The cause and effect of mood disturbance in patients with ankylosing spondylitis

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Context

This MPhil was completed as an intercalated degree between years four and five of my undergraduate medicine course. Throughout my medical studies and whilst conducting this MPhil, I have worked part-time as a healthcare support assistant. It is through this work that I have developed an appreciation for the diverse psychological impacts of chronic physical illness.

As a clinician, I believe it is essential to consider the patient in their entirety, with attention to the intricacies of human emotion. As a researcher, I believe it is important to illuminate the patient experience, whilst acknowledging that findings may not always coincide with conventional medical wisdom.

"Cure sometimes, treat often, comfort always"

Hipprocrates

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Definitions

Throughout this thesis, several expressions are used to describe multiple groups of disease- and mood- related variables. The following phrases have been selected by the author for their ease-of-use:

Disease severity is used as an umbrella term to describe the disease status of patients in relation to three distinct constructs: disease activity, pain and functional impairment.

Mood status is used to describe the individual assessment of depression and anxiety.

Mood disturbance is employed to describe a psychological state where depression and anxiety co-exist.

List of common abbreviations

AS	Ankylosing spondylitis
CES-D	Centre for Epidemiological Studies Depression Scale
CI	Confidence interval
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BDI	Beck Depression Index
DSM	Diagnostic and Statistical Manual of Mental Disorders
HADS	Hospital Anxiety and Depression Scale
HLA	Human leukocyte antigen
ICD	International Classification of Diseases
MCID	Minimal clinically important difference
NRS	Numerical rating scale
OR	Odds ratio
PROM	Patient-reported outcome measure
QoL	Quality of life
SpA	Spondyloarthropathy
TNF	Tumour necrosis factor

Abstract

Ankylosing spondylitis (AS) is a chronic inflammatory disorder, causing progressive pain and stiffness of the spine and peripheral joints. A systematic review of the literature revealed a high prevalence of possible depression (23-36%) and possible anxiety (45-57%) in patients with AS. However, few existing studies have focussed on the relationships between mood and AS severity.

612 participants in a UK cohort of AS patients were included in the baseline postal survey. 470 patients responded to the six month follow-up survey thereafter. Several measures of disease status were collected [disease activity (Bath AS Disease Activity Index), pain (numerical rating scale) and physical function (Bath AS Functional Index)]. Mood was assessed by the Hospital Anxiety and Depression Scale. Improvements or deteriorations in mood and disease status were defined according to minimal clinically important differences in each measure.

298/612 (49%) patients reported depression/anxiety at baseline. Of whom, 166/298 (56%) demonstrated a co-existence of depression and anxiety; 27/298 (9%) had depression only and 105/298 (35%) had anxiety only. Although depression and anxiety were individually associated with increased disease activity, the strongest association was observed in patients with mixed depression and anxiety (OR 7.66, 95% CI 4.10-14.30). Similarly, there were significant associations of mixed depression and anxiety with poor function (OR 5.91, 95% CI 3.17-10.99) and increased pain (OR 4.76, 95% CI 2.56-8.86). In contrast to clinical expectations, there was no association between changes in mood or disease status over six months.

There is a high prevalence and frequent co-occurrence of depression and anxiety in patients with AS. Findings suggested that AS patients with mixed depression and anxiety had increased disease severity, however longer follow-up studies of more than six months

are required to investigate these causal relationships. Anxiety and depression, as well as disease severity, should be considered when treating patients with AS.

CHAPTER 1

Background

1.1 Ankylosing spondylitis

1.1.1 Definitions

Seronegative spondyloarthropathies (SpAs) comprise a heterogeneous group of multisystem inflammatory conditions that share specific clinical characteristics that distinguish them from other rheumatic diseases (Braun and Sieper, 2006). The disorders commonly present with inflammatory back pain, asymmetric peripheral arthritis and the absence of rheumatoid factor: a serological state referred to as *seronegativity.*

Ankylosing spondylitis (AS) is one of several conditions classified as a spondyloarthropathy. The disease is characterised by fluctuating pain and stiffness of the spine and peripheral joints, with variable extra-articular manifestations (Russel, 1998). Although the precise aetiology of AS is unknown, as with other spondyloarthropathies, there is a strong genetic predisposition associated with the HLA-B27 gene (Wordsworth, 1998).

1.1.2 Epidemiology

AS typically presents insidiously in the second to third decade of life (Braun and Sieper, 2007). The female to male ratio is approximately 1:2-3 (Dagfinrud, 2009), however, it is recognised that females tend to have a later onset of clinical disease.

There are approximately 200,000 diagnosed patients with AS in the UK (DoH, 2006); with 2,300 newly diagnosed cases each year (NICE, 2008). The adult prevalence has been estimated to vary between 0.1% and 1.4% depending on the geographical region; with

highest rates found in northern Europe and indigenous peoples of North America (Boonen and Van der Linden, 2006).

Specific geographical estimates reflect the varying prevalence of HLA-B27 positivity. European estimates include a prevalence of 1.1% to 1.4% in northern Norway (Gran et al, 1985) and 0.86% in Berlin, Germany (Braun et al, 1998). The prevalence of AS is notably lower in Asian countries such as Turkey and China, where rates of 0.25% and 0.11% have been reported, respectively (Karkucat et al, 2010, Dai et al, 2003).

1.1.3 Clinical and socioeconomic impact

The most characteristic clinical finding of AS is the presence of sacroiliitis (inflammation of the sacroiliac joints). This is potentially complicated by inflammatory involvement of the entire vertebral column. Frequently, there are limitations in spinal and thoracic mobility (Karapolat, 2008); with one third of patients progressing to severe disabling disease (Zink, 2000). Generally, men tend to have more profound spinal involvement whilst women are more likely to experience peripheral joint symptoms (Braunstein et al, 1982).

Other related disease entities include anterior uveitis, psoriasis, reactive arthritis and inflammatory bowel disease, where associations with the HLA-B27 gene have also been implicated (Elewaut and Matucci-Cerinic, 2009). Rarely, cardiac valve disease, pulmonary fibrosis, amyloidosis and pathological bone fractures result, with a corresponding increase in mortality (Braun and Pincus, 2002). However, the occurrence of these extra-articular conditions is variable among patients and largely unpredictable (Boonen and Van der Linden, 2006).

Similarly to patients with other inflammatory rheumatological disorders, AS patients also experience general somatic symptoms related to the persistence of chronic inflammation. In particular, fatigue has been reported as a major complaint in 65% of AS patients (Jones et al, 1996). Sleep disorders are also common; with an estimated prevalence of 55% (Günaydin et al, 2009).

In addition, patients with AS report substantial disruptions in psychosocial functioning. Exploratory research has elicited patient concerns such as changes in mood, personality and reduced levels of social participation (Hamilton-West, 2009). AS patients have been shown to experience significantly higher levels of body image disturbance when compared to healthy controls, including diminished self-confidence and negative body judgement (Guenther et al, 2010). Male patients have also reported further worries related to sexual dysfunction, namely diminished sexual drive and reduced satisfaction (Dincer et al, 2007).

The socioeconomic impact of AS is undoubtedly concerning. Studies of individuals with established disease have identified lower frequencies of employment than found in the general population. In a Dutch study, overall paid employment was 54% within a cohort of 658 AS patients (Chorus et al, 2002). This was a reduction of 11% when compared with national aged-matched reference data. In the UK, Healey et al (2011) reported similar employment levels of 14% below the national average of those of working age.

Although many patients with AS continue to remain in full-time employment, the individual and societal impact of lost productivity is significant and often unrecognised. A recent UK study on healthcare resource use and work productivity estimated an average cost of almost £3,000 for each patient over a period of three months (Rafia et al, 2012). The majority of this burden was related to costs resulting from unemployment, absenteeism and reduced work productivity.

1.1.4 Diagnosis

1.1.4.a Ankylosing spondylitis

A diagnosis of AS is generally made by combining clinical and radiologic findings (X-ray or Magnetic Resonance Imaging). However, previous years have seen a variation in the diagnostic tools applied in both medical and research settings, as an understanding of the clinical features of AS has developed.

There are two main sets of diagnostic criteria which have been proposed for use in epidemiological studies concerning AS cohorts: the Rome criteria (Kellgren et al, 1963) and the New York criteria (Bennett and Wood, 1968). Both criteria recognise the presence of radiographic sacroiliitis for a definite diagnosis of AS (Table 1.1).

Table 1.1: Original diagnostic criteria for ankylosing spondylitis (AS)

Rome (Kellgren et al 1963)	New York (Bennett and Wood, 1968)
Clinical criteria:	
• Low back pain and stiffness for ≥ three months that is not relieved by rest • Pain and stiffness in the thoracic region • Limited motion in the lumbar spine • Limited chest expansion • History of uveitis	• Low back pain with inflammatory characteristics • Limitation of lumbar spine motion in sagittal and frontal planes • Decreased chest expansion
Radiological criteria:	
• Bilateral sacroiliitis ≥ grade two	• Bilateral sacroiliitis ≥ grade two • Unilateral sacroiliitis ≥ grade three
Diagnosis:	
• Definite AS if one clinical criterion is present with one radiological criterion	• Definite AS if one clinical criterion is present with one radiological criterion

The separate criteria were later criticised by Van der Linden et al (1984); specifically the Rome criteria for its' vague definition of lumbar spine motion and the New York criteria for its' unspecific definition of low back pain. Subsequently, the modified New York criteria were devised and validated (Van der Linden et al, 1984). A diagnosis of AS according to the modified New York criteria requires the presence of low back pain for more than three months with a limitation of lumbar spine motion in both the frontal and sagittal planes.

An overview of the modified New York criteria is provided in Table 1.2.

Table 1.2: Modified New York criteria for ankylosing spondylitis (AS) (Van der Linden et al, 1984)

Clinical criteria:
• Low back pain (≥ three months), improved by exercise but not relieved by rest • Limitation of lumbar spine motion in both the frontal and sagittal planes • Limitation of chest expansion relative to normal values for age and sex
Radiological criteria:
• Bilateral sacroiliitis ≥grade two • Unilateral sacroiliitis ≥ grade three
Diagnosis:
• Definite AS if one clinical criterion is present with one radiological criterion

The modified New York criteria have been widely used among research studies and are nationally recommended for use in clinical settings (BSR, 2004). It is important to note, however, that the diagnostic requirements of the criteria inherently lead to poor sensitivity for early stages of disease, which are not apparent on plain radiographs. As a result, the mean diagnostic delay between onset and diagnosis of AS is estimated to be as long as 8.5 to 11.4 years (Feldtkeller, 2003).

1.1.4.b Spondyloarthropathy

Patients with the early stages of AS or overlapping symptoms with other inflammatory conditions may have an undifferentiated form of spondyloarthropathy (SpA). In an attempt to discriminate SpAs from other rheumatic diseases, such as rheumatoid arthritis (RA), two main sets of criteria have been devised and validated: the Amor criteria (Amor et al, 1990) and the European Spondyloarthropathy Study Group (ESSG) criteria (Van der Linden et al, 1991). Both criteria are presented collectively in Table 1.3 below.

Table 1.3: Diagnostic criteria for spondyloarthropathy (SpA)

Amor criteria (Amor et al, 1990)	**European Spondyloarthropathy Study Group (ESSG) criteria (Van der Linden et al, 1991)**
Clinical criteria:	
• Inflammatory back pain (1) • Unilateral buttock pain (1) • Alternating buttock pain (2) • Enthesitis (2) • Peripheral arthritis (2) • Dactylitis (2) • Acute anterior uveitis (2) • *HLA-B27* positive or family history of spondyloarthropathy (2) Good response to NSAIDs (2) Note: ( ) indicates number of clinical points	Main criterion: • Inflammatory spinal pain or synovitis that is asymmetrical/predominantly lower limb Other clinical criteria: • Sacroiliitis • Alternating buttock pain • Enthesopathy • Positive family history • Inflammatory Bowel disease • Psoriasis • Urethritis/cervicitis/acute diarrhoea occurring within one month before arthritis
Diagnosis:	
• Definite SpA if there is a total of six points or more	• Definite SpA if the main criterion is present with one of the other clinical criteria

The ESSG criteria require the presence of inflammatory back pain or synovitis to make a definitive diagnosis of SpA. Conversely, the Amor criteria contribute a point system according to the presence of different axial and peripheral symptoms. Separate axial and peripheral SpA criteria have recently been devised by the Assessment of Spondyloarthritis International Society (ASAS) (Rudwaleit et al, 2009). However, there are currently few clinical studies which have used these criteria for the identification and recruitment of patients.

1.1.5 Management

1.1.5.1 Assessment of disease severity

Monitoring of disease severity in patients with AS can be challenging, as serological inflammatory markers such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels have been found to be unreliable indicators of clinical disease activity (Sheehan, 1986; Pradeep et al, 2008). Therefore recent years have seen the increasing development and use of several patient-focussed self- and clinician-administered instruments.

The ASAS group have defined six core assessment domains for AS severity in clinical practice: fatigue, functional ability, stiffness, pain, global well-being and spinal mobility (Van der Heijde et al, 1999). Fatigue and functional ability are measured with the Bath AS Disease Activity Index (BASDAI) and the Bath AS Functional Index (BASFI), respectively (Garrett et al, 1994; Calin et al, 1994). Stiffness, pain and global well-being are assessed with numerical rating scales (NRS). Spinal mobility is measured by the Bath AS metrology Index (BASMI) (Jenkinson et al, 1994).

All of these tools, with the exception of the BASMI (a clinically assessed measure), are examples of patient-reported outcome measures (PROMs): self-administered instruments reported directly from patients. Subsequent analyses in this thesis are based on data derived solely from PROMs, including the BASDAI, BASFI and pain NRS. These measures are therefore described in greater detail in Chapter three. It is noteworthy, however, that the BASMI is commonly applied in clinical studies to validate the disease severity scores reported by patients (Brandt et al, 2000; Braun et al, 2002). Therefore, for the purposes of completeness, the BASMI is considered here.

The BASMI quantifies spinal mobility through five examinable measurements of lumbar flexion, lumbar lateral flexion, cervical rotation, tragus to wall and inter-malleolar

distances. Each dimension is given a score between zero and ten; higher scores indicating more severe limitations. The clinician then calculates a final mean score of the sum of the items between zero and ten. The BASMI is considered to be a reliable objective measure of axial status; however, individual clinical assessment of patients may not be feasible in many large cohort studies, due to the time and cost implications.

