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Patterns of comorbidity and their impact on axial spondyloarthritis

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Declaration

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award. This thesis is being submitted in partial fulfilment of the requirements for the degree of PhD. This thesis is the result of my own independent work/investigation, except where otherwise stated. Other sources are acknowledged by explicit references. The views expressed are my own. I hereby give consent for my thesis, if accepted, to be available for photocopying and for interlibrary loan, and for the title and summary to be made available to outside organisations.

Signed: 

Sizheng Steven Zhao

10 November 2020

Acknowledgements

I started my journey on clinical research eight years ago with zero experience. My first paper required so many revisions that it took over a year's worth of tracked changes from first draft to submission. I am grateful to Dr Nicola Goodson for seeing my potential and patiently tutoring me over these years, and for her mentorship in writing this thesis. I thank Dr Dierdre Lane, for being an indispensable source of encouragement and pastoral support, and for her drive and commitment in supervising this PhD to completion. Academia can be a dangerous beast, sucking life from things that actually matter. I have Professor Robert Moots to thank for simultaneously providing me the opportunity to remain in it (through funding this PhD) and reminding me that there is much more.

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Abstract

Background and Aim: Axial spondyloarthritis (axSpA) patients have higher risk of co-existing medical conditions – comorbidities – than the general population, yet management guidelines are largely based on randomised controlled trials that often exclude those with comorbidities. The overarching aim of this thesis was to describe the patterns of comorbidity and their impact on treatment using three real-world axSpA populations.

Methods: Three datasets were used: one from a specialist axSpA service (Aintree cohort) and one from tertiary hospitals in Boston, Massachusetts (Boston cohort), and a longitudinal national axSpA register – the British Society for Rheumatology Biologics Register for axSpA (BSRBR-AS). Chapter 4 compared the prevalence of 39 comorbidities between two axSpA phenotypes – non-radiographic and radiographic axSpA – using the Boston and Aintree cohorts. Cluster analysis was then used to examine how comorbidities co-exist in the Aintree cohort, and how clusters relate to axSpA severity using multivariable regression models. Chapter 5 applied multivariable regression models to baseline BSRBR-AS data to examine whether axSpA disease assessment using various indices were differentially influenced by 14 comorbidities. Chapter 6 applied conditional models to longitudinal data from the BSRBR-AS to investigate the association between comorbidity and treatment response. Chapter 7 focused on the potential causal association of baseline mental health symptoms on treatment outcomes using marginal models.

Results: The Boston cohort included 775 patients (mean age 53 (SD 17) years, 74% male), Aintree 421 patients (46 (SD 14) years, 69% male), and BSRBR-AS 2042 patients (49 (SD 15) years, 67% male). Around half of each cohort had at least one comorbidity. Comorbidity patterns and counts were similar between radiographic and non-radiographic axSpA in Boston (mean 1.5 vs. 1.3, respectively) and Aintree cohorts (1.4 vs. 1.3). Mental health conditions tended to co-exist and were associated with greater axSpA disease severity. In the baseline BSRBR-AS data, each additional comorbidity was associated with higher BASDAI (Bath AS Disease Activity Index) by 0.40 units (95% CI 0.27, 0.52) and ASDAS (AS Disease Activity Score) by 0.09 units (95% CI 0.03, 0.15). Among 994 BSRBR-AS patients starting TNF inhibitors (TNFi), those with multiple comorbidities had similar absolute improvement in disease activity but reduced improvement in function (by 1.0 unit in BASFI at 6 months) and health-related quality of life (2.3 ASQoL units). Compared to those with less than mild depressive symptoms, patients with moderate-severe symptoms had reduced response at 6 months, by approximately 2 BASDAI units and 0.9 ASDAS units. Patients with moderate-severe anxiety symptoms had increased treatment discontinuation (HR 1.59; 95% CI 1.12 to 2.26) than those with less than mild anxiety.

Conclusions: Comorbidities are highly prevalent in axSpA, in particular cardiovascular and mental health disorders. Comorbidities are associated with axSpA disease activity at baseline and adverse treatment outcomes, particularly depression and anxiety. These results have important clinical and policy implications for the current approach to disease assessment. Clinicians should record and refer comorbidities for optimal management, particularly mental health disorders.

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Glossary

AS	Ankylosing spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASDAS-MI	Ankylosing Spondylitis Disease Activity Score major improvement (reduction by 2 or more units)
ASQoL	Ankylosing spondylitis quality of life questionnaire
axSpA	Axial spondyloarthritis
BASDAI 50/2	50% or 2-unit reduction in BASDAI
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
bDMARDs	Biologic disease-modifying antirheumatic drugs
BMI	Body mass index
BSRBR-AS	British Society for Rheumatology Biologics Register for Ankylosing Spondylitis
CCI	Charlson Comorbidity Index
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
csDMARDs	Conventional synthetic disease-modifying antirheumatic drugs
CVD	Cardiovascular diseases
DAS28	Disease activity score – 28 joints
EAMs	Extra-articular manifestations
EHRs	Electronic health records
EQ5D	EuroQol questionnaire - 5 dimensions
ESR	Erythrocyte sedimentation rate
GEE	Generalised estimating equations
HADS	Hospital anxiety and depression scale
HLA-B27	Human leukocyte antigen B27
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
ICD	International Classification of Diseases codes
IMD	Index of Multiple Deprivation
IPCW	Inverse probability of censoring weight
IPTW	Inverse probability of treatment weight
MMI	Multimorbidity index
MS	Multiple sclerosis
NICE	National Institute for Health and Care Excellence
Nr-axSpA	Non-radiographic axial spondyloarthritis
NSAIDs	Non-steroidal anti-inflammatory drugs
PsA	Psoriatic arthritis
QoL	Quality of life
RA	Rheumatoid arthritis
RCTs	Randomised controlled trials
RDCI	Rheumatic Disease Comorbidity Index

SCQ	Self-reported comorbidity questionnaire
SpA	Spondyloarthritis
TB	Tuberculosis
TIA	Transient ischaemic attack
TNFi	Tissue necrosis factor inhibitors
VAS	Visual analogue scale

Publications

The work presented in this thesis formed the basis of the following publications:

1. Zhao S, Robertson S, Reich T, Harrison NL, Moots RJ, Goodson NJ. Prevalence and impact of comorbidities in axial spondyloarthritis: systematic review and meta-analysis. Rheumatology 2020;59(supplement 4): iv47–-57 [Chapter 2]
2. Zhao S, Hong C, Cai T, Chang X, Huang J, Ermann J, Goodson NJ, Solomon DH, Cai T, Liao KP. Incorporating natural language processing to improve classification of axial spondyloarthritis using electronic health records. Rheumatology 2020;59(5):1059-1065 [Chapter 3]
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9. Zhao S, Goodson NJ, Robertson S, Gaffney K. Smoking in spondyloarthritis: unravelling the complexities. Rheumatology 2020;59(7):1472-81
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14. Zhao S, Lyu H, Solomon DH, Yoshida K. Improving rheumatoid arthritis comparative effectiveness research through causal inference principles: systematic review using a target trial emulation framework. Ann Rheum Dis 2020;79:883-890
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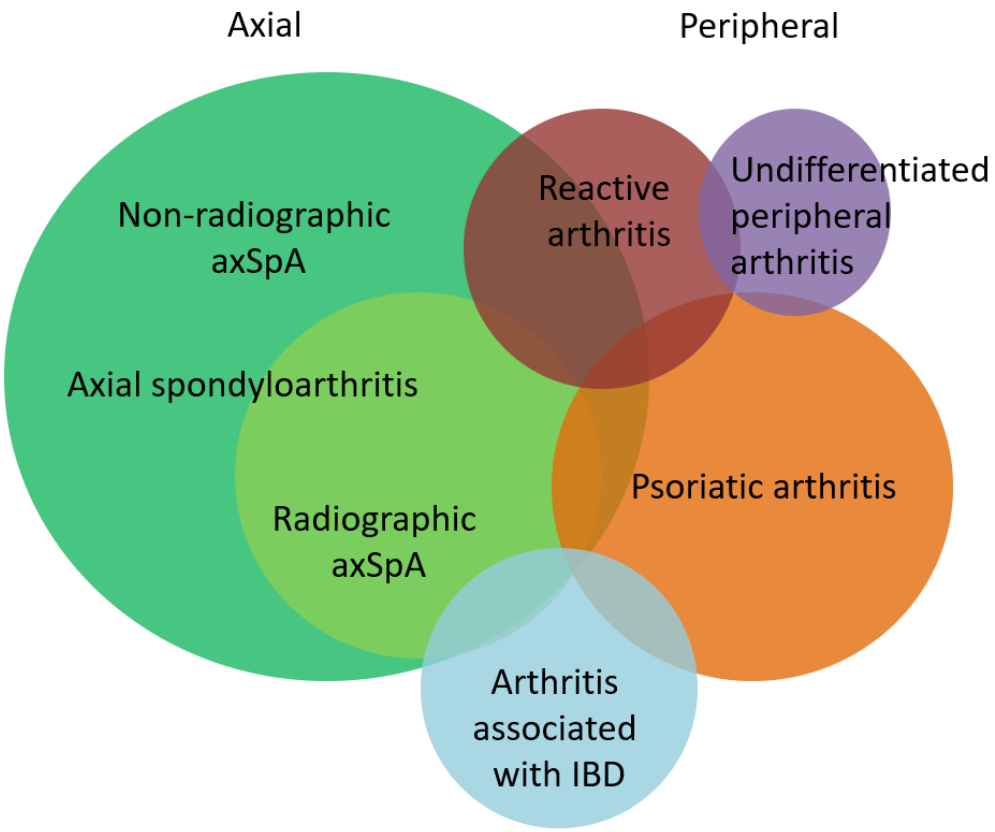
Chapter 1: Introduction

This chapter provides an overview of axial spondyloarthritis (axSpA). Aspects of the disease that are necessary to provide a background for the thesis are described, including clinical features, epidemiology, diagnosis and classification, pathophysiology, and management. This chapter will also introduce the importance of comorbidities and related terminology.

1.1 What is axial spondyloarthritis?

The concept of seronegative spondyloarthritides was first introduced by Moll and Wright in the 1970s [1]; seronegativity for rheumatoid factor, along with clinical features, helped distinguished it from rheumatoid arthritis. The more modern term 'spondyloarthritis' (SpA) includes several pathomechanistically related diseases, such as the prototype ankylosing spondylitis (AS), reactive arthritis, and SpA associated with psoriasis or inflammatory bowel disease (IBD) (Figure 1.1) [2].

Figure 1. 1: The spondyloarthritides.



Adapted from the Assessment of SpondyloArthritis international Society (ASAS) slide library (www.asas-group.org). axSpA, axial spondyloarthritis; IBD, inflammatory bowel disease.

These diseases share similar clinical features and a common association with the human leukocyte antigen B27 (HLA-B27). From a practical viewpoint (e.g., for management), SpA can be grouped into disease that has predilection for the axial or peripheral joints [3]. Patients can, and often do, have both patterns of joint involvement; those with purely axial disease at presentation can develop peripheral arthritis over time and vice versa. This thesis will focus entirely on axial SpA.

Axial spondyloarthritis (axSpA) is a relatively recent disease concept that includes AS, as well as 'non-radiographic axSpA' (nr-axSpA). AS can be considered an advanced stage of the disease spectrum, which is characterised by abnormal, excessive bone formation in the axial skeleton. Nr-axSpA was introduced to recognise early disease without observable damage on plain radiographs [2]. Some consider the two as difference conditions, as only a minority of nr-axSpA progress to AS [4,5].

1.1.1 Clinical features

AxSpA patients can have a diverse combination of disease features that develop in varying chronological order. The commonest presentation is chronic inflammatory back pain: lower back and/or buttock pain that improves with activity and non-steroidal anti-inflammatory drugs (NSAIDs), often causing nocturnal wakening and, upon waking, early morning stiffness. Unlike other adult rheumatic diseases, symptoms of axSpA typically begin at a relatively young age. The mean age of symptom onset in UK cohorts is the early 20s [6,7] - a critical time for education, career, social networks and development of personal identity in general. Consequently, axSpA significant impacts quality of life and work productivity over the life course, at costs to both the individual and the economy [8]. Symptoms of poor mental health are common [9], and this is at least partly due to uncertainty and frustration through the often prolonged delay to diagnosis (mean of 6.7 years [10]).

Peripheral articular features – arthritis, enthesitis and dactylitis – are present in around half of axSpA patients and contribute to additional symptom burden [11]. Arthritis, or synovitis, affect around 29% of patients [12], causing pain, stiffness and functional limitation as in rheumatoid arthritis (RA). Unlike RA, joint involvement is more often asymmetrical, oligoarticular, and associated with a better prognosis (i.e., less structural damage). There is evidence to suggest that synovitis in axSpA is preceded by, and may be a result of cytokine spill over from, adjacent enthesitis [13].

Enthesitis involves localised inflammation at the point of ligament, tendon or capsule insertion into the bone. Enthesitis is common, present in 29-35% of axSpA patients, and can cause widespread pain and tenderness not only in the limbs, but also at spinous processes, costochondral junctions, sternal articulations and iliac crests [12]. These symptoms can present challenges to axSpA diagnosis and management, since widespread tenderness can also be caused by fibromyalgia [14].

Another peripheral feature is dactylitis. It is present in around 6% of axSpA patients and is characterised by inflammation and circumferential thickening of whole digits [12]. Dactylitis may also be a manifestation of enthesitis: inflammation of multiple digital entheseal insertions result in flexor tenosynovitis and extensive soft-tissue swelling outside the joint capsule [13]. It is a cardinal feature of another member of the SpA family, psoriatic arthritis (PsA), where it is present in a quarter of patients and may be associated with greater radiographic damage [15].

1.1.2 Extra-articular manifestations (EAMs)

AxSpA is also strongly associated with extra-articular, or extra-skeletal, manifestations. The prevalence of uveitis among axSpA patients is 26%, while 9% have psoriasis and 7% IBD [16]. The hazard of uveitis was 16-fold higher (95% CI 11.6 to 20.7), psoriasis 50% higher (95% CI 1.1 to 1.9) and IBD 3-fold higher (95% CI 2.3 to 4.8) in axSpA (n=4101) than age- and sex-matched controls (n=28,591) in the UK primary care population [17]. Presence of one EAM can influence the chances of having others [18]. Research into their pathophysiology has improved understanding of the axSpA disease mechanism (Section 1.3). The presence of EAMs also help diagnosis and classification of axSpA (Section 1.4). Patients with EAMs often require collaborative cross-specialty management, which is relevant for healthcare resource use [16]. Most importantly, EMAs impact quality of life and work outcomes, and have also been associated with greater disease activity, functional impairment and radiographic progression in axSpA [18].

1.1.2.1 Acute anterior uveitis (AAU)

Anterior uveitis is defined by inflammation of the anterior uvea (iris and ciliary body) and can be acute (<3 months duration) or chronic (≥3 months). AAU is, by definition, self-limiting and usually managed with topical corticosteroids. It is typically unilateral and recurrent in around half of patients [19]. Symptoms include acute onset of eye redness,

pain, photophobia and miosis. Visual acuity is generally preserved but can be reduced in 8% of cases [20].

AAU occurs in around a quarter of axSpA patients – higher in HLA-B27 positive individuals. Its prevalence becomes higher with longer disease duration as reported in meta-regression of published studies (17% among studies reporting with a mean disease duration of <10 years to 39% with a mean disease duration of >20 years) [20]. AAU and SpA likely share the same underlying disease mechanism [21]. It may the first clinical manifestation of axSpA. In the SENTINEL study of 798 patients with anterior uveitis, over half of patients were found to have axSpA - 70% if HLA-B27 positive [22]. AAU also impacts treatment decisions; monoclonal antibodies to TNF reduce incidence and relapse of AAU, whereas etanercept is less efficacious (see Section 1.5.3.2).

1.1.2.2 Psoriasis

Psoriasis is characterised by keratinocyte proliferation, which results in erythematous, scaly plaques on the body, as well as nail deformities. The disease is not limited to the skin – there are significant associations with metabolic syndrome and depression [23]. Thirty percent of psoriasis patients develop articular involvement, including SpA. Conversely, around 9% of axSpA patients have psoriasis; these individuals are also more likely to have peripheral joint involvement [24].

Due to shared inflammatory pathways, many treatments are approved for psoriasis, PsA and axSpA. Some drugs, such as ustekinumab (IL12/23 inhibitor), guselkumab (IL23 inhibitor), and apremilast (phosphodiesterase 4 inhibitor) are effective for psoriasis but not axial symptoms. Interestingly, around 1.5 to 5% of patients treated with TNFi develop paradoxical psoriasis [25]; the mechanism of which is not yet fully understood.

1.1.2.3 Inflammatory bowel disease

Inflammatory bowel disease (IBD) includes ulcerative colitis (mostly affecting continuous portions of the colon), Crohn's disease (skip lesions anywhere from mouth to anus), and indeterminate colitis. Approximately 10% of patients with IBD develop arthritis – the most common extra-intestinal manifestation [26]. Conversely, around 7% of axSpA patients are diagnosed with IBD [16] and over half have microscopic inflammatory gut lesions [27]. Microscopic bowel inflammation has been associated with more extensive inflammation of the sacroiliac joints [28]. Co-existing IBD and axSpA impacts treatment decisions for both treating specialties; for example, vedolizumab (integrin inhibitor) and ustekinumab are

effective treatments for IBD but not for concurrent axSpA, whereas etanercept for axSpA is not effective for IBD.

1.2 Epidemiology

1.2.1 Prevalence and incidence

Estimates for the prevalence of axSpA vary according to geography (mostly due to background HLA-B27 prevalence), sampling method and disease definition. Most epidemiological studies have focused on AS, where the mean prevalence was estimated as 0.19% in Europe (95% CI calculated from reported data: 0.13 to 0.28%) and 0.32% in North America (95% CI 0.19 to 0.53%) [29]. The incidence of AS was estimated to be 7 cases per 100,000 in both continents [30]. Similar studies of axSpA are scarce. Extrapolating from chronic back pain populations, the prevalence of axSpA in the US and Netherlands were both 0.7% [31,32]. There are no studies of axSpA incidence.

1.2.2 Non-environmental risk factors

AS has traditionally been described as a disease of young males. Earlier studies quoted male:female ratios as high as 9:1, although males only outnumber females by 2-3:1 in more recent studies [30]. This is more likely due to phenotypic differences between the sexes rather than a true difference in prevalence, since sex ratios in early stages of the disease process (i.e., before progression to ankylosis) are typically balanced [12].

Genetic factors are estimated to contribute >90% of the overall susceptibility to AS, half of which due to HLA-B27 and other major histocompatibility complex (MHC) genes [33]. The prevalence of HLA-B27 is around 80% in advanced AS cohorts, but lower in nr-axSpA. The risk of AS was 63% in one monozygotic twin if the other was affected [34]. In one Icelandic study, first degree relatives of AS patients had a 76-fold higher risk of having the condition [35].

1.2.3 Environmental risk factors

Recent studies demonstrated distinctive microbial signature (e.g., abundance of *Ruminococcaceae*) in gut biopsies and faeces of patients with AS/SpA compared with controls [37,38]. This rekindled interest in dietary risk factors, originally ignited by the hypothesis that Klebsiella infection is a trigger for axSpA. There is indeed evidence that diet

has a strong impact on the composition of the gut microbiota [39]. However, no specific dietary components have been identified that can impact the risk or severity of AS. Studies of the gut microbiome have not confirmed the Klebsiella hypothesis.

The most studied environmental risk factor is cigarette smoking. Smoking is a major risk factor for the incidence and severity of RA, and it is also a causal contributor to numerous comorbidities and mortality in all rheumatic diseases. However, its role in axSpA risk and treatment response is less clear. A body of work was performed in parallel to this thesis, since smoking is intimately related to comorbidities but not commonly included as one. In brief, smoking is consistently associated with greater axSpA disease severity and risk of psoriasis and uveitis flares [7,40]. However, evidence for an independent causal role of smoking on axSpA incidence and treatment response had important methodological limitations [9,41,42] (see list of Publications).

1.3 Pathophysiology

Around 80% of axSpA patients are positive for HLA-B27 [2]. This association remains the strongest between any disease and an MHC antigen. However, the precise mechanism(s) through which it causes disease is unclear. It may induce cellular stress and cytokine production directly or through protein misfolding, present 'arthrogenic' microbial peptides to cytotoxic T-cells, and/or cause disease through modulation of the skin and bowel microbiome [2].

AxSpA differs from autoimmune diseases, such as RA, that are typically characterised by T and B cell dysfunction, disease-specific autoantibodies, and female predominance. Instead, it has more in common with auto-inflammatory diseases, where localised stress at specific tissue sites lead to abnormal innate immune responses. AxSpA is clinically, genetically and pathophysiologically related to barrier dysfunction diseases such as psoriasis and IBD; many features of axSpA occur at sites of high mechanical stress, such as those of the sacroiliac joints, spine and entheses [21].

The interplay between genetic predisposition and mechanical stress has become clearer in recent decades. HLA-B27 misfolding and bowel inflammation both induce IL23 expression. IL23 responsive resident T cells, thought responsible for abnormal innate immune response to mechanical stress, have been found at the entheses and aortic root. Overexpressing IL23 in mice activates these T cells to produce peripheral and axial enthesitis, aortitis and uveitis.

IL23 also activates T helper (Th17) cells that produce IL17A/F and TNF [43]. There is evidence to suggest they, and other related cytokines, contribute to the osteoproliferation that characterises AS [2]. The role of these downstream cytokines has been confirmed by clinical efficacy of their blockade [2].

1.4 Diagnosis and Classification

Diagnostic and classification criteria are seldom interchangeable. This distinction is sometimes neglected, partly because the same clinical, laboratory and imaging features are often used for both diagnostic and classification purposes in axSpA. Diagnostic criteria are 'a set of signs, symptoms, and tests developed for use in *routine clinical care* to guide the care of individual patients [44].' In contrast, classification criteria are 'standardised definitions that are primarily intended to enable clinical studies to have uniform cohorts for research [44].' Diagnostic criteria need to account for disease heterogeneity and have high sensitivity (as well as specificity), whereas classification criteria create homogeneous patient groups and need to have high specificity (rather than sensitivity).

1.4.1 Diagnosis

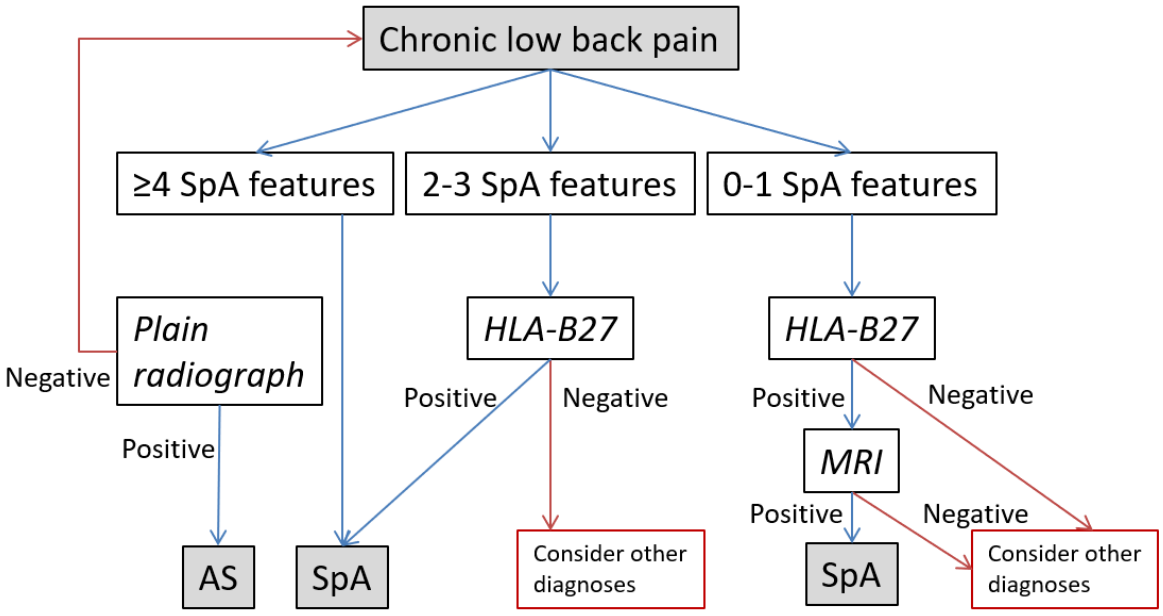
There are no diagnostic criteria for axSpA (or any members of the SpA family), which is unlikely to change [44]. There are many problems with applying diagnostic criteria, such as their dependence on the disease prevalence and range of differential diagnoses (i.e., the pre-test probability). Nevertheless, algorithms, such as the one shown in Table 1.1, can aid diagnostic decisions by providing relative 'importance' of each disease feature [45]. The Assessment of SpondyloArthritis international Society (ASAS) used this data to propose a diagnostic algorithm shown in Figure 1.2.

Table 1. 1: Likelihood ratios to aid diagnosis of axial spondyloarthritis.

Disease feature	Likelihood ratio if present	Likelihood ratio if absent
HLA-B27	9.0	0.11
Sacroiliitis on MRI	9.0	0.11
Anterior uveitis	7.3	
Positive family history*	6.4	0.72
Good response to NSAIDs	5.1	0.27
Dactylitis	4.5	
Peripheral arthritis	4.0	
Inflammatory bowel disease	4.0	
Heel pain (enthesitis)	3.4	
Inflammatory back pain	3.1	0.33
Psoriasis	2.5	
Raised CRP/ESR	2.5	0.63

Adapted from Rudwaleit et al [45].
*Family history for axSpA, reactive arthritis, psoriasis, IBD or anterior uveitis.
HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Figure 1. 2: Diagnostic algorithm for axial spondyloarthritis by the Assessment of SpondyloArthritis international Society (ASAS).



Adapted from van den Berg et al. 2013 [46]. HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging; SpA, spondylarthritis.

1.4.2 Classification

In the absence of diagnostic criteria, features selected for classification are often used to assist the diagnostic process. Describing the evolution of the axSpA concept retrospectively can be confusing using current terminology; to clarify, AS and SpA are longstanding concepts but axSpA was not defined until 2009. The first criteria for the classification of AS was introduced in 1961 [47]. This was subsequently developed into the modified New York criteria in 1984 [48], shown in Box 1.1.

The modified New York criteria require a substantial degree of structural damage of the sacroiliac joints that typically occur in advanced stages of the disease process; these criteria are therefore unable to classify early disease. Patients with peripheral symptoms are also excluded. Partly in response to these limitations, ASAS developed further classification criteria for SpA in 2009 [49,50].

Box 1.1: The modified New York criteria for ankylosing spondylitis.

A. Diagnosis
    1. Clinical criteria:
        a) Low back pain and stiffness for >3 months which improves with exercise, but is not relieved by rest
        b) Limitation of motion of the lumbar spine in both the sagittal and frontal panes
        c) Limitation of chest expansion relative to normal values corrected for age and sex
    2. Radiologic criteria:
        a) Bilateral grade 2-4 sacroiliitis or
        b) Unilateral grade 3-4 sacroiliitis
B. Grading
    1. Definite AS if the radiologic criteria is associated with ≥1 clinical criterion
    2. Probable AS if:
        a) 3 clinical criteria are present
        b) The radiologic criterion is present without any signs or symptoms satisfying the clinical criteria.

Accessibility of MRI to detect early inflammatory changes, as well as the number of effective pharmacological treatments, have both increased in recent decades. Therefore, it became more important to recognise and treat early forms of the disease. To facilitate research and development in this area, ASAS met and developed classification criteria (Box 1.2) for the new entity 'axial SpA' [51]. The equivalent was also developed for 'peripheral SpA' [52], but will not be discussed further in this thesis. This new concept includes the whole spectrum of disease from early non-radiographic forms (nr-axSpA) to more advanced stages when radiographic changes develop (radiographic-axSpA or AS).

Box 1.2. ASAS criteria for axial spondyloarthritis.

In patients with ≥3 months back pain and age at onset <45 years:

- Sacroiliitis on imaging* plus ≥1 SpA feature** (imaging arm) or
- HLA-B27 plus ≥2 SpA features** (clinical arm)

* Sacroiliitis on imaging:

1. Active inflammation on MRI highly suggestive of sacroiliitis associated with SpA;
2. Definite radiographic sacroiliitis (grade ≥2 bilaterally or grade ≥3 unilaterally)

** SpA features include:

1. Inflammatory back pain: any 4 of the following: (1) age at onset <40 years, (2) insidious onset, (3) improvement with exercise, (4) no improvement with rest, (5) pain at night (with improvement upon getting up)
2. HLA-B27 positive
3. Anterior uveitis: confirmed by ophthalmologist
4. Psoriasis: diagnosed by a doctor
5. IBD: diagnosed by a doctor
6. Arthritis (i.e., synovitis): diagnosed by a doctor
7. Dactylitis: diagnosed by a doctor
8. Heel enthesitis: at the Achilles tendon or plantar fascia insertion
9. Good response to NSAIDs: back pain is resolved or much better 24–48h after full dose
10. Elevated CRP: above upper limit of normal without other causes
11. Family history: AS, reactive arthritis, psoriasis, uveitis, or IBD in first- or second-degree relatives.

Meta-analysis of the ASAS criteria performance (from 9 studies, 5739 patients) found high overall sensitivity (82%) and specificity (89%) [53]. The ASAS criteria for axSpA permitted classification via the 'imaging' or the 'clinical' arm (Box 1.2). For the former, the specificity of 'positive MRI' has been questioned, since 28% patients with non-specific back pain have demonstrated similar MRI findings [54]. The definition of a positive MRI finding also has a significant impact on its specificity [55]. The clinical arm has received even greater criticism since it does not require imaging at all. For example, a young, obese, HLA-B27 positive female with fibromyalgia could be misclassified as axSpA if she reports a good response to NSAIDs and is found to have an elevated ESR.

When the United States (US) Food and Drug Administration (FDA) met to consider TNF inhibitors (TNFi) for patients with nr-axSpA, they raised concerns that patients with highly prevalent conditions such as fibromyalgia might be misdiagnosed as nr-axSpA and inappropriately treated. This was one reason why biologic treatment remained unlicensed for nr-axSpA in the USA until March 2019. Research are ongoing to validate the ASAS axSpA criteria and, if needed, to strengthen the MRI imaging definition and weighting of the SpA features.

1.4.3 Differences between radiographic and non-radiographic axial spondyloarthritis

Not all patients with nr-axSpA progress to AS [4]; therefore, there is some controversy over whether or not nr-axSpA is an early form of the axSpA spectrum. There are important differences between the two evident in observational cohorts: AS groups tend to be older, more frequently male, and have higher inflammatory markers and a higher proportion of HLA-B27 positivity than their nr-axSpA counterparts [56–58]. However, both have similar disease features, symptom burden and, importantly, similar response to treatment [59,60]. ASAS-EULAR (the European League against Rheumatism) recommends a unified treatment approach for all axSpA patients [61]. How management should be delivered for these two conditions has not yet been fully elucidated; for example, whether comorbidities differ between AS and nr-axSpA is not yet known.

1.5 Management

This section is largely based on the 2016 ASAS-EULAR recommendations [62] – the only set developed by an international society (ASAS). Discussion is limited to aspects that are particularly relevant to this thesis, namely disease assessment and pharmacological management.

1.5.1 Assessment

ASAS has endorsed outcome measures for use in a range of settings [62]. The core set recommended for routine management [63] is shown in Box 1.3. BASDAI is a 6-item questionnaire, from which a score is derived ranging from 0 (low) to 10 (high disease activity). Spinal pain is assessed using two questions in the ASAS recommendations, one for pain from AS, and another for pain from AS *at night*. In routine UK clinical practice, only the former is used. BASFI is an average score from 10 questions, ranging from 0 (low) to 10 (high functional impairment). Components of these indices are shown in Box 1.4. In the UK, treatment using biologics require mandatory assessment of BASDAI and spinal pain. For disease monitoring, ASAS-EULAR recommendations also specify the need to assess EAMs [62]. Other important patient reported outcomes, including health-related quality of life (core to the ASAS-EULAR overarching principle of management), are discussed in Chapter 3.

Box 1.3: Core outcome set recommended for routine management.

- BASDAI, the Bath AS disease activity index
- Spinal pain
- BASFI, the Bath AS disease functional index
- Patient global
- Fatigue (BASDAI question 1)
- Duration of morning stiffness (BASDAI question 6)
- Spinal mobility (chest expansion, modified Schober, occiput to wall distance, cervical rotation, lateral lumbar flexion; note that these are not the same as items in BASMI)
- 44 swollen joint count
- Entheses (using a validated tool)
- Acute phase reactants (CRP or ESR)

Box 1.4: Components of key patient reported outcome measures used to monitor axSpA patients.

BASDAI

1. How would you describe the overall level of fatigue/tiredness you have experienced?
2. How would you describe the overall level of AS neck, back or hip pain you have had?
3. How would you describe the overall level of pain/swelling in joints other than the neck, back or hips you have had?
4. How would you describe the overall level of discomfort you have from any areas tender to touch or pressure?
5. How would you describe the overall level of morning stiffness you have had from the time you wake up?
6. How long does your morning stiffness last from the time you wake up?

Spinal pain

How would you describe the overall level of pain you have experienced in your spine during the past week?

BASFI

Level of ability with each of the following activities during the past week:

1. Putting on your socks or tights without help or aids (e.g., sock aid).
2. Bending forward from the waist to pick up a pen from the floor without an aid.
3. Reaching up to a high shelf without help or aids (e.g., helping hand).
4. Getting up out of an armless dining room chair without using your hands or any other help.
5. Getting up off the floor without help from lying on your back.
6. Standing unsupported for 10 min without discomfort.
7. Climbing 12 to 15 steps without using a handrail or walking aid. One foot at each step.
8. Looking over your shoulder without turning your body.
9. Doing physically demanding activities (e.g., physiotherapy, exercises, gardening or sports).
10. Doing a full day's activities, whether it be at home or at work.

Since the above recommendations, ASAS also introduced the AS disease activity score (ASDAS) [64,65], which has stronger associations with radiographic progression than BASDAI [219]. ASDAS was created with the aim of introducing more validity, discriminative capacity, and objectivity to disease activity assessment. It combines five disease activity variables with only partial overlap. ASAS preferentially recommends the ASDAS-CRP, with ASDAS-ESR as an alternative (Box 1.5).

Box 1.5: The ankylosing spondylitis disease activity score (ASDAS) formulae [8,9].

ASDAS combines three questions from the BASDAI with a patient global score and inflammatory marker (CRP in mg/l or ESR).

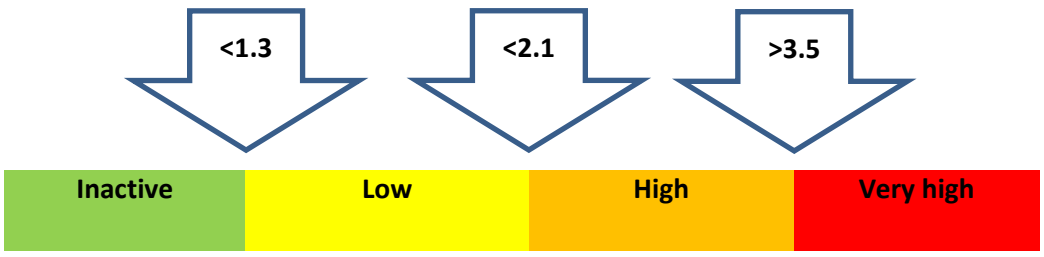
1. Total back pain (BASDAI question 2)
2. Peripheral pain/swelling (BASDAI question 3)
3. Duration of morning stiffness (BASDAI question 6)
4. Patient global: 'How active was your spondylitis on average during the last week?'

ASDAS-CRP = 0.12 x Back Pain + 0.06 x Duration of Morning Stiffness + 0.07 x Peripheral Pain/Swelling + 0.11 x Patient Global + 0.58 x Ln(CRP+1)

ASDAS-ESR = 0.08 x Back Pain + 0.07 x Duration of Morning Stiffness + 0.09 x Peripheral Pain/Swelling + 0.11 x Patient Global + 0.29 x √ESR

Four disease activity states were chosen by consensus with validated thresholds (Figure 1.3). A change of ≥1.1 units is defined as 'clinically important improvement' and ≥2.0 units as 'major improvement' (ASDAS-MI).

Figure 1. 3: Ankylosing spondylitis disease activity score (ASDAS) states.

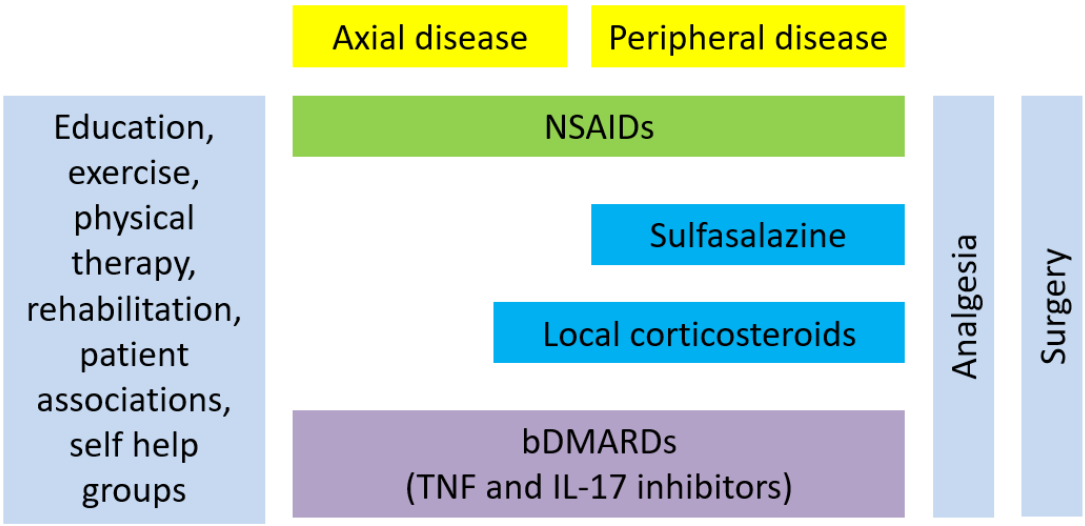


Adapted from references [64,65].

1.5.2 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs inhibit cyclo-oxygenase (COX) to reduce key mediators of inflammation. The maximum tolerated dose is recommended as the first line pharmacological option (Figure 1.4), with response evaluated 2 to 4 weeks later. The ASAS-EULAR, as well as NICE (National Institute for Health and Care Excellence), guidelines recommend trial of at least two agents. Naproxen was able to induce ASAS partial remission in 35% of patients with early disease [66]. Continuous use of celecoxib, a selective COX-2 inhibitor, reduced radiographic progression [67].

Figure 1. 4. ASAS-EULAR recommendations for the management of axial spondyloarthritis



Adapted from van der Heijde et al [62]. bDMARDs, biologic disease-modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; TNF, tumour necrosis factor.

Not all patients are able to tolerate NSAIDs, for example, those with renal or cardiovascular diseases. Non-selective NSAIDs are associated with intestinal relapses in patients with active IBD and increased hospital admissions due to colitis [68]. In axSpA patients with IBD, selective COX-2 inhibitors may be safer alternatives [69,70]. North American guidelines conditionally recommended celecoxib over other NSAIDs for short courses [71]. When patients have sustained high disease activity despite NSAIDs, or develop toxicity, disease-modifying antirheumatic drugs (DMARDs) are recommended.

1.5.3 Disease-modifying antirheumatic drugs (DMARDs)

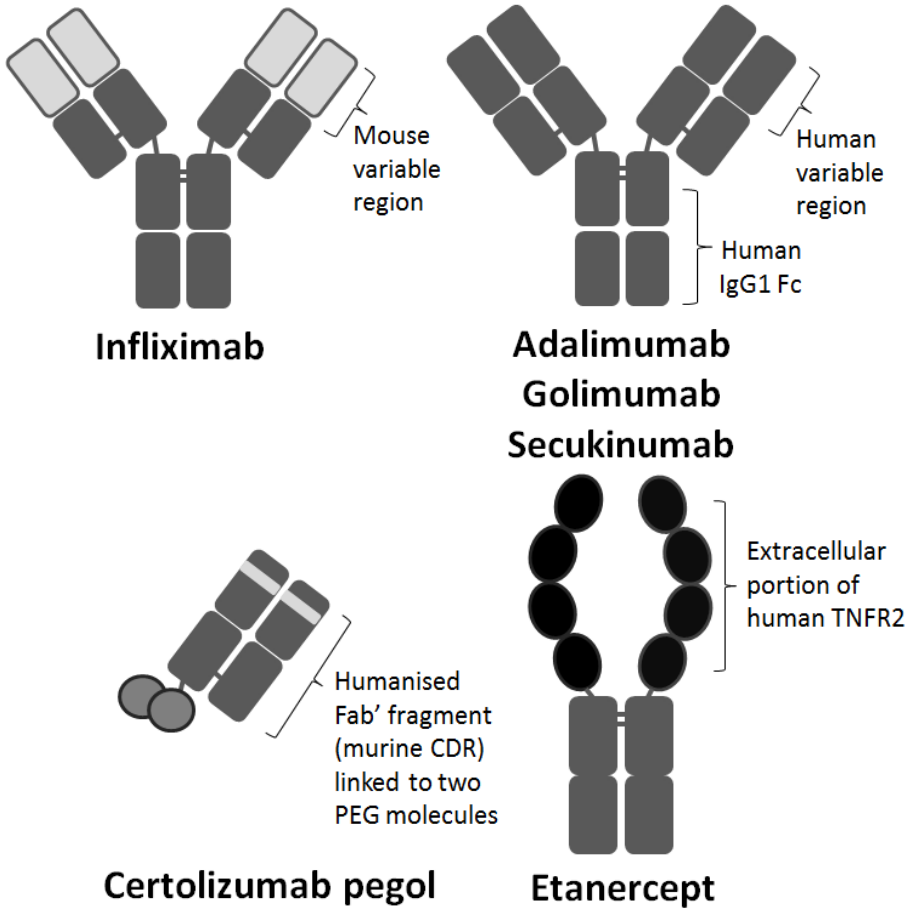
1.5.3.1 Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)

There is evidence that csDMARDs - sulfasalazine, methotrexate and leflunomide - are *not* efficacious for axial symptoms. Patients with purely axial disease should not normally be treated with csDMARDs [62], although sulfasalazine may be considered in patients with peripheral joint involvement.

1.5.3.2 Biologic disease-modifying antirheumatic drugs (bDMARDs)

bDMARDs have revolutionised the treatment for those with sustained high disease activity despite the above treatment options. These are large, complex protein molecules that target specific cytokines, or their receptors, involved in the inflammatory pathway. Several TNF inhibitors (TNFi) have been approved for axSpA (Figure 1.5). All except infliximab have indications for both radiographic and nr-axSpA. TNFi for nr-axSpA was approved more recently: 2016 in the UK, and 2019 in the US (only certolizumab pegol). In the UK, biosimilar infliximab, adalimumab and etanercept are widely in use. In 2016, a new class of bDMARDs became available for AS patients in the UK – secukinumab (IL17A inhibitor).

Figure 1. 5 Biologic disease-modifying antirheumatic drugs licenced for axSpA.



All except etanercept are monoclonal antibodies. All are TNF inhibitors except secukinumab, which blocks IL17A. TNFR2, TNF receptor 2; Fc, fragment crystallisable region.

Approximately half of patients started on TNFi achieve BASDAI 50 (50% reduction in BASDAI, sometimes labelled as BASDAI 'major response') at 3 months [42,72]. The efficacy of bDMARDs with regard to musculoskeletal signs and symptoms are comparable, although no head-to-head trials are available. Their efficacy for EAMs, however, differ significantly. Monoclonal antibodies against TNF are efficacious for both uveitis and IBD, whereas etanercept may not be optimal for the former and has no efficacy in the latter [62]. Etanercept may also be less efficacious for psoriasis [62]. The secukinumab trial in Crohn's disease was terminated early because rates of adverse events and efficacy were worse than placebo [73]. In trials of psoriasis, PsA and AS, exacerbations and new onset of IBD occurred [74]. Therefore, secukinumab should be used with caution or avoided in patients with significant bowel symptoms even without a definitive diagnosis of IBD.

1.5.3.3 Targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs)

tsDMARDs are small molecule drugs that have specific intracellular targets of action. Apremilast (phosphodiesterase 4 inhibitor) is licensed for psoriasis and PsA, but has failed to demonstrate any difference from placebo in AS [75]. A more recent addition to the rheumatologists' armamentarium is the group of Janus kinase (JAK) inhibitors. Tofacitinib – a JAK1/3 inhibitor already licenced for RA and PsA – showed superior efficacy to placebo in a phase 2 trial of AS patients (67% of active arm achieved ASAS 20% improvement, 27% higher than placebo [76,77]). Another phase 2 trial also demonstrated efficacy of filgotinib (selective JAK1 inhibitor) over placebo in AS [78]. Although none are currently licenced (September 2020), it is likely that JAK (and other kinase) inhibitors will play an important role in future axSpA management.

1.6 Comorbidity

Patients with axSpA frequently have other co-existing conditions – comorbidities – by chance or resulting from the disease process and its treatment. To provide holistic care, with the patient (rather than the disease) at the centre, clinicians need a proactive and pragmatic approach to managing comorbidities. Many conditions directly impact management, yet randomised controlled trials – the gold standard evidence-base – seldom include patients with comorbidities, thus the benefit/risk of these aforementioned pharmacological therapies are largely unknown. There is a pressing need for research about the impact of comorbidities on the disease process and their impact on treatment options to fill this gap in evidence-based practice. This section introduces why comorbidities are important for clinicians and researchers, accompanied by clarification of terminology.

1.6.1 Comorbidity or multimorbidity

The worldwide population is ageing, particularly in developed countries like the UK and United States. A 2012 study in the UK provided a clear demonstration of how comorbidity burden increases with age (Figure 1.6) [79]. Patients attending rheumatology clinics with multiple disorders are increasingly the norm. This demographic shift has occurred in parallel with increasing specialisation of disease management, aimed at improving the quality of care. It is essential that specialists remain proactive in identifying and managing comorbidities, not only because fragmented care can be inefficient [80] (e.g., several

healthcare providers treating overlapping conditions) but also because patients benefit from being treated holistically.

Figure 1. 6: The number of co-existing conditions increases with age.

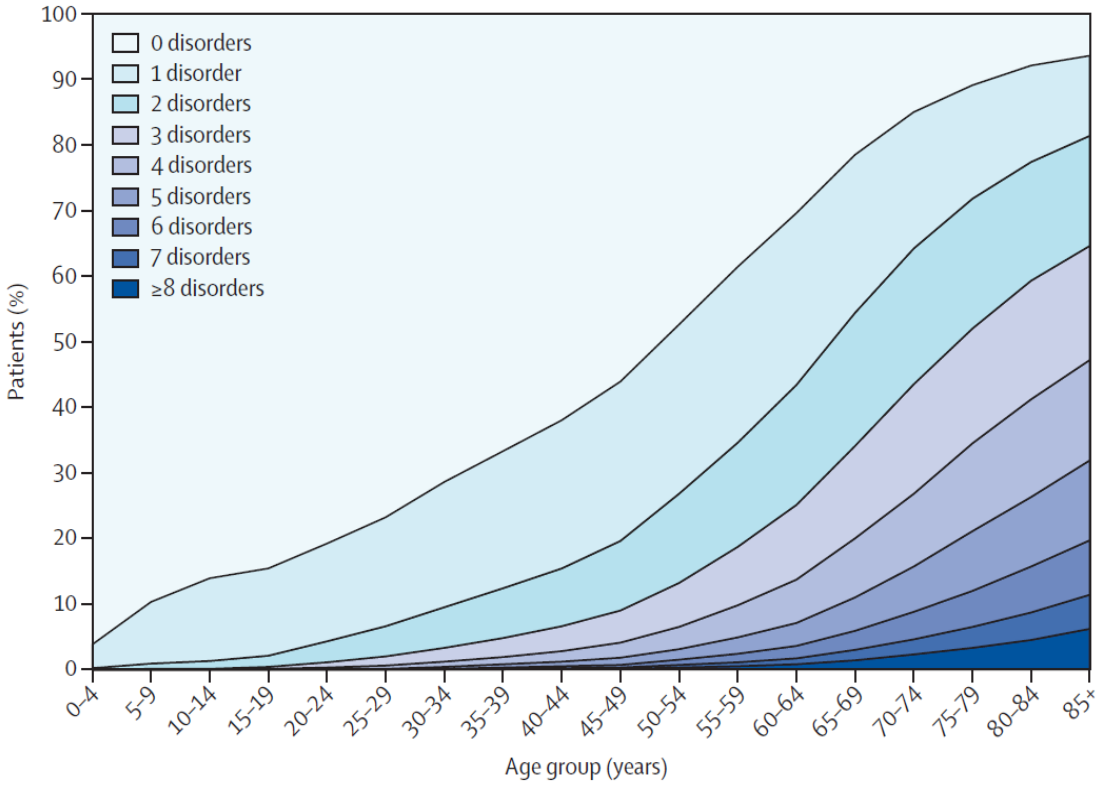


Figure from Barnett et al 2012 [79].

The co-existence of two or more conditions is a seemingly simple concept but has a range of interpretations and definitions. 'Comorbidity' is defined by the co-existence of distinct morbidities in addition to an index disease of interest. This perspective is common in hospital settings, where each specialty manages the index disease and its manifestations, but often refers comorbidities to other healthcare providers. 'Multimorbidity' is a more patient-centred concept that refers to the co-existence of any two chronic conditions. This viewpoint is typical for primary care settings, but the two are not mutually exclusive. While the philosophy behind 'multimorbidity' is how patient-care should be delivered, 'comorbidity' will be used throughout this thesis for clarity and familiarity.

What counts as a 'morbidity' is also debated. EAMs share the same underlying pathophysiology as axial disease and are thus considered disease features, not comorbidities. This definition is not without problems; for example, conduction and

valvular defects of the heart also share mechanisms with axial inflammation [43], but would be more commonly considered as cardiovascular comorbidities. A helpful delineation is observed from RCTs: EAMs are actively included, while comorbidities are generally excluded. There is further ambiguity between comorbidity and complications, most notably regarding osteoporosis and fractures: reduced bone mineral density of the spine is considered a comorbidity but is related to effects of localised inflammation in the spine (i.e., the disease process); fractures can be due to vertebral fusion (complication) or osteoporosis (comorbidity). Chronic comorbidities are most commonly counted, but some indices also include acute conditions (e.g., myocardial infarction), health-related risk factors (e.g., obesity and hypertension) and/or symptoms (e.g., back pain and urinary incontinence) [81–83]. For example, hypertension is a risk factor for coronary heart disease and stroke, but also has a diagnostic definition and requires long-term management like many chronic diseases.

The choice of which comorbidities to include depends somewhat on whether they are studied as outcomes (e.g., do bDMARDs increase risk of infections?) or exposures (does depression impact treatment response?). Rather than focusing on one definition, this thesis will examine aspects related to comorbidity from a flexible standpoint, to identify and contribute to areas of unmet research need.

1.7 Summary

AxSpA is a complex condition that presents with a range of disease features and unique challenges for management. Its onset in early adulthood can be deleterious to education, career, relationships, and mental health; improving care for axSpA patients is important as the disease has potential to disrupt the entire life-course. Although effective targeted treatments are increasingly available, most clinical trials have excluded patients with comorbidities. Description of comorbidity burden and patterns are scarce. How comorbidities impact axSpA outcomes, such as treatment response, are unclear. There is a pressing need for research into comorbidities in axSpA to inform and support holistic, evidence-based management.

Chapter 2: Background Literature Review

This chapter systematically reviews the literature on comorbidities in axSpA and discusses areas in need of further research to support the aims and objectives of this thesis.

2.1 Introduction

Comorbidities are common in people with chronic rheumatic diseases. This may be due to shared risk factors, consequences of inflammation or its treatment (e.g., long-term NSAIDs). Comorbidities are associated with adverse health outcomes such as poorer physical function, quality of life, work productivity, and mortality [84]. Some, such as renal, cardiovascular and gastrointestinal diseases, influence treatment decisions [85]. A holistic, patient-centred approach is therefore essential in rheumatology, yet randomised controlled trials – the gold-standard on which management guidelines are largely based – often exclude patients with comorbidities. Observational research using real-world data are important in addressing this unmet need, but studies have historically been heterogeneous in design and quality.

The majority of axSpA comorbidity research has focused on one or a few closely related conditions within one organ system; for example, depression in axSpA [9], or cardiovascular diseases (CVDs) in axSpA [86]. While this approach is valid for assessing the impact of one comorbid disease on axSpA and vice versa, it does not reflect the real-world setting where patients frequently have multiple inter-related comorbidities. Studying a broad range of comorbidities helps quantify their collective 'burden' on health, which in turn provides context for the relative importance of, and relationship between, individual conditions. For example, what are the relative impacts of CVDs and depression on outcomes such as quality of life? When commissioning interventions, which should be prioritised? Are there 'clusters' of commonly co-existing comorbidities, such that the presence of one should trigger screening for others? These are some of many unmet research-needs in axSpA that motivated this thesis. This chapter begins by reviewing descriptive epidemiological studies of comorbidities in axSpA and then moves on to their impact on disease outcomes. A detailed discussion follows, focusing on directions and methodological approaches for this thesis.

2.2 Aims

1. To describe the prevalence of commonly reported comorbidities in patients with axSpA and how they compare to control populations.
2. To summarise what is known about the impact of comorbidity burden on longitudinal outcomes in patients with axSpA.
3. To discuss implications of the systematic review findings on the aims and methodology of this thesis.

2.3 Methods

A systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. The protocol was pre-registered with PROSPERO (CRD42019151105). Full details on methods and results for this review are published in reference [84]. Medline, PubMed, Scopus and Web of Science were searched for relevant literature on 27th of September 2019, using the following search terms: (ankylosing spondylitis [MeSH] OR axial spondyloarth*) AND (multimorbidy [MeSH] OR comorbidity [MesH] OR polymorbid* OR multi-morbid* OR co-morbid* OR poly-morbid*). No additional date or language restrictions were used. Bibliographies of all eligible studies were also manually searched to identify additional titles. The review was updated on 30th of September 2020 to include articles published over the last 12 months. 'PICO' was defined as:

- Participants/population: Studies of axSpA, whether defined by classification criteria or otherwise.
- Intervention/exposure: Not applicable for Aim 1. For Aim 2, 'exposure' was the presence of any or individual comorbidities versus none.
- Comparator/control: For Aim 1, incidence and prevalence of comorbidities were compared against controls. The definition of the control group could be healthy (i.e., without rheumatic diseases) or general populations (i.e., including rheumatic disease).
- Outcome: Aim 1 'outcomes' of interest were incidence and prevalence of comorbidities. Aim 2 examined axSpA-specific (e.g., treatment response or disease severity indices) and general outcomes (e.g., mortality).

Published conference abstracts were considered, as some prevalence studies may not be published as full articles but nevertheless have sufficiently detailed methodology and results. Reviews, comments, and editorials were excluded.

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 distinguished studies of comorbidity from, e.g., cardiovascular risk. Studies that used non-representative sampling (highly selective recruitment or randomised controlled trials) or had a samples size of less than 30 (to avoid unreliable prevalence estimates) were excluded. Extra-articular manifestations (EAMs) were excluded from the list of comorbidities, since they share pathogenesis with and aid diagnosis of axSpA (thereby determining study inclusion) [87,88].

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. Studies were assessed for risk of bias using an adapted version of the Newcastle Ottawa Scale.

For Aims 1 and 2, meta-analysis was performed for comorbidities reported by at least three studies. Pooled prevalence estimates were reported as percentages (95% confidence interval, I^2 statistic), using random-effects models (DerSimonian-Laird). Double arcsine transformation was used, since 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).

2.4 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 [89–91], from which the paper by Nikiphorou et al was selected since it restricted to participants fulfilling ASAS criteria. Two articles used the OASIS registry [92,93]; Stolwijk et al was selected as it reported a greater range of comorbidities. The larger of 2 studies using United States' claims data by Walsh et al was included [94,95]. Flowchart of the selection process is shown in Figure 2.1.

The 40 included studies are summarised in Table 2.1 [7,86,90,93,95–129]. Sample size ranged from 74 to 21,872 [107,108]. Twenty-one studies used European cohorts [7,96,98,100,102,106,108–110,112–114,116,118,119,121–123,128–130], 7 were from Asia [101,104,111,115,117,124,125], 6 North America [86,95,97,103,126,127], 1 Argentina [120], 1 Australia [99] and 4 were multinational [90,93,105,107]. Mean age of study samples ranged from 29 (China [115]) to 59 (UK [109]). Mean BASDAI ranged from 3.4 (China [115]) to 7.6 (Australia, cohort initiating TNFi [99]).

AxSpA was defined using classification criteria in 20 studies (7 using the modified New York criteria only, 13 using the ASAS and/or mNY criteria), diagnostic codes in 14, physician diagnosis in 3 and self-report in 1. The number of comorbidities studied ranged from 3 to 43 (excluding EAMs). Most studies used non-validated lists, while 13 used a validated index either directly or indirectly (to inform which comorbidities to include, e.g., Kang et al [101]): 3 used the Charlson Comorbidity Index (CCI), 2 Elixhauser Comorbidity Index (ECI), 3 self-reported comorbidity questionnaire (SCQ), 2 Rheumatic Disease Comorbidity Index (RDCI), 2 multimorbidity index (MMI) and 1 Functional Comorbidity Index. EAMs were included as comorbidity in a minority (5 out of 40 studies), while 2 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 since they were not dedicated studies of comorbidities, thereby losing one point for bias. Taking this into account, most studies scored 4 or 5 out of a possible 6 points indicating minimal bias (summary in Table 2.1, detailed risk of bias assessment is presented in Appendix 10.1, Table S2.1 and Figure S2.1).

Figure 2. 1: PRISMA flowchart of study selection for each of the study aims.

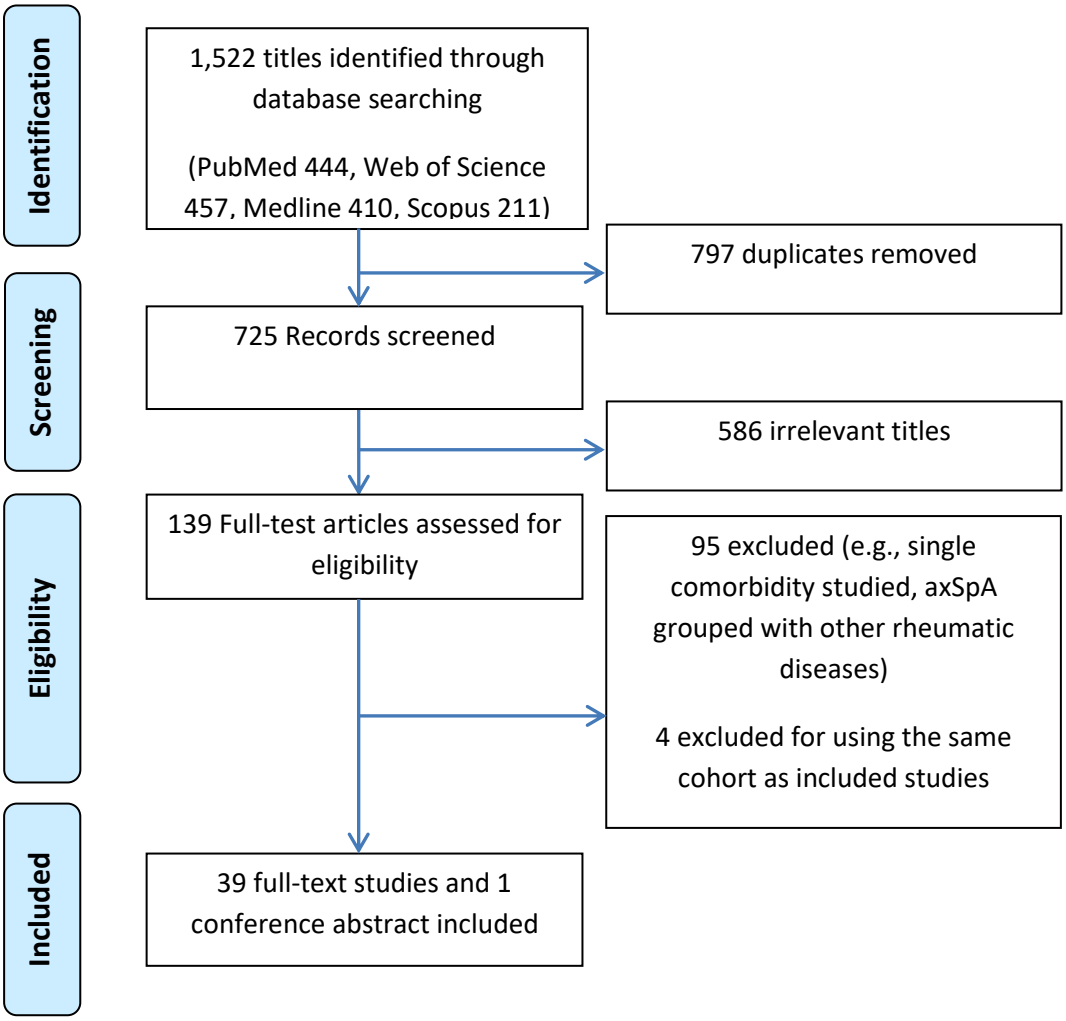


Table 2. 1: Summary of characteristics of studies included in the systematic review of comorbidities in axial spondyloarthritis.

Study	Country	Sample Size	Diagnosis	Mean Age	Males %	BASDAI	Data source	Comorbidity Ascertainment	Number of Comorbidities	NOS
Boonen 2001 [96]	Netherlands	658	AS (physician diagnosed)	na	71%	na	Hospital	Self-reported	19	3
Han 2006 [97]	USA	1843	AS (ICD)	47	60%	na	Health insurance	ICD	8	4
Ara 2008 [98]	UK	147	AS (mNY)	51 (11)	87%	4.3 (2.3)	Hospital	Physician diagnosed	3	5
Oldroyd 2009 [99]	Australia	198	AS (physician diagnosed, starting TNFi)	45 (12)	72%	7.6	Hospital	Self-reported	19	3
Salaffi 2009 [100]	Italy	164	AS (mNY)	52 (9)	81%	5.5 (1.7)	Hospital	Self-reported	SCQ	3
Kang 2010 [101]	Taiwan	11701	AS (ICD)	67% <45yrs	79%	na	Health insurance	ICD	31 ECI	4
Bremander 2011 [102]	Sweden	935	AS (ICD)	52 (15)	67%	na	Population register	ICD	7	4
Gladman 2011 [103]	Canada	1108	axSpA (mNY/ASAS)	31 (12) at diagnosis	74%	4.7 (2.5)	Hospital (SPARCC)	Physician diagnosed	5	5
Bodur 2012 [104]	Turkey	1381	AS (mNY)	39 (11)	75%	52% ≥4	Hospital	Physician diagnosed	6	5
Ward 2013 [105]	USA, Australia	801	AS (mNY)	Median 46	73%	na	Hospital (PSOAS)	Unclear	12	3
Stolwijk 2014 [131]	Netherlands, Belgium	98	AS (physician diagnosed, starting TNFi)	54 (11)	70%	3.8 (2.2)	Hospital (OASIS)	Medical records	11 SCQ	5
Dougados 2015 [106]	France	708	SpA (26% mNY, 70% ASAS)	34 (9)	46%	60% >4	Hospital (DESIR)	Physician diagnosed	12	5
Hammoudeh 2015 [107]	Egypt, Kuwait, Qatar, Saudi Arabia	74	AS (unclear, 85% had	na	na	na	Hospital	Physician diagnosed	4	4

			radiographic sacroiliitis)							
Haroon 2015 [86]	Canada	21473	AS (ICD)	46	53%	na	Health insurance	ICD	8	4
Kristensen 2015 [108]	Sweden	21872	AS (ICD)	Median 46	52%	na	Hospital	ICD	7	3
Ahmed 2016 [109]	UK	94	AS (Read code)	59 (13)	87%	na	Primary care	Read code	4	4
Essers 2016 [110]	UK	3809	AS (Read code)	46% <40years	71%	na	Primary care	Read code	11	4
Exarchou 2016 [130]	Sweden	8600	AS (ICD)	42 (13) at diagnosis	66%	na	Hospital	ICD	12	3
Garip 2016 [111]	Turkey	110	AS (mNY)	40 (10)	68%	4.9 (1.9)	Hospital	Patient reported then cross checked with medical records	8	4
Maas 2016 [112]	Netherlands	461	axSpA (mNY/ASAS)	45 (13)	66%	3.8 (2.3)	Hospital	Self-reported	15 mSCQ	3
Cook 2018 [113]	UK	1254	AS (self-reported)	Median 59	63%	na	Population research cohort	Self-reported	7 from FCI, not all reported	2
Iannone 2018 [114]	Italy	213	SpA (ASAS)	48 (13)	54%	na	Hospital	Self-reported	mRCDI	3
Jiang 2018 [115]	China	364	SpA (ASAS)	29 (8)	81%	3.4 (2.0)	Hospital	medical records and interview	24	5
Krüger 2018 [116]	Germany	10208	AS (ICD)	57	61%	na	Health insurance	ICD	9 CCI	4
Lee 2018 [117]	Korea	1111	AS (ICD)	51% <45yrs	65%	na	Health insurance	ICD	CCI	4
Lindström 2018 [118]	Sweden	2577	AS (ICD, starting TNFi)	44 (13)	71%	20% ≥4	Hospital (SRQ)	ICD and prescriptions	6	4
Ljung 2018 [119]	Sweden	346	AS (mNY)	56 (15)	75%	na	Hospital	Medical records	43	5

Nikiphorou 2018 [90]	Multinational - 22 Countries	3370	SpA (ASAS)	43 (14)	66%	3.7 (2.4)	Hospital	Physician diagnosed	10 RDCI	6
Sommerfleck 2018 [120]	Argentina	86	axSpA (mNY/ASAS)	Median 46	80%	na	Hospital (ESPAXIA)	Patient interview and medical records	10	5
Walsh 2018 [94]	USA	6679	AS (ICD)	51 (14)	61%	na	Health insurance	ICD	20	4
Zhao 2019 [7]	UK	2420	axSpA (mNY/ASAS)	49 (15)	68%	4.8 (2.5)	Hospital (BSRBR-AS)	Physician diagnosed	15	5
Claudepierre 2019 [121]	France	827	AS (ICD)	50 (14)	57%	na	Health insurance	ICD	9	4
Fernandez-Carballido 2020 [122]	Spain	738	AS (mNY)	48 (12)	74%	na	Hospital	Unclear	14 CCI	4
Fitzgerald 2019 [123]	Ireland	734	axSpA (78% mNY, 94% ASAS)	45 (12)	77%	Median 3.9	Hospital (ASRI)	Physician diagnosed	12	5
Hong 2019 [124]	Singapore	262	axSpA (mNY/ASAS)	32 (13)	79%	3.6 (1.9)	Hospital	Physician diagnosed	3	5
Png 2019 [125]	Singapore	189	axSpA (ASAS)	38 (13)	76%	38% ≥4	Hospital	Unclear	5	3
Singh 2019 [126]	USA	10990	AS (unclear)	na	50%	na	Hospital	Unclear	6	1
Zhao 2019 [127]	USA	775	axSpA (ASAS)	53 (17)	74%	na	Hospital	ICD	39	4
Zhao 2019 [128]	UK	419	axSpA (ASAS)	46 (14)	69%	5.8 (2.5)	Hospital	Physician diagnosis and medication	38	5
Redeker 2019 [abstract] [129]	Germany	1776	AS (ICD)	56	54%	na	Health insurance	ICD	9 ECI	4

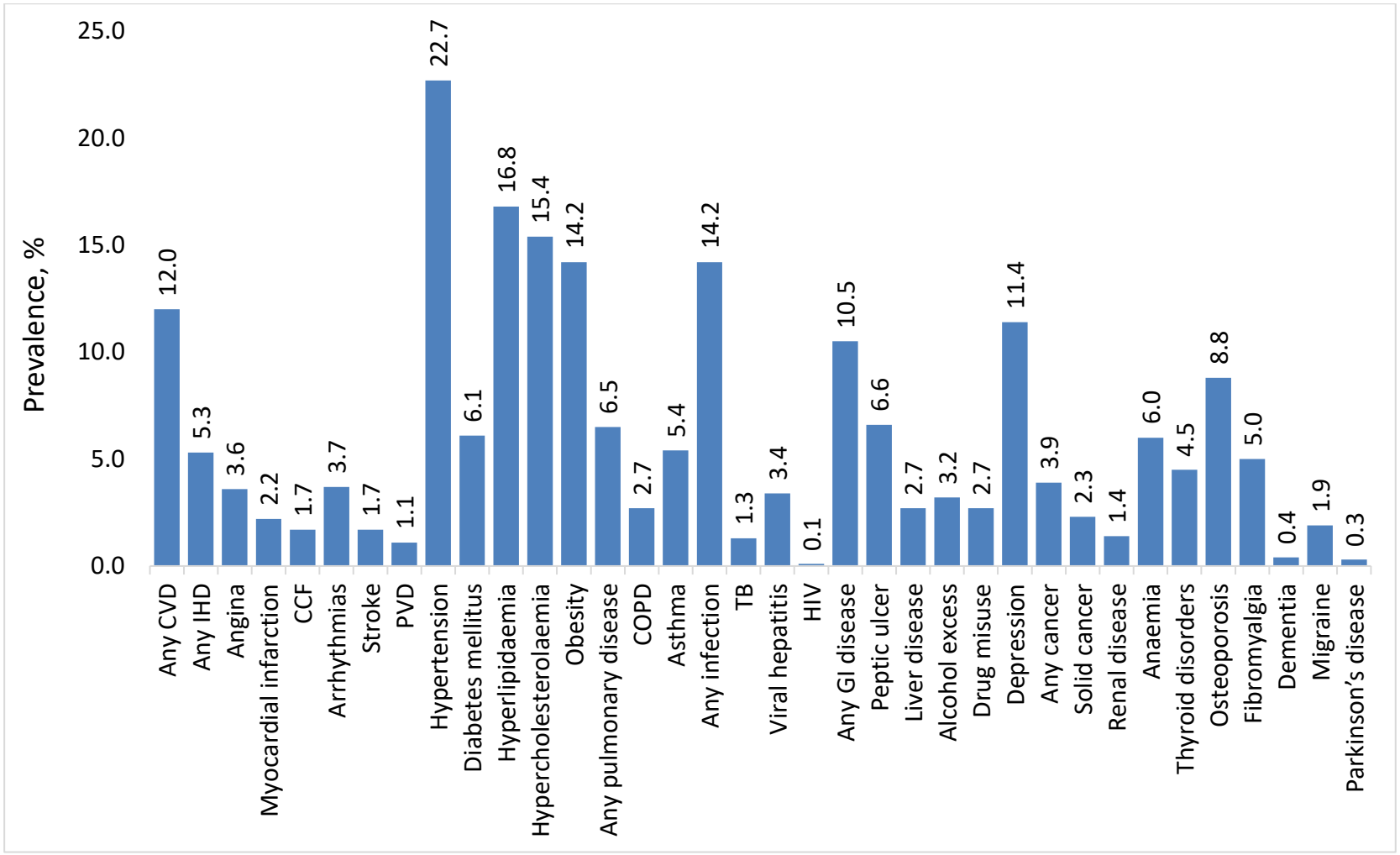
na, not available; NOS, Newcastle-Ottawa Score for bias; mNY, modified New York criteria; ASAS, Assessment of SpondyloArthritis international Society criteria; axSpA, axial spondyloarthritis; AS, ankylosing spondylitis; ICD, International Statistical Classification of Diseases; CCI, Charlson Comorbidity Index; SCQ, self-reported comorbidity questionnaire; RDCI, Rheumatic Disease Comorbidity Index; ECI, Elixhauser Comorbidity Index.

2.4.1 Prevalence of comorbidities

A total of 40 studies reported prevalence of individual comorbidities with a combined sample size of 121,485 patients [7,86,90,94,97–99,101–113,115,116,118–121,123–132]. All studies reported one or more diseases of the cardiovascular system. Diverticulitis, irritable bowel syndrome, venous thromboembolism and bronchiectasis are examples of infrequently (reported by ≤2 studies) included conditions.

Pooled prevalence estimates of individual comorbidities (reported by ≥3 studies) are summarised in Figure 2.2 with further details provided in Table 2.2. The top five most prevalent comorbidities reported were hypertension (23%), hyperlipidaemia (17%), hypercholesterolaemia (15%), obesity (14%) and any infection (14%). There was significant heterogeneity for most of the meta-analyses. Forest and funnel plots of the 37 meta-analyses were published in reference [84]. Some examples of most frequently reported comorbidities are shown in Figures 2.3 to 2.5.

Figure 2. 2: Pooled prevalence of individual comorbidities reported by three or more studies.



CVD, cardiovascular disease; CCF, congestive cardiac failure; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; PVD, peripheral vascular disease.

Table 2. 2: Meta-analysis estimates for prevalence of individual comorbidities in the included studies.

	No. of studies	Pooled prevalence	95% confidence interval	I^2, %	Range
Any cardiovascular disease	13	12.0	5.9 to 19.3	95	2.7 to 34.4
Any ischaemic heart disease	19	5.3	3.7 to 7.2	99	0.9 to 16.2
Angina	6	3.6	1.2 to 6.9	96	1.2 to 7.0
Myocardial infarction	10	2.2	1.4 to 3.1	91	0 to 7.2
Heart failure	12	1.7	1.2 to 2.3	94	0.5 to 5.8
Arrhythmias	8	3.7	1.9 to 6.0	95	1.0 to 14.0
Stroke	19	1.7	1.3 to 2.3	96	0 to 5.5
Peripheral vascular disease	9	1.1	0.6 to 1.9	97	0.2 to 2.8
Hypertension	36	22.7	16.6 to 29.3	100	4.5 to 73.0
Diabetes mellitus	33	6.1	4.8 to 7.6	98	0.3 to 18.0
Hyperlipidaemia	11	16.8	10.1 to 24.7	100	4.2 to 33.1
Hypercholesterolaemia	7	15.4	6.8 to 26.5	99	6.8 to 26.5
Obesity	7	14.2	1.7 to 33.5	100	0.2 to 27.3
Any pulmonary disease	7	6.5	3.0 to 11.1	98	1.9 to 15.5
COPD	9	2.7	1.2 to 4.7	98	0.6 to 8.8
Asthma	9	5.4	3.3 to 8.0	98	0.5 to 11.3
Any infection	4	14.2	2.9 to 30.7	100	4.6 to 32.9
TB	8	1.3	0.6 to 2.4	92	0 to 3.8
Viral hepatitis	6	3.4	0.9 to 7.3	97	0.6 to 18.6
HIV	3	0.1	0.04 to 0.3	13	0 to 0.3
Any gastrointestinal disease	6	10.5	3.2 to 20.9	99	1.0 to 31.3
Peptic ulcer	13	6.6	3.2 to 10.9	99	1.1 to 20.9
Liver disease	10	2.7	0.7 to 5.9	99	0 to 12.0
Alcohol excess	4	3.2	0.0 to 8.3	99	0.3 to 9.4
Drug misuse	3	2.7	0.4 to 6.6	96	1.1 to 4.8
Depression	19	11.4	7.0 to 16.6	100	2.0 to 31.0
Any cancer	18	3.9	0.9 to 8.7	100	0.3 to 29.5
Solid cancer	4	2.3	0.7 to 4.6	96	0.6 to 12.0
Renal disease	15	1.4	1.0 to 1.8	93	0.1 to 2.7
Anaemia	6	6.0	2.0 to 11.7	97	1.0 to 14.1
Thyroid disorders	8	4.5	0.2 to 12.3	99	0.2 to 28.2
Osteoporosis	12	8.8	5.1 to 13.2	99	3.4 to 31.0
Fibromyalgia	6	5.0	1.2 to 11.0	100	0.4 to 14.6
Dementia	4	0.4	0.1 to 0.8	74	0 to 0.8
Migraine	3	1.9	0.9 to 3.3	83	1.3 to 3.0
Parkinson's disease	3	0.3	0.2 to 0.4	0	0.1 to 0.3
Multiple sclerosis	4	0.4	0.3 to 0.6	0	0.1 to 0.5

Stroke includes cerebrovascular accidents and transient ischaemic attacks. COPD, chronic obstructive pulmonary disease.

Figure 2. 3: Forest plot for meta-analysis of hypertension prevalence.

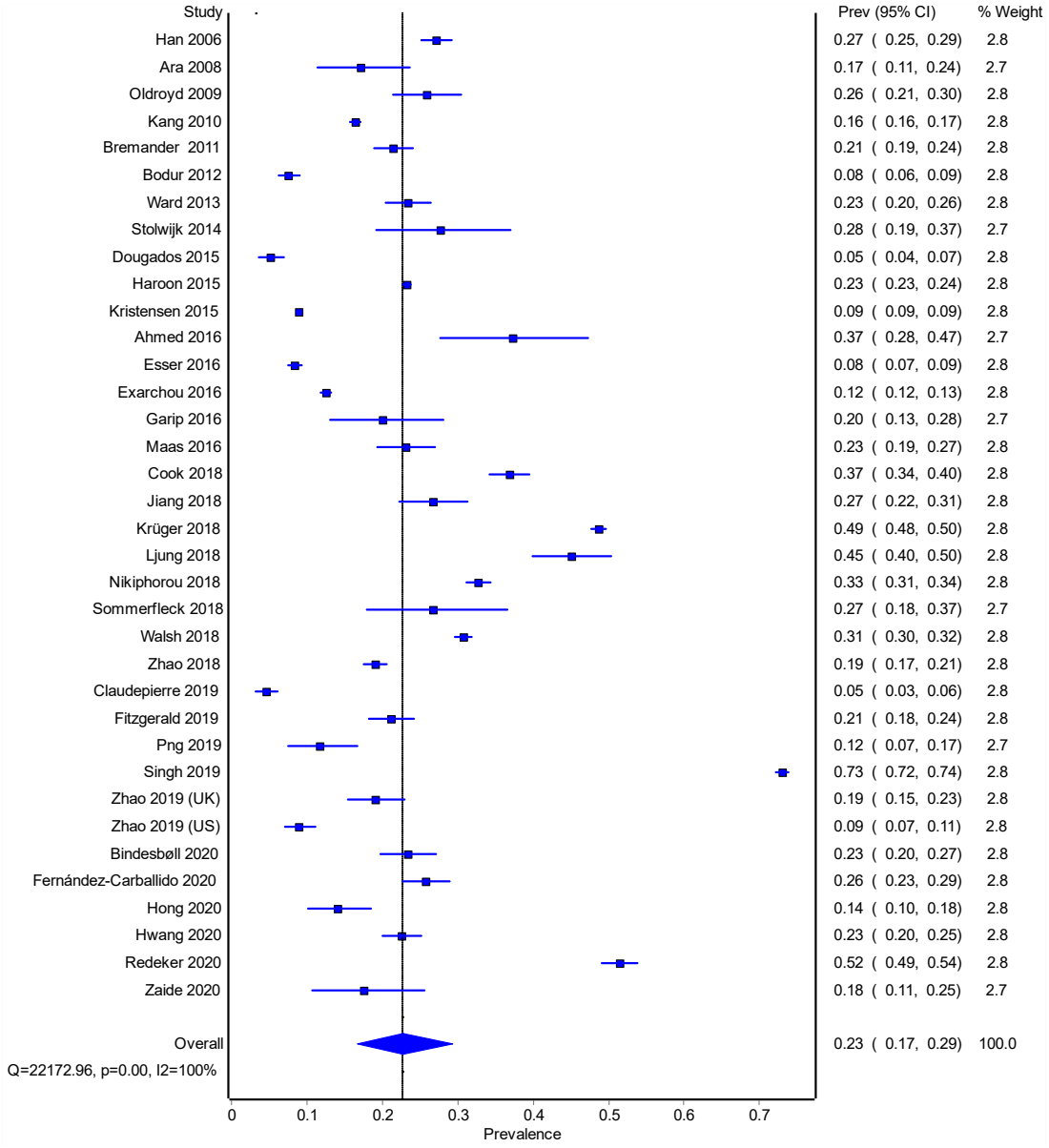


Figure 2. 4: Forest plot for meta-analysis of diabetes mellitus prevalence.

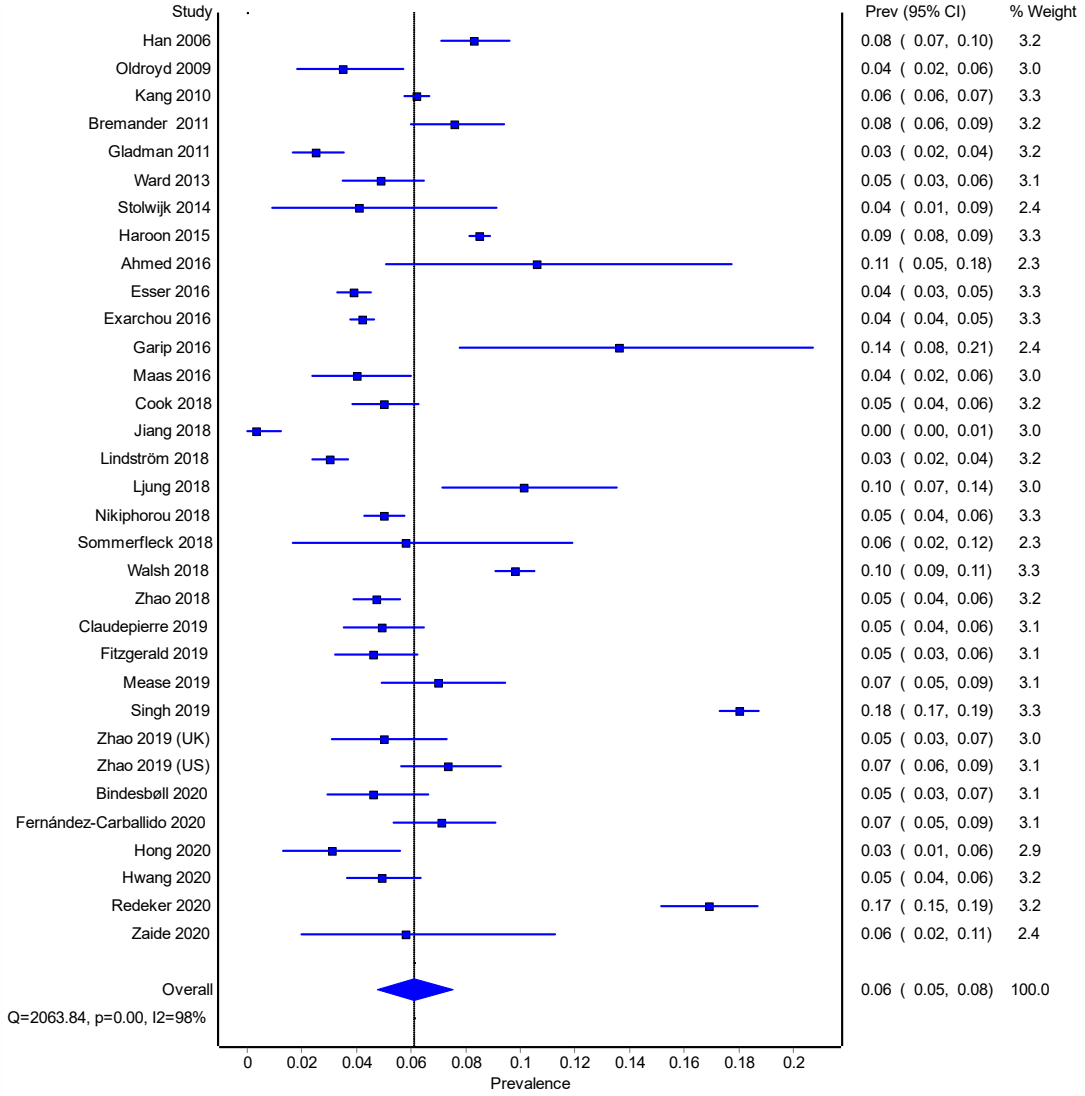
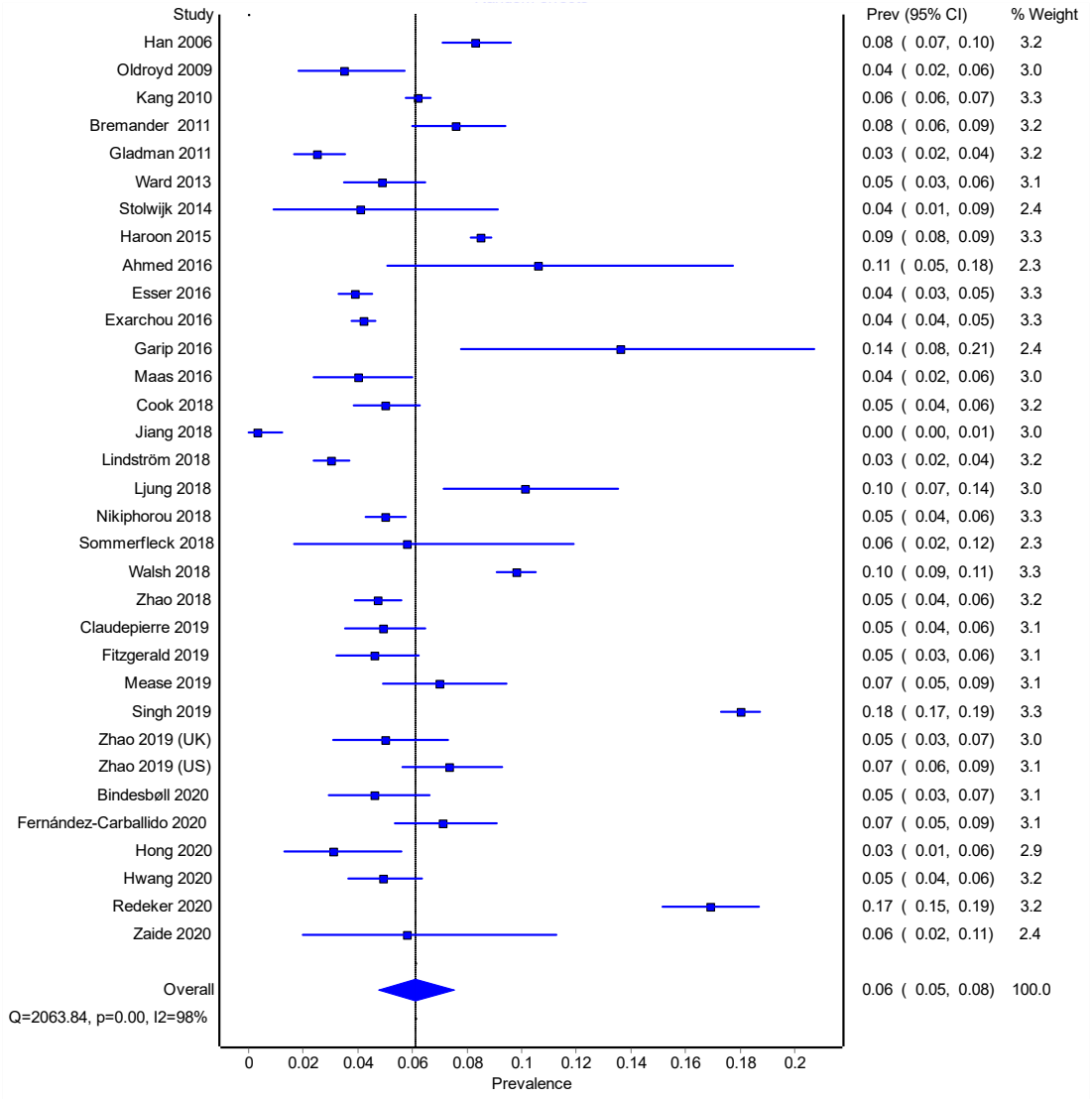


Figure 2. 5: Forest plot for meta-analysis of depression prevalence.



