Multimorbidity is Common in Axial Spondyloarthropathy and is Associated with Worse Disease Outcomes: Results from the ASRI cohort

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Key Indexing Terms:

Spondyloarthropathies; Axial Spondyloarthopathy; Multiple chronic conditions; Outcome measures.

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Funding

ASRI is supported by an unrestricted grant from Pfizer Pharmaceuticals and AbbVie Pharmaceuticals. GF is a recipient of the Bresnihan-Molloy Scholarship from the Royal College of Physicians of Ireland, funded by AbbVie pharmaceuticals. The funders had no role in the design of the study, collection of the data, analysis and interpretation of the data or any part of manuscript preparation.

Conflict of interest: The authors declare no conflicts of interest.

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Running head: Multimorbidity in Axial Spondyloarthopathy

ABSTRACT

Objective

Multimorbidity, the co-existence of 2 or more conditions in an individual, is associated with morbidity and mortality in the general population. This study aims to describe the prevalence of multimorbidity in axial spondyloarthropathy (axSpA) and assess its association with disease outcome measures.

Methods

This cross-sectional study was conducted within the Ankylosing Spondylitis Registry of Ireland (ASRI) cohort. Structured standardised assessment was performed. Multimorbidity was considered as the presence of at least 1 physician-diagnosed chronic condition (excluding extra-articular manifestations) in addition to axSpA. Validated outcome measures were collected: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), Health Assessment Questionnaire (HAQ), AS Quality of Life (ASQoL), Bath AS Metrology Index (BASMI). Adjusted multiple regression was performed to investigate the association between multimorbidity and disease outcomes.

Results

A total of 734 patients from 12 centres were included: 77% male, mean (SD) age 45 (12) years. Of the cohort, 55% (n=403) are multimorbid. Multimorbid patients are significantly ($p<0.01$) older than axSpA-only patients (50 (12) v 40 (11) years). Obesity is the most prevalent chronic condition, affecting 27%. Multimorbid patients have more severe disease than patients with axSpA only. After adjusting for confounders, multimorbidity was associated with higher BASDAI (ß=0.7, 95% CI 0.34 to 1.05), BASMI (ß=0.45, 95% CI 0.09 to 0.80), BASFI (ß=0. 5, 95% CI 0.23 to 0.78), HAQ (ß=0.07, 95% CI 0.00 to 0.13) and ASQoL (ß=0.87, 95% CI 0.28 to 1.46).

Conclusion

Multimorbidity is prevalent in axSpA and is associated with more severe disease.

INTRODUCTION

The dramatic increase in life expectancy of modern times is an important accomplishment (1, 2). Population growth has been accompanied by many challenges (3, 4), including projected increases in age-related expenditure and associated economic burden. A simple aspiration to live longer is no longer the goal. A delayed onset of morbidity and functional decline, termed "compression of morbidity" (5), is now the ambition, where people live longer but with less chronic disease. Unfortunately, it appears that old age is instead accompanied by a greater disease burden (6), namely noncommunicable diseases, now the biggest threat to mortality worldwide (7).

In order to cope with ageing populations, health systems must adapt (3). Current clinical practise guidelines focus on individual co-morbidities, without giving adequate guidance on managing patients with multiple chronic conditions (8). However, with pressure to delay the onset of functional decline and facilitate people to remain effective members of society for longer, swapping the concept of co-morbidity for multimorbidity is needed (8). Multimorbidity shifts our focus from a narrow view of considering each condition in isolation to a more holistic approach, whereby the patient is considered as the centre of care and all aspects of their condition are considered together (8, 9).

Although the definition can vary, multimorbidity is widely accepted as the presence of 2 or more chronic conditions in the one individual, without specifying the index disease (10). Multimorbidity estimates range from 13-95%, with prevalence increasing with age (11, 12). Multimorbid patients have increased mortality, more disability, worse quality of life and greater utilisation of healthcare resources (13-15); in some cases, 25% of the population accounts for more than 50% of health utilisation (15). Musculoskeletal disease (MSD) is common in multimorbidity patterns (16) and serves to intensify the impact (17, 18).

In rheumatoid arthritis (RA), 62-65% of patients are multimorbid (19, 20). Multimorbid RA patients have worse physical function (9) and lower rates of disease control (21).