1.1.5.2 Assessment of quality of life

The World Health Organisation defines quality of life (QoL) as “an individual’s perception of their position in life in the context of the culture and value systems in which they live” (WHO, 1997). Over the last decade there has been considerable debate concerning the assessment of QoL for patients with AS. The challenge has been to develop a tool which elicits the unique disease impacts of AS, with applicability in both clinical and research settings. Currently three AS-specific measures exist: the AS Quality of Life (ASQoL) questionnaire (Doward et al, 2003), the Patient Generated Index-AS (PGI-AS) (Haywood et al, 2003) and the Evaluation of AS Quality of Life (EASi-QoL) questionnaire (Haywood et al, 2010).

All of these measures are assessed by self-reported questionnaires. The most recently developed measure, the EASi-QoL, consists of four separate domains: disease activity, physical function, social participation and emotional wellbeing. Unlike the ASQoL and the PGI-AS, the EASi-QoL provides individual scores for each of the dimensions of QoL. The separate domain for emotional wellbeing reflects the acknowledgement of psychological outcomes as fundamental components of QoL.

1.1.5.3 Treatment

There is no curative treatment for AS. Unlike with RA, disease modifying drugs have been found to be of minimal benefit (Chen et al, 2006a, 2006b). Therefore, current treatment regimens aim to relieve symptoms and prevent the development of stiffness and flexion

deformities. The mainstays of treatment are non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy intervention (McVeigh and Cairns, 2006). A BASDAI score of four or more is suggestive of suboptimal disease control. These patients are considered eligible for biological therapies such as tumour necrosis factor (TNF) inhibitors, known as anti-TNFs (NICE, 2008).

Anti-TNF therapies have been shown to significantly improve disease activity, mobility, function and pain in patients with AS (Zochling et al, 2009), although the relatively high costs and the increased susceptibility of patients to serious infections, make initiation of therapy a difficult decision for both the patient and clinician (BSR, 2004). Furthermore, anti-TNF medication is not suitable for all patients, with contraindications in pregnancy and individuals with severe cardiac, hepatic and renal impairment (NICE, 2008).

Joint replacement and spinal corrective surgery are reserved for those patients with advanced structural disease, which medical treatment cannot improve.

1.2 Anxiety and depression

1.2.1 Definitions

Anxious and depressive states are considered as physiological manifestations of mental distress. Anxiety is often described as feelings of unease, apprehension and worries about the future, whilst depression refers to a state of low mood; associated with emotions of sadness and hopelessness. These symptoms occur on a continuum of severity; becoming pathological through their persistence and interference with everyday life (Bjelland, 2004).

1.2.2 Prevalence in the general population

In the UK, the point prevalence of depression has been reported at 2.6% for adults living in private households (Singleton et al, 2001). Similarly, an international study by the World Health Organisation (WHO) found a one year prevalence of depression of 3.2% in

patients with no other medical conditions (Moussavi et al, 2007). When subjects with other chronic co-morbidities were included, these figures rose dramatically to as high as 23%. Anxiety has been less widely studied; however, a recent systematic review reported a pooled one-year prevalence of 10.6% within the general population (Somers et al, 2006).

Depression and anxiety occur frequently together. In her meta-analysis, Clark (1989) found that 56% of individuals with a depressive disorder also had an anxiety disorder at some time in their lives. The occurrence of depression in anxious patients was also common, however this varied according to the type of anxiety disorder (20-63%). Furthermore, it is widely reported that cases of pure depression, in the absence of anxiety, are relatively infrequent when compared to the number of cases of anxiety (Alloy et al, 1990, Mineka et al, 1998).

It is therefore recognised that depression and anxiety are common disorders of the general population, even when considering individuals without medical co-morbidities. Although anxiety is less widely studied than depression, it is important to consider that these psychological states rarely occur in isolation. Individuals with medical co-morbidities are known to be at higher risk of developing anxiety and depression (NICE, 2009a).

1.2.3 Clinical and socioeconomic impact

Depression is established as the fourth leading cause of disability worldwide; accounting for 4.4% of total disability adjusted life years (Ustun et al, 2004). The independent impact of depression on physical function was investigated in the Medical Outcomes Study across three American sites (Wells et al, 1989). Functioning in outpatients with depressive symptoms was comparable with or worse to the unique effects of other chronic medical conditions such as diabetes, heart disease and arthritis. Patients with co-morbid depression and chronic physical illness demonstrated a significant additive deterioration.

Anxiety has also been shown to significantly impact on clinical outcomes. A study of 280 primary care patients explored the unique effects of different types of anxiety disorder

(Stein et al, 2005). When controlling for depression and other chronic medical conditions, it was found that panic disorder, post-traumatic stress and social phobia were all similarly associated with functional impairment and a reduction in health-related quality of life. Notably, the effect of generalised anxiety disorder was non-significant, probably due to its extensive co-morbidity with major depression.

Depression and anxiety are important public-health problems, with increasing burdens on individuals and healthcare services. In the UK, the annual cost for services and lost employment has been estimated at £7.5 billion for depression and £8.9 billion for anxiety (McCrone et al, 2008). Wittchen et al (2000) also reported a reduction in work productivity of 10% or more in patients with mixed depression and anxiety. Furthermore, the co-existence of depression and anxiety has also been associated with an increase in medical utilisation, symptom severity and chronicity of symptoms (Hirschfield, 2001).

1.2.4 Diagnosis

The improved recognition of depression and anxiety in primary care is central to current international strategies for understanding mental health (WHO, 2001). Assessment of depression and anxiety is particularly important in patients with physical comorbidities where mood disturbance occurs more frequently (NICE, 2009a).

The disorders are assessed by registration of the patient's subjective symptoms and impairment during a specified time period, through interviews or questionnaires (Bjelland, 2004). Symptoms of mood disturbance are complex, including varying degrees of cognitive, behavioural and somatic disturbances. Assessment is also confounded by the presence of general somatic symptoms such as fatigue and insomnia, which may manifest as a result of both physical and psychiatric illness.

Depression and anxiety are presently defined by two main classification criteria: the International Classification of Diseases 10 (ICD-10) (WHO, 1992) and the Diagnostic and

Statistical Manual of Mental Disorders IV (DSM-IV) (American Psychiatric Association, 2000). According to both classifications, the patient must be symptomatic for at least two weeks for a diagnosis of major depressive disorder and six months for a diagnosis of generalised anxiety disorder.

The DSM-IV (table 1.4) is considered the gold standard for depression according to national guidelines (NICE, 2009b), and is often used for the validation of new patient-reported outcome measures (PROMs). There are two hallmark symptoms of depression: low mood and diminished interest or pleasure in everyday activities (anhedonia). Other possible clinical symptoms include cognitive problems such as reduced concentration and somatic complaints such as appetite and sleep disturbances.

Table 1.4: Diagnostic criteria for major depressive episode (American Psychiatric Association, 2000)

Main criteria:
• Low/depressed mood • Diminished interest or loss of pleasure in almost all activities (anhedonia)
Other clinical symptoms:
• Significant weight change or appetite disturbance • Sleep disturbance (insomnia or hypersomnia) • Psychomotor agitation or retardation • Fatigue or loss of energy • Feelings of worthlessness • Diminished ability to think or concentrate; indecisiveness • Recurrent thoughts of death/suicide plans or attempts
Diagnosis:
• At least five symptoms within a two week period, including one main criterion • Symptoms cause impairment in social or occupational functioning

The diagnosis of an anxiety disorder is nosologically complex. The DSM-IV classifies anxiety into several categorical subtypes including generalised anxiety (Table 1.5), panic,

phobic, post-traumatic stress and obsessive-compulsive disorders. The most common of these is generalised anxiety disorder, which is classified according to the main criterion of excessive worry, accompanied by other clinical symptoms such as restlessness and irritability.

Table 1.5: Diagnostic criteria for Generalised Anxiety Disorder (American Psychiatric Association, 2000)

Main criterion:
• Difficulty to control excessive anxiety or worry
Other clinical symptoms:
• Restlessness • Being easily fatigued • Difficulty concentrating/ irritability • Muscle tension • Sleep disturbance
Diagnosis:
• Main criterion and three other symptoms, occurring most days over six months

The ICD-10 and DSM-IV also include suggested criteria for the diagnosis of mixed anxiety and depressive disorder. This diagnosis is recommended when patients present with a constellation of depressive and anxious symptoms, yet neither disorder is clearly predominant.

Although structured interviews are considered to be the gold standard, questionnaires are increasingly applied in many clinical and research settings, due to their simplicity, low cost and reliability (Fitzpatrick, 1998). Survey methods are practically advantageous; enabling assessment of large populations, including patients in remote locations. Furthermore, the use of standardised questions ensures precise measurement. PROMs are particularly useful in assessing mood disturbance, as mood disorders are often difficult to diagnostically define and largely influenced by observer subjectivity.

Instruments which have been frequently used to assess mood in epidemiological studies include the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983); Beck Depression Inventory (BDI) (Beck et al, 1961); Centre for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977); Patient Health Questionnaire 9 (PHQ-9) (Spitzer et al, 2001) and the State-Trait Anxiety Inventory (STAI) (Spielberger et al, 1970). The HADS questionnaire assesses both depression and anxiety, while the other measures assess depression (BDI, CES-D, PHQ-9) or anxiety (STAI) only.

Each of these PROMs has its own distinct constructs and psychometric properties. Furthermore, each measure assesses different symptoms and severities of mood disturbance, with variable diagnostic thresholds. For example, the HADS depression subscale consists of seven items pertaining to the cognitive and emotional impacts of depression; with normal, possible and probable outcomes. Conversely, the BDI is a 21-item inventory which includes additional questions concerning physical symptoms such as weight loss and fatigue. The outcomes of the BDI are normal, mild, moderate and severe. Both tools are similar in that they assess depressive symptoms over the last week.

The properties of the mood assessment measures which have been applied specifically in studies of patients with ankylosing spondylitis are reported in further detail in the literature review in Chapter two.

1.2.5 Management

It is important to detect depression and anxiety as they have considerable clinical and socioeconomic impacts, yet respond well to appropriate treatment. Both depression and anxiety have been shown to benefit from a variety of psychological and pharmacological interventions. A wide range of psychotherapies are available, including cognitive behavioural therapy (CBT), interpersonal therapy and non-directive counselling (NICE, 2006). In addition, newer antidepressants such as selective serotonin re-uptake inhibitors

(SSRIs) have proven to be an effective treatment for patients with co-existence of depressive and anxious symptoms (Nutt, 1997).

1.3 Anxiety and depression in rheumatological disorders

Psychiatric disorders are common in patients with rheumatological disease, as are they in many chronic pain populations. A UK survey of 203 patients found that 33.5% of patients referred to specialist rheumatology services had a diagnosis of depression, generalised anxiety or panic disorder as defined by the DSM-IV criteria (Maiden, 2003).

When depression or anxiety co-exists with rheumatological disease, it may be that the psychiatric symptoms are a pathogenic cause or consequence of the physical illness, or a coincidental occurrence (Rodin et al, 1991). It has also been proposed that adverse psychological responses may lead to an additional stress-induced activation of cellular inflammation, further contributing to a worsening in disease activity in patients affected by inflammatory conditions, such as rheumatoid arthritis (Davis et al, 2008).

1.3.1 Inflammatory rheumatological disorders

In this section, anxiety and depression are discussed in relation to patients with inflammatory rheumatological disorders, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). These conditions are important to consider as these patients share similar symptoms to patients with ankylosing spondylitis (AS). In particular, age and sex matched groups of patients with RA and AS show similar levels of disability, pain, and reductions in well-being (Zink, 2000). This section concludes with a discussion of the theories surrounding the occurrence of anxiety and depression in patients with AS.

1.3.1.1 Rheumatoid arthritis

Numerous studies have examined the psychological wellbeing of patients with RA. A meta-analysis of twelve independent studies found significantly higher levels of

depression in RA patients when compared to healthy controls (Dickens et al, 2002). In a recent study of 169 RA patients possible anxiety was found in 35.3% of patients and possible depression in 28.3% of patients (Covic et al, 2012). Mixed depression and anxiety was common, with 21.8% of patients reporting a co-existence of depression and anxiety.

Concurrent and prospective levels of depression and anxiety have been positively associated with disease activity in patients with RA (Overman et al, 2012). Pain has also been implicated as a main causal mechanism for depression in RA (Dickens et al, 2002, Wolfe, 2009), however, individual cognitive responses and coping strategies have been suggested to mediate this link (Basler, 1993).

1.3.1.2 Systemic lupus erythematosus

Particularly high levels of depression and anxiety have been reported in patients with SLE. In a study of 120 patients with diagnosed SLE, 37% were reported to have possible depression and 60% were reported to have possible anxiety (Tench et al, 2000). Longitudinal changes in depression and anxiety have also been shown to positively correlate with disease activity in patients with SLE (Ward et al, 2002). However, it should be born in mind that neuropsychiatric disturbance can occur as a result from the direct inflammatory effect of SLE on the brain (Hanly, 2005).

1.3.1.3 Ankylosing Spondylitis

There is no clinical evidence that the inflammatory processes in AS directly affect the brain. Hence, the development of psychiatric symptoms in AS is likely to be an emotional reaction to the burden of sustained physical illness, rather than from immunopathogenic mechanisms. The negative impact of AS has been reported across a wide range of physical domains; including pain, stiffness, fatigue and sleep disturbance; symptoms which inevitably interfere with psychological functioning.

In 2010, the National AS society published a document entitled ‘Looking Ahead’. The aim of the report was to support both clinicians and patients in achieving optimal management for AS. The report raises awareness of the problems that patients with AS may face, which are often under-recognised. Specific concerns included diagnostic uncertainty, inconsistent monitoring and inequalities in access to appropriate healthcare and treatments. The document concludes by highlighting the extensive psychosocial impacts of AS, with a recommendation for further studies to fully explore the impacts of AS on patients.

Following interviews with RA patients, Bury (1988) described the onset of illness as a major disruptive experience *or bibliographic disruption*; whereby the patient is forced to reassess their future plans and expectations. This concept may be even more relevant for patients with AS, where onset is often considerably earlier than RA. The initial non-specific symptoms can make a definite diagnosis of AS elusive; thus creating profound insecurity at a time when young adults are faced with important decisions concerning their independence. Furthermore, the progressive nature of AS requires continual physical, psychological and social adjustment throughout the entirety of the patient’s life.

Even when a diagnosis of AS is made, disease progression is variable; ranging from minimal to widespread disability (Brophy et al, 2002). The erratic evolution of extra-articular symptoms and complex co-morbidities adds to the individual burden of disease (Boonen and Van der Linden, 2006). Unpredictable exacerbations of inflammatory activity can create feelings of apprehension and helplessness. In addition, the physical effects of reduced height and stooped body posture contribute to the development of social phobias and feelings of self-consciousness (Hamilton-West and Quine, 2009).

