and axSpA-specific indices, compared to patients with isolated axSpA (table 3). For instance, EQ5D was lower by 0.25 units in both clusters compared to patients with isolated axSpA. Disease

activity was higher by 0.9 units in the depression-anxiety cluster and 1.8 units in the fibromyalgia-IBS cluster. There were no overall differences in ESR or CRP, except patients with concurrent dyspepsia had 0.5mg/dl lower CRP than those with isolated axSpA (P=0.008); this was not reproduced in sensitivity analyses with imputed missing data (supplementary table 3).

Patients in the largest cluster (hypertension-CHD) had statistically similar outcome measures as those without comorbidity. Patients in C7 (alcohol problems-osteoporosis) reported worse global health and function with similar effect sizes to the depression-anxiety cluster, although this was not statistically significant. Patients with other psychoactive substance misuse reported significantly worse global health by 1.6 units; they also showed a trend of having higher BASDAI.

Sensitivity analysis using multiple imputation for missing data produced similar results (supplementary table 3). Cluster analysis using only morbidities prevalent in at least two patients showed similar clusters (supplementary table 4).

Discussion

In this cross-sectional study, we found that comorbidity was common among patients with axSpA. Several comorbidity clusters were identified, each with only a small number of predominant conditions reflecting the overall low number of conditions among those with comorbidity. Depression-anxiety and hypertension-coronary heart disease formed the most common disease clusters. All comorbidities within the clusters were compatible with shared patho-aetiological mechanisms. Patients in the depression-anxiety clusters and fibromyalgia-IBS clusters reported worse quality of life, global health, fatigue, disease activity, pain and functional impairment. Our data did not provide evidence that any comorbidity clusters were significantly associated with ESR or CRP.

The prevalence of individual morbidities in this study were consistent with those reported in the recent worldwide ASAS-COMOSPA cohort which had similar age and gender distributions,

although ASAS-COMOSPA included patients with both axial and peripheral SpA [22]. The proportion with at least one comorbidity was higher in our cohort (61% vs 51%), but this is likely due to the larger number of conditions we included. Our cohort had a greater proportion of current smokers (35% vs 29%), which may explain the higher prevalence of coronary heart disease (6% vs 1%). Interestingly, the prevalence of hypertension in our cohort was lower (19% vs 34%). ASAS-COMOSPA included single-measurement blood pressure thresholds in their definition of hypertension, which may lead to over-diagnosis [23]. Osteoporosis was also less common (6% vs 13%), which may be under-documented since a previous study [24] found a 9% prevalence of osteoporosis in a subgroup of this cohort (defined by T-score≤-2.5, as was in ASAS-COMOSPA).

Depression and fibromyalgia were not described in ASAS-COMOSPA. The prevalence of depression reported in our cohort was very similar to results from a prior meta-analysis in axSpA (16% vs 15%) [25]. Fibromyalgia (5%) was likely under-diagnosed, compared to prevalence reported using meta-analysis (13%) and found by screening questionnaire in the British Society for Rheumatology Biologics Register for AS (21%) [26,27]. Associations between clusters dominated by these two conditions and patient-reported outcome measures were similar in magnitude to those reported in other studies [25–27,7]. In previous meta-analysis, depression was additionally associated with objective measures such as ESR and the Bath AS metrology index [25]. Baseline depression has also been shown to reduce treatment response in RA [28] but further studies are needed in axSpA.

The prevalence of conditions included in our study has also been described in the general UK population and an RA cohort [3,6]. We cannot directly compare prevalence figures, since these studies identified conditions using diagnostic codes; results were nevertheless similar apart from the notably higher prevalence of depression in our axSpA cohort (16% compare with 5% in

RA and 8% in the UK population). AxSpA is a chronic condition with early age at disease onset, which may impact psychological well-being more than diseases that develop in later life.

Differences in patient characteristics across the comorbidity clusters were consistent with existing literature. Both fibromyalgia [29] and thyroid disorders [30] were more prevalent among females which, given these clusters were predominantly female, explains the higher prevalence of peripheral joint involvement and lower prevalence of radiographic disease and HLA-B27 positivity [31]. The prevalence of cardiovascular disease and osteoporosis both increase with age, as does the risk of uveitis [32].