A growing body of work has examined the burden of co-morbidities in axSpA (22-26). Mortality is known to be increased in axSpA patients compared to age- and sex-matched controls (25-27). The recent Assessment of SpondyloArthritis Society (ASAS) – COMOSPA study (23) has outlined the comorbidity profile of axSpA patients, particularly highlighting the frequency of osteoporosis and peptic ulcer disease. Cardiovascular-related co-morbidity is also more prevalent in AS (28, 29). Co-morbidity adds to the burden of disease in SpA patients, adversely influencing physical function and quality of life (24). ASAS/European League Against Rheumatism (EULAR) recommendations for management of axSpA suggest that treatment should be tailored to take comorbidities into consideration (30), but no specific guidelines are available. However, little is known about the burden of multimorbidity in axSpA, despite recognition that better knowledge of multimorbidity is crucial to allow sustainable models of care to be established (8). In modern society, increasing emphasis is being placed on compression of morbidity, therefore it is important to understand the impact of multimorbidity in axSpA patients. To our knowledge, there is no literature looking at the prevalence of multimorbidity and associated relationships in patients with axSpA.

Therefore, the aims of this study are to determine:

1. prevalence of multimorbidity within a well-characterised real-life axSpA cohort
2. relationships between multimorbidity and disease outcomes.

MATERIALS AND METHODS

ASRI study design & patient recruitment

This study was conducted within the framework of the Ankylosing Spondylitis Registry of Ireland (ASRI) cohort. ASRI is a large observational cross-sectional multicentre cohort study, which is ongoing. It was established in 2013, with the primary objective to measure the burden of axSpA disease in the Irish population and identify predictors of poor disease outcome.

Consecutive patients are invited to partake in ASRI if they have a clinical diagnosis of axSpA, made by a Rheumatologist, and have attended secondary or tertiary care in the preceding 3 years. Patients are excluded if they have cognitive or other impairment which prohibits informed consent. Each centre has a designated sub-investigator with responsibility for local oversight. Accuracy of the data collected is monitored quarterly by PG. The primary investigator (FOS) has responsibility for overall oversight of the database. To date, 12 centres in Ireland have recruited patients and contributed data to ASRI.

Written informed consent is obtained from all patients. Ethical approval was originally obtained from the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (REC reference: 2013/21/06) and was subsequently approved in each participating centre.

Data collection

A trained study investigator collected data according to a standard protocol in a structured face-to-face visit. The medical record was reviewed as required to obtain information not available directly from the patient. The following data was entered into an electronic centralised report form:

- Demographics: age, sex, ethnicity, marital status, employment status, alcohol intake, smoking status (current/past/never), family history of SpA (AS, AxSpA, psoriasis or psoriatic arthritis).
- Disease characteristics: age of symptom onset, duration of disease, delay to diagnosis, history of extra-articular manifestations (EAM) (uveitis, psoriasis, inflammatory bowel disease), other SpA features (enthesitis, dactylitis, peripheral arthritis), current and previous treatment (non-steroidal anti-inflammatories (NSAIDs), methotrexate, sulfasalazine, biologics), human leukocyte antigen (HLA)-B27 status, highest recorded erythrocyte sedimentation rate (ESR), current ESR (measured on the day), highest recorded C-reactive protein (CRP), current CRP (measured on the day).
- Morbidities: considered present if patient had history of physician diagnosis of any of the following conditions known to be prevalent in SpA (23): ischaemic heart disease, cerebrovascular disease, hypertension, hyperlipidaemia, diabetes mellitus, peptic ulcer disease, tuberculosis, osteoporosis, depression, cancer (melanoma, non-melanoma skin cancer, lung, breast, gastrointestinal, genitourinary, lymphoma, haematological, other). Additionally obesity (recorded as a body mass index (BMI) of greater than 30 mg/kg^2, as per the WHO criteria, based on the weight and height measurements taken by the investigator during the assessment) and alcohol excess (considered as an alcohol consumption of greater than 21 units in men and 14 units in women, as per national guidelines (31), and was based on the patient's self-report of alcohol consumption) were collected. Patient medical records were used as required to confirm the presence or absence of each of these co-morbidities. EAMs were not considered as additional morbidities.
- Physical examination: tragus-to-wall, cervical rotation, chest expansion, modified Schober test, lumbar side flexion, intermalleolar distance – all performed according to standardised technique (32); current blood pressure, height (measured in centimetres), weight (measured in kilograms), waist circumference (measured in cm).