1.4 Conclusion

Patients with AS suffer from a wide range of clinical symptoms from a young age, with an unpredictable disease course for the rest of their lives. When considering the breadth of potential clinical impacts, it is not uncommon that patients with established disease present a substantial socioeconomic burden (Boonen and Van der Heijde, 2004). There are direct NHS and personal expenses associated with the increased use of health resources, and indirect costs related to unemployment, work disability and absenteeism (Rafia et al, 2012).

Clinical assessment of disease severity is challenging in patients with AS. However, the development of patient-reported outcome measures (PROMs), such as the Bath indices, has provided a standardised approach for measuring and understanding the patient experience. Existing PROMs encompass several aspects of AS severity, including disease activity, pain and functional impairment. In addition, emotional wellbeing is recognised as an important dimension in the assessment of quality of life in AS patients (Haywood et al, 2010). Although AS-specific PROMs for mood do not exist, generic mood PROMs provide a reliable means of assessing mood in large cohorts of patients with a wide variety of medical conditions.

Both depression and anxiety have been reported as common features in patients with chronic inflammatory diseases, such as Rheumatoid Arthritis (RA), and have been suggested to play an important role in the severity of the patient's symptoms (Overman et al, 2012). It is therefore perhaps surprising that the presence of mood disorders in patients with AS has been less commonly studied than in patients with RA, although the same clinical factors exist in both diseases (Zink, 2000).

1.5 Aims and structure of this thesis

The main research aims for this thesis are as follows:

(i) to summarise the existing evidence on the prevalence of depression and anxiety in AS, and their associations with disease severity.

(iia) to assess the unique and combined associations of depression and anxiety on disease severity.

(iib) to assess the unique and combined associations of disease severity on depression and anxiety.

(iiia) to determine the predictive relationships of depression and anxiety on disease severity.

(iiib) to determine the predictive relationships of disease severity on depression and anxiety.

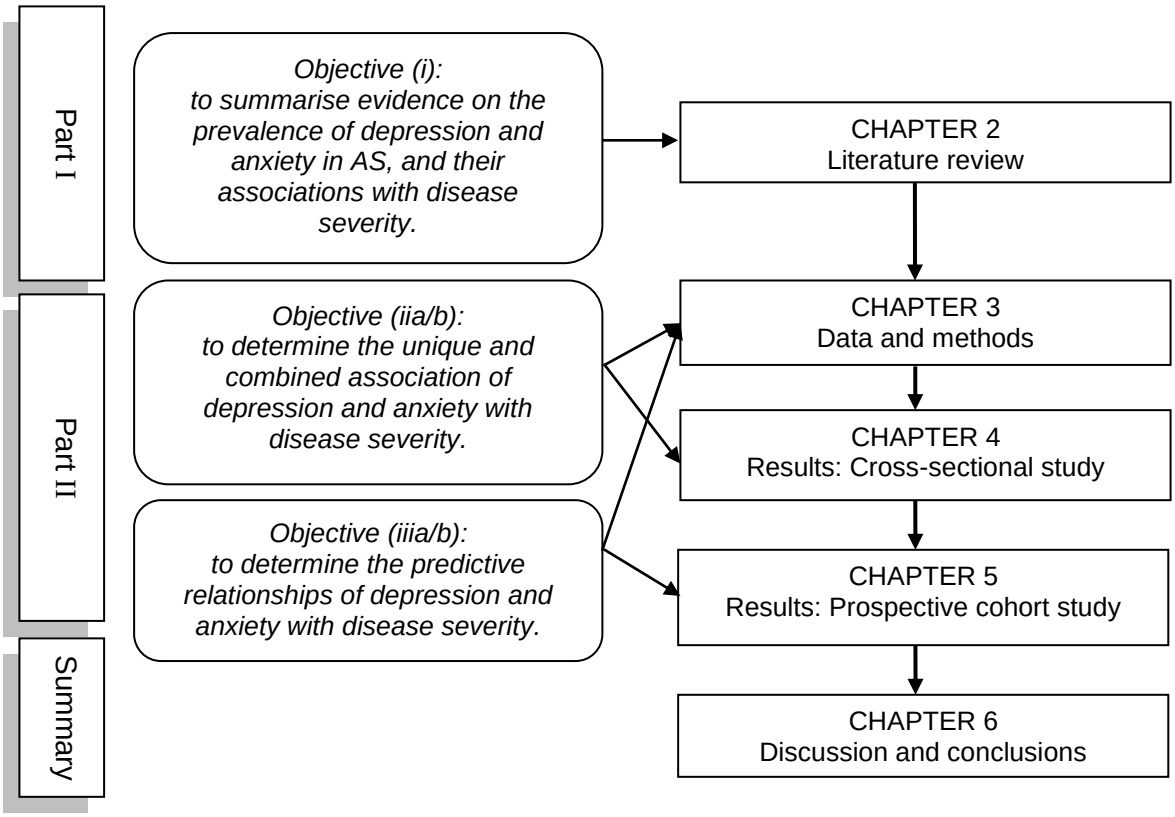
The remainder of this thesis is divided into two parts illustrated in Figure 1.1. The first part of the thesis relates to aim (i) and the second part of the thesis relates to aims (ii) and (iii).

Part I: literature review (Chapter two). This part of the thesis presents a systematic review of the evidence on the prevalence of depression and anxiety in patients with AS, whilst identifying studies which have considered their relationships with disease severity.

Part II: cross-sectional and prospective cohort studies (Chapters three to five). This part of the thesis covers the methods and results from a multisite UK observational cohort study of AS patients. The analytical methods for this study are described in Chapter three; however, cross-sectional and prospective results are presented separately in Chapters four and five, respectively. Following each set of results, there is a summary of principle findings.

Finally, Chapter six provides a conclusion and discussion of all of the results from this study, with recommendations for clinical practice and future research.

Figure 1.1: Schematic overview of this thesis



Part I

Literature review

CHAPTER 2

Literature Review

2.1 Aims and objectives

Recent years have seen an increasing interest in the impact of psychological variables on the patient's individual illness experience and perception of well-being. However, few reports have actually focussed on depression and anxiety as primary outcomes for patients with ankylosing spondylitis (AS). This Chapter therefore aims to summarise the existing evidence on the prevalence of depression and anxiety in AS, and their associations with a range of patient- and disease-related factors.

The specific objectives of this review are:

(i) to determine how the prevalence of anxiety and depression is influenced by how mood is measured in patients with AS.

(ii) to compare the prevalence of anxiety and depression across clinical settings (primary versus secondary/tertiary care) and the general population.

(iii) to assess the unique and combined relationships of anxiety and depression with AS severity.

(iv) to identify potential confounding factors (eg. patient characteristics) for the relationship between mood and AS severity.

This Chapter provides a description of the methods used to identify the searchable published and unpublished literature. A narrative synthesis of the results is provided, with cross-study comparisons based on mood outcome measures, clinical setting and patient characteristics. The strengths and limitations of the identified studies are also considered.

2.2 Methods

2.2.1 Search Strategy

A systematic review protocol was formulated between 22nd August and 31st August 2011. The protocol was reviewed by the research information manager from the Primary Care Research Institute, Keele (JJ). The full protocol is shown in Appendix A.1.

Search terms

Search terms comprised of key words for ankylosing spondylitis, combined with terms associated with anxiety, depression or both. Medical subject headings (MeSH) and individual database thesauruses identified relevant index terms. In addition, the search evolved based on the search strategies employed by relevant papers and the Cochrane Depression, Anxiety and Neurosis review group (Churchill et al, 2012).

The search terms used were:

i. "ankylosing spondylitis" and related terms in the title and/or abstract of the paper.

AND,

ii. "mood" and related terms in the title and/or abstract of the paper.

OR,

iii. "anxiety" and related terms in the title and/or abstract of the paper.

OR,

iv. "depression" and related terms in the title and/or abstract of the paper.

OR,

v. "neurosis" and related terms in the title and/or abstract of the paper.

The search strategy used in the Medline database is presented in Table 2.1. All terms within a column were combined with the OR operator. Subsequently, all of the "ankylosing spondylitis" and "mood disorder" terms were combined with the AND operator. Full search strategies with other database results are found in Appendix A.2.

Some terms were truncated (*) to allow for multiple endings of relevant words. For example, searching for spondyloarth* included references to spondyloarthropathy, spondyloarthropathies and spondyloarthritis. Variations in spelling were also accounted for, such as spondyloarthopathy and spondylarthropathy.

Table 1: Medline search strategy for ankylosing spondylitis with depression and anxiety

	Ankylosing Spondylitis	Mood disorder			
		General mood	**Anxiety**	**Depression**	**Neurosis**
Search terms	1. Ankylosing ADJ Spondyl*	1. Mood*	1. Anxiet*	1. Depress*	1. Neurosis
	2. Spondylitis, Ankylosing *(MeSH)*	2. Mood disorders *(MeSH)*			
	3. Spondyloarth*	3. Emotion*	2. Anxious*	2. Depression *(MeSH)*	2. Neurotic
	4. Spondylarth*	4. Emotions *(MeSH)*			
	5. Spondylitis	5. Affective	3. Anxiety *(MeSH)*	3. Depressive disorder *(MeSH)*	3. Neuroses
	6. Spondylarthritis *(MeSH)*	6. Affect *(MeSH)*			
	7. Spondylarthopathies *(MeSH)*	7. Affective symptoms *(MeSH)*	4. Anxiety disorder *(MeSH)*		4. Neurotic disorders *(MeSH)*
	8. Spondylitis *(MeSH)*				
Combined search	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	1 OR 2 OR 3 OR 4	1 OR 2 OR 3	1 OR 2 OR 3 OR 4
	Overall combination: (Ankylosing Spondylitis) AND (General mood OR Anxiety OR Depression OR Neurosis)				

Note: * = truncated, ADJ = adjacent, MeSH = Medical Subject Headings

Data sources

Five electronic bibliographic databases were searched using the National Health Service (NHS) interface between 1st and 30th September 2011. An email alert service identified subsequently published articles up to July 2012. The databases were searched from 1950 onwards, or from the date of inception. These included:

- **Medline** (from 1950)
- **Cinahl** (from 1981)
- **Embase** (from 1980)
- **PsycINFO** (from 1950)
- **British Nursing Index – BNI** (from 1985).

Reference lists of relevant articles were also scrutinised in order to identify preceding studies undiscovered through database searching. In addition, citation tracking and a conference index search were performed in the Web of Science database (1970 to November 2011). Conference proceedings from international rheumatology conferences were sought by combining the original search strategy with the term 'Rheumatology' in the conference index option.

Inclusion Criteria

The search aimed to identify all original studies in English, French or German languages with:

(i) Ankylosing spondylitis (AS) or spondyloarthropathy (SpA) patients who were 16 and over.
(ii) Validated patient-reported outcome measures (PROMs) of anxiety and/or depression.

Studies of SpA patients were included, as these studies may include patients with AS. It was also hypothesised that patients with SpA may have a lower prevalence of mood

disturbance than patients with AS, as the diagnosis for SpA is more general; including patients with earlier disease and potentially lower levels of disease severity.

It was recognised that many of the existing mood PROMs may have been developed before validation techniques were fully established, but these may have proven to be clinically effective over time. More recently developed questionnaires, however, were expected to have been validated with comparison to either an existing mood PROM or a semi-structured interview such as the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV).

Clinical setting

Studies recruiting from the following settings were accepted:

(i) Specialist care (secondary/tertiary)

(ii) Primary care

(iii) General population (eg. National AS Society)

Specialist care settings were included in the review as patients with AS are predominantly managed in these settings (Malaviya and Ostor, 2011). It was hypothesised that there could be an increased prevalence of depression and anxiety in tertiary care, compared to secondary care, as patients travelling longer distances and those successfully achieving referral to tertiary services are likely to have either more severe disease or be better self-advocates (personal communication; J. Packham, 2012).

However, it was found to be impractical to differentiate between secondary and tertiary care research studies because many published studies combine data from secondary and tertiary care centres. The precise boundary between secondary and tertiary care is often unclear and poorly defined within published studies. In addition, the health care systems in different countries define secondary and tertiary care in different ways.

Studies within primary care and the general population were also included, as almost one third of patients with diagnosed AS do not currently engage with a specialist rheumatology service (Hamilton et al, 2011). It is also recognised that over 80% of all patients presenting in general practice with depressive and anxious symptoms are managed entirely in primary care (Goldberg and Huxley, 1992). In addition, inclusion of these studies would allow comparisons between clinical settings; thus establishing whether a difference in the prevalence of depression and anxiety exists.

Study design

The following study designs were accepted:

(i) Cross-sectional

(ii) Prospective cohort

(iii) Case-control

(iv) Interventional (eg. randomised controlled trials)

Cross-sectional and prospective cohort studies were identified as being the most appropriate means of assessing the prevalence of depression and anxiety. Cross-sectional and baseline data from prospective cohorts are able to describe the frequencies of variables at a single time point. In addition, prospective cohort studies are useful when assessing the predictive relationships between variables of interest (i.e. mood and disease severity) over time.

Case-control and interventional studies were also accepted if they reported baseline mood assessments specifically for AS or SpA patients. Patient data following any research intervention was not considered. Although the strict exclusion criteria that often accompany these study designs may introduce an unwanted selection bias, it was felt that inclusion of these studies would broaden the scope of the review, by encompassing as many relevant studies as possible.

Exclusion Criteria

Studies were excluded based on six criteria:

(i) Non-human.

(ii) Inappropriate study design (reviews, editorials and qualitative studies).

(iii) Children and adolescents (Age < 16).

(iv) Studies only reporting outcomes on personality disorders.

(v) Patients selected based on disease severity (disease activity, pain or function).

(vi) Patients exposed to surgical intervention as a result of complications related to AS.

The justifications for exclusion criteria (iii)-(vi) are given below.

According to the diagnostic criteria produced by the International League of Associations for Rheumatology (ILAR), inflammatory back pain onset before the age of 16 years is classified as a subset of enthesitis-related juvenile idiopathic arthritis (Fink et al, 1995). Such patients are considered to retain this diagnostic label through adulthood. Furthermore, a specific diagnosis of AS in young patients is difficult due to the presence of undifferentiated symptoms and lack of radiographic evidence. Therefore, studies including patients under the age of 16 were excluded.

Personality disorder is a non-specific psychiatric diagnosis. Anxious and depressive personality traits refer to enduring patterns of behaviour which typically develop in childhood or early adolescence (Semple and Smyth, 2009). The relationship between the subsequent development of AS and mood disturbance is therefore difficult to establish. Furthermore, the term ‘Neurotic personality’ also refers to mania and emotional instability, which are beyond the scope of this review.

Samples selected based on disease severity or surgical exposures are likely to have more severe disease; presenting a selection bias. Therefore, these studies were excluded in order to provide accurate estimates of depression and anxiety in a general population of AS patients.