A key strength of this study was the range and number of comorbidities, selected based on their importance in the general population rather than their relationship to the index disease. The latter approach is common among studies of comorbidity, many of which include diseases based on prevalence or availability of data and may overlook important conditions. We extracted comorbidity data from diagnoses documented in clinical notes, which are likely more accurate than those obtained from patient-recall or administrative diagnostic codes alone. Several sources of clinical information were reviewed to reduce the possibility of missing diagnoses.

Severe axSpA is likely to increase the risk of depression, and depression is known to impact the experience and reporting of pain [25,33]. We cannot draw conclusions on the direction of causation due to the cross-sectional design of this study. However, our aim was to identify patient-clusters that may benefit from additional management. Our results may have limited generalisability to all axSpA cohorts, since this study was conducted at a specialist centre that served an area with high levels of deprivation. Since this study used data from each patient's first clinic visit, the numbers using TNF inhibitors was low. This may also explain the low prevalence of current NSAID-use; referral may be driven by lack of response to previously prescribed, and thus discontinued, NSAIDs. We did not have data on cumulative NSAID exposure, which would be more relevant for comorbidities. We did not correct for multiple

testing since all outcomes measured the same underlying construct - disease severity - and were not completely independent. Although consistent associations across several outcomes are reassuring, care should be taken when interpreting isolated significant results (such as the association between global health and other substance misuse). Lastly, certain objective outcome measures were lacking in this study: most of our data were collected from before the introduction of the AS disease activity score (ASDAS), and BASMI was not routinely measured. We also did not have any measure of severity for each comorbid condition.

In other chronic rheumatic conditions, such as gout, cluster analyses of comorbidities included conditions that could be considered part of the disease process [17]. For instance dyslipidaemia, hypertension, obesity and hyperuricaemia are components of the metabolic disease pathway. Including these high-prevalence disease features/manifestations would dominate and impair clustering of rarer comorbidities. This was an additional reason for excluding extra-articular manifestations from our analyses. However, it would be interesting to repeat our analysis in older axSpA cohorts with a higher comorbidity burden.

In conclusion, comorbidity is common among patients with axSpA which was frequently driven by concurrent cardiovascular and mental-health disorders. Patients with comorbid depression-anxiety and fibromyalgia-IBS reported worse overall quality of life, global health, fatigue and axSpA disease activity. These results highlight the importance of comorbidities and will inform healthcare professionals in the delivery more patient-centred management of axSpA.

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Table 1. Patient and disease characteristics of patients according to whether they have isolated axial spondyloarthritis (axSpA) or axSpA with comorbidities.

	Isolated axSpA n=164	axSpA with comorbidities n=255	P-value
Age, mean (SD) years	40.0 (12.9)	49.0 (14.1)	<0.001
Male	114 (70%)	177 (69%)	0.980
Modified New York criteria for AS	135 (82%)	210 (82%)	0.990
HLA-B27 positive*	66 (62%)	92 (56%)	0.340
Age at symptom onset, mean (SD) years	25.7 (0.8)	28.8 (0.8)	0.008
Symptom duration, median (IQR) years	10.6 (3.8 to 20.1)	18.9 (8.4 to 30.2)	<0.001
BMI, mean (SD)	27.4 (5.2)	28.7 (5.9)	0.045
Deprivation index, median (IQR)**	2.0 (1.0 to 6.0)	2.0 (1.0 to 5.0)	0.290
Current smoker	53 (34%)	84 (35%)	0.450
Ex-smoker	23 (15%)	46 (19%)	
Never smoked	78 (51%)	108 (45%)	
NSAIDs	31 (19%)	40 (16%)	0.392
Peripheral joint involvement	40 (26%)	73 (30%)	0.480
Uveitis	39 (25%)	61 (24%)	0.880
Psoriasis	33 (21%)	40 (16%)	0.180
IBD	19 (12%)	21 (8%)	0.190
Disease severity measures:			
EuroQoL, median (IQR)	0.6 (0.1 to 0.8)	0.5 (-0.02 to 0.7)	<0.001
Global health, median (IQR)	4.8 (2.3 to 6.4)	5.2 (3.5 to 7.1)	0.005
Fatigue, median (IQR)	5.1 (3.0 to 7.1)	6.3 (3.8 to 7.7)	0.021
BASDAI, median (IQR)	5.6 (3.6 to 7.2)	6.4 (3.9 to 8.1)	0.011
Spinal pain, median (IQR)	6.0 (3.0 to 8.0)	7.0 (4.0 to 8.0)	0.029
BASFI, median (IQR)	4.5 (2.2 to 6.7)	6.8 (4.1 to 8.4)	<0.001
ESR (mm/hr)	10.0 (5.0 to 27.0)	13.0 (5.0 to 29.0)	0.067
CRP (mg/L)	4.0 (1.0 to 17.0)	5.0 (1.0 to 12.0)	0.800