2.4.2 Comorbidity in axSpA vs. controls

Eleven studies compared comorbidities between axSpA and control groups [86,94,97,101,102,109,110,113,116,121,130]. Six studies selected controls without AS or inflammatory rheumatic diseases [86,95,110,113,116,121], while 5 others did not specify or selected from the whole population [97,101,102,109,130]. All studies compared prevalence; 9 used pairwise comparisons or odds ratios (OR) and 2 used standardised mortality ratios (SMR). All except one study [121] matched for at least age and sex. Cardiovascular comorbidities were the most commonly described. Almost all individual comorbidities were more prevalent in axSpA populations than matched controls (Table 2.3).

Table 2. 3: Comparison of comorbidity prevalence between axSpA and controls.

	Effect estimate	Control group	Comorbidity	Effect size	95% CI
Han 2006 [97]	OR (arbitrary time) matched for age, sex, region, time in health plan	All patients from claims database	Hypertension	1.34	1.19 to 1.51
			Ischaemic heart disease	1.26	1.02 to 1.56
			Heart failure	1.85	1.27 to 2.70
			Stroke	1.72	1.30 to 2.28
			PVD	1.57	1.13 to 2.18
			Diabetes	1.18	0.98 to 1.43
			Hyperlipidaemia	1.21	1.07 to 1.36
Kang 2010 [101]	conditional OR (arbitrary time) matched for age, sex, income, level of urbanisation	All patients from a subset of the same claims database from which cases were selected	Hypertension	1.87	1.75 to 1.99
			Ischaemic heart disease	2.74	2.15 to 3.49
			Heart failure	1.42	1.17 to 1.73
			Cardiac arrhythmias	1.82	1.58 to 2.09
			PVD	1.37	1.08 to 1.74
			Stroke	1.01	0.87 to 1.17
			Hyperlipidaemia	1.81	1.50 to 2.18
			Migraine	1.46	1.35 to 1.57
			COPD	3.24	2.38 to 4.40
			Asthma	0.98	0.88 to 1.10
			Restrictive/ILD	1.08	0.70 to 1.66
			Diabetes without complications	1.11	0.98 to 1.22
			Diabetes with complications	0.92	0.78 to 1.09
			Hypothyroidism	2.06	1.80 to 2.37
			Obesity	0.86	0.52 to 1.41
			Renal failure	1.11	0.86 to 1.42
			Liver disease	1.93	1.80 to 2.07
			Peptic ulcer disease	3.63	3.39 to 3.88
			Hepatitis	2.02	1.81 to 2.26
			HIV	1.11	0.52 to 2.39
			Tuberculosis	1.71	1.23 to 2.36
			Deficiency anaemias	2.74	2.36 to 3.18
			Alcohol	1.34	0.93 to 1.93
			Drug	1.11	0.91 to 1.34
			Depression	1.97	1.72 to 2.26
			Psychoses	1.65	1.43 to 1.90
			Metastatic cancer	0.71	0.28 to 1.82
			Solid tumour without metastasis	1.01	0.84 to 1.20
Breman der 2011 [102]	SMR	General population with at least 1 clinic visit and any diagnosis	Hypertension	1.98	1.72 to 2.28
			Ischaemic heart disease	2.20	1.77 to 2.70
			Myocardial infarction	1.32	0.81 to 2.04
			Diabetes	1.41	1.10 to 1.78
			AV block	3.97	1.90 to 7.30
			Dyslipidaemia	1.26	0.89 to 1.72
			Osteoporosis	4.33	2.96 to 6.11
Haroon 2015 [86]	OR (at baseline)	Patients without AS from health	Hypertension	1.40	1.35 to 1.45
			PVD	2.21	1.46 to 3.36
			Diabetes	1.29	1.22 to 1.36

	matched for age, sex, local health network	administrative database	Chronic kidney disease Dementia Cancer	2.45 1.06 1.59	2.15 to 2.79 0.89 to 1.28 1.53 to 1.64
Ahmed 2016 [109]	OR (arbitrary time) matched for age, sex	All patients from the primary care database	Hypertension Ischaemic heart disease Diabetes Hyperlipidaemia	1.73 1.12 1.24 1.33	1.07 to 2.79 0.54 to 2.36 0.59 to 2.61 0.65 to 2.74
Essers 2016 [110]	OR (at baseline) matched for age, sex, calendar time, practice	CPRD patients without RA, PsA, SLE or vasculitis	CVD Ischaemic heart disease Myocardial infarction Stroke Heart failure PVD Hypertension Renal failure Hypercholesterolaemia Diabetes	1.14 1.27 1.35 0.95 1.53 1.06 1.09 0.44 1.01 1.31	0.98 to 1.32 1.07 to 1.50 1.04 to 1.75 0.69 to 1.31 0.98 to 2.39 0.75 to 1.50 0.96 to 1.23 0.18 to 1.09 0.85 to 1.19 1.10 to 1.56
Exarcho u 2016 [130]	OR (arbitrary time) matched for age, sex, county	Census population (i.e., not the same population as cases, which were from a national secondary care register)	CVD Hypertension Ischaemic heart disease Heart failure VTE Stroke Diabetes Infection Malignancy Lung disease	1.97 3.01 1.81 2.74 1.83 1.57 1.18 2.03 1.33 2.20	1.87 to 2.07 2.78 to 3.26 1.64 to 2.00 2.33 to 3.23 1.46 to 2.28 1.36 to 1.81 1.06 to 1.32 1.93 to 2.14 1.19 to 1.48 1.82 to 2.65
Cook 2018 [113]	SMR	UK biobank participants without AS, RA, PsA or SLE	Hypertension Angina Myocardial infarction Stroke Diabetes COPD Depression	1.2 1.4 1.3 1.5 1.0 2.0 1.5	1.1 to 1.3 1.1 to 1.7 1.0 to 1.7 1.0 to 2.0 0.8 to 1.3 1.6 to 2.6 1.2 to 1.8
Krüger 2018 [116]	OR (after diagnosis) matched for age, sex inpatient stay, CCI prior to diagnosis	Patients without AS from claims database	Hypertension Dyslipidaemia Refraction and accommodation Depression Fibromyalgia	1.19 1.02 1.41 1.45 3.06	1.14 to 1.24 0.98 to 1.07 1.34 to 1.47 1.38 to 1.54 2.65 to 3.53
Walsh 2018 [94]	OR (at baseline) Matched for age, sex, geographic location, calendar year	Patients without AS from claims database	Hypertension CVD Ischaemic heart disease Angina Myocardial infarction Stroke PVD VTE	1.24 1.26 1.31 1.60 1.42 1.27 1.06 1.38	1.16 to 1.31 1.19 to 1.34 1.15 to 1.50 1.22 to 2.11 1.10 to 1.85 1.01 to 1.59 0.85 to 1.32 1.05 to 1.81

			Dyslipidaemia Diabetes Asthma Peptic ulcer disease Cancer Osteoporosis Fracture Depression Parkinson's disease MS Obstructive sleep apnoea	1.07 0.92 2.01 2.86 1.25 4.17 4.55 1.95 1.25 1.82 1.80	1.00 to 1.14 0.84 to 1.01 1.63 to 2.48 2.08 to 3.92 1.11 to 1.39 3.45 to 5.04 3.03 to 6.83 1.77 to 2.15 0.72 to 2.17 1.16 to 2.85 1.62 to 2.01
Claudepierre 2019 [121]	unadjusted OR	Patients without AS from claims database	Hypertension Ischaemic heart disease Stroke Diabetes Arrhythmia Solid tumour Haematological malignancy Depression	2.5 1.1 1.8 0.9 4.3 0.8 2.1 2.1	1.6 to 3.9 0.6 to 1.9 0.7 to 4.5 0.6 to 1.3 1.9 to 9.6 0.6 to 1.3 0.7 to 6.8 1.3 to 3.6

Stroke includes cerebrovascular accidents and transient ischaemic attacks. CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; GI gastrointestinal; MS, multiple sclerosis; PVD, peripheral vascular disease; VTE, venous thromboembolism.

For the nine studies reporting OR (or from which OR would be calculated), comorbidities reported by ≥3 studies were pooled using meta-analysis (summarise in Figure 2.6 with further details in Table 2.4). The three most frequently reported comorbidities were hypertension, diabetes, and ischaemic heart disease. The largest effect sizes were: 84% higher odds of congestive heart failure in axSpA compared to controls; and 80% higher odds for depression. Heterogeneity was high for all meta-analysis estimates. Forrest and funnel plots for 10 meta-analyses were published in reference [84].

Figure 2. 6: Meta-analysis estimates for odds ratios comparing comorbidities between axSpA and control groups.

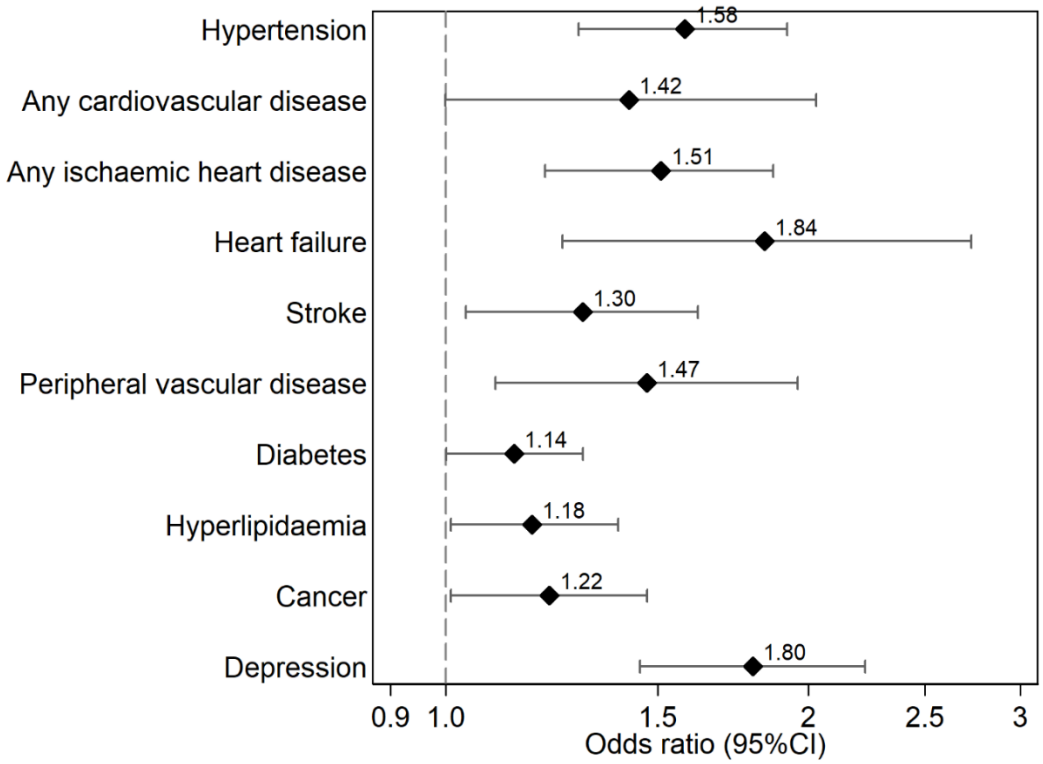


Table 2. 4: Meta-analysis estimates for odds ratios of comorbidities compared between axSpA and control groups.

	Number of studies	Pooled OR	95% confidence interval	I^2, %	OR range
Hypertension	9	1.58	1.29 to 1.92	98	1.09 to 3.01
Any cardiovascular disease	3	1.42	0.999 to 2.03	99	1.14 to 1.97
Any ischaemic heart disease	7	1.51	1.21 to 1.87	87	1.10 to 2.74
Heart failure	4	1.84	1.25 to 2.73	89	1.42 to 2.74
Stroke	6	1.30	1.04 to 1.62	81	0.95 to 1.80
Peripheral vascular disease	5	1.47	1.10 to 1.96	83	1.06 to 2.21
Diabetes	8*	1.14	1.001 to 1.30	83	0.90 to 1.31
Hyperlipidaemia	5	1.18	1.01 to 1.39	94	1.02 to 1.46
Cancer	5**	1.22	1.01 to 1.47	93	0.80 to 1.59
Depression	4	1.80	1.45 to 2.23	92	1.45 to 2.10
Meta-analysis was only performed for conditions reported by 3 or more studies. *Diabetes without complications selected. **Solid cancer without metastasis chosen Stroke includes cerebrovascular accidents and transient ischaemic attacks.					

2.4.3 Comorbidity and disease outcomes

Seventeen studies reported the association between comorbidity burden and axSpA outcomes (Table 2.5).

2.4.3.1 Cross-sectional designs

Most studies were cross-sectional. Overall, axSpA patients with comorbidities had higher disease activity and functional impairment, more severe pain, and poorer quality of life than those without comorbidities. ESR and CRP were generally not significantly different between those with and without comorbidities.

Three studies reported work-related measures. 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) [90]. Stolwijk et al found that the SCQ score was associated with stopping work due to disability, but only in those with BASDAI<4 [131]. Boonen et al reported 3 fold higher odds of inability to perform paid work in AS patients with comorbidities than without [96]. No studies examined the relative contributions of individual comorbidities within this context.

Table 2. 5: Cross-sectional studies examining the impact of comorbidity on disease indices in axial spondyloarthritis.

	How comorbidity was examined	**Outcome**	**Results (shown as pairwise comparison, or effect size; 95% confidence interval)**
Boonen 2001 [96]	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 to 5.09)
Ariza-Ariza 2009 [133]	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 [100]	SCQ	BASDAI	SCQ was associated with increased BASDAI, no effect size or p-value reported.
Stolwijk 2014 [131]	SCQ mSCQ CCI RDCI	BASFI Quality of life (SF36)	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.

		Work disability (stopped due to disability)	SCQ and mSCQ were associated with work disability in BASDAI<4 (but not ≥4); CCI and RDCI were not.
Garip 2016 [111]	Presence or absence (9 comorbidities)	Multiple outcomes (see next column)	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 [119]	Each of 4 comorbidity categories	Multiple outcomes (see next column)	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 [90]	RDCI	Multiple outcomes (see next column)	In multilevel multivariable linear or logistic models, RDCI was associated with: BASFI (ß=0.37; 0.30 to 0.43), EQ5D (ß=-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).
Fernandez-Carballido 2019 [132]	Modified CCI (cancer definitions pooled)	BASFI	CCI was not associated with BASFI (ß=0.03; CI -0.13 to 0.20) in multivariable linear model.
Fitzgerald 2019 [123]	Presence or absence (12 comorbidities)	Multiple outcomes (see next column)	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 (ß=0.70; 0.34 to 1.05), BASMI (ß=0.45; 0.09 to 0.80), BASFI (ß=0.50; 0.23 to 0.78), HAQ (ß=0.07; 0.00 to 0.13),

			ASQoL (ß=0.87; 0.28 to 1.46).
	Number of comorbidities		The number of comorbidities was also significantly associated with: BASDAI (ß=0.23; 0.09 to 0.37), BASMI (ß=0.20; 0.05 to 0.34), BASFI (ß=0.21; 0.10 to 0.32), HAQ (ß=0.03; 0.01 to 0.06), ASQoL (ß=0.25; 0.02 to 0.49).
Redeker 2019 [abstract] [129]	ECI excluding rheumatic diseases	BASDAI BASFI	In multivariable linear models, each unit increase in ECI was associated with: BASDAI (ß=0.12; 0.07 to 0.17), BASFI (ß=0.10; 0.04 to 0.17).
Zhao 2019 (US) [127]	Modified MMI (39 comorbidities)	Pain ESR CRP	Comorbidity was present in 51%. MMI count was associated with pain (ß=0.21; 0.04 to 0.38), ESR (ß=2.04; 0.65 to 3.42), CRP (ß=4.93; 2.88 to 6.98) in age and sex adjusted linear models.
Zhao 2019 (UK) [128]	Presence or absence (38 comorbidities based on MMI)	Multiple outcomes (see next column)	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/hr) 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.
Work status (working or not); Absenteeism (time off due to health reasons); Presenteeism (reduced productivity at work); CCI, Charlson Comorbidity Index; ECI, Elixhauser Comorbidity Index; SCQ, self-reported comorbidity questionnaire; RDCI, Rheumatic Disease Comorbidity Index; MMI, multimorbidity index.			

2.4.3.2 Longitudinal designs

There were six longitudinal studies (Table 2.6) [86,114,117,118,130,134]. Three reported increased all-cause and 'vascular' mortality among axSpA patients with comorbidities [86,117,130]. Three others examined treatment outcomes [114,118,134].

Table 2. 6: Longitudinal studies examining the impact of comorbidity on disease outcomes in axial spondyloarthritis.

	How comorbidity was examined	Outcome	Results (95% confidence interval)
Haroon 2015 [86]	Each of 7 comorbidities including IBD	'Vascular' (cardio- and cerebrovascular) mortality	Dementia (HR, 2.62; 1.32 to 5.23) and PVD (HR, 6.79; 2.45 to 18.84) were significantly associated with vascular mortality, but not diabetes, CKD, IBD or cancer.
Exarchou 2016 [130]	Each of 5 'general' comorbidities	Mortality	CVD (HR 1.99; 1.58 to 2.49), DM (HR 1.92; 1.51 to 2.45), Chronic pulmonary disease (HR 3.03; 2.27 to 4.05), Malignancy (HR 1.67; 1.32 to 2.12), Infections (HR 2.01; 1.68 to 2.34) were each independent predictors of mortality in separate multi-adjusted Cox models.
Iannone 2018 [114]	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) mRCDI was a significant independent predictor of drug discontinuation (HR 1.53; 1.02 to 2.29) and ASDAS remission (HR 0.43; 0.20 to 0.92) in multi-adjusted Cox models
Lee 2018 [117]	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 to 1.13), but not physical disability (OR 1.01; 0.95 to 1.08).
Lindström 2018 [118]	Each of 6 comorbidities	TNFi discontinuation	CVD (HR 1.24; 1.08 to 1.43),

			Affective disorder (HR 1.81; 1.54 to 2.13), Chronic lung disease (HR 1.49; 1.22 to 1.82), Malignancy (HR 1.36; 1.06 to 1.74), were associated with TNFi discontinuation in unadjusted Cox models, but not Diabetes (HR 1.36; 0.99 to 1.87) or CKD (HR 0.79; 0.41 to 1.52)
Macfarlane 2020 [134]	Count of 14 comorbidities	TNFi response	Per unit increase in comorbidity count was associated with: ASAS20 (OR 0.65; 95% CI 0.50 to 0.84. OR_{adj} not significant, not provided) ASAS40 (OR 0.57; 0.42 to 0.79. OR_{adj} 0.64; 0.45 to 0.92) ASDAS improvement by ≥1.1 (OR 0.60; 0.44 to 0.82. OR_{adj} 0.57; 0.37 to 0.88) ASDAS <2.1 (OR 0.51; 0.35 to 0.75. OR_{adj} 0.60; 0.38 to 0.95)
ASDAS, Ankylosing spondylitis disease activity score; ASAS20, ASAS Response Criteria designed for clinical trials: improvement of at least 20% and an absolute improvement of at least 10 units on a 0-100 scale in at least three of the following: patient global assessment, pain assessment, function (BASFI), and inflammation (BASDAI); CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; IBD, inflammatory bowel disease; OR, odds ratio; RDCI, Rheumatic Disease Comorbidity Index.			

2.4.3.2.1 Mortality outcomes

Lee et al studied comorbidity burden using CCI, where each unit increase was associated with 7% higher odds of all-cause mortality [117]. Haroon et al found that dementia and PVD were associated with increased vascular mortality, but not diabetes, chronic kidney disease, IBD or cancer [86]. All comorbidities in the study by Exarchou et al were each significantly associated with all-cause mortality; AS patients with chronic pulmonary disease were at particularly higher risk of death (HR 3.0; 95% CI 2.3 to 4.1) [130].

2.4.3.2.2 Treatment outcomes

Iannone [114] et al showed that mRCDI was significantly correlated (by Spearman's rank) with the number of biologic switches, however, the Kaplan Meier curves showed no difference between mRDCI of 1 and 0, while the mRDCI≥2 group separated after approximately 1 year. These curves were difficult to interpret as they suggested: 1)

discontinuation was assessed at (large intervals of) discrete times, and 2) >90% of those with mRDCI 0 or 1, but 0% of those with mRDCI≥2, remained on treatment at end of follow-up (approximately month 60). This clearly non-(log-)linear relationship with mRDCI was then modelled adjusting for gender and disease duration, showing mRDCI to be a significant predictor of drug discontinuation (HR 1.53; 95CI 1.02 to 2.29) for 635 patients with rheumatic diseases overall; no results were reported for the 213 SpA patients. Cox models were also used to assess (discrete-)time-to-remission (ASDAS<1.3) and reported HR 0.43 (95% CI 0.20 to 0.92) for the comorbid SpA subgroup.

The second study, by Lindström et al [118], examined risk of TNFi discontinuation in unadjusted Cox models for each of: cardiovascular disease (HR 1.24; 1.08 to 1.43), affective disorder (HR 1.81; 1.54 to 2.13), chronic lung disease (HR 1.49; 1.22 to 1.82), malignancy (HR 1.36; 1.06 to 1.74), diabetes (HR 1.36; 0.99 to 1.87) and chronic kidney disease (HR 0.79; 0.41 to 1.52). These effect estimates did not account for confounding, thus are difficult to interpret causally.

The third study used a sample of 335 BSRBR-AS participants to show continuous comorbidity count as a predictor of binary response [134] . The investigators showed each additional comorbidity to reduce odds of achieving clinically important improvement in ASDAS (≥1.1) by 43% (95% CI 0.37 to 0.88) and ASDAS<2.1 by 40% (95% CI 0.38 to 0.95) within 10 weeks to 9 months of treatment initiation.

2.5 Discussion

This systematic review aimed to summarise existing research on comorbidities in axSpA and identify unmet needs to inform aims of this thesis. A large body of literature consistently showed that comorbidities are common among axSpA patients, more so than age- and sex-matched controls. Comorbidities were also consistently associated with greater disease severity in mostly cross-sectional studies. However, research into the impact of comorbidity burden on longitudinal outcomes in patients with axSpA were relatively scarce. Methodological approaches were highly heterogenous, for example, in the type and number of conditions included.

A strength of this review is the breadth of the literature search, allowing a hypothesis-free (in terms of comorbidity selection) overview of the topic. It was not feasible to additionally combine results from studies of individual comorbid conditions in axSpA, which may have provided further insight. However, this thesis aimed to examine comorbidities overall rather than a priori comorbid diseases of interest. 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. These factors will impact pooled prevalence estimates. 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.

2.5.1 Prevalence of comorbidities

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 poorer than in the general population [135]. 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 [135]. They focused on six conditions – CVDs, depression, infections, malignancies, peptic ulcer, and osteoporosis – 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 [136], but

this may be limited by feasibility in daily practice - the six comorbidities alone require a 93-item reporting form.

Almost all comorbidities examined were more prevalent in axSpA patients than age- and sex-matched controls. AxSpA patients had markedly increased odds for depression and CVDs. 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 ischaemic heart disease were no different between axSpA and controls after adjusting for NSAID-use [110]. Congestive 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 to controls [137,138]. Heart failure can have significant impact on function and quality of life [139], thus optimal symptom management is important for patients already burdened by their rheumatic disease.

In all studies, comorbidities were studied individually or as a count. Future studies should complement such analyses by interrogating the contribution of individual comorbidities in the context of comorbidity clusters [128] and their combined impact. To address these unmet needs, this thesis will examine individual conditions and total comorbidity burden in parallel. How individual comorbidities co-exist will also be examined. Existing studies described comorbidity epidemiology in AS or axSpA populations, but none have directly compared comorbidity patterns between AS and non-radiographic axSpA. These diagnoses of the axSpA spectrum have similar symptom burdens and clinical features, but AS cohorts differ from their nr-axSpA counterparts in being more frequently male and having higher levels of CRP [56,57]. Comorbidity patterns are different between the sexes (e.g., prostate disorders or osteoporosis) [140], while systemic inflammation is a risk factor for many comorbidities [141]. Characterising comorbidity burden in AS and nr-axSpA subgroups is important since comorbidities influence treatment decisions and disease outcomes [142].

The type and number of conditions included were highly heterogenous. The number of included comorbidities in this review ranged from 3 to 43. Most studies used investigator-

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 [143], 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 [9]). Some studies used indices that were weighted and validated for outcomes unrelated to their research question. Methodological approaches for comorbidity research could benefit from similar standardisation as suggested for clinical practice [144]. The following section will discuss comorbidity indices in detail and justify the approach used in this thesis.

2.5.2 Methods for studying comorbidity

There is a plethora of tools and checklists for measuring comorbidity in the clinical literature [145]. Conditions are typically selected based on some consensus of their perceived importance, or on prognostic factors such as mortality. They can be patient-reported or derived from routine healthcare data. Individual conditions can be added as a count or weighted according to their impact on outcomes such as mortality or quality of life. Severity may also be considered for some conditions (e.g., malignancies and diabetes). Choice of which index to use should be based on the population and outcome of the original validation studies; for example, using the Charlson Comorbidity Index (CCI) – originally validated for inpatient mortality – may not be suitable for studying quality of life in outpatient settings. This is particularly relevant for weighted indices, whereas a simple count of the number of conditions will be less tied to specific outcomes. For example, 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) [131]. Studies should avoid using weighted indices that have not been validated for their main outcome of interest.

The CCI and ECI were both validated using hospital inpatients and may be less suitable for primarily outpatient specialties such as rheumatology. The CCI has also been adapted into a self-administered comorbidity questionnaire (SCQ) which asks about 13 comorbidities [146]. Both indices were validated to predict mortality (ECI additionally for cost and length of stay). RDCI was developed in patients with rheumatic and musculoskeletal diseases and is better at predicting mortality and functional disability than the CCI [147].

Only the SCQ was validated against health-related quality of life – a priority outcome in chronic disease management. One other index in the RA literature is an adapted version of

the list of 40 chronic conditions in the Barnett et al multimorbidity study of the Scottish primary care population [79]. Barnett et al selected these diseases based on 1) recommendations from systematic review, 2) the quality and outcomes framework of the UK general practice contract, and 3) long-term disorders identified as important by NHS Scotland [79]. Radner et al validated the index against the CCI and functional comorbidity index in two large RA samples [148]. The authors created a count version of the index and another weighted for health-related quality of life, but the latter was not meaningfully superior. Key characteristics of some of these tools are compared in Table 2.7.

Table 2. 7: Comparison of five common comorbidity tools in rheumatic diseases research.

	Charlson [149]	Elixhauser [150]	SCQ [146]	RDCI [147]	Multimorbidity index [148]
Year	1987	1998	2003	2007	2015
Number of conditions	16 (severity distinguished in 3)	30 (severity distinguished in 2)	13 (plus up to 3 additional)	11	40
Self-reported	No	No	Yes	Yes	No
Original population	Inpatients	Inpatients	Inpatients	RA, lupus, OA and fibromyalgia	RA
Original outcome	One-year mortality	Length of stay, hospital costs, and hospital mortality	Quality of life, prescriptions	Mortality, hospitalization, disability, and costs	Health-related quality of life
Weighted	Yes	Weighted and unweighted	No	Yes	Weighted and unweighted
Comorbidities	Myocardial infarction Congestive heart Failure Peripheral vascular disease Cerebrovascular disease Dementia COPD Connective tissue disease Peptic ulcer disease Diabetes mellitus (un/complicated) Renal disease Para/Hemiplegia Leukaemia	Congestive heart failure Cardiac arrhythmias Valvular disease Pulmonary circulation disorders Peripheral vascular disorders Hypertension Paralysis Neurodegenerative disorders Chronic pulmonary disease Diabetes mellitus (un/complicated)	Heart disease High blood pressure Lung disease Diabetes Ulcer or Stomach disease Kidney disease Liver disease Anaemia or other blood disease Cancer Depression Pain and swelling in joints other than the back Osteoporosis Fractures	Lung disease Heart attack Stroke Other cardiovascular disease Hypertension Fracture Depression Diabetes Cancer Peptic ulcer or stomach problems	Glaucoma Irritable bowel syndrome Schizophrenia/bipolar disorder Learning disability Anorexia/bulimia Migraine Prostate disorders Diverticulitis Chronic sinusitis Hypertension Cancer Diabetes Atrial fibrillation Constipation Multiple sclerosis

	Malignant lymphoma Solid tumour Liver disease (mild-moderate/severe) HIV/AIDS	Hypothyroidism Renal failure Liver disease Peptic ulcer disease, no bleeding AIDS/HIV Lymphoma Metastatic cancer Solid tumour without metastasis Rheumatoid arthritis/collagen vascular diseases Coagulopathy Obesity Weight loss Fluid and electrolyte disorders Blood loss anaemia Deficiency anaemia Alcohol abuse Drug abuse Psychosis Depressions	Up to 3 additional conditions		Substance misuse Osteoporosis Psoriasis eczema Coronary heart disease Hearing loss Stroke/TIA Peripheral vascular disease Chronic kidney disease Inflammatory bowel disease Thyroid disorders Asthma Obesity Chronic liver disease Heart failure Bronchiectasis Depression Anxiety/neurotic disorders Alcohol problems Blind or low vision Parkinson Dyspepsia COPD Hepatitis Epilepsy Dementia

AIDS, acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease; OA, osteoarthritis; RDCI, rheumatic disease comorbidity index; SCQ, self-administered comorbidity questionnaire; TIA, transient ischaemic attack.

AxSpA studies require additional considerations for which comorbidities should be included. For example, the SCQ includes osteoarthritis, back pain and RA that may be difficult for patients to distinguish from axSpA when self-reported [131]. The MMI includes inflammatory bowel disease and psoriasis that are not considered comorbidities, since they share pathogenesis with and aid diagnosis of axSpA [87,88]. EAMs are common, partly because they are included in the disease definition; including uveitis (prevalence around 25% [151]) in comorbidity lists will dominate many less common conditions in analyses. Furthermore, including EAMs in the modified SCQ did not improve its validity [152]. These distinctions and their supportive evidence only emerged in more recent years. Two studies in this review included cigarette smoking as a comorbidity. The distinction between comorbidity and risk factor is not absolute (take for example hypertension).

2.5.3 Association with axial spondyloarthritis outcomes

In this literature review, the presence of comorbidities was consistently associated with greater axSpA disease severity as assessed by a range of indices. Individuals with more severe axSpA may be at higher risk of developing comorbidities directly (e.g., depression) or indirectly through treatment (e.g., dyspepsia or renal disease from NSAIDs). Conversely, many comorbidities (e.g., heart failure or COPD) will directly impact physical function and fatigue, while others (e.g., depression) may indirectly influence the perception and reporting of pain. In two individuals with identical underlying axSpA disease activity, the one with multiple comorbidities will likely report higher subjective symptom burden. This is highly relevant to axSpA management where most disease indices are completely patient reported (e.g., BASDAI, spinal pain, BASFI). Whether more objective indices (e.g., ASDAS) are less influenced by comorbidities has not been investigated. This is an important clinical question since many treatment decisions rely on these indices. For example, eligibility for bDMARDs in the UK is partly determined by BASDAI, which may be modified by the presence of comorbidities that influence fatigue and pain. This thesis will address this unmet need by investigating how robustly various outcomes (e.g., BASDAI vs. ASDAS) are related to comorbidities such as depression.

Evidence beyond cross-sectional associations between comorbidities and axSpA severity were comparatively scarce. Increased mortality in individuals with multiple comorbidities has been repeatedly described in other populations [153] and replicated among axSpA patients. Only three studies examined longitudinal associations with treatment outcomes, each with important methodological limitations. Comorbid axSpA patients consistently had

more severe axSpA, which will influence how treatment response is defined. For example, patients with higher disease activity will need to achieve greater absolute improvement to reach a low disease activity or remission state, compared to those with less active disease. Prior studies have only analysed these potentially problematic binary response definitions. The choice of response definition has both statistical (power and bias) and philosophical (which matters more to patients or health economics) implications. A better approach would be to provide a range of complementary response definitions, and additionally include absolute change in disease indices (rarely used in the general rheumatology literature and not at all in the reviewed axSpA studies) and time to treatment discontinuation. Outcome definitions and justification for selection will be discussed in greater detail in the Methods chapter.

2.5.4 Summary of literature review

Comorbidities are common among axSpA patients and are associated with greater axSpA severity. Several unmet research needs of clinical relevance were identified, namely whether comorbidities differ between AS and nr-axSpA populations, whether comorbidities co-exist, whether they are differentially associated with disease activity indices, and whether they influence response to TNFi therapy. There is also need for improved methodological approaches, namely the assessment of comorbidities and definitions of treatment outcomes.

2.6 Thesis Aims and Objectives

The main aim of this thesis is to describe the patterns and impact of comorbidity in axial spondyloarthritis using real-world patient populations. This body of work will approach comorbidity as a count ('comorbidity burden') and individual conditions to understand how they contribute to disease severity and treatment response. Three distinct populations – each with unique strengths and limitations – will be used to answer specific objectives and results from one data source will be validated in another where possible.

The objectives were to:

1. To describe the prevalence and patterns of comorbidities in axSpA and examine whether they differ between AS and nr-axSpA.
2. To investigate whether and how comorbidities co-occur among people with axSpA and whether these patient 'clusters' are associated with axSpA disease severity.
3. To determine whether comorbidities influence axSpA disease severity and compare whether these indices are differentially affected.
4. To examine whether baseline comorbidity burden is associated with response to TNF inhibitors.

As the thesis evolved, analyses addressing the above objectives repeatedly pointed to mental health conditions as a prevalent and important comorbidity. Thus, an additional objective was added:

5. To examine the impact of baseline depression and anxiety on response to TNF inhibitors.

Chapter 3: Methods

This chapter describes the study populations that will be use and how their data were collected and prepared for analyses. The main statistical methods used in this thesis will also be described.

3.1 Study populations

Three axSpA datasets were used for this thesis. The Aintree and Boston axSpA studies used cross-sectional data obtained from routine tertiary healthcare records. The British Society for Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS) was a nationwide longitudinal pharmacovigilance study, recruiting from secondary and tertiary rheumatology centres across the UK. The next three sections (3.2 to 3.4) describe the population context for each study, their study designs, and methods used to prepare the data for analyses. Section 3.5 introduces the common statistical methods used.

3.2 Aintree axial spondyloarthritis registry

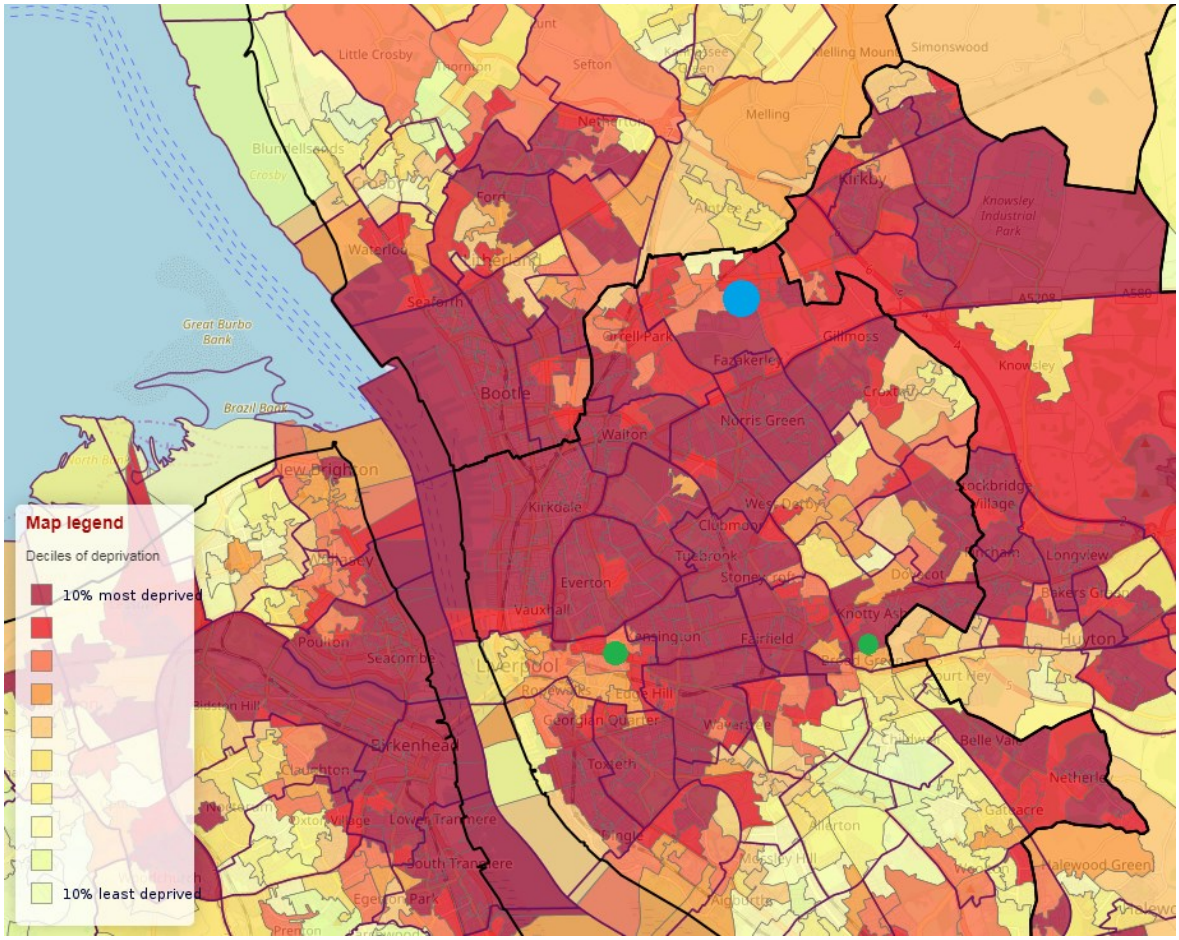
3.2.1 Local population

Liverpool is a city in the North West of England with a population of 466,000 according to the most recent (2011) census [154]. It is a relatively young population; nearly half are aged 16 to 44 compared with 39% nationally. Only 14% of the overall population are of Black, Asian, and Minority Ethnicities, which is less diverse than figures for England and Wales (19%). Residents, particularly in the North of the city (where Aintree hospital is located), are predominantly White.

Liverpool was the fourth most deprived local authority in England in 2015 [155]. Nearly half of the city is in the national top 10% most deprived areas, which are concentrated in the North (Figure 3.1). Twenty-two percent have university or higher degree qualifications and 29% have no qualifications, compared to 27% and 23%, respectively, for England and Wales. Deprivation is also reflected in the population's general health; Liverpool has lower levels of self-reported good health and higher levels of self-reported bad health than the national average (Figure 3.2). One third of the population have at least one morbidity and

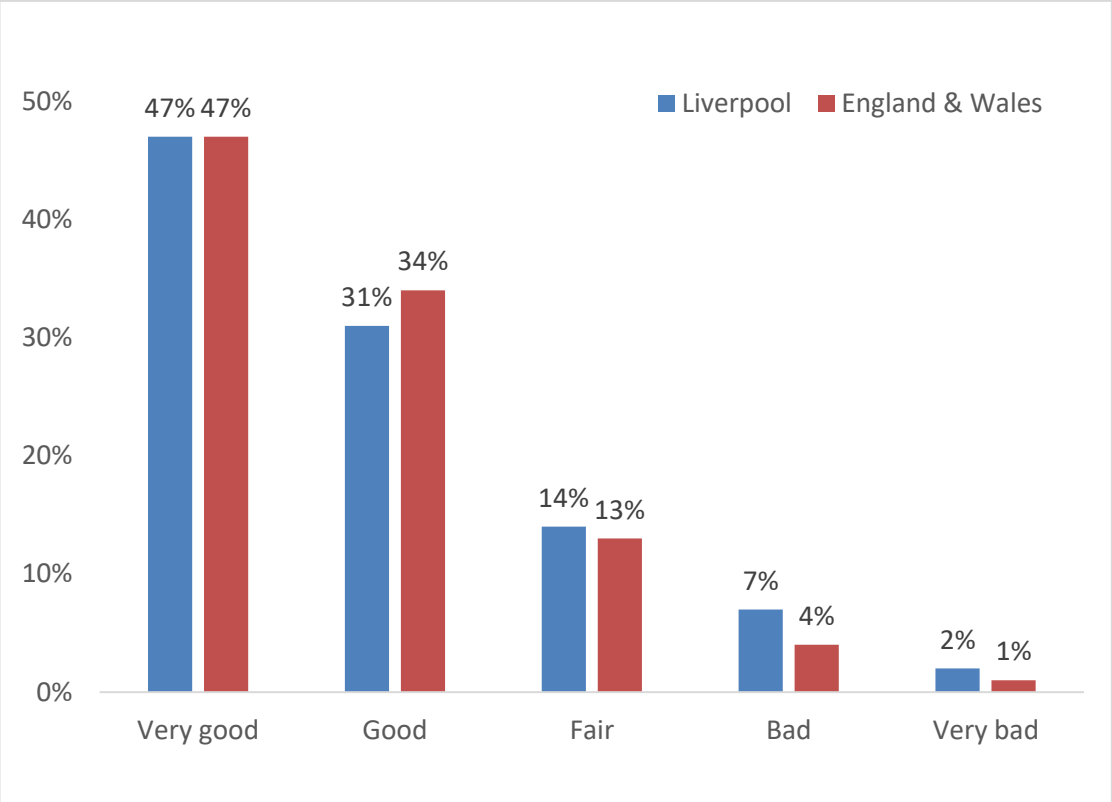
15% have multimorbidity [155]. The 2016-2018 life expectancy estimates for Liverpool (males 76 years, females 80 years) were approximately 3 years lower than the national average [154].

Figure 3. 1: Map showing relative deprivation in Liverpool, using the post-code-based Index of Multiple Deprivation.



Aintree University Hospital (blue) and Royal Liverpool and Broadgreen University Hospitals (green) are shown by coloured dots. (Image from dclgapps.communities.gov.uk)

Figure 3. 2: Self-reported level of general health in Liverpool from the 2011 UK census.



Data from the 2011 UK census [154].

3.2.2 Health provision and the Aintree University Hospital spondyloarthritis service

There are two large university teaching hospitals in Liverpool that are in the process of merging (at the time of writing) to form 'Liverpool University Hospitals'. Aintree University Hospital mainly serves the North Liverpool population from 3 Clinical Commissioning Groups (CCGs): Liverpool, Knowsley, and Sefton. The Royal Liverpool and Broadgreen University Hospital sites (Figure 3.1) serve Central and South Liverpool, although coverage by these hospitals overlap significantly.

Aintree University Hospital hosts the main academic rheumatology centre in Merseyside and provides the only specialist spondyloarthritis service in Liverpool. Most Aintree axSpA patients come from North Liverpool. AxSpA patients from other parts of the region are predominantly managed in general rheumatology clinics of nearby hospitals. The specialist SpA service also accepts referrals (e.g., complex cases) from other parts of the region. At Aintree, almost all SpA patients are eventually seen in the specialist spondyloarthritis service which served around 600 patients from 2014 to 2018.

At the first clinic visit, new patients complete a set of questionnaires, undergo a detailed clinical history and examination, followed by relevant investigations such as serum inflammatory makers and imaging. Questionnaires used in the clinic are for routine care purposes only, to assess disease activity and facilitate clinical assessment (e.g., BASDAI, BASFI, health-related quality of life). Clinical assessment is semi-structured including, for example, SpA features from classification criteria, past medical history, and social history (smoking status, pack-years, and alcohol status). Once a diagnosis of SpA is made or confirmed, patients are followed-up annually at a minimum. Axial SpA patients are generally seen in the dedicated axSpA clinic, which includes parallel reviews by a physiotherapist. Patients also have access to hydrotherapy as indicated.

3.2.3 Electronic Health Records (EHRs)

At the time of writing, the Aintree site uses a combined electronic health record (EHR) system. Medway Sigma (System C Healthcare) was introduced in 2009 including 10 years of backdated patient records. This system holds:

1) Patient identifiable information,
2) Text-documents of dictated clinic letters,
3) EDMS (Engineering Document Management System) of scanned hand-written (in- and outpatient) clinical notes,
4) Results of investigation such as blood tests and imaging reports, and
5) Integrated PACS (Picture Archiving and Communication System) images.

There is a separate electronic prescription system (predominantly used for inpatient care), which was not used for this study as outpatient medication were not consistently captured. Medication data were instead extracted from clinical letters and notes.

3.2.4 Study design

The Aintree axSpA registry was created by the thesis author with ethical approval granted by the National Research Ethics Committee in August 2015 (15/LO/1519). Individual patient consent was not required for this study. Active data collection continued to April 2018, and the study was formally ended in May 2020 to allow completion of analyses. It was a cross-sectional observational study of consecutive axSpA patients at their first contact with the specialist SpA service (i.e., retrospective inception population). The registry held pseudo-anonymised data, but it was possible to trace patients via a secured key file if required.

3.2.4.1 Eligibility

Although all types of SpA are seen in the specialist service, only physician diagnosed axSpA patients were eligible for inclusion into the study. Patients were required to be adults (≥18 years) fulfilling the ASAS criteria for axial SpA or modified New York criteria for AS [15, 16]. PsA patients with axial involvement were also included if they met these criteria. Existing patients who did not have records of their baseline visit (e.g., pre-EHR coverage) were excluded.

3.2.4.2 Representativeness

As discussed above, a small minority of patients are referred from regions outside of North Liverpool; these patients may have more complex disease on average. It is also possible that patients on stable conservative management (e.g., NSAIDs only) are more likely to stop attending clinic. Patients who became lost to follow-up before 2015 would not have been included in the study, which could bias the sample toward more severe cases. Both instances are likely to be rare. Aintree's annual report records a population of 330 thousand [156]; therefore 600 cases would give a prevalence of 0.18%, which is similar to the prevalence estimated for European (0.19% [29]). Of note, there is a significant proportion of patients who are only managed in primary care, to whom this study's conclusions may not apply. In Scotland, two-thirds of all axSpA patients are managed in primary care only [157].

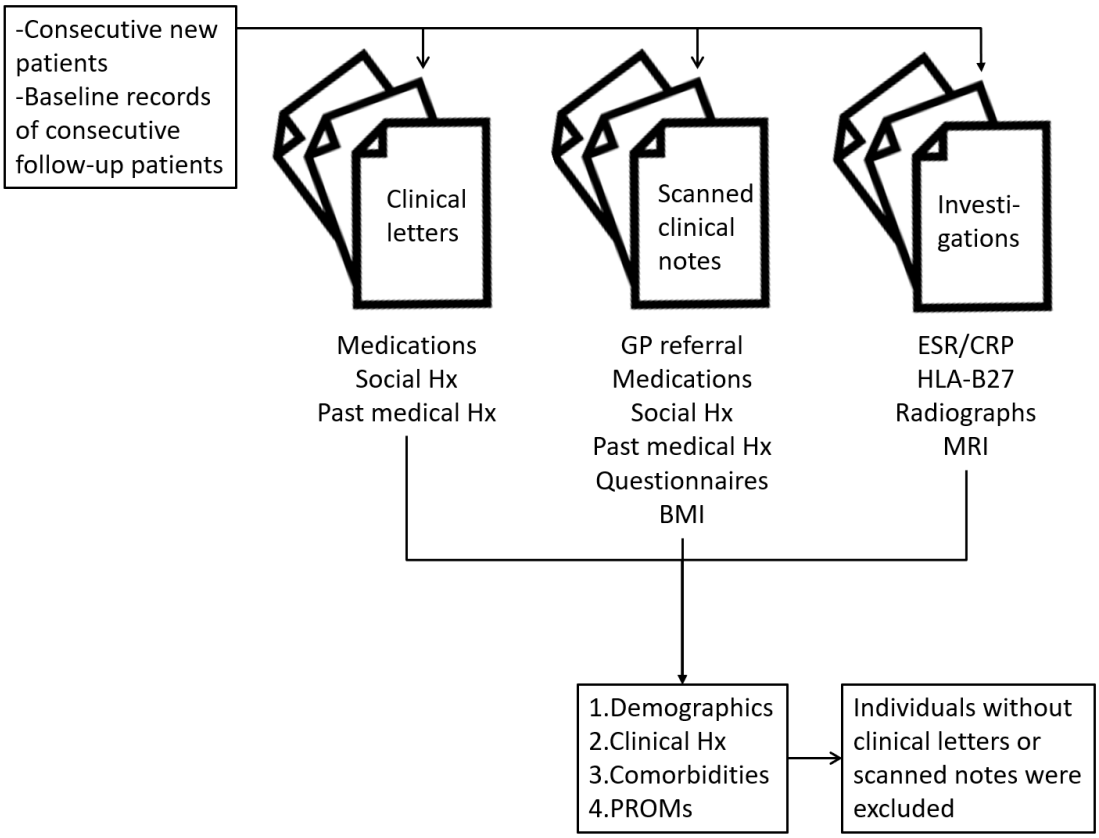
3.2.4.3 Data collection

Each patient's baseline (i.e., first clinic assessment) data were entered into the registry by two means: 1) prospective entry of consecutive new patients attending the SpA service, and 2) retrospective entry of consecutive follow-up-review patients, which increased the efficiency of patient accrual. The baseline visit was not necessarily when the diagnosis was made. For example, newly referred patients may have managed their axSpA for many years in the community or by other centres. Conversely, patients may not be diagnosed until after a series of assessments.

Data were obtained by manual review of each patient's electronic health records, predominantly clinic letters (by rheumatology physicians and specialist nurses), scanned notes, and investigation results. To improve accuracy and validity, collection of each variable was checked in duplicate by two trained medical (Master of Research) students.

Any discrepancies were resolved through discussion. The data collection process is summarised in Figure 3.3.

Figure 3. 3: Summary of data collection for the Aintree axial spondyloarthritis registry.



For each consecutive patient attending the Aintree SpA service, three components of electronic health records were manually reviewed by the thesis author. All variables were validated by a trained medical student (duplicated extraction). Only patients who had records of their baseline assessment were eligible (e.g., follow-up patients whose baseline assessment predated available electronic records would not be eligible). Two patients, who had records missing all relevant components of clinical letters and notes, were excluded. No record was kept of the number of individuals failing to meet eligibility criteria, but the SpA service was estimated to have served 600 patients from 2014 to 2018, inclusive. BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hx, history; PROMs, patient reported outcome measures.

Box 3.1 shows the variables collected for each patient. In addition to basic demographics, socioeconomic status was approximated using Index of Multiple Deprivation (IMD) based on post-codes of England [158]. Decile 1 relates to the top 10% most deprived areas whilst decile 10 represents the least deprived areas. Height and weight were measured for each patient, from which body mass index (BMI) was calculated as weight (in kilograms) divided by height (metres) squared.

Box 3. 1: Variables collected in the Aintree axSpA registry, organised into four linked datasets.

1) Basic and demographic information

- Age (at baseline, i.e., first clinic visit), gender, age at symptom onset, age at diagnosis, Index of Multiple Deprivation.
- Clinical diagnosis, HLA-B27 status, CRP (mg/L), ESR (mm/hr)
- Imagining (i.e., radiographic sacroiliitis, positive MRI)

2) Detailed clinical history:

- Peripheral joint involvement, uveitis, psoriasis, inflammatory bowel disease
- Body mass index (BMI)
- Medications
- Smoking, pack-years; Alcohol, units/week; Illicit drug use

3) Comorbidities (see Box 3.2)

4) Questionnaire data:

- BASDAI, Spinal pain, BASFI (described in Chapter 1)
- EQ5D 3-level version [159]. Responses were converted into a single index value, which reflects the health state is according to the preferences of the UK general (1 for 'best health state', and 0 for 'worst health state equalling death')
- Fatigue visual analogue scale (VAS): How would you describe the level of fatigue/tiredness you have experienced in the past week? (0: no fatigue, 100: worst fatigue ever experienced)
- Global health VAS: How would you describe your general state of health today? (0: best imaginable heath state, 100: worst imaginable health state)

The semi-structured clinical assessment routinely recorded age at symptom onset, CRP, ESR, and SpA features (Chapter 1, Box 1.2, page 35) as they are pivotal for diagnosis and classification. HLA-B27 was not always tested, for example, when the clinical picture was highly indicative of a diagnosis. All medications were recorded from clinic letters and confirmed against GP referral documents where available. Only summary-level results for imaging investigations were collected for the study, i.e., presence of radiographic sacroiliitis or bone marrow oedema without grading or further description.

Routine clinic questionnaires were scanned into EDMS. Numerical rating scale (i.e., integers from 1 to 10) version of the BASDAI, spinal pain and BASFI were used. In addition, patients completed the 3-level version of the descriptive EQ-5D (i.e., without the visual analogue scale, EQ5D-VAS), and single questions on fatigue and general health. No additional questionnaires were given to patients specifically for the study. Data were stored in a Microsoft Access relational database, with the four datasets linked by a unique study identification number.

3.2.4.4 Comorbidity ascertainment

There are several indices commonly used to measure comorbidity burden. Among them, the multimorbidity index (MMI) by Radner et al [148] was selected for use in assessing comorbidities in this study for the following reasons: 1) it assesses the largest number of conditions, 2) it is unweighted and 3) it has been validated in patients with rheumatic diseases against health-related quality of life [148]. Weighted indices such as the Charlson [149] and Elixhauser [150] indices were validated for inpatients and mortality or inpatient-related outcomes. They are less suitable for chronic diseases predominantly managed in outpatient settings. The rheumatic disease comorbidity index (RDCI) - although validated in rheumatic diseases - is also weighted and only includes 11 conditions [147].

Further adaptations to the original MMI were made for the Aintree axSpA registry, with discussion involving senior academic rheumatologists. Extra-articular manifestations - inflammatory bowel disease and psoriasis - were excluded. ‘Painful conditions’ was changed to fibromyalgia. Osteoporosis was added because of its importance in chronic rheumatic musculoskeletal diseases. The final list of 39 comorbidities is shown in Box 3.2. Body mass index (BMI) was systematically measured in all patients. Given this differential ascertainment of obesity (compared to other comorbidities) and the greater amount of information held by BMI as a continuous variable (compared to obesity), obesity was not included in analyses using the Aintree data.

Box 3. 2: List of 39 comorbidities in the Aintree axial spondyloarthritis registry.

- Alcohol problems
- Anorexia or bulimia
- Anxiety and other neuroses
- Asthma
- Atrial fibrillation
- Blind or low vision
- Bronchiectasis
- Cancer
- Chronic kidney disease
- Chronic liver disease
- COPD
- Chronic sinusitis
- Constipation
- Coronary heart disease
- Dementia
- Depression
- Diabetes mellitus
- Diverticular disease
- Dyspepsia
- Epilepsy
- Glaucoma
- Hearing loss
- Heart failure
- Hypertension
- Irritable bowel syndrome (IBS)
- Learning disability
- Migraine
- Multiple sclerosis
- Obesity
- Parkinson's disease
- Peripheral vascular disease
- Prostate disorders
- Psychoactive substance misuse
- Schizophrenia or bipolar
- Stroke or TIA
- Thyroid disorders
- Viral hepatitis
- **Fibromyalgia**
- **Osteoporosis**

Comorbidity list based on the multimorbidity index (MMI) [148] with modifications highlighted in bold. COPD, chronic obstructive pulmonary disease; TIA, transient ischaemic attack.

Presence of each comorbidity was sought from each patient's clinical records. The 'diagnosis' list in each rheumatology clinic letter was the main source of comorbidity information. This was supported by GP records, which were provided in most referral documents. Some comorbidities were assumed to be present if the patient's medication were highly suggestive of an underlying condition (Table 3.1).

Table 3. 1: Comorbidities assumed to be present if history and medications were suggestive of the condition.

Condition	Suggestive medication
Hypertension	Prescribed anti-hypertensives in the absence of kidney or heart disease
Dyspepsia	Prescribed proton pump inhibitors or H2 receptor blockers in the absence of glucocorticoids or NSAIDs
Coronary heart disease	Prescribed antianginals (e.g. nitrates) or secondary prophylaxis combinations (e.g., statin, antiplatelet and beta-blocker/ACE inhibitor) in the absence of other indications.
Diabetes	Prescribed oral hypoglycaemics or insulin.
Irritable bowel syndrome (IBS)	Prescribed mebeverine in the absence of other intestinal diseases
Constipation	Prescribed laxatives without gastroenteric diseases such as chronic liver disease or IBS.
Depression	Prescribed selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, or tricyclics in the absence of any neuropsychiatric conditions or chronic pain.
Fibromyalgia	Prescribed duloxetine, pregabalin or gabapentin in the absence of neuropsychiatric conditions or neuropathic pain.
Other psychoactive substance misuse	Includes documented use of cannabis.
Alcohol problems	Includes documented weekly alcohol use of ≥50 units for men or ≥35 units for women. These thresholds are defined by UK government as high risk drinking [160].

3.2.4.5 Sample size considerations

Sample size calculations are subtly different when describing data without invoking hypothesis testing, but nevertheless relevant for precision (i.e., standard error). The primary aim of the Aintree axSpA study was to describe the prevalence of comorbidities. Standard error of a proportion is given by:

$$SE = \sqrt{\frac{p(1-p)}{N}}$$

Where p is the proportion (or prevalence), and N is the sample size. The 95% confidence interval (i.e., alpha=0.05) is p±1.96*SE. A correction (±0.5/N) is made for using a normal approximation for a discrete distribution, i.e., 95% CI = p±1.96*SE±0.5/N. The relationship between prevalence, sample size and precision are illustrated in Table 3.2; sufficient precision is where the 'margin of error' is smaller than the prevalence estimate. For example, a sample size of >1000 is required to provide sufficient precision (i.e., margin of error <0.5%) for a comorbidity with 0.5% prevalence.

However, sample size is often not a decision in many observational studies; examples include secondary analysis of existing registries, or when the available patient population imposes a ceiling of sample size. Instead, investigators are recommended to estimate whether there is sufficient power (or in this case precision) to pursue their analysis, given the sample size [161].

Using the above described method of case identification, a sample of 421 axSpA patients was achieved at the time of analysis. This would allow conditions with >1.2% prevalence to be estimated with sufficient precision. It was therefore anticipated that 1) confidence intervals for the population prevalence estimate would include zero for rarer conditions, and 2) rarer comorbidities are likely to have zero cases in this study. In a study of RA using the same list of comorbidities, a sample size of 876 was able to capture at least one case of all but one comorbidity [148].

A once popular practice is to calculate post hoc power of an analysis. This is simply an alternative way of expressing the p-value and provides no additional information [162]. Instead, each chapter will begin by estimating whether there is sufficient power given the sample size (using G*Power version 3.1.9). Precision of effect estimates will then form part of discussions.

Table 3. 2: Relationship between sample size and precision for different prevalence estimates.

p	N	SE without correction	±0.5/N correction	'Margin of error'	Lower 95% CI limit	Upper 95% CI limit
10%	100	3.0%	0.5%	6.4%	3.6%	16.4%
	500	1.3%	0.1%	2.7%	7.3%	12.7%
	1000	0.9%	0.1%	1.9%	8.1%	11.9%
5%	100	2.2%	0.5%	4.8%	0.2%	9.8%
	500	1.0%	0.1%	2.0%	3.0%	7.0%
	1000	0.7%	0.1%	1.4%	3.6%	6.4%
1%	100	1.0%	0.5%	2.5%	<0%	3.5%
	500	0.4%	0.1%	1.0%	0.0%	2.0%
	1000	0.3%	0.1%	0.7%	0.3%	1.7%
0.5%	100	0.7%	0.5%	1.9%	<0%	2.4%
	500	0.3%	0.1%	0.7%	<0%	1.2%
	1000	0.2%	0.1%	0.5%	0.0%	1.0%
0.1%	100	0.3%	0.5%	1.1%	<0%	1.2%
	500	0.1%	0.1%	0.4%	<0%	0.5%
	1000	0.1%	0.1%	0.2%	<0%	0.3%

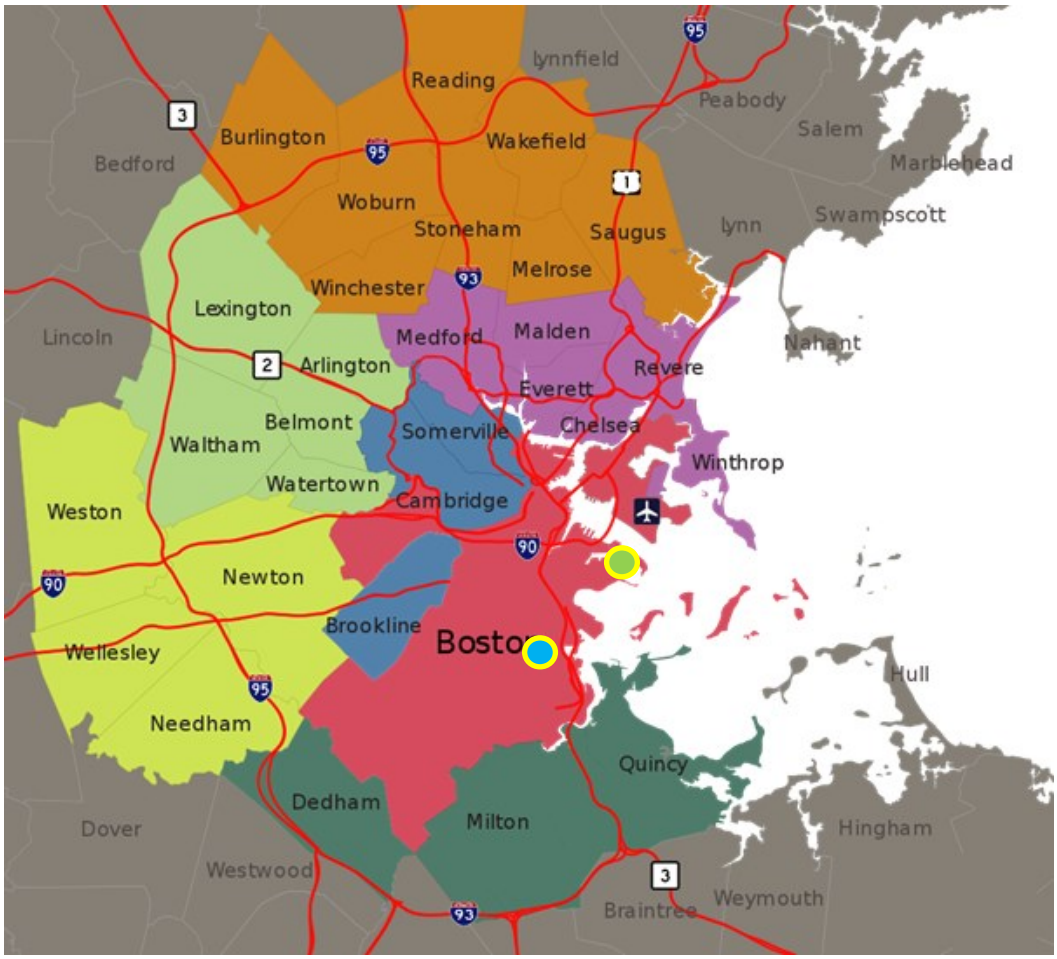
P, proportion/prevalence; N, sample size; SE, standard error; 95% confidence interval = p± 'margin of error'

3.3 Boston axial spondyloarthritis study (Massachusetts, USA)

3.3.1 Local population

Boston is the capital of the state of Massachusetts, United States (US), with a population of 695 thousand according to the 2018 census [163]. It is also the centre of the larger metropolitan area known as Greater Boston which, depending on the geographic definition, is home to 5 to 8 million people (Figure 3.4). Like Liverpool, the Boston population is relatively young, with half the population between 20 and 49 years of age. However, Boston has significantly greater ethnic diversity (44% white, 22% black, 20% Hispanic and 9% Asian) and higher educational attainment (51% with university or higher degrees).

Figure 3. 4: Boston city within Greater Boston.



The Brigham and Women's Hospital (blue) and Massachusetts General Hospital (green) shown in circles. (Reuse with permission from commons.wikimedia.org)

There are no metrics of socioeconomic status equivalent to the UK's Index of Multiple Deprivation. The Greater Boston area has the 6th largest economy in the US and 12th largest in the world (by 2008 estimates [164]). But there is great disparity in wealth [165]; 18% of Boston residents live below the poverty line (defined as minimum necessary to meet the basic needs of a family unit), compared to 10% for the state of Massachusetts.

3.3.2 Health provision

3.3.2.1 Healthcare in the United States (US)

Unlike the UK's NHS, healthcare facilities in the US are predominantly run by private sector businesses. A single clinic visit can cost several hundred dollars and an average three-day inpatient stay may cost tens of thousands of dollars depending on the type of care needed. Most Americans access healthcare through insurance, paid either privately or by their employer, to reduce such costs. The US government also provides state-managed, low-cost, public insurance: Medicare is eligible to people over the age of 65, disabled adults and those with end-stage renal disease. Medicaid provides health insurance to those who cannot afford it, to children in lower-income families, and sometimes to the disabled.

The insurance premium is not the only cost; there are also deductibles (analogous to the 'excess' in UK insurance), co-insurance (a proportion that individuals have to pay alongside the insurer), and/or 'co-pays' (co-payments; a fixed-amount payment each time care is accessed), the amount of each varies with different insurance policies. Furthermore, not all insurance plans cover all aspects of care; for example, until the Affordable Care Act ('Obamacare') in 2010 that standardised essential care, some plans did not cover prescriptions or non-emergency services. Not all plans provide access to all providers; that is, insurers may give access to certain physicians, hospitals, pharmacies, networks, etc., while another may not. These factors mean that there is great disparity in who can, or chooses to, access certain health services.

3.3.2.2 Healthcare in Boston

Partners HealthCare is a not-for-profit conglomerate of over 20 hospitals and primary care centres in the Greater Boston area. Around 1.5 million patients are seen each year in Partners hospitals [166]. It was founded in 1994 by two large tertiary care hospitals, the Brigham and Women's Hospital and Massachusetts General Hospital (Figure 3.4). Both are academic tertiary hospitals affiliated with Harvard Medical School. Together, they run the largest hospital-based research program in the world.

There are around 30 rheumatologists in the Brigham and Women's hospital, among whom SpA patients are dispersed. Although there is no dedicated SpA service, some rheumatologists do have it as a sub-specialty interest.

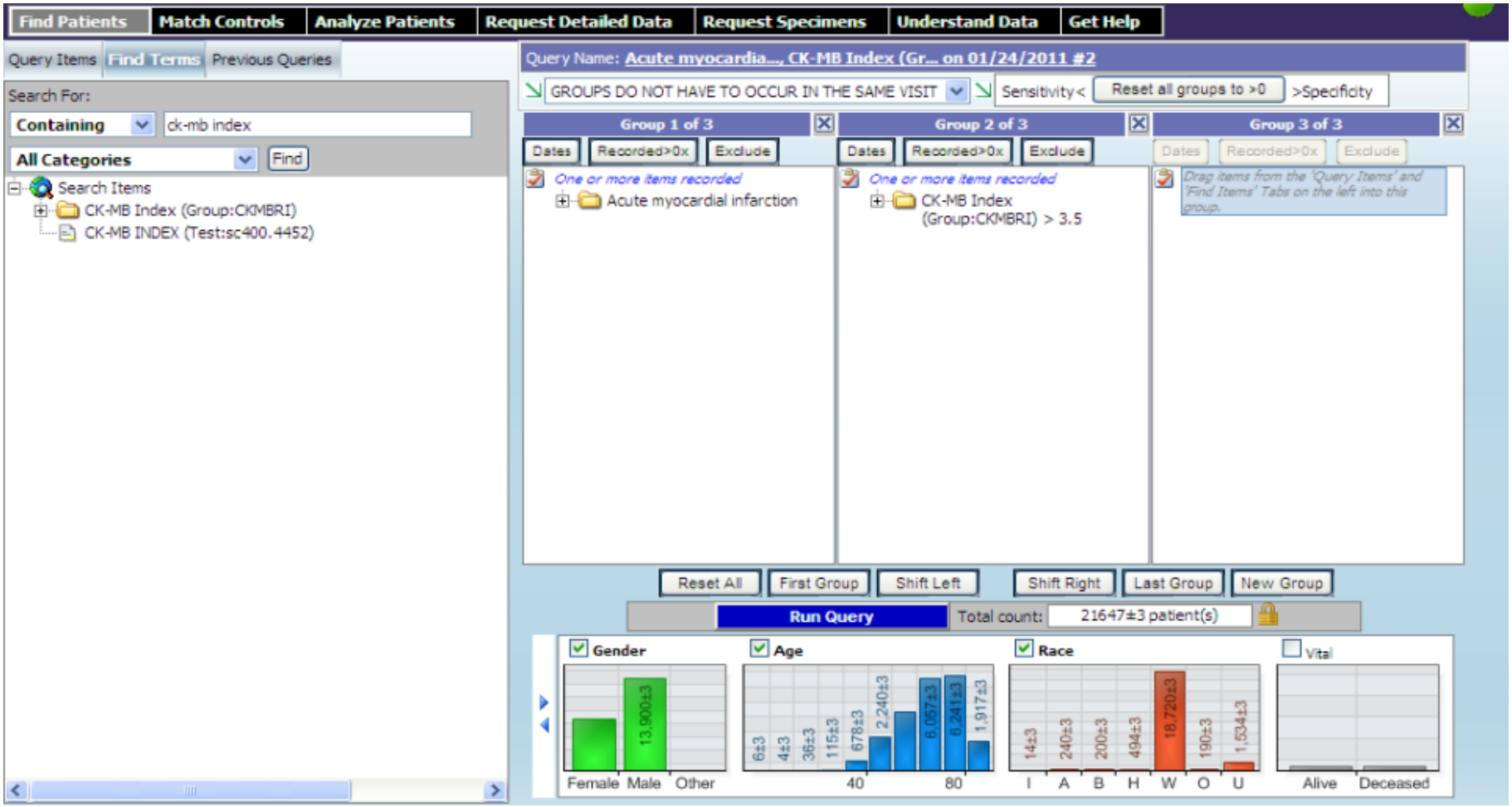
The American College of Rheumatology guidance for axSpA management resembles those from the UK and Europe, but there are differences in routine practice. First, uptake of the term 'axial spondyloarthritis' (first defined by predominantly European researchers) came much later. Until March 2019 (when the first biologic was licenced for non-radiographic axSpA in the US), many continued to exclusively use 'ankylosing spondylitis'. This is partly because the billing code system (International Classification of Diseases, ICD) was not updated to include axSpA until version 11 (to come into effect in 2022), and partly because of concerns in distinguishing non-radiographic axSpA from other differentials (namely fibromyalgia). Second, access to biologic drugs are at the discretion of the rheumatologist and the patient's insurer. Unlike the UK (and much of Europe), there are no criteria required to commence or continue biologic therapy. Thus, many outcome measures, such as BASDAI or ASDAS, are not recorded. in the Partners' electronic health records, the only consistently recorded patient-reported outcome is the pain visual analogue scale, which patients complete in the waiting room.

3.3.3 Electronic Health Records (EHRs) and the Research Patient Data Registry (RPDR)

Use of EHR started in 1996 for Brigham and Women's Hospital and 1994 for Massachusetts General Hospital. An internally developed Longitudinal Medical Record (LMR) system was initially used. This was superseded by EHR from Epic Systems in 2015. This system provides a single platform where all aspects of healthcare records (e.g., prescriptions, clinic letters, investigation results) are entered and accessed. Together, LMR and Epic EHR have facilitated care for approximately 7 million patients.

Partners HealthCare also has a Research Patient Data Registry (RPDR) – a centralised clinical data registry that gathers information from EHR and other hospital systems, as well as existing research data (Figure 3.5).

Figure 3. 5: The Research Patient Data Registry (RPDR).



Example query for acute myocardial infarction cases with a certain test result. (Image taken from RPDR training manual: https://content.research.uconn.edu/pdf/storrs/rits/RITSeminarResearchRepository.pdf)

RPDR is not an inherent component of the Epic EHR. It is an online, self-service system that allows registered users to, for example, identify patients for clinical trials or audit care provision. It also controls and audits access to patient data for research, thereby ensuring security of patient information. The RPDR can be used to: 1) obtain aggregate numbers (i.e., no individual-level data) of patients that meet user-defined criteria (e.g., diagnosis, medication, investigations) to help assess study feasibility, without institute review board (IRB) approval, and 2) request detailed identifiable patient records from the aforementioned searches, but only with an IRB approved study protocol.

3.3.4 Study design

The Boston axSpA study was set up by the thesis author. The Partners HealthCare Institutional Review Board approved all aspects of this study (2018P001840/PHS) in August 2018. Individual patient consent was not required. All data processing and analyses were completed in November 2018 and IRB approval ended in August 2020. It was a cross-sectional observational study of axSpA patients identified from Partners EHR. Requests for data from all Partners sites were submitted to, and processed by, the RPDR. Patient data were identifiable (via unique hospital number and date of birth) and were stored and processed on secure drives held at the Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital.

3.3.4.1 Eligibility

The Partners EHR contains over 7 million patient-records. A feasible approach of identifying axSpA patients among this number was therefore necessary. There is no dedicated Partners SpA service from which potentially eligible patients could be identified. It was also not possible to restrict records to rheumatology departments. Potentially eligible patients were identified from the entirety of Partners EHR using automated searches in RPDR.

Since the prevalence of axSpA was expected to be low (0.2 to 0.5% [167]), a search strategy with high specificity (at costs to sensitivity) was necessary to make subsequent manual review feasible. For example, using published criteria (at least 1 ICD code for AS [168]) returned tens of thousands of records with low prevalence of true axSpA. More stringent search criteria were therefore developed. Aggregate data provided by RPDR facilitated an iterative process to refine the search strategy. Ultimately, the search combined ICD codes with a simple text-search of radiology reports: ≥3 ICD-9 or 10 codes for AS (720.x or M45.x)

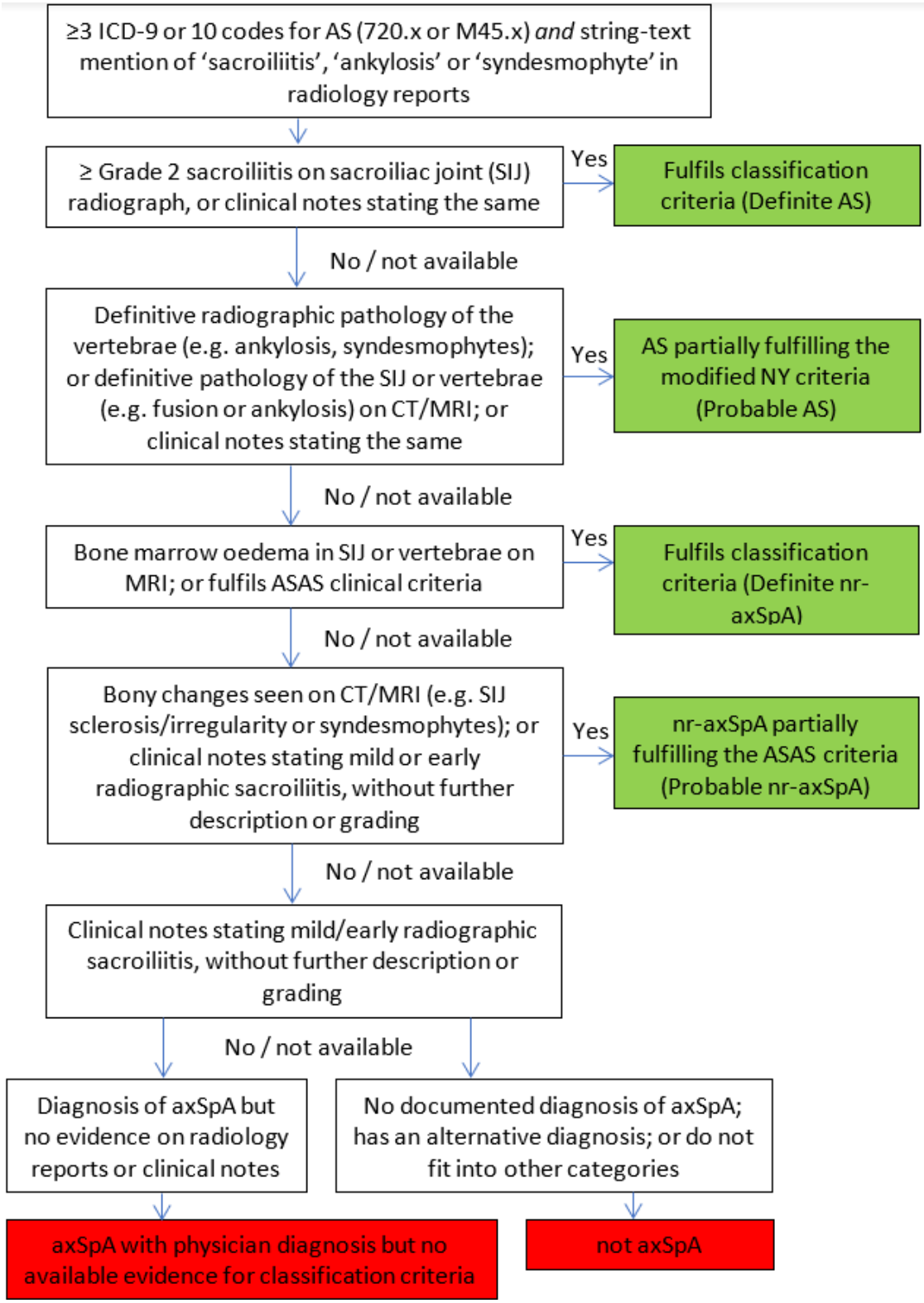
≥7 days apart *and* string-text mention of 'sacroiliitis', 'ankylosis' or 'syndesmophyte' (whether present or absent) in radiology reports, including plain X-rays, MRIs or CT scans.

This created a population with higher prevalence of cases, which was then manually reviewed. Each adult (≥18 years of age) fulfilling classification criteria were eligible for the study. Patients with a clinical diagnosis of axSpA were classified as AS if they fulfilled the modified New York criteria [169], and as nr-axSpA if they fulfilled ASAS criteria for axSpA [170] but not the modified New York criteria.

Since this was primarily a clinical rather than research cohort, investigations required for classification were not always available; for example, when patients attend with a previously established diagnosis. This was particularly true for imaging data. Patients incompletely fulfilling classification criteria were labelled as 'Probable' AS if they had imaging pathology consistent with AS (e.g. ankylosis of the vertebrae or sacroiliac joint fusion) on plain-film radiographs, CT or MRI; patients with less definitive changes on CT/MRI (e.g. sacroiliac joint sclerosis/irregularity) were labelled as 'Probable' nr-axSpA. Both Definite (fulfilling full criteria) and Probable cases of AS and nr-axSpA were eligible for inclusion. Patients with a clinical diagnosis of axSpA upon manual medical record review but no supportive imaging evidence or medical notes, and those with ICD codes but no formal clinical diagnosis of axSpA, were excluded. A flow-chart of the case selection process is shown in Figure 3.6.

During the cohort development process, a probabilistic method of case-identification was developed using Natural Language Processing (i.e., of free-text records). These algorithms were able to identify a larger number of patients without imposing the strict eligibility criteria of ≥3 ICD codes [171]. However, a manually confirmed sample was preferred for this thesis.

Figure 3. 6: Classification process for axSpA patients.



Severity of sacroiliitis was determined using a combination of radiology reports and scoring by a trained rheumatologist. Both Definite and Probable cases (in green) were included, while cases with insufficient/no evidence (in red) were not. ASAS: Assessment of Spondyloarthritis International Society; NY: New York; SIJ: sacroiliac joint; nr-axSpA: non-radiographic axial SpA.

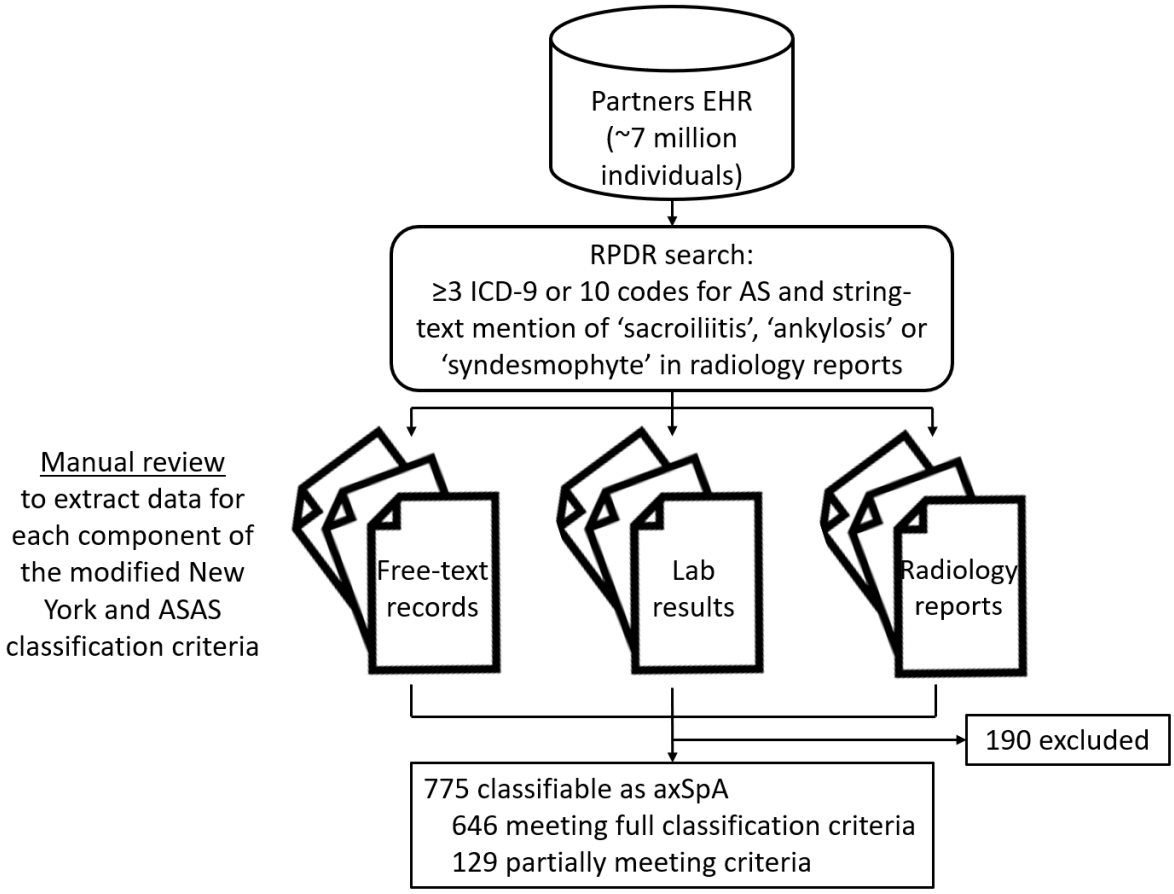
3.3.4.2 Representativeness

The Boston cohort may differ in representability for several reasons. First, there is great disparity in wealth and access to healthcare. Patients with underlying axSpA may not present to healthcare services, or decline referral to rheumatology recommended by, for example, physiotherapists or primary care clinicians. AxSpA patients without insurance or those with plans that do not cover relevant tests, referrals, or treatments (i.e., those from lower socioeconomic groups), are unlikely to be represented unless they are eligible for Medicaid. In a similar Partners study of rheumatoid arthritis, 96% of the cohort were white [148], which does not reflect the local diversity. Second, the Partners group includes two large tertiary academic hospitals but also over 20 affiliated primary care centres. The latter may provide better representation of the general axSpA population in theory. However, in practice, most records came from rheumatology departments of the two academic hospitals. Third, the way in which eligibility was defined will likely restrict the study to patients with longer disease duration or more severe disease.

3.3.4.3 Data collection

Records of potentially eligible patient from all historical encounters with Partners HealthCare were downloaded, including in- and outpatient records, medication/pharmacy records, laboratory results (HLA-B27, ESR and CRP) and radiology reports. Records include all free-text documents and coded data (e.g., ICD and prescription codes); scanned records were not included. Patients' unique identifiers were used to access their records on Epic EHR where review of radiological images was required. A summary of the data processing is shown in Figure 3.7.

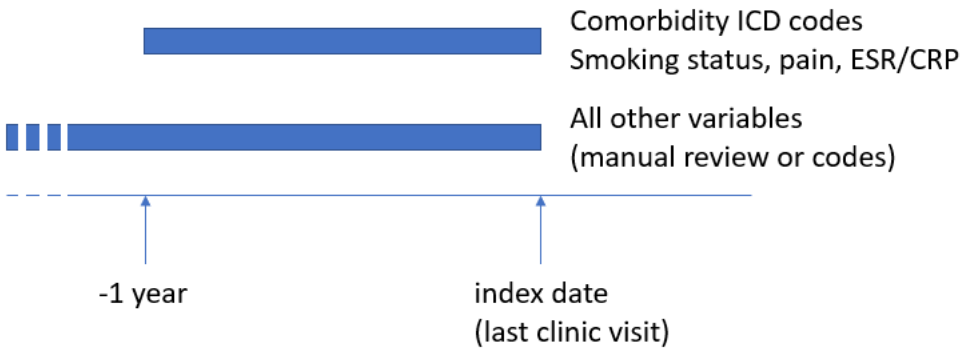
Figure 3. 7: Summary of data processing for the Boston axial spondyloarthritis study.