- Dual-energy x-ray absorptiometry (DXA): most recent DXA result was obtained (if performed) and osteoporosis defined according to the World Health Organisation (WHO) (33).

Outcome measures

The following validated patient-reported outcomes were collected:

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI): measured on a scale of 0-10; higher scores indicate more severe disease (34).
- Bath AS Functional Index (BASFI): measured on a scale of 0-10; higher scores indicate worse function (35).
- Health Assessment Questionnaire (HAQ): assessed on a scale of 0-3; 0 indicates no disability and 3 indicates large burden of disability (36).
- AS Quality of Life (ASQoL): assessed on a scale of 0-18; higher scores indicate worse QoL (37).

Bath AS Metrology Index (BASMI) assessed spinal mobility on a scale of 0-10; higher scores indicate worse spinal mobility (32).

Multimorbidity

Morbidity is defined as the presence of a chronic condition in a patient. We defined multimorbidity as the presence of at least two chronic conditions in one person (10, 38). Severity of multimorbidity was assessed by counting the number of chronic conditions in addition to axSpA present in an individual (20, 39). Of note, EAMs were not considered a separate morbidity.

Statistical analysis

Descriptive statistics are presented as mean with standard deviation (SD), median with 25th and 75th percentiles or frequencies with percentage as appropriate. Independent 2-tailed T-tests, Mann-Whitney U test or Analysis of Variance (ANOVA) were performed on continuous data as indicated to explore differences between groups. Chi-square tests compared categorical variables. Tukey's honestly significant difference (HSD) test controlled for multiple comparisons.

We developed separate models determining the association between (1) being multimorbid and (2) worsening multimorbidity, defined by number of additional chronic conditions, and disease outcome measures. BASDAI, BASMI, BASFI, ASQoL and HAQ were individually treated as dependent variables. Initially we explored univariable demographic, treatment and disease-related characteristics associated with each outcome. To control for the effects of these characteristics, we built a model using all variables with a p-value of <0.1 in univariable analysis and performed hierarchical regression, entering variables in blocks of demographics, treatment and disease-related variables prior to assessing the effect of multimorbidity. Age and gender were controlled for in every model. Adjusted R^2 was used to determine the additional variation explained by each block of variables entered. The final models retained variables that significantly improved the fit.

The appropriate assumptions for each statistical test were met. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 24.

RESULTS

Baseline characteristics

At time of database extraction in February 2018, the ASRI cohort contained 734 patients, from 12 Rheumatology centres representing all geographical regions of Ireland. Seventy-seven percent (n=536) of the patients in ASRI are male, with a mean (SD) age of 45 (12) years and a median (IQR) disease duration of 16 (9 to 27) years. The baseline demographic and clinical characteristics of the ASRI cohort are outlined in table 1.

Multimorbidity profile of ASRI cohort

Fifty-five percent of the cohort (n=403) is multimorbid i.e. at least one chronic condition in addition to axSpA: 25% (n=180) has 1 additional chronic condition, 16% (n=118) has 2 additional chronic conditions, 8% (n=57) has 3 additional chronic conditions and 7% (n=48) has 4 or more additional chronic conditions.

The most prevalent chronic condition is obesity, affecting 27% (n=192) of the population, followed by hypertension (n=155, 21%), hyperlipidaemia (n=119, 16%) and depression (n=76, 10%). Thirty percent (n=222) of patients have cardiovascular comorbidity i.e. at least one of IHD, cerebrovascular disease, hypertension, hypercholesterolaemia. Remaining conditions are outlined in figure 1.

Thirty-nine patients (5.3%) report a prior diagnosis or had a diagnosis recorded in the medical record of osteoporosis. Only 19.5% (n=143) had previously had a DXA, of which 95 hip and 94 spine DXA results were available (results of DXAs performed in private facilities or primary care were not universally available): 58% had low BMD at the hip (43% osteopenia, 15% osteoporosis) and 50% had low BMD at the spine (33% osteopenia, 17% osteoporosis).

Comparison of multimorbid and non-multimorbid patients

Demographics/clinical characteristics

Multimorbid patients are older, with longer disease duration and longer delay to diagnosis than axSpA-only patients (see table 1). Multimorbid patients have similar CRP and ESR to the axSpA-only cohort. Gender and HLA-B27 status have no effect on the presence or absence of multimorbidity. The prevalence of psoriasis is higher in multimorbid patients than axSpA-only patients (21% versus 15%, p=0.02). Uveitis and IBD are equally prevalent in both groups.

