

Multimorbidity in Axial Spondyloarthritis and Its Association with Disease Outcomes: Results from the Ankylosing Spondylitis Registry of Ireland Cohort

Gillian Fitzgerald^{ID}, Phil Gallagher, and Finbar D. O'Shea^{ID}

ABSTRACT. *Objective.* Multimorbidity, the coexistence 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 spondyloarthritis (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 standardized 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), and 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 centers were included: 77% male, mean (SD) age 45 (12) years. Of the cohort, 55% (n = 403) were multimorbid. Multimorbid patients were significantly ($p < 0.01$) older than axSpA-only patients [50 (12) vs 40 (11) yrs]. Obesity was the most prevalent chronic condition, affecting 27%. Multimorbid patients had more severe disease than patients with axSpA only. After adjusting for confounders, multimorbidity was associated with higher BASDAI (β 0.7, 95% CI 0.34–1.05), BASMI (β 0.45, 95% CI 0.09–0.80), BASFI (β 0.5, 95% CI 0.23–0.78), HAQ (β 0.07, 95% CI 0.00–0.13), and ASQoL (β 0.87, 95% CI 0.28–1.46).

Conclusion. Multimorbidity is prevalent in axSpA and is associated with more severe disease. (First Release October 1 2019; J Rheumatol 2020;47:218–26; doi:10.3899/jrheum.181415)

Key Indexing Terms:

SPONDYLOARTHROPATHIES
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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

From the Department of Rheumatology, St. James's Hospital; Department of Clinical Medicine, Trinity College Dublin; Department of Rheumatology, St. Vincent's University Hospital, Dublin, Ireland.

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G. Fitzgerald, MB BCH, BAO, MRCPI, Rheumatologist, PhD candidate, Department of Rheumatology, St. James's Hospital, and Department of Clinical Medicine, Trinity College Dublin; P. Gallagher, RGN, Department of Rheumatology, St. Vincent's University Hospital; F.D. O'Shea, MB BCH, BAO, MRCPI, Consultant Rheumatologist, General Physician, Department of Rheumatology, St. James's Hospital, and Department of Clinical Medicine, Trinity College Dublin.

Address correspondence to Dr. G. Fitzgerald, Department of Rheumatology, St. James's Hospital, Dublin, Ireland.

E-mail: gifitzge@tcd.ie

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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 burden⁶, in particular noncommunicable diseases, which are now the biggest threats to mortality worldwide⁷.

To cope with aging populations, health systems must adapt³. Current clinical practice guidelines focus on individual comorbidities, without giving adequate guidance on managing patients with multiple chronic conditions⁸. However, with pressure to delay the onset of functional decline and to allow people to remain effective members of society for longer, swapping the concept of comorbidity for multimorbidity is needed⁸. 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 center 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 1 individual, without specifying the index disease¹⁰. Multimorbidity estimates range from 13% to 95%, with prevalence increasing with age^{11,12}. Multimorbid patients have increased mortality, more disability, worse quality of life, and greater use of healthcare resources^{13,14,15}; in some cases, 25% of the population accounts for more than 50% of healthcare use¹⁵. Musculoskeletal disease (MSD) is common in multimorbidity patterns¹⁶ and serves to intensify the effect^{17,18}.

In rheumatoid arthritis (RA), 62–65% of patients are multimorbid^{19,20}. Multimorbid patients with RA have worse physical function⁹ and lower rates of disease control²¹.