2.2.2 Inclusion procedure

Records from individual databases were combined and then manually searched in order to identify and exclude duplicate articles. These were then screened systematically by title and then by abstract. Titles were accepted if they referred to general rheumatology or autoimmune populations, followed by examination of the abstract and/or paper for data specific to patients with ankylosing spondylitis or spondyloarthropathy.

All titles were screened by the author (NCM). A sample of 43 titles (10% of records retrieved from database searching) were reviewed by a second reviewer (JP). There was 95% agreement on titles to be included (41/43). The two titles concerning disagreement related to qualitative exploration of the patients' illness experience. Following discussion, these were included with the intention of screening the abstract and paper for validated mood PROMs.

Relevant papers were obtained electronically, then through local libraries and finally via the interlibrary loan system. Attempts were also made to contact authors for clarification on mood outcome measures, and the criteria for defining clinical anxiety or depression, if unreported.

2.2.3 Methodological quality assessment

A checklist was devised to assess the methodological quality of the final included studies, as existing appraisal tools were inappropriate (Table 2.2). All papers were quality assessed for bias based on ten selected criteria adapted from the Quality in Prognostic

Studies (QUIPS) appraisal tool (Hayden et al, 2006). Methodological bias of each study was assessed in relation to four separate domains:

- Study participation (criteria 1-3)
- Outcome measurement (criteria 4-6)
- Confounding measurement and account (criteria 7-8)
- Analytical methods (criteria 9-10)

Each of the ten criteria were graded based on options of ‘yes’, ‘partly’, ‘no’ or ‘unclear’. The options coincided with a numerical grading system of 3 to 0, respectively, combining to form an overall score of methodological quality between 0 and 30 (lowest grade 0, highest grade 30). Higher scores indicated increased methodological quality. Further guidance for the scoring system can be found in Appendix A.3.

All English papers were independently assessed by two of the reviewers (NCM and JP). Cases of disagreement were resolved through discussion and consensus opinion, with involvement of a third reviewer (VS). Non-English full papers were assessed only by NCM, with guidance from a translator, who was a native speaker or had gained higher qualifications in the languages.

The numerical grading system served as a means of comparing reviewer agreement between each of the four quality domains, and did not serve as a means of excluding any studies from the qualitative synthesis. Papers pertaining to the same study were first assessed individually, with extraction of data unique to each paper. A final score for methodological quality was given based on the highest score from the related papers.

Table 2.2: Methodological quality appraisal checklist for full-text articles

Bias related to study participation	**Comments:**
1. The source population is adequately described ☐ Yes ☐ Partly ☐ No ☐ Unclear	
2. The sampling frame and recruitment are adequately described ☐ Yes ☐ Partly ☐ No ☐ Unclear	
3. The inclusion/exclusion criteria are adequately described ☐ Yes ☐ Partly ☐ No ☐ Unclear	
Bias related to outcome measurement	**Comments:**
4. A clear definition of the outcome of interest is provided including the level and extent of the outcome construct ☐ Yes ☐ Partly ☐ No ☐ Unclear	
5. The outcome measure and method is adequately valid to limit misclassification bias ☐ Yes ☐ Partly ☐ No ☐ Unclear	
6. The clinical significance of the anxiety/depression scores is adequately described, including cut-offs ☐ Yes ☐ Partly ☐ No ☐ Unclear	
Bias related to confounding measurement and account	**Comments:**
7. All important potential clinical confounders are described ☐ Yes ☐ Partly ☐ No ☐ Unclear	
8. The study does not exclude known clinical confounders ☐ Yes ☐ Partly ☐ No ☐ Unclear	
Bias related to Analytical methods	**Comments:**
9. There is sufficient presentation of data ☐ Yes ☐ Partly ☐ No ☐ Unclear	
10. There is no selected reporting of results ☐ Yes ☐ Partly ☐ No ☐ Unclear	

2.2.4 Data extraction

An Excel database was used to evaluate data concerning the study population, sample characteristics, study design, and mood assessment measures. Studies with data in multiple papers were combined and counted as a single study within the review. When baseline data was reported separately for different sample groups, data was extracted in the form of combined means or percentages.

2.3 Results

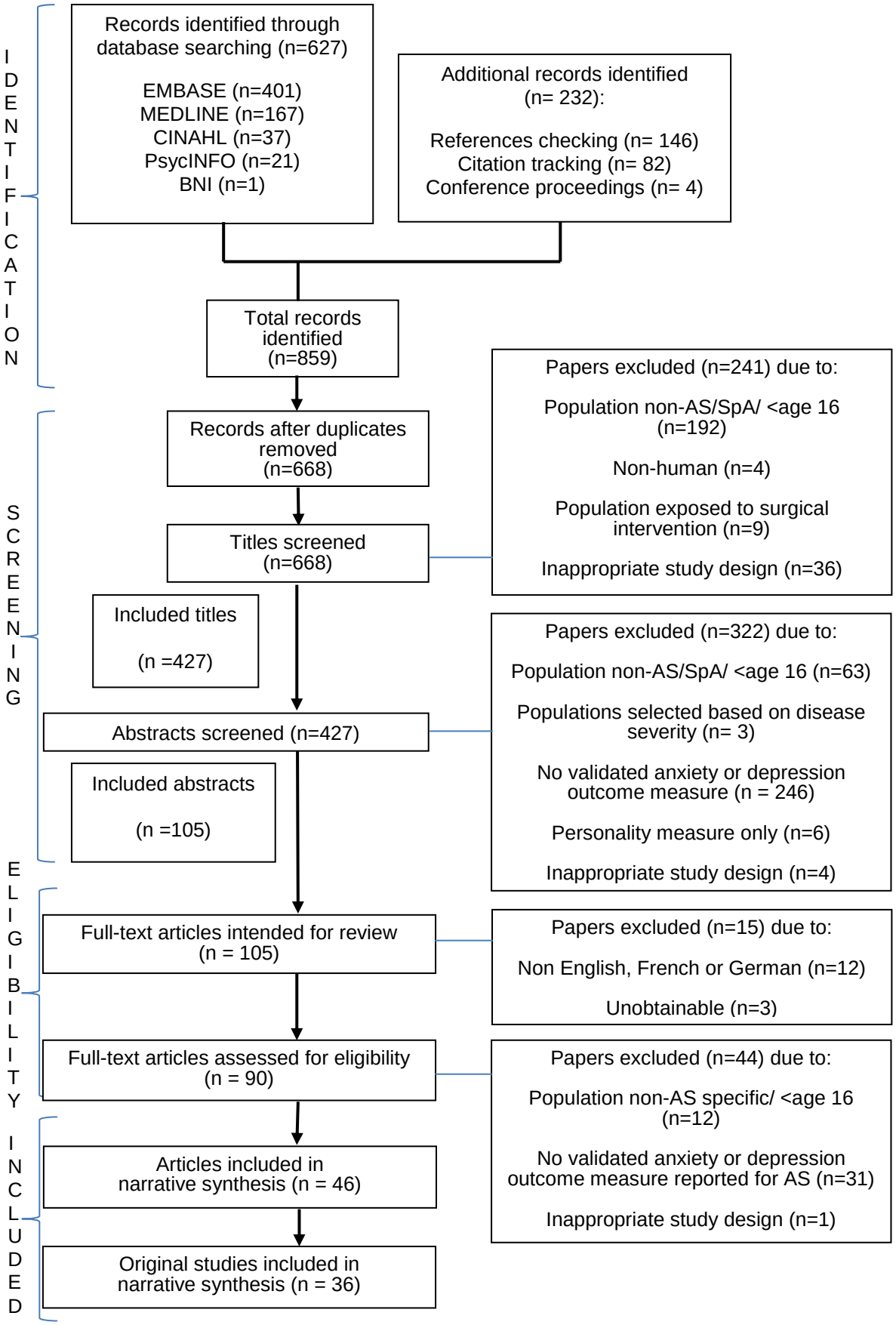
This section details the results of the inclusion process, followed by descriptions of the methodological quality and study characteristics of articles chosen for inclusion in the final review. The prevalence of depression and anxiety is then presented according to different assessment tools, clinical settings and patient characteristics. Finally, studies which have reported the associations of depression and anxiety with AS severity are considered.

2.3.1 Search strategy and inclusion

Figure 2.1 presents a summary of the search results and reasons for exclusion at title, abstract and full-text levels. Following the removal of duplicates, 435 records were identified through database searching and 232 additional records through reference checking, citation tracking and conference index searching collectively. Only four of the 232 additional records met the inclusion criteria for the review, demonstrating a rigorous initial search strategy. One of these articles was identified through citation tracking; three were retrieved from the conference index search.

In total, 46 publications comprising 36 original studies were included in the review. The studies were clinically and methodologically diverse; therefore a qualitative synthesis was performed.

Figure 2.1: Overview of search results and inclusion process



Note: AS = Ankylosing Spondylitis; SpA = Spondyloarthropathy.

2.3.2 Methodological quality assessment

Table 2.3 presents the results of the quality assessment according to the four domains.

Table 2.3: Quality appraisal scores of 36 included studies

	Quality Assessment domain				
First author(s) (year)	**(I) /9**	**(II) /9**	**(III) /6**	**(IV) /6**	**Overall /30**
Analay et al (2003)	5	4	2	4	15
Assassi et al (2009, 2010, 2011)	8	7	4	5	24
Barlow et al (1993, 1994)	8	8	4	5	25
Barlow et al (2001)	9	9	5	5	28
Barlow et al (2010)	5	2	4	6	17
Basler and Rehfisch (1989, 1991)	6	7	4	4	21
Baysal et al (2011)	7	5	3	6	21
Bodur et al (2011)	8	7	5	5	25
Bradna et al (2004)	4	5	4	4	17
Cagliyan et al (2007)	8	6	3	4	21
Cakar et al (2007)	8	9	5	5	27
Cakar et al (2009)	7	7	5	4	23
Cay et al (2011)	8	5	3	5	21
Da Costa et al (2009, 2011)	9	9	4	6	28
Dincer et al (2007)	6	8	2	5	21
Durmus et al (2009)	7	7	2	4	20
Guenther et al (2010)	5	8	4	5	22
Gunaydin et al (2009)	8	9	3	6	26
Hamilton-West and Quine (2007)	9	7	5	5	26
Healey et al (2006, 2009, 2010, 2011)	9	9	5	5	28
Hider et al (2002)	6	5	4	5	20
Juanola-Roura et al (2005)	4	6	1	5	16
Karapolat et al (2008)	8	7	3	4	22
Karapolat et al (2009)	8	7	3	4	22
Karatay et al (2004)	6	5	4	3	20
Kobayashi-Gutierrez et al (2009)	6	9	2	4	21
Lim et al (2005)	8	7	4	2	21
Marengo et al (2008)	7	5	5	5	22
Martindale et al (2006, 2010)	9	9	4	4	27
Ortancil et al (2010)	5	7	2	5	19
Pirildar et al (2004)	6	8	3	6	23
Pritchard et al (2010)	5	6	5	5	21
Rau et al (2008)	5	8	4	4	21
Roussou et al (1997)	8	5	4	3	20
Ward (1999)	9	4	3	5	21
Yang et al (2010)	3	5	1	5	14

Note: (I) = study participation; (II) = outcome measurement; (III) = confounding measurement and account; (IV) = analytical methods

There was considerable variability in the quality domain scores across studies. The study participants were generally well-described, with lower scores found in conference abstracts compared to full-text papers. The outcome measures were also well defined; although many studies did not report cut-offs for defining clinically significant mood symptoms. There were no studies that described all of the potential clinical confounders. 19 (52.8%) studies did not report prevalence frequencies for depression or anxiety; reporting mean depression/anxiety scores only.

2.3.3 Characteristics of included studies

Appendix A.4 displays the detailed characteristics of 36 included studies.

2.3.3.1 Participant characteristics

The literature was distributed between three main countries: Germany, Turkey and the UK. Most patients were recruited from hospitals or specialist rheumatology centres. 33 studies included patients which were reported to have a diagnosis of ankylosing spondylitis and three studies included patients with a more general diagnosis of spondyloarthropathy. The majority of studies identified AS patients according to the modified New York criteria for AS (n=19). Other criteria included the American College of Rheumatology criteria (n=3) and clinical diagnoses by unspecified means (n=11).

Studies varied with respect to sample size (n=15 to n=1224), mean age (28 years to 52 years) and mean disease duration (6 years to 24 years). Samples were predominantly male, and five studies investigated men only.

2.3.3.2 Study designs

The majority of studies were cross-sectional (n=16). The remaining studies consisted of three prospective cohort designs, seven case-control studies and ten experimental trials.

The interventions in the trials varied, including group exercise, home exercise, cognitive behavioural therapy, motivational interviewing and written emotional disclosure.

2.3.3.3 Mood outcome measures

There was significant variation in the psychological outcome measures used by each study. 20 studies assessed depression only and 16 studies assessed both depression and anxiety. There were no studies identified that reported anxiety PROMs only. The outcome measures consisted of nine clinically validated assessment tools and an independently validated questionnaire. All of the instruments that were identified in the studies were considered validated PROMs that have been used in a wide variety of clinical and research settings to assess mood. One study examined two instruments, while all other studies used a single instrument. The identified assessment tools were as follows:

- Beck Depression Index (BDI) (n=14)
- Hospital Anxiety and Depression Questionnaire (HADS) (n=9).
- Centre for Epidemiological Studies Depression (CES-D) (n=4)
- Zung self-rating depression and anxiety scales (SRS) (n=3)
- Von Zerssen Abjective Mood scale (AMS) (n=2)
- Patient Health Questionnaire 9 (PHQ-9) (n=1)
- Hamilton Anxiety Rating Scale (HAMS) (n=1)
- State-Trait Anxiety Inventory (STAI) (n=1)
- Arthritis Impact Measurement Scale (AIMS) (n=1)
- Symptom checklist-90 (SCL-90) (n=1)

The HADS, STAI, AMS and AIMS questionnaires contain questions specific to cognitive and emotional symptoms. While the BDI, CES-D, HAM-A, PHQ-9, Zung and SCL-90 questionnaires also include questions relating to somatic symptoms, such as sleep disturbance, fatigue and loss of appetite.

Further background information concerning each mood PROM is presented in table 2.4.