Impact of multimorbidity on disease outcomes

Across all disease outcome measures, multimorbid patients have more severe disease than patients with axSpA-only (see table 1). Disease outcome measures also correlate with the burden of multimorbidity, which is measured by the number of additional chronic conditions: as the burden of multimorbidity increases, BASDAI scores worsen (see table 2 for all outcomes measures).

The cohort was subsequently compared in 3 groups: (a) axSpA-only, (b) multimorbid with 1 additional chronic condition, (c) multimorbid with 2 or more additional chronic conditions. Disease outcome measures were all significantly higher in patients with multimorbidity compared to patients with axSpA-only, regardless of the number of chronic conditions (see table 3). However, when comparing within the patients with multimorbidity, only BASMI, BASFI and HAQ were significantly higher in patients with 2 or more additional conditions compared to patients with 1 additional condition. There was no difference in BASDAI and ASQoL scores between the multimorbid cohort with 2 or more additional conditions and 1 additional condition (see table 3; ANOVA analysis presented in supplementary table 1).

Regression analysis

Multimorbid versus non-multimorbid

In adjusted analyses (see table 4), when compared to patients with axSpA only, being multimorbid is associated with a higher BASDAI of 0.7 (95% CI 0.34 to 1.05), BASMI of 0.45 (95% CI 0.09 to 0.80), BASFI of 0.5 (95% CI 0.23 to 0.78), HAQ of 0.07 (95% CI 0.00 to 0.13) and ASQoL of 0.87 (95% CI 0.28 to 1.46).

Severity of multimorbidity

In separate models investigating the association between severity of multimorbidity and outcomes (see table 4), the presence of each additional condition was associated with a higher BASDAI of 0.23 (95% CI 0.09 to 0.37), BASMI of 0.20 (95% CI 0.05 to 0.34), ASQoL of 0.25 (95% CI 0.02 to 0.49), HAQ of 0.03 (95% CI 0.01 to 0.06) and BASFI of 0.21 (95% CI 0.10 to 0.32).

DISCUSSION

There is growing interest in multimorbidity. Multimorbid patients have complex needs, requiring cohesive individualised patient-centred strategies, rather than the traditional disease-focused model of care, in order to meet the needs of a rapidly expanding population (8). The negative consequences of multimorbidity are well-outlined in the general population (12, 13, 15), but much less is known about its impact in axSpA patients. Our study found multimorbidity is common in axSpA patients, affecting over half (55%) of this large well-characterised cohort. Additionally, multimorbidity is associated with worse disease outcomes than those with axSpA alone.

The prevalence in our cohort is higher than in the general population, where the prevalence of multimorbidity is around 23% (12), although estimates vary from 13% to 95% (11, 39) depending on age-group and definition of multimorbidity used. Prevalence of multimorbidity is also higher in primary care populations than the general population (40). Musculoskeletal diseases (MSD) are common in patients with multimorbidity (16) and multimorbidity is equally prevalent in RA, affecting over 60% of patients (20), therefore it is unsurprising that multimorbidity is common in axSpA patients.

In our study, we defined the differences between multimorbid and axSpA-only patients. Multimorbid axSpA patients have longer disease duration, longer delay to diagnosis and are on average 10 years older than patients with axSpA only, a similar trend to other populations where multimorbidity increases with age (12, 41). However, with multimorbid axSpA patients averaging 50 years, younger than that seen in primary care practice populations and in RA (12, 19), multimorbidity is not exclusive to the elderly in axSpA.

A systematic review of the general population found an association between women and multimorbidity (11). However, literature is conflicting in RA, where both no gender effect (19) and

a predominance of women in the multimorbid group (42) have been shown. Males and females are equally affected by multimorbidity in our study.

Obesity is the most common morbidity, affecting 26% of our cohort. The prevalence of hypertension (21%) and hypercholesterolaemia (16%) is lower in our study than in ASAS-COMOSPA, but frequency of ischaemic heart disease (3%) and cerebrovascular disease (2%) is similarly low (23). Cardiovascular morbidity is common (30%) in multimorbid patients in our study, reflecting international trends (7). Depression is prevalent in our study, affecting 10% of patients, as is alcohol excess (9%).