A growing body of work has examined the burden of comorbidities in axial spondyloarthritis (axSpA)^{22,23,24,25,26}. Mortality is known to be increased in axSpA patients compared to age- and sex-matched controls^{25,26,27}. The Assessment of Spondyloarthritis international Society-COMorbidities in SPondyloArthritis (ASAS-COMOSPA) study²³ has outlined the comorbidity profile of patients with axSpA, particularly highlighting the frequency of osteoporosis and peptic ulcer disease. Cardiovascular-related comorbidity is also more prevalent in AS^{28,29}. Comorbidity adds to the burden of disease in patients with SpA, reducing physical function and quality of life²⁴. ASAS/European League Against Rheumatism recommendations for management of axSpA suggest that treatment should be tailored to take comorbidities into consideration³⁰, 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 established⁸. In modern society, increasing emphasis is being placed on compression of morbidity; therefore, it is important to understand the effect of multimorbidity in patients with axSpA. To our knowledge, there is no literature looking at the prevalence of multimorbidity and associated relationships in patients with axSpA.

Therefore, the aims of our study are to determine (1) the prevalence of multimorbidity within a well-characterized real-life axSpA cohort, and (2) relationships between multimorbidity and disease outcomes.

MATERIALS AND METHODS

Ankylosing Spondylitis Registry of Ireland (ASRI) study design and patient recruitment. This study was conducted within the framework of the ASRI cohort. ASRI is a large observational cross-sectional multicenter 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 that prohibits informed consent. Each center has a designated subinvestigator with responsibility for local oversight. Accuracy of the data collected is monitored quarterly by (author) PG. The

primary investigator (author FOS) has responsibility for overall oversight of the database. To date, 12 centers in Ireland have recruited patients and contributed data to ASRI.

Written informed consent was 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 center.

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 were entered into an electronic centralized 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 extraarticular manifestations [EAM; uveitis, psoriasis, inflammatory bowel disease (IBD)], other SpA features (enthesitis, dactylitis, peripheral arthritis), current and previous treatment (nonsteroidal antiinflammatories, methotrexate, sulfasalazine, biologics), 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 SpA²³: ischemic heart disease (IHD), cerebrovascular disease, hypertension (HTN), hyperlipidemia, diabetes mellitus, peptic ulcer disease, tuberculosis, osteoporosis, depression, cancer (melanoma, nonmelanoma skin cancer, lung, breast, gastrointestinal, genitourinary, lymphoma, hematological, other). Additionally, obesity and alcohol excess were noted. Obesity was recorded as a body mass index $> 30 \text{ mg/kg}^2$, as per the World Health Organization (WHO) criteria, based on the weight and height measurements taken by the investigator during the assessment. Alcohol excess was considered as alcohol consumption > 21 units/week in men and 14 units/week in women, as per national guidelines³¹, and based on the patient's self-report of alcohol consumption. Patient medical records were used as required to confirm the presence or absence of each of these comorbidities. EAM 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 standardized technique³²; current blood pressure, height (measured in cm), weight (measured in kg), waist circumference (measured in cm).
- Dual-energy x-ray absorptiometry (DEXA): most recent DEXA result was obtained (if performed) and osteoporosis defined according to WHO³³.

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 disease³⁴.
- Bath AS Functional Index (BASFI): measured on a scale of 0–10; higher scores indicate worse function³⁵.
- Health Assessment Questionnaire (HAQ): assessed on a scale of 0–3; 0 indicates no disability and 3 indicates large burden of disability³⁶.
- AS Quality of Life (ASQoL): assessed on a scale of 0–18; higher scores indicate worse QOL³⁷.
- Bath AS Metrology Index (BASMI) assessed spinal mobility on a scale of 0–10; higher scores indicate worse spinal mobility³².

Multimorbidity. Morbidity is defined as the presence of a chronic condition in a patient. We defined multimorbidity as the presence of at least 2 chronic conditions in 1 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, EAM were not considered a separate morbidity.

Statistical analysis. Descriptive statistics are presented as mean with SD, median with 25th and 75th percentiles, or frequencies with percentage as

appropriate. Independent 2-tailed t tests, Mann-Whitney U test, or ANOVA were performed on continuous data as indicated to examine differences between groups. Chi-square tests compared categorical variables. The Tukey honestly significant difference 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 investigated 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 < 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 sex 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 < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 24 (IBM Corp.).