*HLA-B27 available for 269 patients.
**Index of multiple deprivation deciles, with 1 representing the top 10% most deprived areas and 10 the most affluent.
Fatigue and global health were single-question visual analogue scales, ranging from 0 (worst) to 10 (best).
EuroQoL, 5-domain quality of life measure; BASDAI, Bath AS disease activity index; BASFI, Bath AS Functional index.

Table 2. Prevalence of comorbidities in each of 11 patient clusters with more than 1 patient.											
Cluster	1	2	3	4	5	6	7	8	9	10	11
Number of patients	164	31	50	18	4	88	19	9	16	14	2
Hypertension			1 (2)	3 (17)		**72 (82)**	4 (21)	1 (11)			
Depression		3 (10)	**42 (84)**	4 (22)		15 (17)			1 (6)	1 (7)	
Anxiety and other neuroses		2 (6)	**7 (14)**		**4 (100)**	2 (2)					
Schizophrenia or bipolar						3 (3)			1 (6)	1 (7)	
Osteoporosis		1 (3)	5 (10)				**14 (74)**			1 (7)	
Alcohol problems		1 (3)	1 (2)	1 (6)		6 (7)	**9 (47)**				
Other psychoactive substance misuse						1 (1)	1 (5)		**16 (100)**		
Chronic liver disease				1 (6)		1 (1)	1 (5)				
Viral hepatitis			1 (2)			1 (2)			1 (6)		
Migraine			6 (12)					1 (11)		1 (7)	
Epilepsy*		1 (3)	3 (6)							1 (7)	
Thyroid disorders			1 (2)			3 (3)		**9 (100)**			
Diabetes			4 (8)			15 (17)	2 (11)				
Atrial fibrillation						3 (3)					2 (100)
Coronary heart disease			1 (2)			**21 (24)**	1 (5)			1 (7)	
Heart failure						2 (2)	1 (5)				
Stroke and TIA			1 (2)			4 (5)	1 (5)				
Peripheral vessel disease							1 (5)				
COPD			3 (6)			12 (14)	1 (5)				
Asthma*						3 (3)	1 (5)			**14 (100)**	
Chronic sinusitis						1 (1)					
Prostate disorders						5 (6)					
Fibromyalgia			2 (4)	**13 (72)**	1 (25)	2 (2)		1 (11)			
Irritable bowel syndrome			1 (2)	**10 (56)**		3 (3)				1 (7)	
Diverticular disease			1 (2)			4 (5)					
Constipation*			1 (2)			3 (3)					
Cancer**			4 (8)								
Chronic kidney disease		3 (10)				6 (7)	1 (5)				
Dyspepsia*		**29 (94)**	1 (2)	3 (17)					2 (13)		
Glaucoma						13 (15)					
Parkinson's disease											1 (50)

*Currently treated. **Cancer diagnoses in the past 5 years. Cells with zero prevalence were left empty for clarity. Bold text highlights dominant morbidities in each cluster. Clusters 12, 13, 14 and 15 were omitted: each had only 1 patient (chronic sinusitis, blind or low vision, multiple sclerosis, and learning disability). TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary diseases.