Table 2.4: Patient-reported outcome measures for mood status

Author (year)	Assessment tool	Originally advised interpretation
Zigmond and Snaith (1983)	HADS (Hospital anxiety and depression scale)	Maximum anxiety/depression score 21. 8–10 possible anxiety/depression, >10 probable anxiety/depression.
Beck et al (1961)	BDI (Beck depression inventory)	Maximum depression score 63. 5–13 mild depression, 14–20 moderate depression, >21 severe depression.
Radloff (1977)	CES-D (Centre for epidemiologic studies-depression questionnaire)	Maximum depression score 60. ≥16 clinical depression.
Zung (1965)	Zung SDS (Zung self-rating depression scale)	Maximum depression score 80. 50–59 mild depression, 60–69 moderate depression, >69 severe depression.
Zung (1971)	Zung SAS (Zung self-rating anxiety scale)	Maximum anxiety score 80. 45-59 mild to moderate anxiety, 60-74 marked to severe anxiety, 75-80 extreme anxiety.
Spitzer et al (2001)	PHQ-9 (Patient Health Questionnaire-9)	Maximum depression score 27. 5-9 mild depression, 10-14 moderate depression, 15-19 moderately severe depression, 20-27 severe depression.
Hamilton (1959)	HAM-A (Hamilton Anxiety Rating Scale)	Maximum anxiety score 56. 18-24 mild to moderate anxiety, 25-30 moderate to severe Anxiety, >30 severe anxiety
Spielberger et al (1970)	STAI-T (State Trait Anxiety Inventory)	Maximum anxiety score 80. Higher scores indicate higher levels of anxiety.
Meenan et al (1980)	AIMS (Arthritis Impact Measurement Scale)	Maximum anxiety/depression score 10. Higher scores indicate higher levels of anxiety/depression.
Von Zerssen (1976)	Von Zerssen adjective mood scale (AMS)	Maximum depression score 56. Scores ≥18 poor mood status.
Duckro et al (1985)	SCL-90 (Symptom checklist-90)	Maximum anxiety/depression score 36. Higher scores indicate higher levels of anxiety/depression.

2.3.4 Prevalence of depression and anxiety

In the following section, the prevalence of depression and anxiety is initially considered in relation to the individual assessment tools. Secondly, there is a comparison of results according to the different clinical settings. Finally, a review of the results in relation to different patient characteristics is provided.

2.3.4.1 Assessment tool

Two mood assessment tools were used frequently in the studies: the Hospital Anxiety and Depression questionnaire (HADS) and the Beck Depression Index (BDI). As there were insufficient studies reporting data from the other assessment tools, these were not considered separately.

Hospital Anxiety and Depression scale

More AS patients were assessed by the HADS questionnaire collectively than any other PROM. These studies were predominantly conducted in the UK. Amongst the nine original studies, six studies reported the prevalence of anxiety and depression and two studies presented mean scores only. One study reported a mean score for depression only.

Table 2.5 presents the characteristics and HADS scores of AS patients from nine original studies, in order of decreasing methodological quality. The prevalence of possible and probable depression ranged from 25.0% to 32.4% and 9.8% to 13.6%, respectively. Possible anxiety was found in 44.6% to 57.0% of patients, and probable anxiety in 20.2% to 29.6%. A study by Baysal et al (2011) applied different cut-off values of ≥7 for depression and ≥10 for anxiety. As expected, depression was high (39.8%) and anxiety was relatively low (19.5%), due to the lower cut-off for depression, and higher cut-off for anxiety.

The mean depression scores ranged from 5.04 to 6.67; all mean scores being within the higher limits of the normal range. The mean anxiety scores ranged from 6.41 to 8.60; with

mean scores of ≥8 in two studies. There was a wide dispersion amongst the studies reporting standard deviations for both depression and anxiety; thus reflecting the full breadth of psychological experience.

Table 2.5: Study characteristics, HADS scores and frequencies of depression and anxiety for patients with ankylosing spondylitis

Reference, first author (year)	Study Population	Inclusion (I)/Exclusion (E) criteria	Sample Size (% male)	Mean depression score ± SD if reported	Mean anxiety score ± SD if reported	Defined HADS-D (D) and HADS-A (A) cut-off	N (%) depression	N (%) anxiety
Healey et al (2006, 2009, 2010, 2011)	Postal survey 10 UK secondary care centres	I – random database selection E - learning disability, poor English, pregnancy	612 (72)	5.04	6.41	≥8	198 (32.4)	273 (44.6)
			556 (72)	Not reported	not reported	≥11	75 (13.5)	122 (22.0)
Barlow et al (2001)	Postal survey NAAS and outpatient clinics	I - age 16-65 E- diagnosis after age 40	133 (73)	5.51	8.05	≥8	41 (31.0)	65 (48.9)
Martindale et al (2006, 2010)	Single hospital review group Lancashire	I - booked appointments E - other serious illness, pregnancy	89 (83)	5.35 ± 4.32	6.76 ± 4.48	≥11	11 (9.8)	18 (20.2)
Baysal et al (2011)	5 outpatient clinics east Turkey	I – not reported E - other serious illness	243 (86)	6.67 ± 4.24	7.46 ± 4.02	D ≥7, A ≥10	96 (39.8)	47 (19.5)
Rau et al (2008)	Rehab. clinic, Germany	I - pain duration > 3 months E –poor German	27 (not reported)	not reported	not reported	≥11	3 (11.11)	8 (29.63)
Hider et al (2002)	NASS and outpatients Cannock, UK	I - not reported E -not reported	40 (73)	5.85	8.60	not reported	not reported	not reported
Barlow et al (2010)	Hospital clinics Coventry and Warickshire	I - not reported E -not reported	29 (86)	5.60 ± 3.38	7.6 ± 3.85	≥8*	7 (25)	17 (57)
Pritchard (2010)	Outpatient clinics, UK	I – not reported E-not reported	73 (89)	Median 4 (IQR 2-8)	Median 6 (IQR 4-10)	not reported	not reported	not reported
Hamilton-West and Quine (2007)	NASS and outpatient clinics	I - daily pain, age >18, E - not reported	68 (66)	5.42 ± 3.61	not reported	not reported	not reported	not reported

Note: HADS= Hospital Anxiety and Depression Scale; AS = ankylosing spondylitis; NAAS = national ankylosing spondylitis society; SD=standard deviation; IQR = interquartile range. * Cut-off score obtained from author.

Beck Depression Index

The Beck Depression Index (BDI) was reported in the largest number of studies; predominantly in studies from Turkey. Table 2.6 details the study characteristics of 13 studies reporting the mean BDI scores of patients with AS and SpA, in order of decreasing methodological quality. One study has been disregarded due to an inherent discrepancy found within the paper concerning the reported mean BDI score and percentage prevalence, where a cut-off of 13 was given (Pirildar et al, 2004).

From the 13 remaining studies, only three reported the prevalence of depression. Frequencies were given according to the mild, moderate or severe depression ranges of the BDI. A variation of single cut-off scores were selected by the different studies, falling within the range of each severity category. This made cross-study comparisons challenging, however, as would be predicted, the percentage prevalence of depression increased in association with a reduction in diagnostic threshold. The frequency of depression ranged from 10.7% to 23.1%.

In contrast to the mean HADS scores, mean BDI scores demonstrated considerable variability across studies; ranging from 5.9 to 20.0. This heterogeneity may be due to a number of factors. Firstly, five of the 11 studies were designed as trial-based studies; with varying inclusion and exclusion criteria. Secondly, lower scores were found in the two studies which included patients with a more general diagnosis of SpA; suggesting that depression may be more common amongst AS patients than those patients with general spondyloarthropathy. Thirdly, all of the studies which had used the BDI had relatively small sample sizes, therefore increasing within-study variability.

Table 2.6: Study characteristics, BDI scores and frequencies of depression for patients with ankylosing spondylitis

Author (year)	Study Population	Inclusion (I)/Exclusion (E) criteria	Sample size (% male)	Mean BDI score ± SD if reported	Defined BDI cut-off	N (%) depression
Bodur et al (2011)	Inpatient/outpatient clinics, Turkey	I - age 16-65 E - diagnosis > age 40	54 (80)	18.6 ± 9.2	Not reported	Not reported
Cagliyan et al (2007)	Outpatient clinics Turkey	I – able to tolerate exercise E - lumbar disc herniation pain, comorbidity	46 (83)	18.35	Not reported	Not reported
Cakar et al (2007)	Military academy, Turkey	I - military service E- not reported	53 (100)	Not reported	≥25	6 (10.7)
Cakar et al (2009)	Military academy, Turkey	I - military service E- not reported	121 (100)	14.48	Not reported	Not reported
Dincer et al (2007)	Outpatient clinics Turkey	I - sexually active E - systemic disease, hip OA, psychiatric disorder	68 (100)	14.9 ± 9.4	Not reported	10 (15)
Durmus et al (2009)	Clinical setting not reported, Turkey	I - no regular exercise in last six month E - systemic disease, anti-TNF therapy	43 (81)	9.51	Not reported	Not reported
Karapolat et al (2008)	Outpatient clinics, Turkey	I - age 18-75 E - systemic disease, severe co-morbidity, regular exercise in last six month	38 (68)	8.21	Not reported	Not reported
Karapolat et al (2009)	Outpatient clinics, Turkey	I - age 18-75, able to swim/exercise, no regular exercise E - systemic disease, active arthritis, anti-TNF therapy	37 (73)	7.16	Not reported	Not reported
Karatay et al (2004)	Clinical setting not reported, Turkey	I – not reported E – not reported	27 (81)	14.77 ± 13.95	Not reported	Not reported
Lim et al (2005)	Outpatients, Korea	I – no regular exercise in last six month E - systemic disease, medication change	50 (78)	20	Not reported	Not reported
Analay et al (2003)	Outpatients, Turkey	I - age 18-55, participate in group exercise E - systemic disease, reduced hip/knee movement, DMARDS, regular exercise in last three month	45 (84)	5.89	Not reported	Not reported
Cay et al (2011)	Outpatients, Turkey	I - live in Antalya, Turkey E - learning disability, psychotropic drugs, renal/hepatic impairment	15 (not reported)	9.59 ± 1.91	Not reported	Not reported
Juanola-Roura et al (2005)	Outpatients, Spain	I – not reported E – not reported	160 (not reported)	Not reported	≥18	37 (23.10)

Note: BDI= Beck Depression Index, AS = Ankylosing Spondylitis, TNF= tumour necrosis factor**,** SD = standard deviation, OA = osteoarthritis

Other mood assessment measures

The third commonly applied measure was the Centre for Epidemiological Studies depression questionnaire (CES-D). Amongst the four studies that reported CES-D scores, two adaptations of the CES-D were used: the CES-AR and the CES-Dr. Despite the use of the different adapted scales, the frequencies of possible depression were similar, ranging from 32% to 36%. This was slightly higher than the possible depression frequencies reported by studies using the HADS questionnaire.

Three studies reported data based on the Zung self-rating depression scale (SRS). Only one study was a full paper, reporting a frequency of 27.4% for mild depressive symptoms, when a cut-off of ≥50 was applied (Gunaydin et al, 2009). This is similar to the prevalence of possible depression according to the HADS questionnaire. The study with the largest number of patients (n=1224) also reported the highest frequency of depression (45.5%) in the review (Yang et al, 2010), however, limited information was provided concerning the patient characteristics and diagnostic threshold.

Two German studies with small sample sizes used the Von Zerssen abjective mood scale to assess depression; both reporting mean scores within the range for *normal* symptoms. The Patient Health Questionnaire-9 (PHQ-9), Hamilton Anxiety Rating Scale (HAM-A), State Trait Anxiety Inventory (STAI-T), Arthritis Impact Measurement Scale (AIMS) and Symptom checklist-90-R (SCL-90-R) were only featured in single studies. All of these studies only reported mean assessment scores, with no data on the prevalence of anxiety or depression.

An independent questionnaire developed by Ward (1999) found clinically significant depression in 28.7% and anxiety in 28.6% of a sample of 175 patients; where construct validity was demonstrated with the CES-D. In addition, 50.6% of patients expressed concerns about their appearance and 50.3% had worries about their future. These results

are similar to the other validated questionnaires; thus demonstrating consistently high levels of depression and anxiety in AS patients.

2.3.4.2 Clinical setting

No studies were identified that recruited from primary care. Therefore, insufficient data was available to compare the prevalence of mood disturbance among primary and secondary/tertiary care cohorts.

When comparing the studies conducted in the UK, it was apparent that the highest HADS scores were reported by those studies which included patients from the National AS Society (NASS): a patient run society which patients choose to join. This is particularly noticeable with anxiety; where mean scores of ≥8 were reported. However, there was no significant difference in mood disturbance among NASS members and secondary care patients when HADS scores were compared within a single study (Barlow et al, 2001).

Only one study included hospital inpatients (Bodur, 2011). This study reported a particularly high mean BDI score of 18.6. However, given that this study was based on a small sample size (n=54), it was not possible to conclude that AS inpatients had a different emotional experience than AS outpatients.

2.3.4.3 Patient characteristics

Diagnostic criteria

Among the 36 original studies, only three investigated the presence of depression/anxiety in patients with SpA. Two of these studies reported BDI scores and one study reported CES-D scores. The BDI scores appeared generally lower when compared to the other studies of AS patients. However, the highest frequency of depression in the review was reported from the study with CES-D scores for SpA patients (Da Costa et al, 2011). It was

therefore difficult to form generalisable comparisons between AS and SpA patients, due to conflicting evidence from a limited number of studies.

Gender

The increased risk of depression amongst female AS patients has been previously reported (Barlow et al, 1994). However, a conference abstract from one large study reported significantly higher levels of anxiety but not depression in female patients (Healey et al, 2006). Analysis of the influence of gender across all of the studies was otherwise constrained by the small number of females in other studies.

Disease duration

There did not appear to be any association between disease duration and mood scores across the studies. For example, similar mean HADS-D scores of 5.51 and 5.85 were reported by two studies with mean AS durations of 28 and 13 (Barlow et al, 2001, Hider et al, 2002). Within the individual studies, only two studies referred to the relationship between mood and AS duration, providing contrasting evidence. Martindale et al (2006) reported non-significant correlations between depression or anxiety with disease duration, whereas, Karatay et al (2004) reported a moderate significant correlation.

Marital status

There were no studies identified that referred to the relationship between mood and the marital status of patients with AS or SpA. Furthermore, no studies reported any data concerning marital status. Therefore, the contribution of marital status to depression or anxiety could not be assessed.

Employment

Few studies provided the employment characteristics of their study samples, whilst only one study investigated the relationship between mood and employment status (Healey et

al, 2011). In this study, depression was independently associated with outcomes of unemployment and absence from work.

Social deprivation

Only one study measured the deprivation status of its participants (Healey et al 2010). In this study, significant differences in the frequencies of possible depression among patients of varying degrees of deprivation were reported. The prevalence of depression was as high as 60% in the quintile of patients with the highest deprivation. Anxiety was found to be non-significant; however, only mild forms of anxiety were investigated.