RESULTS

Baseline characteristics. At the time of database extraction in February 2018, the ASRI cohort contained 734 patients, from 12 rheumatology centers 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 (interquartile range) disease duration of 16 (9–27) 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 ($n = 403$) are multimorbid (i.e., at least 1 chronic condition in addition to axSpA): 25% ($n = 180$) have 1 additional chronic condition, 16% ($n = 118$) have 2 additional chronic conditions, 8% ($n = 57$) have 3 additional chronic conditions, and 7% ($n = 48$) have 4 or more additional chronic conditions.

The most prevalent chronic condition is obesity, affecting 27% ($n = 192$) of the population, followed by HTN ($n = 155$, 21%), hyperlipidemia ($n = 119$, 16%), and depression ($n = 76$, 10%). Thirty percent ($n = 222$) of patients have cardiovascular comorbidity (i.e., at least 1 of IHD, cerebrovascular disease, HTN, or hypercholesterolemia). 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 DEXA, of which 95 hip and 94 spine DEXA results were available (results of DEXA performed in private facilities or primary care were not universally available): 58% had low bone mineral density (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 (Table 1). Multimorbid

patients have similar CRP and ESR to the axSpA-only cohort. Sex and HLA-B27 status have no effect on the presence or absence of multimorbidity. The prevalence of psoriasis is higher in multimorbid patients than in axSpA-only patients (21% vs 15%, $p = 0.02$). Uveitis and IBD are equally prevalent in both groups.

Effect of multimorbidity on disease outcomes. Across all disease outcome measures, multimorbid patients have more severe disease than patients with axSpA only (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 outcome measures).

The cohort was subsequently compared in 3 groups: (1) axSpA only; (2) multimorbid with 1 additional chronic condition; and (3) 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 (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 (Table 3; ANOVA analysis presented in Supplementary Table 1, available from the authors on request).

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

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

DISCUSSION

There is growing interest in multimorbidity. Multimorbid patients have complex needs, requiring cohesive individualized patient-centered strategies rather than the traditional disease-focused model of care, to meet the needs of a rapidly expanding population⁸. The negative consequences of multimorbidity are well outlined in the general population^{12,13,15}, but much less is known about its effect in patients with axSpA. Our study found multimorbidity is common in patients with

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

Characteristics	Whole Population, n = 734	axSpA Only, n = 331	Multimorbid, n = 403	p [†]
Male	563 (76.7)	251 (75.8)	312 (77.4)	0.61
Age, yrs, mean (SD)	45 (12.4)	39.6 (10.7)	49.5 (12)	< 0.01
Disease duration, yrs	16 (9, 27)	13 (7, 20)	20 (12, 32)	< 0.01
Delay to diagnosis, yrs	6 (2, 11)	5 (2, 10)	7 (3, 13)	< 0.01
White	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 ^Δ , T score, mean (SD)				
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
Extraspinal 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 NSAID	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 median (25th quartile, 75th quartile), or n (%), unless otherwise specified. Values in bold face are statistically significant. * HLA-B27 status unknown in 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). ^Δ Most recent BMD results. [§] Refers to values at time of recruitment. ASAS: Assessment of Spondyloarthritis international Society; ASQoL: Ankylosing Spondylitis Quality of Life index; axSpA: axial spondyloarthritis; BMD: bone mineral density; HAQ: Health Assessment Questionnaire; IBD: inflammatory bowel disease; mNY: modified New York; NSAID: nonsteroidal antiinflammatory drugs; TNFi: tumor necrosis factor inhibitor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BMI: body mass index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index.

axSpA, affecting over half (55%) of this large well-characterized cohort. Additionally, multimorbidity is associated with worse disease outcomes than in 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 population⁴⁰. MSD is common in patients with multimorbidity¹⁶ and multimorbidity is equally prevalent in RA, affecting over 60% of

patients²⁰; therefore, it is unsurprising that multimorbidity is common in patients with axSpA.

