

# Prevalence and impact of comorbidities in axial spondyloarthritis: systematic review and meta-analysis

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## Abstract

**Objectives.** Comorbidities are common in people with axial spondyloarthritis (axSpA). In this systematic review and meta-analysis, we aimed to: (i) describe the prevalence of commonly reported comorbidities, (ii) compare comorbidities between axSpA and control populations, and (iii) examine the impact of comorbidity burden on axSpA outcomes.

**Methods.** We systematically searched Medline, PubMed, Scopus and Web of Science using a predefined protocol in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. We excluded studies of only one comorbid condition or a few closely related diseases within one organ system. Where possible, meta-analysis was performed using random-effects models.

**Results.** A total of 40 studies were included for analysis. 36 studies reported prevalence of comorbidities, amounting to a combined sample size of 119 427 patients. The number of comorbidities studied ranged from 3 to 43. The most prevalent individual comorbidities were hypertension (pooled prevalence 23%), hyperlipidaemia (17%) and obesity (14%). Eleven studies consistently showed higher prevalence of comorbidities in axSpA than controls, particularly large differences were seen for depression [pooled odds ratio (OR) 1.80] and heart failure (OR 1.84). Comorbidities (total number of and individual conditions) were also associated with axSpA disease activity, functional impairment, quality of life, work productivity and mortality.

**Conclusions.** Comorbidities are common in axSpA, particularly cardiovascular diseases and risk factors. Most comorbidities were more prevalent in axSpA patients than in control populations. Overall comorbidity burden, and many individual conditions, were associated with axSpA outcomes including worse disease severity, work productivity and mortality.

**Key words:** Ankylosing spondylitis, axial spondyloarthritis, comorbidity, multimorbidity, systematic review, meta-analysis

### Rheumatology key messages

- Comorbidities are common in axSpA patients, particularly hypertension (prevalence 22%), hyperlipidaemia (17%) and obesity (14%).
- Comorbidities were more prevalent in axSpA than controls, with  $\geq 80\%$  higher odds for heart failure and depression.
- Comorbidities were associated with poorer patient-reported outcomes, work productivity, treatment response and mortality.

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## Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease predominantly affecting the spine. It can be divided into 'radiographic' (ankylosing spondylitis, AS) and 'non-radiographic' (nr-axSpA), depending on whether definitive structural changes are evident on plain

radiographs of sacroiliac joints. Patients with axSpA are at higher risk of other medical conditions than the general population, partly due to shared risk factors, consequences of inflammation or its treatment (e.g. long-term NSAIDs). The majority of axSpA patients have at least one comorbid medical condition in addition to any extra-articular manifestations [1]. The collective ‘burden’ of these comorbidities has been reported to associate with poorer function, quality of life and work-related outcomes [2]. They are also important considerations in routine clinical practice where renal impairment, infections, cardiovascular and gastrointestinal diseases will all influence treatment decisions [3]. Some are also key drivers of mortality [4]. A holistic, patient-centred care provision model is therefore essential in rheumatology, yet comorbidity research to inform such practices have been heterogeneous in design and quality.

The majority of prior research have focused on one or a few closely related comorbidities in one organ system; examples include cardiovascular diseases and bone health. While this approach is valid for assessing the impact of one comorbid disease on axSpA, it does not reflect the real-world setting where patients frequently have multiple inter-related comorbidities. When studies include several comorbidities, their methods are often diverse. Some count the number of conditions in varying lists (often arbitrarily) defined by the researchers, which may overlook important comorbidities, while others use indices that are weighted for outcomes unrelated to their topic of study (e.g. using the Charlson Comorbidity Index to study functional outcomes).

The aims of this systematic review and meta-analysis were to: (i) describe the prevalence of commonly reported comorbidities, (ii) compare the incidence and/or prevalence of comorbidities between axSpA and control populations, and (iii) examine the impact of comorbidity burden on axSpA outcomes.

## Methods

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5]. The protocol for this review was pre-registered in advance (PROSPERO: CRD42019151105). We searched Medline, PubMed, Scopus and Web of Science for relevant literature in September 2019, using the following search term: (ankylosing spondylitis OR axial spondyloarth\*) AND (multimorbid\* OR comorbid\* OR polymorbid\* OR multi-morbid\* OR co-morbid\* OR poly-morbid\*).

Studies of axSpA (whether defined by classification criteria or otherwise) were included if they reported the prevalence or incidence of comorbidities or their impact on disease outcomes. We also included studies that did not primarily examine comorbidities but reported their prevalence in detail. Studies were excluded if they focused on only one comorbid condition (e.g. stroke only) or a few closely related diseases in one organ system (e.g. cardiovascular diseases only). This is to

distinguish studies of comorbidity from, say, cardiovascular risk. We also excluded studies that used non-representative sampling (highly selective recruitment or criteria randomized controlled trials) or had a samples size of <30 (to avoid unreliable prevalence estimates). Published conference abstracts were considered, as some prevalence studies may not be published as full articles but nevertheless have sufficiently detailed methodology and results. Bibliographies of all eligible studies were also manually searched to identify additional titles. Reviews, comments and editorials were excluded.