An automated search was performed (using criteria adapted to balanced positive predictive value and feasibility) to identify 965 individuals with high probability of having axSpA. Their records were then manually reviewed by the thesis author (without validation) to assess eligibility (defined by classification criteria). 190 individuals were excluded because they did not have a clearly documented physician diagnosis of axSpA (thus classification criteria not applicable) or did not meet classification criteria. Imaging definitions were adapted (e.g., accepting ankylosis on CT); these individuals were labelled as partial or 'Probable' cases. ASAS, Assessment of SpondyloArthritis international Society; AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; EHR, electronic health records; ICD-9, International Classification of Diseases codes version 9; RPDR, Research Patient Data Registry.

To determine eligibility, data relevant to AS and axSpA classification criteria were manually extracted from all available free-text records prior to the date of the latest clinical record for each patient (i.e., the index date). Coded EHR data (e.g., medication) were also extracted from all historical data. Exceptions to this included ICD codes for comorbidity, smoking status, pain score and CRP/ESR results, which were extracted from the 1-year period prior to the index date (Figure 3.8). Smoking status was assumed as current and non-current based on the presence of ICD codes for smoking. All ICD codes used for this study are shown in Appendix Table S3.1. A summary of variables collected are shown in Box 3.3. Data were stored in Microsoft Excel spreadsheets.

Figure 3. 8: Time ranges from which data were obtained from electronic health records for the Boston axSpA study.



All variables, whether by manual review or coded data, were obtained from all historical records prior to the date of the last clinic visit. The exceptions were comorbidity ICD codes, smoking status, pain score and inflammatory markers, which were from one year prior to the index date.

Box 3. 3: Variables collected in the Boston study.

Variables from manual review:

- Relevant pathological findings from sacroiliac joint and/or spine radiograph, CT, MRI.
- Onset <45 years, uveitis, psoriasis, inflammatory bowel disease (IBD), peripheral arthritis, enthesitis, dactylitis, response to NSAIDs, HLA-B27 status and family history (of AS, psoriasis, uveitis, reactive arthritis or IBD).

Variables from coded EHR data:

- Age at index date, gender, BMI, smoking status
- HLA-B27, ESR, CRP
- Pain VAS
- Comorbidities in Box 4.4; psoriasis, IBD.
- Medication: biologic DMARDs (Adalimumab, Etanercept, Infliximab, Golimumab, Certolizumab pegol, Secukinumab, Ustekinumab), conventional synthetic DMARDs (Sulfasalazine, Methotrexate, Leflunomide), NSAIDs (Ibuprofen, Naproxen, Indomethacin, Celecoxib, Diclofenac, Meloxicam) and Prednisone.

3.3.4.4 Comorbidity ascertainment

The same list of 39 comorbidities in were used for this study. In order to include only chronic and ongoing conditions, ICD codes within a year prior to the index date were extracted. The presence of one ICD code in this period was used to define presence of a comorbidity. The full list of ICD codes used for each of the 39 conditions are shown in the Appendix (Table S3.1).

There are well-described limitations of using claims data for epidemiological research. One consideration at the time of data collection was the window in which to collect comorbidity ICD codes. Possible approaches included using: 1) all available historical codes, 2) codes within a defined window, or 3) codes in the most recent encounter. Prior studies in support of each approach were linked to specific comparisons and outcomes of interest that related poorly to the aims of this study [172,173]. We chose the above approach because 1) it was used to develop the MMI [148] and 2) preliminary trials using all historical codes led to

unrealistic prevalence estimates. For example, one prior episode of self-limited reactive depression, or irritable bowel syndrome that was included in a list of differential diagnoses several years before the index date, should not be included as a chronic comorbidity. The duration of available historical records would also vary between individuals and differ in a manner that risks introducing bias.

3.3.4.5 Sample size considerations

Sample size considerations mirror those of the Aintree axSpA study (Section 3.2.4.5). The required sample size to provide sufficiently precise prevalence estimates for most comorbidities (i.e., those with prevalence >0.5%) was 1000. However, identifying cases from such a large data source required an approach that had different limitations on sample size. Less restrictive criteria for identifying potentially eligible patients returned samples that were not feasible to manually review. For example, using one ICD code for AS returned over 10,000 cases with less than 10% having AS. The maximum prevalence that could be estimated with sufficient precision was 0.5%. It was again anticipated that rarer comorbidities would have zero cases in this study population.

3.4 The British Society for Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS)

3.4.1 Background

The British Society for Rheumatology (BSR), along with pharmaceutical partners and the University of Manchester, set up the first nationwide biologics register in 2001 when these therapies became available for the management of rheumatoid arthritis (RA). This registry provided a wealth of safety data for TNF inhibitors, which were subsequently licensed for treatment of axSpA. Transferring observed safety data to the axSpA population is problematic given the older age, higher comorbidity burden and concurrent csDMARD use in RA patients. The BSRBR-AS was therefore created to test the hypothesis that biologic therapy increases the risk of serious infections (i.e., those requiring hospitalisation or death). Secondary objectives of the BSRBR-AS were to examine the relationship between biologic therapy and incidence of malignancy, serious comorbidity, all-cause mortality, and impact on quality of life.

The BSRBR-AS was set up by the University of Aberdeen as a five-year prospective pharmacovigilance study across the UK (Figure 3.9). Recruitment began in December 2012. Initially, the study recruited only patients who met classification criteria for AS. This was amended to include those fulfilling classification criteria for axSpA (i.e., to include nr-axSpA) in November 2014 [15,16]. The study population was recruited into two cohorts: 1) a 'biologic' groups: participants newly exposed to an eligible biologic drug, and 2) a 'non-biologic' group: participants unexposed to these therapies. The sample size was updated after the first year of study recruitment to reflect the number of serious adverse events reported; the study set out to recruit approximately 2000 participants. The final dataset of 2687 participants (downloaded December 2018) was used for all BSRBR-AS analyses in this thesis.

Figure 3. 9: Recruitment sites cross the UK for the BSRBR-AS.

Colours indicate the number of participants per site as of 2017. (Used with permission from the BSRBR-AS newsletter.)

3.4.2 Study design

The BSRBR-AS was a prospective cohort study. Ethical approval was obtained from the National Research Ethics Committee (11/NE/0374) and written informed consent was obtained from all participants. Applications were made to the BSR to perform secondary analyses relating to comorbidities. Once approved, data were securely transferred, stored, and analysed on University of Liverpool computers.

3.4.2.1 Eligibility

Inclusion and exclusion criteria are summarised in Box 3.4 and in the published protocol [14]. Potentially eligible patients were identified by participating hospitals and first informed about the study prior to their rheumatology clinic appointment by means of a letter from their consultant. Patients were then invited to take part upon clinic attendance and provided written informed consent if they accepted participation.

Box 3. 4: Eligibility criteria for the British Society for Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS)

Inclusion:

- Meeting either modified New York [48] or ASAS (imaging or clinical arm) classification criteria [174]
- Age ≥16
- Willing to give consent

Exclusion:

- Previously treated with biologic therapy
- Unable to give consent
- Unable to communicate in English
- Starting biologic therapy which was not one of the following: Adalimumab (Humira), Etanercept (Enbrel or Benepali), Certolizumab pegol (Cimzia)

3.4.2.2 Representativeness

Participants were consecutively recruited from secondary and tertiary hospitals across England, Scotland, and Wales. This should provide a broad and nationally representative cohort of hospital axSpA patients. There are a number of caveats. It is likely that healthier patients in higher socioeconomic categories were more likely to consent to participate. Hospitals with the highest number of recruits tended to be tertiary centres or those with a specialist SpA service, which may bias towards more complex patients. Lastly, recruitment was stratified into two arms with a pre-determined ratio; while each arm may represent biologic treated and naïve patients (at 35:65 respectively), the overall sample may not represent all hospital axSpA populations (i.e., the proportion of patients treated using biologics).

3.4.2.3 Data collection

Each participant was posted a set of questionnaires that collected information summarised in Table 3.3. A reminder letter and phone call or email were sent if necessary.

Table 3. 3: Variables collected at baseline and follow-up in the BSRBR-AS that were requested for this thesis.

		Baseline	Follow-up
Data from clinic visits	Visit date	✓	✓
	Cohort indicator	✓	
	Date of birth, gender, year of symptom onset, year first seen by a rheumatologist, BMI, Index of Multiple Deprivation	✓	
	AS and axSpA classification criteria components, including imaging, HLA-B27, SpA features	✓	
	bDMARD (name, start date, dose, stop date, reason for stopping)	✓	✓
	NSAID and csDMARD use in the past 6 months	✓	
	Uveitis, IBD, psoriasis confirmed physician diagnoses	✓	✓
	Peripheral articular involvement, dactylitis, enthesitis in the past 6 months	✓	✓
	CRP, ESR, BASMI (date of measurement)	✓	✓
	Comorbidities: myocardial infarction, unstable angina, congestive cardiac failure, stroke, hypertension, diabetes, asthma, chronic bronchitis/emphysema (i.e., chronic obstructive pulmonary disease, COPD), peptic ulcer, liver disease, renal disease, tuberculosis, demyelination, depression and cancer.	✓	✓
Data from questionnaires	Questionnaire date	✓	✓
	Smoking (status, frequency, cigarettes/day), alcohol status, education	✓	✓
	BASDAI (including components), spinal pain, BASFI, patient global, BASG, AS quality of life questionnaire, EQ5D-5L, EQ5D-VAS, Chalder Fatigue Scale, Jenkins Sleep Evaluation Questionnaire, Hospital Anxiety and Depression Scale	✓	✓

AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; BMI, body mass index; bDMARD, biologic DMARDs; csDMARD, conventional synthetic DMARDs; IBD, inflammatory bowel disease; BASG, Bath AS global score; EQ5D-5L, EuroQoL 5-domain 5-level.

Follow-up started at bDMARD commencement (which was not necessarily the baseline questionnaire date). For the biologic group, per protocol assessments were at 0, 3, 6, 12 months and annually thereafter. The non-biologic group underwent annual assessments. Additional clinic visits and questionnaires were possible. When participants in the non-biologic group started biologics, they were switched to the biologic group; that is, they contributed follow-up time to both cohorts. Discontinuation of biologics did not change their assigned group. At each follow-up, clinical (extracted from medical records) and self-reported data (from questionnaires) were collected (Table 3.3). Socioeconomic status was approximated using post-code derived Index of Multiple Deprivation (IMD) for each country of the UK, with quintile 1 representing the top 20% most deprived areas and quintile 5 the least [17, 18].

3.4.2.4 Comorbidity ascertainment

Participating centres extracted physician-diagnosed comorbidity data from medical records. The source of this information was predominantly from patient-reported past medical history, supported by GP records, where available. The list of 14 comorbidities included in the BSRBR-AS registry are shown in Box 3.5. These conditions were selected through a consensus meeting of clinicians and researchers, based on commonly recorded comorbidities in routine practice.

Box 3. 5: List of 14 comorbidities recorded in the British Society for Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS) registry.

1. Ischaemic heart disease
2. Heart failure
3. Stroke
4. Hypertension
5. Diabetes mellitus
6. Asthma
7. Chronic obstructive pulmonary disease (COPD)
8. Peptic ulcer disease
9. Liver disease
10. Renal disease
11. Tuberculosis (TB)
12. Demyelinating diseases
13. Depression
14. Cancer

The registry protocol specified 15 comorbidities. There was some uncertainty between angina (which is categorised with ischaemic heart disease) and unstable angina (which is grouped with myocardial infarction as acute coronary syndrome) during the data entering process. Therefore, for this thesis, myocardial infarction and (unstable) angina were

combined as ischaemic heart disease. The BSRBR-AS also assessed fibromyalgia using the survey criteria [175]. It was not included as a comorbidity in this thesis because 1) a different method of ascertainment was used, and 2) data were collected only from September 2015 onwards.

3.4.2.5 Follow-up outcomes

All indices used in the thesis are commonly referred to as 'outcome measures' in existing literature. This has potential to introduce ambiguity by implying longitudinal design, which is particularly relevant since the BSRBR-AS data were used in both cross-sectional and longitudinal analyses. To avoid the use of 'outcome' in cross-sectional designs, indices were referred to as measures of disease severity, including a subset that specifically measure disease activity (i.e., BASDAI, spinal pain, ASDAS, ESR, CRP).

A summary of longitudinal outcome measures collected at each follow-up time point is summarised in Table 3.3 above. This section briefly summarises the properties of some indices that will be used in the thesis but were not previously described in Chapter 1.

3.4.2.5.1 Hospital Anxiety and Depression Score (HADS)

The Hospital Anxiety and Depression Score (HADS) was created to assess symptoms of anxiety and depression in a general medical population [176,177]. It comprises 14 questions, 7 each for the anxiety and depression sub-scales; each item is scored from 0 to 3, to give each sub-scale score a possible range from 0 (none) to 21 (indicating severe symptoms). Its strength includes the parallel assessment of both conditions, which commonly coexist. It excludes questions relating to somatic symptoms that may confound the diagnosis in hospital populations with physical illnesses. Additional details are provided in Chapter 7 – the only data analysis chapter that use the HADS.

3.4.2.5.2 Jenkins Sleep Evaluation Questionnaire

The Jenkins Sleep Evaluation Questionnaire comprises 4 questions, each scored 0 to 5. The total score ranges from 0 to 20 with higher scores indicating poorer sleep [178].

3.4.2.5.3 Chalder Fatigue Scale

The Chalder Fatigue Scale comprises 11 questions scored 0 to 3. It ranges from 0 to 33 with higher scores indicating greater levels of fatigue [179].

3.4.2.5.4 AS quality of life questionnaire

The AS quality of life questionnaire (ASQoL) has 18 questions with the total score ranging from 0 to 18; higher scores indicate poorer health-related quality of life [180].

3.4.2.6 Sample size considerations

Sample size for the BSRBR-AS was calculated to power the primary analysis - comparing the risks of serious infections using time-to-event analysis [181]. Investigators estimated the baseline risk of serious infection as 1.6 cases per 100 person-years and set out to detect a Hazard Ratio of 2 in the biologic cohort compared to the non-biologic cohort (i.e., event rate of 3.2 per 100 person-years), at a ratio of 35 biologic to every 65 non-biologic participants. This required 1184 and 2216 person-years of observation in the biologic and non-biologic cohorts respectively which, according to the protocol [181], could be provided by at least 720 and 1300 participants in each cohort. Power implications of this pre-determined sample size were analysis-specific and discussed in respective chapters.

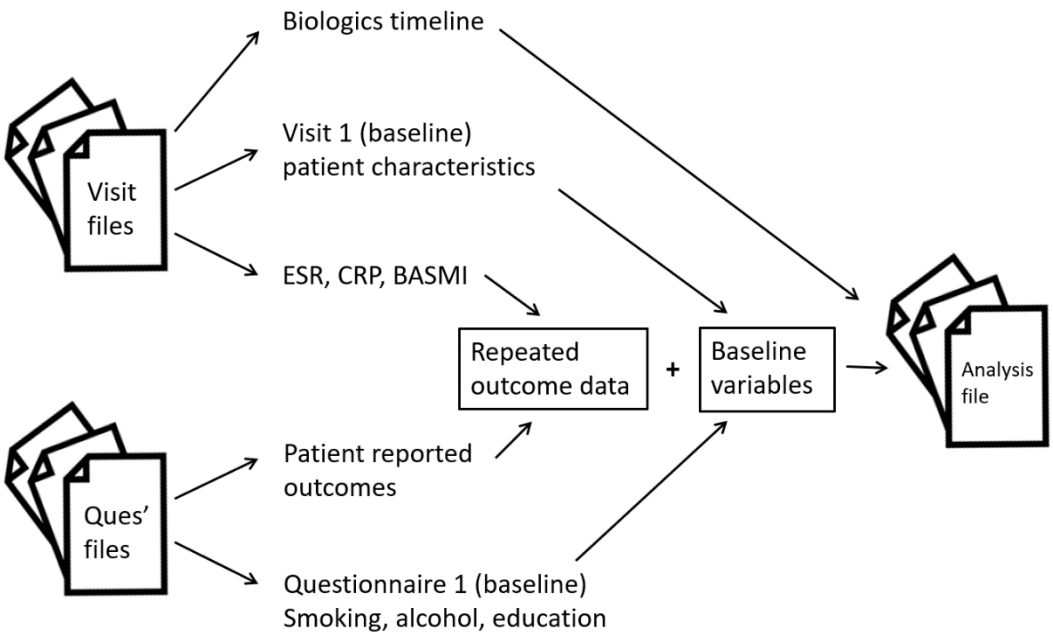
3.4.3 Preparing data for analysis

3.4.3.1 Assembling data files

Data collection for the Aintree and Boston studies were informed by specific aims in this thesis. In contrast, the BSRBR-AS was created for a broad research agenda that did not include the research questions raised in this thesis. This is apparent from, for example, the comorbid conditions that were collected. Data collation from questionnaires and dataset generation were performed by other researchers, which, although to an incredibly high standard, was not tailored for analyses in this thesis. This section summarises the data structure and relevant assumptions made during general data cleaning. Details of data processing are summarised in Appendix 10.2.1.

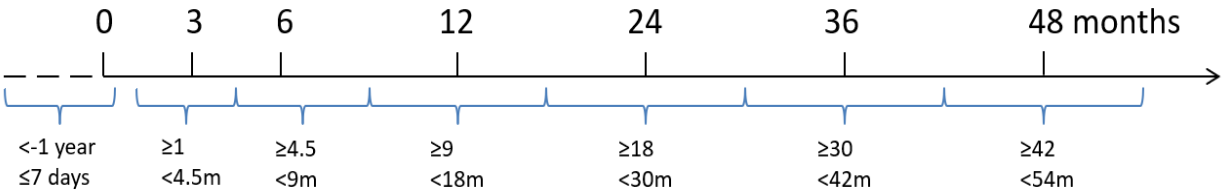
Data from clinic visits and questionnaires were each stored separately, contents of which are shown above in Table 3.3. The visit file was separated into 1) bDMARD data to create a 'treatment timeline' (described in the next section), 2) outcome-related data (ESR, CRP, BASMI), and 3) baseline characteristics. Each questionnaire file was divided into 1) patient-reported outcome measures and 2) data relating to smoking, alcohol, and education. This then allowed time-varying data from visit and questionnaire files to be combined (Figure 3.10). For analyses of treatment response, the treatment timeline was used to inform whether data were obtained while on or off treatment.

Figure 3. 10: Preparation of the analysis file from data files provided by the BSRBR-AS.



Assessments were rarely performed at exact per protocol time-points (Figure 3.11). Individuals could also contribute data (questionnaires or visits) in addition to the follow-up schedule. Questionnaires were not necessarily completed on the day of the clinic assessment. For each time-point, the assessment nearest to the protocol schedule was chosen; for example, if a participant completed questionnaires at months 10 and 13, and attended clinic at months 11 and 12.5, only the month 13 questionnaire and month 12.5 visit were retained. Keeping data processing and analyses consistent with the protocol schedule helps to reduce bias [161] and improve assessment and handling of missing data [182].For example, a participant with one assessment at month 3 is likely different from another with numerous additional clinic visits around the same time (i.e., the number of assessments is informative).

Figure 3. 11: Categorisation of follow-up assessments for the BSRBR-AS registry.



Questionnaires and clinic visits nearest to the per protocol schedule within the above windows were retained for longitudinal analyses. Time 0, or the baseline, was defined differently for analyses of treatment response (as date of treatment initiation date) and non-biologic participants (as baseline visit).

Definition of the baseline (time 0 in the above figure) differed according to whether cross-sectional or longitudinal analyses were performed. For longitudinal analyses of treatment response, baseline was defined as the date of biologic initiation. This date was not always the same as the 'baseline visit' as intended in the protocol due to delayed treatment initiation (e.g., delivery issues, holidays, illness, or personal preference). Baseline inflammatory markers and patient-reported outcomes were only included for analysis if within one year prior to and seven days after the treatment start date. These windows were chosen on the assumption that 1) on average, the disease remains relatively stable pre-treatment and 2) treatment response typically becomes apparent after one week and demonstrable by week 2 in trials [60,183]. Other non-time-varying variables in the visit (e.g., comorbidities, extra-articular manifestations) and questionnaire files (e.g., education) were taken from one year before or after the baseline.

In cross-sectional analyses, 'baseline' was defined as per protocol for the non-biologic cohort and outcome measures from one year before or after the baseline were eligible, since they were not influenced by treatment.

3.4.3.2 The treatment timeline

Longitudinal analyses of treatment response required a clear definition of the treatment timeline, such that only assessments within the treatment period were considered. For example, if a participant permanently stopped treatment at month 6, his/her 9-month outcomes would not be considered. This is particularly relevant when separating response to different treatment courses. For this thesis, only data relating to the first TNF inhibitor were analysed. This decision was taken because 1) baseline data were most consistently

complete for the first drug (the follow-up schedule does not change with biologic switch, thus switch could be between two annual or longer assessments), and 2) it is not valid to combine treatment response in treatment-naïve and -experienced patients, since response is known to differ between them.

Each participant's biologic treatment history was provided in 'wide' format; that is, each individual had one row of data, with details of their first, second, third TNF inhibitor, etc., listed across the same row. This was converted to 'long' format; that is, each individual had multiple rows, each row corresponds to a new treatment course. A pause in treatment of >3 months (e.g., for a prolonged infection) was considered as treatment discontinuation, but a shorter duration was not. Switch to biosimilars (e.g., Enbrel to Benepali) or dose changes were not considered change in treatment; for example, an individual with one row for Enbrel and the next for Benepali would have a combined course of etanercept.

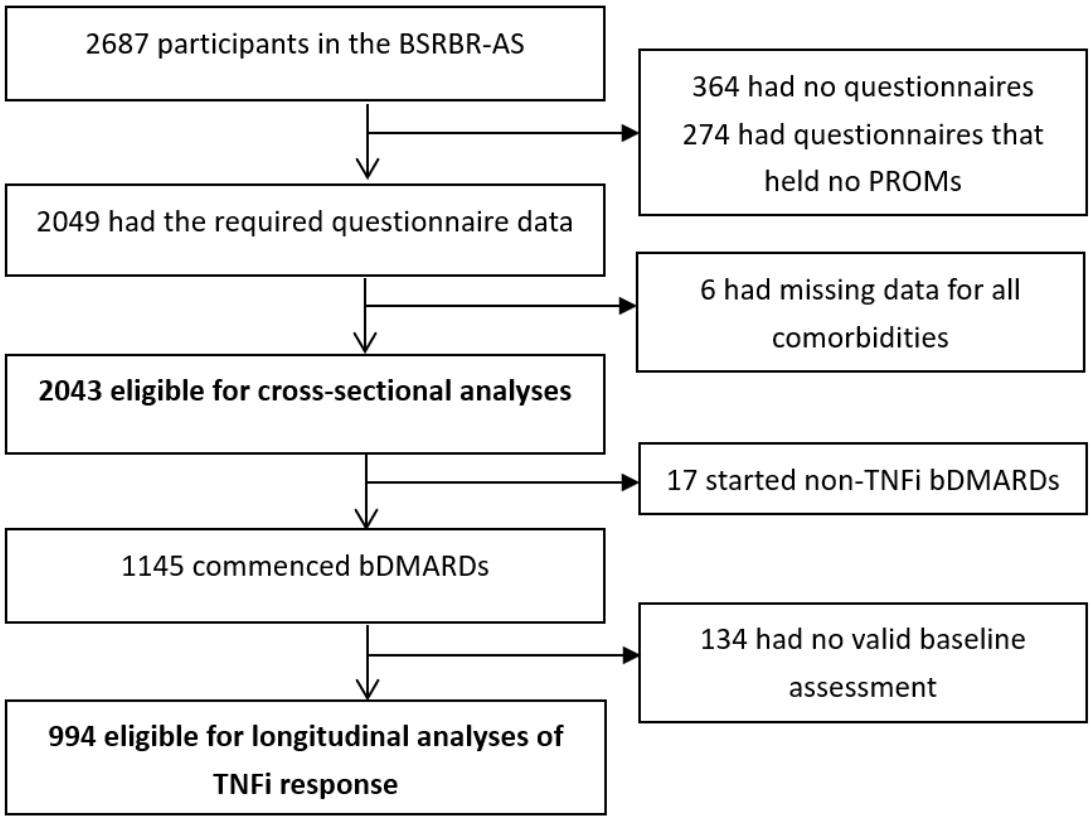
3.4.3.3 Preparing and consolidating existing variables

Once data files were assembled, further data processing and validation were performed. Some SpA features (uveitis, IBD and psoriasis) were recorded twice: once as components of eligibility/classification criteria, and again in the targeted medical history. The latter were physician-confirmed diagnoses specifically relating to the prior 6 months. These duplicates did not always match. If participants had physician-confirmed diagnoses, they were also assumed to fulfil the corresponding ASAS criteria components. HLA-B27 status was also recorded twice: as part of the ASAS criteria, and from the genetics sub-study. Positivity was defined as a positive result from either variable; there were no conflicts regarding positive and negative results from the two variables. Peripheral joint involvement and enthesitis were assumed to be present if swollen joint and enthesitis count, respectively, were recorded as >0.

3.4.3.4 Exclusions

Eligibility for the analysis population were unique to each analysis and will be described in respective chapters. For example, the cross-sectional design of Chapter 5 included all participants who had a valid assessment, which is defined differently for those who start bDMARDs and those who do not. Chapters 6 and 7 included only participants who start on TNF inhibitors with valid baseline assessments. A summary is shown in Figure 3.12.

Figure 3. 12: Summary of exclusions used for BSRBR-AS analyses.



bDMARD, biologic disease modifying antirheumatic drugs; PROMs, patient-reported outcome measures; TNFi, TNF inhibitor.

3.5 Statistics

This section describes the common statistical methods used throughout the thesis, including basic descriptive statistics, linear and generalise linear regression, and longitudinal analyses (time-to-event and repeated measures). All datasets were imported into Stata version 13 (College Station, TX).

3.5.1 Analysis approach

Statistical approaches can be broadly considered to serve one of three purposes: description, prediction, or causal inference [184]. *Description* provides a quantitative summary of the data, ranging in complexity from mean/median to cluster analysis. *Prediction* links input to output, for example, correlation coefficients or 'machine learning' methods such as neural networks. Not all predictors are, or need to be, causative factors – factors that change the outcome if modified. Distinguishing causation from association has become an increasing focus for the data sciences [185]. *Causal inference* differs from prediction in that it requires expert knowledge to specify the question, relevant data sources and the underlying causal structure. The thesis follows the prevailing school of thought that causation can only be claimed for exposures that can be manipulated under a (hypothetical) experiment ('no causation without manipulation'). Although analyses in this thesis were carefully considered, comorbidity status generally cannot be manipulated; therefore, conclusions should not be interpreted as strictly causal. Further discussions are provided in respective chapters.

Regardless of the confidence with which causation can be claimed, this thesis focused on inference between comorbidities and outcomes. Thus, coefficients for other variables in multivariable models were not presented. This avoids the 'Table 2 fallacy' – derived from the practice of presenting effect estimates for all independent variables in 'Table 2' [186]. Many journals actively forbid this approach [187], since observed associations between these covariates and the outcome are not part of a priori aims, do not undergo consideration for confounding, and are thus subject to bias. Throughout this thesis, results – particularly from regression models – were presented primarily as graphs of effect estimates or predicted values to facilitate interpretation. Raw model outputs, including values of the confidence intervals, were included in the Appendices.

3.5.2 Exposure and outcome definitions

The main 'exposure' or independent variable of interest in this thesis was comorbidity. For descriptive purposes, results for individual conditions and total count were presented. Chapter 2 showed that comorbidity could be included in different forms in regression modelling. Since each has strengths and limitations, all variable types were used where possible:

1. Binary variable (i.e., presence or absence of comorbidity) provides results that are the simplest to interpret but has limited amount of information;
2. Continuous variable captures more information, but assumes a linear relationship with the outcome;
3. Categorical variable allows examination of the linear assumption. However, very few patients have high comorbidity count, thus necessitating grouping of higher counts (e.g., into 0, 1, 2 and ≥3 comorbidities);
4. Comorbidities can also be examined as individual conditions, which provides granular information but at the cost of statistical power (e.g., due to the high number of comparisons and the low prevalence of some comorbidities)

In longitudinal analyses, treatment response can be assessed using various definitions of change from baseline. Methodology research (that was performed in parallel but not included in the thesis) demonstrated the potential for very different conclusions to be drawn using different definitions [41,42]. For chapters on treatment response, three approaches were therefore used:

1. Binary response at a specified time point. This is the commonest response definition used by existing studies and clinical trials. They fall into two categories that are described in the next section: a fixed reduction (e.g., 50% reduction in BASDAI) or a disease state (e.g., ASDAS inactive disease). There are many well-described methodological issues with binary outcomes [188]. For example, binary response thresholds are harder to achieve for individuals with higher baseline disease activity. Adjustment for the baseline disease activity is necessary, but introduces bias [41]. However, binary outcomes are favoured for their ease of interpretation for clinicians and patients alike. Patients may also care more about achieving a certain disease state (e.g., 'inactive disease') rather than other outcome definitions. They are included in this thesis predominantly for consistency and comparability with existing literature.

2. Continuous response or absolute change from baseline over follow-up. The simplest approach is to measure change from baseline at a fixed time point, but assessing continuous change in repeated assessments over time is more informative and statistically efficient.
3. Time to treatment discontinuation. This outcome is commonly used with real-world (particularly administrative claims) data where disease severity indices are often not available. It is, in effect, a composite outcome that captures ineffectiveness, intolerance, but also factors unrelated to treatment/disease (e.g., social circumstances, not attending follow-up). Data relating to causes of discontinuation were limited in the BSRBR-AS as shown in previous work [189] and discussed in greater detail in the relevant chapters.

As alluded to above, there are a wide range of binary outcomes in widespread use. For this thesis, four binary outcomes were chosen:

1. BASDAI 50/2: 50% or 2-units reduction in BASDAI from baseline. This outcome is used in routine clinical practice in the UK to determine response and eligibility to continue treatment [190].
2. BASDAI<4: This has been used to define 'low disease activity', deduced from the fact that BASDAI≥4 was defined as high disease activity for early trials of TNFi (and therefore implemented in policy), although the cut-off was not evidence-based and has never been validated.
3. ASDAS major improvement (ASDAS-MI): ≥2-unit reduction in ASDAS.
4. ASDAS<2.1: a validated threshold indicating 'low disease activity' (Chapter 1).

BASDAI was chosen for its direct relevance to UK clinical practice, and ASDAS for its relevance to continental Europe. Clinical trial outcomes such as ASAS40 (≥40% improvement and an absolute improvement from baseline of ≥2 units in ≥3 of the following domains: back pain, patient global, BASFI and inflammation without any worsening in the remaining domain) were deliberately excluded because they were not designed for use in observational data.

3.5.3 Descriptive statistics

Throughout the thesis, simple descriptive statistics (Table 3.4) were used to describe and compare the appropriate types of data. It is common for analysts to apply statistical tests for 'normality' of a continuous variable's distribution (e.g., Kolmogorov-Smirnov or

skewness-kurtosis tests). These tests are over-sensitive, particularly when sample sizes are large. Whether distributions were normally distributed - for the purposes of descriptive statistics (as well as for linear model residuals, see later) - was decided using visual inspection of kernel density plots juxtaposed against a normal distribution.

Table 3. 4: Simple descriptive statistical tests used in the thesis.

Data type	Description	Comparison between 2 groups	Comparison between ≥3 groups
Categorical	Number (percentage)	Chi-squared. Fisher's exact when expected value of any cell is ≤5. Non-parametric test for trend when ordered categorical (e.g., deprivation index)	
Non-normally distributed	Median (interquartile range)	Wilcoxon rank-sum test	Kruskal Wallis test
Normally distributed	Mean (standard deviation)	Independent samples t-test (two-sided)	One-way analysis of variance (ANOVA)

3.5.4 Generalised linear regression models

A simple regression model describes the relationship between a dependent variable, y, and an independent variable, x. In its simplest form, the association between two continuous variables are modelled. The regression line formula is $y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$, where β_1 gives the slope of the regression line, i.e., the change in y for one-unit change in x. The intercept, β_0, is the value of y when x is zero. Due to potentially broad range of unmeasured determinants, y varies for any given value of x, which is combined in an error term Ɛ or 'residual'. The relationship between y and x are assumed to be linear, not unduly influenced by outliers, and correctly specified (i.e., model adequate) [191]. The model residuals and assumptions were tested for each linear model in this thesis, but not shown.

The above simple linear regression model can be extended to a linear combination of multiple covariates – a multivariable model: $y_i = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p + \varepsilon_i$, where x represents a collection of p variables ($x_1, x_2, \ldots x_p$). Coefficient β_1 is the change in y for one-unit increase in x_1, holding all other variables in the model constant.

Linear models can be generalised to accommodate other outcome variable types; for example, logistic models for binary outcomes. In the logistic model, the log-odds of the

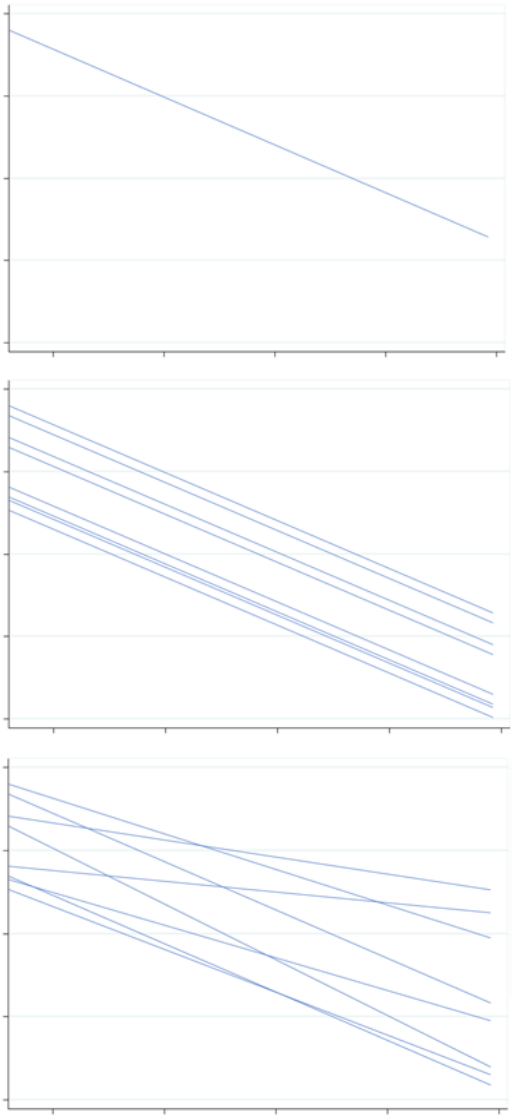
outcome is linearly related to x: $\log\left[\frac{P(x)}{1-P(x)}\right] = \beta_0 + \beta_1 x$. Exponentiating β_1 gives the odds ratio associated with one-unit increase in x. Generalisation to multiple predictors is the same as for linear models. Unlike ordinal least square in linear models, logistic models use maximum likelihood to estimate parameters; that is, parameter are estimated to maximise the likelihood (or joint probability) for the observed data under the chosen model. Models were examined for adequacy (Hosmer-Lemeshow test), influential datapoints, and linearity (between log-odds and x) [191].

3.5.6 Mixed effects models and GEE (Generalised Estimating Equations)

All tests and models discussed so far assume independent (i.e., non-clustered) data. When comparing effects of treatment on BASDAI over repeated follow-ups, each participant's follow-up BASDAI would be related to values at the baseline and other time points. Different methods are required for such analyses. A brief summary of their principles relevant to this thesis are discussed here.

Linear mixed effects (also known as random effects or multilevel) models accommodate non-independent data and, more importantly, examine effects between and within individuals. They differ from simple linear models in the way which variance (error) is partitioned. Each cluster, in this case each patient over time, can be given their own intercept and/or slope (Figure 3.13).

Figure 3. 13: Linear mixed models.



Simple linear

$y_i=\beta_0+\beta_1 x_i+\varepsilon_i$

Random intercept

$y_{ij}=\beta_{0j}+\beta_1 x_{ij}+\varepsilon_{ij}$

$\beta_{0j} = \beta_0+u_j$

Random intercept and slope

$y_{ij}=\beta_{0j}+\beta_{1j} x_{ij}+\varepsilon_{ij}$

$\beta_{0j} = \beta_0+u_{0j}$

$\beta_{1j} = \beta_1+u_{1j}$

Demonstration of three approaches to modelling repeated BASDAI of eight patients over time: simple linear model combining data points from all 8 patients (top); allowing different starting BASDAI (random intercept) for each patient assuming change overtime is constant (middle); or allowing different starting and change in BASDAI, i.e., random intercept and random slope (bottom).

Generalised estimating equations (GEE) are also commonly used for repeated measure analyses. The syntax in Stata is not dissimilar to mixed models. However, there are key differences. Mixed models provide conditional estimates, or individual effects (hence random effects for individuals), that is, 'if two individuals are randomly selected from a

population and both have identical covariate values, the person with one comorbidity would have an outcome value which is, on average, β units higher'. GEE assess marginal effects, that is, population-level effects or 'average change in outcome per unit change in exposure'. Results from marginal and conditional models coincide for continuous outcomes, but not necessarily for binary and time-to-event outcomes. Thus, marginal estimates should not be used to make inferences about individuals under these circumstances. For context, randomised controlled trials assess marginal effects (and so do observational emulations thereof [161], e.g., using inverse-probability weighting).

GEE is robust against misspecification of the correlation structure (discussed in greater detail in Appendix 10.2.2). However, GEE requires stronger assumptions about missing data (Missing Completely At Random) than mixed models (Missing At Random) (Section 3.5.8) [192]. Marginal structural models (discussed in Chapter 7) can only be used with GEE.

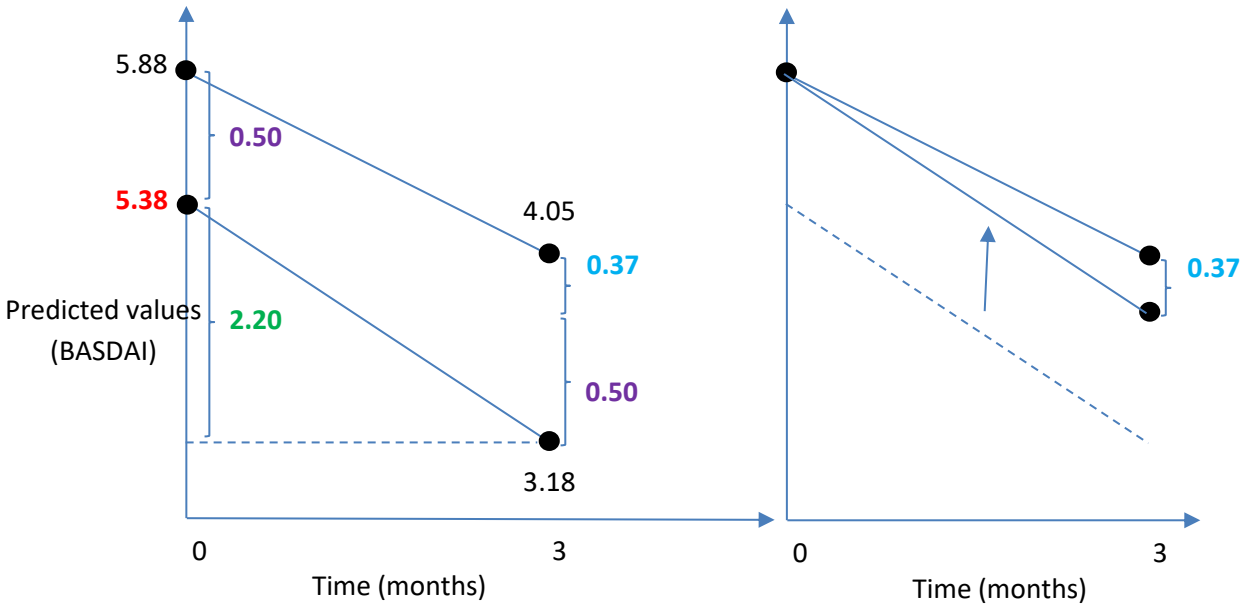
3.5.6.1 Interpretation of interaction terms

For both mixed models and GEE, difference over time between 'exposure' groups were compared using interaction terms between the group and time. Clarifying the interpretation for interaction terms is essential for understanding the results. There is a not uncommon misconception that interaction terms are not required, and that the coefficient for the 'exposure' (i.e., here the dependent variable comorbidity) represents the difference in longitudinal change (e.g., as applied in reference [193]). The following explains why this is incorrect. Take for example the output shown in Table 3.5 when modelling BASDAI (repeated over time) against comorbidity (as binary) and follow-up time (as categorical). (For simplicity covariates are omitted; when they are included later in the results, interpretations remain analogous when all covariates take the value of 0 or the reference.)

Table 3. 5: Example output from mixed model with BASDAI as the outcome to explain the interpretation of interaction terms.

		Coefficient	95% CI
Constant		5.38	(4.48 to 6.28)
Follow-up indicator variables	0.FU	reference	
	3.FU	-2.20	(-2.42 to -1.98)
	6.FU	-2.71	(-2.94 to -2.48)
	12.FU	-2.65	(-2.90 to -2.41)
	24.FU	-2.76	(-3.08 to -2.44)
	36.FU	-3.03	(-3.48 to -2.57)
Comorbidity present (no comorbidity as reference)		0.50	(0.17 to 0.82)
Interaction terms (month 0 and no comorbidity omitted)	3.FU#Comorbidity	0.37	(-0.02 to 0.76)
	6.FU#Comorbidity	0.22	(-0.18 to 0.62)
	12.FU#Comorbidity	0.05	(-0.38 to 0.48)
	24.FU#Comorbidity	-0.21	(-0.75 to 0.32)
	36.FU#Comorbidity	0.45	(-0.26 to 1.16)
FU, follow-up at numbered month. #, interaction term.			

Figure 3. 14: Demonstration of how coefficients from a mixed model with interaction terms are plotted as predicated values



On the left, Table 3.5 results are plotted as 5.38 vs. 5.88 (=5.38+0.50) at month 0, and 3.18 (=5.38-2.20) vs. 4.05 (=3.18+0.50+0.37) at month 3. The right shows that this is analogous to comparing differences after balancing the baseline.

The mean BASDAI at baseline is **5.38** (the constant) in those without comorbidities; that is, when the follow-up time indicator and comorbidity both take the value of 0. Those with comorbidities have **0.50**-units higher BASDAI (coefficient for comorbidity) when the follow-up takes the value of 0. For those without comorbidities, month 3 BASDAI falls by a mean of **2.20**-units from baseline (month 3 coefficient). Those with comorbidities have 0.87 (=**0.37**+**0.50)**-unit higher BASDAI at month 3 (interaction coefficient plus baseline difference). Note that the baseline difference in disease activity (**0.50**) is incorporated into the difference at month 3, thus the interaction term coefficient indicates the difference in change from baseline between groups at each follow-up; in this example, the difference (**0.37**) was not statistically significant (see below). Additional 'adjustment' for the baseline value is therefore not necessary. (This approach also avoids the causal conundrum of baseline adjustment). Had the model not used interaction terms, the two groups' trajectories would be parallel, with the coefficient for comorbidity simply representing the baseline difference (carried over time).

To make interpretation easier, predicted values (using -*marginsplot*- command in Stata) are shown graphically (Figure 3.14, left panel), with asterisks indicating statistical significance of the interaction term at the $p<0.05$ level. Note that statistical significance here does not relate to the difference between the two predicted values at month 3 (4.05 and 3.18), rather it is the departure from the baseline difference, or 'difference accounting for the baseline' (Figure 3.14, right panel).

3.5.7 Survival analysis

Survival analysis accounts for whether the event occurred as well as time to event (e.g., treatment discontinuation). Survival analysis allows 'right-censored' data (when follow-up is stopped before the event occurs) to be included in analyses. The probability of remaining event-free at time t (i.e., the survival function, S(t)) is estimated using the Kaplan-Meier estimator. The Kaplan-Meier curve 'drops' at observed event times and is flat in the intervening period. Curves can be compared using the log-rank test, that tests the hypothesis that the survival distribution is equal at all times.

S(t) is related to the hazard function, h(t), which is the short-term event rate for individuals who have not yet experienced the outcome event. The hazard ratio HR(t) is simply a ratio of h(t) between two groups. In their simplest form, proportional hazards models assume that the hazard ratio does not vary with time, i.e., HR(t)=HR. In these models, the linear

predictor is linked through log-transformation to the HR: $\log[HR(x)] = \log\left[\frac{h(t|x)}{h0(t)}\right] = \beta x$, where $h(t|x)$ is the hazard at time t for an observation with predictor value x, and $h_0(t)$ is the baseline hazard (hazard at time t with predictor at zero). This equation solves to: $\log[h(t|x)] = \log[h_0(t)] + \beta x$, where $\log[h_0(t)]$ is analogous to the intercept in linear models. This log-linear model implies that the log of the hazard changes linearly with each unit change in x. The Cox proportional hazards model was used in this thesis. There are many other approaches, including pooled logistic regression (used with marginal structural models, described in Chapter 7).

Four main diagnostics were performed for each Cox model: model specification, outliers, log-linearity, and proportional hazards [191]. For model specification, Cox-Snell residuals (compared to the cumulative hazard) were used to examine model fit. For log-linearity, higher-order forms of each variable (polynomials) were added to assess model improvement. Proportional hazards were tested by inspecting the Kaplan-Meier estimator and Schoenfeld residuals. Where covariates violated the proportional hazards assumption, the variable was stratified (using the -*strata()*- option of the -*stcox*- command in Stata); i.e., allowing equal coefficients across strata but with a baseline hazard unique to each stratum.

3.5.8 Missing data and multiple imputation

Missing data are problematic because most statistical analyses require a value for each variable. The simplest and commonest approach is to analyse only the cases with complete data; individuals with data missing on any variable are excluded. This can reduce the sample size, power, and introduce bias. Types of missing data can be considered according to their relationship with the non-missing (Box 3.6).

Box 3.6. Missing data mechanisms.

Missing Completely at Random (MCAR): the propensity for missingness is completely random; i.e., there is no relationship between whether a data point is missing and any values in the dataset (missing or observed).

Missing at Random (MAR): systematic relationship between the propensity for missingness and the observed data (but not the missing data); i.e., missingness can be made random by conditioning on certain observed variables.

Missing Not at Random (MNAR): missingness that is explained by the missing data. For example, missing disease activity data after loss of treatment response because treatment was discontinued due to loss of response.

Complete case analysis with MCAR data produces the same result had there been no missing; this is true of cross-sectional or longitudinal data. MAR data can be imputed based on, or weighted to be represented by, observed data to provide unbiased estimates. In longitudinal data, complete case analysis with MAR data can introduce bias when using with some approaches (GEE) but not others (mixed models). MNAR is particularly problematic and requires sophisticated methods that are beyond the scope of this thesis. Complete case analysis in GEE/mixed models – used throughout this thesis – do not 'drop' individuals who do not have complete follow-up at all time points. No imputation was performed for longitudinal analyses. The only exception was when deriving inverse-probability of censoring weights, where the derivation procedure creates a row of data for each person-month (Chapter 7). Values of time-varying variables were carried forward until the next available time point.

The proportion of missing for each relevant variable is described in respective chapters. All primary analyses used complete case only. Sensitivity analysis using multiple imputation was performed for each regression model that used cross-sectional data; only clinically meaningful differences were reported. Models for inverse-probability weights used MICE by default. Multiple imputation by chained equations (*-mi-* command in Stata) handles MAR/MCAR data by creating multiple copies of the dataset (30 used in this thesis) and using the distribution of the observed data and relationships with 'auxiliary variables' to impute missing values (i.e., using them to predict the missing values) of each variable in

turn. Outcome regression was performed on all 30 datasets and combined. Using multiple imputed values reflect the uncertainty around the true value. All covariates in the model of interest were used as auxiliary variables (i.e., variables that are correlated or believed to be associated with missingness).

3.6 Summary

Data used in this thesis were derived from three sources:

- **Aintree axSpA registry**: cross-sectional data from routine clinical records and questionnaires, from 2010 to 2018. This tertiary care dataset included rich and validated comorbidities (39 diseases derived from multiple sources of data by manual review).
- **Boston axSpA study**: cross-sectional data from electronic health records extracted by manual review and using coded data, from 2001 to 2018. This was one of the biggest axSpA cohorts in the US at the time of creation. The same list of 39 comorbidities were derived from ICD codes.
- **BSRBR-AS**: a longitudinal pharmacovigilance study from 2012 to 2017. It contained a wealth of outcomes data for biologic treated and biologic naïve axSpA participants, which allowed examination of treatment response. The list of 15 comorbidities were already collected by the study and provided for secondary analysis for this thesis.

A brief summary of each Results chapter and the dataset used is shown below.

Chapters and Aims	Dataset used		
	Aintree	Boston	BSRBR-AS
Chapter 4: Comorbidities in radiographic vs. non-radiographic axSpA and clustering of comorbidities in axial spondyloarthritis • To describe prevalence of comorbidities among the Boston and Aintree axSpA cohorts. • To compare the prevalence and patterns of comorbidities between AS and nr-axSpA patients, separately in each of the two populations. • To describe axSpA patients according to clusters of comorbidities in the Aintree cohort, and validate results using the Boston data. • To examine whether comorbidity clusters are associated with axSpA disease severity using the Aintree cohort.			
Chapter 5: Comorbidities and disease severity • To compare whether measures of disease activity (BASDAI, spinal pain, ASDAS) and inflammation (CRP/ESR) are differentially influenced by comorbidities. • To replicate these comparisons for other important measures of disease severity (fatigue, function, and health-related quality of life). • To examine whether the patient global component of ASDAS is influenced by comorbidities independent of the other components.			Cross-sectional
Chapter 6: Comorbidities and response to TNF inhibitors • To examine the association between baseline comorbidity status and binary response definitions among those using TNFi. • To examine the association between baseline comorbidity status absolute change in disease activity (BASDAI, spinal pain, ASDAS) and other measures of disease severity. • To examine the association between baseline comorbidity status and TNFi discontinuation.			Longitudinal
Chapter 7: Mental health and response to TNF inhibitors • To describe correlations between depression diagnosis and symptom. • To examine the association between history of depression at baseline and response to TNFi. • To examine the association between baseline symptoms of depression or anxiety and response to TNFi.			Longitudinal

Chapter 4: Comorbidities in radiographic vs. non-radiographic axSpA and clustering of comorbidities in axial spondyloarthritis

This chapter describes the prevalence and pattern of comorbidities and compares them between radiographic (i.e., ankylosing spondylitis) and non-radiographic axial spondyloarthritis, using cross-sectional data from both the Aintree and Boston studies. The same datasets were used to examine how comorbidities co-occur and whether axSpA disease severity differs between these patient-clusters.

4.1 Introduction

AS and non-radiographic axSpA (nr-axSpA) have similar symptom burdens and clinical features [56,57]. AS cohorts differ from their nr-axSpA counterparts in being older, more frequently male and having higher levels of CRP [56,57]. Each of these factors can influence the likelihood of developing comorbidities; for example, comorbidity burden generally increases with age, while some conditions are unique to (e.g., prostate disorders), or are much more prevalent in, one gender (osteoporosis in females) [140]. Systemic inflammation is also a risk factor for many comorbidities, e.g., cardiovascular diseases [141]. Whether comorbidities differ between AS and nr-axSpA groups has not been examined. Characterising their respective comorbidity burden is important since it is associated with several adverse disease outcomes [142].

Prior studies of comorbidities have either examined individual conditions or comorbidity count, which does not account for relationships between diseases (e.g., between hypertension and cardiovascular disease). This chapter addresses this gap in the literature using cluster analysis. Cluster analysis is a set of exploratory statistical techniques that can be used to describe which comorbidities commonly co-occur. It also helps identify patient-groups with disease clusters most associated with disease activity and other outcome measures, who may benefit from additional intervention.

Cross-sectional data from two tertiary centres in Boston (USA) and Aintree (UK), that differ in both socioeconomic context and clinical approaches, will be used to complement each other in all analyses. The Results section will begin with a description of comorbidity prevalence in each patient population.

4.2 Aims

1. To describe prevalence of comorbidities among the Boston and Aintree axSpA cohorts.
2. To compare the prevalence and patterns of comorbidities between AS and nr-axSpA patients, separately in each of the two populations.
3. To describe axSpA patients according to clusters of comorbidities in the Aintree cohort, and validate results using the Boston data.
4. To examine whether comorbidity clusters are associated with axSpA disease severity using the Aintree cohort.

4.3 Methods

4.3.1 Patient populations

4.3.1.1 Boston axial spondyloarthritis study

The Boston axSpA data was extracted from electronic health records (EHR) specifically to address Aim 2 of this chapter. Its sample size is larger than the Aintree study (n=775 vs. n=419); therefore, the primary analyses for Aim 2 focus on the Boston data (for which power calculations were performed), with the Aintree data serving to validate the results. The Boston study holds data on a list of 39 comorbidities (see Chapter 3 Box 3.2, page 88), selected according to their importance to general health, i.e., without assumptions of what might be relevant for axSpA. The accuracy of ICD codes in any study using EHR is a potential limitation, but is unlikely to differ systematically between AS and nr-axSpA groups.

4.3.1.2 Aintree axial spondyloarthritis study

The Aintree axSpA cohort included the same list of 39 comorbidities. Obesity was systematically assessed (all patients were weighed and measured), which makes its ascertainment different from all other comorbidities. The Aintree study has more reliable comorbidity data (from several data sources, cross-checked against medication), in contrast to ICD codes only which were used in the Boston study. It also included a broad selection of disease severity measures relevant to routine practice: axSpA-specific indices (BASDAI, spinal pain, BASFI), ESR, CRP, health-related quality of life (3-level version of EuroQol, EQ5D-3L), global health, and fatigue (see Chapter 3, Box 3.1, page 85). These unique strengths make the Aintree data well-suited for Aims 3 and 4. By contrast, the Boston data only include pain assessment in half of the population.

The two datasets could not be merged for this Chapter due to fundamental differences in which the data were collected. The BSRBR-AS is not suitable for cluster analysis due to the small number of comorbidities recorded (Chapter 3 box 3.5, page 107),

4.3.2 Definition of AS and nr-axSpA

Definitions of AS and nr-axSpA in the Boston data were detailed in Chapter 3 (page 98). In brief, the Boston EHR did not always include imaging data required by the modified New York or ASAS classification criteria. Individuals partially fulfilling these criteria (e.g., sacroiliitis on CT where radiographs were not available) were also included. By contrast, prescribing regulations in the UK require complete assessment of classification criteria components; therefore, AS was defined using the modified New York criteria in the Aintree data, and nr-axSpA defined by meeting the ASAS but not the modified New York criteria.

4.3.3 Statistics

Simple descriptive statistics were used to compare patient characteristics and comorbidities between AS and nr-axSpA groups. Mean, rather than median, comorbidity count was compared; comparison of median and interquartile range (IQR) provides limited information with zero-inflated counts (e.g., median of 1 (IQR 0 to 2) vs. 1 (IQR 0 to 2)). Prevalence of individual comorbidities were compared using Fisher's exact test. Prevalence were displayed as juxtaposing bar-charts to facilitate interpretation. No corrections were made for multiple comparisons, since many comorbidities co-occur and comparisons were not independent.

4.3.3.1 Cluster analysis

For the cluster analysis, obesity was removed from the list of 39 comorbidities for two reasons: 1) BMI was systematically recorded thus ascertainment of this comorbidity differed from all other conditions, and 2) BMI was included in regression models as a continuous variable, which holds more information than a dichotomised variable.

Cluster analysis generates groups of individuals according to their 'similarity' with respect to selected variables, in this case comorbidities. Many different approaches, and combinations thereof, are available [194]. It has been described by some as an 'unsupervised machine learning' method, implying input (or 'supervision') from domain experts is not necessary. However, selection of the analysis method and interpretation of the output both require clinical insight, as discussed below.

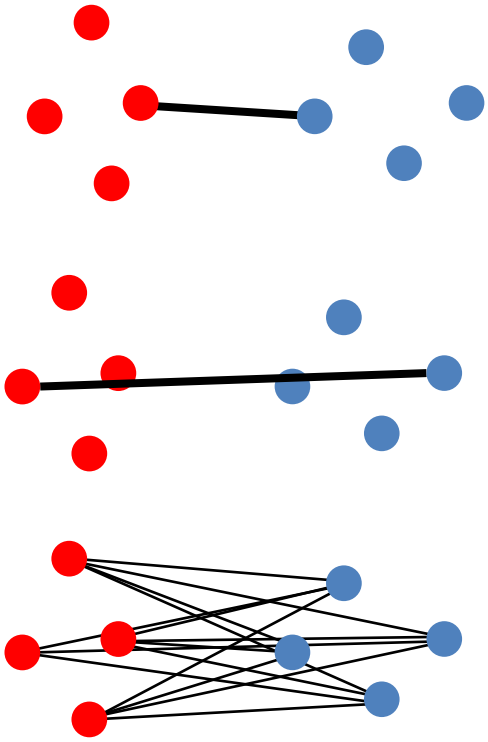
There are many ways to define ‘similarity’. One example is correlation: one can calculate correlation coefficients for each of the many pairs of variables, where sizes of the coefficient indicates the degree of similarity. Doing so with comorbidities presents two problems: first, comorbidities are binary variables (either present or absent in this data); second, patients can ‘correlate’ according to absence of comorbidities. A more appropriate similarity measure is the Jaccard coefficient [194]. It is conceptually simple (Figure 4.1), suitable for binary variables, and does not lend weight to negative matches. Once the similarity measure is chosen, different clustering algorithms are available, for example, single, complete or average linkage. The latter is the most commonly used for its desirable properties (Figure 4.2).

Figure 4. 1: Principle of the Jaccard coefficient.

	Disease A absent (0)	**Disease A present (1)**
Disease B absent (0)	M_{00}	M_{10}
Disease B present (1)	M_{01}	M_{11}

$$\text{Jaccard} = \frac{Area\ of\ overlap}{Area\ of\ union} = \frac{A\ and\ B}{A\ or\ B} = \frac{M11}{M01+M10+M11}$$

Figure 4. 2: Concepts behind common linkage algorithms.



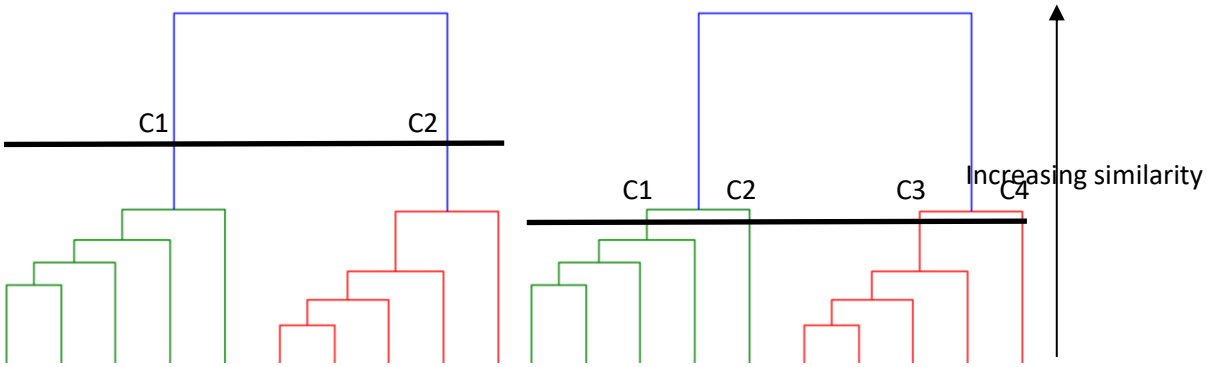
Single linkage: minimum distance; sensitive to outliers and can form clusters where observations between clusters are closer together than within clusters.

Complete linkage: maximum distance; less sensitive to outliers but forms tight clusters that are resistant to merging.

Average linkage: average of all pairwise distances; properties intermediate between single and complete algorithms.

Cluster analysis can be hierarchical or non-hierarchical. The former is more exploratory, while the latter pre-specifies the number of clusters to find when analysts have reason to assume an underlying data structure. The graphical output of hierarchical cluster analyses is like branches of a (upside down) tree, or 'dendrogram' (Figure 4.3). Hierarchical clustering can be agglomerative or divisive; the former starts with individual patients and successively clusters them until the final group contains all patients, while the latter starts with one cluster and separate individuals according to their 'dis-similarity'. Whether using the top-down or bottom-up approach, the analyst needs to decide at what level of similarity to create clusters; 'cutting' the branches near the top will provide fewer clusters and the bottom more (Figure 4.3). The decision can be made according to which makes the most clinical sense or is the most practical (e.g., avoiding hundreds of small clusters or clusters with very few individuals). It can also be based on a more objective measure. Several statistics are available to determine the 'optimum' number of clusters for separation in the Stata software; the default is the pseudo-F statistic.

Figure 4. 3: Example of tree 'dendrogram' from hierarchical cluster analysis.



'Cutting' branches at different levels of similarity will produce different numbers of clusters.

Agglomerative hierarchical analysis was chosen to match the explorative nature of Aim 3, using Jaccard similarity coefficient and average linkage. The optimum number of clusters was determined by the pseudo-F statistic [195]. All prevalent conditions in this cohort were included in the cluster analysis. Small clusters (less than 5 patients) were combined for description and regression. Patient characteristics of, and dominant comorbidities in, each cluster were then described.

4.3.3.1.1 Validating clusters

A common practice when using 'machine learning' methods (including cluster analysis) is to examine the robustness of results using cross-validation; that is, performing the clustering ('training') in a random subset of the data and 'testing' in the remainder, repeatedly. This was not possible in the current dataset due to the limited sample size and power. Other approaches were therefore used to assess robustness of the results. First, the optimal number of clusters were also tested using an alternative method – the Duda-Hart pseudo T-squared statistic (as this is the only other option available in Stata v14). Second, cluster formation may be influenced by rare comorbidities. To test the stability of clustering, the analysis was repeated using the same number of patients, but restricted to comorbidities that were prevalent in ≥2 patients. Third, the cluster analysis was externally validated using the Boston dataset. The aim of the external validation was to test whether main clusters were reproducible; clusters were not anticipated to match that of the main analysis exactly, since the comorbidity burden and its ascertainment were distinctly different.

4.3.3.2 Regression

Each cluster was compared to patients with isolated axSpA (i.e. no comorbidity) using multivariable linear models for each outcome measure as the dependent variable, and cluster as a dummy independent variable. All models were adjusted for age, gender, symptom duration, smoking status, BMI, social deprivation, and current NSAID-use. ESR and CRP were log-transformed prior to regression. There was no correction for multiple comparisons since the outcome variables were closely related constructs that measure underlying severity of disease (i.e., not independent).

4.3.3.3 Power considerations

4.3.3.3.1 Power considerations for comorbidity prevalence between AS and nr-axSpA

As discussed in Chapter 3, pre-determined sample sizes of both the Boston and Aintree studies were unable to provide sufficiently precise prevalence estimates for rarer conditions. The following power calculations were for the larger Boston study. For Aim 1, a sample of 775 would give insufficiently precise prevalence estimates for rarer comorbidities; that is, the 'margin of error' (95% CI divided by 2) would be larger than the prevalence estimate for conditions with ≤0.5% prevalence.

Aim 2 hypothesises a difference between comorbidities in AS and nr-axSpA patients. This should be a comparison of counts (which is non-normally distributed, thus appropriate for Wilcoxon rank-sum test). T-tests were used instead, given 1) the robustness of the t-test for non-normal distributions [196], and 2) the excess of zero-count (no comorbidity; reporting medians of 0 vs. 0 is uninformative). The two-tailed t-test has 99% power, assuming a meaningful difference in comorbidity count of 1 and standard deviation of 2, known sample sizes in each group (669 vs. 135), beta:alpha ratio of 1 (i.e., both types of error equally prioritised); the equivalent power for the rank-sum test is similar (99%). Power for probable values of means and standard deviations are shown in Table 4.1.

Table 4. 1: Examples of statistical power for t-tests.

Mean group 1	Mean group 2	Standard deviation	Power, %
1	2	1	~100
1	1.5	1	99
0.5	0.75	1	86
1	2	2	99
1	1.5	2	86
0.5	0.75	2	65
Calculations based on alpha=0.05, beta=0.2 and sample size of this study			

Pairwise comparisons of individual comorbidity prevalence using Fisher's exact test are sufficiently powered (beta=0.2, alpha=0.05) to detect the differences shown in Table 4.2, without accounting for multiple testing. For example, if a condition has 0.5% prevalence in the AS group, the sample size provides 80% power to detect a difference of 3.9% but no smaller.

Table 4. 2: Relationship between prevalence and difference that can be detected with sufficient power.

Prevalence in the AS group	Difference in prevalence that can be detected with sufficient statistical power
0.5%	3.9%
1.0%	4.6%
5.0%	7.2%
10.0%	9.2%
15.0%	10.5%
20.0%	11.5%

4.3.3.3.2 Power considerations Cluster analysis

As discussed in Chapter 4, the Aintree study sample size was limited by the local patient population and study duration. Approaches to cluster analysis are legion and there are no widely accepted sample size estimation methods. One recent recommendation arising from mathematical simulations [197] suggested 70 observations for each variable (70*39=2730).

The main concern was that insufficient sample sizes could produce unstable clusters – this was addressed using approaches described in Section 4.3.3.1.1.

For the regression model, patient-clusters were entered as dummy variables (i.e., each cluster required one additional degree of freedom) resulting in 18 variables in total. Power depends on the amount of variance explained by each variable. Using an alpha of 0.05, a sample size of 419 provides 80% power (i.e., beta of 0.2) for a cluster explaining ≥2% of total variance. This value is difficult to conceptualise; to illustrate, the proportion of variance (i.e., R^2) in BASDAI explained by age is 0.2%, depression 0.5%, and hypertension 0.02%. For a binary variable such as cluster-membership, a very low prevalence will contribute to a small R^2, although their relationship is not easily predictable.

4.3.3.4 Sensitivity analyses

For the AS vs. nr-axSpA comparison and bDMARD-prescription analysis using Boston data, sensitivity analyses were conducted restricting to only individuals meeting full classification criteria to increase robustness of eligibility. Sensitivity analysis was also performed for the Aintree study by excluding obesity from the comorbidity count. Sensitivity analysis for clustering was described in Section 4.3.3.1.1.

4.4 Results

4.4.1 Prevalence of comorbidities

4.4.1.1 Boston axSpA study

Among 965 patients who fulfilled the initial inclusion criteria, 775 patients (80%) were classified as axSpA and the remainder were excluded. 641 (83%) patients were classified as AS (553 Definite, 88 Probable) and 134 (17%) as nr-axSpA (93 Definite, 41 Probable). The cohort was predominantly male (74%) with a mean age of 53 years (SD 17). HLA-B27 was tested in 58% of patients, among whom 80% were positive. 91% of patient-records were from 2012 to 2018, 63% from 2018.

Patient characteristics according to diagnosis are shown in Table 4.3. AS patients were significantly older (54 (SD 17) vs. 46 (SD 17) years) and more frequently male (77% vs. 64%). HLA-B27 was more frequently tested in nr-axSpA patients, although the proportion of positive results were similar between the two groups. There were no differences in extra-axial manifestations except psoriasis, which was more frequently recorded in AS patients (13% vs. 6%, P=0.035). AS patients also had higher ESR and CRP levels, but pain VAS was similar to the nr-axSpA group. Sensitivity analysis restricting to those with AS and nr-axSpA meeting full classification criteria (i.e., Definite) did not significantly change results (Appendix 10.3: Table S4.1).

Table 4. 3: Characteristics of 775 patients in the Boston axial spondyloarthritis study, overall and compared according to diagnosis.

	All axSpA patients	Ankylosing spondylitis (n=641)	Non-radiographic axSpA (n=134)	P-value
Age, years	52.5 (16.8)	53.8 (16.6)	46.3 (16.5)	<0.001
Male	575 (74%)	490 (77%)	85 (64%)	0.002
BMI, kg/m^2	28.0 (6.1)	28.0 (6.2)	28.0 (5.9)	0.95
Current smoking	88 (11%)	71 (11%)	17 (13%)	0.59
HLA-B27 tested	447 (58%)	359 (56%)	88 (66%)	0.039
HLA-B27 positive	356 (80%)	287 (80%)	69 (78%)	0.75
Family history	103 (14%)	81 (13%)	22 (17%)	0.17
Uveitis	201 (27%)	165 (26%)	36 (29%)	0.57
Psoriasis	90 (12%)	82 (13%)	8 (6%)	0.035
Inflammatory bowel disease	80 (11%)	70 (11%)	10 (8%)	0.29
Peripheral arthritis	136 (18%)	114 (18%)	22 (17%)	0.87
Enthesitis	31 (4%)	24 (4%)	7 (6%)	0.36
Dactylitis	17 (2%)	16 (3%)	1 (1%)	0.23
ESR tested	305 (39%)	255 (40%)	50 (37%)	0.59
ESR result (mm/hr), median (IQR)	13.0 (6.0 to 25.0)	13.0 (6.0 to 27.0)	9.5 (5.0 to 21.0)	0.042
CRP tested	386 (50%)	323 (50%)	63 (47%)	0.48
CRP result (mg/dl), median (IQR)	3.0 (1.1 to 10.4)	3.4 (1.2 to 11.0)	2.2 (0.7 to 5.3)	0.007
Pain VAS available	280 (36%)	227 (35%)	53 (40%)	0.36
Pain VAS	2.4 (3.1)	2.2 (3.0)	3.0 (3.3)	0.12
Comorbidity count*, mean (SD)	1.5 (2.2)	1.5 (2.2)	1.3 (2.2)	0.29

Data are shown as mean (SD) and n (%) unless otherwise specified.
*number of comorbidities among a list of 39 chronic conditions.
BMI, body mass index; IBD, inflammatory bowel disease; IQR, interquartile range; SD, standard deviation; VAS, visual analogue scale.

Overall, a history of bDMARD-use was seen in 55% of Boston patients, csDMARDs in 25%, NSAIDs in 76%, and prednisone in 35% of patients. Ever-prescriptions of each bDMARD was similar between AS and nr-axSpA groups (Table 4.4). NSAID prescription was also similar between the two groups, except meloxicam which was significantly more frequently prescribed in patients with nr-axSpA. Sensitivity analysis restricting to those with AS and nr-axSpA meeting full classification criteria (i.e., Definite) did not significantly change the results (Appendix Table S4.2).

Table 4. 4: Medications used in 775 Boston axSpA patients compared according to diagnosis.

	Ankylosing spondylitis (n=641)	Non-radiographic axSpA (n=134)	P-value
bDMARDs	353 (55%)	70 (52%)	0.55
Adalimumab	205 (32%)	39 (29%)	0.51
Etanercept	190 (30%)	36 (27%)	0.52
Infliximab	85 (13%)	17 (13%)	0.86
Golimumab	26 (4%)	7 (5%)	0.54
Certolizumab pegol	20 (3%)	3 (2%)	0.78
Secukinumab	21 (3%)	4 (3%)	1.00
Ustekinumab	12 (2%)	0	0.24
csDMARDs	158 (25%)	35 (26%)	0.72
Sulfasalazine	81 (13%)	18 (13%)	0.80
Methotrexate	101 (16%)	23 (17%)	0.69
Leflunomide	4 (1%)	3 (2%)	0.10
NSAIDs	480 (75%)	106 (79%)	0.30
Ibuprofen	234 (37%)	61 (46%)	0.051
Naproxen	204 (32%)	49 (37%)	0.29
Indomethacin	157 (24%)	28 (21%)	0.37
Celecoxib	116 (18%)	19 (14%)	0.28
Diclofenac	86 (13%)	23 (17%)	0.26
Meloxicam	58 (9%)	20 (15%)	0.04
Prednisone	223 (35%)	51 (38%)	0.47

bDMARD, biologic disease modifying anti-rheumatic drugs; csDMARD, conventional synthetic DMARD; NSAID, non-steroidal anti-inflammatory drugs.

The median number of comorbidities was 1 (IQR 0 to 2). The mean comorbidity count was 1.5 (SD 2.2) and not statistically different between AS and nr-axSpA groups. Half of all patients had at least one comorbidity. Figure 4.4 shows the distribution of comorbidity count. The prevalence of each comorbidity is shown in Figure 4.5 in order of prevalence. The common comorbidities were anxiety (7.9%), coronary heart disease (7.7%), cancer (7.2%), hypertension (6.1%) and depression (5.2%). Twelve of the 39 conditions had a prevalence of 5% or higher, while 9 diseases had a prevalence of 1% or lower.

Figure 4. 4: Histogram showing comorbidity count among 775 Boston axSpA patients.

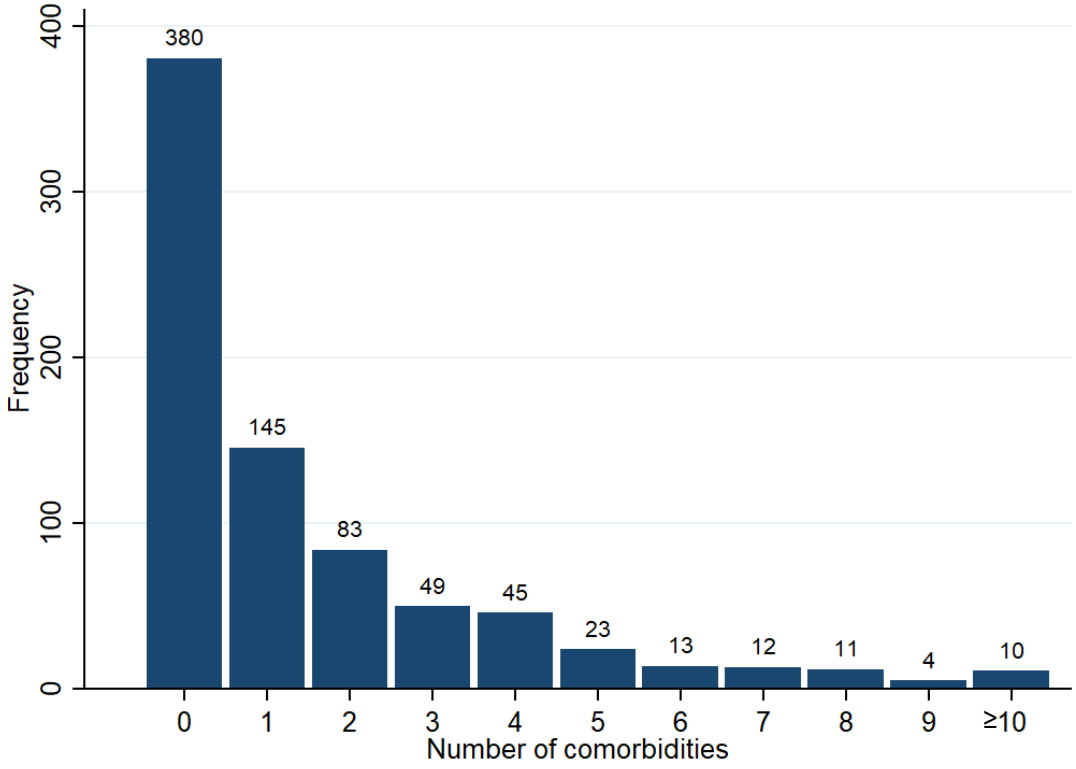
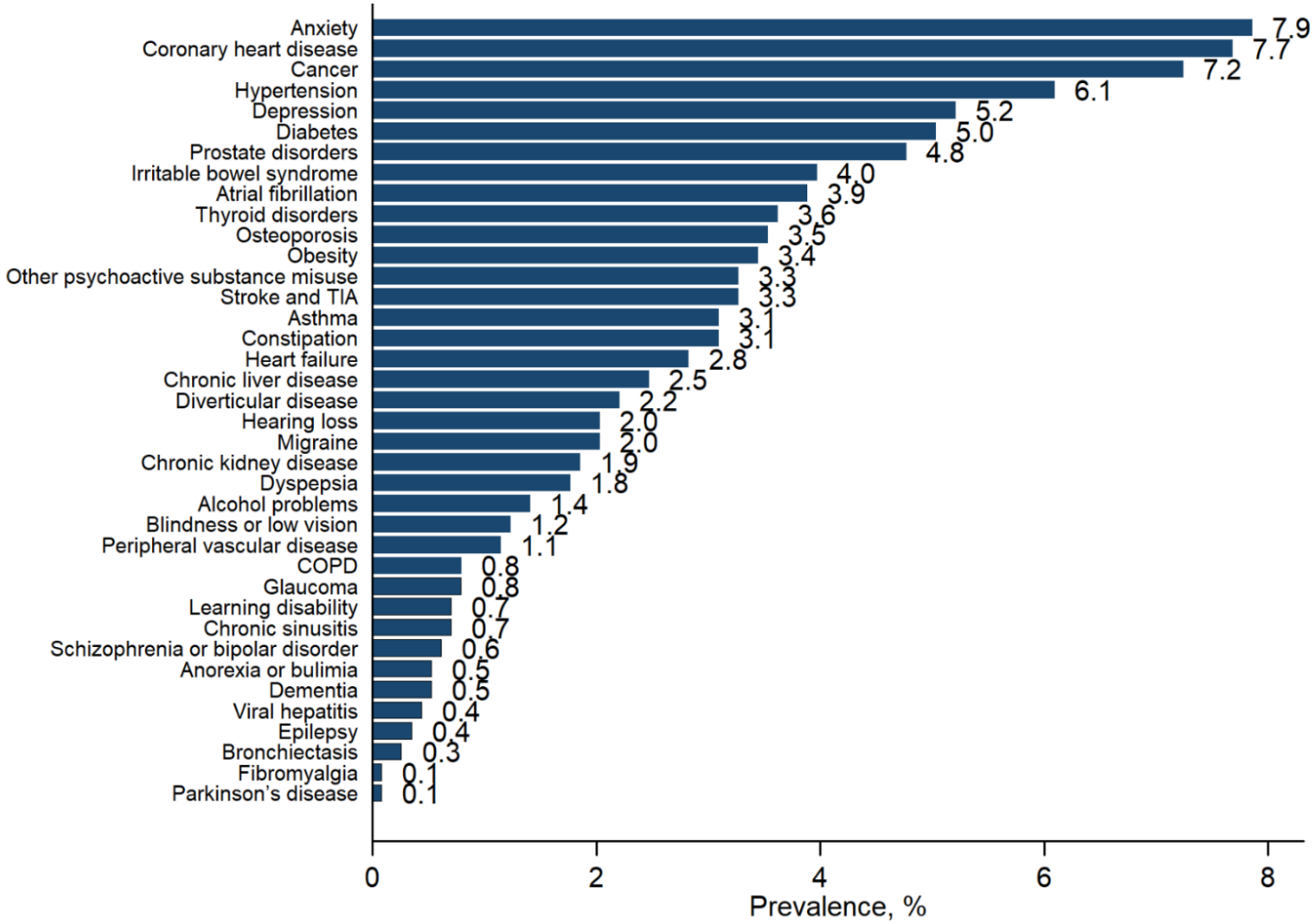


Figure 4. 5: Prevalence of individual comorbidities in the Boston axSpA study.



Compared to those with isolated axSpA, patients with comorbidity were significantly older and had higher mean BMI (Table 4.5). Patients with comorbidities were more likely to be current smokers than those without (18% vs. 4%). These patients were also more likely to have IBD, but not other extra-articular manifestations. Comorbid patients reported similar levels of pain, but had significantly higher ESR and CRP levels.

Table 4. 5: Patient characteristics of the Boston axial spondyloarthritis study according to the presence of comorbidities.

	Isolated axSpA (n=380)	**axSpA with comorbidities (n=395)**	**P-value**
Age, years	46.7 (15.4)	58.0 (16.3)	<0.001
Male	287 (76%)	288 (73%)	0.34
BMI, kg/m^2	27.1 (6.1)	28.7 (6.1)	0.017
Current smoking	15 (4%)	73 (18%)	<0.001
HLA-B27 tested	241 (63%)	206 (52%)	0.002
HLA-B27 positive	194 (80%)	162 (79%)	0.63
Family history	45 (12%)	58 (15%)	0.25
Uveitis	98 (26%)	103 (27%)	0.93
Psoriasis	37 (10%)	53 (14%)	0.11
Inflammatory bowel disease	25 (7%)	55 (14%)	<0.001
Peripheral arthritis	70 (19%)	66 (17%)	0.53
Enthesitis	14 (4%)	17 (4%)	0.66
Dactylitis	9 (2%)	8 (2%)	0.74
ESR tested	122 (32%)	183 (46%)	<0.001
ESR result (mm/hr), median (IQR)	8.5 (4.0, 18.0)	16.0 (7.0, 33.0)	<0.001
CRP tested	168 (44%)	218 (55%)	0.002
CRP result (mg/dl), median (IQR)	2.2 (0.8, 6.8)	5.1 (1.8, 13.6)	<0.001
Pain VAS available	108 (28%)	172 (44%)	<0.001
Pain VAS	2.2 (3.0)	2.5 (3.1)	0.44
Data are shown as mean (SD) and n (%) unless otherwise specified. BMI, body mass index; VAS, visual analogue scale; IQR, interquartile range; SD, standard deviation; IBD, inflammatory bowel disease.			

4.4.1.2 Aintree axSpA registry

The Aintree axSpA registry included 421 patients with established axSpA. Sufficient clinical data were available for 419 patients (2 patients had no accessible electronic health records). The cohort was predominantly male (69%) with a mean age of 46 (SD 14) years. 82% fulfilled the modified New York criteria for AS. HLA-B27 was available in 269 and of these 59% were positive. Two patients were prescribed TNF inhibitors and 17% were currently using NSAIDs at baseline.

Patient characteristics according to diagnosis are shown in Table 4.6. AS patients were significantly older (46 (SD 14) vs. 41 (SD 14) years) and more frequently male (73% vs. 53%). HLA-B27 was more frequently positive among AS patients (66 vs. 30%). AS patients more frequently had EAMs, which was significant for uveitis and psoriasis but not IBD. AS patients had (numerically but not statistically) higher median ESR (12.0 vs. 10.0mm/hr) and CRP (5.0 vs. 3.0mg/dl) levels. All patient reported measures were similar in the AS and nr-axSpA groups. The mean number of comorbidities was 1.3 (SD 1.3) and not statistically different between the AS and nr-axSpA groups.

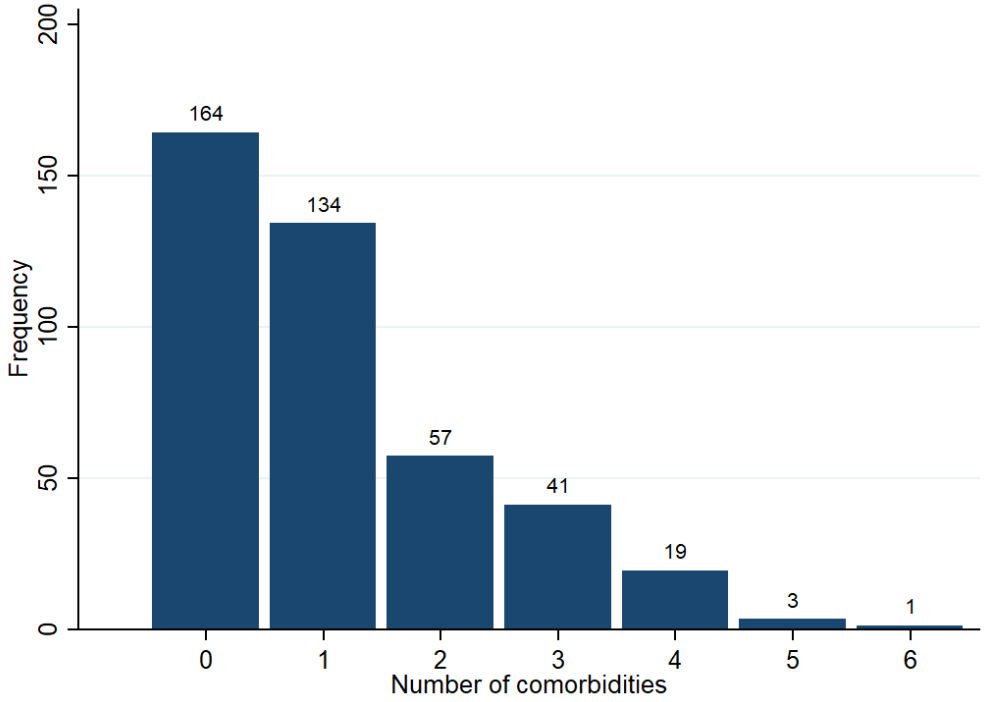
Table 4. 6: Characteristics of 419 patient in the Aintree axial spondyloarthritis registry, overall and according to diagnosis.

	All axSpA patients	Ankylosing spondylitis (n=345)	Non-radiographic axSpA (n=74)	P-value
Age, years	45.5 (14.3)	46.4 (14.2)	41.0 (13.8)	0.003
Male	291 (69%)	252 (73%)	39 (53%)	<0.001
Modified New York criteria for AS	345 (82%)	345 (100%)	0 (0%)	<0.001
HLA-B27 positive*	158 (59%)	141 (66%)	17 (30%)	<0.001
Age at symptom onset, years	27.6 (11.1)	27.0 (10.6)	30.3 (12.4)	0.026
Symptom duration, median (IQR) years	14.6 (6.2, 26.7)	17.0 (8.2, 27.9)	5.9 (2.2, 13.7)	<0.001
BMI, kg/m^2	28.2 (5.7)	28.3 (5.4)	28.1 (7.0)	0.78
Deprivation index**, median (IQR)	2.0 (1.0, 5.0)	2.0 (1.0, 5.0)	2.0 (1.0, 6.0)	0.96
Current smoker	137 (35%)	114 (36%)	23 (32%)	0.30
Ex-smoker	69 (18%)	60 (19%)	9 (13%)	
Never smoked	186 (47%)	147 (46%)	39 (55%)	
Current NSAID use	71 (17%)	54 (16%)	17 (23%)	0.13
Peripheral joint involvement	113 (29%)	75 (23%)	38 (54%)	<0.001
Uveitis	100 (25%)	96 (29%)	4 (6%)	<0.001
Psoriasis	73 (18%)	46 (14%)	27 (38%)	<0.001
Inflammatory bowel disease	40 (10%)	35 (11%)	5 (7%)	0.35
EuroQoL, median (IQR)	0.5 (0.1, 0.7)	0.5 (0.1, 0.8)	0.5 (0.0, 0.7)	0.46
Global health, median (IQR)	5.0 (2.9, 6.8)	5.0 (2.9, 6.9)	5.0 (3.2, 6.3)	0.85
Fatigue, median (IQR)	6.0 (3.3, 7.5)	6.0 (3.2, 7.5)	6.1 (4.2, 7.6)	0.28
BASDAI, median (IQR)	6.1 (3.8, 7.7)	6.0 (3.6, 7.8)	6.6 (4.8, 7.5)	0.29
Spinal pain, median (IQR)	6.7 (4.0, 8.0)	6.0 (3.0, 8.0)	7.0 (5.0, 8.0)	0.31
BASFI, median (IQR)	6.0 (3.2, 8.1)	6.0 (3.1, 8.1)	6.1 (3.9, 7.8)	0.89
ESR (mm/hr)	11.5 (5.0, 28.0)	12.0 (5.0, 28.0)	10.0 (5.0, 29.0)	0.51
CRP (mg/L)	5.0 (1.0, 15.0)	5.0 (1.0, 16.0)	3.0 (1.0, 8.0)	0.14
Comorbidity count, mean (SD)	1.3 (1.3)	1.4 (1.4)	1.3 (1.3)	0.69

Data shown as mean (SD) and n (%) unless otherwise indicated.
*HLA-B27 available for 269 patients.
**Index of multiple deprivation deciles, with 1 representing the top 10% most deprived areas and 10 the most affluent.
Fatigue and global health were single-question visual analogue scales, ranging from 0 (worst) to 10 (best).