In our study, we defined the differences between multimorbid and axSpA-only patients. Multimorbid patients with axSpA 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 those seen in primary care practice populations and in RA^{12,19}, multimorbidity is not exclusive to the elderly in axSpA.

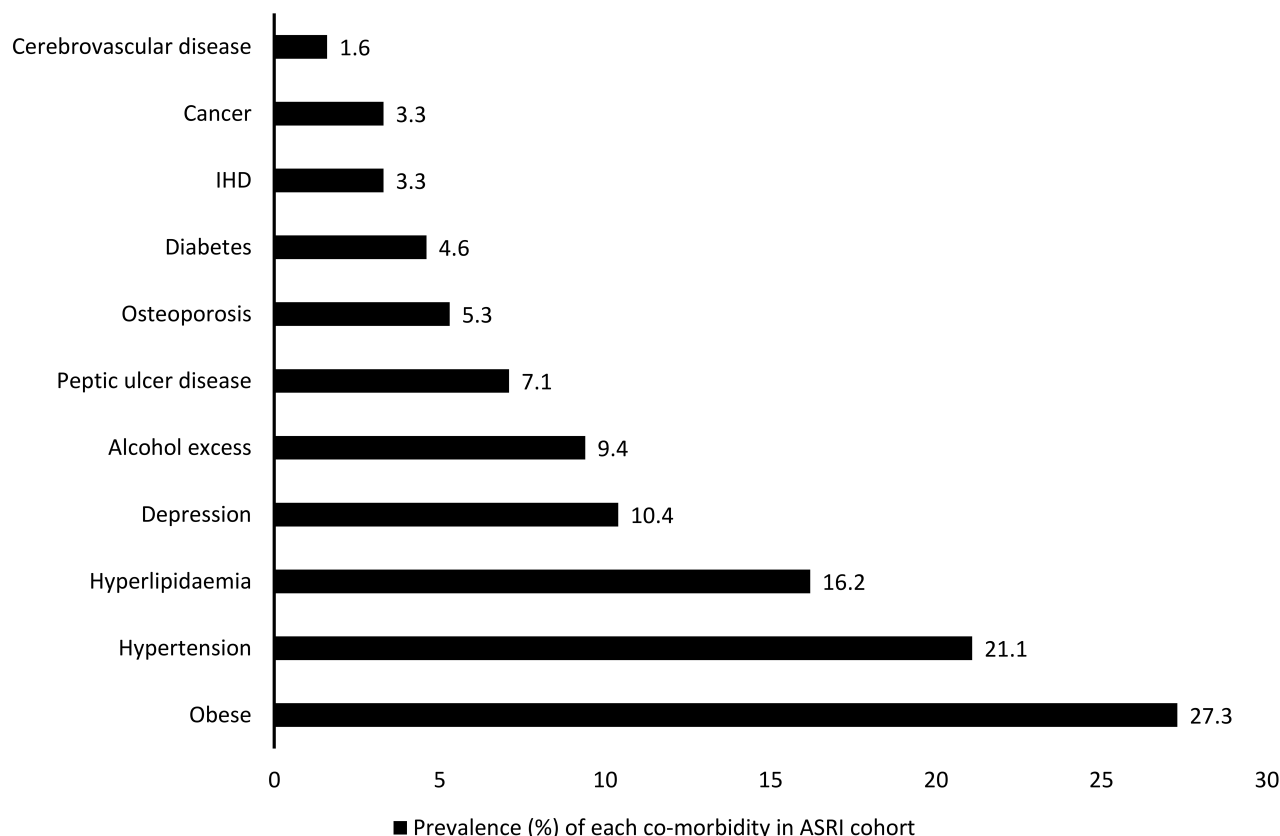


Figure 1. Prevalence of comorbidities in the Ankylosing Spondylitis Registry of Ireland (ASRI), ranked from least to most common. IHD: ischemic heart disease.