Two independent reviewers screened titles and abstracts, assessed full-texts for eligibility and extracted data from qualifying studies. Any discrepancy at each stage was resolved through discussion moderated by a third reviewer. Information from included studies was extracted into predefined tabulated summaries. We excluded extra-articular manifestations (EAMs) from our list of extracted comorbidities, as they share pathogenesis with and aid diagnosis of axSpA [6, 7]. Studies were assessed for risk of bias using adapted versions of the Newcastle Ottawa Scale (details in [supplementary materials](#), available at *Rheumatology* online).

For aims 1 and 2, we performed meta-analyses for comorbidities reported by at least three studies. Pooled prevalence estimates were reported as percentages (95% CI), using random-effects models (DerSimonian-Laird). Double arcsine transformation was used, as traditional weighting methods are problematic when proportions are close to the bound limits. Heterogeneity of meta-analysis estimates were presented using the  $I^2$  statistic. Funnel plots were used to assess risk of publication bias. Analyses were performed using MetaXL version 5.3 (Sunrise Beach, Australia).

## Results

A total of 1522 publications were found from the literature search. After excluding duplicates, irrelevant and ineligible studies, 44 studies remained. Three used data from the ASAS-COMOSpA study [2, 8, 9], from which the paper by Nikiphorou *et al.* was selected because it restricted to participants fulfilling ASAS criteria. Two used the OASIS registry [10, 11]; we kept the paper by Stolwijk *et al.* as it reported a greater range of comorbidities. The larger of two studies using United States’ claims data by Walsh *et al.* was included [5, 12]. Flowchart of the selection process is shown in [Supplementary Fig. S1](#), available at *Rheumatology* online.

The 40 included studies are summarized in [Supplementary Table S1](#), available at *Rheumatology* online. Sample size ranged from 74 to 21 872. A total of 22 studies used European cohorts, seven were from Asia, six North America, one Argentina, one Australia and four were multinational. Mean age of study samples ranged from 29 (China) to 59 (UK). Mean BASDAI ranged from 3.4 (China) to 7.6 (Australian cohort initiating TNFi).

AxSpA was defined using classification criteria in 20 studies (seven using the modified New York criteria

only, 13 using the ASAS  $\pm$ mNY criteria), diagnostic codes in 14, physician diagnosis in three and self-report in one. The number of comorbidities studied ranged from three to 43 (excluding EAMs). Most studies used unvalidated lists, while 13 used a validated index either directly or indirectly (to inform which comorbidities to include, e.g. Kang *et al.* [13]): three used the Charlson Comorbidity Index (CCI), two the Elixhauser Comorbidity Index (ECI), three the self-reported comorbidity questionnaire (SCQ), two the Rheumatic Disease Comorbidity Index (RDCI), two the multimorbidity index and one the Functional Comorbidity Index (see reference [14] for descriptions of each). EAMs were included as comorbidity in a minority (five out of 40 studies), while two considered valvular heart disease and restrictive lung disease as EAMs. Two studies also included smoking as comorbidity. Most studies did not justify their sample size because they were not dedicated studies of comorbidities, thereby losing one score for bias. Taking this into account, scores were mostly 4–5 out of 6 stars (Supplementary Table S2 and Fig. S2, available at *Rheumatology* online) indicating minimal bias.

### Prevalence of comorbidities

A total of 36 studies reported prevalence of individual comorbidities with a combined sample size of 119 427 patients [1, 2, 5, 11, 13, 15–45]. All studies reported one or more diseases of the cardiovascular system; 21 studies included a gastrointestinal or hepatic disorder; 21