2.3.5 Association of depression and anxiety with AS severity

A prospective study of 89 AS patients showed that both anxiety and depression significantly correlated with self-reported disease activity and functional impairment, when measured with the Bath AS Disease Activity Index (BASDAI) and the Bath AS Functional Index (BASFI), respectively (Martindale et al, 2006). At each of the four six-month time intervals, anxiety consistently correlated with disease activity (ranging from 0.58-0.67; all $P<0.001$) and functional impairment (ranging from 0.55-0.67; $P<0.001$). Similarly, depression was quite strongly correlated with disease activity (ranging from 0.64 to 0.67; all $P<0.001$) and comparably more with functional disability (ranging from 0.61-0.71; all $P<0.001$). A weaker association was found with range of movement when this was assessed with the Bath AS metrology index (BASMI).

Martindale et al (2010) then proceeded to examine depression and anxiety in patients with persistently high levels of disease activity (BASDAI ≥4, n=45) compared to patients with persistent quiescent disease (BASDAI <4, n=10). According to the HADS questionnaire, baseline mean depression scores were 9.3 (SD 3.4) in the active group and 1.9 (2.0) in the quiescent group ($p<0.001$). Significant mean differences were also found when

depression and anxiety were analysed at 18 months. However, neither anxiety nor depression increased significantly in the patients with active disease over two years.

A cross-sectional study of 294 patients found that depression contributed significantly to the variance in disease activity and functional impairment (Assassi et al, 2009, 2010) When multiple linear regression analyses were conducted, depression was found to contribute independently to a worsening in BASDAI and BASFI scores, whilst other demographic variables such as gender and employment failed to demonstrate comparable associations. According to the PHQ-9 (range 0-27), each numerical increase in depression resulted in a 0.19 increase in disease activity and a 0.12 increase in functional impairment (both ranges 0-10).

2.4 Discussion

2.4.1 Strengths and limitations of this review

This is the first systematic review which has been conducted concerning psychological factors in ankylosing spondylitis; although several reviews exist relating to patients with rheumatoid arthritis (Anderson et al, 1985; Young, 1992; Dickens et al, 2002). The main strength of this review lies in its broad search strategy. The inclusion of five bibliographic databases and three European languages aided the identification of studies. In addition, international conference abstracts were also included, minimising the risk of publication bias.

A limitation of this review was that many studies did not report a prevalence of mood disturbance, specifically studies conducted outside of the UK. Consequently, these studies were compared based on their mean scores only; with limited information concerning the number of patients with clinically relevant symptoms. Additional international studies may have been identified if more languages were also included;

however, this is unlikely to have greatly influenced the results, as the majority of identified articles were in English.

It was difficult to provide precise estimates of the prevalence of depression and anxiety in AS, due to a wide variation of mood PROMs and cut-offs among studies. Also, there were insufficient studies reporting mean scores and standard deviations for each of the mood PROMs. The pooling of studies with different cut-offs for each mood PROM resulted in the grouping of largely variable results. For example, the prevalence of depression ranged from 9.8% to 32.4% with the HADS-D and 10.7% to 23.1% with the BDI. It was felt that the exact quantitative outcome of a meta-analysis would be difficult to interpret given the subjective nature of mood disturbance and the inherent variability between each mood PROM. A qualitative analysis, however, was sufficient to provide an overarching representation of the prevalence of depression and anxiety in patients with AS, with an appreciation for the methodological and clinical diversity among studies.

2.4.2 Principle findings of this review

2.4.2.1 Prevalence of depression and anxiety in AS

Mild or possible depression and anxiety were the most common subtypes reported in patients with AS, although severe mood disturbance has been less robustly studied. Across all assessment tools, the prevalence of possible or mild depression and anxiety was estimated at 23-36% and 45-57%, respectively. The prevalence of probable depression according to the HADS questionnaire was 10-14% for depression and 20-30% for anxiety. Anxiety was consistently higher than depression in all studies applying the same cut-offs, with mean HADS scores ranging from 5.04 to 6.67 for depression and 6.41 to 8.60 for anxiety.

Normative data for HADS scores among healthy UK residents (n=1792) show mean (S.D) scores of 3.68 (3.07) for depression and 6.14 (3.76) for anxiety; with prevalence rates for

probable depression and anxiety of 3.6% and 12.6%, respectively (Crawford et al, 2001). The proportional relationship between the prevalence of depression and anxiety is similar in AS patients to the general population, but even by modest estimates both are at least twice as common.

In a systematic review of RA patients, the frequency of major depressive disorder was reported as 13-17%. This is similar to the prevalence estimates of probable depression in AS patients. Comparable mean depression scores have also been reported with the BDI when AS and RA patients were assessed concurrently (Bodur et al, 2011). There is no current systematic review on anxiety in RA patients. However, based on the high frequency of anxiety in AS patients, it is likely that the prevalence of anxiety is equivalent, if not higher, than that found in other inflammatory conditions.

No studies of patients with AS in primary care included an assessment of depression or anxiety. However, the author is aware of an on-going UK study within a community cohort of patients with low back pain. This study will be the first to provide data on the prevalence of anxiety and depression in AS patients (personal communication; K. Gaffney, 2012).

From the existing literature, it appears that depression and anxiety may be greater in females and those reporting unemployment and increased deprivation. There does not appear to be an association between depression or anxiety and AS duration, however, few studies have independently assessed this. Surprisingly, the relationship between marital status and mood has not been investigated in AS, despite the well-recognised relationship between unmarried status and depression in the general population (Zung et al, 1983).

2.4.2.2 Assessment of depression and anxiety in AS

Depression has been more widely studied than anxiety in patients with AS, with the majority of studies reporting depression outcomes only. From the studies that reported

depression and anxiety; it was evident that anxiety is even more prevalent than depression in AS patients; indicating a need for clinicians to measure depression and anxiety together.

Studies using the HADS questionnaire showed the least variability in mean depression and anxiety scores; suggesting the HADS questionnaire to be a consistent measure of depression and anxiety in AS patients. The HADS questionnaire is practically advantageous as the anxiety and depression sub-scales are presented together. Also, unlike many of the other mood PROMs, the HADS questionnaire does not contain questions pertaining to somatic symptoms such as fatigue, sleep disturbance and loss of appetite. Such scales may lead to an overestimation of depression and anxiety in patients with AS, due to the presence of AS-related somatic symptoms.

2.4.2.3 Association of depression and anxiety with AS severity

The development of individualised measures, such as the Bath indices, has enabled the standardised assessment of disease severity in AS patients. Over the last decade, studies have increasingly reported Bath indices for AS patients, however, few studies have explored the specific relationships between mood and AS severity.

The association between mood and metrology scores in the literature is modest. Psychiatric disorders in AS tend to be associated with more negative appraisal of symptoms, as demonstrated by self-reported measures for disease activity and function. Patient-reported measures may, in part, reflect individual levels of coping and self-efficacy, and should not be disregarded due to their subjectivity.

From the existing literature, it is evident that both anxiety and depression demonstrate stable correlations with AS severity. Martindale et al (2006) have reported consistent associations between depression and anxiety with disease activity and functional impairment over eighteen months. In addition, cross-sectional analyses have shown

depression to contribute significantly to the variance in disease activity and function (Assassi et al, 2009, 2010). However, this study did not account for anxiety.

2.5 Gaps in current literature

Mean anxiety scores have been shown to be significantly higher than mean depression scores in UK residents (Herrmann, 1997). Despite this, studies concerning anxiety in AS patients are lacking. In addition, studies among the general population highlight the frequent co-existence of depressive and anxious symptoms (Sartorius et al, 1996). However, there are currently no studies that have considered the combined impact of depression and anxiety for patients with AS.

Few studies exist that provide data for mood or disease severity at more than one time point. No studies exist which have examined the predictive relationships between mood disturbance on subsequent disease severity. Although Martindale et al (2010) report a non-significant increase in depression or anxiety in patients with active disease; larger studies are required to investigate these predictive relationships.

Large cross-sectional studies are required to clarify the relationship of depression and anxiety with other physical and social factors in AS patients. Multivariate analyses of new or existing studies would provide valuable information on the unique and combined associations of depression and anxiety with AS severity.

Part II

Cross-sectional and prospective cohort studies

CHAPTER 3

Data and methods

The preceding literature review has identified depression and anxiety as common problems for patients with ankylosing spondylitis (AS). The remainder of this thesis aims to expand on current research by examining the cause and effect of depression and anxiety in a six-month cohort study of AS patients. This Chapter introduces the specific objectives for this study, followed by an explanation of the study design and methods used to analyse the baseline and follow-up data.

Preliminary note: throughout this study, the phrase *disease severity* is used to describe three measures of AS severity: disease activity, pain and function. *Mood status* is used to describe the individual assessment of depression and anxiety. The term *mood disturbance* is employed to describe a psychological state where depression and anxiety co-exist. Detailed definitions for each measure of disease severity and mood status are found later in this Chapter.

3.1 Aims and objectives

Sections 3.1.1 and 3.1.2 outline the objectives for the cross-sectional study (baseline) and prospective cohort study (baseline and follow-up), respectively.

3.1.1 Cross-sectional study

The main aim of the cross-sectional study is to examine the unique and combined association of depression and anxiety with disease severity.

The specific objectives for the cross-sectional study are as follows:

(i) to describe the prevalence of depression and anxiety in relation to the socio-demographic and disease-specific characteristics of AS patients.

(ii) to assess the association of depression and anxiety on disease severity.

(iii) to assess the association of disease severity on depression and anxiety.

(iv) to evaluate the association of mood disturbance on disease severity.

(v) to evaluate the association of disease severity on mood disturbance.

3.1.1 Prospective cohort study

The main aim of the prospective cohort study is to examine the predictive relationships of depression and anxiety with disease severity.

The specific objectives for the longitudinal cohort study are as follows:

(i) to compare the baseline characteristics of responders and non-responders to the six-month follow-up survey.

(ii) to describe the individual patient variability for clinically significant changes in depression, anxiety and disease severity.

(iii) to determine the relationships between baseline depression and anxiety with clinically significant changes in disease severity.

(iv) to determine the relationships between baseline disease severity with clinically significant changes in depression and anxiety.

3.2 Recruitment and data collection

The data analysed in this thesis has been taken from an existing dataset used originally to evaluate a new AS-specific measure of quality of life: the evaluation of ankylosing spondylitis quality of life (EASi-QoL) questionnaire (Haywood et al, 2010). The design and implementation of the baseline and follow-up surveys were carried out before the commencement of this thesis; with no involvement of the author. Data collection was completed between July 2007 and May 2008.

A sample of 1,000 AS patients were randomly selected from the registers of ten secondary care rheumatology centres across the UK. Subjects were eligible for the study if they had a confirmed diagnosis of AS according to the modified New York criteria; with no age or gender specification. Patients with learning disability, pregnancy or an inadequate understanding of the English language were excluded.

Eligible patients were sent an information letter inviting them to self-complete a copy of the baseline questionnaire (Appendix A.5) and a form for written consent to participate in the study. Postal reminders were sent at two and four weeks after survey distribution to non-responders. The study was approved by the North Staffordshire local research ethics committee and the ten National Health Service (NHS) trusts. As a result of ethical approval, there was no demographic data regarding the non-responders at baseline.

Six months after returning the baseline questionnaires, patients were asked to complete a further postal questionnaire. Only responders to the baseline survey were included in the follow-up phase of the study. Identical mailing procedures were applied.

3.3 Patient characteristics

The following section describes the measures used to assess the baseline socio-demographic and disease-specific characteristics of the baseline responders.

3.3.1 Socio-demographic characteristics

Age was recorded by asking patients to provide their date of birth (Appendix A.5, Section C, part 1, question 1). Age was then calculated by subtracting the date of birth from the date on which the baseline questionnaire was completed. Patients were subsequently divided into four age groups: <40, 40-49, 50-59 and ≥60 years.

Gender was recorded by asking patients to 'cross' a box for either male or female (Appendix A.5, Section C, part 1, question 2).

Marital status was assessed with the question ‘‘What is your current marital status?’’. Patients were provided with four options: 1) married/cohabiting, 2) single, 3) divorced/separated and 4) widowed (Appendix A.5, Section C, part 1, question 7). Marital status was then divided into two categories: married/cohabiting and unmarried. All patients that reported being single, divorced or widowed were categorised as unmarried.

Employment status was established by asking patients to indicate their current work status according to eight options: 1) employed 2) retired, 3) unemployed/seeking work, 4) not working due to ill health 5) retired due to ill health, 6) house-wife/husband, 7) full/part time education and 8) other (Appendix A.5, Section C, part 2, question 1). In order to distinguish between individuals with early or normal retirement, patients were asked to provide the age at which they were last employed (Appendix A.5, Section C, part 2, question 2b). Normal retirement age was defined as ≥65 years for males and ≥60 for females (Department for Work and Pensions, 2012).

Subsequently, all employment categories were collated into a dichotomous variable to aid interpretation of the results. The chosen categories were employed/normal retirement and unemployed/early retirement. Employed/normal retirement included all patients that were currently employed or had retired from normal retirement age. The unemployed category included patients with early retirement and those retired or not working due to ill health. Students, house-wives/husbands and those patients indicating ‘other’ were excluded, as these patients did not fall into either employment category.

Deprivation status for each patient was recorded according to the overall Index of Multiple Deprivation (IMD) of their local areas at the time of the survey (Office of the Deputy Prime Minister, 2004). The IMD is based on geographically defined regions within England known as lower-level Super Output Areas (SOAs). Each SOA is given a ranking according to seven aspects of social deprivation: income, employment, health and disability, education, housing and services, living environment and crime. Patients in this

study were categorised into the least deprived quintile (20%), middle three quintiles (60%) and most deprived quintile (20%).

3.3.2 Disease-specific characteristics

Disease duration was defined according to the duration which patients had been diagnosed with AS and the duration which patients had experienced symptoms of AS.

Diagnosis duration was established by asking patients to provide the year in which they were first diagnosed with AS (Appendix A.5, Section B, part 1, question 1). The duration was then calculated by subtracting the year of diagnosis from 2008: the year in which data collection was complete. Diagnosis duration was then organised into the following year groups: <10, 10-19, 20-29 and ≥30.

Symptom duration was recorded by asking patients how many years they had had symptoms from AS (Appendix A.5, Section B, part 1, question 2). The durations were then organised into the same year categories as diagnosis duration.

3.4 Disease severity status

Disease severity was assessed in the baseline and follow-up questionnaires. The following section describes the assessment properties of three measures of disease severity: disease activity, pain and function. This is followed by an explanation of their use in the cross-sectional and prospective cohort studies.

3.4.1 Disease activity

Disease activity was assessed by the Bath AS Disease Activity Index (BASDAI) (Garrett et al, 1994) The BASDAI consisted of six questions pertaining to the symptoms of pain, stiffness and fatigue experienced over the preceding week (Appendix A.5, Section B, part 6). Each item was scored between zero and ten according a series of visual analogue

scales. A final mean score from the sum of the items was calculated (0-10). Higher scores signified increased disease activity.