Obesity is not always included in multimorbidity scores, with it only counted as a chronic condition in 5 of 39 multimorbidity counts in a systematic review in 2011 (43). However, obesity was only officially recognised as a disease in 2013 (44). As it has a clear negative impact on mortality (45) and represents a growing public health challenge, it is worthy of being considered in a multimorbidity count (41), thus our decision to include it.

In ASAS-COMOSPA, osteoporosis was the most frequent co-morbidity, affecting 13% of the cohort (23). The prevalence of self-reported osteoporosis in our study is 5.3%. However, systematic screening isn't feasible in the context of a registry study. Using the DXA data available in a minority of the cohort, 17% have osteoporosis. However, this may be an overestimation of the population prevalence, as patients referred for DXA assessment likely had risk factors making a diagnosis of osteoporosis more probable, thus the true prevalence is expected to fall between 5 and 17%, closer to that reported in ASAS-COMOSPA.

The second aim of this study is to determine the association between multimorbidity and disease outcomes in axSpA. We demonstrate an association between multimorbid patients and worse disease outcomes, using both subjective and objective outcome measures. As the severity of multimorbidity increases, so too do disease outcome scores. Our results reflect the general population, where multimorbidity is associated with impaired function and worse quality of life,

particularly if a rheumatic disease is involved (46), and RA, where multimorbid patients have more severe disease and more fatigue than patients with RA only (19, 47). Nikiphorou et al (24) similarly demonstrated that a rising comorbidity burden is associated with worse QoL in SpA patients.

However, what differentiates our study from those which focus on co-morbidity is we demonstrate that simply being multimorbid, i.e. having any additional condition to axSpA, is associated with worse outcomes compared to patients with axSpA alone. The difference in outcomes between axSpA-only and being multimorbid is more marked than the difference for each additional condition thereafter. This has potential to be a clinically useful finding, which could provide physicians with a simple method to identify patients at risk of poor outcomes.

We would like to acknowledge some limitations. Firstly, the cross-sectional design of this registry study prohibits comment on causality, therefore we can merely observe the association between multimorbidity and severe disease. Secondly, the absence of information on co-morbidities not collected within the framework of ASRI represents a potential limitation. However, our study reports the co-morbidities known to occur most commonly in SpA, as outlined in ASAS-COMOSPA (23), with the exception of infections (hepatitis B prevalence of 3.5% in SpA worldwide). In Ireland the prevalence of hepatitis B is known to be very low (<0.1%) (48), therefore it is unlikely to have influenced the results. Additionally, pulmonary disease is not collected in ASRI. However, although abnormalities on high-resolution computed-tomography imaging of the thorax are common (49), the clinical significance of these is unknown (50), therefore we are confident that not including a measure of the prevalence of pulmonary disease is unlikely to have significantly affected the prevalence of multimorbidity. Thirdly, alcohol intake is based on patients own report. It has been well established that patients tend to underestimate their alcohol consumption. All efforts were made to establish an accurate alcohol intake, but it is possible that intake was under-reported, thus under-estimating the prevalence of alcohol excess. Fourthly, our population is

overwhelmingly Caucasian, therefore extrapolating the results of our study to other ethnicities is not possible.

However, our study has many strengths. It is a large study, with a well characterised cohort. The homogenous nature of our patients reduces variation that could be introduced from diverse backgrounds. Additionally, it contains real-life data, providing clinicians with relevant and clinically useful information. It is also novel, as the first study to examine prevalence estimates of multimorbidity in axSpA. To date, studies have primarily focused on individual comorbidities in axSpA, along with their impact on disease outcomes/management. Focusing on individual conditions takes the focus away from the patient; different conditions are considered the index disease by different clinicians, all aiming for best control of their disease of interest, without necessarily considering its impact on other diseases, potentially leading to fragmented care (8, 9). Multimorbidity brings the focus back to the patient, not the disease. Further research is needed to further delineate the impact of multimorbidity in our patients. Specifically, prospective longitudinal studies are needed to investigate the development of multimorbidity in axSpA and its impact on disease outcomes over time.

In conclusion, we have demonstrated that multimorbidity is prevalent in axSpA patients and that the presence of multimorbidity is associated with worse disease outcomes.