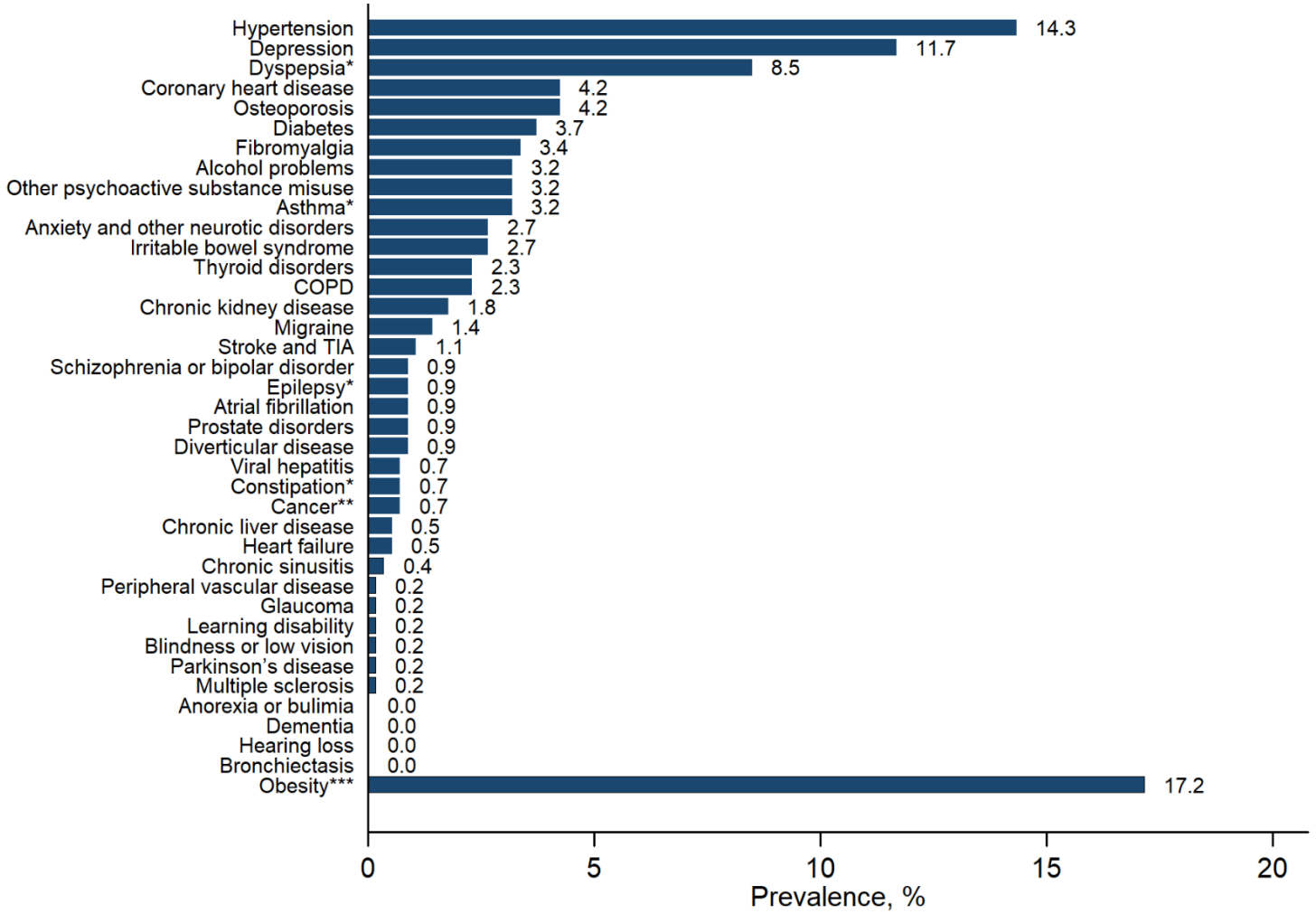
At least one comorbidity was seen in 286 (68%) axSpA patients. Figure 4.6 shows the distribution of comorbidity count. The median number of comorbidities was 1 (IQR 0 to 2). The mean was 1.3 (SD 1.3). Excluding obesity, the median and IQR of comorbidities remained unchanged, but mean was 1.1 (SD 1.2).

Figure 4. 6: Histogram showing comorbidity count among 419 Aintree axial spondyloarthritis patients.



The prevalence of each comorbidity is shown in Figure 4.7, in order of prevalence. Obesity was present in 23% (derived from systematically assessed BMI). Excluding obesity, the most common comorbidities were hypertension (14.3%), depression (11.7%) and dyspepsia (8.5%). Only six of the 38 conditions had a prevalence of over 5%, while 16 diseases had a prevalence of 1% or lower. No patients had dementia, hearing loss, bronchiectasis or anorexia.

Figure 4. 7: Prevalence of individual comorbidities in the Aintree axial spondyloarthritis registry.



*Currently treated. **New diagnosis in last 5 years. ***Obesity was defined through systematic assessment of BMI. TIA, transient ischaemic attack.

Compared to those with isolated axSpA, Aintree patients with comorbidities were significantly older (mean 49 (SD 14) vs. 40 (SD 13) years) and had higher mean BMI. Comorbid patients reported significantly worse disease activity (BASDAI and spinal pain), functional impairment, health-related quality of life, global health, and fatigue. There were no significant differences in ESR or CRP levels (Table 4.7). These comparisons were repeated with obesity excluded from the comorbidity count (Appendix 10.3: Table S4.3); results were not significantly different.

Table 4. 7: Patient characteristics the Aintree axial spondyloarthritis registry according to the presence of comorbidities.

	Isolated axSpA (n=133)	**axSpA with comorbidities (n=286)**	**P-value**
Age, years	39.5 (13.0)	48.3 (14.1)	<0.001
Male	94 (71%)	197 (69%)	0.71
Modified New York criteria for AS	111 (83%)	234 (82%)	0.68
HLA-B27 positive*	51 (60%)	107 (58%)	0.77
Symptom duration, median (IQR) years	10.6 (4.6, 20.0)	17.5 (7.1, 30.1)	<0.001
BMI***, kg/m^2	27.4 (5.2)	28.7 (5.9)	0.045
Deprivation index**, median (IQR)	3.0 (1.0, 6.0)	2.0 (1.0, 5.0)	0.08
Current smoker	42 (34%)	95 (35%)	0.32
Ex-smoker	17 (14%)	52 (19%)	
Never smoked	64 (52%)	122 (45%)	
NSAIDs	21 (16%)	50 (17%)	0.67
Peripheral joint involvement	34 (28%)	79 (29%)	0.95
Uveitis	33 (27%)	67 (24%)	0.56
Psoriasis	27 (22%)	46 (16%)	0.19
Inflammatory bowel disease	14 (11%)	26 (9%)	0.49
EuroQoL, median (IQR)	0.6 (0.1, 0.8)	0.5 (-0.02, 0.7)	0.012
Global health, median (IQR)	4.9 (2.1, 6.5)	5.1 (3.3, 7.0)	0.041
Fatigue, median (IQR)	5.5 (3.2, 7.1)	6.1 (3.6, 7.6)	0.15
BASDAI, median (IQR)	5.6 (3.5, 7.2)	6.3 (4.0, 8.1)	0.014
Spinal pain, median (IQR)	6.0 (3.0, 8.0)	7.0 (4.0, 8.0)	0.014
BASFI, median (IQR)	4.2 (2.1, 6.2)	6.7 (3.9, 8.3)	<0.001
ESR (mm/hr)	8.0 (5.0, 23.5)	13.0 (6.0, 30.0)	0.006
CRP (mg/L)	3.0 (0.0, 16.0)	5.0 (1.0, 15.0)	0.21

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

4.4.2 Comorbidities in AS vs. nr-axSpA

4.4.2.1 Comparison of comorbidities in AS and nr-axSpA among Boston patients

There were no statistically significant differences in prevalence of the 39 chronic conditions between AS and nr-axSpA groups, except chronic kidney disease which was higher in AS patients (3% vs. 0%, p=0.035) (Figure 4.8). Sensitivity analysis restricting to those with AS and nr-axSpA meeting full classification criteria did not significantly change results (Appendix 10.3: Table S4.4).

4.4.2.2 Comparison of comorbidities in AS and nr-axSpA among Aintree patients

There were no statistically significant differences in prevalence of the 39 chronic conditions between AS and nr-axSpA groups, except irritable bowel syndrome (2% in AS vs. 9% in nr-axSpA, p=0.008) (Figure 4.9). The prevalence of hypertension was higher in AS patients with borderline significance (21% vs. 11%, p=0.05). Depression and fibromyalgia prevalence were numerically higher in nr-axSpA than AS patients, but the difference was not statistically significant.

Figure 4. 8: Prevalence of 39 comorbidities compared between AS and nr-axSpA patients in the Boston study.

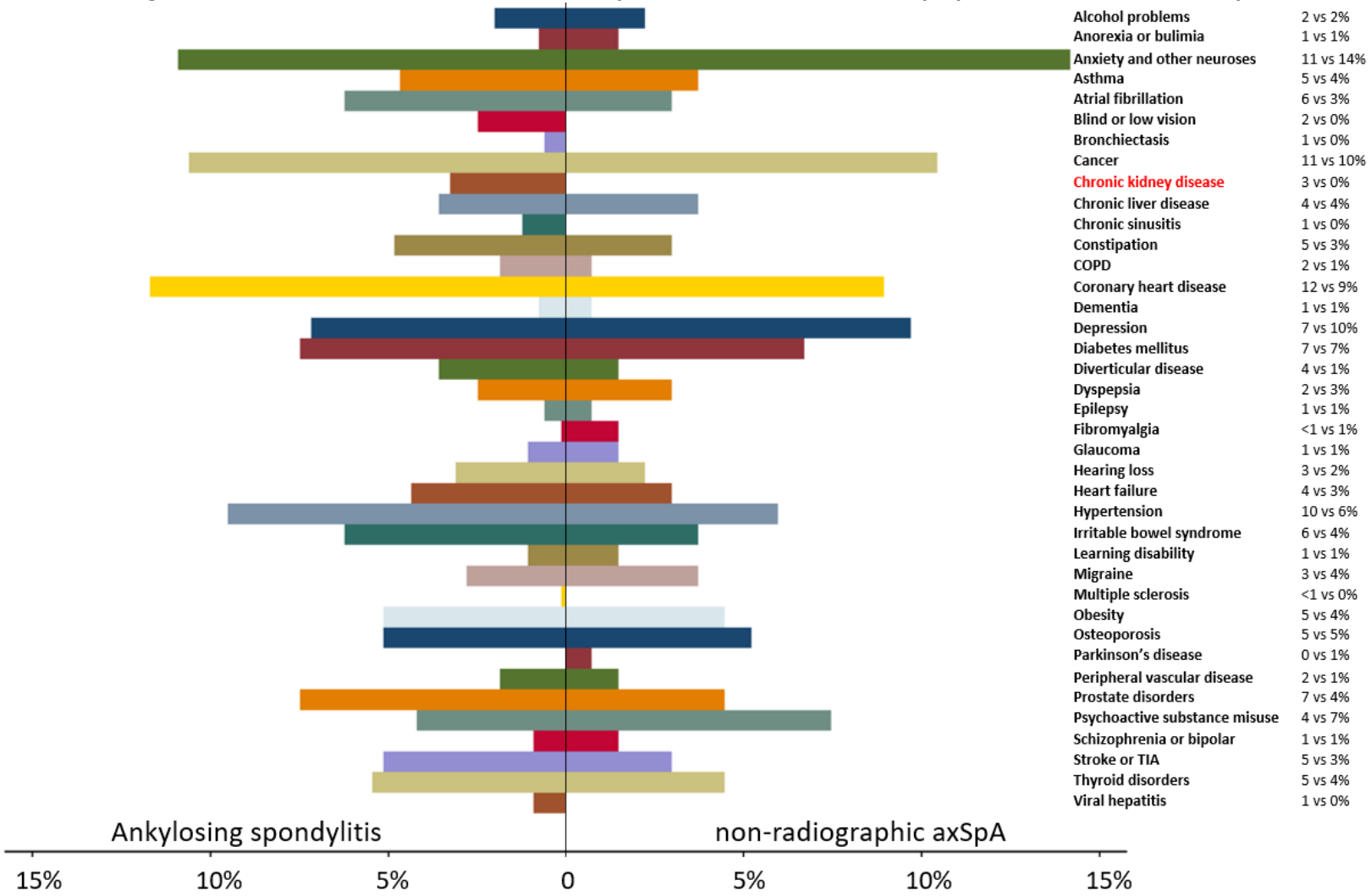
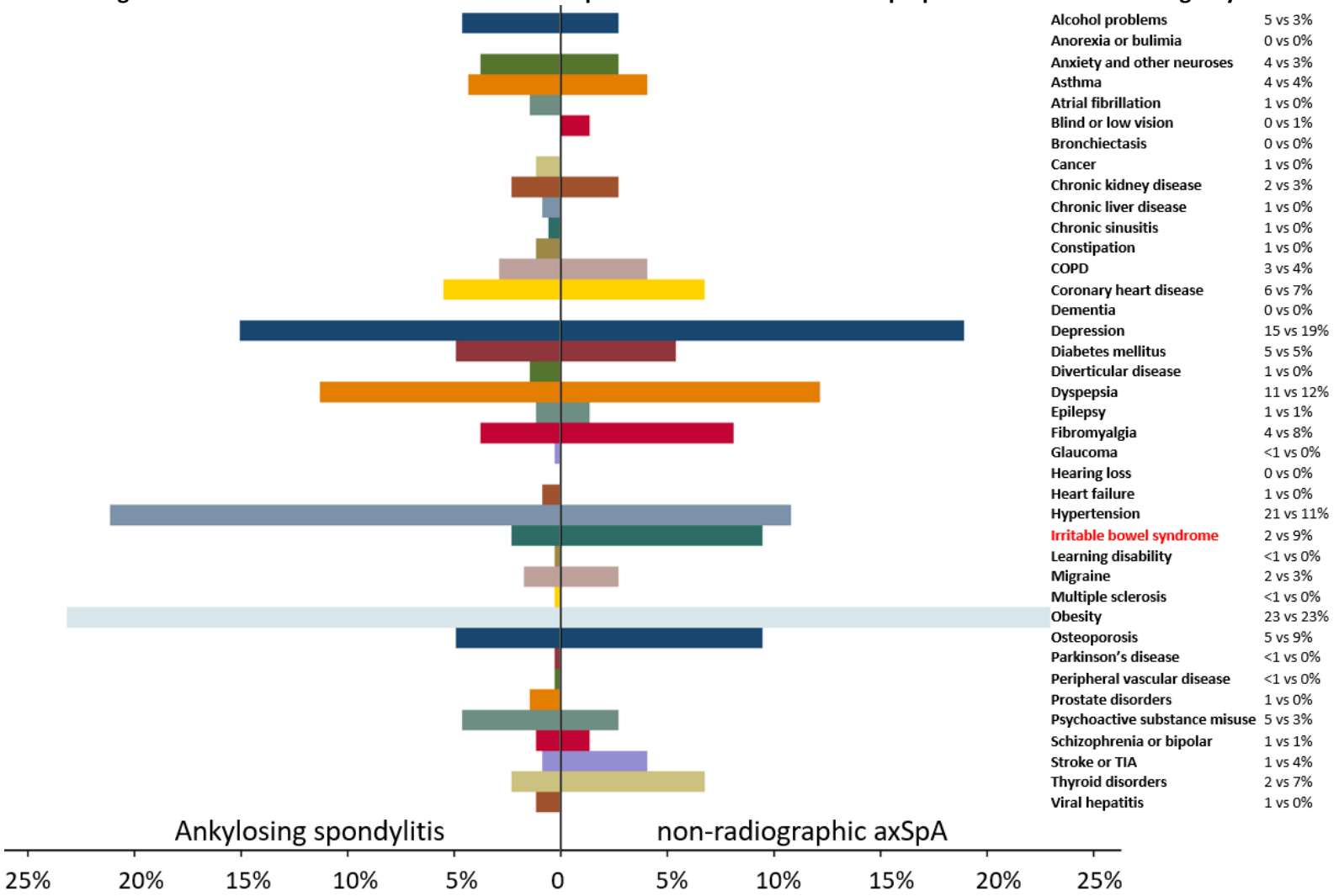


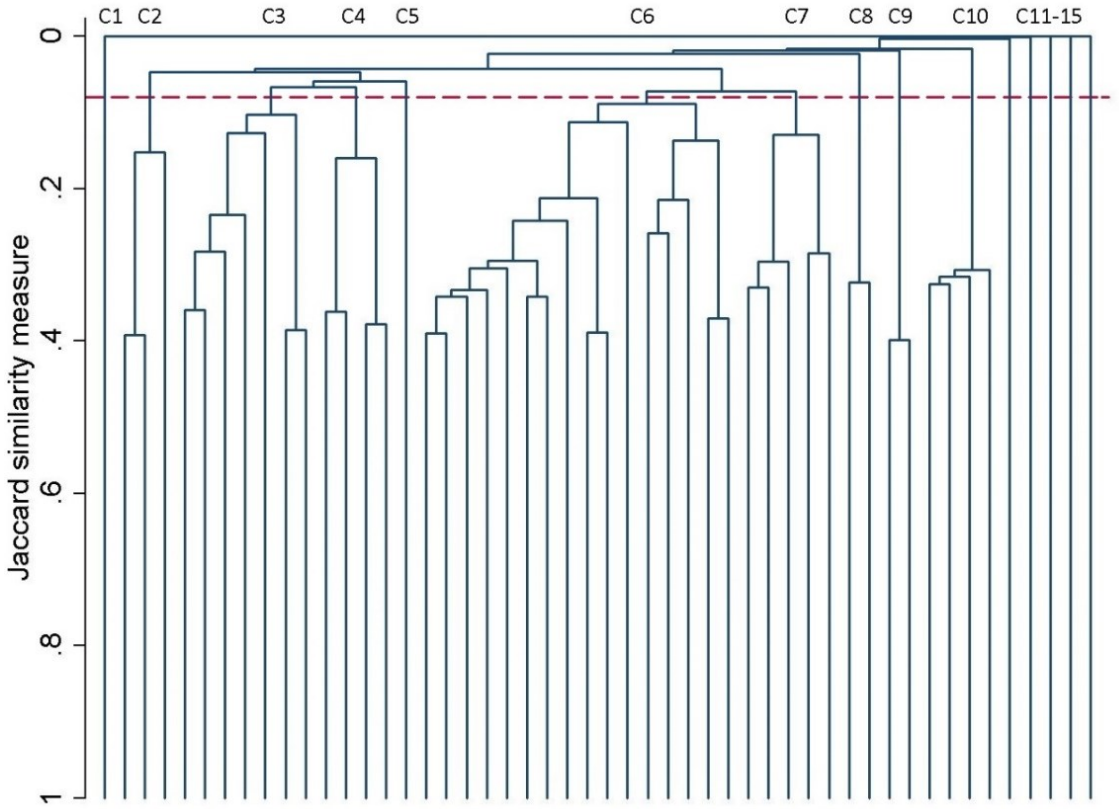
Figure 4. 9: Prevalence of 39 comorbidities compared between AS and nr-axSpA patients in the Aintree registry.



4.4.3 Comorbidity clusters in the Aintree axSpA registry

No patients had dementia, hearing loss, bronchiectasis or anorexia; therefore, these conditions were excluded from the cluster analysis. The diagram from cluster analysis of the remaining 34 conditions is shown in Figure 4.10. The pseudo-F statistic (Appendix 10.3: Table S4.5) identified 15 as the optimum number of clusters, labelled in numerical order from left to right. Clustering generally occurred at low levels of similarity.

Figure 4. 10: Diagram ('dendrogram') from cluster analysis of 419 Aintree patients and 34 comorbidities.



Zero on the y-axis indicates no similarity between clusters. From the bottom, clusters progressive joined (at levels of similarity shown at their union) until a single cluster is formed at the top. The pseudo-F statistic determined the optimum number of clusters, indicated by where the dotted horizontal line intersects with the branches. Clusters are labelled 1 to 15 from left to right based on the dominant comorbidity in the cluster.

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

All other clusters were generally dominated by one to two comorbidities with varying number of other less frequent conditions (Table 4.8). C2 (n=40) was predominantly characterised by patients with concurrent dyspepsia (94%). Clusters 3, 4 and 5 were similar: C3 (n=84) patients most commonly had depression (83%) and anxiety (14%); C4 (n=35) patients frequently had fibromyalgia (72%) and irritable bowel syndrome (IBS, 56%); C5 had only four patients, all with anxiety. Clusters 3 and 5 were combined for further analysis since they both included anxiety and would merge in the next clustering (Figure 4.10).

C6, the largest comorbidity cluster (n=88), was predominantly characterised by hypertension (82%) and coronary heart disease (CHD, 24%). C7 (n=38) commonly had osteoporosis (74%) and alcohol problems (47%). CHD and other cardiovascular diseases feature in both groups, explaining their proximity in Figure 4.10.

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

The fibromyalgia-IBS cluster and thyroid disorders cluster were predominantly female and least frequently had positive HLA-B27 status or met classification criteria for AS (Table 4.9). Patients in the hypertension-CHD cluster and alcohol problems-osteoporosis cluster were the oldest and had a higher prevalence of uveitis. Current NSAID use was lowest among those in the dyspepsia and other substance misuse clusters. Current smoking was highest among those with other substance misuse and lowest among asthma clusters.

Table 4. 8: Prevalence of comorbidities in each of the 11 patient clusters with more than one patient.

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

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

Table 4. 9 Baseline characteristics compared across comorbidity clusters in the Aintree registry.

Cluster		**1**	**2**	**3 and 5**	**4**	**6**	**7**	**8**	**9**	**10**	**11 to 15**
Disease(s)		Isolated axSpA	Dyspepsia	Anxiety and/or depression	Fibromyalgia and/or IBS	Hypertension and/or CHD	Alcohol problems and/or osteoporosis	Thyroid	Other substance misuse	Asthma	Other rare conditions
n		164	31	54	18	88	19	9	16	14	6
Age, years		40.0 (12.9)	47.9 (13.8)	44.1 (11.1)	45.9 (10.6)	56.5 (12.2)	58.0 (8.6)	50.6 (14.7)	31.6 (8.1)	37.7 (12.0)	38.3 (19.4)
Male		114 (70%)	21 (68%)	36 (67%)	7 (39%)	64 (73%)	16 (84%)	2 (22%)	16 (100%)	9 (64%)	6 (100%)
Modified New York criteria for AS		135 (82%)	26 (84%)	41 (76%)	12 (67%)	81 (92%)	15 (79%)	5 (56%)	14 (88%)	11 (79%)	5 (83%)
HLA-B27 positive*		66 (62%)	8 (44%)	17 (47%)	6 (43%)	31 (66%)	7 (70%)	2 (33%)	9 (64%)	6 (50%)	6 (100%)
BMI		27.4 (5.2)	28.2 (4.6)	29.2 (6.3)	29.7 (8.9)	29.2 (5.7)	30.0 (4.7)	28.4 (2.2)	24.4 (5.0)	29.9 (5.8)	24.5 (6.0)
Deprivation index**		2.0 (1.0, 6.0)	2.0 (1.0, 5.0)	2.0 (1.0, 4.0)	1.5 (1.0, 6.0)	2.0 (1.0, 5.0)	5.0 (1.0, 6.0)	3.5 (1.0, 7.5)	1.5 (1.0, 4.0)	1.0 (1.0, 5.0)	3.5 (1.0, 7.0)
Smoking	Current	53 (34%)	12 (44%)	23 (43%)	4 (25%)	22 (27%)	6 (33%)	1 (13%)	15 (94%)	1 (8%)	0
	Ex	23 (15%)	5 (19%)	8 (15%)	4 (25%)	22 (27%)	4 (22%)	1 (13%)	0	1 (8%)	1 (20%)
	Never	78 (51%)	10 (37%)	22 (42%)	8 (50%)	39 (47%)	8 (44%)	6 (75%)	1 (6%)	10 (83%)	4 (80%)
NSAIDS		31 (19%)	2 (6%)	12 (22%)	3 (17%)	13 (15%)	4 (21%)	2 (22%)	1 (6%)	2 (14%)	1 (17%)
Peripheral joint involvement		40 (26%)	10 (34%)	15 (28%)	7 (41%)	19 (23%)	7 (37%)	4 (44%)	3 (20%)	6 (43%)	2 (33%)
Uveitis		39 (25%)	4 (14%)	6 (11%)	6 (35%)	33 (38%)	8 (42%)	1 (11%)	1 (6%)	2 (14%)	0
Psoriasis		33 (21%)	5 (17%)	11 (21%)	2 (12%)	12 (14%)	2 (11%)	3 (33%)	3 (19%)	2 (14%)	0
IBD		19 (12%)	3 (10%)	5 (9%)	3 (18%)	7 (8%)	1 (5%)	0	0	1 (7%)	1 (17%)

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

4.4.3.1 Validation of cluster analysis results

4.4.3.1.1 Cluster number using an alternative algorithm

The optimal number of clusters determined using the pseudo T-squared statistic was 12 (Appendix 10.3: Table S4.5). The only difference compared to the main analysis was that Clusters 3 (depression/anxiety), C4 (fibromyalgia/IBS) and C5 (anxiety) were combined into one cluster.

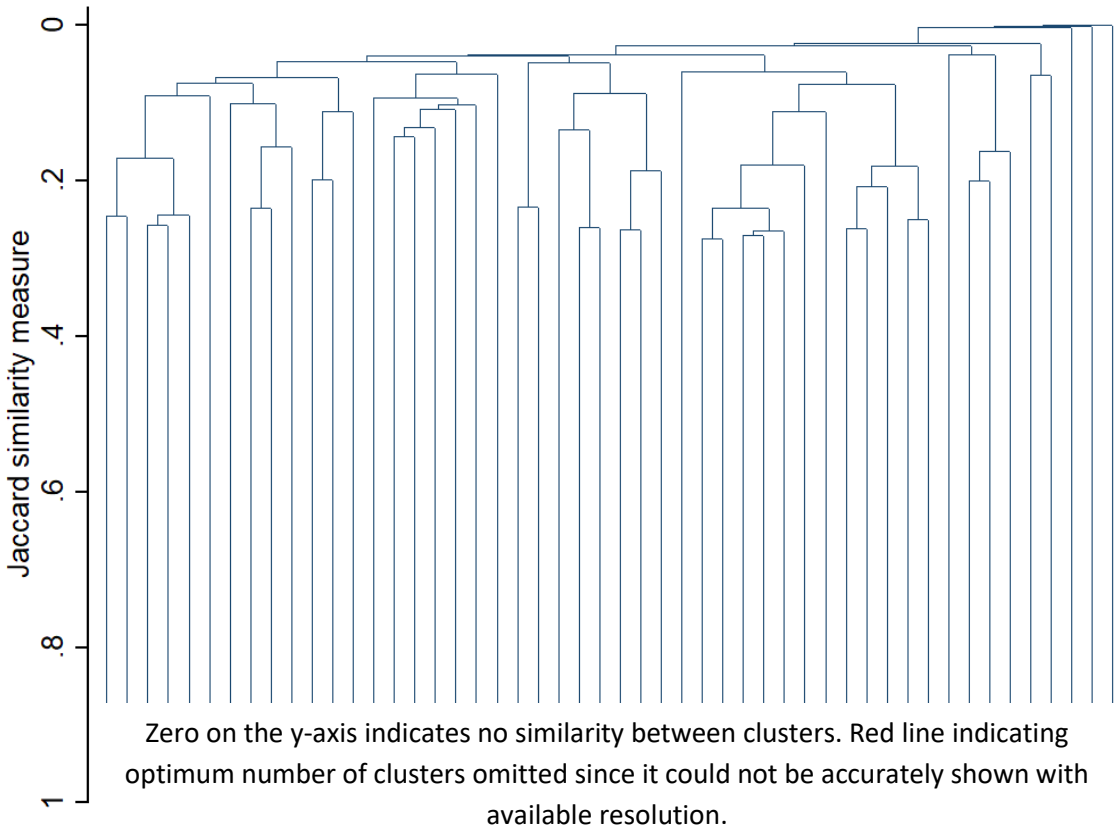
4.4.3.1.2 Excluding rare comorbidities

Cluster analysis using the 28 comorbidities that were prevalent in at least two patients showed the same clusters (Appendix 10.3: Table S4.6).

4.4.3.1.3 Externally validation of clusters using the Boston data

Repeating the cluster analysis using the Boston data (n=775, mean number of comorbidities 1.5 (SD 2.2)) revealed broadly similar patient-clusters. The dendrogram is shown in Figure 4.11.

Figure 4. 11: Dendrogram from cluster analysis of 775 Boston patients and 39 comorbidities.



Zero on the y-axis indicates no similarity between clusters. Red line indicating optimum number of clusters omitted since it could not be accurately shown with available resolution.

Ten clusters (C) were identified (Table 4.10); the corresponding pseudo-F and pseudo T-squared statistics are shown in Appendix 10.3: Table S4.7. The right-most three clusters in Figure 4.11 were most distinct from (i.e., least similar to) other clusters: C10, the largest cluster was formed by patients with no comorbidities; C9 (fibromyalgia) and C8 (dementia) had only three patients between them.

C1 to C3 were closely related. C1 (n=118) was dominated by cardiometabolic comorbidities (atrial fibrillation, coronary heart disease, heart failure, hypertension, diabetes, obesity) and cancer. C2 (n=58) was dominated by cancer. C3 (n=42) by gastrointestinal (dyspepsia, chronic liver disease, diverticular disease) and prostate diseases. The second largest cluster, C4 (n=127), was dominated by anxiety, depression, other substance misuse, and also constipation. C5 (osteoporosis, n=17) and C6 (glaucoma and blindness, n=4) were small, closely related clusters. C7 (n=26) was dominated by asthma and migraine.

As in the main analysis using the Aintree axSpA dataset, patients with no comorbidities were generally younger (47 (SD 15) years) and less frequently current smokers (4%) (Table 4.11). Patients in the cardiometabolic cluster were older (64 (SD 15) years) and had higher BMI (31 vs. 27 in the no comorbidity cluster). The mental health and substance misuse cluster had the highest prevalence of smoking (31%) – almost twice that of the group with the next highest prevalence.

Table 4. 10: Prevalence of comorbidities in each cluster with in the Boston axSpA study as external validation.

Cluster	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Number of patients	118	58	42	127	17	4	26	1	2	380
Atrial fibrillation	**33 (28)**	2 (3)		9 (7)						
Alcohol	2 (2)		1 (2)	13 (10)						
Anorexia and other neuroses	2 (2)			4 (3)		1 (25)	1 (4)			
Anxiety	5 (4)	4 (7)	2 (5)	**77 (61)**						
Asthma	4 (3)		3 (7)	11 (9)			**17 (65)**			
Blind or low vision	8 (7)			6 (5)		**2 (50)**				
Bronchiectasis				1 (1)	2 (12)		1 (4)			
Cancer	**30 (25)**	**35 (60)**	6 (14)	10 (8)	1 (6)					
Coronary heart disease	**59 (50)**		5 (12)	22 (17)			1 (4)			
Chronic liver disease	5 (4)		**14 (33)**	9 (7)						
Chronic sinusitis	1 (1)	3 (5)	1 (2)	3 (2)						
Chronic kidney disease	16 (14)	2 (3)	1 (2)	2 (2)						
COPD	7 (6)		3 (7)	1 (1)	1 (6)	1 (25)				
Dementia	3 (3)			1 (1)				**1 (100)**		
Depression	7 (6)	3 (5)	5 (12)	**44 (35)**						
Diabetes mellitus	**39 (33)**		2 (5)	12 (9)	1 (6)	1 (25)	2 (8)			
Diverticular disease	5 (4)		**14 (33)**	6 (5)						
Epilepsy	2 (2)			3 (2)						
Fibromyalgia				1 (1)					**2 (100)**	
Glaucoma	2 (2)		1 (2)	2 (2)		**4 (100)**				
Hearing loss	4 (3)	9 (16)	5 (12)	5 (4)						
Heart failure	**26 (22)**			5 (4)			1 (4)			
Hypertension	**45 (38)**	**1 (2)**	4 (10)	13 (10)	3 (18)		3 (12)			
Irritable bowel syndrome	3 (3)		2 (5)	39 (31)			1 (4)			
Learning disability	1 (1)	3 (5)	1 (2)	3 (2)		1 (25)				
Migraine	2 (2)		1 (2)	9 (7)			**11 (42)**			

Cluster	1	2	3	4	5	6	7	8	9	10
MS		1 (2)								
Obesity	**26 (22)**	3 (5)	2 (5)	7 (6)			1 (4)			
Osteoporosis	9 (8)	2 (3)	1 (2)	10 (8)	**17 (100)**	1 (25)				
Other psychoactive substance misuse	1 (1)		1 (2)	**35 (28)**						
Parkinson's disease	1 (1)									
Prostate disorders	16 (14)	3 (5)	**20 (48)**	14 (11)		1 (25)				
Peripheral vessel disease	6 (5)	4 (7)		4 (3)						
Schizophrenia or bipolar	2 (2)		1 (2)	4 (3)		1 (25)				
Stroke	17 (14)	8 (14)		12 (9)						
Thyroid disorders	8 (7)	10 (17)		18 (14)	**4 (24)**		1 (4)			
Constipation	1 (1)		1 (2)	**33 (26)**						
Dyspepsia	4 (3)		**11 (26)**	3 (2)			2 (8)			
Viral hepatitis	2 (2)	1 (2)	1 (2)	2 (2)						

*Currently treated. **Cancer diagnoses in the past 5 years. Cells with zero prevalence were left empty for clarity. Bold text highlights dominant morbidities in each cluster. Clusters 12 (2 patients with AF) and 13 (1 with sinusitis) were omitted.
TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary diseases.

Table 4. 11 Baseline characteristics compared across comorbidity clusters in the Boston study.

Cluster	**10**	**1**	**2**	**3**	**4**	**7**	**5, 6, 8, 9**
Disease(s)	Isolated axSpA	Cardiometabolic	Cancer	GI and prostate	Anxiety, depression, substance misuse	Asthma & migraine	Other rarer diseases
n	380	118	58	42	127	26	24
Age, years	46.7 (15.4)	63.5 (14.5)	58.3 (16.4)	60.3 (15.5)	53.3 (15.7)	47.1 (18.4)	63.0 (14.8)
Male	287 (76%)	100 (85%)	40 (69%)	38 (90%)	88 (69%)	9 (35%)	13 (54%)
AS*	309 (81%)	103 (87%)	49 (84%)	38 (90%)	103 (81%)	21 (81%)	18 (75%)
HLA-B27 positive**	194 (80%)	44 (75%)	20 (77%)	21 (84%)	56 (81%)	11 (73%)	10 (83%)
BMI	27.1 (6.1)	30.7 (5.8)	27.9 (6.5)	28.4 (4.2)	28.1 (6.1)	29.1 (8.2)	23.6 (3.9)
Current smoking	15 (4%)	16 (14%)	4 (7%)	7 (17%)	40 (31%)	4 (15%)	2 (8%)
NSAIDS	98 (26%)	28 (24%)	15 (26%)	15 (36%)	30 (25%)	6 (23%)	9 (39%)
Peripheral joint involvement	37 (10%)	21 (18%)	9 (16%)	7 (17%)	10 (8%)	1 (4%)	5 (22%)
Uveitis	25 (7%)	18 (16%)	8 (14%)	9 (21%)	12 (10%)	6 (23%)	2 (9%)
Psoriasis	70 (19%)	18 (16%)	13 (23%)	11 (26%)	17 (14%)	4 (15%)	3 (13%)
IBD	14 (4%)	8 (7%)	2 (4%)	2 (5%)	4 (3%)	0 (0%)	1 (4%)

Data shown as mean (SD), median (interquartile range) or n (%).
*modified New York criteria adapted for the Boston study to include sacroiliitis by other imaging modalities.
**HLA-B27 available for 447 patients.

4.4.4 Associations between patient-clusters and disease indices in the Aintree study

Aintree axSpA patients in the depression-anxiety clusters (C3 and C5), and fibromyalgia-IBS cluster (C4) reported poorer health-related quality of life, global health, fatigue, and axSpA-specific indices, compared to patients with isolated axSpA (Table 4.12). To facilitate interpretation, model coefficients and confidence intervals are also displayed graphically in Figure 4.12. For example, EQ5D-3L was lower by 0.25 units in both clusters compared to patients with isolated axSpA. Disease activity was higher by 0.9 units in the depression-anxiety cluster and 1.8 units in the fibromyalgia-IBS cluster. There were no overall differences in ESR or CRP, except patients with concurrent dyspepsia had 0.5mg/dl lower CRP than those with isolated axSpA (P=0.008).

Patients in the largest cluster (hypertension-CHD) had statistically similar axSpA severity as those without comorbidity across all patient-reported measures. Patients in C7 (alcohol problems-osteoporosis) reported worse global health and function with similar effect sizes to the depression-anxiety cluster, although this was not statistically significant. Patients with other psychoactive substance misuse reported significantly worse global health by 1.5 units; they also showed a trend of having higher BASDAI.

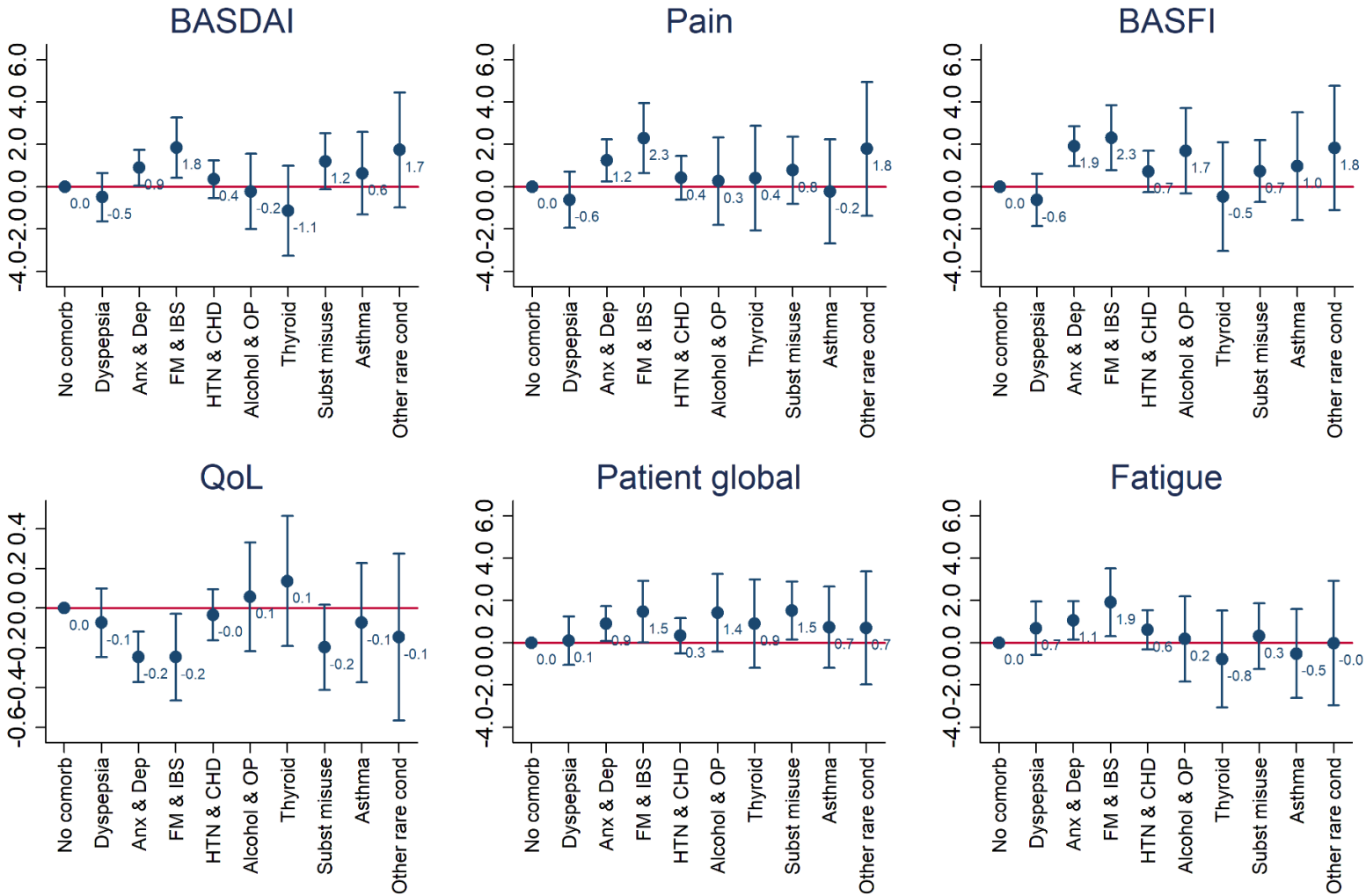
This analysis could not be replicated for the Boston study as these disease indices were not recorded.

Table 4. 12: Disease indices compared between each comorbidity cluster and axial spondyloarthritis patients with no comorbidity.

Cluster	**1**	**2**	**3 and 5**	**4**	**6**	**7**	**8**	**9**	**10**	**11 to 15**
Disease(s)	Isolated axSpA	Dyspepsia	Anxiety and/or depression	Fibromyalgia and/or IBS	Hypertension and/or CHD	Alcohol problems and/or osteoporosis	Thyroid	Other substance misuse	Asthma	Other rare conditions
n	164	31	54	18	88	19	9	16	14	6
EQ5D-3L	reference	-0.07 (-0.25, 0.10)	-0.25 (-0.37, -0.12)	-0.25 (-0.47, -0.03)	-0.03 (-0.16, 0.10)	0.06 (-0.22, 0.33)	0.14 (-0.19, 0.46)	-0.20 (-0.41, 0.02)	-0.07 (-0.37, 0.23)	-0.15 (-0.57, 0.27)
Global health	reference	0.1 (-1.0, 1.3)	0.9 (0.1, 1.7)	1.5 (0.01, 2.9)	0.3 (-0.5, 1.2)	1.4 (-0.4, 3.3)	0.9 (-1.2, 3.0)	1.5 (0.1, 2.9)	0.7 (-1.2, 2.7)	0.7 (-2.0, 3.4)
Fatigue	reference	0.7 (-0.6, 1.9)	1.1 (0.2, 2.0)	1.9 (0.3, 3.5)	0.6 (-0.3, 1.5)	0.2 (-1.8, 2.2)	-0.8 (-3.1, 1.5)	0.3 (-1.2, 1.9)	-0.5 (-2.6, 1.6)	-0.02 (-3.0, 2.9)
BASDAI	reference	-0.5 (-1.6, 0.7)	0.9 (0.1, 1.8)	1.8 (0.4, 3.3)	0.4 (-0.5, 1.2)	-0.2 (-2.0, 1.6)	-1.1 (-3.3, 1.0)	1.2 (-0.1, 2.5)	0.6 (-1.3, 2.6)	1.7 (-1.0, 4.5)
Spinal pain	reference	-0.6 (-1.9, 0.7)	1.2 (0.3, 2.2)	2.3 (0.6, 4.0)	0.4 (-0.6, 1.5)	0.3 (-1.8, 2.3)	0.4 (-2.1, 2.9)	0.8 (-0.8, 2.4)	-0.2 (-2.7, 2.2)	1.8 (-1.4, 5.0)
BASFI	reference	-0.6 (-1.9, 0.6)	1.9 (1.0, 2.9)	2.3 (0.8, 3.9)	0.7 (-0.3, 1.7)	1.7 (-0.3, 3.7)	-0.5 (-3.0, 2.1)	0.7 (-0.7, 2.2)	1.0 (-1.6, 3.5)	1.8 (-1.1, 4.8)
ESR*	reference	-0.34 (-0.84, 0.15)	-0.02 (-0.40, 0.35)	-0.26 (-0.91, 0.38)	-0.26 (-0.64, 0.11)	-0.02 (-0.78, 0.74)	-0.51 (-1.47, 0.45)	0.35 (-0.25, 0.95)	-0.42 (-1.30, 0.46)	-0.07 (-1.30, 1.16)
CRP*	reference	-0.80 (-1.38, -0.21)	-0.04 (-0.49, 0.41)	-0.05 (-0.82, 0.72)	-0.38 (-0.83, 0.07)	-0.53 (-1.49, 0.42)	-0.02 (-1.17, 1.13)	-0.13 (-0.85, 0.59)	-0.49 (-1.54, 0.55)	-0.21 (-1.68, 1.26)

Data shown as regression coefficients (95% confidence interval). For EuroQol, higher values indicate better health-related quality of life (e.g. cluster 4 had 0.25-unit poorer QoL). For all other measures, higher values indicate more severe disease (e.g. cluster 4 had 1.5-unit poorer global health).
Coefficients derived from models using each outcome measure as independent variable, and cluster as a dummy variable with isolated axSpA as the reference group. Models adjusted for age, gender, symptom duration, deprivation, current NSAID-use, and smoking status.
Global health and fatigue were measured by single-item questions with 0 as best/no fatigue and 10 as worst.
*ESR and CRP were log-transformed using Ln(ESR) and Ln(CRP+1).
EQ5D-3L, 5-domain 3-level version of the EuroQoL quality of life measure; BASDAI, Bath AS disease activity index; BASFI, Bath AS Functional index; IBS, irritable bowel syndrome; CHD, coronary heart disease.

Figure 4. 12: Disease indices compared between each comorbidity cluster and axial spondyloarthritis patients with no comorbidity, show graphically.



Data shown as regression coefficients (95% confidence interval). For EQ5D-3L, higher values indicate better quality of life. For all other measures, higher values indicate more severe disease.

FM, fibromyalgia; IBS, irritable bowel syndrome; HTN, hypertension; CHD, coronary heart disease; OP, osteoporosis; BASDAI, Bath AS disease activity index; BASFI, Bath AS functional index; QoL, quality of life measured using EQ5D-3L.

4.5 Discussion

This chapter used two cross-sectional axSpA populations to describe comorbidity prevalence and patterns. In both populations, over half of all patients had at least one comorbid condition. Overall pattern and burden of comorbidity were similar between patients with AS and nr-axSpA. Several comorbidity clusters were identified, each with only a small number of predominant conditions. Depression-anxiety and hypertension-coronary heart disease were the most common disease clusters in both axSpA cohorts. Patients in the depression-anxiety clusters and fibromyalgia-IBS clusters had more severe disease consistent across all patient-reported outcomes.

4.5.1 Prevalence of comorbidities

Differences in demography and socioeconomic context between Boston and Aintree cohorts offer interesting comparisons. Boston patients were, on average, older (mean age 53 vs. 46 years) and less likely to be current smokers (11 vs. 35%) compared to Aintree patients. BMI, extra-articular manifestations, and inflammatory makers between the two cohorts were virtually identical. Patients with comorbidities had higher inflammatory markers in both studies, but statistical significance was reached only in the Boston analysis; this could be due to selective testing (comorbid patients were more likely to be tested) or greater statistical power. Interestingly, the prevalence of IBD was higher in Boston patients with comorbidities than without, which was not observed in the Aintree data. This difference may be due to limitations of ICD codes used in the Boston data.

The mean (1.5 vs. 1.3) and range (0 up to 13 vs. 6) of comorbidity count differed between the Boston and Aintree studies. Direct comparison of comorbidity prevalence has limited meaning given differences in age and methods of data collection. Manual chart review supported by GP and medication records (Aintree) is more likely to capture comorbidities than diagnostic codes (Boston). Clinical practice may also explain some key discrepancies, for example, systematic recording of BMI (obesity in 17% of Aintree vs. 3.4% of Boston patients) and blood pressure (hypertension in 14% of Aintree vs. 6.1% of Boston patients). Boston patients had higher prevalence of anxiety (7.9 vs. 2.7%), coronary heart disease (7.7 vs. 4.2%), and cancer (7.2 vs. 0.7%) than Aintree patients. These differences are more challenging to explain without knowing the validity of ICD codes for these conditions, but may partly be explained by the older age of the Boston cohort.

The mean number of comorbidities (1.5) in the Boston axSpA study was similar to the 1.6 conditions reported among rheumatoid arthritis patients, using the same index and ICD codes in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) [198]. The BRASS cohort was older (mean age 58 years) than this axSpA group (mean age 53 years). Notably, axSpA subjects had a higher prevalence of anxiety (11% vs. 4% of BRASS); this adds to an increasing body of literature highlighting the importance of mental health in these patients [199].

The prevalence of individual morbidities in the Aintree cohort were consistent with those reported in the worldwide ASAS-COMOSPA cohort which had similar age and gender distributions, although ASAS-COMOSPA included patients with both axial and peripheral SpA [200]. The proportion with at least one comorbidity was higher in the Aintree cohort (61% vs. 51%), but this is likely due to the larger number of conditions included. The Aintree cohort had a greater proportion of current smokers (35% vs. 29% of ASAS-COMOSPA), which is compatible with the relative deprivation in this area of Liverpool (see Chapter 3, Section 3.2.1). This may also explain the higher prevalence of coronary heart disease (6% vs. 1%) in the Aintree cohort. Interestingly, the prevalence of hypertension in the Aintree data was lower (19% vs. 34% in ASAS-COMOSPA). The ASAS-COMOSPA study used single-measurement blood pressure thresholds in their definition of hypertension, which may lead to over-diagnosis [201]. Osteoporosis was also less common (6% vs. 13%), which may be under-documented since a previous study [202] found a higher (9%) prevalence of osteoporosis in a subgroup of this cohort (defined by T-score≤-2.5, as was in ASAS-COMOSPA).

Some comorbidities are likely under-represented in both cohorts. For example, fibromyalgia prevalence (0.1% in Boston and 3.4% in Aintree) were much lower than the prevalence reported using meta-analysis (13%) and found by screening questionnaire in the British Society for Rheumatology Biologics Register for AS (21%) [203,204].

4.5.2 Comorbidities in AS vs. nr-axSpA

There were no differences in the prevalence of HLA-B27 positivity between AS and nr-axSpA groups in the Boston study, while the difference was marked in the Aintree data (66% positive in AS and 30% positive in nr-axSpA). Similar discrepancies exist in existing literature and may be explained by different approaches to the diagnostic work-up. AS subgroups in both populations had higher inflammatory markers and greater proportion of males [205,206]. These results support the hypothesis that both diagnoses belong to the

same disease spectrum, and that males and those with higher inflammatory markers are more likely to progress to radiographic damage [207]. Although data on disease severity measures were limited in the Boston data, subjective measures of pain were similar between diagnoses. All patient-reported disease measures were similar between AS and nr-axSpA in the Aintree data. This is consistent with more detailed outcome measures from the Corrona SpA registry, where the two groups had similar disease activity, functional impairment, and health-related quality of life [205]. These results are supportive of guidelines that recommend a unified treatment approach for all axSpA patients [61].

The only statistically significant differences in prevalence of individual morbidities between AS and nr-axSpA patients were chronic kidney disease (in Boston cohort) and IBS (in Aintree cohort). Higher prevalence of chronic kidney disease in AS patients may be related to their older age and longer exposure to NSAIDs. Higher IBS (along with fibromyalgia and depression) prevalence in nr-axSpA may be due to higher psychosomatic burden due to more challenging (and therefore likely delayed) diagnosis, or from misdiagnosis of fibromyalgia as nr-axSpA. These differences should not be over-interpreted in the context of multiple comparisons.

Results from the Boston study confirms those from the Corrona SpA registry that bDMARDs are widely used for nr-axSpA in clinical practice [205]. This is consistent with the ACR/SAA/SPARTAN treatment recommendations for AS and axSpA [208], although bDMARDs were not licensed for this indication in the US when this study was conducted. Clinicians were likely relying on a clinical diagnosis rather than classification criteria for making treatment decisions. The proportions of patients prescribed bDMARDs and csDMARDs (55% and 25%, respectively) were similar to those reported in Corrona SpA registry (67% and 36%) [205]. A history of bDMARD-use was seen in 55% of Boston patients, csDMARDs in 25%, NSAIDs in 76%, and prednisone in 35% of patients.

4.5.3 Comorbidity clusters and associations with disease severity

In the main analysis using the Aintree cohort, each comorbidity cluster had only a small number of predominant conditions reflecting the low number of conditions among those with comorbidity. All comorbidities within each cluster had shared patho-aetiological mechanisms. Depression-anxiety and hypertension-coronary heart disease formed the most common disease clusters, which were externally validated in the Boston axSpA study. The higher comorbidity burden in the Boston cohort resulted in clusters dominated by a higher number of conditions; for example, the cardiometabolic cluster additionally included

atrial fibrillation, heart failure and obesity, compared to results from the Aintree cohort. Another notable difference was the clustering of mental health and other substance misuse disorders. The latter was shown to be associated with disease severity indices with clinically important (but statistically non-significant) effect sizes. It also highlights the intimate link between mental and physical health.

Differences in patient characteristics across the Aintree comorbidity clusters were consistent with the existing literature. Both fibromyalgia [209] and thyroid disorders [210] are generally more prevalent among females, which explains the high proportion of female patients in these clusters and also the higher prevalence of peripheral joint involvement and lower prevalence of radiographic disease and HLA-B27 positivity [211]. The prevalence of uveitis increases with age [16], which explains its higher prevalence in the older hypertension-CHD and alcohol problems-osteoporosis clusters.

In the Aintree cohort, patients in the depression-anxiety clusters and fibromyalgia-IBS clusters reported worse health-related quality of life, global health, fatigue, disease activity, pain, and functional impairment. Associations between these two clusters and patient-reported outcome measures were similar in magnitude to those reported in other studies [199,203,204,142]. However, none of the comorbidity clusters were significantly associated with ESR or CRP in the present study. In a previous meta-analysis, depression was additionally associated with objective measures such as ESR and BASMI [199]. Severe axSpA is likely to increase the risk of depression, and depression is known to impact the experience and reporting of pain [199,212]. Direction of causation could not be determined due to the cross-sectional design of this study. This is less relevant when the aim is to identify patient-clusters that may benefit from additional management. Baseline depression has been shown to reduce treatment response in longitudinal studies of RA [213], but whether this is true for axSpA patients is not yet known.

Although consistent associations across several outcomes are reassuring, care should be taken when interpreting isolated significant results (such as the association between global health and other substance misuse). Several clusters (e.g., asthma, thyroid and other rare diseases) had low prevalence, which partly contributed to the lack of precision in their effect estimate. For example, the cluster for other rare conditions was associated with clinically significant effect sizes in BASDAI, pain and BASFI, but these were not statistically significant. Larger studies using standardised recording of comorbidities and disease indices are needed to study them in greater detail.

4.5.4 Strengths and limitations

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

There were several limitations. For the Boston study, identifying cases from historical EHR data is challenging in the context of evolving terminology and classification criteria. There are no ICD-9 or -10 codes for axSpA, and using ICD code alone to classify AS has limited accuracy [168]. The high positive predictive value (80%) of the search strategy likely came at the cost of reduced sensitivity, in particular the ability to identify nr-axSpA cases. Requiring three or more ICD codes and radiological keywords may have selected individuals with more advanced disease, which may explain the older age of the cohort. Nevertheless, the proportion of AS cases (83%) was similar to that of the Corrona SpA registry (76%) [205].

In the US, patients can, and do, change their hospitals and care-providers such that diagnoses are often made at prior institutions and by different providers; therefore, data may not be consistently available for variables such as disease or symptom duration. Disease severity indices were not systematically collected. Treatment decisions in the US are made by the provider together with the patient; insurance companies do not require documentation of BASDAI to prescribe biologics. However, the available pain data was consistent with analyses of other disease indices in the Aintree axSpA and Corrona SpA registries [205].

Using ICD codes to derive comorbidities may have limited accuracy for certain diseases. However, any inaccuracies with ICD codes are likely to be the same for both AS and nr-axSpA groups and would not result in directional bias. Coded EHR medication data could not be used to determine current use of individual drugs. Furthermore, NSAIDs might be bought over the counter, and infliximab could be prescribed on infusion charts and not coded. It is also possible for patients to consult and receive treatment from

rheumatologists outside of Partners HealthCare, which would not be coded. The proportion of patients who had ever used prednisone was high. This could be explained by short courses prescribed for symptom flares or for other co-existing conditions.

The main methodological limitation for the cluster analysis was the lack of internal (e.g., cross-) validation of the cluster analysis. Clustering results were, however, supported by a range of sensitivity analyses, including the use of an independent, external dataset.

Results from these analyses may have limited generalisability to all axSpA cohorts, since both studies were conducted at tertiary centres. Lastly, some important disease indices were lacking in both studies, namely ASDAS and BASMI. This precluded comparison of whether associations with subjective and more objective measures of disease activity.

4.6 Summary

Comorbidities were common in both axSpA populations and similar between AS and nr-axSpA. These findings highlight the importance of identifying and managing comorbidities in these patients and support a unified management approach for the full spectrum of axSpA. Comorbidity co-existed in clusters, which consisted mostly of concurrent cardiovascular or mental-health disorders. Patients with comorbid depression-anxiety and fibromyalgia-IBS reported worse overall health-related quality of life, global health, fatigue and axSpA disease activity. These results highlight the importance of identification and optimisation of comorbidities, particularly mental health, and holistic patient-centred management of axSpA.

Chapter 5: Comorbidities and disease assessment in axSpA

This chapter examines whether assessment of axSpA disease activity and other measures of disease severity are influenced by the presence of comorbidities, using cross-sectional data from the BSRBR-AS registry.

5.1 Introduction

The previous chapter showed that axSpA patients with comorbidities reported more severe disease (including disease activity, functional impairment, fatigue, etc.) than those without. This may be explained, at least in part, by the subjectivity of patient-reported outcome measures. Prior studies have shown that patient perspectives of disease activity are more associated with function and fatigue, whereas physician assessments are more related to metrology and CRP [214]. Patients' experience of axSpA symptom severity may be influenced by coexisting conditions; for example, cardiorespiratory diseases can significantly reduce physical function [90,215], while concurrent depression and fibromyalgia influence fatigue [216]. Many treatment decisions depend on patient-reported disease activity despite these limitations; for example, eligibility to commence and continue biologics are defined using thresholds of BASDAI and spinal pain in the UK [190].

The AS disease activity score (ASDAS) was developed to address some of these concerns around disease activity assessment [217,218]. ASDAS combines three questions from BASDAI with CRP/ESR and the patient global score (see Chapter 1, Box 1.5, page 39), analogous to the disease activity score – 28 joints (DAS28) for rheumatoid arthritis (RA). Unlike BASDAI, it has been shown to associate with radiographic progression [219]. However, whether ASDAS is robust to the influence of comorbidities compared to patient-reported disease activity has not been examined. In RA, comorbidity count inflates DAS28 through the patient global score, independently of swollen/tender joints and inflammatory markers [220]. The patient global score is given more weight than all other patient-reported components in the ESR-based ASDAS formula and surpassed only by the 'back pain' component in the CRP-based formula. It is unknown whether the same vulnerability exists for ASDAS. Understanding whether and how comorbidities influence assessment of disease activity is crucial given their high prevalent [84,221]. This chapter addresses these unmet

research needs, namely how comorbidities influence the assessment of disease activity and other disease indices.

5.2 Aims

1. To compare whether measures of disease activity (BASDAI, spinal pain, ASDAS) and inflammation (CRP/ESR) are differentially influenced by comorbidities.
2. To replicate these comparisons for other important measures of disease severity (fatigue, function, and health-related quality of life).
3. To examine whether the patient global component of ASDAS is influenced by comorbidities independent of the other components.

5.3 Methods

The BSRBR-AS was used to address these aims as it includes a wealth of axSpA disease severity measures. Sufficient data was collected from which ASDAS could be derived, which was not possible in the Aintree and Boston cohorts. Cross-sectional baseline data were used from both biologic (i.e., pre-treatment data) and non-biologic groups.

5.3.1 Comorbidity

The count of 14 comorbidities was considered in three ways (as described in Chapter 3, Section 3.5.2) as: binary (no comorbidity vs. at least one), continuous, categorical (0, 1, 2, ≥3) and individual conditions.

5.3.2 Assessment of disease activity and severity

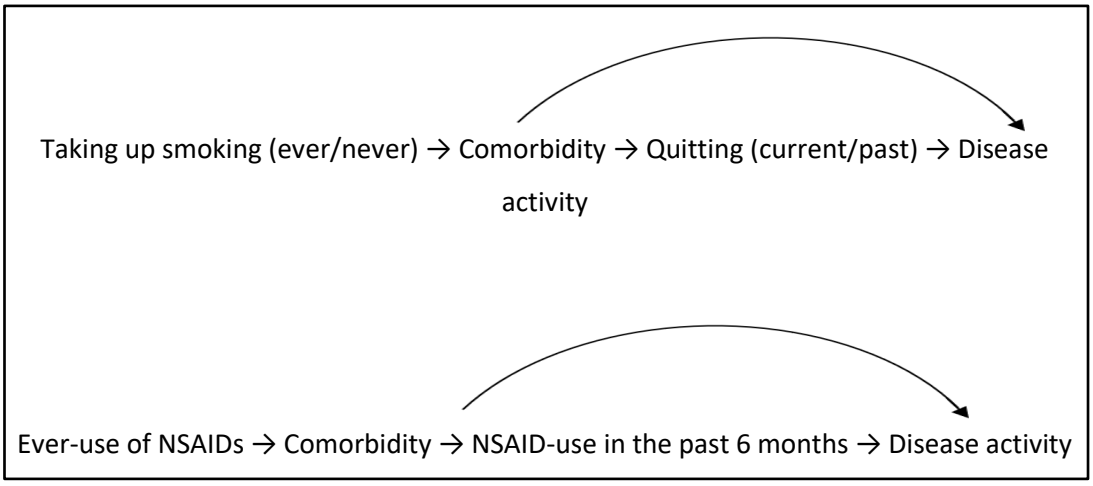
Disease severity is a multifaceted concept. For this thesis, 'severity' included disease activity and other indices such as functional impairment. Disease activity was assessed using BASDAI, ASDAS, spinal pain, CRP (mg/dl) and ESR (mm/hr) [180]. ASDAS was calculated using the following: ASDAS-CRP = 0.12 x Back Pain + 0.06 x Duration of Morning Stiffness + 0.07 x Peripheral Pain/Swelling + 0.11 x Patient Global + 0.58 x Ln(CRP+1), or ASDAS-ESR = 0.08 x Back Pain + 0.07 x Duration of Morning Stiffness + 0.09 x Peripheral Pain/Swelling + 0.11 x Patient Global + 0.29 x √ESR [218].

Functional impairment was assessed using BASFI and BASMI [180]. Fatigue was measured using the Chalder Fatigue Scale Likert scale (CFQ) and health-related quality of life using the AS quality of life questionnaire (ASQoL) [179,222].

5.3.3 Covariates

Covariates were determined *a priori* including age, gender (female as referent), BMI, smoking status (ever/never), socioeconomic status (as continuous variable) and educational attainment (as dummy variables). Socioeconomic status was approximated using post-code derived Index of Multiple Deprivation, with quintile 1 representing the top 20% most deprived areas and quintile 5 the least deprived [158,223]. Smoking was categorised as ever and never, since comorbidities will influence smoking cessation behaviour (see causal diagram in Figure 5.1). Similarly, use of NSAIDs in the past 6 months is an intermediate variable rather than confounder (Figure 5.1)

Figure 5. 1. Causal diagrams to justify covariate selection.



Smoking is directly causal for several comorbidities, thus ever-exposure to smoking will be associated with increased risk of developing certain comorbidities. However, those with comorbidities will be more likely to stop smoking. Adjusting for current/past smoking status (an intermediate variable) would attenuate effect of comorbidity on outcomes, while adjusting for ever-smoking would not.

Historical use of NSAIDs will likely impact development of comorbidities such as peptic ulcer disease. However, NSAID use was only captured for the preceding 6 months. It is likely that comorbidity onset pre-dated this. Adjusting for NSAID-use in the past 6 months (an intermediate variable) would attenuate effect of comorbidity on outcomes.

Age, gender, and BMI are associated with both comorbidity and axSpA disease severity. Deprivation and education are causal factors for lifestyle, which is a latent variable associated with both comorbidity and disease severity. These hypothesised confounding

relationships were tested in the data: education was strongly associated with comorbidity count and BASDAI; deprivation was strongly associated with BASDAI but not comorbidity count. Potential confounders strongly associated with the outcome should be included, even if only weakly associated with the 'exposure' [224]. These variables were therefore included as covariates.

5.3.4 Statistics

Descriptive statistics were used to summarise comorbidity prevalence and compare participants with and without comorbidities. CRP and ESR were transformed using ln(CRP+1) and ln(ESR) in regression models.

In addition to three variable-types for comorbidity count, the independent contribution of individual comorbidities to each disease activity and other disease severity measures was also examined, by adding all 14 comorbidities into linear models, and adjusting for the same covariates. Individual conditions may be closely related to others (e.g., hypertension and ischaemic heart disease shown in Chapter 4); variance inflation factor [191] was used to check for multicollinearity. Correction for multiple testing was not performed since dependent variables measure a shared underlying construct of disease severity; that is, tests were not independent [225].

To examine whether comorbidity count or individual comorbid conditions independently inflated the patient global score, the above analyses were repeated for patient global and comorbidity count or individual comorbidities, but additionally adjusting for other components of the ASDAS (three BASDAI questions and CRP). Throughout, model coefficients and 95% confidence intervals were displayed graphically with detailed results provided in the Appendix 10.4.

5.3.4.1 Power considerations

The primary analysis examined the association between the number of comorbidities against BASDAI using multivariable linear regression. Education was entered as a dummy variable (i.e., as 5 variables), giving a total of 11 variables. Using alpha of 0.05, a sample size of 2043 provides 80% power (i.e., beta of 0.2) if comorbidity count explains ≥0.4% of the total variance. These power estimates remain practically unchanged for secondary analyses that examine individual comorbidities (i.e., 14 additional variables, total 25 variables). Statistical power was reduced for analyses of other disease severity outcomes where the proportion missing was greater.

7.3.4.2 Sensitivity analyses

Some comorbidities, including heart failure, cancer, TB and demyelinating diseases, are routinely sought for during the workup for TNF inhibitor therapy. These comorbidities may therefore be more prevalent in the biologic cohort due to differential ascertainment alone. Equally, presence of certain comorbidities may channel patients into (e.g., renal/peptic ulcer disease and inability to use NSAIDs) or away from (e.g., cancer) the biologic group. All analyses were repeated in the non-biologic cohort only.

For analyses of comorbidity and the patient global score, successful adjustment for other components of ASDAS required adequate covariate overlap between comparison groups; extrapolating beyond overlap can introduce bias. Patients were therefore matched on all covariates (gender, ever-smoking, education, deprivation index, quintiles of age and BMI, and tertiles of the three ASDAS questions and ln(CRP+1)) in sensitivity analyses, using coarsened exact matching [226].

5.4 Results

Among a total of 2687 participants, 2043 (76%) were included for analysis; exclusions were due to missing questionnaires (n=364, 14%), missing comorbidity data (n=6, 0.2%) and questionnaires completed outside the eligible window (n=274, 10%). Included and excluded participants were generally similar (Appendix 10.4: Table S5.1), except the latter were younger (mean 44 (SD 13) vs. 49 (SD 15) years, p<0.001) and had younger age of symptom onset (mean 28 (SD 13) vs. 29 (SD 14) years, p=0.015) and clinically non-significantly lower ESR (median 9 vs. 13 mm/hr, p=0.035) and BASMI (median 3.2 vs. 3.8, p=0.022).

The population included in the analyses were predominantly male (67%) with mean age of 49 (SD 15) years (Table 5.1). Classification criteria for AS was fulfilled by 1316 (65%). HLA-B27 status was available for 74% of participants and was positive in 79% of these cases. Thirty one percent were in the biologic group but had not yet commenced treatment.

Those with comorbidities were significantly older (54 (SD 15) vs. 45 (SD 14) years), had higher BMI (29 (SD 6) vs. 27 (SD 5) kg/m^2) and lower educational attainment. Although there were more ever-smokers in the group with comorbidities (63 vs. 50%), a larger proportion had quit (43 vs. 32%). NSAID use in the preceding 6 months was less common among those with comorbidities. Participants with comorbidity also had higher disease activity, more fatigue, function impairment and lower health-related quality of life.

Table 5. 1: Baseline characteristics of 2043 participants from the BSRBR-AS registry.

		All participants (n=2043)	axSpA without comorbidities (n=1127)	axSpA with ≥1 comorbidity (n=886)	P-value
Age, years		49.1 (14.7)	45.3 (13.5)	53.9 (14.8)	<0.001
Males		1382 (68%)	742 (66%)	615 (69%)	0.078
Meeting modified New York criteria		1340 (66%)	703 (62%)	613 (69%)	0.001
Age at symptom onset, years		29.1 (11.8)	28.4 (11.3)	30.1 (12.3)	0.001
Symptom duration, years		20.0 (14.6)	16.9 (13.4)	23.8 (15.3)	<0.001
HLA-B27 positive*		1193 (79%)	702 (80%)	471 (76%)	0.11
BMI, kg/m^2		27.7 (5.5)	26.7 (4.9)	28.9 (6.0)	<0.001
Smoking status	Never smoked	900 (44%)	563 (50%)	323 (37%)	<0.001
	Ex-smoker	743 (36%)	355 (32%)	379 (43%)	
	Current smoker	394 (19%)	207 (18%)	181 (20%)	
Education	Secondary school	648 (32%)	335 (30%)	308 (35%)	<0.001**
	Apprenticeship	191 (9%)	92 (8%)	97 (11%)	
	Further education college	620 (30%)	318 (28%)	289 (33%)	
	University degree	417 (21%)	275 (25%)	134 (15%)	
	Further degree	157 (8%)	102 (9%)	53 (6%)	
Deprivation index, median (IQR)		3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	0.26
NSAID use in past 6 months		1486 (73%)	865 (77%)	596 (68%)	<0.001
DMARD use in past 6 months		201 (13%)	103 (12%)	96 (15%)	0.13
BASDAI, median (IQR)		4.9 (2.6, 6.8)	4.4 (2.3, 6.6)	5.5 (3.3, 7.3)	<0.001
Spinal pain, median (IQR)		5.0 (2.0, 7.0)	3.0 (1.0, 7.0)	5.0 (2.0, 8.0)	<0.001
ASDAS*		2.3 (1.1)	2.2 (1.1)	2.4 (1.1)	<0.001
CRP (mg/dL), median (IQR)*		0.6 (0.2, 1.9)	0.6 (0.2, 1.8)	0.6 (0.2, 2.0)	0.50
ESR (mm/hr), median (IQR)*		11.0 (5.0, 23.0)	10.5 (5.0, 23.0)	11.5 (5.0, 24.0)	0.28
Fatigue, median (IQR)		14.0 (11.0, 19.0)	14.0 (11.0, 18.0)	15.0 (11.0, 20.0)	<0.001
ASQoL, median (IQR)		8.0 (3.0, 13.0)	7.0 (3.0, 12.0)	10.0 (5.0, 15.0)	<0.001
BASFI, median (IQR)		4.4 (2.0, 7.0)	3.6 (1.5, 6.1)	5.7 (2.9, 7.9)	<0.001
BASMI, median (IQR)*		3.8 (2.2, 5.4)	3.2 (2.0, 4.8)	4.4 (2.8, 6.0)	<0.001

Data shown as mean (SD) and n (%) unless otherwise indicated.
*Not all variables had complete data; HLA-B27 was available for 74% of participants, BASMI 75%, ASDAS 78%, CRP 78%, ESR 39%.
**non-parametric test for trend.
ASDAS, AS disease activity score; ASQoL, AS quality of life; BASDAI, Bath AS disease activity index; BASFI, Bath AS functional index; BASMI, Metrology Index; questionnaire; BMI, body mass index; Deprivation index, 1=most deprived, 5=least deprived; IQR, interquartile range.

The distribution of comorbidity count is shown in Figure 5.2; 44% of participants had at least one of the 14 comorbidities. The median number of comorbidities was 0 (IQR 0 to 1) and the mean was 0.7 (SD 0.9). The prevalence of each comorbidity is shown in Figure 5.3. The most common comorbidities were hypertension (28%), depression (23%), and asthma (15%). Only four of the 14 conditions had a prevalence of ≥5%, while five diseases had a prevalence of 1% or lower.

Figure 5. 2: Histogram showing comorbidity count among 2043 participants of the BSRBR-AS.

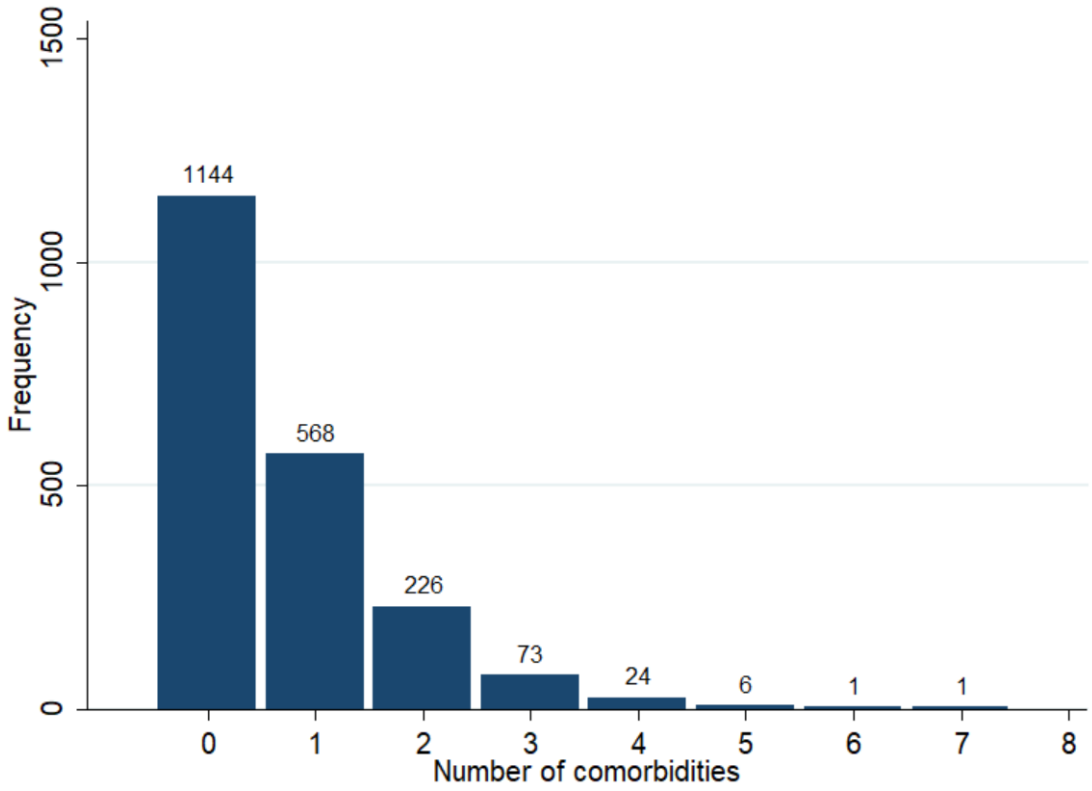
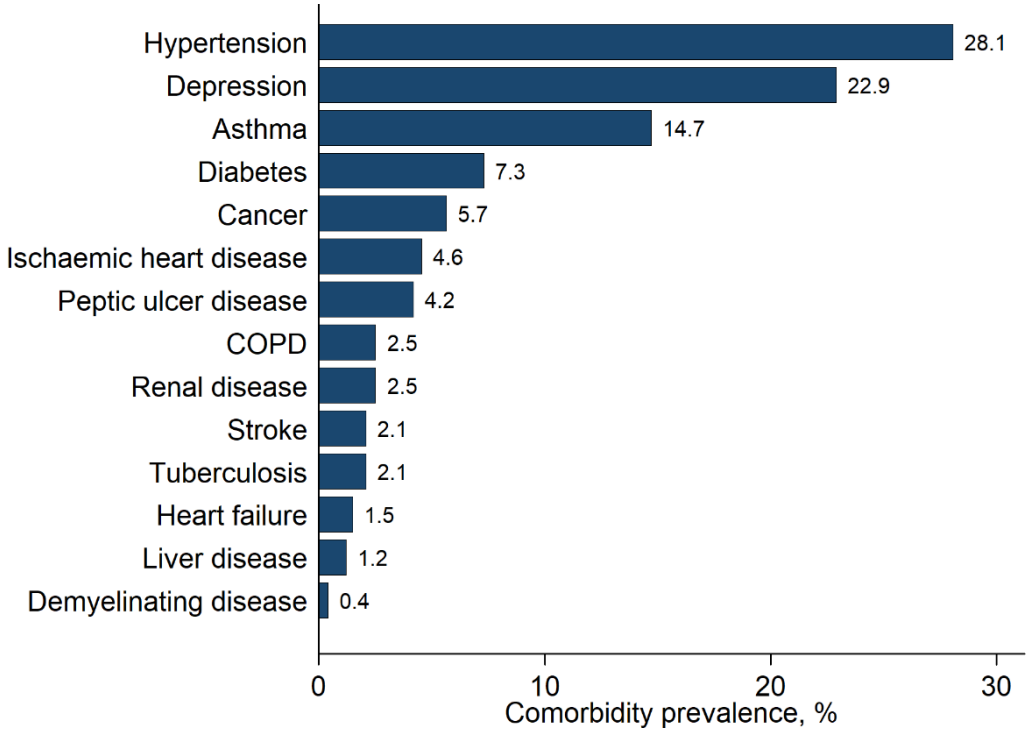


Figure 5. 3: Prevalence of comorbidities among 2043 participants of the BSRBR-AS.

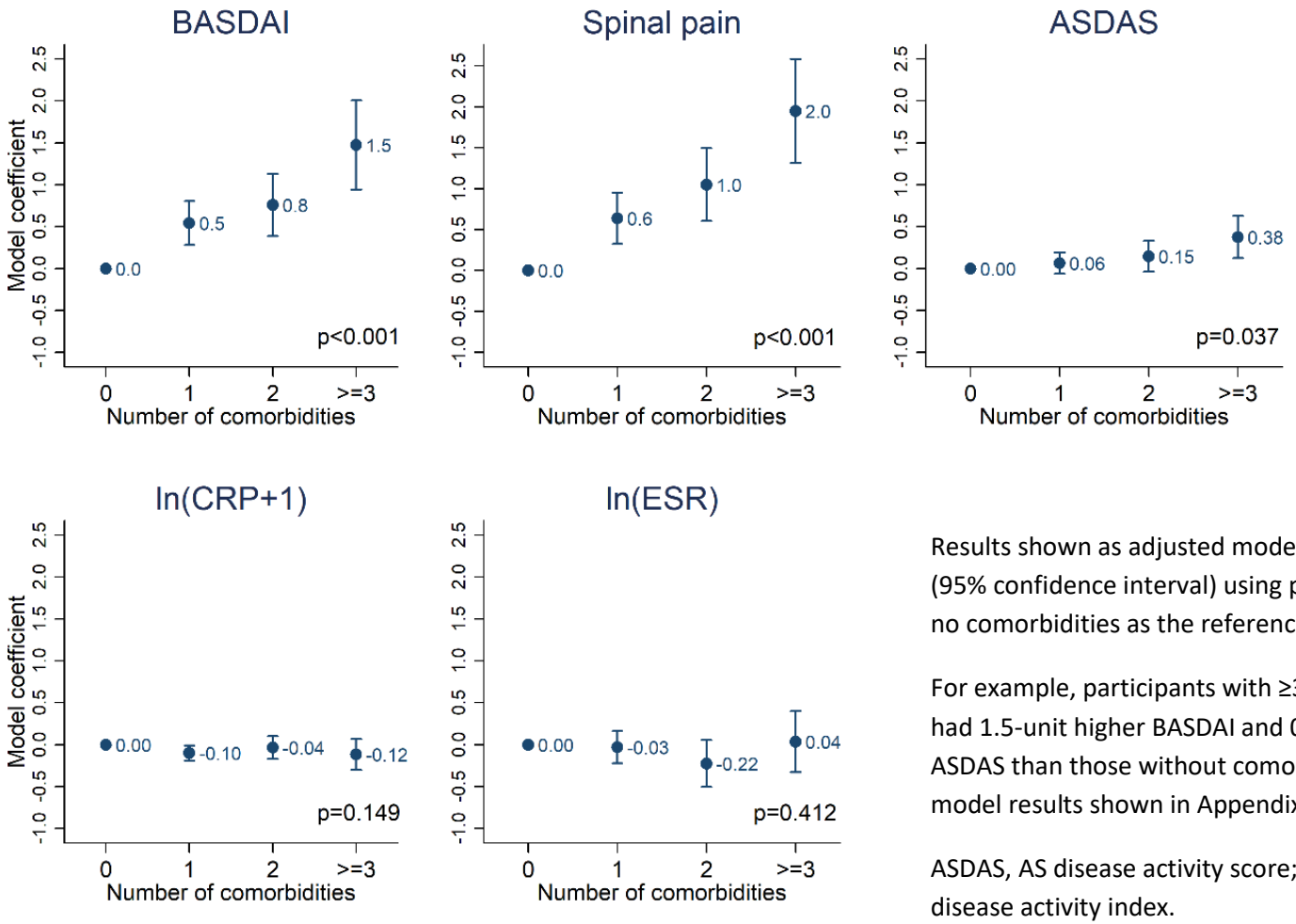


5.4.1 Comorbidities and disease activity

With comorbidity count as a continuous variable, each additional comorbidity was associated with higher BASDAI by 0.40 units (95% CI 0.27 to 0.52) and spinal pain by 0.53 (95% CI 0.37 to 0.68). Figure 5.4 shows these relationships with comorbidity count as a categorical variable (with full model coefficients shown in Appendix 10.4: Table S5.2)**.** For each additional comorbidity, ASDAS was higher by 0.09 units (95% CI 0.03 to 0.15). Those with 1 or 2 comorbidities did not have higher ASDAS than those with no comorbidities in terms of statistical or clinical significance. Comorbidity count was not associated with log-transformed CRP (β=-0.03 (back-transformed effect size -0.03mg/dL); 95% CI -0.07 to 0.02) or log-transformed ESR (β=-0.03 (i.e., 0.97mm/hr); 95% CI -0.12 to 0.06).

Independent associations between each comorbid condition and disease activity are shown in Figure 5.5. Participants with depression, heart failure and peptic ulcer diseases had consistently higher disease activity than those without each of these conditions. For example, participants with depression had 0.9-unit higher BASDAI and spinal pain than those without, after accounting for covariates and all other comorbidities. Effect sizes were smaller for ASDAS. The only comorbidities associated with CRP and ESR were COPD and asthma, respectively; the back-transformed effect sizes for CRP (0.5mg/dL) and ESR (0.7mm/hr) were not clinically meaningful.

Figure 5. 4: Association between comorbidity count and disease activity.

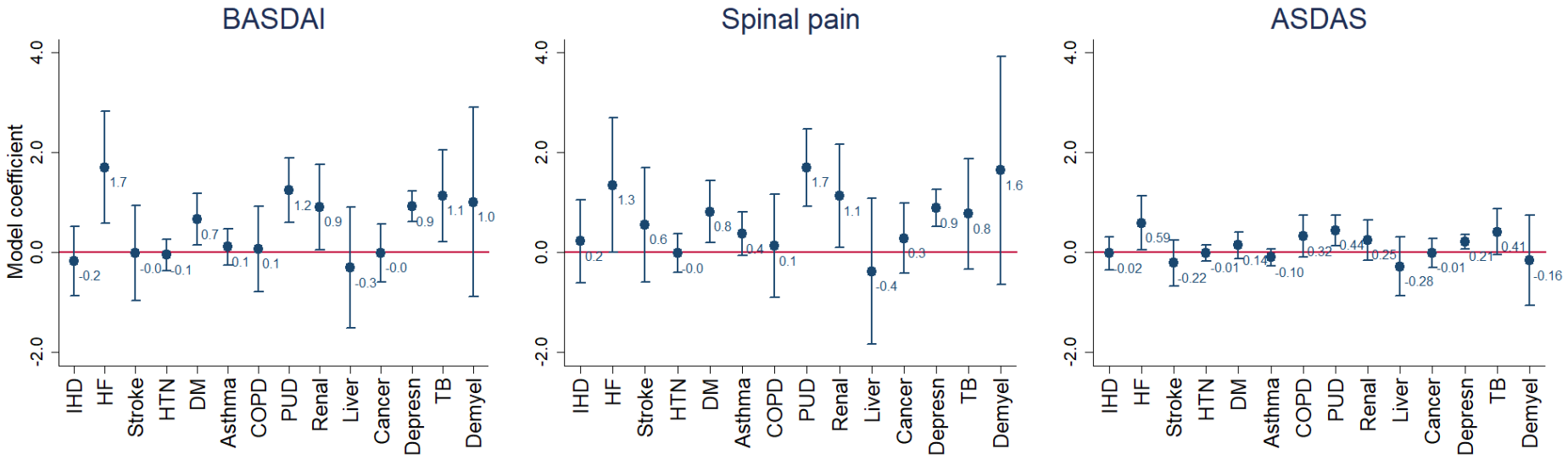


Results shown as adjusted model coefficients (95% confidence interval) using participants with no comorbidities as the reference group.