3.4.1.1 Cross-sectional study

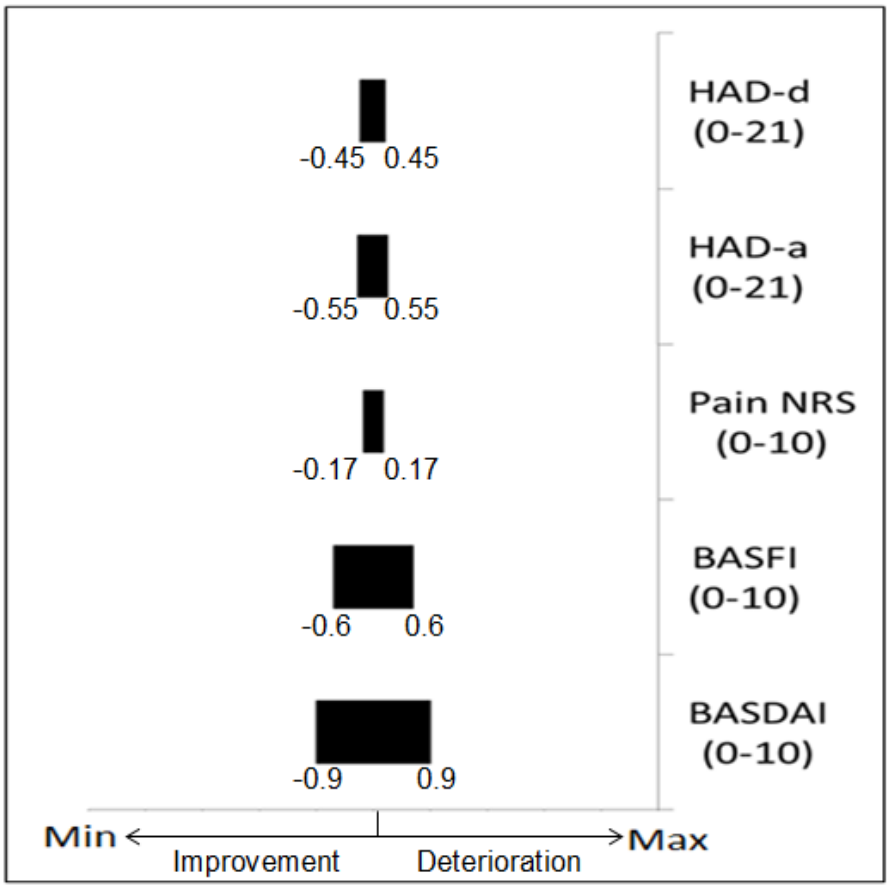
Baseline disease activity was assessed according to binary categories of <4 and ≥4 on the BASDAI scale. Patients with a BASDAI score of ≥4 were considered to have increased disease activity, consistent with national guidelines for defining active disease (NICE, 2008).

3.4.1.2 Prospective cohort study

Baseline disease activity scores were used as a continuous variable. When change in disease activity was the outcome, change (follow-up – baseline) was defined according to three categories: deterioration, stable or improvement. These categories were coded according to a minimal clinically important difference (MCID) of 1.0 on the BASDAI scale. This MCID was taken from a previous study of AS patients, following two weeks of physiotherapy intervention (Pavy et al, 2005). The MCID represents the smallest improvement considered worthwhile by the patient (Copay et al, 2007).

Figure 3.1 shows the MCID for disease activity and other subsequent outcome measures in this study. The MCID for disease activity is considered here as an example of how each MCID was used. A clinically important change in disease activity was defined as a decrease or increase of 1.0 or more on the BASDAI scale (0-10). Deterioration in disease activity was defined as a difference of 1.0 or more. Improvement was defined as a difference of -1.0 or more. Patients that reported a change in BASDAI score ranging from -0.9 to 0.9 were classified as stable.

Figure 3.1: Minimal clinically important differences for mood and disease severity



Note: HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = HADS-anxiety domain. BASDAI = Bath AS Disease Activity Index; NRS = numerical rating scale; BASFI = Bath AS Functional Index. Shaded areas represent patients with stable change according to the minimal clinically important difference (MCID).

3.4.2 Pain

Pain levels were indicated on a single numerical rating scale (NRS) for pain. Patients were asked how much AS-related pain they had experienced over the last week. (Section B, part 4, question 1). The scale ranged from zero to ten; zero was labelled as ‘no pain’ and ten was labelled as ‘most severe pain’. A final score between zero and ten was recorded. Higher scores were indicative of greater pain intensity.

3.4.2.1 Cross-sectional study

Baseline pain scores were dichotomised into <4 and ≥4 on the pain NRS. A cut-off of ≥4 was chosen, as this score is recommended by clinical guidelines (NICE, 2008) and is commonly reported for identifying patients with active disease in clinical trials (Dougados et al, 2001; Wanders et al, 2005).

3.4.2.2 Prospective cohort study

Baseline pain scores were used as a continuous variable. When change in pain was the outcome, a clinically important change in pain was defined as deterioration, stable or improvement according to an MCID of 0.18. This MCID was adapted from a previous observational study of patients with chronic pain over one month (Angst et al, 2008). A MCID for pain in AS patients could not be found; therefore a study of patients with chronic pain was chosen, as this was the closest clinical match relevant to AS. An explanation of how this MCID was used to categorise patients in this study is found in figure 3.1.

3.4.3 Functional impairment

Functional impairment was measured by the Bath AS Functional Index (BASFI) (Calin et al, 1994). The BASFI consisted of ten questions concerning functional limitations over the last week. The questions related to problems specifically experienced by patients with AS, such as problems with bending forward and climbing stairs (Appendix A.5, Section B, part 5). All questions were presented as visual analogue scales between zero and ten, with higher scores indicating greater functional disability. A mean of the sum of the items was calculated (0-10). Higher scores were consistent with increased levels of functional impairment.

3.4.2.1 Cross-sectional study

Baseline scores for functional impairment were dichotomised into BASFI scores of <4 and ≥4. A cut-off on the BASFI for increased functional impairment could not be found in

existing clinical guidelines. However, a BASFI of ≥4 was chosen to define worse functional impairment, as this cut-off has also been used as an outcome for increased disease severity in other studies of AS patients (Pham et al, 2003; Lubrano et al, 2007).

3.4.2.2 Prospective cohort study

Baseline function scores were used as a continuous variable. When change in function was the outcome, a clinically important change was defined as deterioration, stable or improvement, according to a MCID of 0.7. This MCID was previously reported by AS patients, following two weeks of physiotherapy intervention (Pavy et al, 2005). An explanation of how this MCID was used to categorise patients in this study is found in figure 3.1.

3.5 Mood status

Measures for depression and anxiety were included in the baseline and follow-up questionnaires. Anxiety was assessed with the anxiety domain (HADS-A) and depression was assessed with the depression domain (HADS-D) of the Hospital Anxiety and Depression scale (HADS) (Zigmond and Snaith, 1983). Each domain consisted on seven questions relating to a variety of cognitive and emotional symptoms experienced over the last week (Appendix A.5, Section A, part 3).

Questions for anxiety related to symptoms such as worrying thoughts, restlessness and panic. Questions for depression explored symptoms of low mood, anhedonia and cognitive impairment. Each question was marked between zero and three, where higher scores indicated an increased frequency of symptoms. The sum of the seven items was then calculated, providing an overall domain score between zero and 21. Higher scores indicated increased severity of depressive or anxious symptoms.

3.5.1 Cross-sectional study

Frequencies of depression and anxiety were calculated according to cut-offs of ≥8 and ≥11 on each HADS domain, as these cut-offs were originally recommended for defining possible and probable cases, respectively (Zigmond and Snaith, 1983). A cut-off of ≥8 was chosen in subsequent baseline analyses, in order to include all patients with clinically significant mood symptoms. Furthermore, this cut-off allowed comparability with the majority of existing studies, which have reported mild or possible levels of mood disturbance in AS patients (Barlow et al, 2004; Gunaydin et al, 2009; Healey et al, 2011).

Anxiety and depression were then grouped collectively under the same variable of *mood disturbance*. There were three main reasons for this. Firstly, the conditions frequently co-exist and are considered to be clinically related constructs (Kaufman and Charney, 2000). Secondly, there has been a recent move towards the collective evaluation of anxiety and depression among epidemiological studies (Stordal et al, 2003; Kunik et al, 2005; Walters et al, 2011; Covic et al, 2012). Thirdly, the current literature does not account for the combined causes or effects of co-morbid depression and anxiety in AS, although this would be clinically useful when managing patients with an amalgamation of mood-related symptoms.

3.5.2 Prospective cohort study

Baseline scores for depression and anxiety were used as a continuous variable. When changes in depression or anxiety were the outcome, clinically important changes in depression and anxiety were defined according to MCIDs of 0.46 and 0.56, respectively (Angst et al, 2008). These MCIDs were adapted from a previous observational study of patients with chronic pain over one month. Depression and anxiety were not assessed collectively in the prospective cohort study, as the MCIDs, and thus definitions of change for these measures, were different. An explanation of how these MCIDs were used to categorise patients in this study is found in figure 3.1.

3.6 Analytical methods

The statistical package for the social sciences (SPSS) software version 20.0 was used for all statistical analyses in this thesis. The analytical methods for the cross-sectional and prospective cohort studies are described in Sections 3.6.1 and 3.6.2 respectively.

Note: the term *potential confounding variables* is used to describe the analyses which controlled for the following patient characteristics: age, gender, symptom duration, marital status, employment status and social deprivation. Symptom duration was chosen, opposed to diagnosis duration, for all of the multivariate analyses, as this was thought to be a more accurate estimation of disease duration due to the diagnostic delay often occurring in AS (Feldtkeller, 2003).

3.6.1 Cross-sectional study

This section outlines the methods used to analyse the baseline data in relation to the objectives given in Section 3.1.1.

Baseline responders were initially summarised according to their socio-demographic and disease-specific characteristics. In addition, average scores for depression, anxiety and disease severity were reported according to the mean scores for each outcome measure.

3.6.1.1 Prevalence of depression and anxiety

The numbers and percentages of patients with possible and probable depression or anxiety were calculated. Patients with different socio-demographic and disease-specific characteristics (Section 3.3) were compared by the Pearson's Chi-square test for statistically significant differences in prevalence.

Subsequently, the numbers and percentages of patients with possible mood disturbance, depression only or anxiety only were calculated. Mean depression and anxiety scores were recorded for each group.

3.6.1.2 Association of depression and anxiety on disease severity

Logistic regression was used to assess both the unadjusted and adjusted associations of depression and anxiety on disease severity. Increased disease activity (BASDAI ≥4), pain (NRS ≥4) and function (BASFI ≥4) were assessed as separate outcome variables, compared to patients with scores of <4. Subsequently, a final adjusted model was created which included depression, anxiety and all of the potential confounding variables. Odds ratios with 95% confidence intervals were reported.

3.6.1.3 Association of disease severity on depression and anxiety

Logistic regression was performed with depression (HADS-D ≥8) and anxiety (HADS-A ≥8) as separate outcome variables, compared to patients with scores of <8 for each measure. Unadjusted analyses were performed with increased disease activity, pain and function as independent variables. All potential confounding variables were then entered in a final adjusted model. Odds ratios with 95% confidence intervals were reported.

3.6.1.4 Association of mood disturbance on disease severity

The numbers and percentages of patients with increased disease severity were recorded in a cross-tabulation with the following mood categories: normal, depression only, anxiety only and mixed depression and anxiety.

Logistic regression was performed with increased disease activity (BASDAI ≥4), pain (NRS ≥4) and function (BASFI ≥4) as separate outcome variables, compared to patients with scores of <4 for each measure. Unadjusted analyses were performed with mood disturbance as an independent variable. Categories of interest were depression only (HADS-D ≥8), anxiety only (HADS-A ≥8) and mixed depression and anxiety (HADS-D ≥8 and HADS-A ≥8). All potential confounding variables were then entered in a final adjusted model. Odds ratios with 95% confidence intervals were reported.

3.6.1.5 Association of disease severity on mood disturbance

Multinomial logistic regression was used to assess the association of each measure of disease severity on three outcomes for mood disturbance: depression only (HADS-D ≥8), anxiety only (HADS-A ≥8) and mixed depression and anxiety (HADS-D ≥8 and HADS-A ≥8). Normal mood was chosen as a reference category (HADS-D <8 and HADS-A <8). A series of unadjusted analyses were performed with increased disease activity, pain and function as independent variables. All potential confounding variables were then entered in a final adjusted model. Odds ratios with 95% confidence intervals were reported.

3.6.2 Prospective cohort study

This section outlines the methods used to analyse the baseline and follow-up data in relation to the objectives given in section 3.1.2.

3.6.2.1 Characteristics of follow-up responders

For the purposes of this thesis, six-month responders were identified based on those patients who provided item responses for all of the measures of disease status and mood.

Categorical differences in age, gender, disease duration, marital status, employment and deprivation between responders and non-responders were assessed by the Pearson's Chi-squared test. Mean differences in disease severity and mood were assessed with independent t-tests.

3.6.2.2 Variability of change in mood and disease severity

Paired t-tests were performed on each outcome measure, in order to establish any significant mean differences between responders over six months.

The individual differences in mood and disease severity were calculated by subtracting the baseline scores from the follow-up scores for each patient. A clinically significant

change was defined according to minimal clinically important differences (MCIDs) for each measure (Pavy et al, 2005; Angst et al, 2008) (Figure 3.1).

Cumulative probability plots were then devised to depict the variability of change in depression, anxiety and each of the disease severity measures. The plots provided the numbers and percentages of patients who deteriorated, improved or remained stable according to each MCID.

3.6.2.3 Association of baseline depression and anxiety on clinically significant changes in disease severity

The bivariate association between baseline mood scores and a clinically significant change in disease severity was investigated by the one way ANOVA test, with linear trend analysis. The mean baseline scores for depression and anxiety were compared according to categories of change for disease activity, pain and function. Change in each measure of disease severity was defined as deterioration, stable or improvement according to the MCIDs. It was hypothesised that mean baseline mood scores would decrease in the following order for changes in disease status: deterioration → stable → improvement.

Three multinomial logistic regression analyses were then performed to explore the multivariate relationships between baseline mood scores and clinically significant changes in disease severity. Separate outcomes of disease activity, pain and function were assessed according to deteriorations or improvements defined by the MCIDs for each measure. The reference category was stable, according to a change within the MCID. Firstly, an unadjusted analysis was performed with depression and anxiety as continuous variables. Separate adjusted models were then created which included depression, anxiety and all of the potential confounding variables from the baseline survey. It was hypothesised that increased levels of depression and anxiety would be positively associated with deterioration and negatively associated with improvement in disease status.