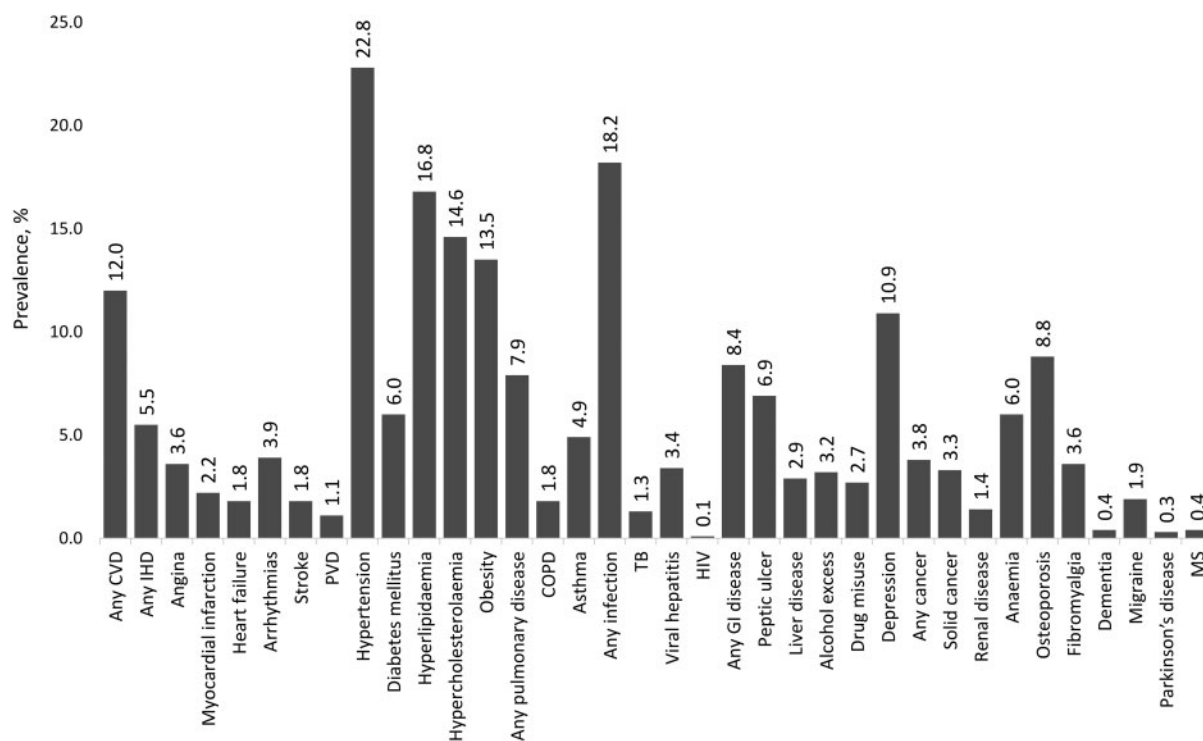
included cancers; 18 pulmonary disorders; 16 mental health disorders (anxiety or depression). The most frequently studied individual comorbidities were hypertension (33 studies), diabetes (30) and stroke (18); all other were reported by 16 or fewer studies. Diverticulitis, irritable bowel syndrome, venous thromboembolism and bronchiectasis are examples of infrequently (reported by  $\leq 2$  studies) included conditions (full list in Supplementary Table S3, available at *Rheumatology* online).

Pooled prevalence estimates of individual comorbidities are summarized in Fig. 1 with further details in Table 1. The top five most prevalent comorbidities were hypertension (22.3%), any infection (18.3%), hyperlipidaemia (17.1%), obesity (13.5%) and any cardiovascular disease (CVD, 12.3%). There was significant heterogeneity for the majority of meta-analyses. Stratifying by axSpA definition (i.e. diagnostic code, modified New York, ASAS $\pm$ mNY criteria) did not improve heterogeneity or give significantly different prevalence estimates (data not shown). Forrest and funnel plots of the 36 meta-analyses are provided in supplementary materials, available at *Rheumatology* online.

### Comorbidities in axSpA compared with controls

Eleven studies compared comorbidities between axSpA and control groups [5, 13, 15–18, 20, 26, 36, 37, 41]. Six studies selected controls without AS or inflammatory rheumatic diseases, while five others did not specify or

Fig. 1 Pooled prevalence of individual comorb conditions reported by  $\geq 3$  studies