For example, participants with ≥3 comorbidities had 1.5-unit higher BASDAI and 0.38-unit higher ASDAS than those without comorbidities. Full model results shown in Appendix Table S7.2.

ASDAS, AS disease activity score; BASDAI, Bath AS disease activity index.

Figure 5. 5: Association between each comorbid condition and disease activity.



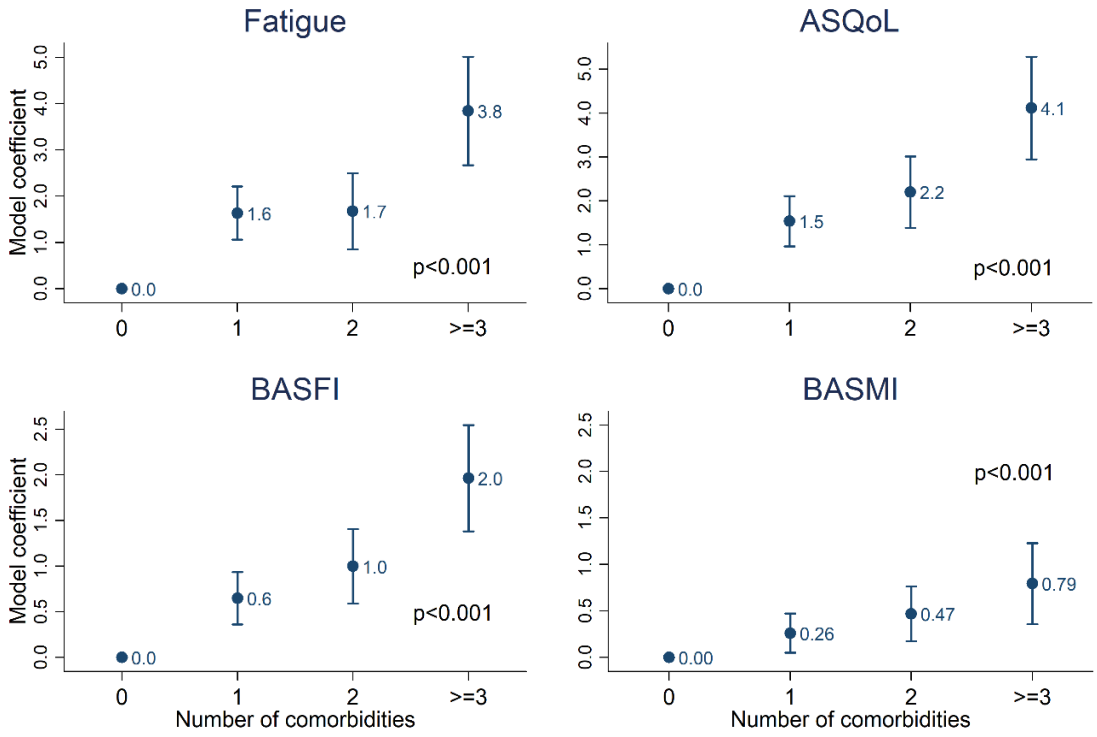
Results shown as adjusted model coefficients (95% confidence interval) compared to participants without each condition. For example, participants with heart failure (HF) had 1.7-unit higher BASDAI and 0.59-unit higher ASDAS than those without HF. Full model results shown in Appendix 10.4: Table S5.3. ASDAS, AS disease activity score; BASDAI, Bath AS disease activity index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; IHD, ischaemic heart disease; PUD, peptic ulcer disease.

5.4.2 Comorbidities and other measures of disease severity

Comorbidity count (as a continuous variable) was associated with significantly worse fatigue (β=1.05; 95% CI 0.76 to 1.33), health-related quality of life (β=1.18; 95% CI 0.90 to 1.46) and functional impairment (β=0.55; 95% CI 0.41 to 0.69). The effect size was smaller for BASMI (β=0.22; 95% CI 0.12 to 0.33) than BASFI. Figure 5.6 shows these relationships with comorbidity count as a categorical variable.

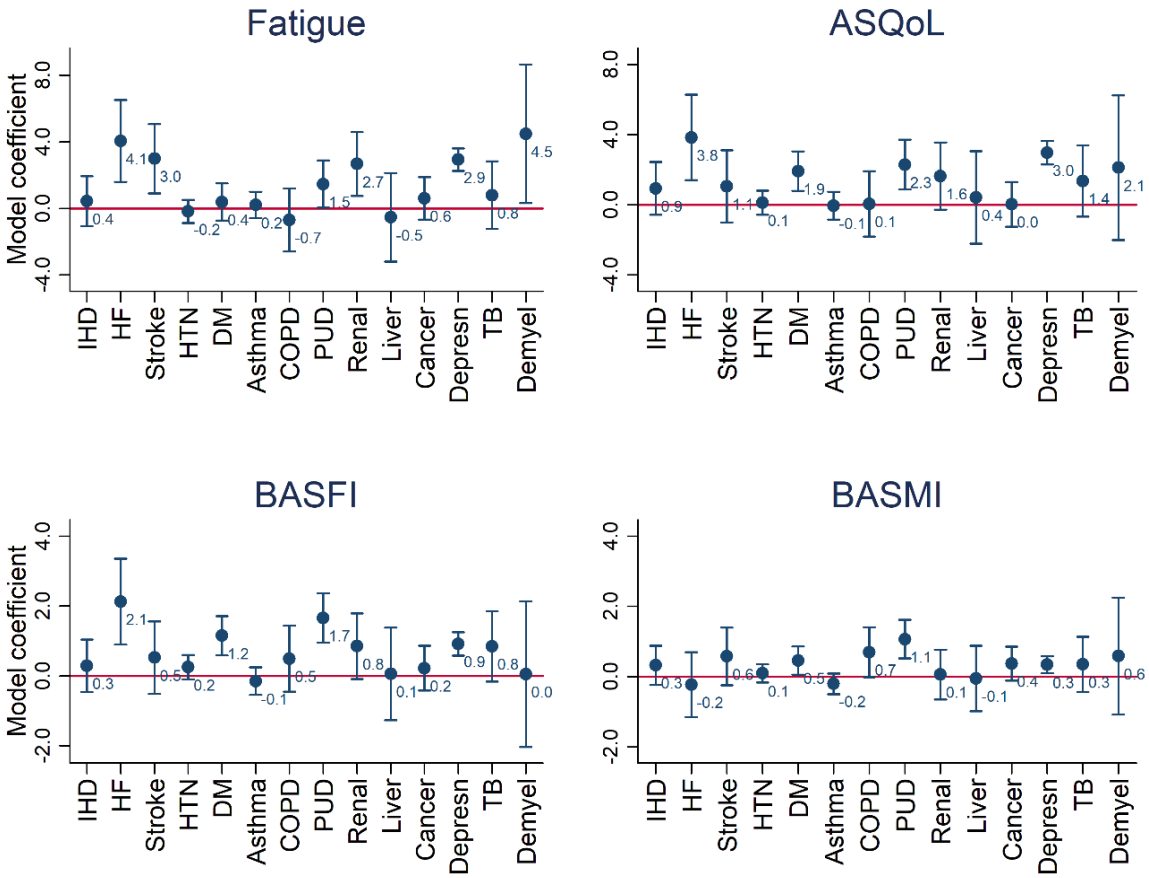
Independent associations between each comorbid condition and the four disease severity measures are shown in Figure 5.7. Participants with heart failure, depression and peptic ulcer disease had consistently worse fatigue, quality of life and functional impairment than those without, accounting for covariates and all other comorbidities. Diabetics had poorer function and quality of life, while participants with stroke had greater fatigue.

Figure 5. 6: Association between comorbidity count and other measures of disease severity



Results shown as adjusted model coefficients (95% confidence interval) using participants with no comorbidities as the reference group. For example, participants with ≥3 comorbidities had 2.0-unit higher BASDAI and 0.79-unit higher BASMI than those without. Full model results shown in Appendix 10.4: Table S5.4. ASQoL, AS quality of life questionnaire; BASFI, Bath AS functional index; BASMI, Bath AS metrology index.

Figure 5. 7: Association between each comorbid condition and other measures of disease severity.

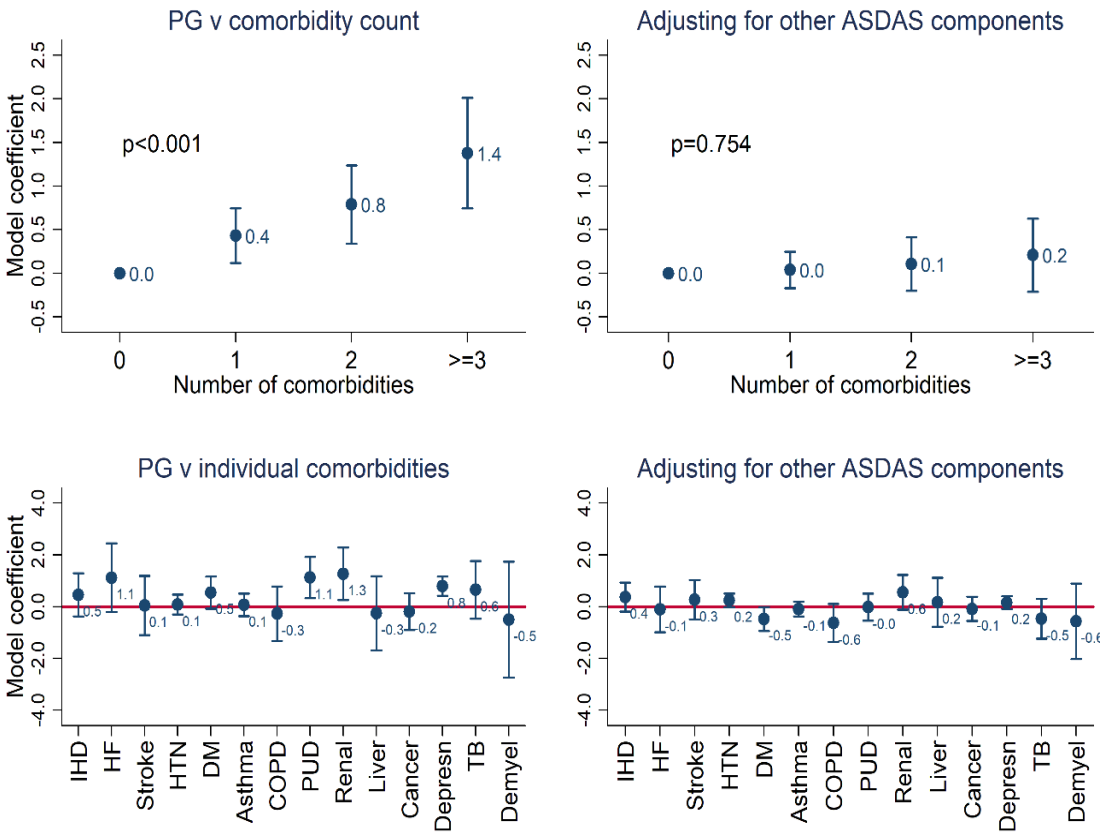


Results shown as adjusted model coefficients (95% confidence interval) compared to participants without each condition. Full model results shown in Appendix 10.4: Table S5.5. ASQoL, AS quality of life questionnaire; BASFI, Bath AS functional index; BASMI, Bath AS metrology index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; IHD, ischaemic heart disease; PUD, peptic ulcer disease.

5.4.3 Independent influence of comorbidity on the patient global score

Patient global score increased (suggesting an increase in disease severity) with the number of comorbidities, but not independently of other ASDAS components (Figure 5.8). Depression, peptic ulcer, and renal diseases were significantly associated with patient global score, but not when additionally adjusting for other ASDAS components.

Figure 5. 8: Association between comorbidities and the patient global score.



Top panels show comorbidity count vs. PG without (top left) and with adjustment for other components of ASDAS (top right). Bottom panels show associations between PG and individual comorbid conditions. Results shown as model coefficients (95% confidence interval). ASDAS, AS disease activity score; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; IHD, ischaemic heart disease; PG, patient global score; PUD, peptic ulcer disease.

5.4.4 Sensitivity analysis

There were some differences when biologic and non-biologic cohorts were compared (Appendix 10.4: Table S5.6). Participants in the biologic arm of the BSRBR-AS registry were younger, less frequently HLA-B27 positive or met the classification criteria for AS, more often current smokers, and resided in more deprived areas. They also had significantly more severe disease across all indices. Participants in the biologic cohort had an overall similar comorbidity burden (mean number 0.7 (SD 0.9) vs. 0.7 (SD 0.9)) to those in the non-biologic cohort. However, they less frequently had stroke (1 vs. 2%, p=0.04), hypertension (15 vs. 21%, p=0.003), cancer (2 vs. 5%, p<0.001), and more often had peptic ulcer (4 vs. 2% p=0.006) and depression (21 vs. 13% p<0.001). Despite these differences, results from the sensitivity analysis restricted to the non-biologic cohort did not meaningfully change effect estimates, although precision was reduced (i.e., confidence intervals widened) with smaller sample sizes (Appendix 10.4: Figure S5.1 and S5.2). Results using coarsened exact matching to adjust for other components of ASDAS were not meaningfully different (data not shown).

5.5 Discussion

This chapter used cross-sectional, pre-treatment data from the BSRBR-AS to examine associations between comorbidity and measures of disease severity. Unlike BASDAI and spinal pain (subjective measures of disease activity), ASDAS was not associated with comorbidity count or individual comorbidities at a clinically meaningful effect size. Although the patient global component of ASDAS was influenced by coexisting morbidities, they did not inflate ASDAS through the patient global score independently of other ASDAS components. Other patient-reported measures of disease severity (function, fatigue, and health-related quality of life) were significantly associated with comorbidity count and individual comorbidities. When making treatment decisions, clinicians should be mindful of the potential impact of comorbidities on patient reported measures of disease activity, and consider additionally assessing disease activity using ASDAS when comorbidities are present.

These results complement those from the ASAS-COMOSPA study, where comorbidity burden (assessed using RDCI) was associated with poorer BASFI, health-related quality of life (EuroQol) and work-related outcomes, despite using a slightly different list of comorbid conditions [90]. The current analyses additionally demonstrated that BASMI – a physician derived outcome often considered objective – is also significantly associated with comorbidity count, albeit with smaller effect sizes than BASFI. Importantly, ASDAS was found to be comparatively robust to the impact of coexisting morbidities. Unlike BASDAI and spinal pain, the relationship between comorbidity count and ASDAS was not completely linear, which may be explained by the weighting of ASDAS components. ASDAS was not significantly different between participants without comorbidities and those with one or two. There was a statistically significant difference in ASDAS between those with ≥3 and no comorbidities, but the mean difference of 0.38 is not clinically significant (meaningful change = 1.1). Using an unweighted comorbidity count was preferable, since RCDI was weighted for inpatient outcomes (mortality, hospitalization, disability, and costs) that may not be appropriate to study axSpA-specific measures. It also allowed examination of the relationship between comorbidity and outcomes in more detail: depression, diabetes, heart failure, peptic ulcer, and renal diseases (and to a smaller and less consistent extent stroke) were the most significant contributing conditions. Most of these conditions are relative (or potentially absolute depending on severity) contra-indications for NSAIDs – the first and only line of pharmacological therapy before bDMARDs. Patients with high cardiovascular risk, renal or peptic ulcer diseases, who cannot use NSAIDs, are more likely

to experience more severe symptoms of axSpA and their impact on other aspects such as fatigue. This channelling away from NSAIDs and towards bDMARDs was supported by the higher prevalence of peptic ulcer disease in the biologic than non-biologic cohort of the BSRBR-AS (Appendix 10.4: Table S5.6). Equally, cardiovascular, renal, and peptic ulcer disease may also result from long-term exposure to NSAIDs due to severe symptoms. These are limitations arising from the cross-sectional design and lack of historical NSAID data. The data does, however, suggest that more objective measures such as ASDAS and BASMI are influenced by comorbidities to a lesser extent than patient-reported indices.

In RA, patient global score increased with the number of comorbidities, independently of tender/swollen joint count, CRP and physician global [220]. Among axSpA participants in these analyses, patient global score was significantly associated with comorbidity count. This is potentially concerning since it is given more weight than almost all patient-reported components of the ASDAS. Reassuringly, the patient global score did not appear to inflate ASDAS independent of its other components. These observations support the use of ASDAS particularly when comorbidities are present and likely to influence other patient-reported outcome measures. Further longitudinal studies are needed to assess whether comorbidities influence treatment response as measured by different outcomes (e.g., BASDAI vs. ASDAS). Longitudinal studies on comorbidities as 'exposure' (rather than outcome) in axSpA are scarce. Preliminary results from the BSRBR-AS suggests that comorbidity may be one of very few potentially modifiable predictors of treatment response [134].

5.5.1 Strengths and limitations

A key strength of this study is its large sample size representative of a national axSpA population, for whom a wide range of disease measures were collected. Ascertainment of comorbidities was robust, using physician diagnoses from medical records. There were also some limitations. Cross-sectional data do not inform causal direction; however, it is more plausible that comorbidity burden influences experience and reporting of disease activity, rather than vice versa. First, baseline disease activity is less likely to influence past medical history (albeit baseline may reflect disease activity history). Second, the difference between subjective and more objective indices suggest subjectivity is relevant. Comorbidities were selected through a consensus meeting of clinicians and researchers to support the primary drug safety aims; therefore some (e.g., neurological) comorbidities were not compared. However, included comorbidities were broadly representative of important diseases when

compared to prior axSpA research [84]. Low prevalence of some conditions (e.g., heart failure, liver, and demyelinating diseases) meant that their effect estimates had significant uncertainty. Severity (e.g., for heart failure) and more granular descriptions (e.g., cancer type) for comorbidities were not available but would have provided useful information. Some comorbidities (TB, heart failure, cancer, and demyelinating diseases) are of special interest when considering TNF inhibition therapy; they may be recorded more systematically in patients. However, restricting analyses to the non-biologic cohort did not meaningful change results. Lastly, the wording of the patient global question can be highly variable [227]. For example, the patient global question in DAS28 can be worded to assess arthritis-related disease activity or global health (the recommended phrasing in RA is 'Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?'). The patient global question in the BSRBR-AS was specific to spondyloarthritis activity in the past week; therefore, other versions may not be equally robust in the presence of comorbidities.

5.6 Summary

Patient-reported axSpA measures are influenced by comorbidities. This is important for routine practice as around half of all patients have at least one comorbidity. ASDAS seems to be less influenced by the presence of comorbidities. ASDAS was not disproportionately inflated by the effect of comorbidities on the patient global score, as was shown for DAS28 in rheumatoid arthritis. In routine clinical practice, clinicians should consider additionally collecting ASDAS to assess disease activity in patients with multiple comorbidities, including but not limited to depression. Additional studies are needed to examine the impact of comorbidity burden on longitudinal disease severity and response to treatment. This will be addressed in the next Chapter.

Chapter 6: Comorbidities and response to TNF inhibitors

This chapter uses longitudinal data from the BSRBR-AS to examine whether the presence of comorbidities at baseline is associated with response to TNF inhibition treatment. Analyses will approach response using common binary definitions, change in continuous outcome indices over time, and time to treatment discontinuation.

6.1 Introduction

Previous chapters showed that comorbidities are common and are associated with greater axSpA severity. Comorbidities may also impact management (e.g., eligibility for treatment escalation) through the way in which axSpA disease activity is assessed. Despite this, research into the impact of comorbidities on treatment response are scarce. This is an important unmet need for two reasons: First, up to half of patients do not respond to their first TNF inhibitor (TNFi) [228], thus identifying potentially modifiable factors are important for clinical practice. Second, if some axSpA disease indices are inflated in the presence of comorbidities, comorbid patients may have persistently high scores – thereby at risk of having treatment discontinued – despite successfully supressing axSpA inflammation.

Of the three existing studies [114,118,134], most rely on binary response definitions, such as a certain degree of improvement (e.g., 50% improvement in BASDAI) or disease state (e.g., ASDAS low disease activity, <2.1). These outcomes are problematic in observational data where starting disease activity differ between groups under comparison: those with higher baseline disease activity are simultaneously more able to achieve the former (because there is more 'room' for improvement) and less able to achieve the latter (because greater absolute improvement is required), compared to those with lower disease activity. Consider a participant with ASDAS of 3.6 at baseline and another with ASDAS 2.2; an identical reduction by 1 unit in both would achieve 'inactive disease' status for the latter while the former would still have 'high disease activity'. This is true regardless of the 'exposure' of interest; smokers, those from more deprived areas or with lower education attainment, or any group with high disease activity at baseline, would all be less likely to achieve binary response. Thus, absolute improvement in disease activity is likely to differ from the binary response derived from the same index. (These limitations have been examined in detail in publications related to the thesis project [41,42].) Adjustment for the

baseline disease activity is necessary, but controversial [41], since it is unlikely a confounder (i.e., baseline disease activity will not *cause* comorbidities) and more likely a mediator (i.e., comorbidities influence baseline disease activity as a causal intermediate to response, as shown in the previous chapter).

Untangling the role of comorbidities on the treatment response is important for clinical practice, which requires more than one approach to defining response. This chapter addresses this unmet research need using binary response definitions, change in continuous outcome indices over time, and time to treatment discontinuation.

6.2 Aims

1. To examine the association between baseline comorbidity status and binary response definitions among those using TNFi.
2. To examine the association between baseline comorbidity status absolute change in disease activity (BASDAI, spinal pain, ASDAS) and other measures of disease severity.
3. To examine the association between baseline comorbidity status and TNFi discontinuation.

6.3 Methods

6.3.1 Patient population

Participants in the BSRBR-AS who started on their first TNFi (including those who switched from the non-biologic group) were eligible for inclusion in this analysis. Eligible individuals were required to have a clinic visit or questionnaire within 1 year before, or 7 days after, the TNFi start date, from which the baseline value of time-varying data (i.e., measures of disease activity and severity) was obtained. Time-invariant data could come from any assessment time if missing at baseline; all variables except disease activity indices were considered time-invariant in this analysis.

6.3.2 Comorbidity

The count of 14 comorbidities was analysed as three variable types: binary (comorbidity vs. none), continuous, and categorical (0, 1, ≥2; or 0, 1, 2 ≥3 where possible) (see Chapter 3, Section 3.5.2). Many existing studies select one approach often without justification; performing analyses using all three can reveal comparative merits or deficiencies of each. This subpopulation of TNFi initiators in the BSRBR-AS was not sufficient in size to explore individual comorbidities as was performed in the previous chapter.

6.3.3 Outcomes

6.3.3.1 Binary response definitions

The first aim used the following common binary response definitions at 6 months: BASDAI 50/2 (50% or 2-unit reduction), ASDAS major improvement (ASDAS-MI, ≥2-unit reduction), low disease activity defined as BASDAI<4 or ASDAS<2.1 (see Chapter 3, Section 3.5.2). Participants with missing baseline BASDAI or ASDAS were excluded. Where the 6-month assessment was missing but participants remained on the drug, they were considered as having responded if they demonstrated response at 3 or 12 months. Both assumptions are justifiable since participants were unlikely to remain on the drug if they lost or did not have a response, as per prescribing guidelines in the UK [190]. Participants who discontinued treatment within 6 months for any reason were considered as non-responders.

Using the above definitions for the binary response, individuals who stayed on treatment (i.e., no stop date) but did not have assessments recorded at 3, 6 or 12 months would have missing response values. In sensitivity analyses, these individuals were assumed to have responded at 6 months if they remained on treatment beyond 12 months. This was not included in the main analysis because patients without a documented stop date could be on treatment or lost to follow-up.

The first two response definitions are derivatives (in part for BASDAI 50/2) of absolute reductions. They should be less effected by baseline disease activity except through a 'floor effect' of the index (e.g., someone starting with BASDAI of 2 cannot possibly decrease by more than 2). The low disease activity definitions would be affected by issues relating to differing baseline values, as discussed above.

6.3.3.2 Change in continuous outcome indices over time

The second aim examines the absolute change in disease activity (BASDAI, spinal pain, ASDAS); that is, change from baseline over follow-up time. Assessing continuous change in repeated assessments made over time is more efficient and informative than imposing one time point.

These analyses were repeated for other disease outcomes including functional impairment, health-related quality of life, fatigue, and sleep (see Chapter 3 for descriptions of these indices). Response was assessed only in the first 3 years (up to 36 months + 6 months' window = 42 months) because the number at each sequential follow-up dropped dramatically (see Results below).

For continuous change in disease indices, mixed effects models are able to handle data Missing At Random (i.e., systematic relationship between the propensity for missingness and the observed data, but not the missing data [192]). No imputation for baseline or longitudinal values were required.

6.3.3.3 Time to treatment discontinuation

The final aim examines time to any-cause discontinuation. Treatment duration was analysed as continuous time from start to discontinuation of treatment was derived from respective dates. Censoring was defined by the last visit for those who did not discontinue treatment.

A small number of participants were commenced on TNFi but did not have any subsequent assessments by visit or questionnaire, thus their time on-drug were unknown. These individuals with zero follow-up time would, by definition, be excluded from all time-to-event analyses. They can contribute (their baseline characteristics) to the analysis by having an arbitrarily small time assigned. In the primary analysis, each were assigned 0.001 days' follow-up (approximately 1.5 minutes) which does not affect the overall person-time.

Cause-specific discontinuation was not assessed as part of the primary aims because previous work using the BSRBR-AS showed limitations in this data [189]. There is often overlap between how inefficacy and adverse events are defined and reported. For example, therapy is more likely to continue in the face of mild adverse events if they are highly effective for symptom control; inflammation in previously unaffected peripheral joints may be reported as an adverse event, when it would more appropriately reflect lack of disease

control and efficacy. Before 2016 – that is, most of the study period (2012-2017) – NICE stipulated that patients who did not demonstrate initial or maintained response to treatment would not be funded to use a second TNFi [17, 18]. However, switching to a second TNFi was allowed if discontinuation was due to the development of a treatment-related adverse event. This may have influenced labelling of discontinuation as adverse events or other reasons. These errors would not affect the analysis of all-cause discontinuation.

6.3.4 Covariates

The following covariates were determined *a priori*: age, gender (female as reference), BMI, Index of Multiple Deprivation (IMD, as a continuous variable) and educational attainment (as dummy variables). Smoking was not included since analyses performed in parallel to this thesis did not demonstrate a convincing causal role with treatment-related outcomes [42,189].

Baseline disease activity is a controversial covariate. Existing literature have both justifiably included and excluded it as a covariate. Debate on this topic necessitates the distinction and definition of causation, as discussed in Chapter 3; a summary is given in this section. Part of the definition for a confounder is that it is a cause for the exposure (here comorbidity) and outcome. High disease activity *at baseline* does not cause comorbidity. It is more likely that comorbidities influence baseline assessment, in which case adjusting for a causal intermediate (a mediator) would be inappropriate. However, not accounting for baseline disease activity is problematic for some binary definitions of response (see above) and does not give the effect of the exposure independent of baseline disease activity.

6.3.5 Statistics

Descriptive statistics were used to describe comorbidity prevalence in this analysis cohort and compare participant with and without comorbidities.

6.3.5.1 Logistic regression

Each of the four binary response variables were used in turn as the dependent variable. Comorbidity count was modelled as the independent variable, adjusting for covariates. Odds ratios were reported without, then with, adjustment for baseline values of the disease index of interest; the latter were displayed graphically to aid interpretation.

Interactions between the comorbidity variable and each covariate (i.e., effect modification age, gender, etc.) were tested.

6.3.5.2 Mixed effect model

The principles of mixed effect models and interaction terms were discussed in Chapter 3. In summary, differences in baseline values of each index is accounted for by the intercept and does not require additional adjustment. Comparison instead focuses on the interaction-term coefficients, which represents the *additional* difference in change from baseline. To facilitate interpretation, predicted values are shown graphically, with an asterisk indicating statistical significance of the interaction term at the $p<0.05$ level. Note that statistical significance refers to the departure from the baseline difference, or 'difference accounting for the baseline' (see Chapter 3, Figure 3.14).

6.3.5.3 Time-to-event analyses

TNFi discontinuation is equivalent to drug 'survival'. Kaplan-Meier curves were used to show the shape of the survival function for each group (comorbidity was used as binary and categorical). The log-rank test was used to test whether their survival distributions are equal. The relationship between comorbidity history at baseline (binary and categorical) and discontinuation was then modelled using Cox models, adjusting for covariates. Interaction between comorbidity and all covariates were tested. Where covariates violated the proportional hazards assumption, non-proportional variables were stratified (see Chapter 3, Section 3.5.7).

6.3.5.4 Power considerations

Power calculation for logistic regression remains an active area of research. The commonest 'rule-of-thumb' is to have at least 10 'events' (i.e., responders) per independent variable. The number of events would therefore need to be 90 for models of binary comorbidity and 100 for categorical (assuming 3 categories). Adjusting for baseline disease activity would require 10 additional events. Assuming a 50% response, a sample of 994 would provide sufficient events per variable. There are two caveats. First, this rule-of-thumb is not based on robust mathematics nor does it perform well in simulations [229]. Alternatives were developed mainly for prediction models (using metrics related to out-of-sample prediction performance) that are difficult to apply here [229]. Second, the number of events will be very small when categorising comorbidity count; for example, around 150

participants have just one comorbidity (thus 75 events) and 60 have two or more (thus 30 events). These analyses will be underpowered.

Power calculations for mixed models are extremely complex, many of which are simulation-based, and are not available in software such as Stata and G*Power. They also require a range of assumptions that, if taken from the output of an already performed model, essentially become a transformation of its p-value (i.e., post-hoc power).

For a Cox model with none:≥1 comorbidities ratio of 2:1, alpha 0.05 and power 0.8, the number of events (TNFI discontinuation) needed is 3198 for a 10% reduction in hazard (i.e., HR 0.9), 713 for 20%, and 279 for 30% [230]. There were approximately 300 discontinuations in the analysis population. Therefore, the present analyses will be underpowered to detect an effect size smaller than 30% risk of discontinuation in those with compared to without comorbidities. As above, power will be further reduced when comorbidity count is categorised.

6.3.5.5 Sensitivity analyses

The UK prescribing guidelines should mean that all participants have BASDAI ≥4 at TNFi initiation. Some participants had lower values; the commonest example is a participant who had BASDAI<4 within a year before TNFi initiation but did not have any other assessments recorded prior to (or within 7 days of) starting treatment. It is also possible that the initiation date was recalled with error. In the first set of sensitivity analyses, these individuals were excluded from the analysis set.

Second, missing binary outcomes were imputed as response if patients remained on drug for longer than one year (see Section 6.3.3.1).

The third set of sensitivity analyses additionally adjusted for smoking status (ever/never) and alcohol status (ever/never) in turn. These are potential confounders, although evidence of their causal link with the outcome (required for confounder definition) are equivocal. Baseline employment status was reported as a predictor in a subsequent BSRBR-AS publication [134], but this data was not available for this thesis. Note that employment status – a time-varying covariate – is unlikely to serve as a confounder.

The final sensitivity analysis, other variance-covariance structures were tested for one outcome, BASDAI, in linear mixed models. Three are available in Stata: ‘independent’, one variance parameter per random effect and all covariances 0; ‘exchangeable’, equal

variances for random effects and one common pairwise covariance; and 'unstructured', all variances and covariances to be distinctly estimated (Appendix 10.2.2).

6.4 Results

Among 2687 participants in the BSRBR-AS, 1145 (43%) started on biologics. Of this group, 17 (1.5%) were excluded for using non-TNFi bDMARD, and 134 (12%) for having no valid baseline assessment within the accepted time window. Thus 994 (87%) were eligible for the current analysis. TNFi initiators included and excluded from the analysis set were similar in all baseline characteristics except the former were more often male (68 vs. 60%) (Appendix 10.5:Table S6.1). Sample sizes for individual analyses in the subsections below vary according to the amount of missing data for each variable. The analysis cohort was predominantly (68%) male with a mean age of 45 (SD 13) years (Table 6.1). Participants with comorbidities were significantly older, had higher BMI, and less frequently had university education than those without; they also used NSAIDs less frequently in the past 6 months and had more severe disease across all indices.

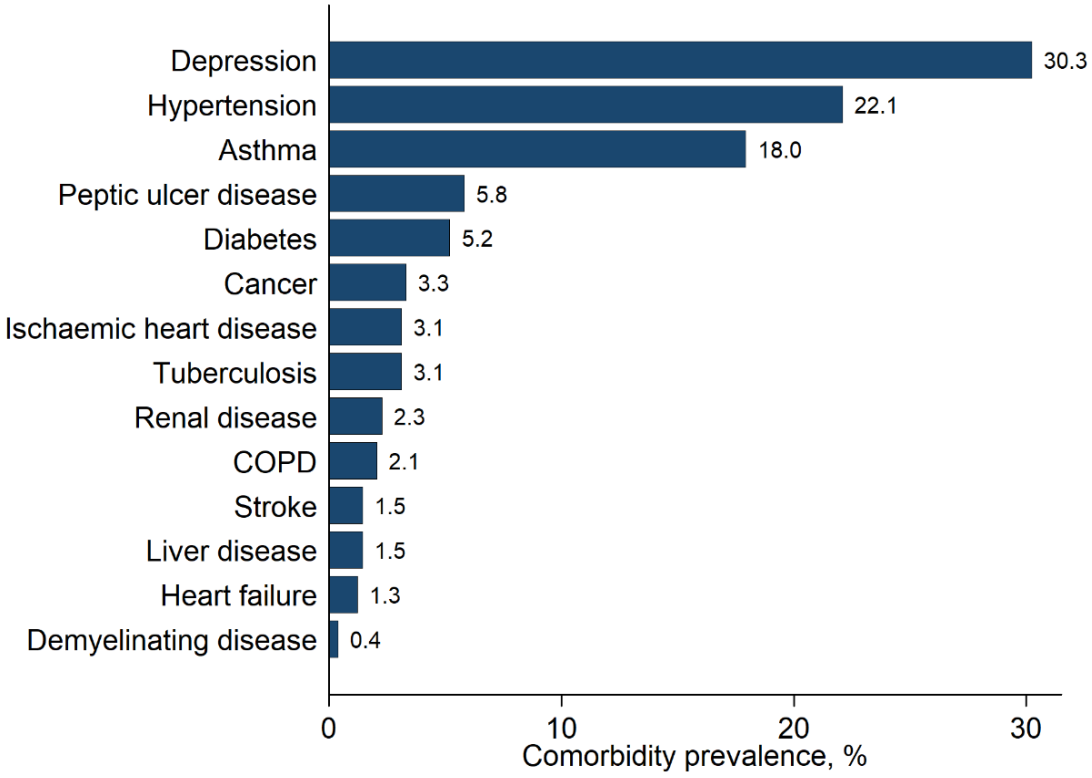
Table 6. 1: Baseline characteristics of 994 BSRBR-AS participants in the longitudinal analysis cohort.

		All participants (n=994)	axSpA without comorbidities (n=671)	axSpA with ≥1 comorbidity (n=323)	P-value
Age, years		44.7 (13.4)	43.0 (12.7)	48.3 (14.2)	<0.001
Males		679 (68%)	468 (70%)	211 (65%)	0.17
Meeting modified New York criteria		597 (60%)	394 (59%)	203 (63%)	0.24
Age at symptom onset, years		28.6 (11.3)	28.3 (10.9)	29.4 (12.1)	0.13
Symptom duration, years		16.0 (12.6)	14.7 (12.0)	18.9 (13.4)	<0.001
HLA-B27 positive*		540 (74%)	382 (76%)	158 (71%)	0.12
BMI, kg/m^2		28.1 (5.8)	27.5 (5.6)	29.2 (6.1)	<0.001
Smoking status	Never smoked	351 (40%)	251 (42%)	100 (35%)	0.093
	Ex-smoker	291 (33%)	188 (32%)	103 (36%)	
	Current smoker	241 (27%)	155 (26%)	86 (30%)	
Education	Secondary school	289 (33%)	184 (31%)	105 (36%)	0.022**
	Apprenticeship	82 (9%)	56 (10%)	26 (9%)	
	Further education college	276 (31%)	175 (30%)	101 (35%)	
	University degree	178 (20%)	138 (23%)	40 (14%)	
	Further degree	53 (6%)	36 (6%)	17 (6%)	
Deprivation index, median (IQR)		3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	0.12
NSAID use in past 6 months		734 (75%)	509 (77%)	225 (70%)	0.023
DMARD use in past 6 months		146 (15%)	104 (16%)	42 (13%)	0.29
BASDAI, median (IQR)		6.7 (5.3, 7.8)	6.5 (5.1, 7.7)	7.2 (6.0, 8.2)	<0.001
Spinal pain, median (IQR)		7.0 (5.0, 8.0)	7.0 (5.0, 8.0)	7.0 (6.0, 8.0)	<0.001
ASDAS*		2.9 (0.8)	2.8 (0.8)	3.0 (0.8)	<0.001
BASFI, median (IQR)		6.5 (4.5, 8.1)	6.1 (4.1, 7.7)	7.1 (5.4, 8.6)	<0.001
ASQoL, median (IQR)		13.0 (9.0, 16.0)	12.0 (8.0, 15.0)	14.0 (11.0, 17.0)	<0.001
Fatigue, median (IQR)		17.5 (14.0, 21.0)	17.0 (13.0, 21.0)	19.0 (15.0, 23.0)	<0.001
Sleep, median (IQR)		14.0 (8.0, 18.0)	13.0 (8.0, 17.0)	15.0 (10.0, 19.0)	0.003

Data shown as mean (SD) and n (%) unless otherwise indicated.
**non-parametric test for trend.
IQR, interquartile range; BMI, body mass index; BASDAI, Bath AS disease activity index; ASDAS, AS disease activity score; BASFI, Bath AS functional index; ASQoL, AS quality of life questionnaire.

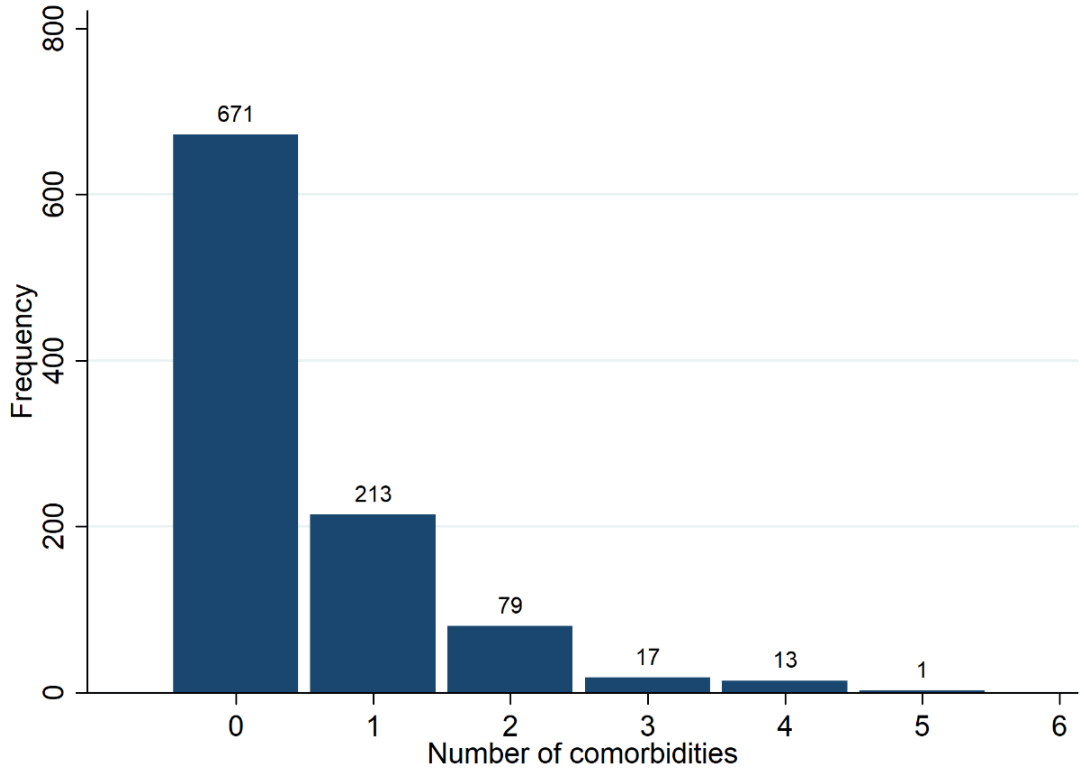
Prevalence of individual comorbidities are shown in Figure 6.1. Again, there were no difference between those included and excluded from analysis (Appendix 10.5: Table S6.1).

Figure 6. 1: Comorbidity prevalence in the treatment response analysis cohort.



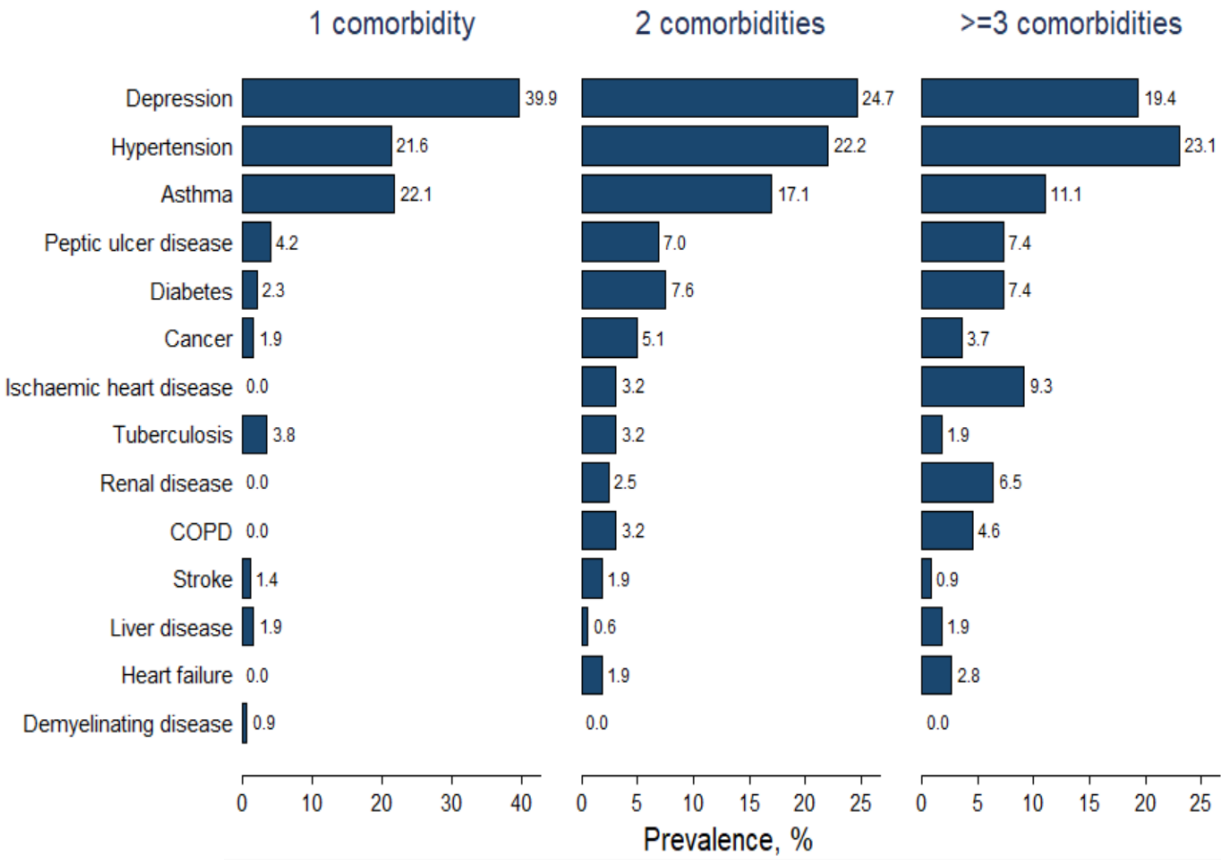
The distribution of comorbidity count is shown in Figure 6.2. The proportion with any comorbidity in this subgroup of TNFi initiators was lower than the whole BSRBR-AS cohort (32 vs. 44%); the mean number of comorbidities was 0.5 (SD 0.8) in this subgroup compared to 0.7 in the entire study population (see Chapter 5). Only around 1 in 5 had one comorbidity and 1 in 10 had two or more comorbidities.

Figure 6. 2: Histogram showing comorbidity count among 944 participants initiating TNF inhibitors in the BSRBR-AS.



When comorbidity count was categorised, the most prevalent condition was depression among those with only one comorbidity (Figure 6.3).

Figure 6. 3 Prevalence of individual comorbidities among those with only one comorbidity, and in two other comorbidity count categories.



COPD, chronic obstructive pulmonary disease.

To facilitate navigation of the following results, combinations of comorbidity and outcome variable-types will be reported in sections as indicated:

	Binary comorbidity status (≥1 vs. 0)	Continuous comorbidity count	Categorical comorbidity count
Aim 1: Binary response	6.4.1.1	6.4.1.1	6.4.1.2
Aim 2: Change in continuous outcome	6.4.2.1	6.4.2.2	6.4.2.3
Aim 3: Time to treatment discontinuation	6.4.3 (Kaplan-Meier only)	6.4.3.1	6.4.3.1

6.4.1 Binary response outcome

6.4.1.1 Binary and continuous comorbidity variables vs. binary outcome

The proportion of participants achieving binary responses varied from 26% to 52% depending on the definition (Table 6.2). There were no significant interactions in any of the models. Models for BASDAI<4 and ASDAS<2.1 showed reduced effect sizes for comorbidity after adjusting for baseline values of BASDAI and ASDAS, respectively. For example, participants with comorbidity (vs. none) had 30% lower odds of achieving BASDAI<4, but this reduced to 19% when accounting for baseline differences in BASDAI between the two groups. In contrast, comorbidity effect sizes increased after such adjustment for models of BASDAI 50/2 and ASDAS-MI. For example, participants with comorbidity (vs. without) had 4% lower odds of achieving BASDAI 50/2, but this increased to 13% when adjusting for baseline differences in BASDAI.

Table 6. 2: Association between comorbidity and binary response at 6 months.

	No. achieving response	**Comorbidity variable**	**Odds ratio without adjusting for baseline disease activity**	**Odds ratio adjusting for baseline disease activity**
BASDAI 50/2	312 (51%)	Binary	0.96 (0.65 to 1.40)	0.87 (0.59 to 1.28)
		Continuous count	0.88 (0.70 to 1.10)	0.81 (0.64 to 1.02)
ASDAS-MI	130 (26%)	Binary	0.94 (0.57 to 1.55)	0.69 (0.39 to 1.22)
		Continuous count	0.88 (0.63 to 1.21)	**0.66 (0.46 to 0.94)**
BASDAI<4	316 (52%)	Binary	0.70 (0.47 to 1.03)	0.81 (0.54 to 1.22)
		Continuous count	**0.73 (0.57 to 0.92)**	0.82 (0.64 to 1.05)
ASDAS<2.1	168 (34%)	Binary	0.95 (0.59 to 1.51)	0.98 (0.62 to 1.57)
		Continuous count	0.84 (0.62 to 1.14)	0.87 (0.64 to 1.18)

Binary comorbidity variable compared 0 (reference) vs. ≥1 comorbidities.
Bold text highlights statistically significant results.
BASDAI 50/2, 50% or 2-unit reduction in BASDAI; ASDAS-MI, major improvement i.e. ≥2-unit reduction.
Full model coefficients including covariates are shown in Appendix 10.5: Table S6.2 and S6.3.

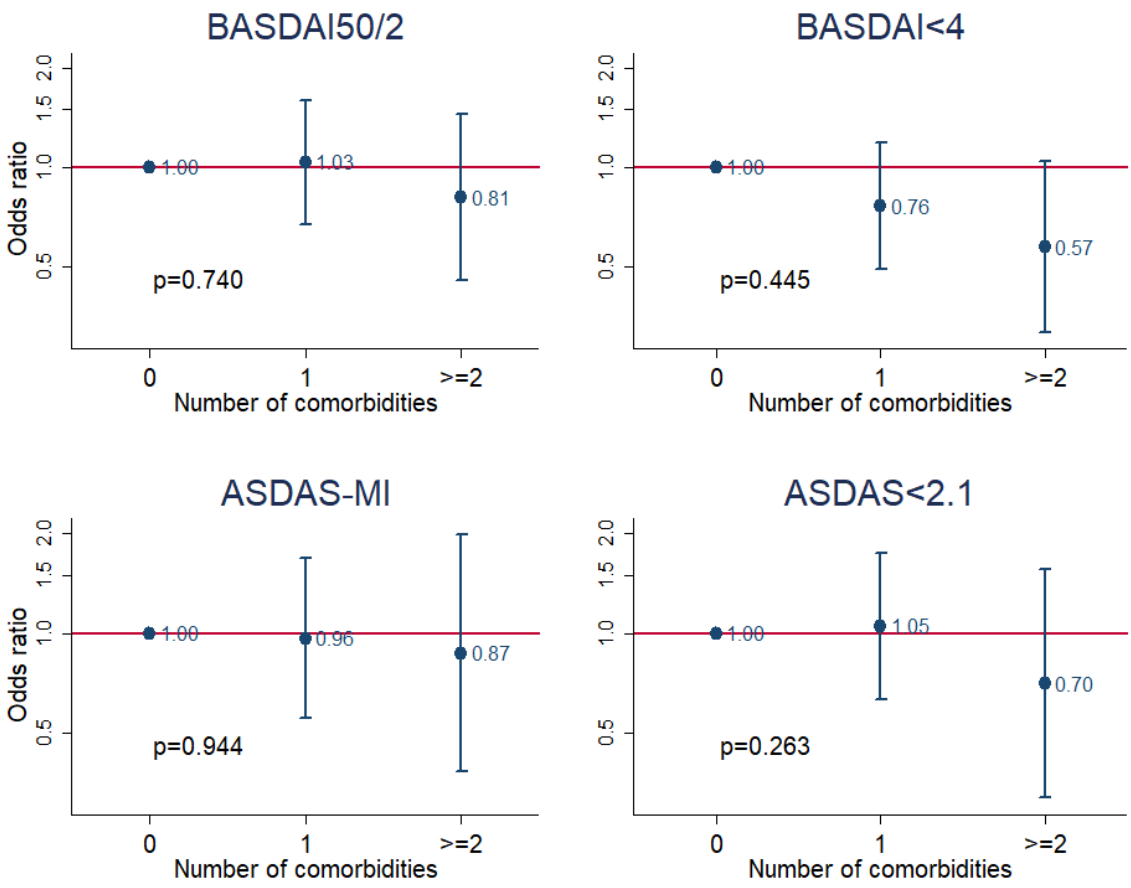
The following results refer to models adjusted for baseline disease activity. Participants with comorbidity (vs. none) had a 2% to 31% reduced odds of achieving a binary response at 6 months (Table 6.2), but none were statistically significant. Using comorbidity count as a continuous variable showed a 13% to 34% reduced odds of achieving a binary response at 6 months for each additional comorbidity.

Effect sizes were not dissimilar when using binary and continuous comorbidity in Table 6.2, suggesting that the relationships between comorbidity count and outcome were not linear. For example, odds of BASDAI 50/2 were reduced by 19% per additional comorbidity yet the presence of any comorbidity reduced it by 13%.

6.4.1.2 Categorical comorbidity count vs. binary outcome

No participants with ≥3 comorbidities achieved ASDAS-MI or ASDAS<2.1 and very few achieved BASDAI 50/2 or BASDAI<4; therefore, the top category was replaced as ≥2 comorbidities. Figure 6.4 shows that the odds of achieving each binary response was not statistically significantly different with increasing number of comorbidities, without adjusting for baseline values of each index. Effect sizes for BASDAI<4 (43% reduction) and ASDAS<2.1 (30% reduction) were, however, clinically significant when comparing ≥2 vs. no comorbidities.

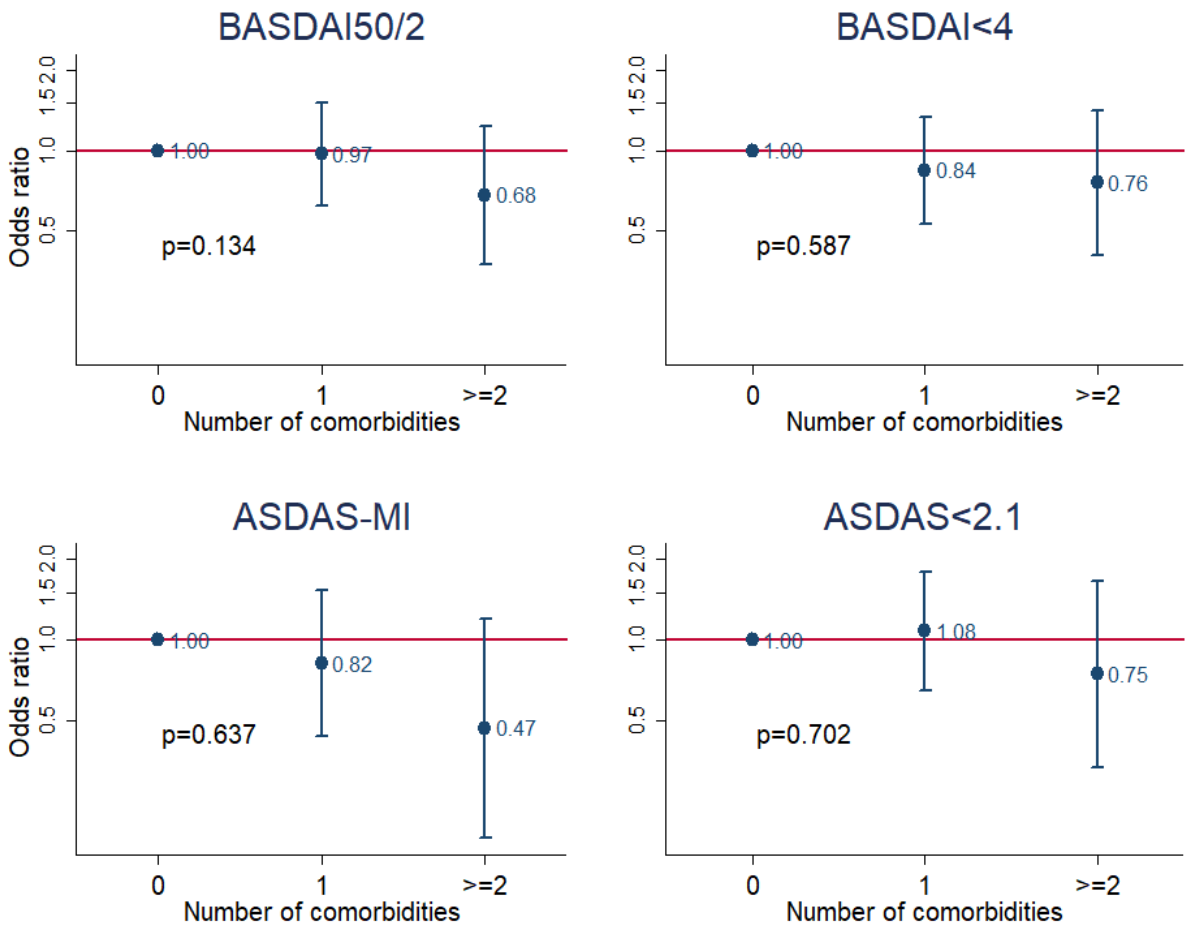
Figure 6. 4: Associations between comorbidity count categories and binary responses at 6 months.



Model coefficients shown in Appendix 10.5: Table S6.4. BASDAI 50/2, 50% or 2-unit reduction in BASDAI; ASDAS-MI, major improvement i.e. ≥2-unit reduction.

Results from the same models, additionally adjusting for the baseline values of each index, showed analogous changes in effect sizes as described above for binary comorbidity (that is, increased effect estimates of BASDAI 50/2 and ASDAS-MI, but decreased for low disease activity states). Equivalent plots are shown in Figure 6.5.

Figure 6. 5: Associations between comorbidity count categories and binary responses at 6 months, additionally adjusting for baseline values of respective indices.

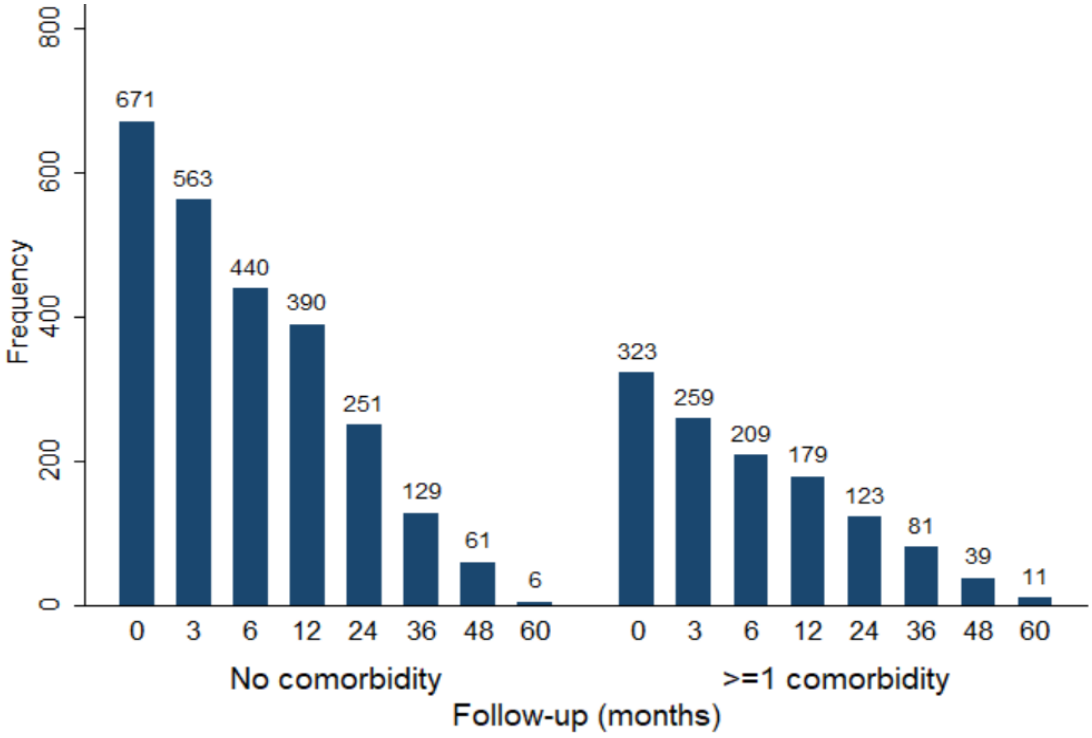


Model coefficients shown in Appendix 10.5: Table S6.4. BASDAI 50/2, 50% or 2-unit reduction in BASDAI; ASDAS-MI, major improvement i.e. ≥2-unit reduction.

6.4.2 Change in continuous outcome indices over time

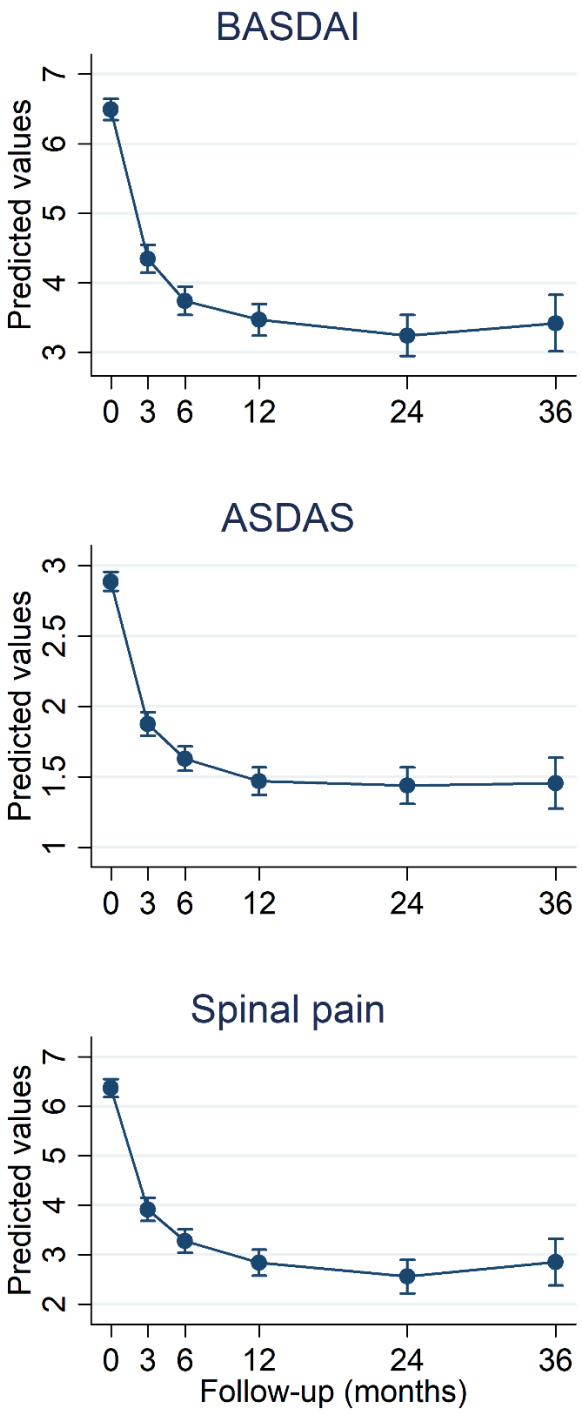
The number of participants with follow-up declined over time (Figure 6.6); therefore, analyses were restricted to the first 3 years (as discussed in the Methods section).

Figure 6. 6: Number of participants with follow-up at each per protocol assessment time, according to comorbidity status.



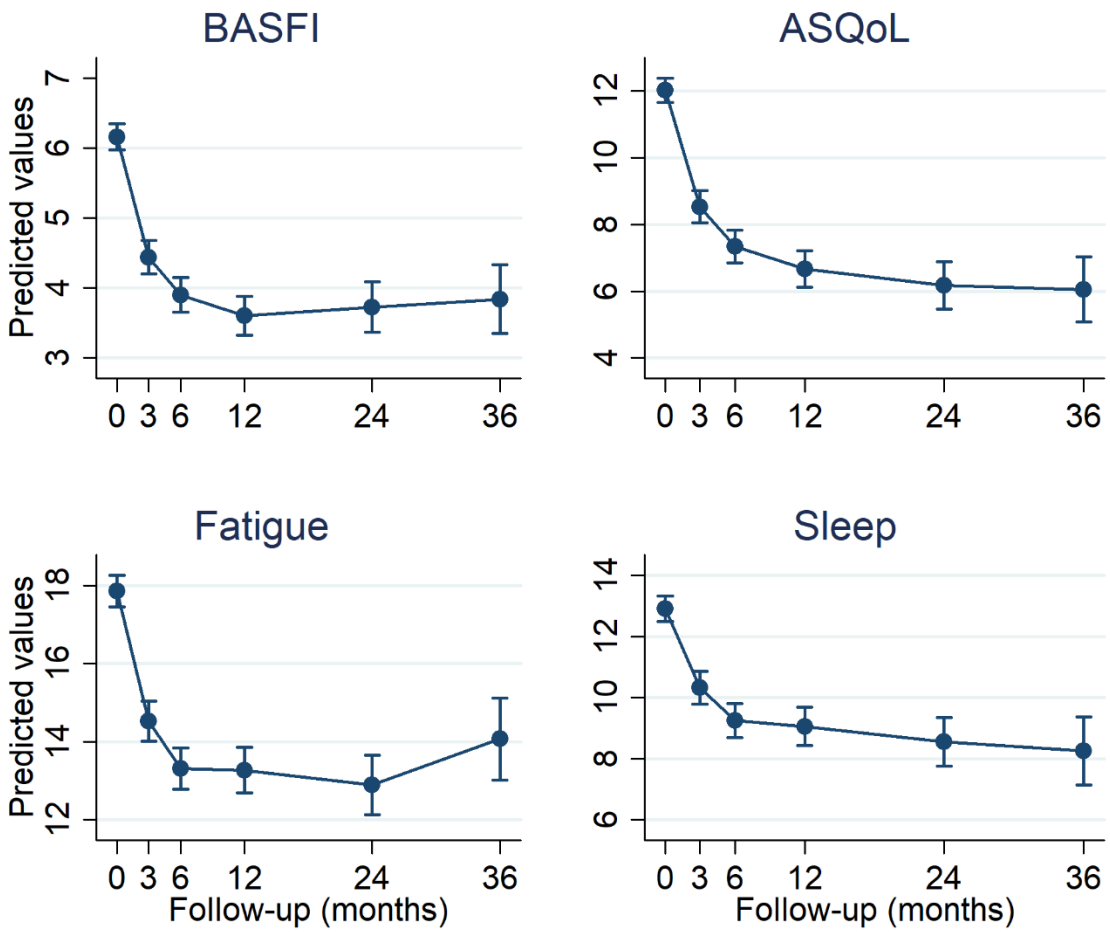
The average trajectories of BASDAI, ASDAS, and spinal pain disease indexes are shown in Figure 6.7. Other disease severity measures followed a similar trajectory (Figure 6.8)

Figure 6. 7: Change in average disease activity after starting TNF inhibitors in the analysis sample.



BASDAI, Bath AS disease activity index; ASDAS, AS disease activity score.

Figure 6. 8: Change in average disease severity indices after starting TNF inhibitors in the analysis sample.

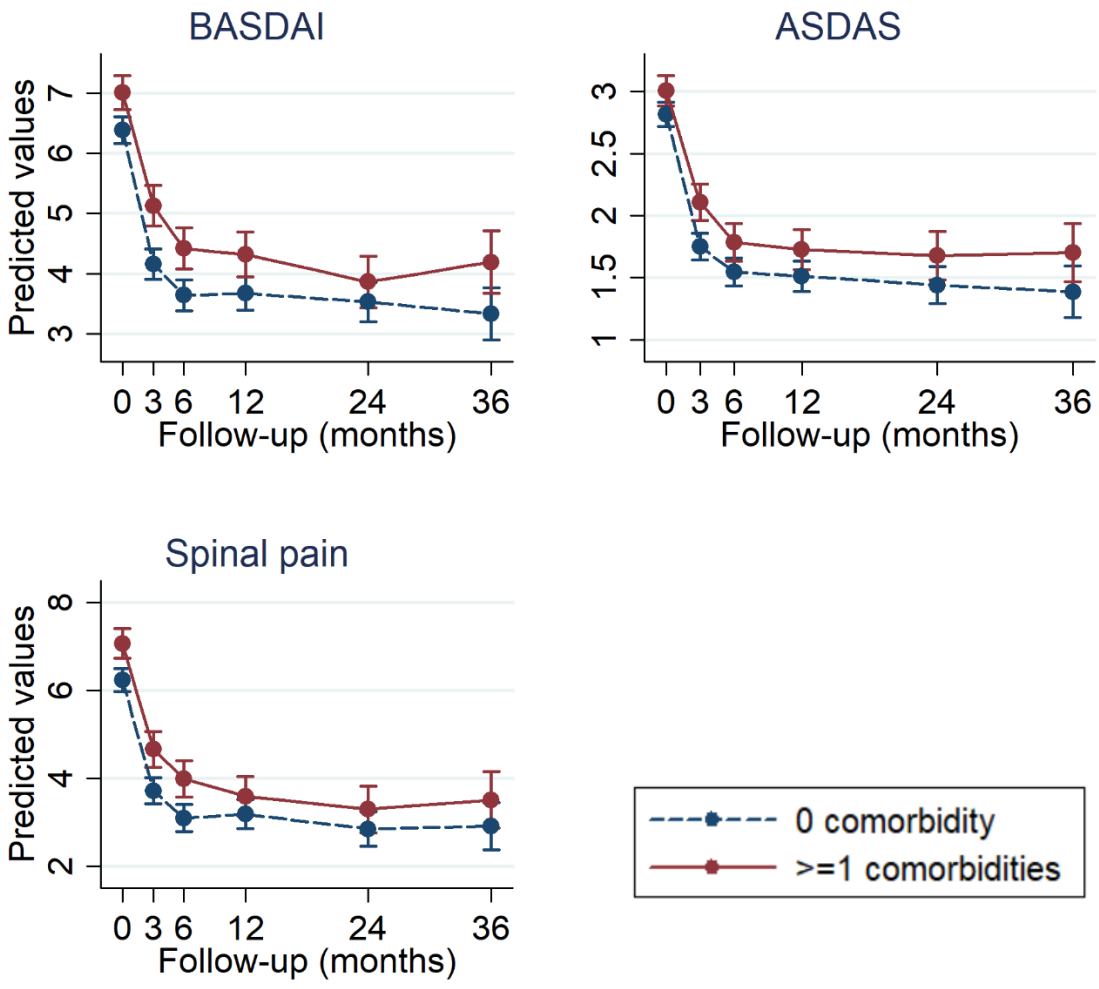


ASQoL, AS quality of life questionnaire; BASFI, Bath AS functional index.

6.4.2.1 Binary comorbidity status vs. continuous outcome

Figure 6.9 compares model-predicted values of each disease activity measure between participants with and without comorbidity at baseline. Participants with comorbidity (red) had higher disease activity at baseline than those without (dashed blue), but the absolute change in disease activity was similar (i.e., lines are parallel) between the two groups. Each of the three disease activity indices decreased significantly over follow-up, compared to the baseline.

Figure 6. 9: Change in disease activity in response to TNF inhibitors, in participants with and without comorbidities.



ASDAS, AS disease activity score; BASDAI, Bath AS disease activity index.

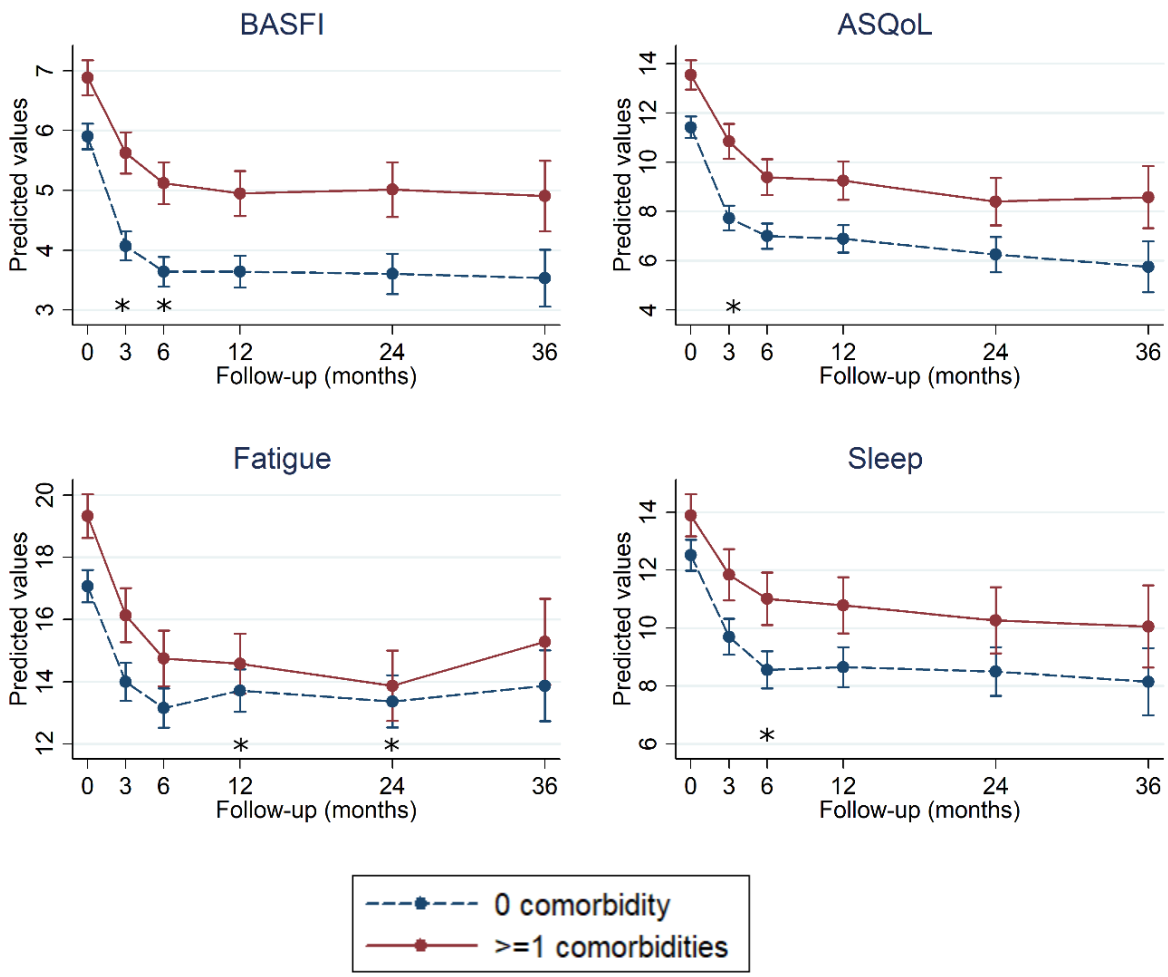
The model coefficients for Figure 6.9 are shown in Table 6.3 (interpretation discussed in Chapter 3, Section 3.5.6). For example, using the BASDAI, 734 participants with complete covariate data contributed 1998 follow-up assessments to the model; the baseline BADSAI was 6.4 among those with no comorbidities (derived from the constant, plus model-prediction at mean age (44 years), deprivation index (2.9), BMI (27), and weighted gender and education such that comparison groups had balanced categories) and 7.0 among those with ≥1 comorbidities. BASDAI changed by -2.2 units after 3 months of treatment in the group with no comorbidities, and -1.8 units (-2.2 plus the interaction term 3.FU#Comorbidity coefficient 0.4) in those with ≥1 comorbidities (contribution from covariates omitted for simplicity). The interaction term coefficient has a confidence interval that includes the null, indicating that the difference in change between the comparison groups were not statistically significant. All coefficients for each categorical time in Table 6.3 (i.e., improvement after treatment) were statistically significant, but the interaction term coefficients were not. Note that difference in ASDAS at baseline between those with and without comorbidity (0.12 units) was not statistically significant.

Table 6. 3: Coefficients from mixed effects models of baseline comorbidity status vs. disease activity over time.

	BASDAI	**ASDAS**	**Spinal pain**
N, participants (follow-ups)	734 (1998)	707 (1872)	734 (2009)
Constant	**5.38 (4.48 to 6.28)**	**2.12 (1.75 to 2.50)**	**5.39 (4.35 to 6.42)**
3.FU	**-2.20 (-2.43 to -1.97)**	**-1.06 (-1.17 to -0.95)**	**-2.49 (-2.78 to -2.20)**
6.FU	**-2.71 (-2.94 to -2.47)**	**-1.26 (-1.37 to -1.15)**	**-3.09 (-3.39 to -2.80)**
12.FU	**-2.66 (-2.91 to -2.41)**	**-1.29 (-1.41 to -1.17)**	**-2.99 (-3.30 to -2.67)**
24.FU	**-2.78 (-3.09 to -2.47)**	**-1.35 (-1.50 to -1.20)**	**-3.28 (-3.67 to -2.89)**
36.FU	**-3.04 (-3.46 to -2.63)**	**-1.43 (-1.64 to -1.22)**	**-3.31 (-3.84 to -2.78)**
Comorbidity*	**0.50 (0.17 to 0.83)**	0.12 (-0.03 to 0.26)	**0.74 (0.35 to 1.13)**
3.FU#Comorbidity	0.37 (-0.03 to 0.77)	0.15 (-0.04 to 0.33)	0.16 (-0.34 to 0.66)
6.FU#Comorbidity	0.22 (-0.18 to 0.62)	0.06 (-0.13 to 0.25)	0.15 (-0.35 to 0.66)
12.FU#Comorbidity	0.05 (-0.39 to 0.48)	0.03 (-0.17 to 0.24)	-0.38 (-0.93 to 0.17)
24.FU#Comorbidity	-0.21 (-0.73 to 0.30)	0.05 (-0.20 to 0.30)	-0.30 (-0.95 to 0.36)
36.FU#Comorbidity	0.44 (-0.22 to 1.09)	0.18 (-0.13 to 0.49)	-0.01 (-0.84 to 0.82)
*≥1 comorbidity vs. none. Covariate coefficients omitted. Bold text highlights statistically significant results. FU, follow-up at numbered month. #, interaction term.			

The analogous comparisons for other disease severity indices are shown in Figure 6.10 and Table 6.4. Participants without comorbidities at baseline had significantly greater improvement in BASFI at the 3- and 6-month assessments, by approximately 0.5 units. Interaction terms for health-related quality of life, fatigue and sleep were not overall significant. Note that the asterisks for fatigue at 12 and 24-month show a significant deviation in the opposite direction; that is, difference at baseline was significantly reduced (by around 1.5 units) at months 12 and 24.

Figure 6. 10: Change in other measures of disease severity in response to TNF inhibitors, in participants with and without comorbidities.



ASQoL, AS quality of life questionnaire; BASFI, Bath AS functional index.

Table 6. 4: Coefficients from mixed effect models of baseline comorbidity status vs. disease severity measures over time.

	BASFI	Quality of life	Fatigue	Sleep
N, participants (follow-ups)	736 (2013)	732 (1989)	735 (2010)	736 (2003)
Constant	**2.10 (0.99 to 3.20)**	**9.47 (7.30 to 11.63)**	**16.5 (14.1 to 19.0)**	**9.46 (6.87 to 12.05)**
3.FU	**-1.83 (-2.04 to -1.62)**	**-3.61 (-4.08 to -3.13)**	**-3.03 (-3.65 to -2.41)**	**-2.79 (-3.39 to -2.18)**
6.FU	**-2.26 (-2.49 to -2.04)**	**-4.31 (-4.80 to -3.82)**	**-3.79 (-4.43 to -3.15)**	**-3.91 (-4.54 to -3.29)**
12.FU	**-2.23 (-2.46 to -1.99)**	**-4.35 (-4.88 to -3.82)**	**-3.16 (-3.85 to -2.47)**	**-3.74 (-4.40 to -3.07)**
24.FU	**-2.24 (-2.53 to -1.95)**	**-4.82 (-5.47 to -4.17)**	**-3.43 (-4.27 to -2.58)**	**-3.80 (-4.61 to -2.98)**
36.FU	**-2.42 (-2.81 to -2.02)**	**-5.70 (-6.57 to -4.82)**	**-3.05 (-4.20 to -1.90)**	**-4.30 (-5.42 to -3.18)**
Comorbidity*	**0.49 (0.11 to 0.87)**	**1.56 (0.79 to 2.33)**	**2.07 (1.17 to 2.96)**	**0.98 (0.05 to 1.91)**
3.FU#Comorbidity	**0.49 (0.12 to 0.87)**	**1.05 (0.22 to 1.88)**	0.05 (-1.03 to 1.14)	0.75 (-0.31 to 1.80)
6.FU#Comorbidity	**0.52 (0.14 to 0.91)**	0.66 (-0.19 to 1.51)	-0.42 (-1.52 to 0.69)	**1.24 (0.17 to 2.32)**
12.FU#Comorbidity	0.36 (-0.05 to 0.77)	0.37 (-0.54 to 1.28)	**-1.35 (-2.54 to -0.16)**	0.78 (-0.38 to 1.93)
24.FU#Comorbidity	0.39 (-0.10 to 0.87)	0.18 (-0.89 to 1.26)	**-1.49 (-2.89 to -0.08)**	0.37 (-1.00 to 1.74)
36.FU#Comorbidity	0.58 (-0.03 to 1.20)	**1.41 (0.05 to 2.78)**	-0.32 (-2.11 to 1.48)	0.91 (-0.84 to 2.66)
*≥1 comorbidity vs. none. Covariate coefficients omitted. Bold text highlights statistically significant results. FU, follow-up at numbered month. #, interaction term.				

6.4.2.2 Continuous comorbidity count vs. continuous outcome

Comorbidity count was also modelled as a continuous variable, but results could not be shown graphically. Coefficients are shown in Table 6.5. Using BASDAI as the example: model-predictions show that for each additional comorbidity, the BASDAI response was approximately (since covariate contributions unaccounted) 0.2 units smaller at 3 and 6 months, although these interaction coefficients were not statistically significant. The same model for BASFI showed 0.3 units reduced response at 3 months for each additional comorbidity, and 0.4 units at 6 months, which were both statistically significant.

Table 6. 5: Coefficients from mixed effect models of baseline continuous comorbidity count vs. disease severity measures over time.

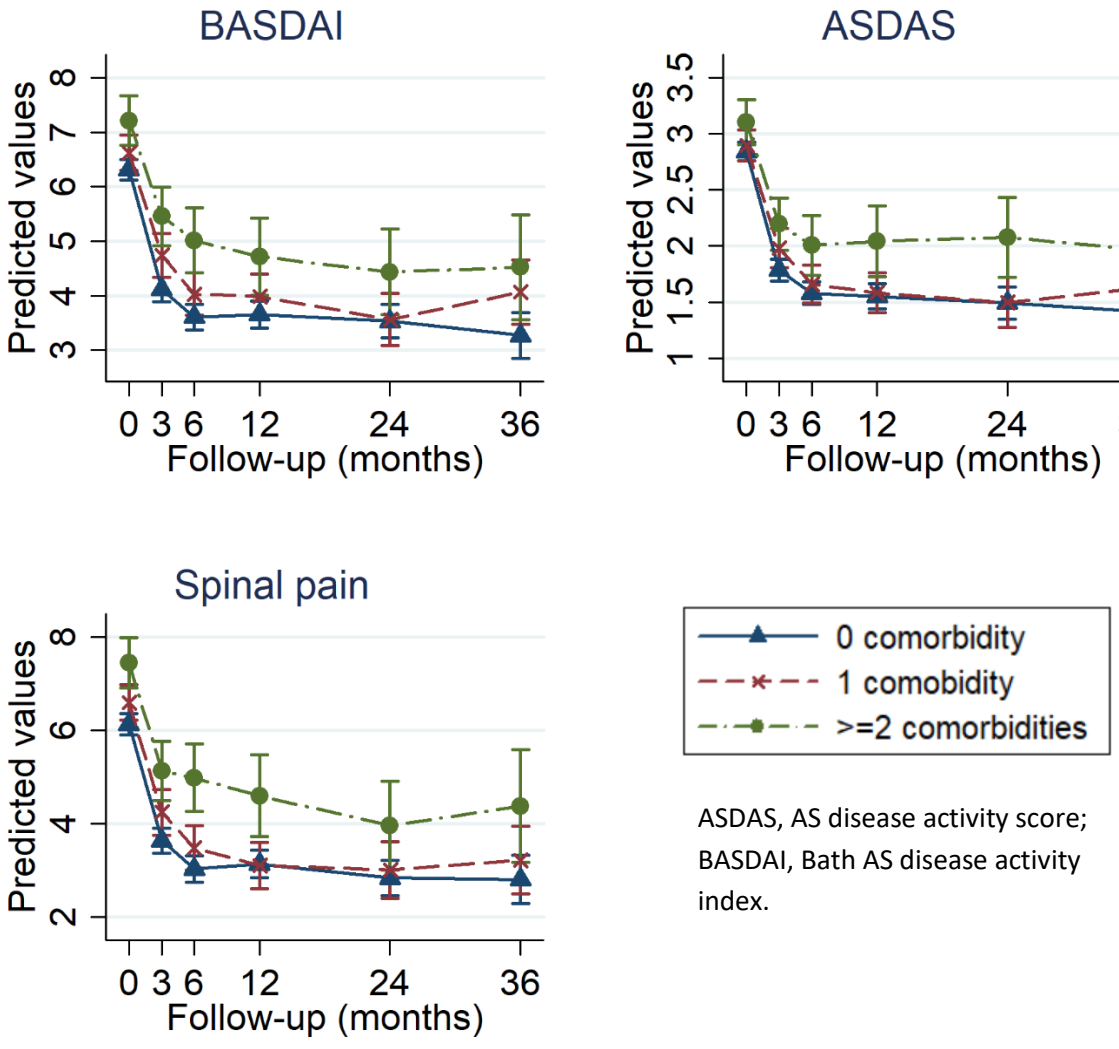
	BASDAI	ASDAS	Spinal pain	BASFI	Quality of life	Fatigue	Sleep
N, participants (follow-ups)	734 (1998)	707 (1872)	734 (2009)	736 (2013)	732 (1989)	735 (2010)	736 (2003)
Constant	**5.59 (4.69 to 6.49)**	**2.2 (1.83 to 2.58)**	**5.69 (4.66 to 6.72)**	**2.37 (1.27 to 3.47)**	**10.1 (7.96 to 12.2)**	**17.1 (14.7 to 19.5)**	**9.79 (7.18 to 12.3)**
3.FU	**-2.19 (-2.40 to -1.97)**	**-1.06 (-1.16 to -0.95)**	**-2.48 (-2.76 to -2.21)**	**-1.81 (-2.02 to -1.61)**	**-3.61 (-4.07 to -3.16)**	**-3.10 (-3.69 to -2.51)**	**-2.75 (-3.33 to -2.18)**
6.FU	**-2.74 (-2.97 to -2.52)**	**-1.28 (-1.39 to -1.17)**	**-3.16 (-3.44 to -2.88)**	**-2.29 (-2.50 to -2.08)**	**-4.45 (-4.92 to -3.98)**	**-3.93 (-4.55 to -3.32)**	**-3.94 (-4.54 to -3.35)**
12.FU	**-2.66 (-2.90 to -2.42)**	**-1.31 (-1.42 to -1.19)**	**-3.06 (-3.36 to -2.75)**	**-2.22 (-2.45 to -2.00)**	**-4.48 (-4.98 to -3.97)**	**-3.25 (-3.91 to -2.59)**	**-3.69 (-4.33 to -3.04)**
24.FU	**-2.85 (-3.14 to -2.55)**	**-1.38 (-1.52 to -1.24)**	**-3.33 (-3.70 to -2.96)**	**-2.24 (-2.52 to -1.96)**	**-4.97 (-5.58 to -4.35)**	**-3.52 (-4.33 to -2.72)**	**-3.82 (-4.60 to -3.04)**
36.FU	**-2.99 (-3.39 to -2.59)**	**-1.42 (-1.62 to -1.22)**	**-3.33 (-3.84 to -2.82)**	**-2.42 (-2.80 to -2.04)**	**-5.79 (-6.63 to -4.96)**	**-3.07 (-4.17 to -1.98)**	**-4.25 (-5.32 to -3.19)**
Comorbidity count*	**0.36 (0.17 to 0.55)**	**0.10 (0.01 to 0.18)**	**0.53 (0.30 to 0.75)**	**0.40 (0.18 to 0.62)**	**1.00 (0.55 to 1.44)**	**1.22 (0.70 to 1.74)**	**0.57 (0.03 to 1.11)**
3.FU#Comorbidity count	0.22 (-0.01 to 0.46)	0.09 (-0.01 to 0.20)	0.09 (-0.19 to 0.38)	**0.30 (0.08 to 0.53)**	**0.71 (0.23 to 1.20)**	0.17 (-0.45 to 0.80)	0.44 (-0.18 to 1.05)
6.FU#Comorbidity count	0.24 (-0.01 to 0.50)	0.08 (-0.04 to 0.20)	0.27 (-0.04 to 0.59)	**0.44 (0.20 to 0.67)**	**0.81 (0.27 to 1.35)**	0.03 (-0.66 to 0.71)	**0.99 (0.32 to 1.66)**
12.FU#Comorbidity count	0.05 (-0.24 to 0.34)	0.06 (-0.07 to 0.19)	-0.11 (-0.47 to 0.25)	0.27 (-0.001 to 0.54)	0.58 (-0.03 to 1.18)	-0.8 (-1.60 to 0.01)	0.49 (-0.28 to 1.25)
24.FU#Comorbidity count	-0.02 (-0.36 to 0.32)	0.11 (-0.06 to 0.27)	-0.11 (-0.52 to 0.29)	0.29 (-0.03 to 0.62)	0.45 (-0.23 to 1.13)	-0.86 (-1.75 to 0.02)	0.34 (-0.53 to 1.20)
36.FU#Comorbidity count	0.25 (-0.20 to 0.69)	0.13 (-0.08 to 0.35)	0.05 (-0.51 to 0.61)	**0.45 (0.03 to 0.87)**	**1.31 (0.39 to 2.24)**	-0.12 (-1.33 to 1.10)	0.62 (-0.57 to 1.80)

*as a continuous variable, i.e., change with each additional comorbidity. Covariate coefficients omitted.
Bold text highlights statistically significant results.
FU, follow-up at numbered month. #, interaction term.