Table 3. Differences in baseline characteristics compared between each comorbidity cluster and axial spondyloarthritis patients with no comorbidity.											
Cluster		1	2	3 and 5	4	6	7	8	9	10	11 to 15
Disease(s)		Isolated axSpA	Dyspepsia	Anxiety and/or depression	Fibromyalgia and/or IBS	Hypertension and/or CHD	Alcohol problems and/or osteoporosis	Thyroid	Other substance misuse	Asthma	Other rare conditions
n		164	31	54	18	88	19	9	16	14	6
Age, years		40.0 (12.9)	47.9 (13.8)	44.1 (11.1)	45.9 (10.6)	56.5 (12.2)	58.0 (8.6)	50.6 (14.7)	31.6 (8.1)	37.7 (12.0)	38.3 (19.4)
Male		114 (70%)	21 (68%)	36 (67%)	7 (39%)	64 (73%)	16 (84%)	2 (22%)	16 (100%)	9 (64%)	6 (100%)
Modified New York criteria for AS		135 (82%)	26 (84%)	41 (76%)	12 (67%)	81 (92%)	15 (79%)	5 (56%)	14 (88%)	11 (79%)	5 (83%)
HLA-B27 positive*		66 (62%)	8 (44%)	17 (47%)	6 (43%)	31 (66%)	7 (70%)	2 (33%)	9 (64%)	6 (50%)	6 (100%)
BMI		27.4 (5.2)	28.2 (4.6)	29.2 (6.3)	29.7 (8.9)	29.2 (5.7)	30.0 (4.7)	28.4 (2.2)	24.4 (5.0)	29.9 (5.8)	24.5 (6.0)
Deprivation index**		2.0 (1.0, 6.0)	2.0 (1.0, 5.0)	2.0 (1.0, 4.0)	1.5 (1.0, 6.0)	2.0 (1.0, 5.0)	5.0 (1.0, 6.0)	3.5 (1.0, 7.5)	1.5 (1.0, 4.0)	1.0 (1.0, 5.0)	3.5 (1.0, 7.0)
Smoking	Current	53 (34%)	12 (44%)	23 (43%)	4 (25%)	22 (27%)	6 (33%)	1 (13%)	15 (94%)	1 (8%)	0
	Ex	23 (15%)	5 (19%)	8 (15%)	4 (25%)	22 (27%)	4 (22%)	1 (13%)	0	1 (8%)	1 (20%)
	Never	78 (51%)	10 (37%)	22 (42%)	8 (50%)	39 (47%)	8 (44%)	6 (75%)	1 (6%)	10 (83%)	4 (80%)
NSAIDS		31 (19%)	2 (6%)	12 (22%)	3 (17%)	13 (15%)	4 (21%)	2 (22%)	1 (6%)	2 (14%)	1 (17%)
Peripheral joint involvement		40 (26%)	10 (34%)	15 (28%)	7 (41%)	19 (23%)	7 (37%)	4 (44%)	3 (20%)	6 (43%)	2 (33%)
Uveitis		39 (25%)	4 (14%)	6 (11%)	6 (35%)	33 (38%)	8 (42%)	1 (11%)	1 (6%)	2 (14%)	0
Psoriasis		33 (21%)	5 (17%)	11 (21%)	2 (12%)	12 (14%)	2 (11%)	3 (33%)	3 (19%)	2 (14%)	0
IBD		19 (12%)	3 (10%)	5 (9%)	3 (18%)	7 (8%)	1 (5%)	0	0	1 (7%)	1 (17%)

Data shown as mean (SD), median (interquartile range) or n (%).
*HLA-B27 available for 269 patients.
**Index of multiple deprivation deciles, with 1 representing the top 10% most deprived areas and 10 the most affluent.

Table 4. Differences in outcome measures compared between each comorbidity cluster and axial spondyloarthritis patients with no comorbidity.