**TABLE 1** Meta-analysis estimates for prevalence of individual comorbidities

	<i>n</i>	Pooled prevalence	95% CI	<i>I</i> <sup>2</sup> , %	Range
Any cardiovascular disease	12	12.0	5.8, 19.9	100	2.7, 34.4
Any ischaemic heart disease	15	5.5	3.7, 7.5	99	0.9, 16.2
Angina	6	3.6	1.2, 6.9	96	1.2, 7.0
Myocardial infarction	11	2.2	1.4, 3.1	91	0, 7.2
Heart failure	10	1.8	1.2, 2.4	95	0.5, 5.8
Arrhythmias	7	3.9	1.2, 7.8	98	1.0, 14.0
Stroke	18	1.8	1.3, 2.3	96	0, 5.5
Peripheral vascular disease	9	1.1	0.6, 1.9	97	0.2, 2.8
Hypertension	33	22.8	16.4, 29.8	100	4.5, 73.0
Diabetes mellitus	30	6.0	4.6, 7.5	99	0.3, 18.0
Hyperlipidaemia	11	16.8	10.1, 24.7	100	4.2, 33.1
Hypercholesterolaemia	5	14.6	4.0, 29.6	99	4.3, 27.0
Obesity	7	13.5	2.2, 30.4	100	0.2, 27.3
Any pulmonary disease	8	7.9	2.6, 15.4	99	1.9, 23.4
COPD	8	1.8	0.9, 2.8	94	0.6, 5.0
Asthma	8	4.9	2.9, 7.3	98	0.5, 11.3
Any infection	3	18.2	3.9, 38.4	100	4.6, 32.9
TB	7	1.3	0.5, 2.4	93	0, 3.8
Viral hepatitis	6	3.4	0.9, 7.3	97	0.6, 18.6
HIV	3	0.1	0.04, 0.3	13	0, 0.3
Any GI disease	5	8.4	2.5, 16.9	99	1.0, 31.3
Peptic ulcer	12	6.9	3.3, 11.6	99	1.1, 20.9
Liver disease	9	2.9	0.7, 6.4	99	0, 12.0
Alcohol excess	4	3.2	0.0, 8.3	99	0.3, 9.4
Drug misuse	3	2.7	0.4, 6.6	96	1.1, 4.8
Depression	16	10.9	6.2, 16.7	100	2.0, 31.0
Any cancer	16	3.8	0.7, 9.0	100	0.3, 29.5
Solid cancer	5	3.3	0.3, 8.5	99	0.6, 12.0
Renal disease	15	1.4	1.0, 1.9	93	0.1, 2.7
Anaemia	6	6.0	2.0, 11.7	97	1.0, 14.1
Osteoporosis	12	8.8	5.1, 13.2	99	3.4, 31.0
Fibromyalgia	5	3.6	0.2, 9.7	100	0.4, 13.0
Dementia	4	0.4	0.1, 0.8	74	0, 0.8
Migraine	3	1.9	0.9, 3.3	83	1.3, 3.0
Parkinson's disease	3	0.3	0.2, 0.4	0	0.1, 0.3
MS	4	0.4	0.3, 0.6	0	0.1, 0.5

Stroke includes cerebrovascular accidents and transient ischaemic attacks.

COPD: chronic obstructive pulmonary disease; GI: gastrointestinal; MS: multiple sclerosis.

selected from the whole population. All studies compared prevalence; nine used pairwise comparisons or odds ratios (OR) and two used standardized mortality ratios (SMR). All except one study matched for at least age and sex. Cardiovascular comorbidities were the most commonly described. Virtually all individual comorbidities were more prevalent in axSpA populations than matched controls (Supplementary Table S4, available at *Rheumatology* online).

For the nine studies reporting OR (or from which OR would be calculated), comorbidities reported by  $\geq 3$  studies were pooled using meta-analysis (summarized in Fig. 2 with further details in Table 2). The three most frequently compared comorbidities were hypertension (axSpA groups had 58% higher odds than controls), diabetes (14% higher odds) and ischaemic heart disease (IHD, 51% higher odds). The largest effect sizes were:

84% higher odds of heart failure in axSpA compared with controls; and 80% higher odds for depression. Heterogeneity was high for all meta-analysis estimates. Forrest and funnel plots for 10 meta-analyses are shown in [supplementary materials](#), available at *Rheumatology* online.

Two studies additionally reported incidence of comorbidities after axSpA diagnosis (Table 3). Cook *et al.* found higher risk of developing hypertension, myocardial infarction, stroke, COPD and depression in axSpA patients compared with controls [18]. When Essers *et al.* adjusted for NSAID-use, however, the difference for myocardial infarction and IHD were no longer significantly different between axSpA and controls [20].

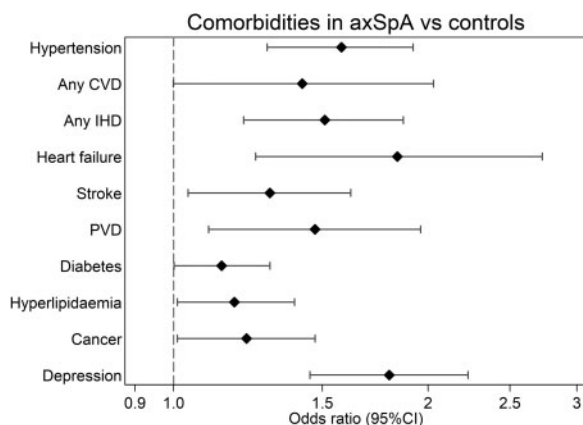
Three studies compared comorbidities between male and females. Bremander *et al.* showed that the difference in osteoporosis prevalence between axSpA and

controls were much higher in males than females (SMR 6.98 vs 3.24) but no different for other comorbidities that they studied [16]. Kang *et al.* reported significantly higher odds of migraine (conditional OR 2.3 vs 1.5), COPD (OR 6.8 vs 2.4) and asthma (OR 1.6 vs 0.8), in female axSpA vs female controls than the equivalent comparison in males [13]. They also found non-significantly higher odds for IHD (OR 4.5 vs 2.3), alcohol (OR 5.0 vs 1.3) and drug (OR 2.2 vs 1.1) abuse/dependence in females. Essers *et al.* reported higher incidence rate ratios for IHD in females than males (1.72 vs 1.07) [20].