6.4.2.3 Categorical comorbidity count vs. continuous outcome

Figure 6.11 shows the differences in disease activity change according to comorbidity count categories (model coefficients shown in Table 6.6). The top category was combined into ≥2 comorbidities due to the small number of participants with ≥3 comorbidities. In summary, there were no statistically significant differences in the absolute change from baseline (i.e., the lines are not statistically different from parallel). Participants with no and one comorbidity had similar graphically depicted trajectories, confirmed by no statistically significant difference in baseline BASDAI (β=0.31; 95% CI -0.06 to 0.68) or ASDAS (β=0.05; 95% CI -0.11 to 0.21). Participants with ≥2 comorbidities had higher BASDAI and ASDAS throughout follow-up. Spinal pain compared between 1 vs. 0 (β=0.47; 95% CI 0.03 to 0.91) and 2 vs. 0 comorbidities (β=1.32; 95% CI 0.74 to 1.91) were significantly different, but changes over time were not.

Figure 6. 11: Change in disease activity according to comorbidity count categories.



ASDAS, AS disease activity score; BASDAI, Bath AS disease activity index.

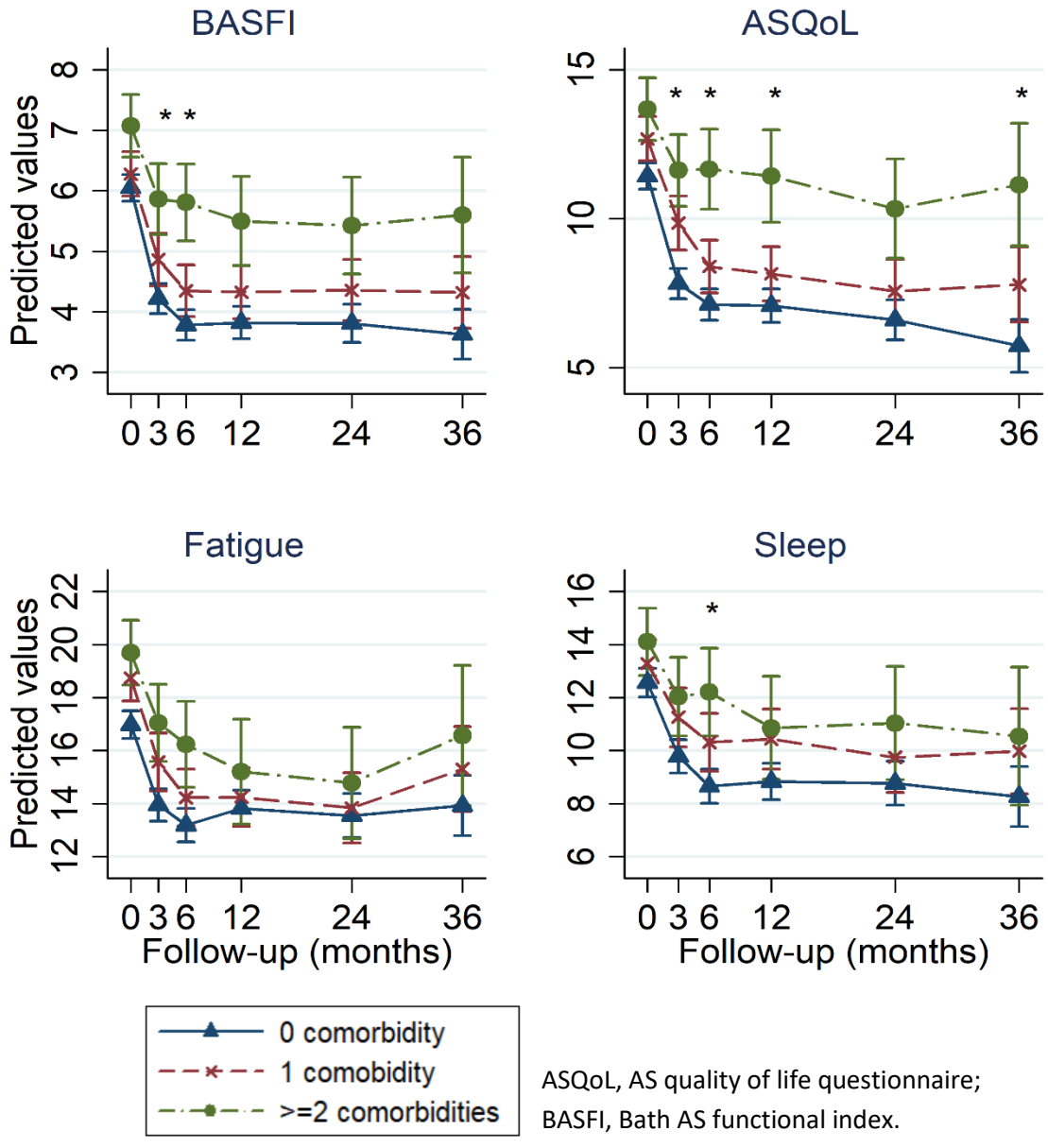
Table 6. 6: Coefficients from mixed effect models of baseline comorbidity count categories vs. disease activity over time.

	BASDAI	ASDAS	Spinal pain
N, participants (follow-ups)	734 (1998)	707 (1872)	734 (2009)
Constant	**5.54 (4.64 to 6.44)**	**2.19 (1.81 to 2.57)**	**5.64 (4.60 to 6.67)**
3.FU	**-2.20 (-2.43 to -1.97)**	**-1.06 (-1.16 to -0.95)**	**-2.49 (-2.77 to -2.20)**
6.FU	**-2.71 (-2.94 to -2.47)**	**-1.26 (-1.37 to -1.15)**	**-3.09 (-3.39 to -2.80)**
12.FU	**-2.66 (-2.91 to -2.41)**	**-1.29 (-1.41 to -1.17)**	**-2.99 (-3.30 to -2.67)**
24.FU	**-2.78 (-3.09 to -2.47)**	**-1.35 (-1.50 to -1.20)**	**-3.29 (-3.67 to -2.90)**
36.FU	**-3.04 (-3.46 to -2.63)**	**-1.43 (-1.64 to -1.22)**	**-3.32 (-3.85 to -2.79)**
1.comcat	0.31 (-0.06 to 0.69)	0.05 (-0.11 to 0.21)	**0.47 (0.03 to 0.92)**
2.comcat	**0.90 (0.40 to 1.40)**	**0.26 (0.04 to 0.48)**	**1.32 (0.74 to 1.91)**
3.FU#1.comcat	0.32 (-0.15 to 0.78)	0.14 (-0.07 to 0.36)	0.13 (-0.45 to 0.72)
6.FU#1.comcat	0.11 (-0.35 to 0.57)	0.03 (-0.19 to 0.24)	-0.02 (-0.60 to 0.55)
12.FU#1.comcat	0.02 (-0.46 to 0.50)	-0.02 (-0.25 to 0.20)	-0.50 (-1.11 to 0.10)
24.FU#1.comcat	-0.28 (-0.85 to 0.30)	-0.05 (-0.33 to 0.23)	-0.30 (-1.04 to 0.43)
36.FU#1.comcat	0.49 (-0.24 to 1.21)	0.15 (-0.19 to 0.49)	-0.06 (-0.97 to 0.85)
3.FU#2.comcat	0.44 (-0.15 to 1.03)	0.15 (-0.13 to 0.42)	0.17 (-0.56 to 0.90)
6.FU#2.comcat	0.51 (-0.13 to 1.15)	0.16 (-0.14 to 0.46)	0.63 (-0.17 to 1.43)
12.FU#2.comcat	0.16 (-0.58 to 0.91)	0.23 (-0.12 to 0.57)	0.13 (-0.81 to 1.08)
24.FU#2.comcat	0.00 (-0.84 to 0.84)	0.32 (-0.08 to 0.72)	-0.20 (-1.24 to 0.84)
36.FU#2.comcat	0.35 (-0.70 to 1.40)	0.29 (-0.23 to 0.82)	0.24 (-1.09 to 1.57)

Comcat, comorbidity category 0 (reference), 1, ≥2. FU, follow-up at numbered month.
Bold text highlights statistically significant results.
#, interaction term.; ASDAS, AS disease activity score; BASDAI, Bath AS disease activity index.

Figure 6.12 shows the differences in change in other measures of disease severity according to comorbidity count categories (model coefficients shown in Table 6.7). Change over time in all four indices were parallel for participants with no and one comorbidity. BASFI was significantly higher at baseline by 1.03 (0.46 to 1.60) in those with ≥2 comorbidities. Moreover, their improvement (i.e., absolute change) over the first 6 months was also significantly smaller than those with no comorbidities (i.e., the gradient of the green line is less 'steep' in the first 6 months). This was also observed for health-related quality of life, which was poorer at baseline and improvement was also smaller.

Figure 6. 12: Change in other measures of disease severity according to comorbidity count categories.



ASQoL, AS quality of life questionnaire;
BASFI, Bath AS functional index.

Table 6. 7: Coefficients from mixed effect models of baseline comorbidity count categories vs. disease severity measures over time.

	BASFI	ASQoL	Fatigue	Sleep
N, participants (follow-ups)	736 (2013)	732 (1989)	735 (2010)	736 (2003)
Constant	**2.33 (1.23 to 3.43)**	**9.90 (7.73 to 12.07)**	**16.8 (14.4 to 19.3)**	**9.69 (7.09 to 12.30)**
3.FU	**-1.83 (-2.04 to -1.62)**	**-3.61 (-4.08 to -3.13)**	**-3.03 (-3.65 to -2.41)**	**-2.79 (-3.39 to -2.18)**
6.FU	**-2.26 (-2.48 to -2.04)**	**-4.31 (-4.80 to -3.82)**	**-3.79 (-4.43 to -3.15)**	**-3.91 (-4.53 to -3.29)**
12.FU	**-2.23 (-2.46 to -1.99)**	**-4.35 (-4.87 to -3.82)**	**-3.16 (-3.84 to -2.47)**	**-3.73 (-4.40 to -3.06)**
24.FU	**-2.24 (-2.53 to -1.95)**	**-4.82 (-5.47 to -4.18)**	**-3.43 (-4.27 to -2.59)**	**-3.80 (-4.61 to -2.98)**
36.FU	**-2.42 (-2.81 to -2.03)**	**-5.70 (-6.57 to -4.83)**	**-3.05 (-4.20 to -1.90)**	**-4.30 (-5.42 to -3.18)**
1.comcat	0.23 (-0.20 to 0.66)	**1.26 (0.39 to 2.13)**	**1.76 (0.75 to 2.78)**	0.72 (-0.34 to 1.78)
2.comcat	**1.03 (0.46 to 1.60)**	**2.25 (1.09 to 3.40)**	**2.72 (1.38 to 4.07)**	**1.54 (0.14 to 2.94)**
3.FU#1.comcat	0.41 (-0.02 to 0.85)	0.77 (-0.19 to 1.74)	-0.14 (-1.41 to 1.12)	0.76 (-0.48 to 1.99)
6.FU#1.comcat	0.33 (-0.10 to 0.76)	0.01 (-0.94 to 0.97)	-0.72 (-1.98 to 0.53)	0.94 (-0.28 to 2.16)
12.FU#1.comcat	0.28 (-0.18 to 0.73)	-0.19 (-1.19 to 0.81)	-1.34 (-2.66 to -0.03)	0.88 (-0.40 to 2.16)
24.FU#1.comcat	0.32 (-0.22 to 0.86)	-0.30 (-1.50 to 0.90)	-1.47 (-3.05 to 0.11)	0.26 (-1.27 to 1.79)
36.FU#1.comcat	0.46 (-0.22 to 1.14)	0.80 (-0.70 to 2.30)	-0.39 (-2.36 to 1.59)	0.99 (-0.95 to 2.93)
3.FU#2.comcat	**0.62 (0.06 to 1.18)**	**1.55 (0.33 to 2.78)**	0.38 (-1.23 to 1.98)	0.72 (-0.84 to 2.28)
6.FU#2.comcat	**1.00 (0.40 to 1.60)**	**2.29 (0.94 to 3.65)**	0.33 (-1.41 to 2.06)	**2.02 (0.31 to 3.72)**
12.FU#2.comcat	0.65 (-0.06 to 1.36)	**2.10 (0.54 to 3.67)**	-1.33 (-3.42 to 0.75)	0.49 (-1.51 to 2.48)
24.FU#2.comcat	0.59 (-0.21 to 1.39)	1.48 (-0.24 to 3.20)	-1.49 (-3.75 to 0.77)	0.73 (-1.51 to 2.97)
36.FU#2.comcat	0.95 (-0.05 to 1.94)	**3.16 (0.97 to 5.34)**	-0.08 (-2.96 to 2.81)	0.74 (-2.06 to 3.54)

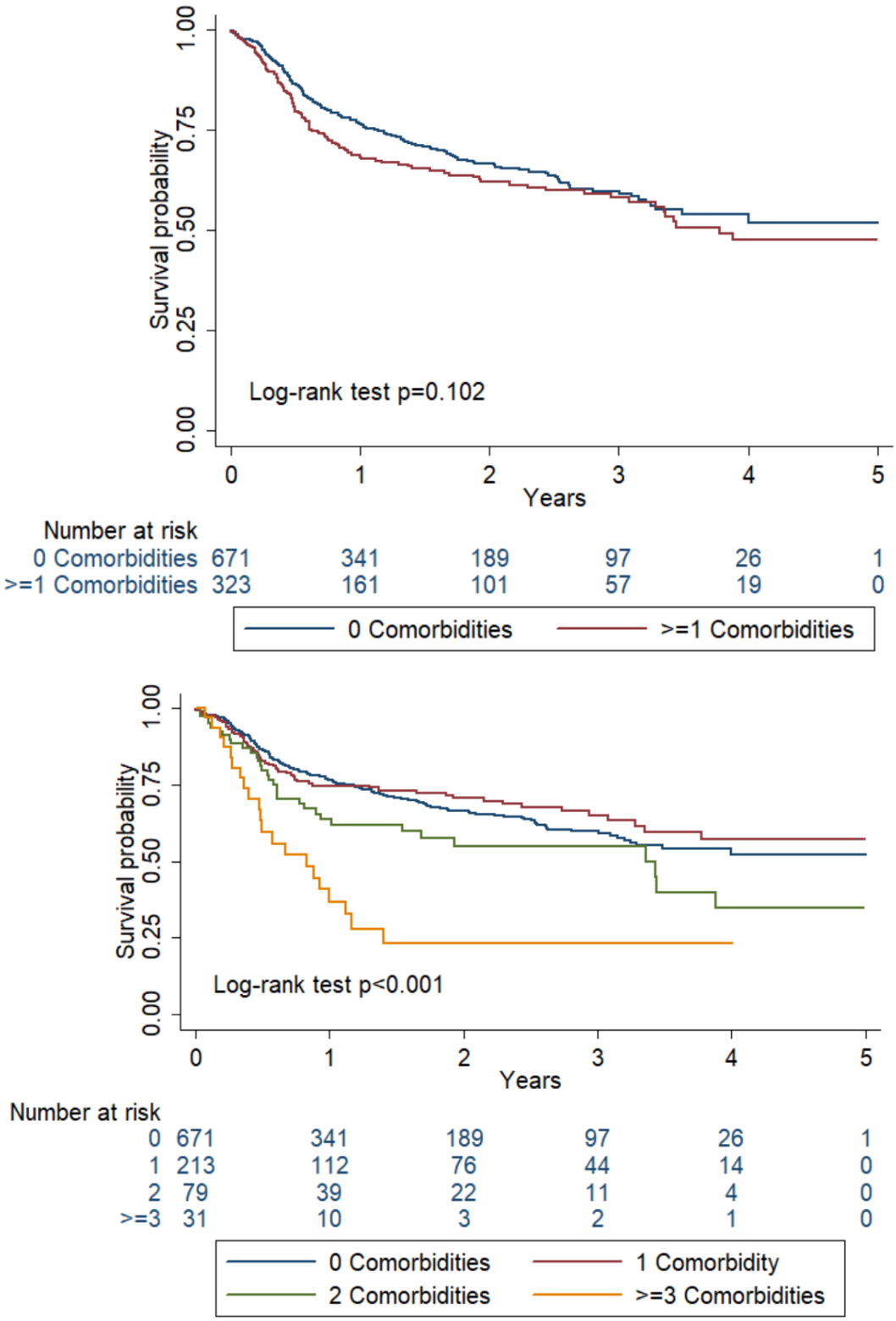
Comcat, comorbidity category 0 (reference), 1, ≥2. FU, follow-up at numbered month.
Bold text highlights statistically significant results.
#, interaction term. ASDAS, AS disease activity score; BASDAI, Bath AS disease activity index.

6.4.3 Time to treatment discontinuation

Of the 994 participants that started TNFi, 18 (1.8%) did not have any post-baseline data and were each assigned one minute of follow-up time. The remaining 976 subjects had 1441 person-years of follow-up, with a mean of 17 (SD 15) months and median of 12 (IQR 6 to 27) months. Thirty one percent of the cohort stopped treatment over the whole study follow-up: 29% of those with no comorbidities, 30% of those with one, 42% two and 68% with ≥3 comorbidities.

The top panel of Figure 6.13 shows overall poorer drug survival in those with comorbidity at baseline than without. The lines are approximately parallel except at around 3 years, suggesting violation of the proportional hazards assumption required for further modelling. (Kaplan-Meier curves were not possible for continuous comorbidity count.) The right panel compares drug survival according to categories of comorbidity count. Log-rank test confirms a statistically significant difference, particularly notable for those with 2 and ≥3 comorbidities.

Figure 6. 13: Kaplan-Meier curves comparing drug survival in participants according to presence of comorbidities.

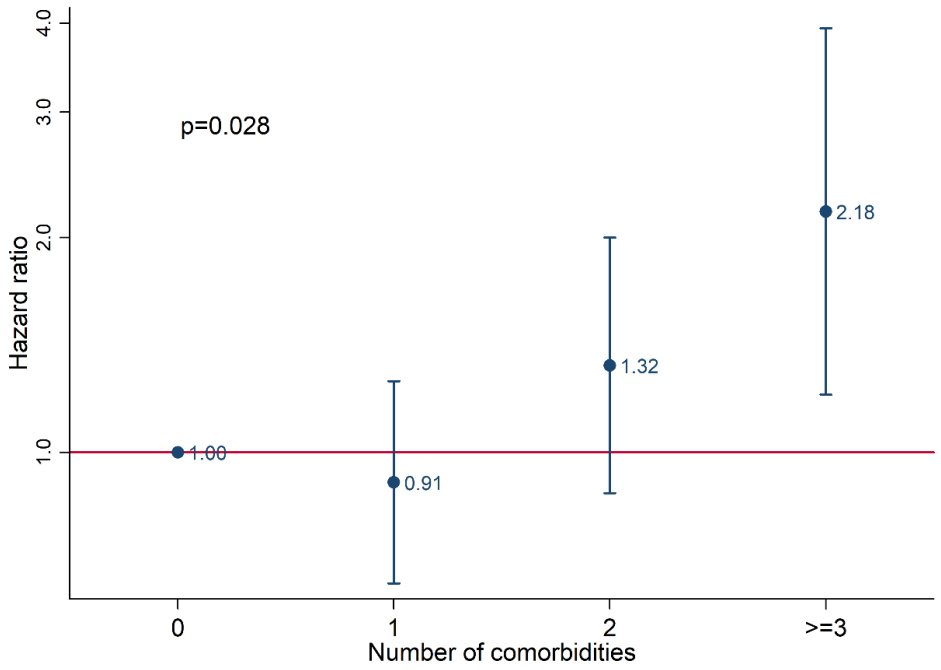


6.4.3.1 Cox models

Modelling for presence vs. absence of comorbidity was not performed due to violation of the proportional hazards assumption indicated by the above Kaplan-Meier curve. Comorbidity count as a single continuous variable was performed for completeness; each additional comorbidity increased the hazard rate of discontinuation by 17% (95%CI 1.02, 1.36). However, this has limited meaning as the relationship with comorbidity count is non-linear (Figure 6.13).

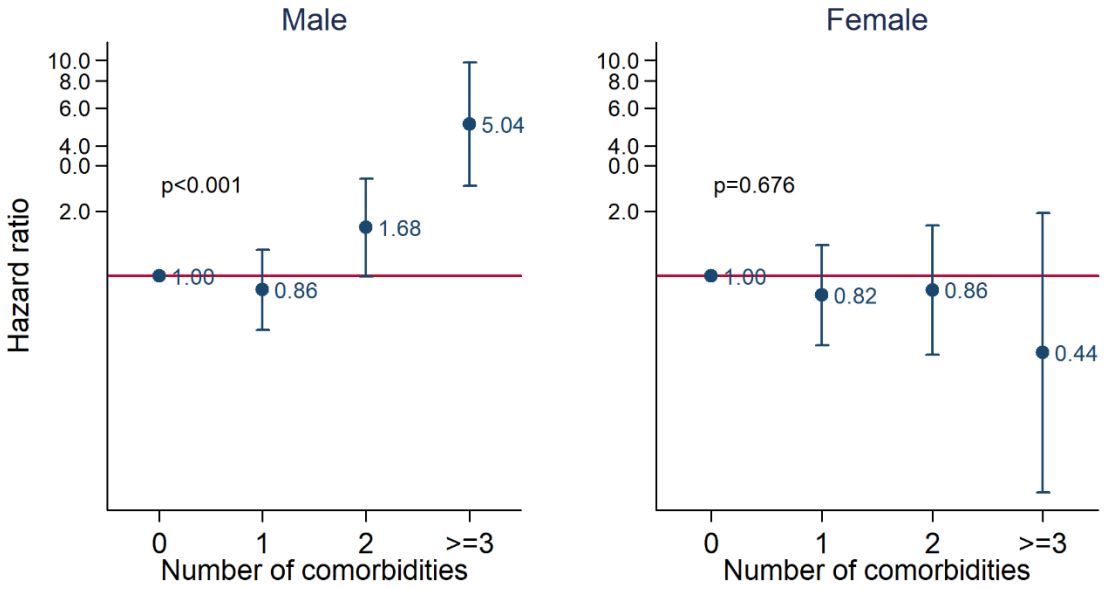
Results from the Cox model of categorical comorbidity count vs. drug discontinuation are shown in Figure 6.14 (model coefficients shown in Appendix Table S6.5). Education was stratified in the model since it was significant in tests for proportional hazards violation. Participants with one comorbidity were not more or less likely to discontinue TNFi compared to those with no comorbidities. The hazard rate of TNFi discontinuation was 32% higher (95%CI 0.88 to 2.00) for those with two comorbidities, but not statistically significant to those without comorbidities. Participants with ≥3 comorbidities had 2.2-fold higher hazard rate (95%CI 1.20 to 3.93) of discontinuation compared to those without comorbidities at baseline (i.e., 2.2 times as many individuals discontinued at any one time, assuming rates are proportional).

Figure 6. 14: TNF inhibitor discontinuation compared according to the number of baseline comorbidities.



Interaction between gender and comorbidity categories were significant across all categories. To aid interpretation, analysis was performed separately in males and females with results plotted in Figure 6.15 (model coefficients shown in Appendix 10.5: Table S6.5). The association between comorbidity and drug survival was present among males, but not females. Males with one comorbidity did not differ in hazard of drug discontinuation compared to those with no comorbidities, but those with 2 comorbidities had 68% higher and ≥3 had over 5-fold higher hazard rates.

Figure 6. 15: Hazard rate of TNF inhibitor discontinuation according to the number of baseline comorbidities, stratified by gender.



6.4.4 Sensitivity analyses

6.4.4.1 Excluding individuals with baseline BASDAI<4

Participants with baseline BASDAI<4 would not ordinarily be eligible for TNFi according to NICE guidance. One explanation is imputation of missing baseline BASDAI from up to a year before TNFi initiation. After excluding these patients, results for the binary outcome, absolute response, and treatment discontinuation analyses were not meaningfully different from the primary analysis (data not shown).

6.4.4.2 Missing binary outcome imputation

Analyses of binary outcomes with imputation significantly changed the proportion of responders, particularly for ASDAS-based variables (due to more missing data with ASDAS). However, analyses of binary, continuous or categorical comorbidity count definitions showed no meaningful differences in results (Appendix 10.5: Table S6.6 and Figure S6.1).

6.4.4.3 Adjusting for additional potential confounders

Results from all models additionally adjusting for ever/never smoking and ever/never use of alcohol were not meaningfully different (data not shown).

6.4.4.4 Testing other variance-covariance structures

Mixed effects models of comorbidity vs. BASDAI using three other variance-covariance structures resulted in no meaningfully difference (data not shown).

6.5 Discussion

In this longitudinal study of response to the first TNF inhibitor, participants with greater comorbidity burden had higher disease activity at baseline that persisted throughout follow-up. Participants with multiple (≥2) comorbidities had significantly poorer absolute improvements in function and health-related quality of life. These individuals also had significantly increased TNFi discontinuation compared to those without comorbidities.

Three studies have previously examined the same topic. Iannone et al showed that mRCDI was significantly correlated (by Spearman's rank) with the number of biologic switches [114]. Kaplan Meier curves showed no difference between mRDCI of 1 and 0, while the mRDCI≥2 group separated after approximately 1 year. These curves were difficult to interpret as they suggested: 1) discontinuation was assessed at large intervals of discrete time, and 2) >90% of those with mRDCI 0 or 1, but 0% of those with mRDCI≥2, remained on treatment at end of follow-up (approximately 60 months). The second study, by Lindström et al [118], examined risk of TNFi discontinuation in unadjusted Cox models for each of: cardiovascular disease (HR 1.24; 1.08 to 1.43), affective disorder (HR 1.81; 1.54 to 2.13), chronic lung disease (HR 1.49; 1.22 to 1.82), malignancy (HR 1.36; 1.06 to 1.74), diabetes (HR 1.36; 0.99 to 1.87) and chronic kidney disease (HR 0.79; 0.41 to 1.52). The third study used an earlier sample of 335 BSRBR-AS participants to show continuous comorbidity count as a predictor of binary response [134]. The investigators showed each additional comorbidity to reduce odds of achieving clinically important improvement in ASDAS (≥1.1) by 43% (95%CI 0.37 to 0.88) and ASDAS<2.1 by 40% (95%CI 0.38 to 0.95) within 10 weeks to 9 months of treatment initiation. These prediction models assumed a log-linear relationship between outcomes and each additional comorbidity, which was shown not to be the case in this study.

Another limitation of these prior studies is that they used only binary definitions of response. To summarise, the decision to adjust for baseline disease activity or not are both fraught with potential bias. By analysing three types of outcomes, this chapter highlights the importance of interpreting each result in the context of the others. For example, it is reasonable to tell patients with comorbidities that they may have lower odds of achieving 'low disease activity' states, but the absolute degree of improvement from pre-treatment disease activity is comparable to those with no comorbidities. Communicating the influence of comorbidities to patients should be more nuanced, depending on whether degree of improvement or a fixed low level of disease activity is more important to the individual.

Existing definitions of response as used for prescribing guidelines, for example in the UK, may need to be reconsidered: a patient starting TNFi with BASDAI of 7 will have higher odds (by 25% in this data) of achieving BASDAI 50/2, while simultaneously having lower odds of BASDAI<4 (by 32%), than an identical individual with starting BASDAI of 6. Which definition of response is more relevant for health-economics remains to be determined. Lastly, many comorbid patients would have been ineligible for randomised controlled trials; this study provided unique insights into how therapeutic effects on function and quality of life differed in comorbid patients – highlighting the need to optimise comorbidities not just axSpA.

The most clinically significant effect sizes came from time-to-event analyses. Interestingly, the association between comorbidity count and TNFi discontinuation was limited to males. Male participants with 1 comorbid condition had similar hazard rate of treatment discontinuation as those with no comorbidities, which concurs with analyses of binary and absolute responses. Male participants with 2 comorbidities had 68% higher hazard rates and ≥3 comorbidities over 5-fold higher. The same was not observed among the female population. Note that the large effect size showing reduced risk of TNFi discontinuation in females with ≥3 comorbidities had a wide confidence interval, arising from just 10 individuals; therefore, it should not be interpreted as being protective. The reasons for these findings are unclear. Data on causes of discontinuation in the BSRBR-AS had limitations (see Methods above) that precluded inclusion into primary analyses; causes did not differ according to gender or the presence of comorbidities (data not shown).

Males had higher prevalence of diabetes but lower prevalence of depression. The high prevalence of depression among female participants and the lack of association between comorbidity count and TNFi discontinuation are not consistent with existing evidence that: 1) depression was negatively associated with disease severity (as shown in prior chapters) and 2) mental health symptoms was a negative predictor of binary treatment response in MacFarlane and colleagues' analysis of the BSRBR-AS [134]. It is also notable that having only one comorbidity was not associated with treatment response or discontinuation, when the commonest condition among those with one single comorbidity was depression (40%, see Figure 6.3). More research is needed to further dissect the role of depression as an independent comorbidity, particularly gender differences in prevalence and symptom reporting.

6.5.1 Strengths and limitations

The strengths of the BSRBR-AS dataset have been discussed in detail in the previous chapter. The systematic approach of the current analysis – using different approaches for comorbidity and outcome variables – provided a contextual overview that prior studies lacked [114,118,134]. Results were also robust to a battery of sensitivity analyses testing several assumptions. There were, however, limitations. Most importantly is the causal interpretation of the role of comorbidity: Did the presence of comorbidities *cause* blunted improvement in function and quality of life and increased treatment discontinuation among males? It would be inappropriate to confidently attribute a causal relationship with treatment response, since many comorbidities are not 'manipulatable' (i.e., one cannot 'assign' individuals to having a *history* of a certain comorbidity in an RCT). Using comorbidity history collected at baseline meant that the complex time-varying relationship between comorbidities and disease activity, before and after TNFi initiation, could not be captured.

Results from analyses of binary response definitions suggested clinically meaningful effect sizes but lacked precision. Results from analysis of change over time should be interpreted with one important caveat: participants who did not respond by the first assessment (usually after 3 months) or those who lost response would have had their treatment stopped under NICE guidance [190]; therefore, record of such high disease activity would be censored. However, such informative censoring should not affect data within the first 3 months [42]. This may help explain the dramatic difference between the relatively unimpressive effect sizes of the response analyses compared to treatment discontinuation. Lastly, analyses of comorbidity count assume that individual comorbidities affect the outcomes equally. This is unlikely to be true and larger studies are required to examine relative contributions of individual conditions in the context of overall comorbidity burden.

6.6 Summary

Participants with multiple (≥2) comorbidities had reduced absolute improvement in function and health-related quality of life compared to those without. Overall, participants with comorbidities generally had reduced odds of achieving binary response definitions compared to those with none, although most effect estimates were small and with uncertainty. They also had significantly higher rate of TNFi discontinuation. Taken together, results can be used to better inform clinicians and educate patients about the likelihood of response to the first TNFi given baseline comorbidity status. Further research is needed to identify potentially modifiable comorbidities that may improve response. This will be the topic of the next Chapter.

Chapter 7: Depression and anxiety and response to TNF inhibitors

This chapter uses longitudinal data from the BSRBR-AS to examine the impact of baseline depression and anxiety on response to TNF inhibitors. This thesis set out to study comorbidities in general, without a priori aims to focus on a single disease group. However, previous chapters have each pointed towards mental health as an important factor in axSpA management.

7.1 Introduction

Symptoms of axSpA commonly begin in early adulthood, which can be a critical time for education, career, and relationships. The consequence of these disruptive symptoms on mental health is compounded by the often-significant delays to diagnosis and treatment [10]. Depression is well-known to influence the experience and reporting of symptoms [231]. This is particularly relevant for assessment of axSpA disease activity, since indices are mostly (e.g., ASDAS) or entirely subjective (BASDAI and spinal pain). Though a recent systematic review identified numerous studies that consistently showed depression to be associated with disease activity [9], none have examined whether they influence longitudinal treatment outcomes.

This chapter includes an in-depth assessment of depression and anxiety and their associations with treatment response. These two mental health comorbidities were chosen because they are the most prevalent and were available in the BSRBR-AS. Studying depression presents unique challenges – namely under-diagnosis and documentation – that can be addressed using the BSRBR-AS data. Diagnosis of depression and depressive symptoms (according to the Hospital Anxiety and Depression Score, HADS) were both recorded to allow comparison.

Unlike other chronic comorbidities, symptoms of depression and anxiety are potentially modifiable, for example, by pharmacological or talking therapies [232]. Estimating the impact of potential mental health interventions on TNFi response could help inform future clinical trials or guidelines. Finding modifiable factors to improve TNFi response is important since up to half do not respond adequately [228] and the number of therapeutic options remains relatively limited compared to rheumatoid arthritis.

7.2 Aims

1. To describe correlations between symptoms and diagnosis of depression.
2. To examine the association between history of depression at baseline and response to TNFi.
3. To examine the association between baseline symptoms of depression or anxiety and response to TNFi.

7.3 Methods

7.3.1 Patient population

Participants in the BSRBR-AS who started on their first TNFi (including those who switched from the non-biologic group) were eligible for inclusion in this analysis. Eligible individuals were required to have a clinic visit or questionnaire within 1 year before, or 7 days after, the TNFi start date, from which the baseline values of time-varying data (i.e., measures of disease activity and severity) were obtained. For aims relating to baseline symptoms of depression or anxiety, only those who completed the baseline HADS questionnaire were eligible.

7.3.2 'Exposures' – baseline depression and anxiety

7.3.2.1 History of depression

The BSRBR-AS recorded physician-confirmed diagnosis (or 'past medical history') of depression as a binary variable. In clinical practice, depression typically remains on a patient's list of diagnoses only when it is currently relevant (i.e., ongoing symptoms or treatment), whereas a resolved depressive episode from many years ago should not. This assumption is difficult to test since the time of diagnosis was not recorded, and reflects the challenges of studying a condition with dynamic symptoms over time. Therefore, mental health symptoms at TNFi initiation were also examined.

7.3.2.2 Symptoms of depression and anxiety

Symptoms of depression and anxiety were measured using the HADS. The original description of the HADS use each sub-scale to describe 'case-ness' (i.e., presence) of depression or anxiety using the following thresholds: 0-7 indicating 'non-cases', 8-10 'doubtful cases', 11-21 'cases' [176,177]. These thresholds were not validated for diagnosis

or classification purposes. For example, the HADS depression sub-scale (HADS-D) does not include all components relevant for diagnostic criteria of depression according to Diagnostic and Statistical Manual of Mental Disorders (e.g., appetite, sleep, and self-harm). HADS-D≥8 was reported to have a sensitivity of 82% and specificity of 74% for major depressive disorder; the corresponding performance for ≥11 was 56% and 92%, respectively [233]. For HADS-A≥8, sensitivity was reported as 90% and specificity 78% [234].

Since HADS reflects symptom severity, commonly used thresholds were labelled as the following: mild (8-10), moderate (11-14) and severe (≥15). Snaith described the 0-7 category as 'being in the normal range' [176]. For convenience, this category was referred to as 'none' (though this includes less than 'mild' symptoms). For models, the moderate and severe groups (i.e., scores ≥11) were combined due to their small numbers.

7.3.3 Outcomes

Outcomes included: 1) binary response (BASDAI 50/2, ASDAS-MI, BASDAI<4, ASDAS<2.1) at 6 months, 2) absolute improvement in disease activity over the first 3 years, and 3) time to treatment discontinuation. In this chapter, only absolute improvement in disease activity (i.e., BASDAI, ASDAS, spinal pain) were considered. This is because causal pathways involving 'downstream' outcomes (e.g., sleep or quality of life that may be mediated by improvement in both disease activity and mental health symptoms) invoke greater complexity and number of assumptions.

7.3.3 Covariates

The following covariates were included: age, gender (female as reference), BMI, Index of Multiple Deprivation (IMD, as a continuous variable) and educational attainment (as dummy variables). Additional covariates included: elevated CRP (defined as per ASAS classification criteria; low as reference), comorbidity count (continuous variable), and baseline values of each outcome measure. Inflammation, measured here using CRP, is a potential confounder since 1) it is suggested to have a causal role in depression [235], 2) 'high CRP' has been shown to be associated with response [236], and 3) depression is less likely to cause elevated CRP, unlike many other comorbidities. The dichotomous variable 'elevated CRP' (recorded for eligibility purposes) was used instead of CRP levels because the latter had higher proportion of missing values at baseline. The presence of other comorbidities may also be a confounder since they will influence mental health and

response. Baseline disease activity was additionally included as a covariate in the marginal models (see below).

Sensitivity analyses additionally included baseline smoking/alcohol status and HLA-B27 status as covariates. Prevalence of HLA-B27 positivity differed between those with and without depression, and has been shown to predict response [236].

7.3.4 Statistics

7.3.4.1 History of depression (Aim 2)

For analyses using history of depression as the independent variable, logistic regression was used for binary response definitions, mixed effects model for change in continuous outcome indices over time (using interaction terms between depression diagnosis and time), and Cox models for time to treatment discontinuation; that is, the same conditional approaches as used in the previous chapter, replacing comorbidity with depression diagnosis. All analyses were adjusted for the above covariates.

These approaches describe association between history of depression and diagnosis, which is inherent in *conditional* models and when using an exposure that cannot be modified (it is not possible to modify a past medical history of depression) [237]. By contrast, symptoms of depression can be modified, thus a *marginal* approach was used to estimate the potential impact of mental health interventions on TNFi response. Further discussion on conditional vs. marginal approaches are given in Appendix 10.6.

7.3.4.2 Symptoms of depression or anxiety (Aim 3)

For symptoms of depression and anxiety, marginal approaches were used: inverse-probability (IP) weighted logistic regression for binary outcomes, IP weighted GEE for absolute response, and marginal structural Cox models (i.e., IP weighted pooled logistic regression) for time to treatment discontinuation. IP weights aim to balance all covariates in the weighted model, thus the outcome models were not additionally adjusted for ('conditioned on') any additional variables.

Marginal approaches estimate the potential change in TNFi response *at the group level* (akin to randomised controlled trials) if mental health symptoms were modified. Studying the causal effect of baseline mental health status has some conceptual challenges. For example, a hypothetical intervention would need to successfully improve baseline mental health symptoms and also their prior history (of unknown duration); this is not equivalent

to a mental health intervention administered at TNFi initiation, but can be considered as one delivered (at an unknown time) before. Nevertheless, IPTW methods are still useful for 'unconfounded descriptive comparisons' [238].

7.3.4.3 Inverse-probability weights

IPTWs were originally devised to compare treatments (hence 'treatment' weights). Although the exposure here is prevalent mental health symptoms, the term 'IPTW' is retained to distinguish it from inverse probability of censoring weights (IPCW, discussed later). IPTWs, in effect, create a hypothetical ('pseudo'-)population where some individuals are upweighted (represented more than once) and others are down-weighted, such that the weighted populations have comparable values of all covariates.

Detailed descriptions of IPTW are given in Appendix 10.6.1. In brief, the numerator was the predicted probability from multinomial logistic model with three-level HADS-categories as the only variable, and the denominator was the same model conditioned on all covariates. This approach to confounding has an important advantage over inclusion of the baseline covariates in the outcome model. IPTW accounts for baseline disease activity without adjusting for it [42]. Baseline covariate balance was checked in the weighted population; one example (balancing between HADS-D groups) is provided in the Results for demonstration.

The marginal risk of treatment discontinuation can be estimated using a marginal approach to Cox models (e.g., standardisation or IPTW). However, an important assumption is that censoring is random; that is, censoring should not differ between exposure groups conditioning on covariates. This can be remediated using IPCWs. Its numerator is the probability of being uncensored at month t, given the individual was uncensored at month t-1, the exposure history (unchanged baseline mental health symptoms) and baseline covariates. The denominator is the same but additionally adjusting for the history of time-varying disease activity.

The product of two weights – baseline time-invariant IPTW and time-varying IPCW – was used in a pooled logistic regression model. Pooled logistic regression is equivalent to a Cox model since the event hazard is small at each time point [239]. (For demonstration, the equivalence of Kaplan-Meier and Cox proportional hazard models using this data is shown in the Appendix 10.6.3). All weights were examined for means close to 1 and extreme values (summary statistics on weights provided in Appendix 10.6: Table S7.3).

To generate the above weights, multinomial logistic models required complete data for all covariates. Multiple imputation was therefore performed (see Chapter 3, Section 3.5.8).

7.3.4.4 Gender interaction

Since treatment discontinuation differed by gender in the previous chapter, and that depression and anxiety are more prevalent among females [240], all analyses took gender into consideration. For descriptive statistics (Aim 1), results were stratified by gender where relevant. For models (Aims 2 and 3), interaction terms were used (e.g., gender-by-depression interaction in the logistic and survival analyses, or gender-by-depression-by-time interaction in the repeated measure analyses). Adding interaction terms into marginal structural models does not require their inclusion into the weights [237].

7.3.4.5 Power considerations

Power considerations were analogous to the previous chapter for analyses using history of depression. Conducting a priori power calculations for analyses using IPTW is difficult since such a calculation is dependent on the weights, which are only known after the analysis has been conducted. In general, IPTW reduces the statistical power [241] through the need for robust standard errors.

7.3.5.6 Sensitivity analyses

First, all analyses were repeated with IP weights including baseline smoking, HLA-B27, and alcohol status. Since HADS sub-scales are correlated with disease activity, HADS categories may have poor overlap in distribution of disease activity (and other covariates). Models that extrapolate to non-overlap areas have limited causal interpretation. In the second sensitivity analysis, overlap was ensured using matching weights, which replaced the numerator with the smallest value weight of the other comparator groups and in doing so emulates a (multi-group propensity score) matched population [242]. Lastly, missing binary outcomes were imputed as response if patients remained on drug for longer than one year (see Section 6.3.3.1).

7.4 Results

Participants with a history of depression at baseline were more often female than those without history of depression at baseline; they were also more frequently current smokers and resided in more deprived areas (Table 7.1). Participants with comorbid depression also had higher disease activity across all three indices. The mean age and proportion of those meeting the modified New York criteria for AS were similar between those with and without a history of depression, but HLA-B27 positivity was significantly more common among those without depression. Those with depression more frequently had other comorbidities, including hypertension, asthma, peptic ulcer, diabetes, and ischaemic heart disease.

Table 7. 1: Baseline characteristics of 994 participants compared according to history of depression diagnosis.

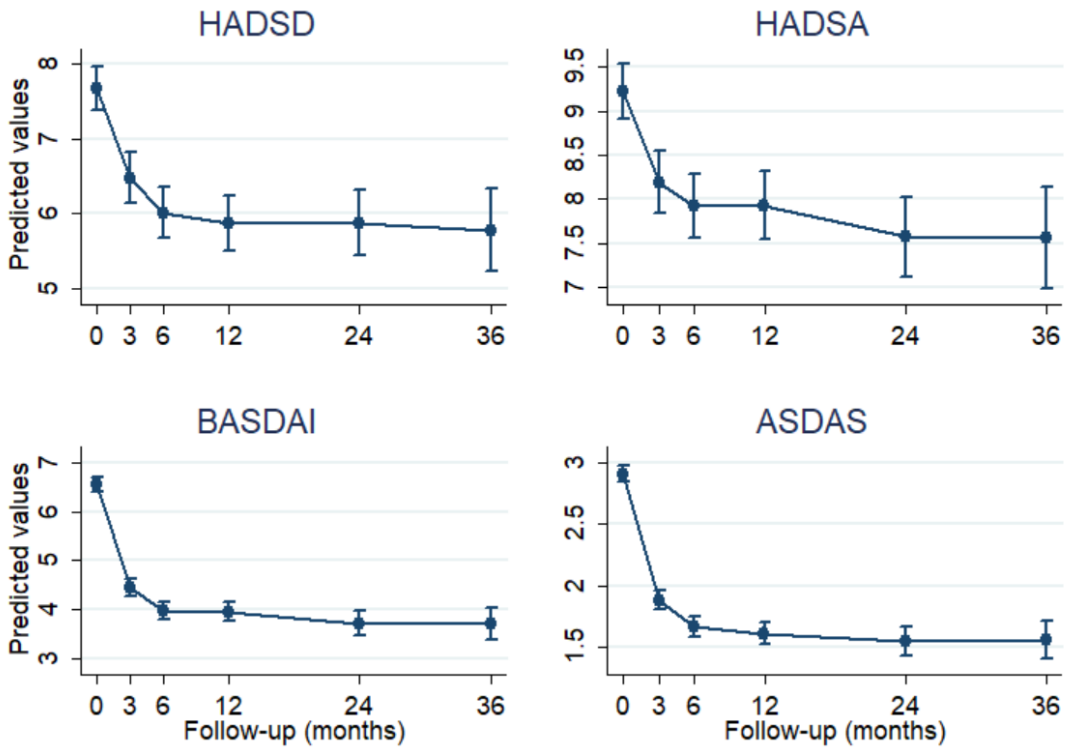
		axSpA with history of depression (n=145)	axSpA without history of depression (n=849)	P-value
Age, years		43.7 (12.0)	44.9 (13.7)	0.35
Males		84 (58%)	595 (70%)	0.005
Meeting modified New York criteria		85 (59%)	512 (60%)	0.71
Age at symptom onset, years		27.0 (10.5)	28.9 (11.4)	0.056
Symptom duration, years		16.7 (11.7)	15.9 (12.8)	0.47
HLA-B27 positive*		67 (64%)	473 (76%)	0.015
BMI, kg/m^2		28.4 (6.5)	28.0 (5.7)	0.45
Smoking status	Never smoked	31 (24%)	320 (43%)	<0.001
	Ex-smoker	43 (33%)	248 (33%)	
	Current smoker	57 (44%)	184 (24%)	
Education	Secondary school	43 (33%)	246 (33%)	0.42
	Apprenticeship	9 (7%)	73 (10%)	
	Further education college	52 (40%)	224 (30%)	
	University degree	19 (15%)	159 (21%)	
	Further degree	8 (6%)	45 (6%)	
Deprivation index		3.0 (1.4)	3.4 (1.5)	0.002
NSAID use in past 6 months		107 (74%)	627 (75%)	0.76
DMARD use in past 6 months		19 (13%)	127 (15%)	0.61
BASDAI, median (IQR)		7.4 (6.2, 8.5)	6.6 (5.2, 7.7)	<0.001
Spinal pain, median (IQR)		7.0 (7.0, 8.0)	7.0 (5.0, 8.0)	<0.001
ASDAS		3.1 (0.8)	2.8 (0.8)	<0.001
Hypertension		24 (16.6%)	82 (9.7%)	0.019
Asthma		24 (16.6%)	62 (7.3%)	<0.001
Peptic ulcer disease		10 (6.9%)	18 (2.1%)	0.004
Diabetes mellitus		9 (6.2%)	16 (1.9%)	0.006
Cancer		3 (2.1%)	13 (1.5%)	0.72
Ischaemic heart disease		7 (4.8%)	8 (0.9%)	0.003
Tuberculosis		1 (0.7%)	14 (1.6%)	0.71
Renal disease		5 (3.4%)	6 (0.7%)	0.014
COPD		6 (4.1%)	4 (0.5%)	0.001
Stroke		1 (0.7%)	6 (0.7%)	1.00
Liver disease		2 (1.4%)	5 (0.6%)	0.27
Heart failure		1 (0.7%)	5 (0.6%)	1.00
Demyelinating disease		0	2 (0.2%)	1.00

Data shown as mean (SD) and n (%) unless otherwise indicated.
ASDAS, AS disease activity score; ASQoL, AS quality of life questionnaire; BASDAI, Bath AS disease activity index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DMARD, disease modifying antirheumatic drug.

7.4.1 Comparison of depression diagnosis and symptoms

HADS was completed by 742 (75%) participants at baseline. Those who did not complete the HADS at baseline were younger (43 vs. 45 years, p=0.005) but otherwise had similar characteristics to participants included in the analysis (Appendix 10.6: Table S7.1). The mean values for the depression and anxiety sub-scale scores were 7.6 (SD 4.1) and 9.2 (SD 4.4), respectively. Average HADS over time showed that symptoms of both depression and anxiety improved after commencing TNFi (Figure 7.1).

Figure 7. 1: Change in HADS sub-scale scores after TNFi initiation, shown alongside change in disease activity.



HADSD, HADS depression sub-scale; HADSA, HADS anxiety sub-scale; BASDAI, Bath AS disease activity index; ASDAS, AS disease activity score

Baseline HADS-depression categories were poorly concordant with history of depression diagnosis (Table 7.2). A quarter of those with history of depression reported HADS values consistent with no depressive symptoms, while 1 in 5 without a history of depression reported at least moderate levels of depression symptoms.

Table 7. 2: Proportion of patients in each HADS depression category according to history of depression.

	axSpA with history of depression (n=145)	axSpA without history of depression (n=849)	p-value
None	31 (27%)	343 (55%)	<0.001
Mild	31 (27%)	161 (26%)	
Moderate	30 (27%)	98 (16%)	
Severe	21 (19%)	27 (4%)	
HADS-D, depression sub-scale. HADS categories: None, ≤7; Mild 8-10; Moderate, 11-14; Severe ≥15.			

HADS depression and anxiety sub-scale scores were highly collinear; those with each category of depression symptoms generally had the similar level of anxiety or none (Table 7.3).

Table 7. 3: Association between HADS anxiety and depression sub-scale categories.

		HADS-D				
		None n=374	Mild n=192	Moderate n=128	Severe n=48	Total N=742
HADS-A	None n=278	218 (58%)	43 (22%)	16 (13%)	1 (2%)	37%
	Mild n=169	86 (23%)	55 (29%)	25 (20%)	3 (6%)	23%
	Moderate n=205	58 (16%)	72 (38%)	57 (45%)	18 (38%)	28%
	Severe n=90	12 (3%)	22 (11%)	30 (23%)	26 (54%)	12%
	Total n=742	100%	100%	100%	100%	100%
HADS-D, depression sub-scale; HADS-A, anxiety sub-scale. Each range from 0 to 21. HADS categories: None, ≤7; Mild 8-10; Moderate, 11-14; Severe ≥15.						

Despite their collinearity, there were subtle differences in baseline characteristics according to HADS anxiety (Table 7.4) and depression categories (Table 7.5). Age and gender were comparable between the four HADS-depression categories. By contrast, increasing severity of anxiety was associated with younger age. Participants reporting mild to severe depressive symptoms had higher BMI compared to those reporting no depressive symptoms, whereas BMI were comparable between anxiety categories. Increasing levels of anxiety and depression were each associated with higher proportions of current and ever smoking and residing in areas with greater deprivation. Participants reporting increasing levels of anxiety or depression also had significantly higher disease activity.

Table 7. 4: Baseline characteristics compared according to baseline HADS depression categories.

		None (n=374)	Mild (n=192)	Moderate (n=128)	Severe (n=48)	P-value
Age, years		45.3 (14.6)	45.5 (13.6)	46.6 (13.0)	42.7 (12.0)	0.44
Males		248 (66%)	133 (69%)	83 (65%)	32 (67%)	0.85
Meeting modified New York criteria		221 (59%)	118 (61%)	69 (54%)	27 (56%)	0.58
Age at symptom onset, years		28.0 (10.7)	29.5 (12.2)	29.8 (12.9)	28.5 (10.8)	0.32
Symptom duration, years		17.3 (13.4)	16.0 (12.5)	16.8 (13.6)	14.2 (11.3)	0.39
HLA-B27 positive		218 (78%)	106 (75%)	70 (74%)	20 (59%)	0.13
BMI, kg/m^2		27.2 (5.2)	29.0 (6.1)	28.9 (6.3)	28.5 (7.1)	0.005
Smoking status	Never smoked	187 (50%)	64 (33%)	41 (32%)	6 (13%)	<0.001
	Ex-smoker	118 (32%)	67 (35%)	42 (33%)	16 (34%)	
	Current smoker	69 (18%)	61 (32%)	45 (35%)	25 (53%)	
Education	Secondary school	107 (29%)	71 (37%)	51 (40%)	22 (50%)	0.006
	Apprenticeship	36 (10%)	16 (8%)	14 (11%)	4 (9%)	
	Further education college	110 (29%)	62 (33%)	40 (31%)	15 (34%)	
	University degree	93 (25%)	34 (18%)	20 (16%)	2 (5%)	
	Further degree	28 (7%)	7 (4%)	3 (2%)	1 (2%)	
Deprivation index		2.9 (1.4)	3.1 (1.4)	3.1 (1.4)	3.7 (1.3)	<0.001
NSAID use in past 6 months		277 (75%)	138 (74%)	89 (70%)	34 (74%)	0.74
DMARD use in past 6 months		44 (12%)	25 (14%)	31 (25%)	7 (15%)	0.009
BASDAI, median (IQR)		6.0 (4.5, 7.2)	7.0 (6.0, 7.8)	7.4 (6.4, 8.6)	8.6 (7.7, 9.6)	<0.001
Spinal pain, median (IQR)		6.0 (4.0, 7.0)	7.0 (6.0, 8.0)	7.5 (6.0, 8.0)	8.0 (7.0, 9.0)	<0.001
ASDAS		2.6 (0.8)	3.1 (0.7)	3.2 (0.7)	3.6 (0.6)	<0.001
History of depression		31 (8%)	31 (16%)	30 (23%)	21 (44%)	<0.001
HADS depression sub-scale		7.0 (3.7)	10.1 (3.5)	11.9 (3.6)	14.8 (3.6)	<0.001
HADS anxiety sub-scale		4.2 (2.0)	8.9 (0.8)	12.1 (1.1)	16.4 (1.1)	<0.001

Data shown as mean (SD) and n (%) unless otherwise indicated.
IQR, interquartile range; BMI, body mass index; BASDAI, Bath AS disease activity index; ASDAS, AS disease activity score; BASFI, Bath AS functional index; ASQoL, AS quality of life questionnaire.

Table 7. 5: Baseline characteristics compared according to HADS anxiety categories.

		None (n=278)	Mild (n=169)	Moderate (n=205)	Severe (n=90)	P-value
Age, years		47.0 (14.7)	45.5 (13.9)	44.6 (13.0)	42.0 (12.9)	0.021
Males		188 (68%)	120 (71%)	131 (64%)	57 (63%)	0.44
Meeting modified New York criteria		165 (59%)	106 (63%)	118 (58%)	46 (51%)	0.33
Age at symptom onset, years		28.3 (11.6)	29.3 (11.1)	28.8 (11.5)	28.8 (12.4)	0.84
Symptom duration, years		18.7 (13.4)	16.2 (13.1)	15.8 (12.7)	13.2 (12.1)	0.003
HLA-B27 positive		174 (81%)	83 (70%)	112 (74%)	45 (70%)	0.092
BMI, kg/m^2		27.8 (5.5)	27.8 (5.1)	28.7 (6.6)	27.8 (6.0)	0.36
Smoking status	Never smoked	138 (50%)	70 (41%)	69 (34%)	21 (23%)	<0.001
	Ex-smoker	90 (32%)	61 (36%)	72 (35%)	20 (22%)	
	Current smoker	50 (18%)	38 (22%)	63 (31%)	49 (54%)	
Education	Secondary school	89 (32%)	60 (36%)	70 (35%)	32 (36%)	0.20
	Apprenticeship	29 (10%)	14 (8%)	19 (9%)	8 (9%)	
	Further education college	81 (29%)	42 (25%)	76 (38%)	28 (32%)	
	University degree	62 (22%)	45 (27%)	27 (13%)	15 (17%)	
	Further degree	16 (6%)	8 (5%)	10 (5%)	5 (6%)	
Deprivation index		2.8 (1.4)	3.0 (1.3)	3.1 (1.4)	3.3 (1.4)	0.015
NSAID use in past 6 months		205 (75%)	125 (75%)	146 (73%)	62 (69%)	0.63
DMARD use in past 6 months		43 (16%)	18 (11%)	35 (18%)	11 (12%)	0.31
BASDAI, median (IQR)		5.9 (4.4, 7.2)	6.6 (5.5, 7.4)	7.3 (6.1, 8.3)	7.7 (6.7, 8.9)	<0.001
Spinal pain, median (IQR)		6.0 (4.0, 8.0)	7.0 (5.0, 8.0)	7.0 (6.0, 8.0)	8.0 (7.0, 9.0)	<0.001
ASDAS		2.6 (0.9)	2.9 (0.7)	3.0 (0.7)	3.2 (0.9)	<0.001
HADS depression sub-scale		4.7 (1.9)	9.0 (0.8)	12.1 (1.0)	16.7 (1.6)	<0.001
HADS anxiety sub-scale		5.0 (3.2)	7.4 (3.2)	9.4 (3.5)	11.9 (3.9)	<0.001

Data shown as mean (SD) and n (%) unless otherwise indicated. IQR, interquartile range; BMI, body mass index; BASDAI, Bath AS disease activity index; ASDAS, AS disease activity score; BASFI, Bath AS functional index; ASQoL, AS quality of life questionnaire.

7.4.2 History of depression vs. treatment outcomes (conditional models)

7.4.2.1 History of depression vs. binary response

The proportion of participants achieving binary response according to each definition is (Table 7.6). As observed in the previous chapter, models for low disease activity (BASDAI<4 and ASDAS<2.1) showed reduced effect sizes after adjusting for baseline values, while effect sizes increased after such adjustment for models of BASDAI 50/2 and ASDAS-MI. Using conservative effect sizes (i.e., baseline adjustment for low disease activity thresholds, but not for BASDAI 50/2 and ASDAS-MI), odds of response was 25 to 47% lower in those with a history of depression than those without.

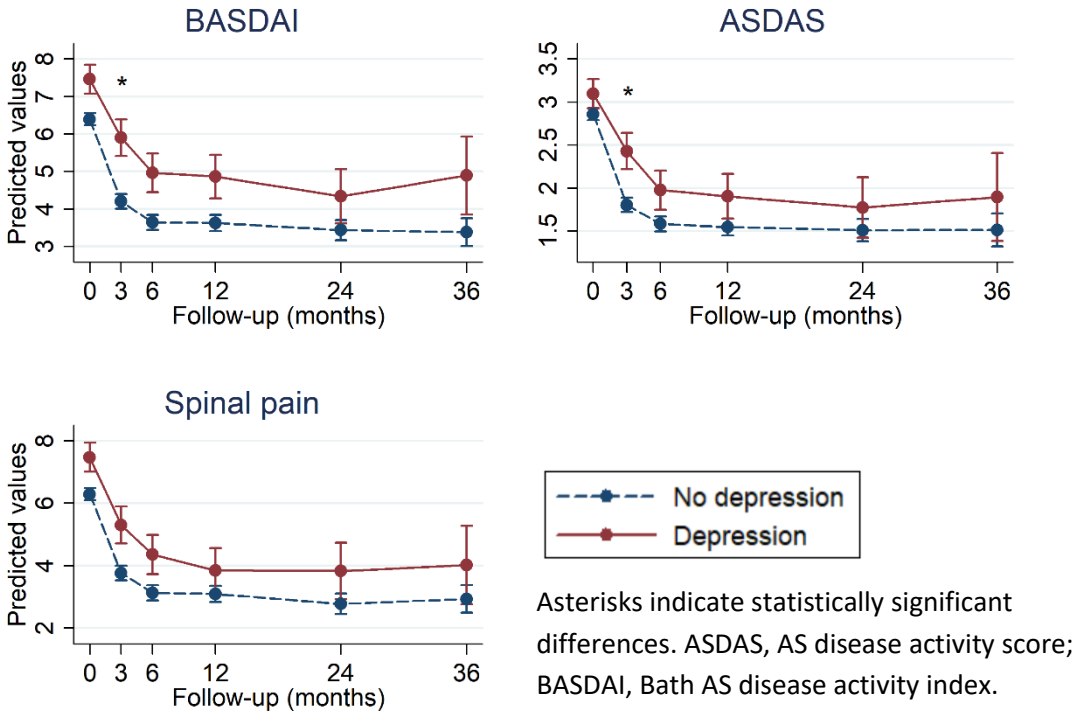
Table 7. 6: Association between history of depression and binary response at 6 months.

	No. achieving response	**Odds ratio without adjusting for baseline disease activity***	**Odds ratio additionally adjusting for baseline disease activity***
BASDAI 50/2	307 (56%)	0.69 (0.40, 1.19)	**0.54 (0.31, 0.96)**
ASDAS-MI	130 (26%)	0.75 (0.36, 1.56)	0.52 (0.23, 1.16)
BASDAI<4	311 (57%)	**0.56 (0.32, 0.99)**	0.73 (0.41, 1.32)
ASDAS<2.1	168 (34%)	**0.50 (0.25, 0.99)**	0.53 (0.26, 1.07)
*Logistic models adjusted for age, gender, BMI, Index of Multiple Deprivation, education, elevated CRP, comorbidity count; full model coefficients shown in Appendix 10.6: Table S7.2. Bold text highlights statistically significant results. BASDAI 50/2, 50% or 2-unit reduction in BASDAI; ASDAS-MI, major improvement i.e. ≥2-unit reduction.			

7.4.2.2 History of depression vs. continuous response (absolute improvement)

Improvements in BASDAI and ASDAS were numerically greater in those without history of depression at baseline, although interaction terms were only statistically different for BASDAI and ASDAS at month 3 (Figure 7.2). For example, BASDAI improvement at month 3 was 0.6 units (95% CI 0.05 to 1.13) greater for those without history of depression (Table 7.7). Interaction terms overall were not statistically significant in any models; differences between groups were also smaller than the clinically important effect size (i.e., smaller than 1 unit for BASDAI and spinal pain, 1.1 units for ASDAS).

Figure 7. 2: Change in disease activity in response to TNF inhibitors according to history of depression at baseline.



Asterisks indicate statistically significant differences. ASDAS, AS disease activity score; BASDAI, Bath AS disease activity index.

Table 7. 7: Coefficients from mixed effects models of history of depression vs. disease activity over time.

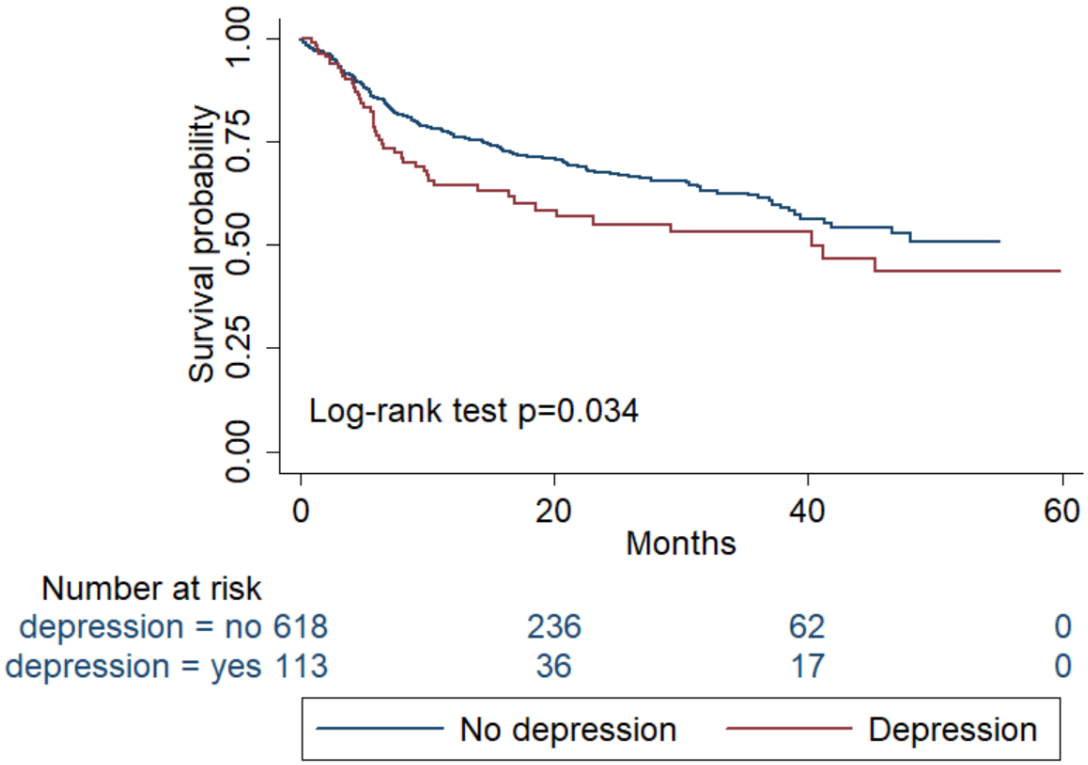
	BASDAI	ASDAS	Spinal pain
N	1998	1872	2009
Constant	5.77 (4.88 to 6.66)	2.15 (1.78 to 2.53)	6.22 (5.20 to 7.25)
3.FU	-2.16 (-2.36 to -1.96)	-1.05 (-1.14 to -0.96)	-2.49 (-2.74 to -2.24)
6.FU	-2.7 (-2.90 to -2.50)	-1.27 (-1.37 to -1.18)	-3.07 (-3.33 to -2.82)
12.FU	-2.67 (-2.89 to -2.46)	-1.3 (-1.40 to -1.19)	-3.07 (-3.34 to -2.79)
24.FU	-2.84 (-3.12 to -2.57)	-1.32 (-1.46 to -1.19)	-3.39 (-3.73 to -3.05)
36.FU	-2.96 (-3.33 to -2.59)	-1.34 (-1.54 to -1.15)	-3.35 (-3.79 to -2.90)
Depression*	0.71 (0.28 to 1.14)	0.16 (-0.02 to 0.35)	0.74 (0.23 to 1.25)
3.FU#Depression	**0.59 (0.05 to 1.13)**	**0.34 (0.09 to 0.59)**	0.34 (-0.34 to 1.02)
6.FU#Depression	0.50 (-0.06 to 1.06)	0.26 (-0.001 to 0.52)	0.31 (-0.40 to 1.02)
12.FU#Depression	0.29 (-0.33 to 0.92)	0.18 (-0.11 to 0.48)	-0.31 (-1.10 to 0.49)
24.FU#Depression	-0.01 (-0.79 to 0.77)	0.09 (-0.30 to 0.48)	0.07 (-0.92 to 1.05)
36.FU#Depression	1.03 (-0.07 to 2.14)	0.36 (-0.20 to 0.91)	0.52 (-0.83 to 1.87)

*Depression vs. none. FU, follow-up at numbered month. #, interaction term.
Bold text highlights statistically significant results.
Mixed models adjusted for age, gender, BMI, Index of Multiple Deprivation, education, elevated CRP, comorbidity count; covariate coefficients omitted.

7.4.2.3 History of depression vs. time to treatment discontinuation

Of the 994 participants that started TNFi, 18 (1.8%) did not have any post-baseline data and were each assigned one minute of follow-up time. The remaining 976 subjects had 1441 person-years of follow-up, with a mean of 17 (SD 15) months and median of 12 (IQR 6 to 27) months. Patients with history of depression at baseline had a significantly higher risk of drug discontinuation (Figure 7.3).

Figure 7. 3: Kaplan-Meier curves comparing drug survival between participant with and without a history of depression.

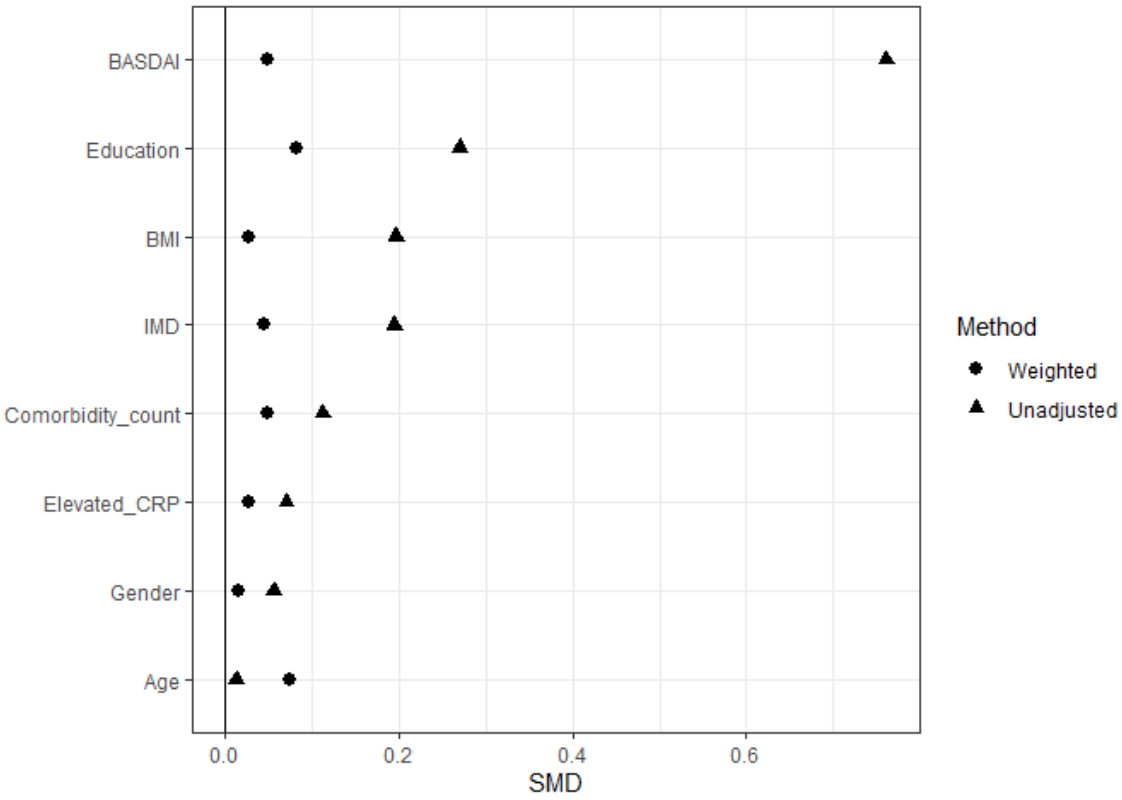


In multivariable (conditional) Cox models, the variable high-CRP violated the proportional hazards assumption and was stratified in the models. The hazard rate of TNFi discontinuation in the group with a history of depression was higher (HR1.17; 95%CI 0.81 to 1.68) than those without a history of depression, but the estimate lacked precision.

7.4.3 Baseline symptoms of depression/anxiety vs. treatment outcomes (marginal models)

This section compares each response definition according to baseline HADS categories. The group categorised as 'none' (i.e., sub-scale <8) was used as the referent. Covariates were balanced using IPTWs (Figure 7.4). All models in this section are marginal (i.e., without covariates). The only exception is for testing gender interactions (Section 7.4.4), where two additional variables – gender and comorbidity-by-gender interaction – were added. All IPTWs had a mean of 1 (see Appendix 10.6: Table S7.3).

Figure 7. 4: Standardised mean differences in each variable before and after inverse probability weighting.

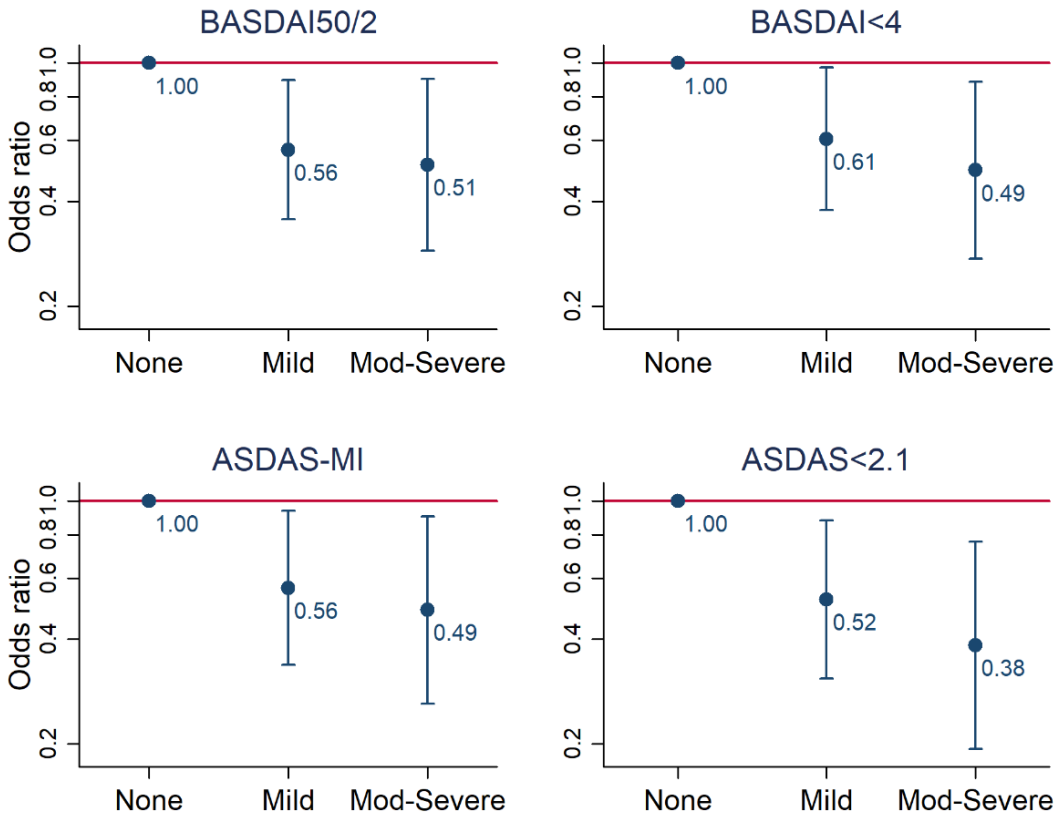


IPTW for analysis of HADS depression categories is shown. SMD <0.1 indicates negligible difference. BASDAI, Bath AS disease activity index; IMD, index of multiple deprivation; SMD, standardised mean difference.

7.4.3.1 Baseline symptoms vs. binary response

The number of individuals included for analysis was 542 for BASDAI-based and 492 for ASDAS-based outcomes. BASDAI50/2 was achieved by 304 (56%), BASDAI<4 by 308 (57%), ASDAS-MI by 129 (26%) and ASDAS<2.1 by 167 (34%). Odds of achieving binary response reduced with increasing severity of baseline depression symptoms (Figure 7.5). In the weighted logistic models, groups with moderate-severe HADS-depression had around half the odds of achieving BASDAI 50/2, BASDAI<4 and ASDAS-MI, and 62% lower odds of ASDAS<2.1 compared to the 'none' group, after accounting for all covariates including differences in baseline BASDAS or ASDAS. Groups with mild depression had 39 to 48% lower odds of achieving these binary responses.

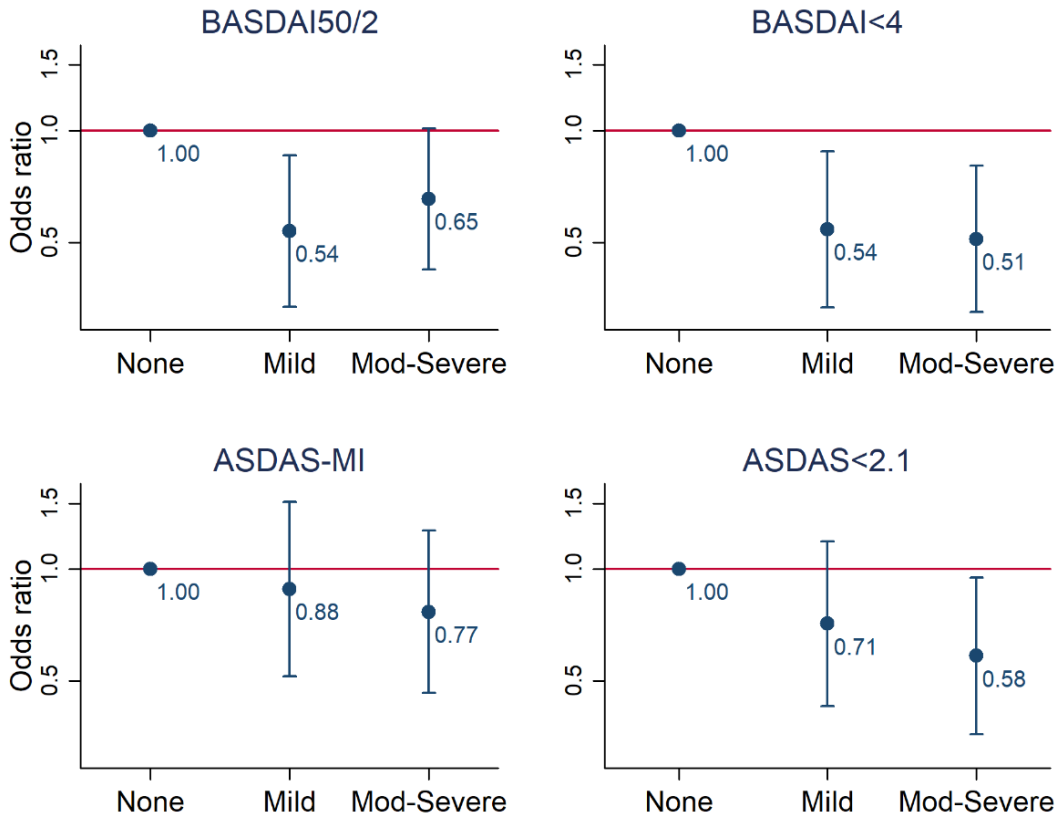
Figure 7. 5: Associations between HADS depression sub-scale categories and binary responses at 6 months.



Model coefficients shown in Appendix 10.6: Table S7.4. HADS-D categories: None, HADSD≤7; Mild, 8-10; Moderate-severe, ≥11. BASDAI 50/2, 50% or 2-unit reduction in BASDAI; ASDAS-MI, major improvement i.e. ≥2-unit reduction.

Compared to the 'none' group for HADS-anxiety, those with mild or moderate-severe anxiety had around half the odds of achieving BASDAI-based responses (Figure 7.6). Using the same referent, the effect sizes were smaller for ASDAS-based definitions. The sole statistically significant comparison was 42% lower odds of achieving ASDAS<2.1 in moderate-severe anxiety vs 'none'.

Figure 7. 6: Associations between HADS anxiety sub-scale categories and binary responses at 6 months.

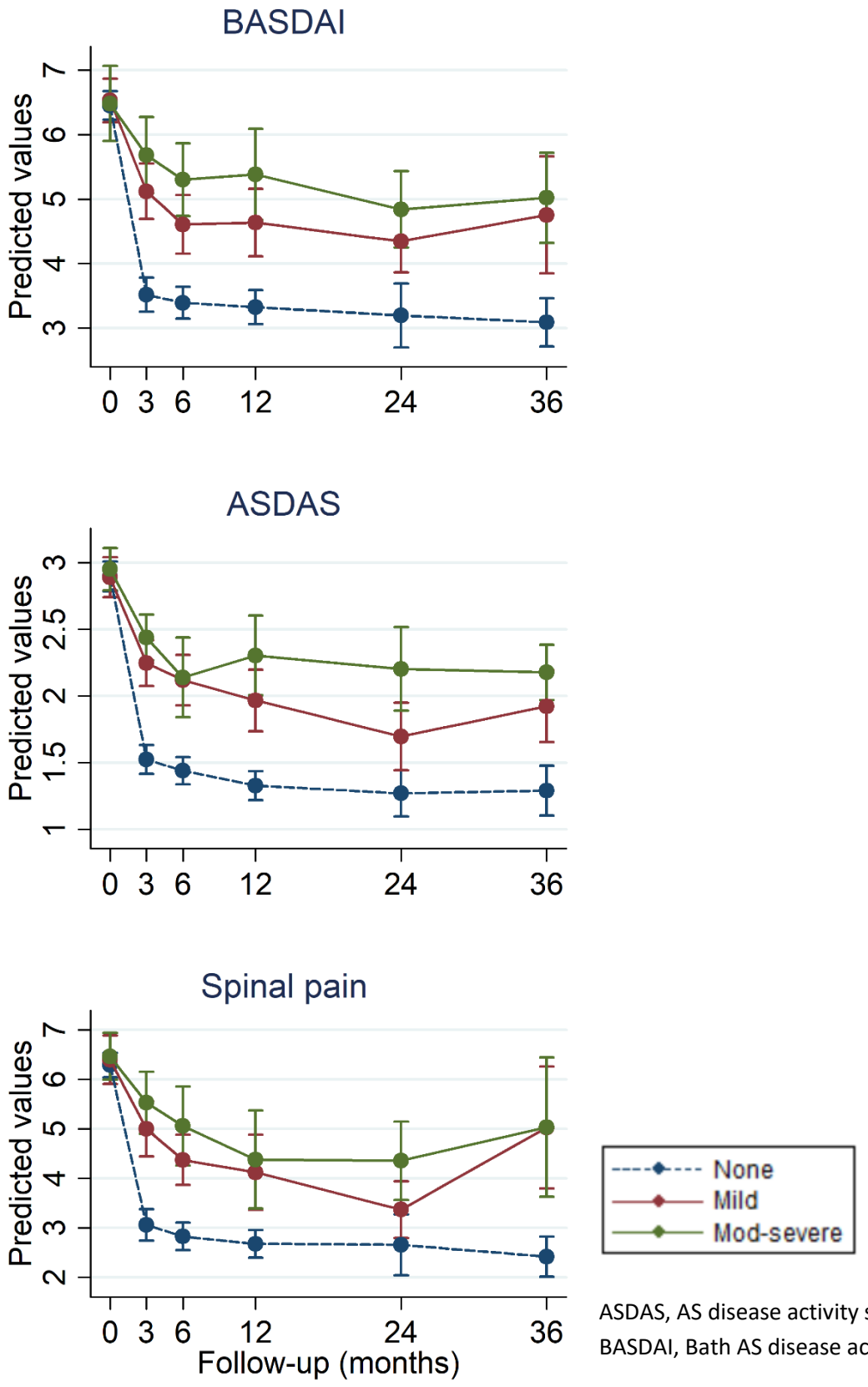


Model coefficients shown in Appendix 10.6: Table S7.4. HADS-A categories: None, HADSA≤7; Mild, 8-10; Moderate-severe, ≥11. BASDAI 50/2, 50% or 2-unit reduction in BASDAI; ASDAS-MI, major improvement i.e. ≥2-unit reduction.

7.4.3.2 Baseline symptoms vs. continuous response (absolute improvement)

Groups reporting mild or moderate-severe baseline depressive symptoms had smaller improvement in all three disease activity indices (Figure 7.7). All data points were statistically significantly different between none vs. moderate-severe depressive symptom groups. For example, the group with no depression at 3-months had approximately 2.1 units greater response in BASDAI, 0.9 units greater response in ASDAS and 2.3 units greater response in spinal pain than the group with moderate-severe depression (Table 7.8). This blunted response persisted throughout the first three years of follow-up. Effect sizes comparing mild vs. 'none' groups were smaller but nevertheless statistically and clinically significant at approximately 1.1- to 1.6-unit greater response in BASDAI, 0.4 to 0.7 units in ASDAS and 0.6 to 2.5 units in spinal pain over 3 years of follow-up.

Figure 7. 7: Change in disease activity in response to TNF inhibitors according baseline HADS depression symptom categories.



ASDAS, AS disease activity score;
BASDAI, Bath AS disease activity index.