ACKNOWLEDGEMENTS

This study was conducted on behalf of the steering committee of the Ankylosing Spondylitis Registry of Ireland. We would like to thank all the patients for participating in this study. We would also like to thank all the personnel in the centres who so willingly and enthusiastically contributed, and continue to contribute, data to ASRI: Blackrock Clinic, Cork University Hospital, Galway University Hospitals, Midland Regional Hospital Tullamore, Our Lady's Hospital Manorhamilton, Our Lady's Hospital Navan, St. James's Hospital, St. Vincent's University Hospital, Tallaght University Hospital, University Hospital Kerry, University Hospital Limerick, University Hospital Waterford.

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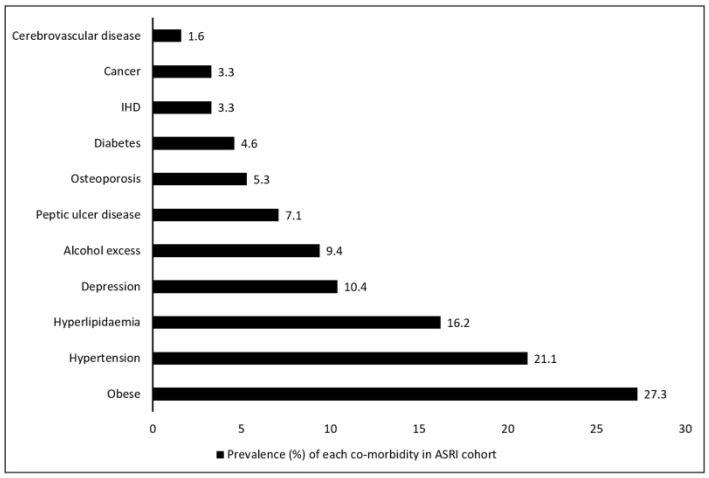

Figure 1: Prevalence of co-morbidities in ASRI cohort, ranked from least to most common. IHD, ischaemic heart disease.

Prevalence of co-morbidities in ASRI, ranked from least to most common.

203x114mm (240 x 240 DPI)

Table 1: Baseline demographic and clinical characteristics of cohort according to multimorbidity status

	Whole population (n=734)	AxSpA only (n=331)	Multimorbid (n=403)	P value†
Males	563 (76.7)	251 (75.8)	312 (77.4)	0.61
Age, years	45 (12.4)	39.6 (10.7)	49.5 (12)	**<0.01**
Disease duration, years	16 (9, 27)	13 (7, 20)	20 (12, 32)	**<0.01**
Delay to diagnosis, years	6 (2, 11)	5 (2,10)	7 (3, 13)	**<0.01**
Caucasian	708 (96.5)	311 (94)	397 (98.5)	**<0.01**
mNY criteria	570 (77.7)	247 (74.6)	323 (80.1)	0.07
ASAS criteria	690 (94)	313 (94.6)	377 (93.5)	0.57
HLA-B27 positive*	502 (91.1)	238 (91.9)	264 (90.4)	0.54
Unemployed¶	166 (22.6)	60 (18.1)	106 (26.3)	**0.01**
Smoker				
• Current smoker	219 (29.8)	106 (32)	113 (28)	**0.02**
• Ex-smoker	207 (28.2)	76 (23)	131 (32.5)	**0.02**
BMD , T-score				
• Hip	-1.2 (1.1)	-1.3 (0.8)	-1.1 (-2, -0.1)	0.38
• Spine	-0.7 (1.9)	-0.9 (1.2)	-0.7 (-2.3, 1.2)	0.30
Waist circumference, cm	95 (85, 104)	88 (81, 96)	101 (91, 110)	**<0.01**
ESR§, mm/h	10 (5, 20)	10 (5, 19)	11 (5, 22)	0.09
CRP§, mg/L	3 (1, 7.7)	2.5 (1, 7)	3 (1, 8)	0.18
BMI, kg/m^2	26.6 (23.9, 30.3)	24.7 (22.9, 27)	29.5 (26, 32.9)	**<0.01**
Extra-spinal manifestations				