#### Association between comorbidity burden and disease outcomes

Seventeen studies reported the association between comorbidity burden and axSpA outcomes (Table 4). In the majority of studies, axSpA patients with comorbidity had higher disease activity and function impairment,

**FIG. 2** Summary of meta-analysis estimates for odds ratios comparing comorbidities between axSpA and control groups



**TABLE 2** Meta-analysis estimates for odds ratios (OR) of comorbidities compared between axSpA and control groups

	<i>n</i>	Pooled OR	95% CI	<i>I</i> <sup>2</sup> , %	OR range
Hypertension	9	1.58	1.29, 1.92	98	1.09, 3.01
Any cardiovascular disease	3	1.42	0.999, 2.03	99	1.14, 1.97
Any ischaemic heart disease	7	1.51	1.21, 1.87	87	1.10, 2.74
Heart failure	4	1.84	1.25, 2.73	89	1.42, 2.74
Stroke	6	1.30	1.04, 1.62	81	0.95, 1.80
Peripheral vascular disease	5	1.47	1.10, 1.96	83	1.06, 2.21
Diabetes	8 <sup>a</sup>	1.14	1.001, 1.30	83	0.90, 1.31
Hyperlipidaemia	5	1.18	1.01, 1.39	94	1.02, 1.46
Cancer	5 <sup>b</sup>	1.22	1.01, 1.47	93	0.80, 1.59
Depression	4	1.80	1.45, 2.23	92	1.45, 2.10

<sup>a</sup>Diabetes without complications selected.

<sup>b</sup>Solid cancer without metastasis selected.

Stroke: includes cerebrovascular accidents and transient ischaemic attacks.

more severe pain and poorer quality of life than those without. ESR and CRP were generally not significantly different.

Three studies reported work-related outcomes. Nikiphorou *et al.* found that RDCI was associated with reduced employment, increased time off due to health reasons (absenteeism) and reduced productivity at work (presenteeism) [2]. Stolwijk *et al.* found that the SCQ score was associated with stopping work due to disability, but only in those with BASDAI < 4 [11]. Boonen *et al.* reported three times higher odds of inability to perform paid work in AS patients with comorbidities than without [48].

Two studies examined treatment outcomes. Iannone *et al.* reported correlation between a modified version of RDCI and number of biological drug switches [49]. The authors also found mRDCI to be a predictor of TNFi discontinuation and poor ASDAS remission response. Lindström *et al.* found CVD, affective disorders, chronic lung disease and malignancy to be associated with increased TNFi discontinuation in unadjusted Cox models, but not diabetes or chronic kidney disease (CKD) [28].

Three studies reported mortality outcomes. Lee *et al.* studied comorbidity burden using CCI, where each unit increase was associated with 7% higher odds of all-cause mortality [50]. Haroon *et al.* found that dementia and peripheral vascular disease (PVD) were associated with increased vascular mortality, but not diabetes, CKD, IBD or cancer [26]. All comorbidities in the study by Exarchou *et al.* were each significant associated with all-cause mortality; AS patients with chronic pulmonary disease were at particularly higher risk of death (HR 3.0) [36].

## Discussion

Comorbidities are common and associated with disease outcomes in axSpA. Meta-analysis pooling results from

**TABLE 3** Studies comparing comorbidity incidence between axSpA patients and controls

	Measure of incidence	Control group	Comorbidity	Effect size	95% CI
Cook 2018 [18]	HR (incidence after AS diagnosis), adjusted for age and sex	UK biobank participants without AS, RA, PsA or SLE	Hypertension	1.1	1.0, 1.3
			Angina	1.2	0.9, 1.7
			MI	1.4	1.0, 1.9
			CVA	1.6	1.1, 2.5
			Diabetes	1.2	0.9, 1.6
			COPD	2.0	1.3, 3.1
			Depression	1.5	1.1, 2.0
Essers 2016 [20]	HR (incidence after AS diagnosis), adjusted for age, sex, NSAID use, smoking, BMI and other medications Incidence rate ratio, adjusted for age and sex	CPRD patients without RA, PsA, SLE or vasculitis	MI		
			Ischaemic heart disease	0.76	0.53, 1.09
			MI		
			Ischaemic heart disease	0.91	0.65, 1.27
			heart disease	1.18	0.96, 1.46

COPD: chronic obstructive pulmonary disease; CPRD: Clinical Practice Research Datalink; CVA: cerebrovascular accident; MI: myocardial infarction.