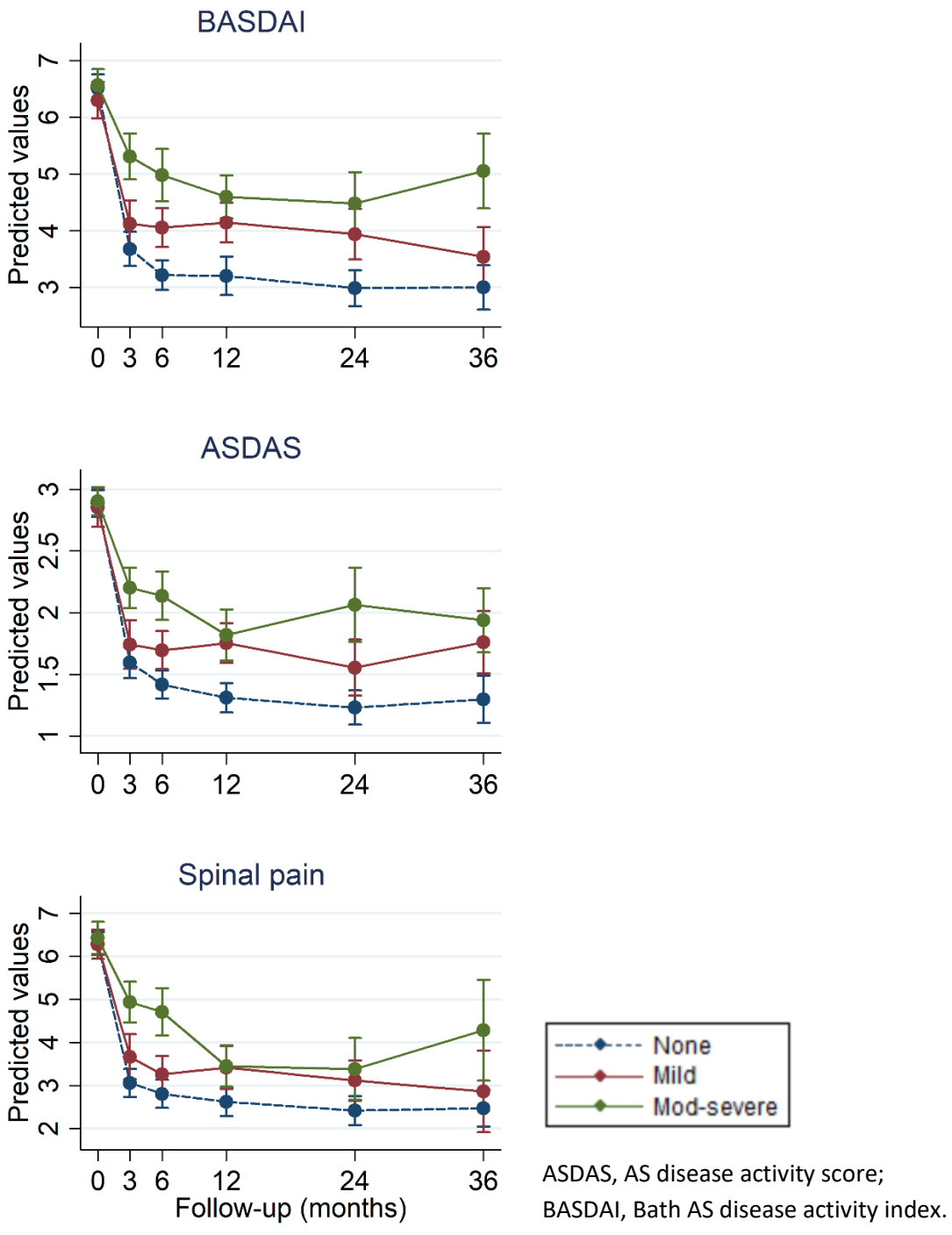
Table 7. 8: Model coefficients for change in disease activity vs. baseline HADS depression symptom categories.

	BASDAI	ASDAS	Spinal pain
N, participants (follow-ups)	738 (2050)	673 (1840)	740 (2065)
Constant	**6.45 (6.23 to 6.68)**	**2.90 (2.78 to 3.01)**	**6.29 (6.04 to 6.54)**
3.FU	**-2.94 (-3.28 to -2.60)**	**-1.37 (-1.52 to -1.22)**	**-3.23 (-3.58 to -2.88)**
6.FU	**-3.06 (-3.38 to -2.75)**	**-1.46 (-1.60 to -1.31)**	**-3.46 (-3.81 to -3.12)**
12.FU	**-3.13 (-3.45 to -2.81)**	**-1.57 (-1.72 to -1.41)**	**-3.61 (-3.96 to -3.26)**
24.FU	**-3.26 (-3.77 to -2.75)**	**-1.63 (-1.84 to -1.42)**	**-3.63 (-4.27 to -2.99)**
36.FU	**-3.37 (-3.79 to -2.95)**	**-1.61 (-1.83 to -1.39)**	**-3.87 (-4.33 to -3.41)**
Mild*	0.08 (-0.32 to 0.48)	0.001 (-0.19 to 0.18)	0.11 (-0.45 to 0.66)
Mod-severe**	0.03 (-0.62 to 0.68)	0.05 (-0.13 to 0.24)	0.17 (-0.34 to 0.69)
3.FU#Mild	**1.53 (0.91 to 2.14)**	**0.73 (0.46 to 0.99)**	**1.83 (1.00 to 2.67)**
6.FU#Mild	**1.14 (0.54 to 1.73)**	**0.69 (0.41 to 0.96)**	**1.44 (0.64 to 2.24)**
12.FU#Mild	**1.23 (0.54 to 1.93)**	**0.64 (0.33 to 0.95)**	**1.34 (0.36 to 2.31)**
24.FU#Mild	**1.07 (0.30 to 1.84)**	**0.43 (0.08 to 0.78)**	**0.61 (-0.16 to 1.37)**
36.FU#Mild	**1.59 (0.60 to 2.57)**	**0.64 (0.27 to 1.01)**	**2.50 (0.92 to 4.08)**
3.FU#Mod-sev	**2.14 (1.33 to 2.95)**	**0.86 (0.60 to 1.12)**	**2.29 (1.54 to 3.05)**
6.FU#Mod-sev	**1.88 (1.18 to 2.58)**	**0.65 (0.36 to 0.93)**	**2.06 (1.12 to 2.99)**
12.FU#Mod-sev	**2.03 (1.19 to 2.87)**	**0.92 (0.56 to 1.28)**	**1.53 (0.42 to 2.63)**
24.FU#Mod-sev	**1.62 (0.93 to 2.30)**	**0.88 (0.47 to 1.28)**	**1.52 (0.45 to 2.60)**
36.FU#Mod-sev	**1.90 (1.03 to 2.78)**	**0.83 (0.51 to 1.15)**	**2.44 (0.94 to 3.94)**

*Mild (8-10) vs. None (<8). **Moderate-severe (≥11) vs. None.
Bold text highlights statistically significant results.
Covariate coefficients omitted. FU, follow-up at numbered month. #, interaction term.

Results were similar for anxiety categories (Figure 7.8). At month 3, the group with no anxiety symptoms had approximately 1.6 units greater response in BASDAI, 0.6 units in ASDAS and 1.8 units in spinal pain than the group with moderate-severe depression (Table 7.9). Effect sizes comparing mild vs. 'none' were also clinically important, by approximately 0.7 to 1.2 units in BASDAI, 0.2 to 0.5 units in ASDAS, and 0.5 to 0.8 units in spinal pain over 3 years.

Figure 7. 8: Change in disease activity in response to TNF inhibitors according baseline HADS anxiety symptom categories.



ASDAS, AS disease activity score;
BASDAI, Bath AS disease activity index.

Table 7. 9: Model coefficients for change in disease activity vs. baseline HADS anxiety symptom categories.

	BASDAI	ASDAS	Spinal pain
N, participants (follow-ups)	738 (2050)	673 (1840)	740 (2065)
Constant	**6.52 (6.28 to 6.76)**	**2.89 (2.78 to 3.00)**	**6.30 (6.04 to 6.57)**
3.FU	**-2.84 (-3.20 to -2.49)**	**-1.29 (-1.45 to -1.13)**	**-3.24 (-3.64 to -2.85)**
6.FU	**-3.3 (-3.64 to -2.96)**	**-1.47 (-1.62 to -1.32)**	**-3.5 (-3.90 to -3.10)**
12.FU	**-3.32 (-3.71 to -2.93)**	**-1.58 (-1.74 to -1.42)**	**-3.68 (-4.09 to -3.27)**
24.FU	**-3.53 (-3.92 to -3.15)**	**-1.66 (-1.83 to -1.48)**	**-3.88 (-4.30 to -3.47)**
36.FU	**-3.52 (-3.98 to -3.06)**	**-1.59 (-1.81 to -1.37)**	**-3.83 (-4.33 to -3.33)**
Mild*	-0.22 (-0.61 to 0.18)	-0.03 (-0.23 to 0.16)	-0.02 (-0.45 to 0.41)
Mod-severe**	0.05 (-0.33 to 0.43)	0.02 (-0.14 to 0.18)	0.13 (-0.32 to 0.58)
3.FU#Mild	**0.66 (0.09 to 1.23)**	0.18 (-0.11 to 0.46)	0.63 (-0.06 to 1.31)
6.FU#Mild	**1.05 (0.50 to 1.61)**	**0.31 (0.05 to 0.57)**	0.47 (-0.18 to 1.12)
12.FU#Mild	**1.16 (0.57 to 1.75)**	**0.48 (0.22 to 0.73)**	**0.81 (0.12 to 1.51)**
24.FU#Mild	**1.17 (0.53 to 1.80)**	**0.36 (0.03 to 0.68)**	**0.72 (0.04 to 1.40)**
36.FU#Mild	0.76 (-0.01 to 1.52)	**0.49 (0.11 to 0.88)**	0.41 (-0.74 to 1.56)
3.FU#Mod-sev	**1.58 (1.05 to 2.12)**	**0.59 (0.35 to 0.82)**	**1.75 (1.12 to 2.38)**
6.FU#Mod-sev	**1.71 (1.12 to 2.31)**	**0.7 (0.45 to 0.96)**	**1.78 (1.07 to 2.48)**
12.FU#Mod-sev	**1.35 (0.79 to 1.90)**	**0.49 (0.23 to 0.76)**	**0.70 (0.07 to 1.33)**
24.FU#Mod-sev	**1.44 (0.74 to 2.14)**	**0.82 (0.46 to 1.18)**	**0.84 (0.02 to 1.66)**
36.FU#Mod-sev	**2.00 (1.19 to 2.82)**	**0.62 (0.27 to 0.98)**	**1.68 (0.39 to 2.97)**

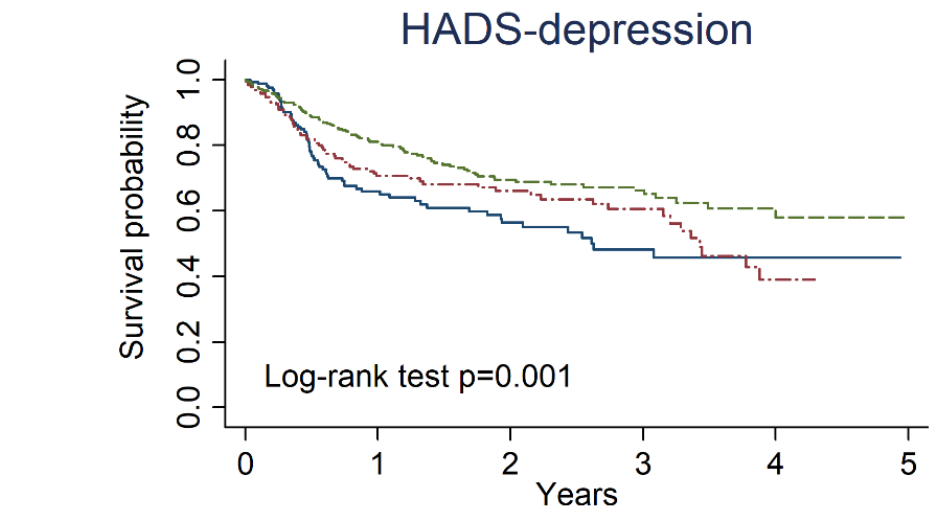
*Mild (8-10) vs. None (<8). **Moderate-severe (≥11) vs. None (<8).
Bold text highlights statistically significant results.
Covariate coefficients omitted. FU, follow-up at numbered month. #, interaction term.

7.4.3.3 Baseline symptoms vs. time to treatment discontinuation

Analyses included 1036 person-years of follow-up, with mean of 17 (SD 15) months and median 12 (IQR 5 to 25) months. Very few individuals had follow-up beyond 4 years.

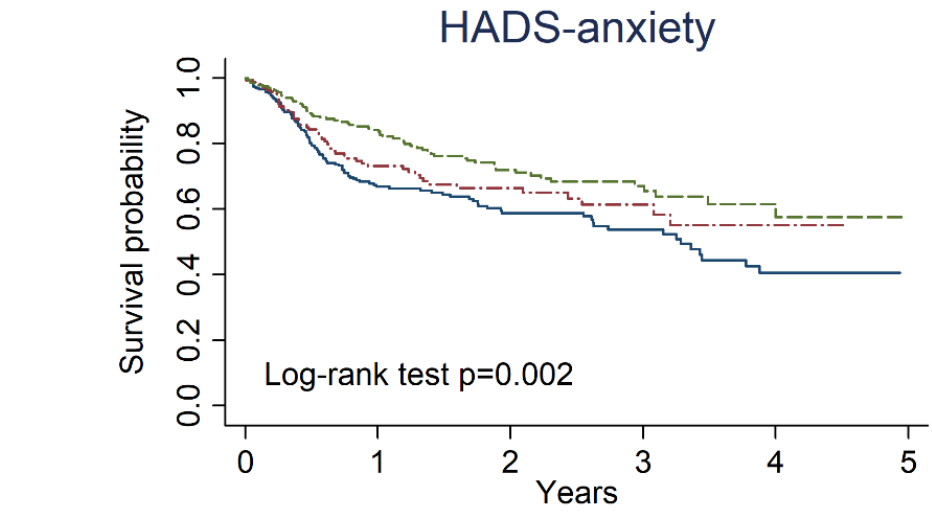
31% of the cohort stopped treatment over the study. 38% of participants with moderate-severe depression discontinued, 35% with mild, 26% with none. 37% of those with moderate-severe anxiety discontinued, 31% with mild, 25% with none. Drug survival according to HADS categories is shown in Figure 7.9.

Figure 7. 9: Kaplan-Meier curves comparing drug survival between participant-groups with different categories of baseline depression and anxiety symptoms.



Number at risk

Mod-severe 172	72	46	23	6	0
Mild 190	97	60	31	7	0
None 368	212	112	61	22	0

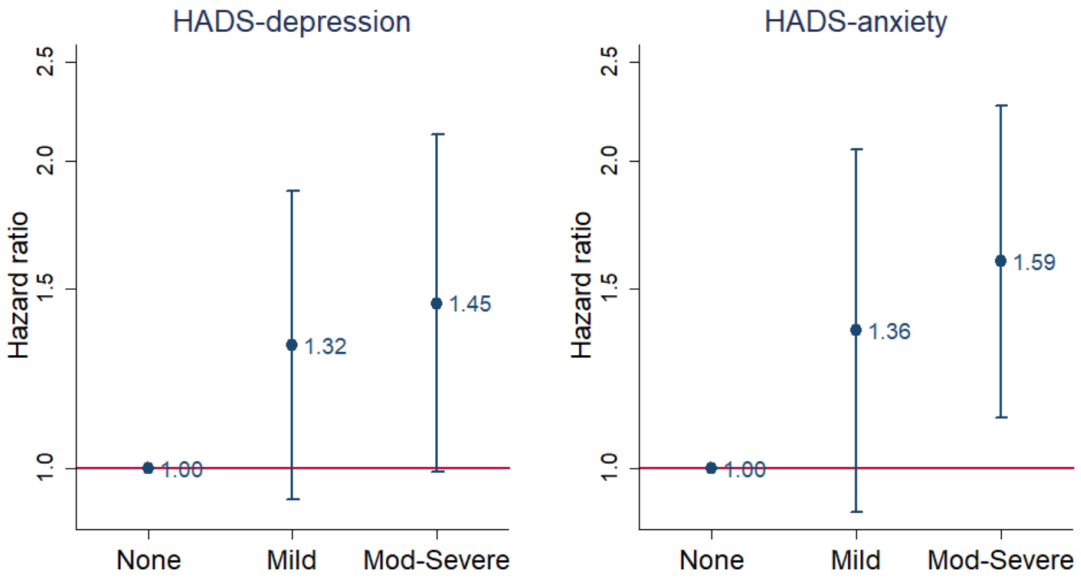


Number at risk

Mod-severe 288	130	77	46	14	0
Mild 167	90	51	24	6	0
None 275	161	90	45	15	0

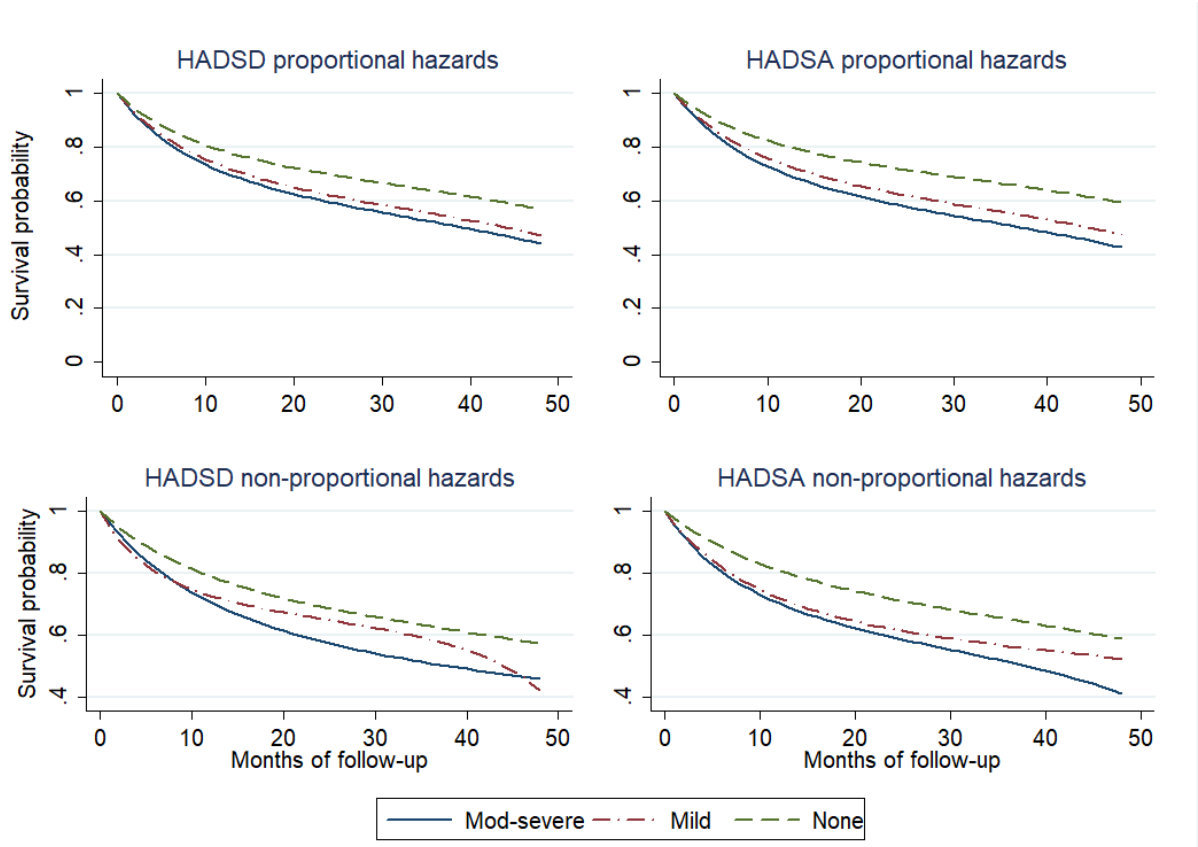
Symptoms of depression or anxiety were associated with greater hazard rate of treatment discontinuation (i.e., greater number of individuals discontinued at any one time, assuming rates are proportional). Compared to the 'none' category for depression, the mild depression group had 32% higher (95% CI 0.93 to 1.87), and moderate-severe group 45% higher (95% CI 0.99 to 2.12), hazard rate of treatment discontinuation (Figure 7.10). Compared to the 'none' category for anxiety, the group with mild anxiety at baseline had 36% higher (95% CI 0.91 to 2.05), and moderate-severe group 59% higher (95% CI 1.12 to 2.26), hazard of TNFi discontinuation.

Figure 7. 10: Treatment discontinuation according to baseline depression or anxiety symptom categories.



Kaplan-Meier estimators in Figure 7.9 suggest potential violation of the proportional hazards assumption. Comparison between none and moderate-severe groups was approximately proportional, as shown by marginal structural Cox models using flexible baseline hazards (Figure 7.11).

Figure 7. 11: TNFi discontinuation modelled using proportional and non-proportional hazards.

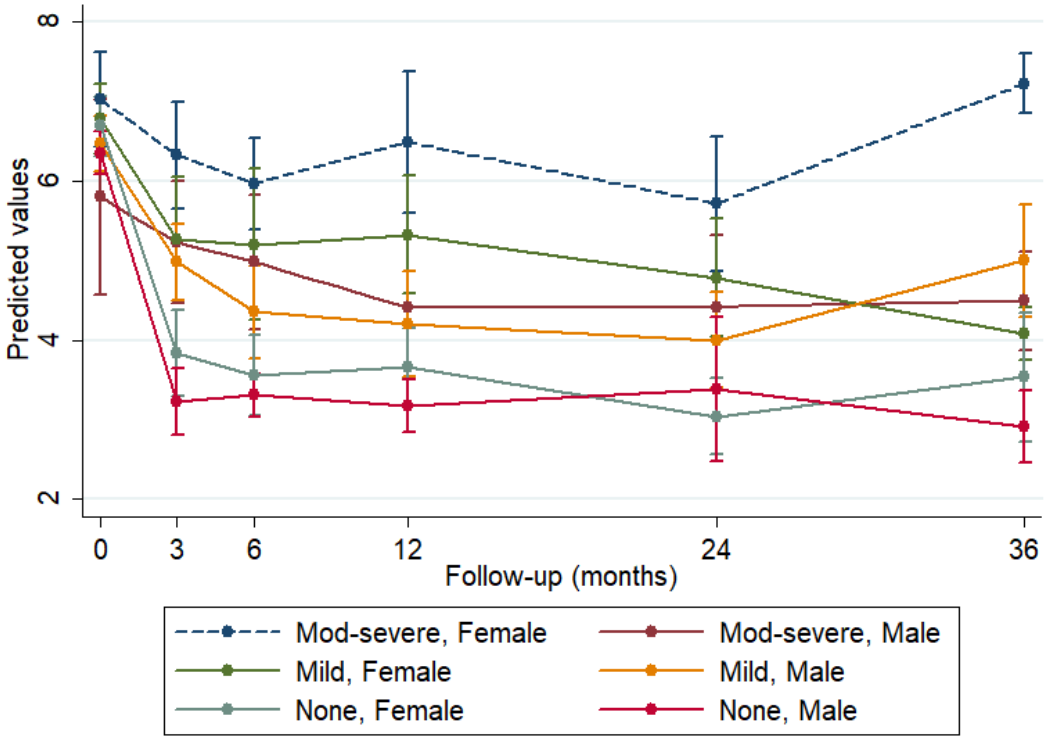


HADSA, hospital anxiety and depression scale – anxiety sub-scale; HADSD, hospital anxiety and depression scale – depression sub-scale.

7.4.4 Gender interactions between baseline depression or anxiety symptoms and each outcome.

All analyses were repeated with consideration of the effect modification by gender (by stratification or interaction). In summary, there were no statistically or clinically significant effect modification in the three aims (data not shown) except one. Marginal longitudinal models of BASDAI according to baseline HADS-depression categories showed significant effect modification by gender. The Wald test p-value for all interaction terms was <0.001. Marginal estimates are plotted in Figure 7.12. Female groups with mild and mod-severe depression had markedly poorer response compared to their male counterparts.

Figure 7. 12: Significant effect modification by gender in the longitudinal analysis of BASDAI according to baseline HADS-depression categories.



7.4.5 Sensitivity analysis

Models using weights that additionally included baseline smoking status, HLA-B27, and alcohol status did not produce significantly different results (data not shown). Analyses repeated using matching weights also did not produce meaningfully different results (data not shown).

7.5 Discussion

In this longitudinal analysis of the BSRBR-AS, history of depression was poorly concordant with depressive symptoms; 1 in 5 of those with no documented depression reported at least moderate symptoms. AxSpA patients with mild to severe symptoms of depression or anxiety had markedly poorer response to their first TNFi compared to those with less than mild symptoms. Interventions to optimise mental health at or before TNFi initiation may dramatically improve treatment response.

In a recent meta-analysis, numerous cross-sectional studies have shown higher disease activity in axSpA patients with depression [9]. Only one prior study – that used an early version of the same BSRBR-AS dataset – examined mental health in the context of treatment response in axSpA [6]. Macfarlane et al used stepwise selection of predictors to show that, for each unit increase in the mental component summary of the SF12 (higher score indicating higher level of health), odds of ASDAS clinically important response (reduction by ≥1.1) and ASDAS low disease activity (<2.1) were significantly increased by 5%. Similarly, ASAS20 response was reduced by 6% for each unit increase in the HADS anxiety subscore. However, predictors do not necessarily have a causal interpretation [20]; for example, stepwise variable selection provides final models that may omit important confounders [21,22]. The current analysis was designed to best approximate a causal interpretation, and extended outcome measures beyond binary response definitions. Such definitions have inherent limitations when using observational data [23]; for example, high baseline DAS28 is a predictor that simultaneously increases odds of ACR70 response and decreases odds of DAS remission in RA [24].

Results of the current analysis are consistent with studies in rheumatoid arthritis using the BSRBR-RA, where history of depression and symptoms of depression were associated with reduced response [243]. The authors used mixed models to examined linear improvement through months 6 and 12, showing an adjusted difference in DAS28 of 0.01 units between

those with and without depression symptoms. This and other effect sizes were an order of magnitude smaller than that deemed clinically meaningful. Contrast this to a difference of proximately 2 BASDAI units and 0.9 ASDAS units between axSpA patients in the moderate-severe and 'none' group for depression, where clinically meaningful differences are around 1 unit for BASDAI and ASDAS [180]. This may be explained by forcing linearity onto a clearly non-linear response trajectory, or the use of the Short-Form 36-item questionnaire which was designed to measure quality of life not to assess depression. The main reason is likely the unique way in which axSpA disease activity is assessed: BASDAI and spinal pain are completely patient-reported. Depression is known to influence the experience and reporting of symptoms [199,231], which is supported by larger effect sizes for BASDAI than (the more objective) ASDAS. Optimising mental health may offer substantial improvements in axSpA treatment response. Conversely, neglecting mental health may lead those with severe mental health symptoms to 'double jeopardy', where apparent inadequate response in disease indices means their TNFi are withdrawn in healthcare systems like the UK.

This study is the first to assess the impact of anxiety on treatment outcomes. Anxiety is often assumed to exist in parallel with depression and thus overlooked in clinical practice and research. Symptoms of both depression and anxiety were associated with treatment discontinuation, but the effect sizes were larger for anxiety: moderate-severe depression (vs. 'none') was associated with 45% higher hazard rate compared to 59% for anxiety. Although correlated, the depression and anxiety are not equivalent. Of those without depressive symptoms, nearly half had at least mild symptoms of anxiety and 1 in 5 had at least moderate. Conversely, 22% of those without anxiety had at least mild symptoms of depression.

Mental health disorders are under-recognised and -diagnosed in axSpA, despite their high prevalence [9] and association with many other important health factors such as alcohol/drug abuse and suicide [143]. Under-diagnosis of depression was clearly demonstrated by the data: 20% of those without a recorded diagnosis of depression reported HADS-D≥11, which has 92% specificity for major depressive disorder [233]. Conversely, diagnosed depression may be treated with variable success; 27% of those with a history of depression reported HADS-D<8. Mental health symptoms are dynamic and should be assessed as such. This likely explains why differences in absolute disease activity improvement were more prominent when using symptoms than history of depression.

These results suggest that symptoms of both depression and anxiety should be systematically screened in routine practice. This allows clinicians to better predict treatment response, but more importantly to highlight individuals who may benefit from interventions to reduce depression and anxiety (medication and/or psychological therapy). Up to half of axSpA patients do not respond to their first TNFi. This study suggests potential for substantial improvements in treatment response (e.g., approximately 2 units in BASDAI) and treatment persistence if severe depression symptoms can be successfully treated. The number of pharmacological options is increasing but as yet not reliably effective in routine practice, while talking therapies can be difficult to access. Improving access to the latter, for example using internet or telephone delivered cognitive behavioural therapy for those with mild to moderate symptoms, may be one solution. Individuals with more severe symptoms will still require one-to-one therapy. RCTs of non-pharmacological mental health interventions in chronic rheumatic disease are needed to find optimal approaches for these prevalent and impactful comorbidities.

7.5.1 Strengths and limitations

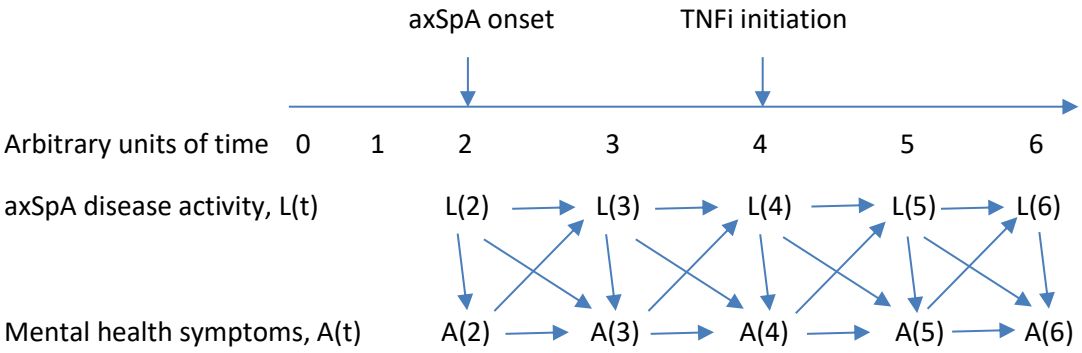
Strengths of the data were discussed in previous chapters; for example, the large sample size recruited from a broad range of rheumatology centres, and use of three response definitions that each lends strength to the overall conclusion. Diagnoses correlate poorly with dynamic and often under-recognised symptoms. Therefore, symptoms of depression/anxiety, rather than documented diagnosis, provide effect estimates that have greater relevance to clinical practice and potential interventions. Results were robust against several sensitivity analyses.

There were also important limitations. Studying the causal effect of baseline mental health symptoms (a 'prevalent exposure') has conceptual difficulty; the implied hypothetical intervention would need to successfully improve baseline symptoms, but also symptoms pre-baseline of unknown duration. This might be considered as an intervention administered before (rather than at) TNFi initiation, but true causal effect sizes are likely to be smaller. Even if more realistic effect estimates were half the size, they still remain larger and more amenable to intervention that other 'modifiable risk factors': Smoking cessation did not convincingly impact treatment outcomes and is difficult to achieve [42,189]; BMI is associated with treatment outcomes [244] but causal effects are conceptually problematic to estimate and interventions practically difficult to implement [245].

Categorising HADS sub-scales will have reduced statistical power and effect sizes. Using IP weights for continuous HADS requires strong assumptions of its distribution; it would also assume a linear relationship between HADS and treatment outcomes, which the above results showed not to hold. Results from weighted GEE models should be interpreted with the limitation that participants who did not respond by the first assessment (usually after 3 months) or those who lost response would have had their treatment stopped under NICE guidance; therefore, record of such high disease activity would be censored. This informative censoring should not affect data within the first 3 months [42]. IP weighting methods are known to inflate variance (reduce precision), for example, through use of robust standard error. A key limitation is that mental health symptoms improve after TNFi initiation; the time-varying interplay between them and axSpA disease activity may be of interest for future analyses. This requires consideration of both time-varying 'exposure' and covariates (Figure 7.13), and is beyond the scope of this thesis [246].

The singular significant result for effect modification by gender should not be over-interpreted. First, binary BASDAI responses were not significantly different according to gender. Second, significant effect modification by gender was not observed for any other indices or treatment discontinuation. Third, the number of females were small leading to uncertainty in the point estimate. Nevertheless, it may be of interest for future studies to examine whether depression differentially affects BASDAI and ASDAS in males and females.

Figure 7. 13: Causal associations between time-varying mental health symptoms and axSpA disease activity, and implications for analytical approaches.



At 'time 2', axSpA symptoms, L(2), influence mental health, A(2), which in turn affects how axSpA symptoms L(3) are experienced and reported. Mental health symptoms at 'time 3', A(3), are simultaneously affected by axSpA symptoms, L(3), and the history of axSpA L(2) and mental health symptoms A(2) before this time point. This complex feedback between exposure and outcome continues to TNFi initiation. When treatment improves L(4), A(4) also improves. Post-treatment axSpA disease activity L(5) is simultaneously affected by treatment (through L(4)) and improvements in mental health A(4).

This complex causal web has important implications for the analysis. Traditional outcome regression 'adjustment' to account for different baseline disease activity between mental health symptom categories is problematic: L(4) is a confounder for A(4), but also a time-varying mediator with respect to $\bar{A}(3)$ (i.e., history of pre-treatment mental health symptoms), and a time-varying confounder that is affected by $\bar{A}(3)$. Conditioning on ('adjusting' for) a time-dependent confounder that is affected by past exposure introduces profound bias, whether in repeated measure [247] or time-to-event analyses [248]. Conditioning on a mediator (post-treatment mental health symptoms) removes the indirect part of the total causal effect of the exposure (total effect = direct effect + indirect effects).

These observations highlight two issues for the current analysis. First, inverse-probability weighting accounts for L(4) without conditioning on it, such that A(4) is not confounded. Second, time-varying post-treatment mental health symptoms cannot simply be 'adjusted for' in GEE or Cox models. To untangle the effect of post-treatment mental health response on post-treatment disease activity, complex causal methods are required (e.g., the mediational g-formula [246]).

7.6 Summary

Baseline history of depression is poorly representative of mental health symptom burden. Symptoms of depression and anxiety at TNFi initiation were each associated with adverse treatment outcomes. Assuming these marginal models provide an adequate approximation of real causal effects, reducing depression symptoms (from moderate-severe to less than mild) at TNFi initiation may improve binary response at 6 months by up to 2-fold, absolute response by as much as 2 BASDAI and 0.9 ASDAS units. Similarly improving anxiety symptoms may reduce treatment discontinuation by up to a third. Taken together, these findings highlight the importance of routinely screening and optimising depression and anxiety. Randomised controlled trials are needed to identify efficacious mental health interventions for axSpA patients.

Chapter 8: Discussion and conclusions

This chapter summarises the major research findings across the thesis and discusses their significance for future research, clinical practice, and wider health policy. Strengths and limitations are outlined, and gaps are identified for further research.

8.1 Summary of findings

The thesis began with a review of the comorbidity literature, which showed axSpA patients to have higher comorbidity burden than control populations [84]. These descriptive studies predominantly approached comorbidities as the outcome (e.g., incidence of cardiovascular disease or cancer), with few examining its impact on and relevance to axSpA management. Of the latter, the majority were studies of individual or related conditions, which lacked context for the relative significance of individual conditions [84]. This context is essential to help identify areas most in need of future research or intervention. Several research needs were identified; for example, the need for a comprehensive description of comorbidity burden and differences between axSpA subgroups, how comorbidities co-occur, their impact on various aspects of axSpA management, and improved study methods. This section summarises findings from this thesis and how they addressed unmet research needs.

8.1.1 Comorbidities in radiographic vs non-radiographic axSpA

Comorbidity burden was measured in two axSpA populations from academic centres in the UK and USA using an adapted version of the multimorbidity index (MMI) [198], which was validated in rheumatic diseases and includes 39 chronic conditions deemed important by multimorbidity researchers and the UK's National Health Service [140]. Comorbidity was common in both study populations; over half of all axSpA patients had at least one additional condition, most frequently belonging to the mental health or cardiometabolic groups [127,128,143]. Mean comorbidity count was higher in the older Boston than Aintree population, in part due to its older age.

The novel contribution to the literature was that comorbidity burden was remarkably similar between AS and non-radiographic axSpA in both Boston and Aintree populations, in terms of individual conditions and the total number of comorbidities. These results were

unexpected given these subgroups differed in age, gender, and inflammatory burden; they support the need for a unified clinical approach to management of the whole axSpA spectrum.

8.1.2 Clustering of comorbidities

Several comorbidity clusters were identified in the Aintree axSpA data. Due to the relatively low comorbidity burden (most patients in this study had only one or two comorbid conditions), clusters were dominated by relatively few diseases. The largest clusters were respectively dominated by mental health and cardiovascular diseases. For external validation, clustering was reproduced in the older Boston axSpA population with higher comorbidity burden. These disease clusters largely confirmed clinical experience: anxiety co-occurs with depression and hypertension with coronary heart disease [249]. Chapter 7 later showed the importance of screening for anxiety when depression is present. An equally important finding was the consistently higher disease severity in groups with anxiety/depression and fibromyalgia/IBS. These patient groups are clearly in need of prioritisation in clinical practice – a conclusion shared by subsequent chapters (namely anxiety/depression; see limitations section for fibromyalgia).

In the validation analysis using the Boston study, substance misuse was clustered with mental health disorders. Substance misuse disorders also showed consistent associations with disease severity, with potentially important but underpowered effect sizes. Subsequent publications using the Boston data confirmed the close relationship between depression and this comorbidity group in greater detail [143].

Describing comorbidity clusters bridges existing study designs that either focus on total counts or individual conditions. This approach could inform screening of other diseases within a cluster when one is present, or identification of patient groups in need of greater prioritisation for research or clinical care.

8.1.3 Comorbidities and disease assessment

Since axSpA symptoms are more severe with increasing comorbidity burden, how should clinicians assess axSpA disease activity in the presence of comorbidities? Chapter 5 addressed this question by comparing whether disease activity measures were differentially influenced by comorbidities in the baseline BSRBR-AS data. Results showed that patient-reported disease activity indices – BASDAI and spinal pain – increased with the number of comorbidities. By contrast, ASDAS was not associated with comorbidity count or individual

comorbidities by a clinically meaningful effect size. The patient global score, although influenced by comorbidities, did not inflate ASDAS independently of other ASDAS components. These results are clinically relevant since many treatment decisions are based on assessments using these indices. Healthcare providers should be mindful of the potential impact of comorbidities on patient reported measures, and consider additionally collecting ASDAS to assess disease activity in patients with multiple comorbidities.

Although the BSRBR-AS comorbidity data differed from the preceding chapters (14 conditions compared to 39 in Boston and Aintree data), depression was again highlighted as highly prevalent (23%) and associated with greater disease severity. When each of the 14 comorbidities were modelled against a range of indices (disease activity plus fatigue, health-related quality of life, and function), depression was consistently and significantly associated with them all.

8.1.4 Comorbidities and response to TNF inhibitors

Patients with comorbidities were significantly more likely to discontinue their treatment. These individuals generally had reduced odds of achieving binary response definitions but had comparable absolute improvement in disease activity, demonstrating that greater absolute improvement is needed to achieve a binary response in those starting with higher disease activity. These subtly different but complementary results highlight the importance of analysing a range of response definitions.

Many comorbid patients would have been ineligible for randomised controlled trials; these results provide unique insights into how therapeutic effects on function and quality of life differed in comorbid patients – highlighting the need to optimise comorbidities as part of axSpA management. Interpreting results of each outcome type in the context of others is important. For example, patients with comorbidities may have comparable absolute improvement yet lower odds of achieving 'low disease activity' states than those with no comorbidities. Communication to patients should be more nuanced. Existing definitions of response as used for prescribing guidelines, for example in the UK, may need to be reconsidered: a patient starting treatment with high BASDAI will have higher odds of achieving BASDAI 50/2, while simultaneously having lower odds of BASDAI<4, than an identical individual with lower starting BASDAI. Which definition of response is more relevant for health-economics remains to be determined.

This chapter's longitudinal design shed further light on causal directions. But is the association between comorbidity and treatment outcome causal? Since comorbidity count cannot be 'modified', it remains difficult to claim causality under this robust definition. Causal interpretation of results should therefore be limited. Comorbidities such as depression can, however, be modified.

8.1.5 Depression and anxiety and response to TNF inhibitors

Baseline history of depression was poorly representative of depressive symptom burden in the BSRBR-AS. Symptoms of depression and anxiety at TNFi initiation were each associated with adverse treatment outcomes. Assuming these marginal models provide an adequate approximation of causal effects, reducing depression symptoms (from moderate-severe to less than mild) at TNFi initiation may improve binary response at 6 months by up to 2-fold, and absolute response by as much as 2 BASDAI and 0.9 ASDAS units. Similarly improving anxiety symptoms may reduce treatment discontinuation by up to a third. These are novel findings in the axSpA literature. By contrast, effect sizes from analyses of other 'modifiable risk factors' such as smoking [41,42] and BMI [250] have been much more modest (or null). These results suggest that symptoms of both depression and anxiety should be systematically screened in routine practice. This allows clinicians to better predict treatment response, but more importantly to highlight individuals who may benefit from interventions to reduce depression and anxiety (e.g., medication and/or psychological therapy).

8.2 Strengths and limitations

8.2.1 Strengths

There are several strengths of this thesis regarding the data, design, analysis, and generalisability. Data for comorbidities and outcomes were robust with little missing data. For example, comorbidity data in the Aintree study were complete for almost all (>99%) patients and validated by multiple researchers and data sources. Comorbidity ascertainment in the BSRBR-AS, though different, was again robustly defined using physician confirmed diagnoses. This is a key advantage over many existing studies that use patient reported diagnoses [93]. Inherent weaknesses of one study was supported by strengths in the other. For example, the potentially limited accuracy of comorbidity ICD codes in the Boston study were supported by more robust Aintree data; limited number of

comorbidities in the BSRBR-AS were supported by comprehensive and standardised comorbidity collection in the Aintree and Boston data.

The design of the two cross-sectional studies were specific to the aims of the thesis, allowing clear axSpA definitions, relevant covariates, and disease indices to be captured where possible. Notably, this allowed a comprehensive list of comorbidities to be standardised across two study populations. The multimorbidity index is also unique in that it is not weighted for a specific outcome and has been validated in rheumatic diseases, which is an advantage over many other commonly used indices. The BSRBR-AS, although not designed to study comorbidities, nevertheless captured most important conditions. Its main strength lies in the large and nationally representative secondary care axSpA population, for whom a wide range of disease measures were collected at regular time points. All three datasets are broadly representative of axSpA populations in secondary/tertiary care. However, they do not represent all axSpA patients in the general population since many are managed in primary care only [157].

Another key strength of this thesis is its methodology. For example, confounder selection has historically relied on suboptimal practices such as stepwise, univariate or other statistical selection [251]. In this thesis, covariate selection was carefully considered with transparent justification (supported by causal graphs) and numerous sensitivity analyses examining additional potential confounders. This more robust approach to confounding is essential for reducing bias and increasing the validity of results. Another weakness of previous research is the heterogenous definition of comorbidity and outcome. Chapter 6 (summarised in Section 8.1.4 above), demonstrated the potential for very different conclusions to be drawn using different outcome definitions (supported by methodology work that was performed in parallel but not included in the thesis [41,42]). Thus, analysis approaches in this thesis included a diverse set of definitions, for example, using a range of approaches for comorbidity (binary, count, individual) and longitudinal outcomes (binary, continuous, time-to-event). Different results highlight the underlying assumptions and limitations of each approach.

In the final results chapter, marginal approaches were chosen to provide results that have a clearer causal interpretation and would be more clinically informative (i.e., emulating output from RCTs), whereas popular conditional approaches may theoretically be less likely concordant with future RCT results.

8.2.2 Limitations

There were three main limitations in this thesis. First, several (mostly sub-)analyses lacked statistical power; for example, regression models of rarer comorbidities (such as peripheral vascular disease) or severe mental health symptom categories. However, most primary analyses were adequately powered. Increasing the sample size of the cohorts employed was not possible: the Aintree and Boston studies sampled from all patients at these centres, while the BSRBR-AS had a predetermined sample size and had completed recruiting. Some statistical methods (weighted GEE) further inflated variance.

Second, the main dataset used in this thesis – the BSRBR-AS – collected a list of conditions tailored for pharmacovigilance rather than comprehensive study of comorbidity. This is an inherent limitation of using pre-collected data. For example, some important conditions were not included (e.g., anxiety or other neuropsychiatric conditions) while conditions seldom included in comorbidity studies were, for example demyelinating diseases and TB. Fibromyalgia was identified as an important comorbidity (Chapter 4) but could not be examined in the BSRBR-AS since it was ascertained differently. However, included comorbidities were broadly representative of important diseases when compared to prior axSpA research [84]. None of the comorbidity data included severity; for example, end-stage renal/liver/heart disease will have very different impact on patients and treatment choices than milder forms. Loss of granularity is somewhat inherent when studying comorbidity burden rather than individual conditions. Chapters 6 and 7 showed that summarising comorbidities into a count may provide limited information for treatment outcomes and may hide the effect of certain comorbidities. Another limitation common to almost all published research is the lack of data on the chronology of comorbidities pre-baseline, which has implications for causal interpretation of some results.

Third, association is not necessarily causation. This is an intrinsic limitation for the cross-sectional designs, which cannot distinguish whether high disease severity (directly or indirectly through its treatment) cause comorbidities or vice versa. For the longitudinal designs, claims of causality depend on the extent of unmeasured confounding (and other modelling assumptions) and the ability to modify the 'exposure', i.e., comorbidities. The latter remains debated [252]. Some relevant confounders such as physical activity and time-varying use of co-medication (e.g., NSAIDs) were not available. Sensitivity analysis methods such as the E-value are available (i.e., size of potential confounder required to explain away the observed results [253]) but not universally accepted [254]. For illustration,

the odds ratio of 0.51 (95%CI 0.29 to 0.90) observed when comparing low disease activity (BASDAI 50/2) at 6 months between moderate-severe vs less than mild depression (Chapter 7) could be explained away by an unmeasured confounder that was associated with both the exposure and outcome by odds ratio of 2.2-fold each, above and beyond measured confounders; weaker confounding could not do so. A single unmeasured confounder of this effect size is highly unlikely.

Additional limitations include the fact that adaptations to the multimorbidity index have not been validated in axSpA. The main adaptation – excluding extra-articular manifestations – has been shown to make no meaningful difference to performance of another comorbidity index [152]. This validation is ongoing as part of research arising from this thesis. Comorbidities were considered as a fixed baseline 'exposure', whereas additional comorbidities are likely to accumulate with time and increasing age in practice. The mean follow-up duration was relatively short for the treatment response analyses, during which accumulation of comorbidities should have been negligible. Accounting for the time-varying nature of comorbidity burden is important for longer-term studies; for example, accumulation of comorbidities substantially accounted for excess mortality among women with RA [255].

8.3 Recommendations for clinical practice

8.3.1 Recording and screening for comorbidities

Comorbidities are more prevalent in axSpA than control populations and are present in the majority of axSpA patients [84]. They influence treatment decisions (e.g., for NSAIDs and bDMARDs [85]), while treatments can cause or contribute to many comorbidities (e.g., cardiovascular and peptic ulcer diseases). Comorbidities are associated with poorer outcomes including disease severity, work productivity and mortality [84]. Rheumatologists, who often follow patients over many years through which comorbidities may accrue, are uniquely positioned to facilitate the optimisation of these co-existing diseases.

Systematic and repeated assessments should be integrated into routine clinical practice to ensure holistic patient-centred management. The 2016 EULAR 'points to consider for comorbidities' recommended rheumatology teams to detect and collect information on comorbidities, liaise with appropriate healthcare providers to treat comorbidities, and

repeat comorbidity reviews [135]. They focused on six conditions: CVD, malignancies, infections, peptic ulcer, osteoporosis, and depression. Others have suggested including additional comorbidities [136], but this may be limited by feasibility in daily practice – the six conditions alone require a 93-item reporting form.

Recording comorbidities may not be enough. This thesis has shown that depression is the most prevalent comorbidity, yet the real burden of mental health in axSpA patients is likely much higher [9] given under-diagnosis is common. Data herein confirmed that diagnosis and symptoms correlate poorly. Mental health has direct relevance to rheumatologists because it significantly impacts treatment response [9,213,243], which may in turn affect long-term outcomes such as disability and quality of life. Suboptimal response to the first TNFi is common in axSpA and may be improved by optimising mental health symptoms. Additional assessment or screening should become part of routine clinical practice. One potential barrier to implementation is not knowing the optimal care pathway when mental health disorders (or indeed other comorbidities) are found.

8.3.2 Optimising and treating comorbidities

Despite the prevalence and impact of comorbidities, their management among patients with chronic inflammatory rheumatic diseases are often suboptimal [135]. The ASAS-COMOSPA study reviewed nearly 4000 SpA patients, and found suboptimal monitoring of comorbidities, particularly relating to vaccinations and some cancers (Figure 8.1) [89]. This highlights the need for holistic patient-centred, rather than single-disease focused, care provision.

Figure 8. 1: Proportion of patients optimally monitored for comorbidities as reported by the ASAS-COMOSPA study.

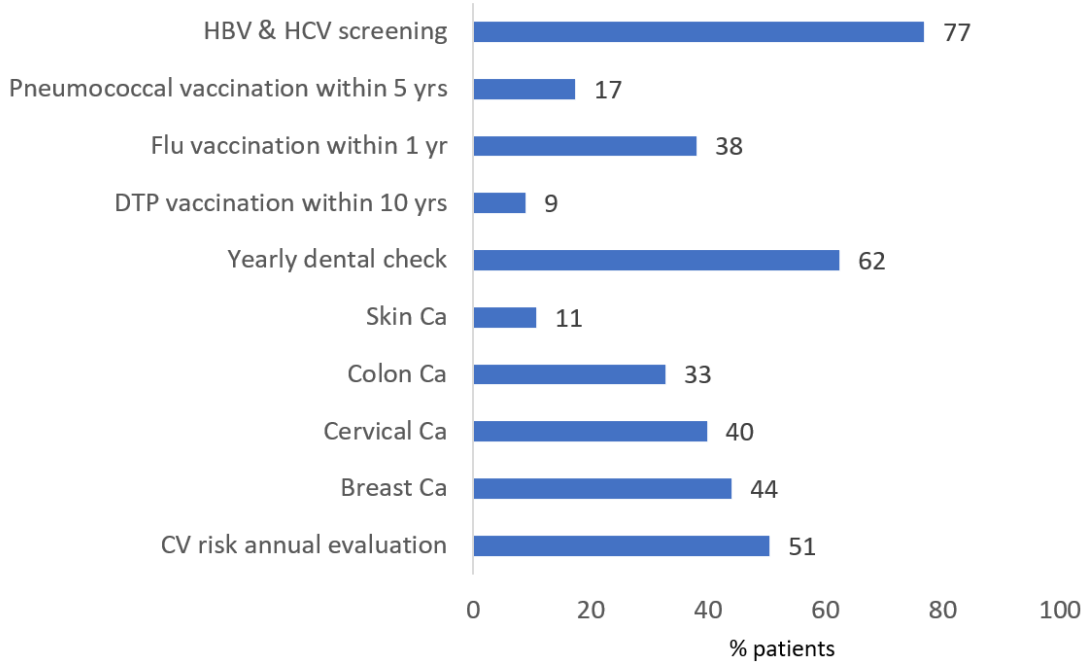


Figure adapted from Molto et al [89]. Ca, cancer; CV, cardiovascular; DTP, diphtheria/tetanus/polio. HBV, hepatitis B virus.

As set out by the EULAR recommendation [135], the first step is to identify and record comorbidities, followed by timely referral to appropriate healthcare services. Rheumatologists, who are accustomed to managing chronic multisystem diseases, are already experienced in facilitating/coordinating such holistic care. For example, axSpA patients often require joint management by ophthalmologists or gastroenterologists. Screening for comorbidities is also not new to rheumatology teams, who already systematically screen for latent or chronic infections and actively take part in their treatment prior to bDMARDs.

Some comorbidities are more challenging to manage. While there are many management options for depression and anxiety, they are often limited by accessibility, effectiveness, or tolerability [256]. Anti-depressants have limited efficacy and acceptability for severe depression and may have little role for milder symptoms. Evidence for talking therapies such as cognitive behavioural therapy (CBT) suggest remarkable effectiveness (e.g., number needed to treat as low as 3) but may not be suitable for more severe symptoms [257]; more

importantly, access to these therapies are often limited and/or accompanied by unacceptably prolonged delays [258].

Unlike many comorbidities, there is often no dedicated healthcare 'department' that takes ownership of mental health management in people with chronic physical conditions. Depression remains underdiagnosed and under-treated in patients with rheumatic conditions [259]. There has been growing integration of psychology into multidisciplinary rheumatology services in recognition of this [260], but currently only 39% of rheumatology departments have access to clinical psychology according to the recent British Society for Rheumatology national audit [261]. Management of rheumatic diseases has evolved significantly with development of protocolised, target-driven management pathways. As a result, patient-encounters have become more pressured with less time to take an exhaustive history or perform a holistic assessment. Assessment aids designed to promptly highlight psychological aspects of rheumatic illness in a busy clinical environment should be considered; for example, the HADS or the 4-question version of the Patient Health Questionnaire (PHQ-4).

8.3.3 Adapting practice in the presence of comorbidities

Chapter 5 showed that ASDAS was less associated with individual comorbidities and comorbidity burden than other indices. For example, individuals with and without comorbidity may have similar ASDAS but markedly different BASDAI. This suggests that routine assessment and monitoring of axSpA patients with multiple comorbidities should additionally include ASDAS. ASDAS is associated with radiographic progression (the axSpA disease process) whereas BASDAI is not [219]. This could mean that escalating to bDMARD based on BASDAI alone may not treat axSpA-specific pathology. However, until prescribing guidelines include ASDAS in healthcare systems such as in the UK, treatment decisions based on this index will be difficult to implement.

Chapter 6 showed that patients with or without comorbidity were able to achieve similar degrees of absolute disease activity reduction irrespective of the index used. This provides reassurance against the potential for 'double jeopardy' in comorbid axSpA patients; that is, having TNFi withdrawn after demonstrating inadequate response due to impact of comorbidities on disease activity assessment, even if axSpA-specific disease activity was improved. Both ASDAS and BASDAI are equally suitable for monitoring treatment response.

Patients and clinicians often benefit from being able to anticipate or predict future response. Results from this thesis should reassure both patients and clinicians that the ability to respond to TNFi, in terms of absolute disease activity reduction, does not appear to be significantly predicted by baseline comorbidity burden. Since comorbid patients start with higher disease activity, they will need greater absolute improvement and thus have lower odds of achieving 'low disease activity' states. Education and communication to patients should include these subtleties. Binary response definitions are used to determine ongoing treatment eligibility in the UK [190] which, along with future research methodology, may need to be reviewed in light of these results (see below). Patients with comorbidities may also find it helpful to know that, on average, it takes slightly longer to experience improvement in disease activity, function, health-related quality of life and sleep. Equally, clinicians may make allowances when assessing response; for example, delaying review by a few weeks, or allowing further reviews if initial response is not demonstrated. It helps both patients and clinicians to know that individuals who have high comorbidity burden, particularly males, are much more likely to discontinue their treatment. More detailed examination of causes of discontinuation, and why they should differ according to gender, are warranted in future studies.

8.3.4 Taking part in pragmatic trials

All three datasets used in this thesis have shown that comorbidities are highly prevalent in real-world patient populations. Despite this, RCTs – the gold-standard in evidence-based medicine – often exclude patients with many of these conditions; Table 8.1 provides some examples of exclusion criteria of TNFi trials in axSpA. This has important implications for routine practice, where guidelines and protocols are mostly derived from RCTs. Evidence-based practice is lacking for patients with certain comorbidities and is dependent on extrapolation.

Table 8. 1 Examples of randomised controlled trials of TNF inhibitors for axSpA and their exclusion criteria.

Trial	Disease	Drug	Exclusion
van der Heijde 2006 [183]	AS (mNY)	Adalimumab (Humira)	active/untreated TB, recent infections requiring antibiotics, hepatitis, HIV, demyelinating disease, multiple sclerosis. Cardiac, renal, neurologic, psychiatric, endocrine, metabolic, malignant, or hepatic diseases.
van der Heijde 2006 [262]	AS (mNY)	Etanercept (Enbrel)	bamboo spine, uncontrolled hypertension, unstable angina pectoris, congestive heart failure, severe pulmonary disease, cancer, demyelinating diseases of the CNS, serious infections.
Huang 2014 [263]	AS (mNY)	Adalimumab (Humira)	active/untreated TB, bamboo spine, unstable EAM (psoriasis, uveitis, IBD), HIV, Hepatitis B/C, recent infection (requiring treatment), listeriosis, histoplasmosis, immunodeficiency, chronic recurring infections, moderate/severe heart failure, recent cerebrovascular accident, demyelinating disease.
Dougados 2014 [264]	Nr-axSpA	Etanercept (Enbrel)	IBD/psoriasis flare within 6m
Landewe 2014 [265]	axSpA	Certolizumab pegol (Cimzia)	chronic/recurring infection, serious/life threatening infection (<6m prior), active/high risk TB, Hepatitis B/C, HIV.
mNY, modified New York criteria for AS; nr-axSpA, non-radiographic axSpA; EAM, extra-articular manifestations; IBD, inflammatory bowel disease.			

The BSRBR-AS chief investigators used an earlier version of the dataset to show that, compared to trial participants, TNFi initiators in the registry were older (by 6 years), more often female, and had poorer function (BASFI and BASMI) despite having similar BASDAI [266]. TNFi initiators in the BSRBR-AS had higher CRP than trial participants, which may be explained by BMI and/or comorbidities that were not reported to allow comparison. Only 41% of those starting TNFi (30% starting adalimumab) in the BSRBR-AS registry would have met eligibility criteria for at least one RCT. This highlights the need for real-world data to complement RCTs.

'Explanatory' RCTs aim to test efficacy under optimal situations, generally favouring those who are better educated, with higher socioeconomic status and better mental/overall health (i.e., those who are likely to adhere to treatment without adverse events). ASAS20 response was achieved by 62% of trial participants which was much higher than in the

BSRBR-AS, where 51% achieved ASAS20 (between 10 weeks and 9 months) among the 39% with available follow-up data [266]. Since those with unavailable data may have discontinued treatment, the true response rate is likely much lower. Differences between trial and real-world populations, between efficacy and effectiveness, are evident [266]; the same is also likely to apply to safety.

There is a 'middle ground' that bridges real-world observational data and explanatory RCTs: pragmatic trials [267]. Pragmatic trials are designed to measure effectiveness under real-world conditions, and (unlike explanatory RCTs that are often set up with regulatory approval in mind) to guide routine clinical practice. Pragmatic trials recruit and randomise representative patients, use clinically relevant comparators (i.e., not placebo), and follow participants over longer periods of time to study safety and other 'hard' (i.e., not surrogate) outcomes (e.g., radiographic progression). Clinicians should be aware of pragmatic trials, take part in them, and promote/demand their use to inform real-world guidelines. Current NICE protocols for guideline development and health technology assessment consider all types of randomised trials and observational studies, but they are nevertheless dominated by explanatory RCTs [268].

8.4 Recommendations for health policy

8.4.1 AxSpA guidelines

The current UK management guidelines from NICE recommend escalating to bDMARDs when high disease activity (typically BASDAI>4) persists despite NSAIDs. Results from this thesis suggest that the BASDAI definition of 'high disease activity' may need to be reconsidered for individuals with high comorbidity burden. ASDAS may be a superior index in preventing escalation to these potentially toxic drugs for symptoms that are not specific to the axSpA disease process.

Once started, NICE recommends that response to TNFi should be assessed at 12 weeks (16 weeks for secukinumab). Treatment should only be continued if there is clear evidence of response (i.e., BASDAI 50/2 response and spinal pain reduction of ≥2 units). NICE includes the following caveat: 'healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires, and make any adjustments they consider appropriate.

[190]' Results from this thesis support additional allowances for response to treatment in the presence of comorbidities, for example, allowing longer for response assessment.

The current response definition (based on BASDAI and spinal pain) is a compromise between 1) absolute response and 2) a fixed threshold for low disease activity/remission. This may be problematic for any patient group with high starting disease activity – for they are simultaneously more able to achieve the former and less able to achieve the latter, compared to those with lower starting disease activity. There are good arguments for both definitions; some patients may only be interested in being 'in remission' or having 'low disease activity', while others would be satisfied with any improvement to their current symptoms. One way for policy makers to decide is to look at the personal and societal benefits from each; for example, if quality of life or work productivity are only improved when remission is achieved, or if they improve proportionately with the degree of absolute disease activity change. Until these studies are available, clinicians should be aware that binary response definitions are highly dependent on starting disease activity and should be interpreted with caution outside of clinical trials.

8.4.2 Healthcare services

The main public health message relates to the need to provide holistic care that addresses comorbidities, particularly co-existing mental health conditions. In 2012, over half of the UK general population over the age of 65 had two or more co-existing chronic conditions [79]; this will continue to increase as the population ages. Patients attending rheumatology clinics with multiple disorders are increasingly the norm. This demographic shift has occurred in parallel with increasingly sub-specialised and protocol-driven disease management; therefore, it is essential that specialists remain proactive in treating patients holistically. Multidisciplinary services may be part of the answer. Some rare conditions, such as Behcet's disease, already benefit from multidisciplinary clinics involving other medical specialties, psychology and social support [260,269]. Similar services have been successful and well-received by patients for SpA [270].

Musculoskeletal and mental health disorders represent some of the biggest disease burdens in the developed world and thus the most likely to co-exist; when they do, there is evidence that they are synergistically detrimental on outcomes such as work [271]. Screening for depression and anxiety in rheumatology services have been discussed above; this should be part of the wider societal effort to improve awareness and provisions for mental health disorders. The World Health Organisation set out its comprehensive Mental

Health Action Plan in 2013 [272]; this was recently echoed by Public Health England's 'Every Mind Matters' campaign [273]. They acknowledge the essential role of mental health in achieving overall health for all people – a fact that rheumatology is increasingly recognising in both clinical practice and research.

Finally, lifestyle factors are directly relevant to rheumatic diseases (e.g., smoking in RA) and indirectly through comorbidities (e.g., SpA patients have higher risk of cardiovascular diseases that can be further increased by poor lifestyle). Education and interventions to promote behavioural change toward healthier lifestyles – e.g., relating to diet, smoking, weight, alcohol, physical activity – should be emphasised to prevent, or improve management of, comorbidities.

8.5 Recommendations for future research

8.5.1 Clinical research

8.5.1.1 Evidence for patient-centred care model

The importance of proactively managing comorbidities in rheumatology was highlighted by EULAR and this thesis, but evidence for its benefit on individual or health economic outcomes are lacking. Such evidence will be needed to support changes in policy, practice, or funding.

A fully patient-centred approach to care is more compatible within the primary, than secondary, care setting. A large pragmatic cluster RCT of 1546 patients in UK primary care compared the effectiveness of patient-centred multimorbidity management to usual care [274]. The '3D intervention' replaced disease-focused reviews with whole-person reviews that included several components thought to be important by this thesis and other research, for example, depression screening, social support, and health promotion. The intervention significantly improved 'patient-centred care' as defined by patient satisfaction, physician/nurse empathy, and compatibility with the 'Chronic Care Model' (organization of health care, clinical information systems, delivery system design, decision support, self-management support, and community resources). However, the primary outcome – quality of life at 15 months – was no different between the intervention and control arms. This finding was consistent with meta-analysis of several previous small trials [275]. There were also no differences in a series of secondary outcomes including HADS, self-rated health,

effect of illness on life, patient-reported treatment burden, medication adherence, or hospital admissions. Cost-effectiveness, in terms of cost per quality-adjusted life year gained, was also equivocal [276].

It is unlikely that similar interventions in secondary care will show superior outcomes given the 3D trial findings. But, as the authors pointed out, improving patient experience is one of the triple aims of health care, thus providing care that is demonstrably more patient-centred is arguably sufficient justification for implementation in itself [274]. Future research, preferably pragmatic trials, should examine the individual and health economic benefits of holistic approaches to comorbidity management in rheumatology services. Successful optimisation of comorbidities, particularly depression, may have direct benefits on axSpA outcomes such as treatment response and, in turn, quality of life and work productivity.

8.5.1.2 Mental health interventions

Preliminary observational data show that clinical psychology interventions integrated into routine rheumatology services can halve psychological distress and reduced need for rheumatology outpatient follow-up by a third [270]. Direct comparison against usual care in pragmatic trials are required to support wide adoption of these integrated interventions. The following examples can inform the design of such trials.

Compared to rheumatologist-led care of RA, nurse-led management (that, among other things, included a 3.3-fold greater provision of psychosocial support and 1.8-fold more education) led to no difference in satisfaction, and no clinically meaningful difference in HADS or quality of life improvement. Nurse-led care also resulted in smaller improvements in perceived self-efficacy, but superior improvements in pain and physical function. Analogous results have been reported for nurse-led (vs GP-led) care of gout that included 1) holistic assessment, education, shared decision making and discussion of illness perceptions, and 2) treat-to-target urate-lowering therapy. Nurse-led care was superior for reducing urate levels and flares; this group also reported superior improvement in the physical component of SF-36 (a quality of life instrument) but not mental health [277]. In both examples, many other clinical parameters (e.g., treatment changes) differed between the trial arms; therefore, it is difficult to attribute results to holistic management.

Future trials should separate direct axSpA interventions from those for optimising mental health. They will also likely need well-defined mental health interventions, rather than non-

specific psychosocial support. Such interventions could include additional cognitive behavioural or related 'talking' therapies for individuals with depression/anxiety, particularly those who have additional psychosomatic symptom burden. These considerations, and the need to expand capacity for mental health research that translates to patient benefit, are relevant to chronic disease management beyond rheumatology.

8.5.1.3 Risk prediction for comorbidities

Although not directly related to this thesis, targeted and individualised approach to comorbidity management should include primary prevention. For example, axSpA patients are at higher risk of depression, fractures and cardiovascular disease [9,278,279]. Identifying individuals at high risk of developing these comorbidities could inform targeted screening or prevention. Such tools for depression or other mental health disorders do not exist, while current population-level prediction algorithms for CVD and fractures are unlikely to be accurate for axSpA populations [280]. Further research is needed to develop and/or optimise risk prediction tools for this patient population.

8.5.1.4 Pragmatic trials

Pragmatic trials have been promoted in several sections of this thesis. This section briefly describes novel designs that are similar to observational registries and should be considered for future research. Challenges in recruiting for a sufficiently large trial on psychosocial interventions were recognised by the Scleroderma Patient-centred Intervention Network (SPIN). The group are using a cohort multiple RCT (also known as 'Trials within Cohorts' or registry-based RCT [281]) design to regularly collect a set of core outcomes from a real-world cohort [282], analogous to the BSRBR-AS. These data are then used to identify potential participants to be assigned to an intervention, who are compared to non-assigned individuals in the cohort. Multiple interventions can be compared, in this case non-pharmacological psychosocial or rehabilitation interventions [282]. One advantage of randomisation using an existing cohort is that all eligible individuals will be offered the intervention, compared with traditional pragmatic RCT design where, for example, 50% of those eligible will be randomised to control. Other differences are shown in Table 8.2.

Table 8. 2: Comparison of registries, registry-based RCTs, and RCTs.

Design	Advantages	Disadvantages
Registries and observational studies	• Ideal for description of standards • Real-world, generalisable cohorts • Large numbers allow for the study of rare events • Relatively inexpensive	• Data quality is variable • Limited use for comparative outcomes research • Confounding
Randomised clinical trials	• Well-designed studies with adequate power • Removes confounding factors	• Highly selected populations • Recruitment often at specialised centres • Often uses surrogate end points • Expensive • Rarely compares interventions that have no economic benefit
Registry-based randomised clinical trials	• Removes confounding • Less-selected patient populations • Large numbers allow for the study of rare events	• Data quality may be variable • Dropout will be higher • Limited outcomes
Adapted from James et al **[283]**.		

8.5.2 Research methodology

This thesis demonstrated the importance of using and reporting a range of different methodological approaches. Future research on comorbidities should consider adopting a combined approach by examining individual conditions in the context of overall comorbidity burden or comorbidity clusters. When using comorbidity count in analyses, weighted scores should not be used for outcomes for which it was not validated. Comorbidity count should not only be dichotomised (present vs absent), since there may be valuable insights offered by continuous or categorical variable types. For example, results from this thesis suggested non-linear relationships between comorbidity count and some treatment outcomes.

This thesis also demonstrated markedly different results when using each of the three definitions of treatment (binary, absolute change, and time-to-discontinuation). Limitations of binary outcome measures on statistical power and causal inference are well-described in the literature [284], yet they remain the preferred and often the only outcome used. Their limitations should be fully acknowledged in future studies, which should preferably be accompanied by analyses using continuous indices. Any patient group with high disease activity at baseline will simultaneously be more able to achieve a fixed or proportional

reduction (because there is more capacity for improvement) and less able to achieve a threshold for low disease activity (because a greater absolute improvement is required). In support of results in this thesis, studies in RA showed that high baseline DAS28 simultaneously increased odds of ACR70 response and decreased odds of DAS remission [285]. Using outcomes from RCTs (e.g., ASAS20 or ACR70), where baseline disease activity is balanced, is inappropriate for observational comparisons when it is not. Adjusting for baseline disease activity may not be a robust solution when using binary outcomes [41].

Future studies should adopt a more considered approach to confounder selection – one that differs according to whether the aim is for prediction or causation [187,251]. For causation, confounder selection should be based on existing knowledge and/or literature review, preferably supported by transparently declared assumptions in the form of causal diagrams. Variable selection methods that are popular for prediction (e.g., univariate screening or stepwise variable selection) should not be used for questions of causation. Researchers should declare the aim of their analysis and highlight limitations in the ability to infer causation. For manipulatable exposures, the gold-standard methodological approach is to use observational data to emulate the design of a hypothetical RCT [161].

8.6 Future research projects related to this thesis

Results from this thesis (and parallel projects on smoking in the BSRBR-AS [7]) have suggested subtle differences between male and female participants, which may be due to the different ways in which they respond to questionnaires generally, and in the context of some comorbidities, such as depression. The axSpA disease process itself is also well-known to differ between sexes, for example, phenotype, prognosis and treatment response [286]. Therefore, future research following on from this thesis will include more detailed examination of gender differences; for example, why treatment discontinuation differs.

Having identified depression and anxiety as a major unmet need within rheumatology, future research should explore – with input from patients and allied health professionals throughout – feasible and acceptable solutions for treatment and strategies for implementation. Clinical psychology input would be ideal but is limited, for example, by funding. A small pilot study of 35 axSpA patients is underway to assess the feasibility and acceptability of internet-delivered CBT for those with depression or anxiety (REC reference 19/NI/0066). This may be promising given its low cost, availability, and acceptability by the

comparatively younger axSpA patients. Lastly, work is ongoing to validate the multimorbidity index (MMI [148]) against other comorbidity indices in an axSpA population. The MMI is comprehensive but labour-intensive to collect. Other, simpler indices (e.g., the self-reported comorbidity index [93]) may be more practical for routine practice.

8.7 Conclusions

Comorbidities are present in the majority of real-world axSpA populations, regardless of the disease stage (i.e., nr-axSpA vs AS). Mental health and cardiovascular comorbidities are by far the most prevalent comorbidities, with mental health having the largest and most consistent impact on axSpA disease assessment and treatment response. These results have important clinical and policy implications for the current approach to disease assessment, including eligibility for initiating (using ASDAS rather than BASDAI) and continuing bDMARDs (using both binary and continuous response definitions). Evidence-based practice is underpinned by RCTs that often exclude comorbid patients. Results of this thesis also highlighted the potential impact of comorbidities on treatment response (e.g., function and health-related quality of life) and discontinuation, that may explain differences between real-world effectiveness and RCT efficacy. Future research will benefit from a broader and more methodologically robust approach to studying comorbidities and treatment outcomes (e.g., comorbidity clusters and outcome-types). Having described the problem of poor response rates to bDMARD treatment, the thesis concluded with a search for a solution: optimising mental health symptoms before or at treatment initiation may provide substantial improvements to treatment response – with effect sizes that are magnitudes larger than seen in RA or with other 'modifiable' risk factors of poor-response (e.g., smoking) in axSpA. Healthcare providers should routinely record and refer comorbidities for optimal management. The importance of multimorbidity – particularly mental health disorders that are often under-recognised – and methodological approaches adopted in this thesis have wider applicability to chronic disease management beyond rheumatology.

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10. Appendices

The chapter includes supplementary data for each chapter, for example, full model coefficients for figures or sensitivity analyses. Tables and figures were numbered to match their respective chapter (e.g., Figure S2.x relates to Chapter 2).

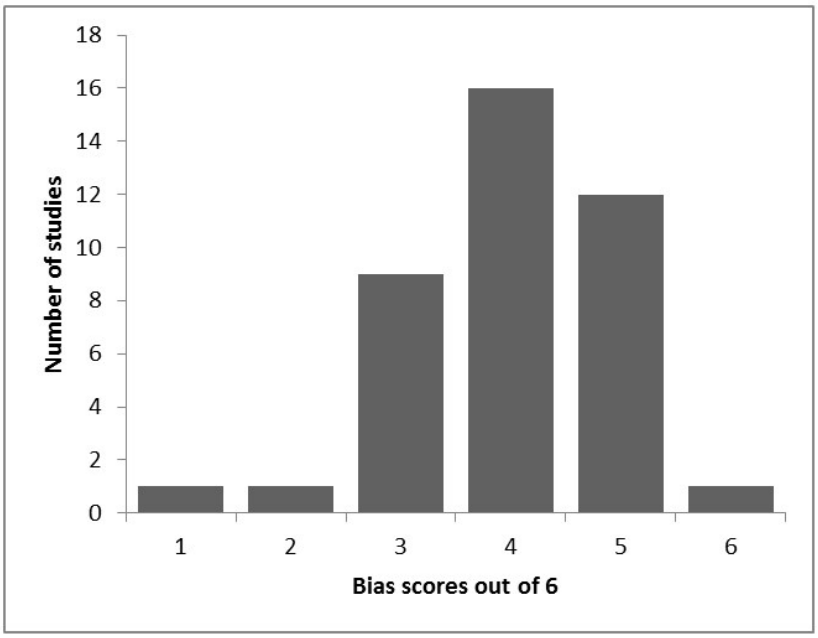
10.1 Appendix for Chapter 2

Table S2. 1: Risk of bias assessment using a modified Newcastle-Ottawa Scale.

Study	Representativeness	Sample Size	axSpA definition	Ascertainment of comorbidities	Total
Ahmed 2016	2	0	1	1	4
Bremander 2011	2	0	1	1	4
Claudepierre 2019	2	0	1	1	4
Cook 2018	2	0	0	0	2
Dougados 2015	1	0	2	2	5
Essers 2016	2	0	1	1	4
Fernandez-Carballido 2019	1	1	2	0	4
Fitzgerald 2019	1	0	2	2	5
Garip 2016	1	0	2	1	4
Gladman 2011	1	0	2	2	5
Hammoudeh 2015	1	0	1	2	4
Haroon 2015	2	0	1	1	4
Jiang 2018	1	0	2	2	5
Kang 2010	2	0	1	1	4
Lindström 2018	1	0	2	1	4
Ljung 2018	1	0	2	2	5
Nikiphorou 2018	1	1	2	2	6
Oldroyd 2009	1	0	2	0	3
Redeker 2019 [abstract]	2	0	1	1	4
Singh 2019	1	0	0	0	1
Sommerfleck 2018	1	0	2	2	5
Stolwijk 2014	1	0	2	2	5
Walsh 2018	2	0	1	1	4
Zhao 2019 (UK)	1	0	2	2	5
Zhao 2019 (US)	1	0	2	1	4
Ara 2008	1	0	2	2	5
Bodur 2012	1	0	2	2	5
Exarchou 2016	1	0	1	1	3
Han 2006	2	0	1	1	4

Hong 2019	1	0	2	2	5
Kristensen 2015	1	0	1	1	3
Krüger 2018	2	0	1	1	4
Maas 2016	1	0	2	0	3
Png 2019	1	0	2	0	3
Ward 2013	1	0	2	0	3
Zhao 2018	1	0	2	2	5
Lee 2018	2	0	1	1	4
Boonen 2001	1	0	2	0	3
Iannone 2018	1	0	2	0	3
Salaffi 2009	1	0	2	0	3
Representativeness: 2 for population or primary care level data, 1 hospital, 0 more selective (e.g. for biologic DMARD treatment). Sample size: 1 if justified, 0 if not. axSpA definition: 2 for classification criteria or physician diagnosis; 1 for diagnostic codes; 0 if self-reported. Ascertainment of comorbidities: 1 if diagnostic code; 0 if self-reported. 0 if unclear/unreported.					

Figure S2. 1: Distribution of bias scores using modified Newcastle Ottawa Scale.



10.2 Appendix for Chapter 3

Table S3. 1: ICD codes used in the Boston axial spondyloarthritis study.

	ICD 9	ICD 10
Atrial fibrillation	427.3x	I48.x
alcohol problems	291.x	F10.x
	303.0x 303.9x	
	305.x	
	357.5	G62.1
	425.5	I42.6
	535.3x	K29.2x
	571.0, 571.1, 571.2, 571.3	K70.x, K70.xx
	760.71	P04.3, Q86.0
	V11.3	Z65.8
Anorexia/bulimia	307.1	F50.0x
	307.51	F50.2
	783.0	R63.0
Anxiety/neurotic disorders	293.84	F06.4
	300.x 301.x 308.x 309.x	F40.x F41.x F42.x F43.x F45.x F48.x F60.x F68.x
	313.0	F93.8
	V62.8	
	V65.2	Z76.5
Asthma	493.xx	J45.x
Blind/low vision	360.41 360.42 438.7	
	362.x 366.x 368.x 369.x	H35.x H25.x H26.x H27.x H28 H53.x H54.x
Bronchiectasis	494.x	J47.x
	748.61	Q33.4
Cancer	140.x to 239.x	C00.x to C96.x, D00.x to D49.x
	338.3	
	357.3	
	365.64	
	377.51	
	377.52	
	377.61	
	377.71	
	511.81	J91.0
	789.51	R18.0
	795.06	R87.614
	795.16	R87.624
	796.76	R85.614
	V10.x	Z85.x
	V58.42	Z48.3
	V71.1	
Coronary heart disease	410.x 411.x 412 413.x 414.x	I20.x I21.x I22.x I23.x I24.x I25.x
	429.2	
	429.7x	I51.x

Chronic liver disease	456.0 456.1 456.2x	I85.1x
	571.x	K70.x to K77.x
	572.2 572.3 572.4 572.8	
	573.x	
	573.0	
	789.1	R16.0
Chronic sinusitis	473.x	J32.x
Chronic kidney disease	249.4	E08.21 E09.21
	250.4x	E11.29 E11.21 E10.29 E10.21
	285.21	D63.1
	403.x	I12.x
	404.x	I13.x
	581.x 582.x 583.x	N04.x
	585.x 586.x 587.x 588.x	N03.x N18.x N19 N25.x N26.x
	753.x	Q61.x
	792.5	R88.0
	996.56 996.68	T85.611x T85.621x T85.631x T85.691x T85.71x
	996.73 996.81	T82.4x T86.1x
	E879.1	Y84.1
	V42.0	Z94.0
	V45.1x	Z99.2
	V56.x	Z49.x
COPD	491.x 491.xx	J41.x J42 J43.x J44.x
Dementia	290.x	F01.x F02.x F03.x
	291.2	F10.27
	292.82	F19.97
	294.1x 294.2x	
	331.x	G30.x G31.x G32.x
Depression	296.2x 296.3x	F32.x F33.x
	296.82	F32.8
	309.0 309.1	F43.21
	311	F32.9
Diabetes	249.x 250.x	E08.x to E13.x
	357.2	E10.42 E11.42 E13.42 E09.42 E08.42
	362.0x	
	366.41	E10.36 E09.36 E08.36 E11.36 E13.36
	648.0x	O24.x
	V45.85	Z96.41
	V58.67	Z79.4
	V65.46	Z46.81
Diverticulitis	562.x	K57.x
Epilepsy	345.x	G40.x
	649.4x	
Fibromyalgia	729.1	
Glaucoma	365.x	H40.x H42.x
	377.14	H47.239
Hearing loss	315.34	F80.4

	388.0x 388.1x 388.2 389.x	H90.x H91.x H93.0x
	744.0x	Q16.x
	V41.2	Z97.4
	V53.2	Z46.1
Heart failure	398.91	I09.81
	402.01 402.11 402.11 402.91	I11.0
	404.9x	I13.0 I13.2
	428.x	I50.x
Hypertension	401.x to 405.x	I10.x to I16.x
	642.x	O10.x O11.x O13.x to O16.x
	796.2	R03.0
	997.91	I97.3
IBD	555.x 556.x 558.x	K50.x 51.x K52.x
IBS	564.x	K58.x K59.x
Learning disability	314.0x 314.1x	F90.x
	315.x	F80.x to F89.x
	V40.0	F81.9
Migraine	346.x	G43.x
Multiple sclerosis	340.x 341.x	G35.x G37.x
Obesity	278.0x	E66.x
	783.1	R63.5
	V85.3x V85.4x	Z68.3x Z68.4
Osteoporosis	733.0x 733.1x	M80.x M81.x
Other substance misuse	292.x 304.x 305.x	F11.x F12.x F13.x F14.x F15.x F16.x F18.x F19.x
	648.3.x	O99.32x
	E962.0	NOD.X
	V65.42	Z71.41
Parkinson's disease	094.82	A52.19
	332.x	G20.x G21.x
	E936.x	T42.76x
Prostate disorders	098.12	A54.22
	098.32	A54.22
	131.03	A59.02
	222.2	D29.1
	600.x 601.x 602.x	N40.x N41.x N42.x
	V10.46	Z85.46
Psoriasis/eczema	696.x	L41.x L41.x
	691.x 692.x	L20.x L30.9
Peripheral vascular disease	249.7x	
	250.7x	
	440.2x 440.3x 440.4	I70.2x I70.3x I70.4x I70.5x I70.6x I70.7x
	443.x	I73.x
	997.2	T81.72XA T81.719A
Schizophrenia/bipolar	295.x	F20.x
	296.x	F30.x F31.x
	V11.0	Z65.8
Stroke/TIA	342.x	G81.x
	430.x to 438.x	I60.x to I69.x

	674.00	O99.419
	V12.54	Z86.73
Thyroid disorders	226	D34
	240.x to 246.x	E00.x to E07.x
	376.21	H05.89
	648.1x	
	E932.7 E932.8	
Constipation	564.0x	K59.0x
Dyspepsia	535.x	K29.x K30.x
	787.1	R12
Viral hepatitis	070.x	B15.x to B19.x
	V02.6x	
Fibromyalgia	729.1	Z79.7
Uveitis	364.x	H20.x
Smoking	305.1x	F17.2xx
	649.0x	O99.33
	989.84	T65.2x

10.2.1 Summary of data preparation for the BSRBR-AS

For the initial analyses of the BSRBR-AS, individual data files were provided by the investigators (e.g., 14 visit files, 9 questionnaire files, one file for deprivation indices, etc.). The following section describes the process with which they were prepared for analysis. Some of the following methods was used by the BSRBR-AS investigators to process final versions of the data. The final version of the BSRBR-AS data was used for analyses shown in the thesis. This version was provided as only 4 files: recruitment data, visits, questionnaires, and TNFi timeline.

Early downloads of the BSRBR-AS dataset included individuals in the non-biologics arm with prior biologic exposure records (could be data entry error or inappropriately recruited). This was checked in the latest download.

Some SpA features (uveitis, IBD, psoriasis) were recorded twice: once as components of ASAS criteria, and again in the targeted medical history that 1) specifically enquires about the past 6 months and 2) are physician confirmed diagnoses. If patients had physician-confirmed records of these features, they should also fulfil the corresponding ASAS components. Inconsistencies were corrected. For descriptions of participant characteristics, physician-confirmed diagnoses were used. A participant with known history of dactylitis, arthritis or enthesitis may not report an episode in the past 6 months; therefore, the SpA criteria were used instead of the targeted medical history for prevalence description. HLA-

B27 status was recorded twice: as component of ASAS criteria and again as its own variable. Overall, positivity was defined as a positive result from either variable. There were no conflicts regarding positive and negative results from the two variables; each helped populate unknown variables in the other.

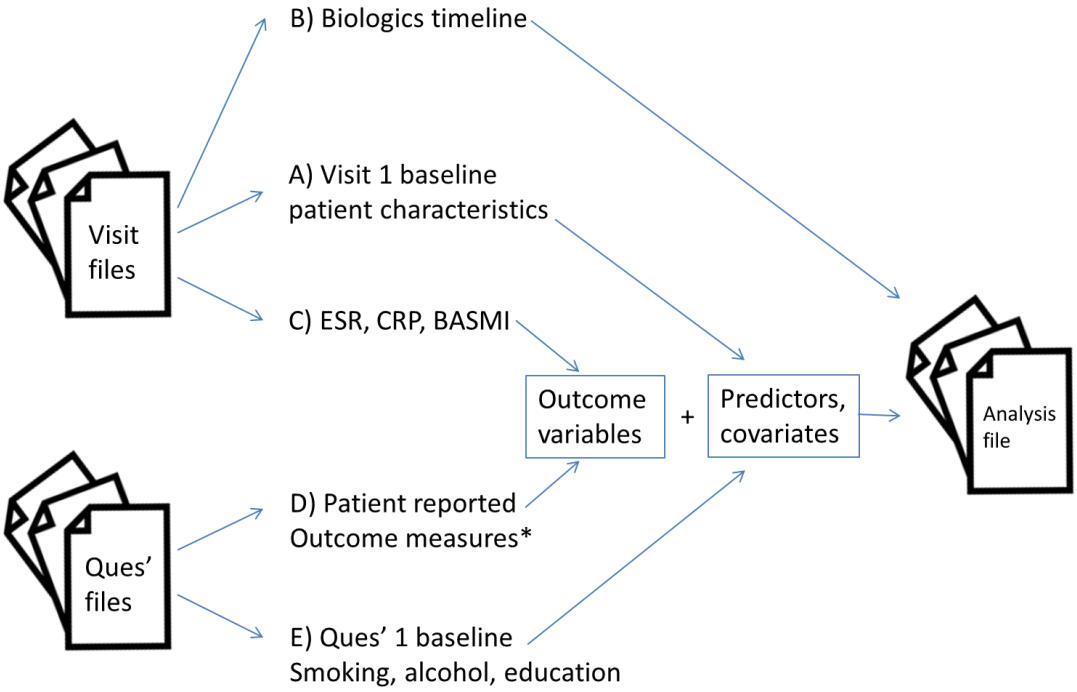
Classification using the modified New York and ASAS criteria were performed. All patients met classification criteria for AS or axSpA: 1757 (65%) met criteria for AS, whilst 2508 (93%) met ASAS criteria for axSpA (imaging criteria met by 2395 and clinical by 1406).

All variables were then renamed and relabelled. The following variables were generated:

- Age (date of first visit – DOB)/365.25
- Year of visit
- Age at symptom onset (year of onset – year of birth)
    - Those with age at symptom onset younger than 5 were replaced as missing
    - Age at symptom onset that were older than age at recruitment were replaced with age at recruitment (i.e., they could be diagnosed at recruitment, but not after recruitment).
- Symptom duration (age – age at symptom onset)
    - Due to discrepancies in the accuracy (decimal places) of above variables, those with negative symptom duration were set to 0.
- Number of comorbidities (sum of 13 comorbidities: hypertension, angina, MI, heart failure, stroke, diabetes, asthma, 'bronchitis', depression, cancer, kidney disease, peptic ulcer, and liver disease)

The first visit file was saved as baseline 'time-independent' characteristics (File A) (Figure S3.1). Visit files (14 in total) were then combined and split into B) biologic information (each visit can have up to 3 entries for biologics information; these were converted from wide into long format), and C) ESR/CRP/BASMI labelled by visit and result dates.