• Peripheral arthritis	239 (33.3)	89 (27.4)	150 (38.2)	**<0.01**
• Enthesitis	125 (17.5)	49 (15.2)	76 (19.3)	0.14
• Uveitis	256 (35.7)	109 (33.6)	147 (37.4)	0.30
• Dactylitis	50 (7)	17 (5.2)	33 (8.4)	0.10
• Psoriasis	131 (18.2)	47 (14.5)	84 (21.3)	**0.02**
• IBD	71 (9.9)	26 (8)	45 (11.2)	0.13
Treatment history				
• Current NSAIDs	373 (50.8)	155 (46.8)	218 (54.1)	0.05
• Current sulfasalazine	29 (4)	13 (3.9)	16 (4)	0.14
• Current methotrexate	47 (6.4)	11 (3.3)	36 (8.9)	0.25
• Lifetime TNFi use	512 (69.8)	229 (69.2)	283 (70.2)	0.76
• Current TNFi	456 (62.1)	207 (62.5)	249 (61.8)	0.84
Disease severity				
• ASQoL, 0-18	6 (1, 12)	3 (0, 9)	7 (3, 13)	**<0.01**
• HAQ, 0-3	0.4 (0, 0.9)	0.3 (0, 0.6)	0.63 (0.25, 1)	**<0.01**
• BASDAI, 0-10	3.9 (2, 5.8)	3 (1.5, 5.4)	4.4 (2.6, 6.2)	**<0.01**
• BASFI, 0-10	3.3 (1.3, 5.6)	2 (0.7, 4.2)	4.5 (2.2, 6.5)	**<0.01**
• BASMI, 0-10	3 (1, 6)	2 (1, 4)	4 (2, 7)	**<0.01**

Data are mean (SD), median (25th quartile, 75th quartile) or n (%). Significant values in bold. * HLA-B27 status unknown in n=183 patients. ¶Patients within employment age but unemployed. † Comparison between axSpA-only and multimorbid patient groups (Independent T-tests for continuous variables, Chi-square analysis for categorical variables). Most recent BMD results. §Refers to values at time of recruitment. ASAS: Assessment of SpondyloArthritis Society; ASQoL: Ankylosing Spondylitis Quality of Life Index; AxSpA: axial spondyloarthropathy; BMD: bone mineral density; HAQ: Health Assessment Questionnaire; HLA: Human leucocyte antigen; IBD, inflammatory bowel disease; IBD: Inflammatory Bowel Disease; mNY: modified New York; NSAIDs: Non-steroidal anti-inflammatory drugs; TNFi: TNF inhibitor.

Table 2: Relationship between increasing multimorbidity and disease outcome measures.

	Increasing multimorbidity	BASDAI	BASFI	BASMI	ASQoL	HAQ
	Rho	***Rho***	***Rho***	***Rho***	***Rho***	***Rho***
	P	**P**	**P**	**P**	**P**	**P**
	n	**n**	**n**	**n**	**n**	**n**
Increasing	…	0.21	0.36	0.35	0.23	0.27
burden of	…	<0.01	<0.01	<0.01	<0.01	<0.01
multimorbidity	…	725	734	713	732	731

Rho: Spearman's correlation coefficient; P: P value; N: number of patients. ASQoL: Ankylosing Spondylitis Quality of Life index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI; Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; HAQ: Health Assessment Questionnaire

Table 3: Comparison of disease outcome scores for patients with axSpA only, multimorbid patients with 1 additional condition and multimorbid patients with 2 or more conditions.

Disease outcome	Group	N	Mean	SD	Tukey's HSD Comparisons†	
					axSpA only	1 additional condition
BASDAI	axSpA only	326	3.5	2.4	…	…
	1 additional condition	178	4.2	2.4	<0.01*	…
	≥ 2 additional conditions	221	4.7	2.3	<0.01*	0.16
BASFI	axSpA only	331	2.7	2.4	…	…
	1 additional condition	180	4.0	2.6	<0.01*	…
	≥ 2 additional conditions	223	4.8	2.6	<0.01*	<0.01*
BASMI	axSpA only	322	2.7	2.3	…	…
	1 additional condition	173	3.6	2.5	<0.01*	…
	≥ 2 additional conditions	218	4.8	2.6	<0.01*	<0.01*
ASQoL	axSpA only	330	5.2	5.3	…	…
	1 additional condition	179	7.5	5.5	<0.01*	…
	≥ 2 additional conditions	223	7.9	5.7	<0.01*	0.76
HAQ	axSpA only	330	0.39	0.45	…	…
	1 additional condition	180	0.57	0.51	<0.01*	…
	≥ 2 additional conditions	221	0.72	0.59	<0.01*	0.01*

†P values presented. * Denotes significant difference. ASQoL: Ankylosing Spondylitis Quality of Life index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; HAQ: Health Assessment Questionnaire; HSD: Honestly Significant Difference; N: number of patients; SD: standard deviation. … denotes duplicate cells left blank.