>100 000 patients showed the most prevalent individual comorbidities to be hypertension, hyperlipidaemia and obesity. There was significant variation in the type and number of conditions included in each study, which will impact the precision of estimates. Almost all comorbidities examined were more prevalent in axSpA patients than age and sex-matched controls, with  $\geq 80\%$  higher odds for heart failure and depression. Comorbidities (total number of and individual conditions) were associated with patient-reported outcomes, work productivity, treatment response and mortality.

Despite the high prevalence of many comorbidities, randomized clinical trials—the gold-standard in evidence-based medicine—routinely exclude patients with these conditions. Clinicians should be mindful of extrapolating results from explanatory trials (i.e. under ideal conditions), while researchers should invest in pragmatic trials that measure effectiveness in routine clinical practice [51]. Comorbidities are essential considerations in the real-world management of axSpA patients. They influence treatment decisions (e.g. for NSAIDs and biologics [3]) and preliminary results also suggest that they impact treatment outcomes [28, 49]. Studies in this review consistently showed higher prevalence of comorbidities in axSpA patients than controls. Yet, in clinical practice, management of comorbidities for patients with chronic inflammatory rheumatic diseases are often worse than in the general population [52]. The 2016 EULAR points to consider for comorbidities recommend rheumatology teams to detect and collect information on comorbidities, liaise with appropriate healthcare providers to treat comorbidities, and repeat comorbidity reviews [52]. They focused on six conditions (CVD, malignancies, infections, peptic ulcer, osteoporosis and depression) that map almost exactly with high-

prevalence comorbidities in our meta-analysis. It may, however, be that under-recognised comorbidities have under-estimated prevalence. Others have suggested including additional comorbidities [53], but this may be limited by feasibility in daily practice – the six comorbidities alone require a 93-item reporting form.

Almost all included comorbidities were more prevalent in axSpA patients than controls. axSpA patients had markedly higher odds for depression and cardiovascular diseases than controls. Symptoms of axSpA typically begin in early adulthood, which is a critical time for careers, relationships and general social and personal identity. Disruptive symptoms—sometimes undiagnosed for many years—may impact life-long mental health trajectory and contribute to depression rates. Unlike RA, axSpA is not typically associated with high levels of systemic inflammation – a key driver of CVD risk. Higher CVD prevalence may be related to treatment in addition to the disease process itself; incidence of myocardial infarction and IHD were no different between axSpA and controls after adjusting for NSAID-use [20]. Heart failure is downstream of many CVDs; thus, higher odds in axSpA may reflect the overall burden and severity of CVDs. It may also be due to more systematic identification when considering TNF inhibitors. These results are consistent with prior studies showing reduced systolic and diastolic function in axSpA patients compared with controls [54, 55]. Heart failure can have significant impact on function and quality of life [56], thus optimal symptom management is important for patients already burdened by their rheumatic disease.

The presence of comorbidities was consistently associated with worse patient-reported axSpA outcomes, such as the BASDAI and BASFI. Future studies should complement such analyses by interrogating the