Figure S3. 1: Preparation of the analysis file from data files provided by the BSRBR-AS.



*15 outcome variables including: disease activity (BASDAI, ASDAS, spinal pain, ESR, CRP), functional impairment (BASFI, BASMI), quality of life (ASQoL, EQ-VAS, EQ5D-3L), BASG, Chalder Fatigue Scale, Jenkins Sleep Evaluation Questionnaire, Hospital Anxiety and Depression Scale.

Questionnaire files (9 in total) were then combined and split into: D) all patient reported outcome measures (patient global, BASG, ASQoL, EQ5D, EQ-VAS, CFQ, JSEQ, HADS, spVAS, BASDAI-Q2/Q3/Q6, BASDAI, BASFI) labelled by questionnaire date, and E) patient characteristics variables (education, smoking, alcohol).

File B) was converted into a treatment timeline:

1. Only patients with a biologic start-date were kept (this includes those in the non-biologic group who later start treatment).
2. Biosimilar names were changed to generic names. For example, switch from Enbrel to Benepali was not considered discontinuation of treatment, based on the assumption that if a serious adverse event or inefficacy occurred with the bio-originator, the patient would receive a different TNFi instead of a biosimilar.
3. For each patient, the earliest start-date for each biologic was selected as the final start-date; the latest biologic stop-date or 'missing' stop-date (i.e., never stopped)

was set as the final stop-date for that biologic. This accounted for those who stop and start the same treatment – which can be assumed to be temporary stops, since inefficacy or serious AE would necessitate permanent cessation. This process also accounted for biosimilar switches.

4. Pauses in treatment of longer than 3 months was considered discontinuation.
5. The last visit or questionnaire date to help create a 'censor' date (relevant for Cox models) for those who do not have a stop-date. (Note many patients do not have further visits but still return questionnaires, for these patients their last questionnaire date was used as censor date instead.)
6. All entries were de-duplicated leaving one entry for each biologic for each patient.

Files C) and D) were merged according to ID and categorised time. At this stage, no imputation was performed. Note carrying forward/backwards is difficult to justify, particularly for baseline values, since treatment is likely to improve all measures. Note also that a patient can have ≤1 questionnaire but still have >1 CRP/ESR/BASMI. This file (C+D) was then merged with the timeline for first biologic (file B) to establish whether the patient was on treatment on that assessment date.

For file E), missing smoking, education and alcohol data at baseline were carried backwards from when they first became available. For example, in the early download of the data, smoking data was missing for 85 patients before this process and 24 after; education 43 to 33; alcohol 98 to 43. File E) was then de-duplicated by patient to give baseline values that was then merged with other baseline characteristics derived from baseline visit file (File A).

For survival analyses, time was defined by duration in days between TNFi start date and: 1) TNFi stop date (main even of interest), 2) last visit date or last questionnaire date if no visit date (censoring). Individuals with zero follow-up time (i.e., started TNFi but did not have further contact with the study) were assigned 0.001 days.

For longitudinal analyses, date of starting first TNFi was used to define the baseline, that is, as the reference point with which the window of acceptable assessments was defined. Baseline data from visits or questionnaires had to come from within 1 year before or 7 days after the TNFi start date. Only assessments made between TNFi start and stop dates (i.e., while on treatment) were included. For any missing disease indices, the last value was carried forward provided it was from within 30 days.

10.2.2 Covariance/correlation structure for longitudinal analyses

Measurements take through time on the same individual are correlated. The correlation (or covariance) between data points can be assumed, for example, to be equal (exchangeable), more closely correlated if closer together in time (auto regressive), different for all pairs of observations (unstructured). Specifying the 'correct' correlation/covariance structure is difficult. For GEE, a temporary assumption can be made before estimating coefficients, with subsequent adjustment to the standard errors to give valid inferences (i.e., Huber-White or 'robust' standard errors). Estimates and standard errors tend to be similar regardless of correlation structure [191].

Covariance structure is analogous for mixed effects models. The random part of the model separates within- and between-individual changes (which is further separated into variance for intercept and slope and their covariance). This has two implications: 1) effects are conditional (i.e., individual, rather than marginal/population-level) and 2) the random effects are of direct interest (c.f. GEE where they are not). A detailed discussion of the variance-covariance structure is beyond the scope of this section, and derived inference not of primary interest in this analysis. In this thesis, the default covariance structure was used ('independent', i.e., equal variances for random effects, all covariances 0). This may or may not be appropriate; therefore, each of the other structures were tested for a single, illustrative model to see whether conclusions were meaningfully changed.

10.3 Appendix for Chapter 4

Table S4. 1: Characteristics of 646 axSpA Boston patients meeting full classification criteria, compared according to diagnosis.

	Ankylosing spondylitis (n=553)	Non-radiographic axSpA (n=93)	P-value
Age, years	52.9 (16.2)	44.4 (14.2)	<0.001
Male	420 (76%)	57 (62%)	0.004
BMI (kg/m2)	27.8 (6.0)	26.5 (4.3)	0.170
Smoking	57 (10%)	10 (11%)	0.900
HLA-B27 tested	334 (60%)	68 (73%)	0.019
HLA-B27 positive	270 (81%)	54 (79%)	0.790
Family history*	74 (13%)	19 (21%)	0.054
Uveitis	148 (27%)	28 (31%)	0.400
Psoriasis	69 (13%)	6 (7%)	0.110
IBD	54 (10%)	6 (7%)	0.350
Peripheral arthritis	101 (18%)	18 (20%)	0.700
Enthesitis	22 (4%)	5 (6%)	0.490
Dactylitis	13 (2%)	1 (1%)	0.450
ESR tested	234 (42%)	39 (42%)	0.950
ESR result (mm/hr) median (IQR)	13.0 (6.0 to 27.0)	8.0 (4.0 to 17.0)	0.019
CRP tested	290 (52%)	48 (52%)	0.880
CRP result (mg/dl), median (IQR)	3.3 (1.2 to 10.6)	2.6 (0.7 to 5.8)	0.034
Pain VAS available	199 (36%)	38 (41%)	0.370
Pain VAS	2.3 (3.1)	2.9 (3.2)	0.250
Comorbidity count**, mean (SD)	1.4 (2.1)	1.1 (1.9)	0.160

Data shown as mean (SD) and n (%) unless otherwise specified.
BMI, body mass index; VAS, visual analogue scale; IQR, interquartile range; SD, standard deviation; IBD, inflammatory bowel disease.
*family history of axial spondyloarthritis, psoriasis, uveitis, reactive arthritis or IBD.
**number of comorbidities among a list of 39 chronic conditions

Table S4. 2: Medications used among 646 axSpA patients meeting full classification criteria, compared according to diagnosis.

	Ankylosing spondylitis (n=553)	Non-radiographic axSpA (n=93)	P-value
bDMARDs	316 (57%)	54 (58%)	0.870
Adalimumab	187 (34%)	31 (33%)	0.930
Etanercept	166 (30%)	25 (27%)	0.540
Infliximab	76 (14%)	13 (14%)	0.950
Golimumab	25 (5%)	5 (5%)	0.789
Certolizumab pegol	18 (3%)	2 (2%)	0.754
Secukinumab	21 (4%)	4 (4%)	0.772
Ustekinumab	10 (2%)	0	0.372
csDMARDs	139 (25%)	24 (26%)	0.890
Sulfasalazine	66 (12%)	12 (13%)	0.790
Methotrexate	94 (17%)	17 (18%)	0.760
Leflunomide	3 (1%)	2 (2%)	0.153
NSAIDs	419 (76%)	78 (84%)	0.086
Ibuprofen	202 (37%)	46 (49%)	0.018
Naproxen	181 (33%)	37 (40%)	0.180
Indomethacin	135 (24%)	22 (24%)	0.870
Celecoxib	103 (19%)	15 (16%)	0.560
Diclofenac	79 (14%)	17 (18%)	0.320
Meloxicam	55 (10%)	16 (17%)	0.038
Prednisone	194 (35%)	37 (40%)	0.380

*Each drug category consists of drugs listed in the remainder of the table. bDMARD, biologic disease modifying anti-rheumatic drugs; csDMARD, conventional synthetic DMARD; NSAID, non-steroidal anti-inflammatory drugs.

Table S4. 3: Characteristics of Aintree axSpA patients according to presence or absence of comorbidities, excluding obesity.

	Isolated axSpA (n=164)	axSpA with comorbidities*** (n=255)	P-value
Age, years	40.0 (12.9)	49.0 (14.1)	<0.001
Male	114 (70%)	177 (69%)	0.98
Modified New York criteria for AS	135 (82%)	210 (82%)	0.99
HLA-B27 positive*	66 (62%)	92 (56%)	0.34
Symptom duration, median (IQR) years	10.6 (3.8 to 20.1)	18.9 (8.4 to 30.2)	<0.001
BMI, kg/m^2	27.4 (5.2)	28.7 (5.9)	0.045
Deprivation index**, median (IQR)	2.0 (1.0 to 6.0)	2.0 (1.0 to 5.0)	0.29
Current smoker	53 (34%)	84 (35%)	0.45
Ex-smoker	23 (15%)	46 (19%)	
Never smoked	78 (51%)	108 (45%)	
NSAIDs	31 (19%)	40 (16%)	0.392
Peripheral joint involvement	40 (26%)	73 (30%)	0.48
Uveitis	39 (25%)	61 (24%)	0.88
Psoriasis	33 (21%)	40 (16%)	0.18
IBD	19 (12%)	21 (8%)	0.19
Disease severity measures:			
EuroQoL, median (IQR)	0.6 (0.1 to 0.8)	0.5 (-0.02 to 0.7)	<0.001
Global health, median (IQR)	4.8 (2.3 to 6.4)	5.2 (3.5 to 7.1)	0.005
Fatigue, median (IQR)	5.1 (3.0 to 7.1)	6.3 (3.8 to 7.7)	0.021
BASDAI, median (IQR)	5.6 (3.6 to 7.2)	6.4 (3.9 to 8.1)	0.011
Spinal pain, median (IQR)	6.0 (3.0 to 8.0)	7.0 (4.0 to 8.0)	0.029
BASFI, median (IQR)	4.5 (2.2 to 6.7)	6.8 (4.1 to 8.4)	<0.001
ESR (mm/hr), median (IQR)	10.0 (5.0 to 27.0)	13.0 (5.0 to 29.0)	0.067
CRP (mg/L), median (IQR)	4.0 (1.0 to 17.0)	5.0 (1.0 to 12.0)	0.80

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

Table S4. 4: Prevalence of 39 comorbidities compared between AS and nr-axSpA patients in the Boston study. Sensitivity analysis restricting to individuals meeting full classification criteria.

		Ankylosing spondylitis (n=553)	Non-radiographic axSpA (n=93)	P-value
1	Alcohol problems	8 (1%)	2 (2%)	0.64
2	Anorexia or bulimia	4 (1%)	0 (0%)	1.00
3	Anxiety and other neuroses	56 (10%)	12 (13%)	0.46
4	Asthma	23 (4%)	3 (3%)	1.00
5	Atrial fibrillation	33 (6%)	1 (1%)	0.05
6	Blind or low vision	16 (3%)	0 (0%)	0.15
7	Bronchiectasis	3 (1%)	0 (0%)	1.00
8	Cancer	56 (10%)	8 (9%)	0.85
9	Chronic kidney disease	17 (3%)	0 (0%)	0.15
10	Chronic liver disease	23 (4%)	4 (4%)	1.00
11	Chronic sinusitis	6 (1%)	0 (0%)	0.60
12	Constipation	22 (4%)	2 (2%)	0.56
13	COPD	9 (2%)	1 (1%)	1.00
14	Coronary heart disease	57 (10%)	7 (8%)	0.57
15	Dementia	4 (1%)	0 (0%)	1.00
16	Depression	40 (7%)	8 (9%)	0.67
17	Diabetes mellitus	39 (7%)	5 (5%)	0.66
18	Diverticular disease	21 (4%)	2 (2%)	0.56
19	Dyspepsia	16 (3%)	4 (4%)	0.51
20	Epilepsy	3 (1%)	0 (0%)	1.00
21	Fibromyalgia	0 (0%)	1 (1%)	0.14
22	Glaucoma	5 (1%)	1 (1%)	1.00
23	Hearing loss	17 (3%)	3 (3%)	1.00
24	Heart failure	18 (3%)	1 (1%)	0.50
25	Hypertension	51 (9%)	2 (2%)	0.022
26	Irritable bowel syndrome	28 (5%)	3 (3%)	0.60
27	Learning disability	6 (1%)	1 (1%)	1.00
28	Migraine	16 (3%)	5 (5%)	0.21
29	Multiple sclerosis	1 (<1%)	0 (0%)	1.00
30	Obesity	28 (5%)	4 (4%)	1.00
31	Osteoporosis	27 (5%)	3 (3%)	0.60
32	Parkinson's disease	0 (0%)	1 (1%)	0.14
33	Peripheral vascular disease	11 (2%)	1 (1%)	1.00
34	Prostate disorders	41 (7%)	4 (4%)	0.38
35	Psychoactive substance misuse	20 (4%)	6 (6%)	0.25
36	Schizophrenia or bipolar	6 (1%)	1 (1%)	1.00
37	Stroke or TIA	27 (5%)	3 (3%)	0.60
38	Thyroid disorders	31 (6%)	4 (4%)	0.81
39	Viral hepatitis	6 (1%)	0 (0%)	0.60

TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary disease.

Table S4. 5: The pseudo F and T-squared statics to determine the optimal number of clusters in the main analysis using the Aintree axSpA study.

Number of clusters	Pseudo-F*	Pseudo T-squared**
5	7.94	0.8
6	6.62	1.9
7	6.07	10.6
8	7.93	12.42
9	9.96	6.96
10	10.52	27.81
11	15.85	26.63
12	19.02	4.38
13	18.32	17.39
14	19.91	12.29
15	21.93	13.56
*The Calinski & Harabasz pseudo-F index; larger values indicating more distinct clusters. **The Duda-Hart pseudo-T-squared values; smaller values indicating more distinct clusters.		

Table S4. 6: Sensitivity analysis using 28 morbidities that were prevalent in at least two patients.

Cluster	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Number of patients	167	40	82	35	5	177	46	12	21	20	21
Hypertension			1 (2)	3 (17)		72 (88)	4 (25)	1 (11)			
Depression		3 (10)	42 (86)	4 (22)		10 (12)	5 (31)		1 (6)		1 (7)
Anxiety and other neuroses		2 (6)	7 (14)		4 (100)						
Schizophrenia or bipolar						3 (4)			1 (6)		1 (7)
Osteoporosis		1 (3)	5 (10)			10 (12)	3 (19)			4 (40)	1 (7)
Alcohol problems		1 (3)	1 (2)	1 (6)		5 (6)	1 (6)			9 (90)	
Other psychoactive substance misuse							1 (6)		16 (100)	1 (10)	
Chronic liver disease				1 (6)		1 (1)				1 (10)	
Viral hepatitis			1 (2)			1 (1)	1 (6)		1 (6)		
Migraine			6 (12)					1 (11)			1 (7)
Epilepsy*		1 (3)	3 (6)								1 (7)
Thyroid disorders			1 (2)			1 (1)		9 (100)			
Diabetes			3 (6)			15 (18)	2 (13)			3 (30)	
Atrial fibrillation						2 (2)	1 (6)				
Coronary heart disease			1 (2)			13 (16)	9 (56)				1 (7)
Heart failure						3 (4)					
Stroke and TIA			1 (2)			3 (4)	1 (6)			1 (10)	
COPD			3 (6)				12 (75)			1 (10)	
Asthma*						4 (5)					14 (100)
Chronic sinusitis						1 (1)					
Prostate disorders						5 (6)					
Fibromyalgia			2 (4)	13 (72)	1 (25)		2 (15)	1 (11)			
Irritable bowel syndrome			1 (2)	10 (56)		3 (4)					1 (7)
Diverticular disease			1 (2)			4 (5)					
Constipation*			1 (2)			2 (2)	1 (6)				
Cancer**			4 (8)								

Chronic kidney disease		3 (10)				6 (7)	1 (6)				
Dyspepsia*		29 (94)	1 (2)	3 (17)		11 (13)	2 (13)		2 (13)		
*Currently treated. **Cancer diagnoses in the past 5 years. Cells with zero prevalence were left empty for clarity. Bold text highlights dominant morbidities in each cluster. Clusters 12 (2 patients with AF) and 13 (1 with sinusitis) were omitted. TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary diseases.											

Table S4. 7: The pseudo F and T-squared statics to determine the optimal number of clusters in the main analysis using the Boston axSpA study.

Number of clusters	Pseudo-F*	Pseudo T-squared**
5	18.42	7.61
6	18.15	24.58
7	24.79	8.27
8	22.32	10.01
9	22.49	14.88
10	23.94	6.8
11	22.95	9.09
12	23.43	8.79
13	22.42	19.09
14	21.8	9.72
15	22.53	9.86

*The Calinski & Harabasz pseudo-F index; larger values indicating more distinct clusters.
**The Duda-Hart pseudo-T-squared values; smaller values indicating more distinct clusters.

10.4 Appendix for Chapter 5

Table S5. 1: Baseline characteristics of BSRBR-AS participants included and excluded from the analysis.

		Included (n=2043)	Excluded (n=644)	P-value
Age, years		49.1 (14.7)	43.9 (13.1)	<0.001
Males		1382 (68%)	446 (69%)	0.47
Meeting modified New York criteria		1340 (66%)	417 (65%)	0.70
Age at symptom onset, years		29.1 (13.8)	27.8 (13.1)	0.015
Symptom duration, years		20.0 (14.6)	16.1 (12.9)	<0.001
HLA-B27 positive*		1193 (79%)	347 (78%)	0.74
BMI, kg/m^2		27.7 (5.5)	27.4 (5.4)	0.33
Smoking status	Never smoked	900 (44%)	104 (37%)	0.060
	Ex-smoker	743 (36%)	107 (38%)	
	Current smoker	394 (19%)	67 (24%)	
Education	Secondary school	648 (32%)	93 (33%)	0.78
	Apprenticeship	191 (9%)	16 (6%)	
	Further education college	620 (30%)	92 (33%)	
	University degree	417 (21%)	52 (19%)	
	Further degree	157 (8%)	27 (10%)	
Deprivation index, median (IQR)		3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	0.21
NSAID use in past 6 months		1486 (73%)	480 (75%)	0.28
DMARD use in past 6 months		201 (13%)	71 (14%)	0.50
CRP (mg/dL), median (IQR)*		0.6 (0.2, 1.9)	0.7 (0.2, 2.0)	0.17
ESR (mm/hr), median (IQR)*		13.0 (5.0, 23.0)	9.0 (4.0, 21.0)	0.035
BASMI, median (IQR)*		3.8 (2.2, 5.4)	3.2 (2.0, 5.0)	0.022

Data shown as mean (SD) and n (%) unless otherwise indicated.
*Not all variables had complete data; HLA-B27 was available for 74% of participants, BASMI 75%, CRP 78%, ESR 39%.
Deprivation index, 1=most deprived, 5=least deprived; IQR, interquartile range; BMI, body mass index; BASMI, Metrology Index.

Table S5. 2: Full model coefficients for the association between comorbidity count categories and disease activity.

	BASDAI	Spinal pain	ASDAS	Ln(CRP+1)	Ln(ESR)
N	1803	1808	1450	1438	699
No comorbidity	reference	reference	reference	reference	reference
1 comorbidity	0.54 (0.28, 0.81)	0.64 (0.33, 0.95)	0.06 (-0.06, 0.19)	-0.10 (-0.19, -0.01)	-0.03 (-0.22, 0.16)
2 comorbidities	0.76 (0.39, 1.13)	1.05 (0.60, 1.50)	0.15 (-0.04, 0.33)	-0.04 (-0.17, 0.10)	-0.22 (-0.51, 0.06)
≥3 comorbidities	1.47 (0.94, 2.00)	1.95 (1.31, 2.59)	0.38 (0.12, 0.63)	-0.12 (-0.30, 0.07)	0.04 (-0.33, 0.40)
Age	-0.03 (-0.03, -0.02)	-0.03 (-0.04, -0.02)	-0.005 (-0.009, -0.0005)	0.004 (0.001, 0.01)	0.01 (0.004, 0.02)
Male sex	-0.42 (-0.66, -0.18)	-0.25 (-0.54, 0.04)	0.06 (-0.06, 0.18)	0.19 (0.11, 0.28)	-0.23 (-0.40, -0.06)
BMI	0.06 (0.04, 0.08)	0.05 (0.02, 0.07)	0.02 (0.01, 0.03)	0.01 (0.004, 0.02)	0.01 (0.0005, 0.03)
Ever-smoker	0.53 (0.30, 0.76)	0.59 (0.32, 0.86)	0.20 (0.09, 0.31)	0.01 (-0.07, 0.09)	0.09 (-0.08, 0.26)
Secondary school	reference	reference	reference	reference	reference
Apprenticeship	-0.32 (-0.73, 0.10)	-0.43 (-0.93, 0.06)	-0.14 (-0.34, 0.06)	-0.10 (-0.24, 0.05)	-0.09 (-0.41, 0.24)
Further education college	-0.46 (-0.74, -0.17)	-0.48 (-0.82, -0.14)	-0.21 (-0.35, -0.07)	-0.04 (-0.14, 0.06)	-0.15 (-0.36, 0.05)
University degree	-0.87 (-1.19, -0.55)	-0.73 (-1.11, -0.34)	-0.38 (-0.53, -0.22)	-0.13 (-0.24, -0.01)	-0.09 (-0.32, 0.14)
Further degree	-1.53 (-1.97, -1.08)	-1.31 (-1.83, -0.78)	-0.60 (-0.81, -0.39)	-0.08 (-0.23, 0.08)	0.06 (-0.26, 0.37)
Deprivation	0.18 (0.10, 0.26)	0.23 (0.13, 0.33)	0.09 (0.05, 0.13)	0.02 (-0.01, 0.05)	0.08 (0.02, 0.14)
BMI, body mass index; COPD, chronic obstructive pulmonary disease; TB, tuberculosis.					

Table S5. 3: Full model coefficients for the association between each comorbidity and disease activity.

	BASDAI	Spinal pain	ASDAS	Ln(CRP+1)	Ln(ESR)
N	1803	1808	1450	1438	699
Ischaemic heart disease	-0.17 (-0.86, 0.52)	0.22 (-0.61, 1.05)	-0.02 (-0.36, 0.31)	-0.10 (-0.34, 0.14)	-0.14 (-0.64, 0.37)
Heart failure	1.70 (0.58, 2.81)	1.34 (-0.00, 2.69)	0.59 (0.05, 1.12)	0.22 (-0.18, 0.62)	0.14 (-0.60, 0.88)
Stroke	-0.02 (-0.96, 0.93)	0.55 (-0.59, 1.69)	-0.22 (-0.68, 0.25)	-0.06 (-0.40, 0.28)	0.07 (-0.69, 0.83)
Hypertension	-0.06 (-0.37, 0.26)	-0.02 (-0.40, 0.36)	-0.01 (-0.17, 0.14)	0.06 (-0.06, 0.17)	0.12 (-0.13, 0.36)
Diabetes	0.66 (0.15, 1.17)	0.81 (0.20, 1.43)	0.14 (-0.13, 0.41)	-0.13 (-0.34, 0.07)	-0.34 (-0.72, 0.03)
Asthma	0.11 (-0.25, 0.47)	0.37 (-0.07, 0.80)	-0.10 (-0.28, 0.07)	-0.10 (-0.23, 0.03)	-0.36 (-0.62, -0.10)
COPD	0.07 (-0.79, 0.92)	0.13 (-0.90, 1.16)	0.32 (-0.10, 0.75)	0.38 (0.07, 0.70)	0.03 (-0.53, 0.60)
Peptic ulcer	1.24 (0.59, 1.88)	1.70 (0.92, 2.47)	0.44 (0.13, 0.75)	-0.15 (-0.37, 0.08)	0.29 (-0.17, 0.75)
Renal	0.91 (0.05, 1.77)	1.13 (0.10, 2.15)	0.25 (-0.15, 0.65)	-0.08 (-0.38, 0.22)	0.32 (-0.36, 1.01)
Liver	-0.31 (-1.52, 0.90)	-0.38 (-1.83, 1.07)	-0.28 (-0.88, 0.31)	-0.07 (-0.50, 0.36)	0.51 (-0.31, 1.33)
Cancer	-0.01 (-0.60, 0.57)	0.28 (-0.42, 0.98)	-0.01 (-0.30, 0.28)	0.04 (-0.17, 0.25)	0.18 (-0.26, 0.62)
Depression	0.92 (0.61, 1.23)	0.88 (0.51, 1.25)	0.21 (0.06, 0.36)	-0.06 (-0.16, 0.05)	0.03 (-0.20, 0.25)
TB	1.13 (0.21, 2.05)	0.77 (-0.34, 1.87)	0.41 (-0.05, 0.87)	-0.08 (-0.42, 0.26)	0.18 (-0.50, 0.85)
Demyelinating	1.00 (-0.89, 2.90)	1.64 (-0.64, 3.91)	-0.16 (-1.07, 0.75)	-0.43 (-1.09, 0.23)	-0.26 (-1.47, 0.96)
Age	-0.02 (-0.03, -0.01)	-0.03 (-0.04, -0.02)	-0.004 (-0.01, 0.0004)	0.003 (-0.0005, 0.01)	0.01 (0.0003, 0.01)
Gender	-0.39 (-0.63, -0.15)	-0.24 (-0.53, 0.05)	0.06 (-0.06, 0.18)	0.19 (0.10, 0.27)	-0.25 (-0.43, -0.08)
BMI	0.06 (0.04, 0.08)	0.05 (0.03, 0.08)	0.02 (0.01, 0.03)	0.01 (0.003, 0.02)	0.02 (0.001, 0.03)
Ever-smoker	0.49 (0.26, 0.72)	0.55 (0.28, 0.83)	0.18 (0.07, 0.29)	0 (-0.08, 0.08)	0.08 (-0.09, 0.25)
Secondary school	reference	reference	reference	reference	reference
Apprenticeship	-0.27 (-0.68, 0.14)	-0.40 (-0.89, 0.10)	-0.13 (-0.33, 0.07)	-0.10 (-0.25, 0.04)	-0.13 (-0.45, 0.20)
Further education college	-0.44 (-0.72, -0.16)	-0.48 (-0.81, -0.14)	-0.20 (-0.33, -0.06)	-0.03 (-0.13, 0.07)	-0.17 (-0.37, 0.04)
University degree	-0.85 (-1.17, -0.53)	-0.72 (-1.10, -0.33)	-0.37 (-0.52, -0.21)	-0.12 (-0.24, -0.01)	-0.13 (-0.36, 0.10)
Further degree	-1.49 (-1.93, -1.05)	-1.27 (-1.80, -0.74)	-0.58 (-0.79, -0.37)	-0.08 (-0.23, 0.07)	-0.02 (-0.34, 0.30)
Deprivation	0.18 (0.10, 0.26)	0.23 (0.13, 0.33)	0.09 (0.05, 0.13)	0.02 (-0.01, 0.05)	0.07 (0.02, 0.13)
BMI, body mass index; COPD, chronic obstructive pulmonary disease; TB, tuberculosis.					

Table S5. 4: Full model coefficients for the association between comorbidity count and other measures of disease severity.

	Fatigue	ASQoL	BASFI	BASMI	Patient global
N	1818	1802	1814	1404	1741
No comorbidity	reference	reference	reference	reference	reference
1 comorbidity	1.64 (1.06, 2.21)	1.54 (0.97, 2.11)	0.65 (0.36, 0.93)	0.26 (0.05, 0.47)	0.43 (0.12, 0.75)
2 comorbidities	1.67 (0.85, 2.50)	2.20 (1.39, 3.01)	1.00 (0.59, 1.41)	0.47 (0.18, 0.76)	0.79 (0.34, 1.24)
≥3 comorbidities	3.84 (2.67, 5.01)	4.12 (2.95, 5.29)	1.96 (1.38, 2.55)	0.79 (0.36, 1.23)	1.38 (0.74, 2.01)
Age	-0.07 (-0.09, -0.05)	-0.07 (-0.09, -0.06)	0.02 (0.01, 0.02)	0.05 (0.04, 0.06)	-0.02 (-0.03, -0.01)
Gender	-0.89 (-1.42, -0.35)	-1.55 (-2.08, -1.02)	-0.22 (-0.49, 0.04)	0.27 (0.07, 0.47)	-0.19 (-0.48, 0.10)
BMI	0.05 (0.01, 0.10)	0.13 (0.09, 0.18)	0.09 (0.07, 0.11)	0.02 (0.00, 0.04)	0.04 (0.02, 0.07)
Ever-smoker	0.52 (0.01, 1.02)	1.51 (1.01, 2.01)	0.72 (0.47, 0.97)	0.26 (0.08, 0.45)	0.50 (0.22, 0.77)
Secondary school	reference	reference	reference	reference	reference
Apprenticeship	-0.06 (-0.97, 0.85)	-0.91 (-1.82, -0.00)	-0.24 (-0.69, 0.21)	-0.29 (-0.62, 0.03)	-0.30 (-0.80, 0.19)
Further education college	-0.11 (-0.73, 0.52)	-1.16 (-1.78, -0.54)	-0.52 (-0.83, -0.20)	-0.38 (-0.61, -0.15)	-0.49 (-0.83, -0.15)
University degree	-0.77 (-1.48, -0.07)	-2.21 (-2.91, -1.51)	-0.94 (-1.29, -0.59)	-0.78 (-1.05, -0.52)	-0.88 (-1.26, -0.50)
Further degree	-1.86 (-2.83, -0.88)	-3.83 (-4.80, -2.87)	-1.75 (-2.23, -1.26)	-0.85 (-1.23, -0.47)	-1.62 (-2.15, -1.09)
Deprivation	0.28 (0.10, 0.46)	0.49 (0.32, 0.67)	0.26 (0.17, 0.35)	0.14 (0.07, 0.20)	0.15 (0.06, 0.25)
ASQoL, AS quality of life questionnaire; BMI, body mass index; COPD, chronic obstructive pulmonary disease.					

Table S5. 5: Full model coefficients for the association between each comorbidity and other measures of disease severity.

	Fatigue	ASQoL	BASFI	BASMI	Patient global
N	1818	1802	1814	1404	1741
Ischaemic heart disease	0.43 (-1.07, 1.94)	0.94 (-0.57, 2.44)	0.29 (-0.46, 1.04)	0.32 (-0.23, 0.88)	0.45 (-0.38, 1.29)
Heart failure	4.06 (1.60, 6.52)	3.84 (1.40, 6.27)	2.12 (0.90, 3.35)	-0.23 (-1.15, 0.69)	1.12 (-0.21, 2.44)
Stroke	2.99 (0.90, 5.08)	1.05 (-1.01, 3.12)	0.52 (-0.52, 1.56)	0.58 (-0.25, 1.40)	0.05 (-1.09, 1.19)
Hypertension	-0.18 (-0.88, 0.51)	0.12 (-0.57, 0.81)	0.25 (-0.10, 0.60)	0.09 (-0.17, 0.35)	0.08 (-0.31, 0.46)
Diabetes	0.39 (-0.74, 1.51)	1.91 (0.78, 3.04)	1.15 (0.59, 1.71)	0.46 (0.05, 0.86)	0.54 (-0.08, 1.16)
Asthma	0.21 (-0.59, 1.00)	-0.06 (-0.84, 0.73)	-0.15 (-0.55, 0.25)	-0.20 (-0.50, 0.09)	0.07 (-0.37, 0.50)
COPD	-0.69 (-2.58, 1.20)	0.05 (-1.81, 1.92)	0.49 (-0.45, 1.43)	0.69 (-0.02, 1.40)	-0.27 (-1.32, 0.78)
Peptic ulcer	1.46 (0.04, 2.88)	2.28 (0.87, 3.70)	1.66 (0.95, 2.37)	1.07 (0.52, 1.62)	1.12 (0.33, 1.91)
Renal	2.67 (0.76, 4.59)	1.64 (-0.28, 3.55)	0.85 (-0.09, 1.79)	0.06 (-0.65, 0.77)	1.26 (0.25, 2.28)
Liver	-0.54 (-3.20, 2.13)	0.42 (-2.21, 3.05)	0.06 (-1.27, 1.39)	-0.05 (-0.98, 0.88)	-0.25 (-1.68, 1.18)
Cancer	0.61 (-0.68, 1.89)	0.03 (-1.25, 1.30)	0.22 (-0.42, 0.86)	0.37 (-0.12, 0.85)	-0.19 (-0.89, 0.51)
Depression	2.93 (2.26, 3.61)	2.97 (2.30, 3.64)	0.92 (0.58, 1.25)	0.34 (0.10, 0.58)	0.79 (0.41, 1.16)
TB	0.80 (-1.22, 2.82)	1.36 (-0.68, 3.39)	0.84 (-0.17, 1.85)	0.35 (-0.44, 1.13)	0.65 (-0.46, 1.75)
Demyelinating	4.49 (0.32, 8.65)	2.12 (-2.00, 6.24)	0.05 (-2.03, 2.13)	0.59 (-1.08, 2.25)	-0.50 (-2.74, 1.74)
Age	-0.05 (-0.07, -0.03)	-0.06 (-0.08, -0.04)	0.02 (0.01, 0.02)	0.05 (0.04, 0.06)	-0.02 (-0.03, -0.01)
Gender	-0.75 (-1.28, -0.22)	-1.48 (-2.01, -0.95)	-0.24 (-0.50, 0.03)	0.24 (0.04, 0.44)	-0.18 (-0.47, 0.11)
BMI	0.07 (0.02, 0.11)	0.14 (0.10, 0.19)	0.09 (0.07, 0.12)	0.02 (0.004, 0.04)	0.04 (0.02, 0.07)
Ever-smoker	0.43 (-0.07, 0.93)	1.39 (0.89, 1.88)	0.67 (0.42, 0.92)	0.23 (0.05, 0.42)	0.44 (0.17, 0.72)
Secondary school	reference	reference	reference	reference	reference
Apprenticeship	-0.07 (-0.97, 0.83)	-0.81 (-1.71, 0.09)	-0.21 (-0.66, 0.24)	-0.28 (-0.61, 0.05)	-0.28 (-0.77, 0.22)
Further education college	-0.09 (-0.70, 0.53)	-1.13 (-1.74, -0.52)	-0.51 (-0.82, -0.20)	-0.38 (-0.60, -0.15)	-0.48 (-0.82, -0.14)
University degree	-0.81 (-1.51, -0.11)	-2.23 (-2.92, -1.54)	-0.95 (-1.30, -0.60)	-0.80 (-1.06, -0.54)	-0.88 (-1.26, -0.50)
Further degree	-1.85 (-2.81, -0.88)	-3.76 (-4.72, -2.80)	-1.72 (-2.21, -1.24)	-0.87 (-1.25, -0.49)	-1.59 (-2.11, -1.06)
Deprivation	0.29 (0.11, 0.47)	0.49 (0.31, 0.66)	0.26 (0.17, 0.35)	0.13 (0.06, 0.20)	0.16 (0.06, 0.26)
ASQoL, AS quality of life questionnaire; BMI, body mass index; COPD, chronic obstructive pulmonary disease; TB, tuberculosis.					

Table S5. 6: Baseline characteristics of participants according to recruitment arm.

		Non-biologic cohort (n=1412)	Biologic cohort (n=631)	P-value
Age, years		51.1 (14.6)	44.5 (13.9)	<0.001
Males		963 (68%)	419 (66%)	0.42
Meeting modified New York criteria		983 (70%)	357 (57%)	<0.001
Age at symptom onset, years		29.1 (13.9)	29.2 (13.6)	0.87
Symptom duration, years		22.0 (15.0)	15.3 (12.6)	<0.001
HLA-B27 positive*		858 (81%)	335 (74%)	0.002
BMI, kg/m^2		27.5 (5.4)	28.1 (5.7)	0.062
Smoking status	Never smoked	655 (47%)	245 (39%)	<0.001
	Ex-smoker	540 (38%)	203 (32%)	
	Current smoker	213 (15%)	181 (29%)	
Education	Secondary school	429 (30%)	219 (35%)	0.12
	Apprenticeship	131 (9%)	60 (10%)	
	Further education college	430 (31%)	190 (30%)	
	University degree	297 (21%)	120 (19%)	
	Further degree	120 (9%)	37 (6%)	
Deprivation index, mean (SD)		2.8 (1.4)	3.1 (1.4)	<0.001
NSAID use in past 6 months		1013 (72%)	473 (75%)	0.20
DMARD use in past 6 months		137 (13%)	64 (13%)	0.72
BASDAI, median (IQR)		3.8 (2.0, 5.8)	6.9 (5.6, 7.9)	<0.001
Spinal pain, median (IQR)		3.0 (1.0, 6.0)	7.0 (5.0, 8.0)	<0.001
ASDAS*		1.9 (1.0)	3.0 (0.8)	<0.001
CRP (mg/dL), median (IQR)*		0.5 (0.2, 1.8)	0.7 (0.2, 2.1)	0.030
ESR (mm/hr), median (IQR)*		9.0 (5.0, 20.0)	14.0 (5.0, 28.0)	<0.001
Fatigue, median (IQR)		13.0 (13.0, 17.0)	18.0 (14.0, 21.0)	<0.001
ASQoL, median (IQR)		6.0 (2.0, 13.0)	13.0 (10.0, 16.0)	<0.001
BASFI, median (IQR)		3.3 (1.4, 5.9)	6.6 (4.8, 8.1)	<0.001
BASMI, median (IQR)*		3.4 (2.0, 5.2)	4.2 (2.8, 5.6)	<0.001
IHD		48 (3%)	15 (2%)	0.27
Heart failure		16 (1%)	5 (1%)	0.64
Stroke		25 (2%)	4 (1%)	0.044
Hypertension		292 (21%)	95 (15%)	0.003
Diabetes		74 (5%)	27 (4%)	0.38
Asthma		129 (9%)	74 (12%)	0.078
COPD		29 (2%)	6 (1%)	0.096
Peptic ulcer		30 (2%)	28 (4%)	0.006
Renal		25 (2%)	10 (2%)	0.86
Liver		9 (1%)	8 (1%)	0.19
Cancer		67 (5%)	11 (2%)	<0.001
Depression		186 (13%)	130 (21%)	<0.001
TB		17 (1%)	12 (2%)	0.23
Demyelinating		6 (<1%)	0 (0%)	0.19

Data shown as mean (SD) and n (%) unless otherwise indicated.
*Not all variables had complete data; HLA-B27 was available for 74% of participants, BASMI 75%, ASDAS 78%, CRP 78%, ESR 39%.

**non-parametric test for trend.
Deprivation index, 1=most deprived, 5=least deprived; IQR, interquartile range; BMI, body mass index; BASDAI, Bath AS disease activity index; BASFI, Bath AS functional index; BASMI, Metrology Index; ASQoL, AS quality of life questionnaire; ASDAS, AS disease activity score; IHD, ischaemic heart disease.

Figure S5. 1: Sensitivity analysis of comorbidity categories restricted to the non-biologic cohort show comparable results for comorbidity count vs. disease severity.

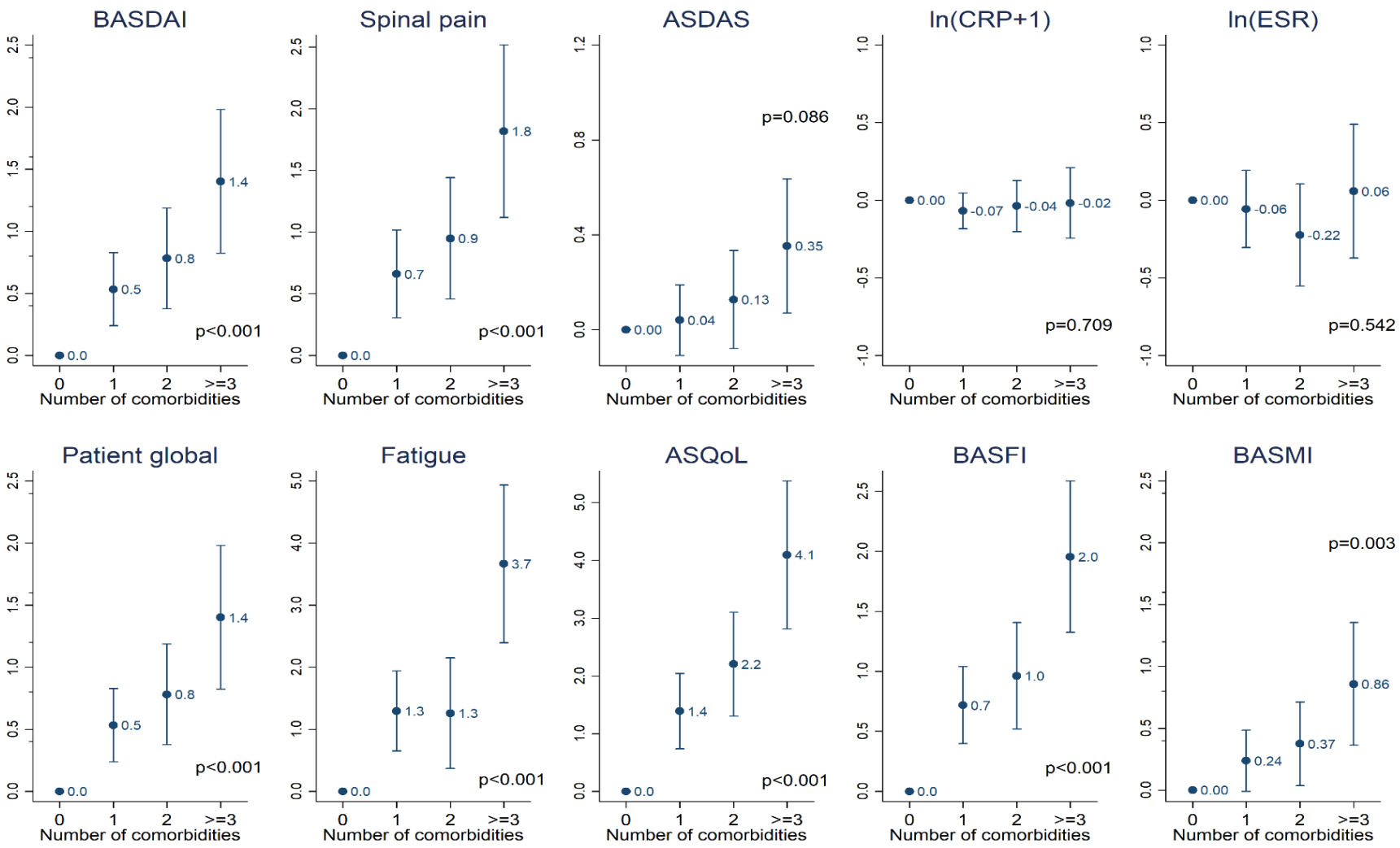
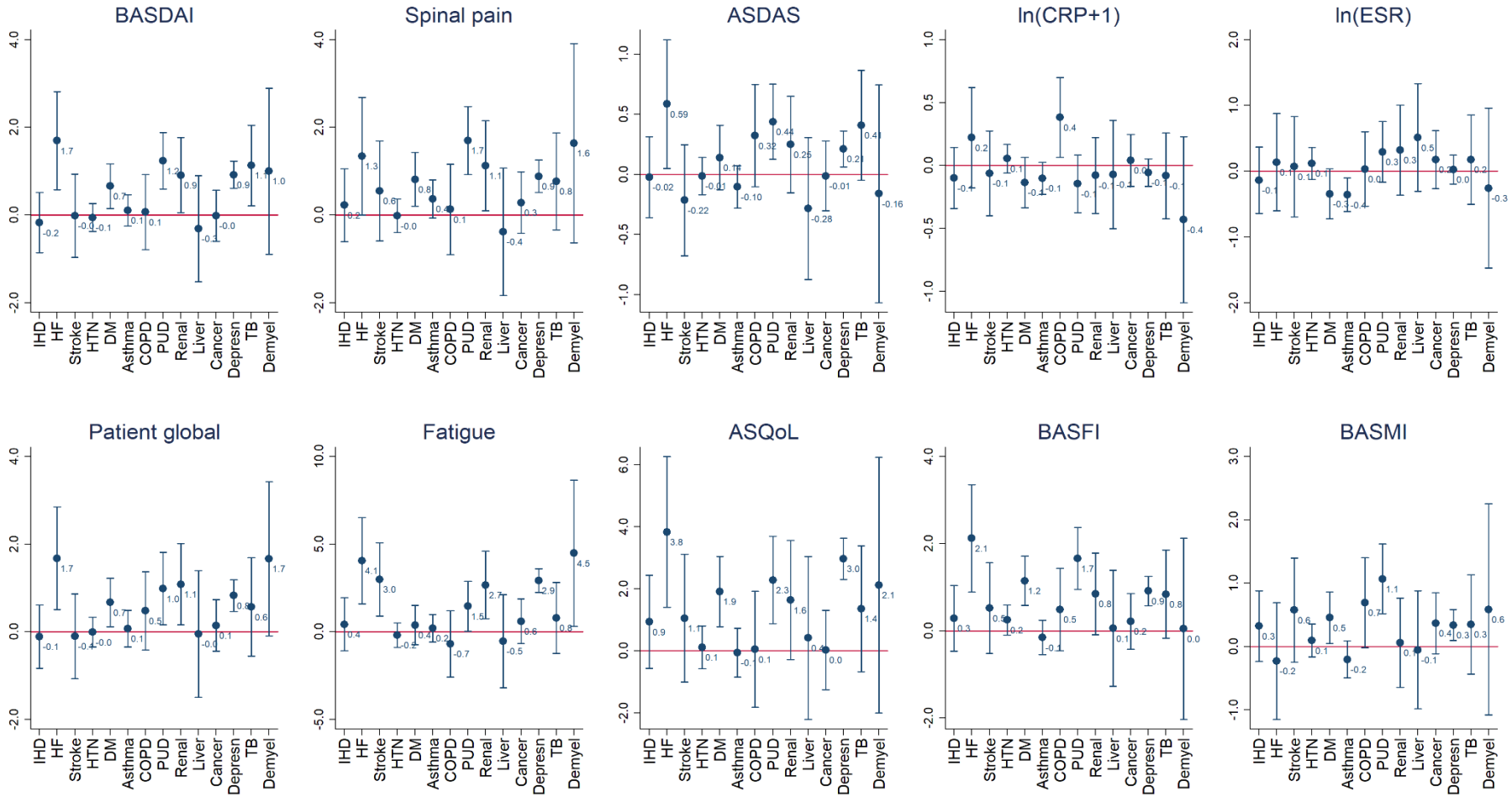


Figure S5. 2: Sensitivity analysis of individual comorbidities restricted to the non-biologic cohort show comparable results for comorbidity count vs. disease severity.



10.5 Appendix for Chapter 6

Table S6. 1: Baseline characteristics of 994 participants included in the longitudinal analysis cohort and 141 who were excluded.

		Included (n=994)	Excluded (n=141)	P-value
Age, years		44.7 (13.4)	43.7 (13.7)	0.40
Males		679 (68%)	84 (60%)	0.044
Meeting modified New York criteria		597 (60%)	90 (64%)	0.41
Age at symptom onset, years		28.6 (13.3)	30.2 (12.2)	0.14
Symptom duration, years		16.0 (12.6)	13.8 (12.1)	0.053
HLA-B27 positive*		540 (74%)	67 (78%)	0.51
BMI, kg/m^2		28.1 (5.8)	27.4 (5.8)	0.24
Smoking status	Never smoked	351 (40%)	52 (40%)	0.88
	Ex-smoker	291 (33%)	45 (35%)	
	Current smoker	241 (27%)	33 (25%)	
Education	Secondary school	289 (33%)	42 (32%)	0.232**
	Apprenticeship	82 (9%)	9 (7%)	
	Further education college	276 (31%)	37 (28%)	
	University degree	178 (20%)	26 (20%)	
	Further degree	53 (6%)	16 (12%)	
Deprivation index, median (IQR)		3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	0.53
Depression		145 (15%)	19 (14%)	0.90
Hypertension		106 (11%)	17 (12%)	0.56
Asthma		86 (9%)	13 (9%)	0.75
Peptic ulcer disease		28 (3%)	7 (5%)	0.18
Diabetes mellitus		25 (3%)	8 (6%)	0.052
Cancer		15 (2%)	5 (4%)	0.085
Ischaemic heart disease		16 (2%)	3 (2%)	0.50
TB		15 (2%)	3 (2%)	0.47
Renal disease		11 (1%)	1 (1%)	1.00
COPD		10 (1%)	1 (1%)	1.00
Stroke		7 (1%)	0	1.00
Liver disease		7 (1%)	2 (1%)	0.30
Heart failure		6 (1%)	2 (1%)	0.25
Demyelinating disease		2 (<1%)	0	1.00

Data shown as mean (SD) and n (%) unless otherwise indicated.
**non-parametric test for trend.
IQR, interquartile range; BMI, body mass index; BASDAI, Bath AS disease activity index; ASDAS, AS disease activity score; BASFI, Bath AS functional index; ASQoL, AS quality of life questionnaire.

Table S6. 2: Full model coefficients for associations between binary comorbidity status (present vs. absent) and binary responses at 6 months.

	Models without adjusting for baseline disease activity				Models additionally adjusting for baseline disease activity			
	BASDAI 50/2	**BASDAI<4**	**ASDAS-MI**	**ASDAS<2.1**	**BASDAI 50/2**	**BASDAI<4**	**ASDAS-MI**	**ASDAS<2.1**
N	534	534	436	436	534	534	436	436
Comorbidities (1 vs. 0)	0.96 (0.65 to 1.40)	0.70 (0.47 to 1.03)	0.95 (0.59 to 1.51)	0.94 (0.57 to 1.55)	0.87 (0.59 to 1.28)	0.81 (0.54 to 1.22)	0.98 (0.62 to 1.57)	0.69 (0.39 to 1.22)
Age	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.02)	0.99 (0.97 to 1.01)	1.00 (0.98 to 1.02)	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.02)	0.99 (0.97 to 1.01)	1.00 (0.98 to 1.02)
Gender	1.67 (1.14 to 2.47)	1.71 (1.15 to 2.54)	1.44 (0.90 to 2.30)	1.38 (0.84 to 2.29)	1.81 (1.22 to 2.68)	1.56 (1.03 to 2.36)	1.47 (0.92 to 2.36)	1.23 (0.71 to 2.12)
Deprivation	0.83 (0.73 to 0.95)	0.79 (0.69 to 0.90)	0.83 (0.71 to 0.97)	0.95 (0.81 to 1.13)	0.81 (0.71 to 0.92)	0.81 (0.71 to 0.93)	0.84 (0.72 to 0.98)	0.92 (0.76 to 1.10)
Secondary school	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Apprenticeship	0.51 (0.26 to 0.99)	0.79 (0.41 to 1.52)	0.92 (0.42 to 1.99)	0.65 (0.27 to 1.56)	0.53 (0.27 to 1.03)	0.71 (0.36 to 1.39)	0.89 (0.41 to 1.94)	0.70 (0.25 to 2.00)
Further education college	1.15 (0.72 to 1.81)	1.50 (0.94 to 2.40)	1.15 (0.67 to 1.99)	1.21 (0.68 to 2.14)	1.24 (0.78 to 1.97)	1.36 (0.84 to 2.22)	1.12 (0.65 to 1.94)	1.60 (0.85 to 3.03)
University degree	1.23 (0.74 to 2.02)	1.92 (1.15 to 3.21)	2.11 (1.19 to 3.71)	1.27 (0.69 to 2.33)	1.38 (0.82 to 2.30)	1.61 (0.95 to 2.73)	2.05 (1.16 to 3.62)	1.74 (0.88 to 3.42)
Further degree	0.82 (0.36 to 1.85)	0.99 (0.43 to 2.26)	0.85 (0.32 to 2.29)	0.40 (0.11 to 1.44)	0.98 (0.42 to 2.26)	0.68 (0.29 to 1.61)	0.78 (0.29 to 2.12)	0.69 (0.17 to 2.82)
BMI	0.93 (0.90 to 0.97)	0.93 (0.90 to 0.97)	0.94 (0.90 to 0.98)	0.9 (0.89 to 0.98)	0.93 (0.90 to 0.96)	0.94 (0.90 to 0.97)	0.94 (0.90 to 0.98)	0.92 (0.88 to 0.97)
Baseline BASDAI/ASDAS					1.18 (1.07 to 1.31)	0.71 (0.64 to 0.80)	0.84 (0.65 to 1.09)	4.23 (2.92 to 6.12)

ASDAS, AS disease activity score; BASDAI 50/2, 50% or 2-unit reduction in BASDAI; ASDAS-MI, major improvement i.e. ≥2-unit reduction; BMI, body mass index; CRP, C-reactive protein.

Table S6. 3: Full model coefficients for associations between continuous comorbidity count and binary responses at 6 months.

	Models without adjusting for baseline disease activity				Models additionally adjusting for baseline disease activity			
	BASDAI 50/2	**BASDAI<4**	**ASDAS-MI**	**ASDAS<2.1**	**BASDAI 50/2**	**BASDAI<4**	**ASDAS-MI**	**ASDAS<2.1**
N	534	534	436	436	534	534	436	436
Comorbidity count	0.88 (0.70 to 1.10)	0.73 (0.57 to 0.92)	0.84 (0.62 to 1.14)	0.88 (0.63 to 1.21)	0.81 (0.64 to 1.02)	0.82 (0.64 to 1.05)	0.87 (0.64 to 1.18)	0.66 (0.46 to 0.94)
Age	1.00 (0.99 to 1.02)	1.00 (0.99 to 1.02)	0.99 (0.98 to 1.01)	1.00 (0.98 to 1.02)	1.00 (0.99 to 1.02)	1.00 (0.99 to 1.02)	0.99 (0.98 to 1.01)	1.00 (0.98 to 1.02)
Gender	1.66 (1.13 to 2.45)	1.71 (1.15 to 2.55)	1.42 (0.89 to 2.27)	1.37 (0.83 to 2.27)	1.81 (1.22 to 2.69)	1.57 (1.04 to 2.37)	1.45 (0.90 to 2.32)	1.18 (0.68 to 2.05)
Deprivation	0.84 (0.74 to 0.96)	0.79 (0.69 to 0.91)	0.84 (0.71 to 0.98)	0.96 (0.81 to 1.13)	0.81 (0.71 to 0.93)	0.82 (0.71 to 0.94)	0.84 (0.72 to 0.98)	0.92 (0.77 to 1.11)
Secondary school	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Apprenticeship	0.52 (0.27 to 1.01)	0.82 (0.42 to 1.58)	0.94 (0.43 to 2.05)	0.66 (0.27 to 1.59)	0.54 (0.28 to 1.06)	0.72 (0.37 to 1.43)	0.91 (0.42 to 1.99)	0.78 (0.27 to 2.23)
Further education college	1.17 (0.74 to 1.85)	1.56 (0.98 to 2.50)	1.18 (0.68 to 2.04)	1.22 (0.69 to 2.17)	1.28 (0.80 to 2.05)	1.4 (0.86 to 2.28)	1.14 (0.66 to 1.99)	1.69 (0.89 to 3.21)
University degree	1.22 (0.74 to 2.01)	1.93 (1.15 to 3.22)	2.09 (1.19 to 3.69)	1.26 (0.69 to 2.32)	1.38 (0.83 to 2.31)	1.61 (0.95 to 2.74)	2.04 (1.16 to 3.60)	1.75 (0.89 to 3.45)
Further degree	0.81 (0.36 to 1.84)	0.98 (0.43 to 2.23)	0.85 (0.32 to 2.28)	0.39 (0.11 to 1.43)	0.98 (0.43 to 2.27)	0.69 (0.29 to 1.62)	0.79 (0.29 to 2.14)	0.69 (0.17 to 2.82)
BMI	0.93 (0.90 to 0.97)	0.93 (0.90 to 0.97)	0.94 (0.90 to 0.98)	0.93 (0.89 to 0.98)	0.93 (0.90 to 0.96)	0.94 (0.90 to 0.97)	0.94 (0.90 to 0.98)	0.93 (0.88 to 0.97)
Baseline BASDAI/ASDAS					1.20 (1.08 to 1.32)	0.72 (0.64 to 0.81)	0.86 (0.66 to 1.11)	4.45 (3.05 to 6.48)

ASDAS, AS disease activity score; BASDAI 50/2, 50% or 2-unit reduction in BASDAI; ASDAS-MI, major improvement i.e. ≥2-unit reduction; BMI, body mass index; CRP, C-reactive protein.

Table S6. 4: Full model coefficients for associations between comorbidity count categories and binary responses at 6 months.

	Models without adjusting for baseline disease activity				Models additionally adjusting for baseline disease activity			
	BASDAI 50/2	BASDAI<4	ASDAS-MI	ASDAS<2.1	BASDAI 50/2	BASDAI<4	ASDAS-MI	ASDAS<2.1
N	534	534	436	436	534	534	436	436
0 comorbidities	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
1 comorbidity	1.03 (0.67 to 1.60)	0.76 (0.49 to 1.18)	0.96 (0.55 to 1.68)	1.05 (0.63 to 1.75)	0.97 (0.62 to 1.51)	0.84 (0.53 to 1.33)	0.81 (0.43 to 1.50)	1.08 (0.65 to 1.80)
≥2 comorbidities	0.81 (0.45 to 1.45)	0.57 (0.32 to 1.04)	0.87 (0.38 to 1.99)	0.7 (0.32 to 1.56)	0.68 (0.38 to 1.23)	0.76 (0.41 to 1.41)	0.47 (0.18 to 1.19)	0.75 (0.34 to 1.67)
Age	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.02)	1.00 (0.98 to 1.02)	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.02)	1.00 (0.99 to 1.02)	1.00 (0.98 to 1.02)	0.99 (0.98 to 1.01)
Gender	1.68 (1.14 to 2.47)	1.71 (1.15 to 2.54)	1.38 (0.83 to 2.29)	1.43 (0.90 to 2.28)	1.81 (1.22 to 2.69)	1.56 (1.03 to 2.36)	1.21 (0.70 to 2.09)	1.46 (0.91 to 2.34)
Deprivation	0.84 (0.73 to 0.95)	0.79 (0.69 to 0.90)	0.96 (0.81 to 1.13)	0.84 (0.71 to 0.98)	0.81 (0.71 to 0.93)	0.81 (0.71 to 0.93)	0.92 (0.77 to 1.10)	0.84 (0.72 to 0.98)
Secondary school	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Apprenticeship	0.52 (0.27 to 1.00)	0.8 (0.41 to 1.55)	0.65 (0.27 to 1.58)	0.94 (0.43 to 2.05)	0.54 (0.27 to 1.05)	0.71 (0.36 to 1.40)	0.74 (0.26 to 2.13)	0.91 (0.42 to 1.99)
Further education college	1.15 (0.73 to 1.83)	1.52 (0.95 to 2.42)	1.21 (0.68 to 2.14)	1.16 (0.67 to 2.00)	1.26 (0.79 to 2.00)	1.37 (0.84 to 2.23)	1.62 (0.85 to 3.07)	1.12 (0.65 to 1.95)
University degree	1.22 (0.74 to 2.02)	1.92 (1.15 to 3.21)	1.27 (0.69 to 2.33)	2.1 (1.19 to 3.70)	1.38 (0.83 to 2.31)	1.61 (0.95 to 2.73)	1.74 (0.88 to 3.43)	2.04 (1.16 to 3.61)
Further degree	0.81 (0.36 to 1.83)	0.98 (0.43 to 2.24)	0.39 (0.11 to 1.43)	0.83 (0.31 to 2.24)	0.97 (0.42 to 2.24)	0.68 (0.29 to 1.61)	0.68 (0.17 to 2.77)	0.77 (0.29 to 2.09)
BMI	0.93 (0.90 to 0.97)	0.93 (0.90 to 0.97)	0.93 (0.89 to 0.98)	0.94 (0.90 to 0.98)	0.93 (0.90 to 0.96)	0.94 (0.90 to 0.97)	0.93 (0.88 to 0.97)	0.94 (0.90 to 0.98)
Baseline BASDAI/ASDAS					1.19 (1.08 to 1.31)	0.72 (0.64 to 0.80)	4.32 (2.97 to 6.28)	0.85 (0.66 to 1.10)

ASDAS, AS disease activity score; BASDAI 50/2, 50% or 2-unit reduction in BASDAI; ASDAS-MI, major improvement i.e. ≥2-unit reduction; BMI, body mass index; CRP, C-reactive protein.

Table S6. 5: Cox model coefficients for risk of discontinuing TNF inhibitor according to the number of baseline comorbidities

	All	Male	Female
N	767	518	249
0 comorbidities	Reference	Reference	Reference
1 comorbidity	0.91 (0.65 to 1.26)	0.86 (0.56 to 1.33)	0.82 (0.48 to 1.39)
2 comorbidities	1.32 (0.88 to 2.00)	1.68 (0.99 to 2.83)	0.86 (0.43 to 1.71)
≥3 comorbidities	2.18 (1.20 to 3.93)	5.04 (2.61 to 9.74)	0.44 (0.10 to 1.96)
Age	1.00 (0.99 to 1.01)	1.01 (1.00 to 1.02)	0.99 (0.97 to 1.01)
Gender*	0.77 (0.58 to 1.01)	n/a	n/a
Deprivation index	1.19 (1.08 to 1.31)	1.22 (1.08 to 1.37)	1.16 (0.99 to 1.36)
BMI	1.02 (1.00 to 1.04)	1.02 (0.99 to 1.05)	1.03 (1.00 to 1.06)
*Female as reference.			

Table S6. 6: Sensitivity analysis for the association between comorbidity and binary response at 6 months, with missing binary outcomes imputed as response if patients remained on drug for longer than one year.

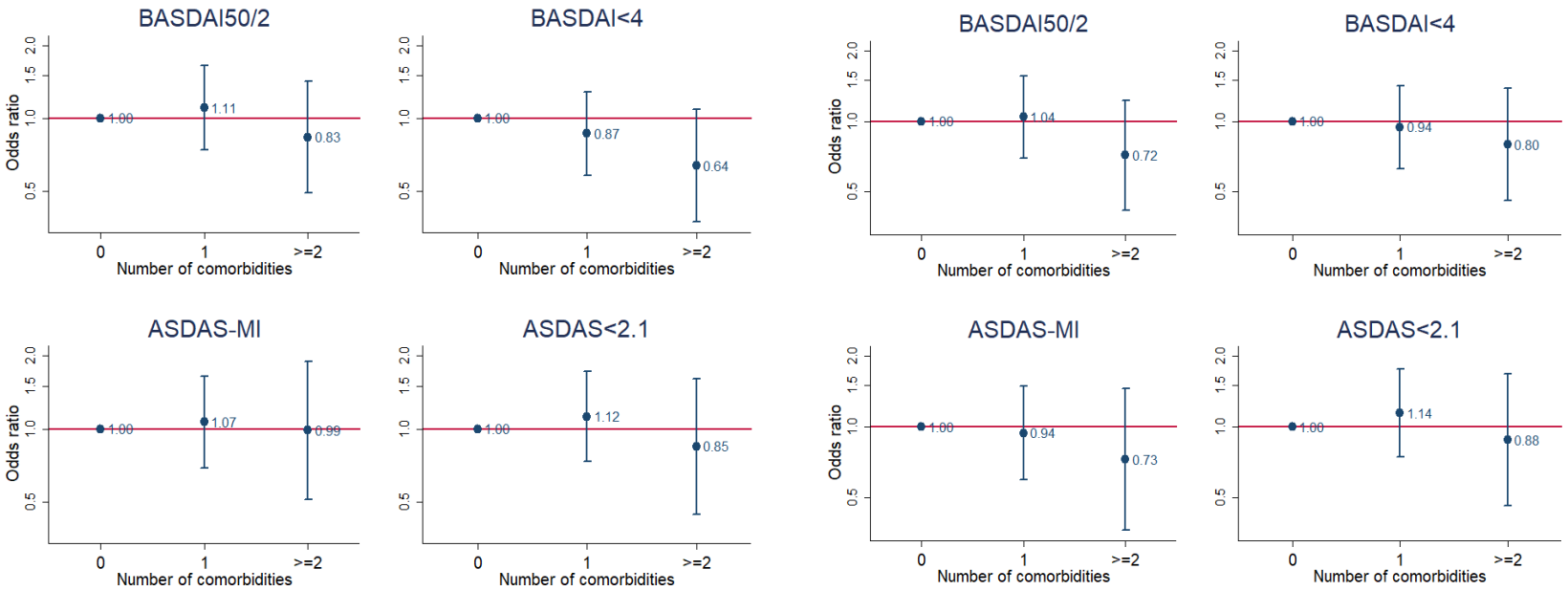
	No. achieving response	Comorbidity variable	Odds ratio without adjusting for baseline disease activity	Odds ratio adjusting for baseline disease activity
BASDAI 50/2	445 (60%)	Binary*	1.01 (0.71 to 1.44)	0.93 (0.65 to 1.33)
		Continuous count	0.92 (0.75 to 1.13)	0.86 (0.70 to 1.06)
ASDAS-MI	130 (26%)	Binary	1.04 (0.70 to 1.55)	0.88 (0.58 to 1.34)
		Continuous count	1.00 (0.78 to 1.28)	0.88 (0.67 to 1.14)
BASDAI<4	449 (60%)	Binary	0.79 (0.55 to 1.12)	0.89 (0.62 to 1.28)
		Continuous count	0.80 (0.65 to 0.99)	0.88 (0.71 to 1.09)
ASDAS<2.1	168 (34%)	Binary	1.04 (0.71 to 1.54)	1.07 (0.72 to 1.58)
		Continuous count	0.96 (0.75 to 1.23)	0.98 (0.77 to 1.25)

*as 0 (reference) vs. ≥1 comorbidities.
BASDAI 50/2, 50% or 2-unit reduction in BASDAI; ASDAS-MI, major improvement i.e. ≥2-unit reduction.
Full model coefficients including covariates are shown in Appendix Table S8.2 and S8.3.

Figure S6. 1: Sensitivity analyses for binary outcomes with missing binary outcomes imputed as response if patients remained on drug for longer than one year.

a) Without baseline adjustment

b) with baseline adjustment



10.6 Appendix for Chapter 7

10.6.1 Inverse-probability weights

Inverse-probability of treatment weighting (IPTW) is often conceptualised as one way of using propensity scores (PS; others being matching, stratifying, and covariate adjustment). Put simply, it is 1 over the probability of being in an exposure group given covariates (i.e., the 'propensity' to be in the exposure group). Thus, IPTW can be considered as 1/PS, or

$$IPTW = \frac{1}{Pr\ [A|L]}$$

where A is the exposure group and L represents all covariates. (The notation is an over-simplification and not strictly correct in representing counterfactuals, which is beyond the scope of this section.) When using IPTW, the overall analysis population size is increased. The weights can be 'stabilised' by replacing the numerator with the probability of being in the exposure group, thus making the mean weight (close to) 1, and the weighted analysis population size (almost) unchanged.

$$Stablised\ IPTW = \frac{Pr\ [A]}{Pr\ [A|L]}$$

Stabilising weights have the additional advantage of reducing the size of extreme weights, which is essential when weights are multiplied, as in marginal structural models discussed later. In this thesis, IPTWs were used only to balance baseline covariates. Since none of the 'exposures' were time-varying (e.g., comorbidity status is measured only at baseline), time-varying IPTWs were not required.

IPTWs are used in marginal (i.e., population level, c.f. conditional or individual) structural (i.e., causal) models. Marginal structural models can be used to analyse repeated measure data (weighted GEE), time-to-event data (weighted pooled logistic regression) or other purposes (e.g., mediation). The marginal risk of treatment discontinuation can be estimated using (a marginal approach to) Cox models (e.g., standardisation or IPTW). However, an important assumption is that censoring (loss to follow-up) is random. This assumption is often violated but can be remediated using inverse probability of censoring weighs (IPCW).

To do so, each individual's follow-up time is discretised into months. This means that someone with x months' follow-up will have x+1 'rows' of data – one for each month. If they had BASDAI assessed every month, each row will have a different BASDAI; if not,

BASDAI from the previous month will be carried forward until the next BASDAI assessment. At each month, IPCWs create weighted populations such that censoring becomes random with respect to baseline covariates and time-varying BASDAI. Stabilised IPCW is constructed as follows:

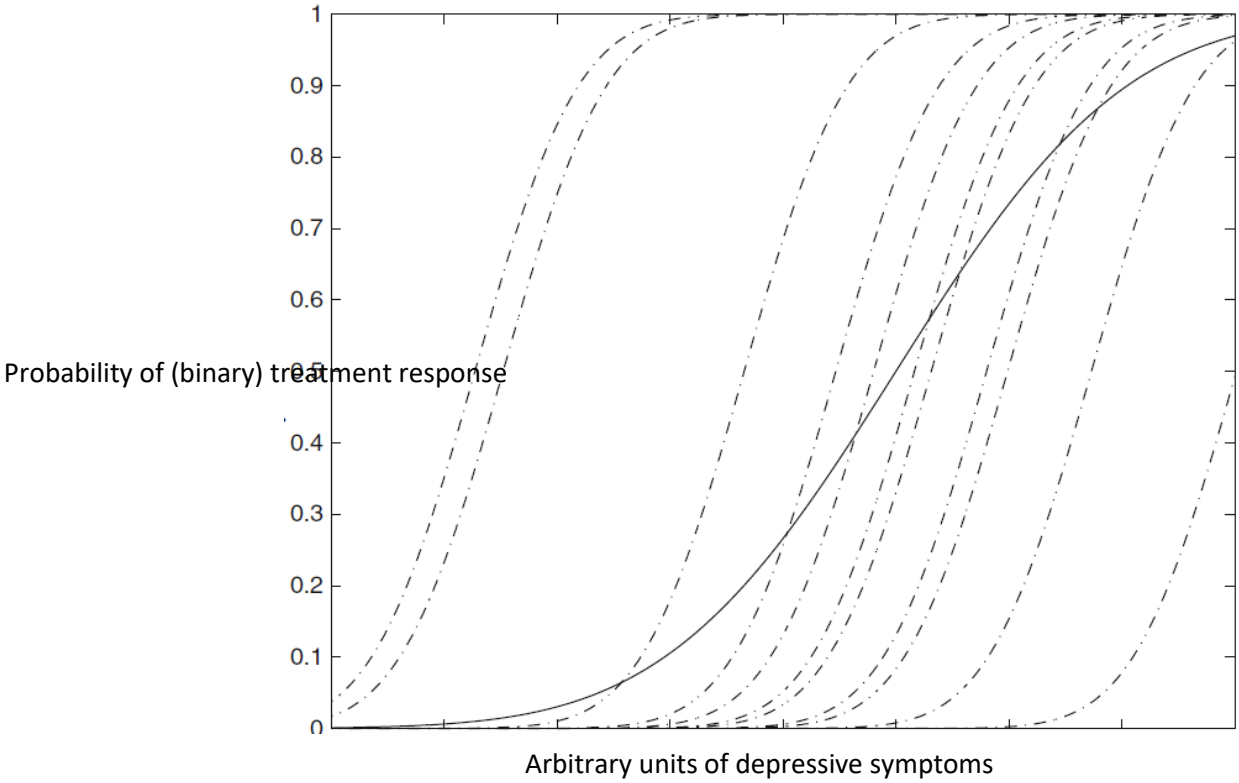
$$\textit{Stabilised IPCW(t)} = \prod_{k=0}^{t} \frac{Pr\,[C(k+1)=0|C(k)=0,\bar{A}(k),L(0)]}{Pr\,[C(k+1)=0|C(k)=0,\bar{A}(k),\bar{L}(k)]}$$

where C(t) is a binary variable taking the value 1 if a subject is censored in month t and 0 otherwise, $\bar{A}$(t) is the exposure history (in this case unchanged), L(0) are baseline covariates including disease activity, and $\bar{L}$(k) is the history of covariates (disease activity at baseline and before censoring). In addition, time is included in both numerator and denominator models in quadratic (i.e., non-linear) form. In this thesis, all stabilised weights, both IPTW and IPCW, were examined for means close to 1 and extreme values. Covariate balance was checked in weighted populations.

10.6.2 Results from marginal and conditional models may not coincide for binary and time-to-event outcomes.

Mixed effects and other conditional models provide conditional estimates, or individual effects, that is, 'if two individuals are randomly selected from a population and both have identical covariate values, the person with one comorbidity would have an outcome value which is, on average, β units higher'. GEE and IP weighted models assess marginal effects, that is, population-level effects or 'average change in outcome per unit change in exposure'. Results from marginal and conditional models coincide for continuous outcomes, but not necessarily for binary and time-to-event outcomes (Figure S6.1). Thus, marginal estimates should not be used to make inferences about individuals under these circumstances. For context, randomised controlled trials assess marginal effects.

Figure S7. 1: Dotted lines show individual/conditional estimates, which do not coincide with population average/marginal estimates in the solid line.



10.6.3 Equivalence between Cox and pooled logistic regression models

This section demonstrates the equivalence between pooled logistic regression and Cox models when the event hazard is small at each time point. The unadjusted HR from the Cox model for time to treatment discontinuation according to history of depression at baseline was HR 1.43 (95% CI 1.04 to 1.97). The same comparison using pooled logistic regression with cubic spline for time (months) with clustered sandwich estimator (for individual participants) gave HR 1.42 (95% CI 1.02 to 1.98). The minor discrepancy explainable by rounding. Figure S7.2 shows Kaplan-Meier estimates using both methods.

Figure S7. 2: Equivalence of Kaplan-Meier estimates derived using continuous (top) and monthly-discrete time (bottom), for Cox and pooled logistic regression.

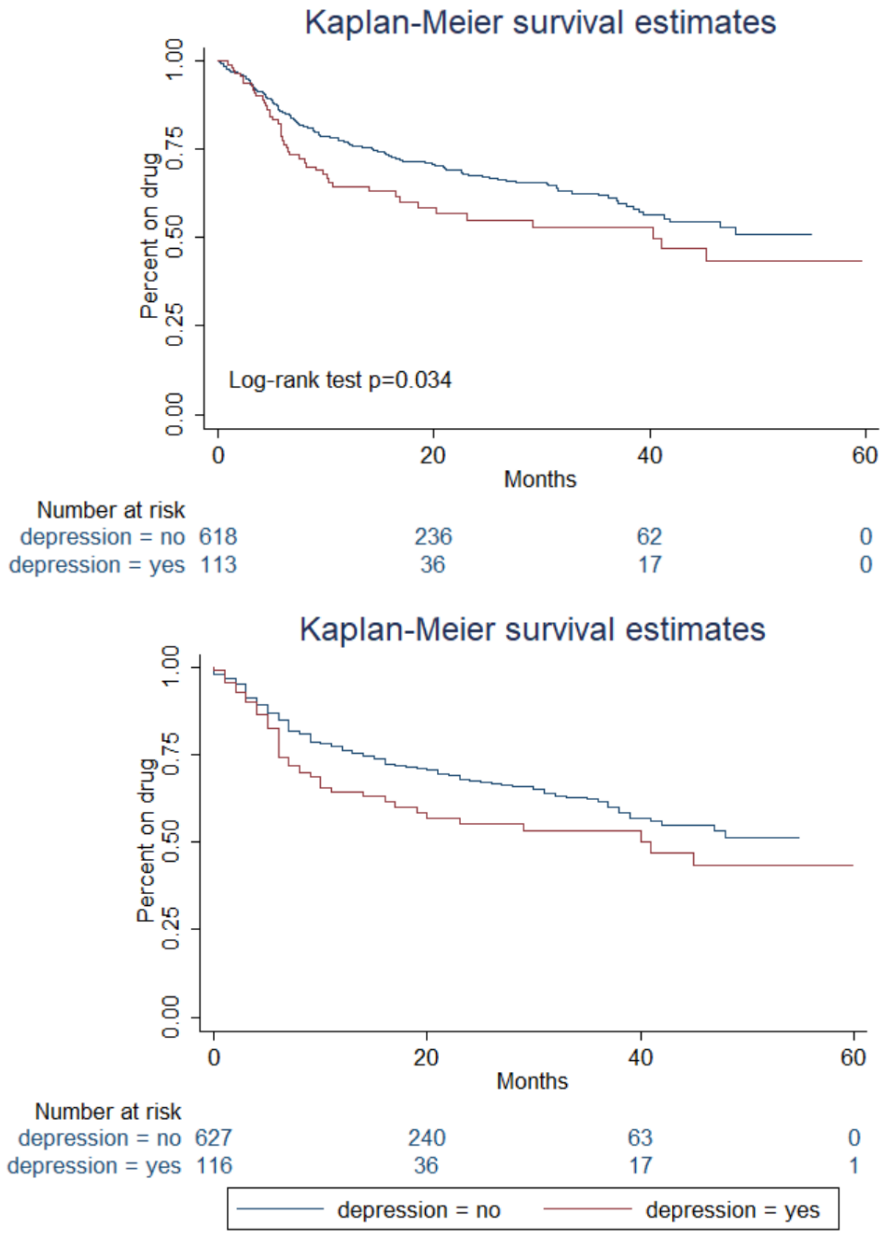


Table S7. 1: Baseline characteristics of BSRBR-AS participants included and excluded from the analysis using HADS.

		Included (n=742)	Excluded (n=252)	P-value
Age, years		45.4 (13.9) (n=742)	42.6 (13.7) (n=252)	0.005
Males		496 (67%)	183 (73%)	0.100
Meeting modified New York criteria		435 (59%)	162 (64%)	0.12
Age at symptom onset, years		28.7 (13.5) (n=742)	28.4 (10.5) (n=252)	0.71
Symptom duration, years		16.7 (13.1) (n=742)	14.2 (13.1) (n=252)	0.008
HLA-B27 positive*		414 (75%)	126 (72%)	0.43
BMI, kg/m^2		28.1 (5.8) (n=653)	28.2 (5.9) (n=217)	0.83
Smoking status	Never smoked	298 (40%)	53 (37%)	0.80
	Ex-smoker	243 (33%)	48 (34%)	
	Current smoker	200 (27%)	41 (29%)	
Education	Secondary school	251 (34%)	38 (27%)	0.15
	Apprenticeship	70 (10%)	12 (8%)	
	Further education college	227 (31%)	49 (35%)	
	University degree	149 (20%)	29 (20%)	
	Further degree	39 (5%)	14 (10%)	
Deprivation quintile	1 - most affluent	134 (18%)	49 (20%)	0.75
	2	161 (22%)	45 (18%)	
	3	145 (20%)	48 (19%)	
	4	148 (20%)	55 (22%)	
	5 - most deprived	153 (21%)	54 (22%)	
NSAID use in past 6 months		538 (74%)	196 (78%)	0.24
DMARD use in past 6 months		107 (15%)	39 (16%)	0.76

Data shown as mean (SD) and n (%) unless otherwise indicated.
*Not all variables had complete data; HLA-B27 was available for 74% of participants
IQR, interquartile range; BMI, body mass index.

Table S7. 2: Full model coefficients for associations between depression diagnosis and binary responses at 6 months.

	Models without adjusting for baseline disease activity				Models additionally adjusting for baseline disease activity			
	BASDAI 50/2	**BASDAI<4**	**ASDAS-MI**	**ASDAS<2.1**	**BASDAI 50/2**	**BASDAI<4**	**ASDAS-MI**	**ASDAS<2.1**
N	475	475	436	436	475	475	436	436
Depression diagnosis	0.69 (0.40, 1.19)	0.56 (0.32, 0.99)	0.75 (0.36, 1.56)	0.5 (0.25, 1.00)	0.54 (0.31, 0.96)	0.73 (0.41, 1.32)	0.52 (0.23, 1.16)	0.53 (0.26, 1.07)
Age	1.00 (0.98, 1.01)	1.00 (0.99, 1.02)	1.00 (0.98, 1.02)	0.99 (0.97, 1.01)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	0.99 (0.97, 1.01)
Gender	1.51 (0.98, 2.31)	1.48 (0.95, 2.30)	1.10 (0.65, 1.86)	1.19 (0.73, 1.93)	1.69 (1.09, 2.62)	1.31 (0.82, 2.08)	1.00 (0.57, 1.78)	1.21 (0.74, 1.97)
Deprivation	0.88 (0.77, 1.02)	0.82 (0.71, 0.95)	1.00 (0.84, 1.19)	0.86 (0.74, 1.01)	0.85 (0.74, 0.99)	0.84 (0.72, 0.98)	0.96 (0.79, 1.16)	0.87 (0.74, 1.02)
Secondary school	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Apprenticeship	0.53 (0.26, 1.07)	0.90 (0.44, 1.82)	0.70 (0.29, 1.72)	1.01 (0.46, 2.23)	0.58 (0.28, 1.19)	0.75 (0.36, 1.57)	0.81 (0.28, 2.35)	0.97 (0.44, 2.14)
Further education college	1.40 (0.86, 2.30)	2.02 (1.21, 3.36)	1.33 (0.74, 2.41)	1.27 (0.73, 2.22)	1.66 (1.00, 2.77)	1.74 (1.02, 2.96)	1.76 (0.91, 3.41)	1.22 (0.70, 2.15)
University degree	1.60 (0.93, 2.76)	2.89 (1.63, 5.13)	1.38 (0.74, 2.58)	2.27 (1.27, 4.06)	1.98 (1.12, 3.50)	2.35 (1.30, 4.25)	1.81 (0.91, 3.61)	2.20 (1.23, 3.95)
Further degree	1.00 (0.41, 2.45)	1.21 (0.49, 3.01)	0.40 (0.11, 1.47)	0.86 (0.32, 2.36)	1.34 (0.53, 3.39)	0.81 (0.32, 2.06)	0.66 (0.16, 2.70)	0.78 (0.28, 2.15)
BMI	0.92 (0.89, 0.96)	0.92 (0.89, 0.96)	0.93 (0.88, 0.97)	0.94 (0.90, 0.98)	0.92 (0.88, 0.95)	0.92 (0.88, 0.96)	0.92 (0.88, 0.97)	0.93 (0.89, 0.97)
Elevated CRP	1.38 (0.91, 2.10)	1.81 (1.18, 2.80)	3.22 (1.81, 5.73)	2.11 (1.30, 3.43)	1.49 (0.97, 2.29)	1.76 (1.12, 2.77)	2.32 (1.26, 4.30)	2.28 (1.39, 3.75)
Comorbidity count	1.05 (0.78, 1.40)	0.84 (0.62, 1.14)	0.99 (0.67, 1.46)	1.05 (0.74, 1.48)	0.95 (0.70, 1.28)	0.96 (0.70, 1.32)	0.75 (0.48, 1.16)	1.09 (0.76, 1.55)
Baseline BASDAI/ASDAS					1.29 (1.15, 1.44)	0.69 (0.61, 0.79)	4.13 (2.82, 6.05)	0.80 (0.61, 1.04)

ASDAS, AS disease activity score; BASDAI 50/2, 50% or 2-unit reduction in BASDAI; ASDAS-MI, major improvement i.e. ≥2-unit reduction; BMI, body mass index; CRP, C-reactive protein.

Table S7. 3: Descriptive summary of all weights used in the analysis.

			n	Mean	SD	Min	Max
IPTW	Depression	BASDAI	738	0.99	0.64	0.30	8.78
		ASDAS	673	0.99	0.61	0.38	8.72
		Spinal pain	740	0.99	0.54	0.39	6.40
	Anxiety	BASDAI	738	1.00	0.47	0.41	3.94
		ASDAS	673	1.00	0.39	0.40	3.52
		Spinal pain	740	1.00	0.39	0.47	5.13
IPCW	Depression		12949	1.00	0.01	0.95	1.07
	Anxiety		12949	1.00	0.01	0.92	1.10
Matching weight	Depression	BASDAI	738	0.08	0.07	0.03	1.00
		ASDAS	673	0.08	0.06	0.03	1.00
		Spinal pain	740	0.12	0.08	0.04	1.00
	Anxiety	BASDAI	738	0.27	0.14	0.10	1.00
		ASDAS	673	0.23	0.11	0.08	1.00
		Spinal pain	740	0.23	0.10	0.10	1.00

ASDAS, AS disease activity score; BASDAI, Bath AS disease activity index; IPTW, inverse probability of treatment weights; IPCW, IP censoring weights; SD standard deviation.

Table S7. 4: Model coefficients for associations between HADS sub-scale categories and binary responses at 6 months.

		BASDAI 50/2	BASDAI<4	ASDAS-MI	ASDAS<2.1
N		542	542	492	492
HADS-D	None	reference	reference	reference	reference
	Mild	0.56 (0.36, 0.89)	0.61 (0.38, 0.97)	0.56 (0.34, 0.94)	0.52 (0.31, 0.88)
	Mod-severe	0.51 (0.29, 0.90)	0.49 (0.27, 0.88)	0.49 (0.26, 0.90)	0.38 (0.19, 0.76)
HADS-A	Mod-severe	reference	reference	reference	reference
	Mild	0.54 (0.34, 0.86)	0.54 (0.33, 0.88)	0.88 (0.51, 1.51)	0.71 (0.43, 1.18)
	None	0.65 (0.42, 1.01)	0.51 (0.33, 0.80)	0.77 (0.46, 1.27)	0.58 (0.36, 0.95)
BASDAI 50/2, 50% or 2-unit reduction in BASDAI; ASDAS-MI, major improvement i.e. ≥2-unit reduction; HADS-D, depression; HADS-A; anxiety sub-scale.					

Table S7. 5: Model coefficients for associations between HADS sub-scale categories and binary responses at 6 months, with missing binary outcomes imputed as response if patients remained on drug for longer than one year.

		BASDAI 50/2	BASDAI<4	ASDAS-MI	ASDAS<2.1
N		665	665	606	606
HADS-D	None	reference	reference	reference	reference
	Mild	0.55 (0.36, 0.85)	0.59 (0.38, 0.92)	0.62 (0.41, 0.95)	0.57 (0.37, 0.89)
	Mod-severe	0.51 (0.31, 0.85)	0.5 (0.30, 0.83)	0.61 (0.37, 1.01)	0.5 (0.30, 0.85)
HADS-A	Mod-severe	reference	reference	reference	reference
	Mild	0.55 (0.36, 0.86)	0.56 (0.35, 0.89)	0.9 (0.57, 1.41)	0.76 (0.49, 1.18)
	None	0.71 (0.48, 1.07)	0.58 (0.38, 0.87)	0.92 (0.62, 1.38)	0.74 (0.49, 1.09)
BASDAI 50/2, 50% or 2-unit reduction in BASDAI; ASDAS-MI, major improvement i.e. ≥2-unit reduction; HADS-D, depression; HADS-A; anxiety sub-scale.					