Cluster	1	2	3 and 5	4	6	7	8	9	10	11 to 15
Disease(s)	Isolated axSpA	Dyspepsia	Anxiety and/or depression	Fibromyalgia and/or IBS	Hypertension and/or CHD	Alcohol problems and/or osteoporosis	Thyroid	Other substance misuse	Asthma	Other rare conditions
n	164	31	54	18	88	19	9	16	14	6
EuroQoL	reference	-0.07 (-0.25, 0.10)	-0.25 (-0.37, -0.12)	-0.25 (-0.47, -0.03)	-0.03 (-0.16, 0.10)	0.06 (-0.22, 0.33)	0.14 (-0.19, 0.46)	-0.20 (-0.41, 0.02)	-0.07 (-0.37, 0.23)	-0.15 (-0.57, 0.27)
Global health	reference	0.1 (-1.0, 1.3)	0.9 (0.1, 1.7)	1.5 (0.01, 2.9)	0.3 (-0.5, 1.2)	1.4 (-0.4, 3.3)	0.9 (-1.2, 3.0)	1.5 (0.1, 2.9)	0.7 (-1.2, 2.7)	0.7 (-2.0, 3.4)
Fatigue	reference	0.7 (-0.6, 1.9)	1.1 (0.2, 2.0)	1.9 (0.3, 3.5)	0.6 (-0.3, 1.5)	0.2 (-1.8, 2.2)	-0.8 (-3.1, 1.5)	0.3 (-1.2, 1.9)	-0.5 (-2.6, 1.6)	-0.02 (-3.0, 2.9)
BASDAI	reference	-0.5 (-1.6, 0.7)	0.9 (0.1, 1.8)	1.8 (0.4, 3.3)	0.4 (-0.5, 1.2)	-0.2 (-2.0, 1.6)	-1.1 (-3.3, 1.0)	1.2 (-0.1, 2.5)	0.6 (-1.3, 2.6)	1.7 (-1.0, 4.5)
Spinal pain	reference	-0.6 (-1.9, 0.7)	1.2 (0.3, 2.2)	2.3 (0.6, 4.0)	0.4 (-0.6, 1.5)	0.3 (-1.8, 2.3)	0.4 (-2.1, 2.9)	0.8 (-0.8, 2.4)	-0.2 (-2.7, 2.2)	1.8 (-1.4, 5.0)
BASFI	reference	-0.6 (-1.9, 0.6)	1.9 (1.0, 2.9)	2.3 (0.8, 3.9)	0.7 (-0.3, 1.7)	1.7 (-0.3, 3.7)	-0.5 (-3.0, 2.1)	0.7 (-0.7, 2.2)	1.0 (-1.6, 3.5)	1.8 (-1.1, 4.8)
ESR*	reference	-0.34 (-0.84, 0.15)	-0.02 (-0.40, 0.35)	-0.26 (-0.91, 0.38)	-0.26 (-0.64, 0.11)	-0.02 (-0.78, 0.74)	-0.51 (-1.47, 0.45)	0.35 (-0.25, 0.95)	-0.42 (-1.30, 0.46)	-0.07 (-1.30, 1.16)
CRP*	reference	-0.80 (-1.38, -0.21)	-0.04 (-0.49, 0.41)	-0.05 (-0.82, 0.72)	-0.38 (-0.83, 0.07)	-0.53 (-1.49, 0.42)	-0.02 (-1.17, 1.13)	-0.13 (-0.85, 0.59)	-0.49 (-1.54, 0.55)	-0.21 (-1.68, 1.26)

Data shown as regression coefficients (95% confidence interval). For EuroQol, higher values indicate better quality of life (e.g. cluster 4 had 0.25-unit poorer QoL). For all other measures, higher values indicate more severe disease (e.g. cluster 4 had 1.5-unit poorer global health).
Coefficients derived from models using each outcome measure as independent variable, and cluster as a dummy variable with isolated axSpA as the reference group.
Models adjusted for age, gender, symptom duration, deprivation, current NSAID-use and smoking status.
Global health and fatigue were measured by single-item questions with 0 as best/no fatigue and 10 as worst.
*ESR and CRP were log-transformed using Ln(ESR) and Ln(CRP+1).
EuroQoL, 5-domain quality of life measure; BASDAI, Bath AS disease activity index; BASFI, Bath AS Functional index; IBS, irritable bowel syndrome; CHD, coronary heart disease.