TABLE 4 Studies examining the impact of comorbidity on axSpA outcomes

	How comorbidity was examined	Outcome	Results (shown as pairwise comparison, or 'effect size; 95% confidence interval')
Ariza-Ariza 2009 [46]	Presence or absence (comorbidity list not described)	Quality of life (EQ5D)	Comorbidity was present in 36%. AS patients with comorbidity reported lower QoL than those without (0.36 vs 0.68, $P<0.001$ ) in unadjusted comparison
Salaffi 2009 [47]	SCQ	BASDAI	SCQ was associated with increased BASDAI, no effect size or $P$ -value reported.
Fernandez-Carballido 2019 [21]	Modified CCI (cancer definitions pooled)	BASFI	CCI was not associated with BASFI ( $\beta = -0.03$ ; $-0.13, 0.20$ ) in multivariable linear model.
Redeker 2019 [abstract] [44]	ECI excluding rheumatic diseases	BASDAI BASFI	In multivariable linear models, each unit increase in ECI was associated with: BASDAI ( $\beta = 0.12$ ; 0.07, 0.17), BASFI ( $\beta = 0.10$ ; 0.04, 0.17).
Zhao 2019 (US) <sup>a</sup> [33]	Modified MMI (39 comorbidities)	Pain ESR CRP	Comorbidity was present in 51%. MMI count was associated with: pain ( $\beta = 0.21$ ; 0.04, 0.38), ESR ( $\beta = 2.04$ ; 0.65, 3.42), CRP ( $\beta = 4.93$ ; 2.88, 6.98) in age and sex adjusted linear models.
Boonen 2001 [48]	Presence or absence (19 comorbidities, not described)	Work disability (inability to perform paid work)	Comorbidity was present in 41%. Odds of work disability higher in AS patients with comorbidities (OR 3.15; 1.96, 5.09)
Stolwijk 2014 [11]	SCQ mSCQ CCI RDCI	BASFI  Quality of life (SF36) Work disability (stopped due to disability)	SCQ and mSCQ were associated with BASFI, but CCI and RDCI were not. SCQ and mSCQ were associated with SF36, but CCI and RDCI were not. SCQ and mSCQ were associated with work disability in BASDAI < 4 (but not $\geq 4$ ); CCI and RDCI were not.
Garip 2016 [23]	Presence or absence (9 comorbidities)	Multiple outcomes	Comorbidity was present in 28%. In unadjusted comparisons, patients with comorbidities reported higher BASDAI (5.1 vs 3.7), BASMI (4.3 vs 3.2), BASFI (5.8 vs 2.4) and energy (52 vs 30), all $P<0.05$ . Differences were not significant for sleep (41 vs 33), social isolation (38 vs 29) or emotional reactions (41 vs 35).
Ljung 2018 [29]	Each of 4 comorbidity categories	Multiple outcomes	In multivariable logistic regression: arrhythmia/valvular disease, atherosclerosis, fractures and obstructive sleep apnoea were not associated with peripheral or extra-articular manifestations, BASMI or CRP.
Nikiphorou 2018 [2]	RDCI	Multiple outcomes	In multilevel multivariable linear or logistic models, RDCI was associated with: BASFI ( $\beta = -0.37$ ; 0.30 to 0.43), EQ5D ( $\beta = -0.03$ ; $-0.04$ to $-0.02$ ), Work status (OR 0.83; 0.76 to 0.91), Absenteeism (OR 1.18; 1.04 to 1.34), Presenteeism (OR 1.42; 1.26 to 1.61).
Fitzgerald 2019 [22]	Presence or absence (12 comorbidities)	Multiple outcomes	Comorbidity was present in 55%. In unadjusted comparisons: axSpA with vs without comorbidity had similar ESR (median 11 vs 10, $P=0.09$ ) and CRP (3 vs 2.5, $P=0.18$ ); similar peripheral and extra-articular features, except psoriasis (21 vs 15%, $P=0.02$ ) and peripheral arthritis (38 vs 27%, $P<0.01$ ), Presence of comorbidity associated with higher: BASDAI ( $\beta = 0.70$ ; 0.34, 1.05), BASMI ( $\beta = 0.45$ ; 0.09, 0.80), BASFI ( $\beta = 0.50$ ; 0.23, 0.78), HAQ ( $\beta = 0.07$ ; 0.00, 0.13), ASQoL ( $\beta = 0.87$ ; 0.28, 1.46).

(continued)

TABLE 4 Continued

	How comorbidity was examined	Outcome	Results (shown as pairwise comparison, or 'effect size; 95% confidence interval')
	Number of comorbidities		The number of comorbidities was also significantly associated with: BASDAI ( $\beta=0.23$ ; 0.09, 0.37), BASMI ( $\beta=0.20$ ; 0.05, 0.34), BASFI ( $\beta=0.21$ ; 0.10, 0.32), HAQ ( $\beta=0.03$ ; 0.01, 0.06), ASQoL ( $\beta=0.25$ ; 0.02, 0.49).
Zhao 2019 (UK) [1]	Presence or absence (38 comorbidities based on MMI)	Multiple outcomes	Comorbidity was present in 61%. In unadjusted comparisons, presence of comorbidity not associated with peripheral or EAM. Patients with comorbidity had worse: EQ5D (0.5 vs 0.6), global health (5.2 vs 4.8), fatigue (6.3 vs 5.1), BASDAI (6.4 vs 5.6), spinal pain (7.0 vs 6.0), BASFI (6.8 vs 4.5), all $P<0.05$ ; but not ESR (13 vs 10mm/h) or CRP (5 vs 4mg/l). In multivariable linear models, anxiety/depression and fibromyalgia/IBS clusters were associated with all outcomes, except ESR and CRP.
Lindström 2018 [28]	Each of 6 comorbidities	TNFi discontinuation	CVD (HR 1.24; 1.08, 1.43), Affective disorder (HR 1.81; 1.54, 2.13), Chronic lung disease (HR 1.49; 1.22, 1.82), Malignancy (HR 1.36; 1.06, 1.74), were associated with TNFi discontinuation in unadjusted Cox models, but not Diabetes (HR 1.36; 0.99, 1.87) or CKD (HR 0.79; 0.41, 1.52).
Iannone 2018 [49]	modified RCDI (adding obesity and renal disease)	Biologic drug use	In SpA patients, mRDCI correlated significantly with the number of biological drug switches (Spearman's rank coefficient 0.26, $P$ -value unreported) mRDCI was a significant independent predictor of drug discontinuation (HR 1.53; 1.02, 2.29) and ASDAS remission (HR 0.43; 0.20, 0.92) in multi-adjusted Cox models.
Haroon 2015 [26]	Each of 7 comorbidities including IBD	'Vascular' (cardio- and cerebrovascular) mortality	Dementia (HR, 2.62; 1.32, 5.23) and PVD (HR, 6.79; 2.45, 18.84) were significantly associated with vascular mortality, but not diabetes, CKD, IBD or cancer.
Exarchou 2016 [36]	Each of 5 'general' comorbidities	Mortality	CVD (HR 1.99; 1.58, 2.49), DM (HR 1.92; 1.51, 2.45), Chronic pulmonary disease (HR 3.03; 2.27, 4.05), Malignancy (HR 1.67; 1.32, 2.12), Infections (HR 2.01; 1.68, 2.34) were each independent predictors of mortality in separate multi-adjusted Cox models.
Lee 2018 [50]	CCI	Mortality Disability (based on spine mobility and radiographic changes)	In multivariable logistic models, CCI was associated with increased all-cause mortality (OR 1.07; 1.01, 1.13), but not physical disability (OR 1.01; 0.95, 1.08).