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

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

Rho: Spearman correlation coefficient; ASQoL: Ankylosing Spondylitis Quality of Life index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath AS Functional Index; BASMI: Bath AS Metrology Index; HAQ: Health Assessment Questionnaire.

A systematic review of the general population found an association between women and multimorbidity¹¹. However, the literature is conflicting in RA, where both no sex effect¹⁹ and a predominance of women in the multimorbid group⁴² 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 prevalences of HTN (21%) and hypercholesterolemia (16%) are lower in our study than in ASAS-COMOSPA, but frequencies of IHD (3%) and cerebro-

vascular disease (2%) are similarly low²³. Cardiovascular morbidity is common (30%) in multimorbid patients in our study, reflecting international trends⁷. Depression is prevalent in our study, affecting 10% of patients, as is alcohol excess (9%).

Obesity is not always included in multimorbidity scores; it is counted as a chronic condition in only 5 of 39 multimorbidity counts in a systematic review in 2011⁴³. However, obesity was not officially recognized as a disease until 2013⁴⁴. Because it clearly increases mortality⁴⁵ and repre-

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 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. — Denotes duplicate cells left blank. 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; axSpA: axial spondyloarthritis.

Table 4A. Adjusted analyses of association between disease outcome measures, and presence of multimorbidity.

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

Table 4B. Adjusted analyses of association between disease outcome measures and severity of multimorbidity.

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

Values are β (95% CI). Variables tested in univariable regression: age, sex, unemployed, delay to diagnosis, current or past smoker, enthesitis, arthritis, dactylitis, uveitis, IBD, psoriasis, CRP, ESR, multimorbid, HLA-B27 positivity, NSAID 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 sex. † P > 0.1 in univariable analysis. ‡ P > 0.05 in multivariable analysis. §: not assessed. 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; β: regression coefficient; NSAID: nonsteroidal antiinflammatory drug; ESR: erythrocyte sedimentation rate; IBD: inflammatory bowel disease; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; TNFi: tumor necrosis factor inhibitor.

sents a growing public health challenge, it is worthy of being considered in a multimorbidity count⁴¹, so we decided to include it.

In ASAS-COMOSPA, osteoporosis was the most frequent comorbidity, affecting 13% of the cohort²³. The prevalence of self-reported osteoporosis in our study is 5.3%. However, systematic screening is not feasible in the context of a registry study. Using the DEXA data available in a minority of the cohort, 17% have osteoporosis. However, this may be an overestimation of the population prevalence, because patients referred for DEXA 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 QOL, particularly if a rheumatic disease is involved⁴⁶, 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 patients with SpA.

However, what differentiates our study from those that focus on comorbidity 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 acknowledge some limitations. First, the cross-sectional design of this registry study prohibits comment on causality; therefore, we can merely observe the association between multimorbidity and severe disease. Second, the absence of information on comorbidities not collected within the framework of ASRI represents a potential limitation. However, our study reports the comorbidities known to occur most commonly in SpA, as outlined in ASAS-COMOSPA²³, 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 common⁴⁹, the clinical significance of these is unknown⁵⁰; 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. Third, alcohol intake is based on the patient's 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 underreported, thus underestimating the prevalence of alcohol excess. Fourth, our population is overwhelmingly white; therefore, extrapolating the results of our study to other ethnicities is not possible.

Our study has many strengths. It is a large study, with a well-characterized cohort. The homogeneous characteristics 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 our knowledge. To date, studies have primarily focused on individual comorbidities in axSpA, along with their effect 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 effect 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 effect of multimorbidity in our patients. Specifically, prospective longitudinal studies are needed to investigate the development of multimorbidity in axSpA and its effect on disease outcomes over time.

We have demonstrated that multimorbidity is prevalent in patients with axSpA and that the presence of multimorbidity is associated with worse disease outcomes.

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