Table 4: Adjusted analyses of association between disease outcome measures and (1) presence of multimorbidity and (2) severity of multimorbidity

	Outcome variables				
	BASDAI	**BASFI**	**BASMI**	**ASQoL**	**HAQ**
(1)	**ß (95% CI)**	**ß (95% CI)**	**ß (95% CI)**	**ß (95% CI)**	**ß (95% CI)**
Independent variables					
Age	0.01 (-0.01 to 0.02)	0.05 (0.04 to 0.06)	0.09 (0.08 to 0.11)	-0.01 (-0.03 to 0.02)	0.01 (0.00 to 0.01)
Gender (male v female)	-0.94 (-1.32 to -0.56)	-0.19 (-0.49 to 0.11)	0.50 (0.11 to 0.89)	-0.55 (-1.10 to 0.09)	-0.07 (-0.15 to -0.01)
Multimorbid (yes v no)	0.70 (0.34 to 1.05)	0.50 (0.23 to 0.78)	0.45 (0.09 to 0.80)	0.87 (0.28 to 1.46)	0.07 (0.00 to 0.13)
BASDAI	§	0.68 (0.62 to 0.73)	§	1.64 (1.52 to 1.76)	0.12 (0.10 to 0.13)
Unemployed (yes v no)	1.62 (1.23 to 2.00)	0.84 (0.52 to 1.15)	1.48 (1.09 to 1.87)	1.39 (0.72 to 2.05)	0.21 (0.13 to 0.28)
Current/past smoker (yes v no)	0.39 (0.07 to 0.71)	0.31 (0.06 to 0.57)	‡	‡	‡
NSAIDs use (yes v no)	1.04 (0.72 to 1.36)	‡	†	‡	‡
ESR	‡	‡	0.03 (0.02 to 0.04)	‡	‡

(2)	BASDAI ß (95% CI)	BASFI ß (95% CI)	BASMI ß (95% CI)	ASQoL ß (95% CI)	HAQ ß (95% CI)
Independent variables					
Age	0.01 (-0.01 to 0.02)	0.05 (0.04 to 0.06)	0.09 (0.07 to 0.11)	-0.01 (-0.03 to 0.02)	0.01 (0.00 to 0.01)
Gender (male v female)	-0.89 (-1.26 to -0.49)	-0.07 (-0.37 to 0.23)	0.64 (0.23 to 1.04)	-0.35 (-0.99 to 0.30)	-0.04 (-0.11 to 0.04)
Worsening multimorbidity	0.23 (0.09 to 0.37)	0.21 (0.10 to 0.32)	0.20 (0.05 to 0.34)	0.25 (0.02 to 0.49)	0.03 (0.01 to 0.06)
BASDAI	§	0.73 (0.67 to 0.78)	§	1.72 (1.61 to 1.84)	0.12 (0.11 to 0.14)
Delay to diagnosis	‡	‡			-0.01 (-0.01 to -0.00)
Unemployed (yes v no)	1.68 (1.29 to 2.07)	†	†	†	†
Current/past smoker (yes v no)	0.38 (0.05 to 0.71)	0.58 (0.20 to 0.96)	‡	‡	‡
NSAIDs use (yes v no)	1.11 (0.79 to 1.44)	‡	‡	‡	‡
ESR	‡	‡	0.03 (0.02 to 0.04)	‡	0.00 (0.00 to 0.01)
IBD	0.74 (0.19 to 1.29)	‡	‡	‡	‡

Variables tested in univariable regression: age, gender, unemployed, delay to diagnosis, current or past smoker, enthesitis, arthritis, dactylitis, uveitis, IBD, psoriasis, CRP, ESR, multimorbid, HLA-B27 positivity, NSAIDs use, csDMARD use, current TNFi use, lifetime history of TNFi use. Variables not included in the above table were not significant in any final model. Every model controlled for age and gender. † P > 0.1 in univariable analysis. ‡ P > 0.05 in multivariable analysis. §: not assessed. ASQoL: Ankylosing Spondylitis Quality of Life score; ß: regression coefficient; CI: confidence interval; IBD: inflammatory bowel disease; MRI: magnetic resonance imaging.