<sup>a</sup>Unpublished data. Absenteeism: time off due to health reasons; CCI: Charlson Comorbidity Index; ECI: Elixhauser Comorbidity Index; MMI: multimorbidity index; Presenteeism: reduced productivity at work; RDCI: Rheumatic Disease Comorbidity Index; SCQ: self-reported comorbidity questionnaire; Work status: working or not.

contribution of individual comorbidities, comorbidity clusters [1], as well as their combined impact. There is also a need to examine how robust various outcomes (e.g. BASDAI vs ASDAS) are to comorbidities such as depression, as they may influence assessment of treatment response. Whether outcomes such as treatment

response and work productivity can be improved by optimizing management of certain comorbidities is an important unanswered question.

Methodological approach for comorbidity research could benefit from similar standardization as suggested for clinical practice [57]. The number of included



comorbidities in this review ranged from 3 to 43. Most studies used author-defined lists that were not validated and selection of diseases was seldom justified. While all studies consistently included CVDs, some important conditions were underrepresented, such as fibromyalgia, alcohol or drug abuse [58] and neurological disorders. Validated comorbidity indices can include rare comorbidities in axSpA (e.g. AIDS and dementia) but not common and important conditions (e.g. depression [59]). None have been validated for use in axSpA patients except the modified SCQ. Stolwijk *et al.* showed that CCI poorly correlated with most axSpA outcomes (e.g. Spearman's  $\rho = -0.01$  for BASDAI) while both CCI and RDCI were poorly associated with BASFI and quality of life (Short Form 36) in multivariable analyses [11]. Validation studies in axSpA are needed for other indices and comorbidity collection based on the 'EULAR 6'. Studies should avoid using weighted indices that have not been validated for their main outcome of interest (e.g. CCI or ECI for functional impairment [21, 44]).

Meta-analysis results should be interpreted with limitations in mind. There was significant heterogeneity in the measurement of comorbidities and relative lack of data on severity. Study samples also differed in age, disease severity and other characteristics. The duration of study in which comorbid diseases were assessed was also variable. These factors will impact pooled prevalence estimates but also highlights the need for greater standardization for future research. Some case-control studies did not explicitly exclude patients with AS or other chronic inflammatory rheumatic diseases from their control population. Comorbidity prevalence in these control populations may therefore be inflated. This is unlikely to meaningfully change the overall result, as inflammatory rheumatic diseases will be uncommon among controls. Once patients develop symptoms of or are diagnosed with axSpA, it is likely that increased healthcare interaction will result in improved identification of comorbidities; therefore, prevalence may be higher than controls by this explanation alone. Well-established comorbidities such as hypertension may undergo more systematic screening and diagnosis than others (e.g. fibromyalgia or depression); results from cases-control comparisons will be inflated for the former group of comorbidities. We were unable to compare comorbidity burden between radiographic and non-radiographic axSpA. Stratified meta-analyses (by classification criteria) did not reveal statistically significant differences in prevalence estimates, which is consistent with the findings of one prior study [33].

In summary, comorbidities are common in axSpA, particularly cardiovascular diseases and risk factors. These items were consistently included in assessments of comorbidities, but diseases belonging to pulmonary, mental health and neurological systems were less frequently included. The vast majority of comorbidities assessed were more prevalent in axSpA patients than in control populations. Overall comorbidity burden, and many individual conditions, were associated with axSpA

outcomes including disease severity, work productivity and mortality. Systematic and repeated assessments should therefore be integrated into routine clinical practice to ensure holistic patient-centred management. Additional studies are needed to validate comorbidity indices for axSpA research.

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## Supplementary data

Supplementary data are available at *Rheumatology* online.

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