3.6.2.4 Association of baseline disease severity on clinically significant changes in depression and anxiety

The bivariate association between baseline disease status scores and a change in mood was investigated by the one way ANOVA test with linear trend analysis. The mean baseline scores for disease activity, pain and function were compared across the change categories of deterioration, stable and improvement for depression and anxiety. Change was defined according to the MCIDs. It was hypothesised that mean baseline disease severity scores would decrease in the following order for changes in mood: deterioration → stable → improvement.

Multinomial logistic regression analyses were then performed to explore the multivariate relationships between baseline disease severity scores and clinically significant change in depression or anxiety. Change was defined according to deteriorations or improvements in the MCIDs for depression and anxiety. The reference category for each of the outcome variables was stable, according to a change within the MCID. Firstly, an unadjusted analysis was performed with continuous variables of disease activity, pain and function. Subsequently, an adjusted model was created which also included potential confounding variables from the baseline survey. It was hypothesised that increased levels of disease activity, functional impairment and pain would be positively associated with deterioration and negatively associated with improvement in depression and anxiety.

CHAPTER 4

Results: cross-sectional study

This Chapter relates to the baseline results from a prospective cohort study of AS patients, based on the methods previously outlined in Chapter three. Firstly, the study is described in relation to the response rates and characteristics of the baseline responders, followed by a presentation of results according to the following five objectives:

(i) to describe the prevalence of depression and anxiety in relation to the socio-demographic and disease-specific characteristics of AS patients.
(ii) to assess the association of depression and anxiety on disease severity.
(iii) to assess the association of disease severity on depression and anxiety.
(iv) to evaluate the association of mixed depression and anxiety on disease severity.
(v) to evaluate the association of disease severity on mixed depression and anxiety.

A summary of principle findings is provided at the end of the Chapter.

4.1 Survey response

612 (61.2%) of the 1000 patients invited to participate in the study, responded to the baseline postal survey. The item response rates for the disease severity measures were 610 (99.7%) for disease activity, 604 (98.7%) for pain and 606 (99.0%) for functional impairment. The response rates for mood were similarly high, with 607 (99.2%) for depression and 605 (98.9%) for anxiety. Among the 612 responders, 596 (97.4) provided item responses for all of the mood and disease severity measures.

4.1.1 Characteristics of responders

The characteristics and mean scores of the baseline responders are presented in table 4.1. Most of the responders were male (72.2%), middle-aged (mean 50.80 years, SD 12.22) and married (73.8%). The majority of patients had established disease, with a mean (SD) symptom duration of 22.37 (12.37) years. Patients also reported a major disruption in work participation, indicated by 42.1% of patients being either unemployed or having retired early. The baseline mean scores for disease activity, pain and function were 4.57 (2.57), 4.79 (2.66) and 4.60 (2.86), respectively, suggesting that patients reported high average levels of disease severity, according to a cut-off of ≥4.

Table 4.1: Baseline patient characteristics and mean scores (SD) of AS patients

	Responded to baseline survey (n=612)
Patient characteristics	
Male gender *n* (%)	438 (72.2)
Mean age (SD)	50.80 (12.22)
Mean AS symptom duration (SD)	22.37 (12.37)
Mean AS diagnosis duration (SD)	17.26 (11.68)
Married/cohabiting *n* (%)	446 (73.8)
Employed/normal retirement *n* (%)	331 (57.9)
Least deprived *n* (%)	93 (19.9)
Mid deprived *n* (%)	282 (60.2)
Most deprived *n* (%)	93 (19.9)
Patient-reported outcome measures (PROMS)[a]	
Mean HADS-D (SD)	5.88 (4.22)
Mean HADS-A (SD)	7.44 (4.47)
Mean BASDAI (SD)	4.57 (2.57)
Mean Pain NRS (SD)	4.79 (2.66)
Mean BASFI (SD)	4.60 (2.86)

[a] HADS-D score 0-21: higher scores indicate greater depression; HADS-A score 0-21: higher scores indicate greater anxiety; BASDAI score 0-10: higher scores indicate increased disease activity; BASFI score 0-10: higher scores indicate greater functional impairment; Pain NRS score 0-10: higher scores indicate more pain.

Note: SD = standard deviation; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain. BASDAI = Bath AS Disease Activity Index; NRS = numerical rating scale; BASFI = Bath AS Functional Index.

4.2 Prevalence of depression and anxiety

According to the HADS depression domain (HAD-D), 413 (68.0%) patients had normal symptoms; 194 (32.0%) possible depression (HADS-D ≥8) and 90 (14.8%) probable depression (HADS-D ≥11). Frequencies of anxiety (HADS-A) were comparably higher, with 334 (55.2%) patients reporting normal symptoms; 271 (44.8%) possible anxiety (HADS-A ≥8) and 140 (23.1%) probable anxiety (HADS-A ≥11). Tables 4.2 and 4.3 illustrate the prevalence of depression and anxiety, respectively.

Table 4.2: Prevalence of depression in AS according to patient characteristics

Variable *(n=607)*	**No depression (HADS-D <8)**		**Possible depression (HADS-D ≥8)**		**P-value**
	n	*%*	*n*	*%*	
Total	413	68.0	194	32.0	
Gender					
male	301	69.0	135	31.0	0.544
female	111	66.5	56	33.5	
Age					
20-39 years	85	72.0	33	28.0	
40-49 years	98	68.1	46	31.9	0.155
50-59 years	65	38.5	65	38.5	
>60 years	122	71.8	48	28.2	
Symptom duration					
< 10 years	59	70.2	25	29.8	
10-19 years	124	69.7	54	30.3	0.447
20-29 years	83	62.9	49	37.1	
>30 years	127	70.9	52	29.1	
Diagnosis duration					
< 10 years	121	68.0	57	32.0	
10-19 years	135	70.7	56	29.3	0.299
20-29 years	76	71.7	30	28.3	
>30 years	55	60.4	36	39.6	
Marital status					
Married/cohabiting	311	70.2	132	29.8	0.119
unmarried	99	63.5	57	36.5	
Employment					
employed/normal retired	262	80.1	65	19.9	<0.001***
unemployed/early retired	127	52.7	114	47.3	
Deprivation					
least	70	75.3	23	24.7	
middle	201	71.8	79	28.2	<0.001***
most	49	53.2	43	46.7	

Note: HADS-D=Hospital Anxiety and Depression Scale-depression. *p <0.05, **p <0.01, ***p<0.001

Table 4.3: Prevalence of anxiety in AS according to patient characteristics

Variable *(n=605)*	**No anxiety (HADS-A <8)**		**Possible anxiety (HADS-A ≥8)**		**P-value**
	n	*%*	*n*	*%*	
Total	334	*55.2*	271	44.8	
Gender					
male	256	58.9	179	44.1	0.004**
female	76	45.8	90	54.2	
Age					
20-39 years	66	56.4	51	43.6	
40-49 years	75	52.4	68	47.6	0.387
50-59 years	87	51.5	82	48.5	
>60 years	102	60.0	68	40.0	
Symptom duration					
< 10 years	49	59.0	34	41.0	
10-19 years	95	53.7	82	46.3	0.831
20-29 years	70	53.0	62	47.0	
>30 years	99	55.3	80	44.7	
Diagnosis duration					
< 10 years	96	54.5	80	45.5	
10-19 years	105	55.0	86	45.0	0.814
20-29 years	62	58.5	44	41.5	
>30 years	47	51.6	44	48.4	
Marital status					
Married/cohabiting	256	57.9	186	42.1	0.028*
unmarried	74	47.7	81	52.3	
Employment					
employed/normal retired	213	65.5	112	33.8	<0.001***
Unemployed/early retired	104	43.2	137	56.8	
Deprivation					
least	58	63.0	34	37.0	
middle	161	57.7	118	42.3	0.069
most	43	46.7	49	53.3	

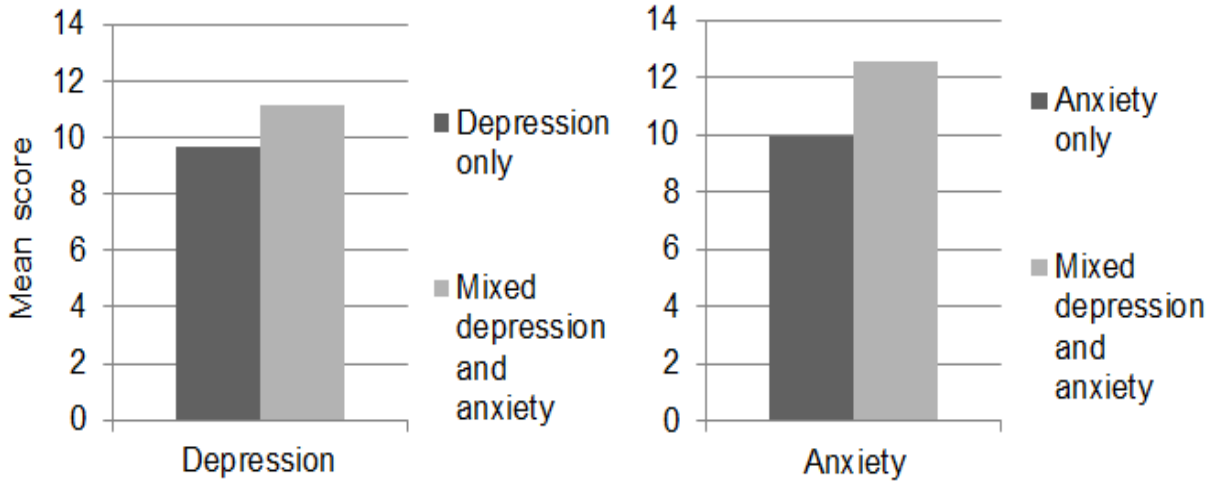
Note: HADS-A=Hospital Anxiety and Depression Scale-anxiety. *p <0.05, **p <0.01, ***p<0.001

The prevalence of possible depression was significantly higher in patients with early retirement/unemployment (n=114, 47.3%, p <0.001) and increased deprivation (p<0.001). Conversely, the prevalence of possible anxiety was significantly higher in females (n=90, 54.2%, p=0.004), patients with unmarried status (p=0.028) and early retirement/unemployment (p<0.001). Patient age, symptom duration and diagnosis duration were all found to be non-significant (all p≥0.05).

Among the 194 patients who reported possible depression, 166 (85.6%) also reported possible anxiety and 27 had depression only. The occurrence of isolated anxiety was noticeably more frequent, with 105 patients reporting anxiety only. When considering all of the baseline responders, a staggering 298 (48.7%) patients were affected by depression, anxiety or both.

Patients with mixed depression and anxiety had significantly higher mean depression and anxiety scores when compared to patients with depression or anxiety only (figure 4.1). The mean depression score increased from 9.65 (SD 1.63) in the depression only group to 11.12 (SD 2.96) in the mixed depression and anxiety group. Mean anxiety scores also increased from 9.92 (SD 2.01) to 12.51 (SD 3.15). This finding was clinically important as the mean scores for depression and anxiety crossed the higher severity thresholds of ≥11 on the HADS scale when both disorders were present

Figure 4.1: Mean scores of patients with mixed depression and anxiety



4.3 Association of depression and anxiety on disease severity

Table 4.4 presents the results of the adjusted and unadjusted logistic regression analyses for the associations of depression and anxiety on disease activity, pain and function. Full tables including all of the potential confounders are found in Appendix A.6.

Table 4.4: Association of depression and anxiety on increased disease severity in patients with ankylosing spondylitis (AS)

	Disease severity status[a]								
	BASDAI ≥4 (n=337)			**Pain NRS ≥4** (n=376)			**BASFI ≥4** (n=332)		
Independent variable	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**[b]	**Adjusted OR (95% CI)**[c]	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**[b]	**Adjusted OR (95% CI)**[c]	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**[b]	**Adjusted OR (95% CI)**[c]
Depression									
Normal (HADS-D <8) (n=413)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Possible depression (HADS-D ≥8) (n=194)	6.53 (4.30-9.92)***	3.79 (2.36-6.09)***	2.83 (1.51-5.29)***	4.46 (2.94-6.77)***	2.78 (1.72-4.50)***	2.12 (1.12-3.99)*	6.21 (4.12-9.37)***	4.62 (2.89-7.39)***	3.77 (1.99-7.15)***
Anxiety									
Normal (HADS-A <8) (n=334)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Possible anxiety (HADS-D ≥8) (n=271)	4.74 (3.34-6.75)***	2.60 (1.73-3.90)***	2.84 (1.66-4.87)***	3.58 (2.51-5.11)***	2.21 (1.46-3.34)***	2.30 (1.34-3.93)**	3.33 (2.37-4.68)***	1.64 (1.09-2.45)*	1.62 (0.93-2.83)

Note: BASDAI = Bath AS disease activity index; NRS = numerical rating scale; BASFI = Bath AS functional index; HADS-D = Hospital Anxiety and Depression Scale - depression domain; HADS-A = Hospital Anxiety and Depression Scale - anxiety domain; OR = odds ratio; CI = confidence interval.
* p <0.05, ** p <0.01, *** p<0.001.

[a] reference categories: BASDAI, BASFI or Pain NRS scores <4.

[b] controlling for mood variables presented.

[c] multivariable model controlling for gender, age, symptom duration, marital status, employment, deprivation and mood variables presented.

Patients with depression demonstrated significant unadjusted associations with increased disease activity (OR 6.53, 95% CI 4.30-9.92), pain (OR 4.46, 95% CI 2.94-6.77) and functional impairment (OR 6.21, 96% CI 4.12-9.37). Slightly lower, yet significant unadjusted associations were also found with anxiety on disease activity (OR 4.74, 95% CI 3.34-6.75), pain (OR 3.58, 95% CI 2.51-5.11) and function impairment (OR 3.33, 95% CI 2.37-4.68).

Following adjustment with all of the mood and potential confounding variables, depression was significantly associated with disease activity (OR 2.83, 95% CI 1.51-5.29), pain (OR 2.12, 95% CI 1.12-3.99) and function impairment (OR 3.77, 95% CI 1.99-7.15); and anxiety was significantly associated with disease activity (OR 2.84, 95% CI 1.66-4.87) and pain (OR 2.30, 95% CI 1.34-3.93). Unlike depression, anxiety did not demonstrate an independent association with functional impairment.

4.4 Association of disease severity on depression and anxiety

There were significant unadjusted associations of disease activity, pain and function on outcomes of depression and anxiety (Table 4.5). These associations were similar to those found in the unadjusted analyses of depression and anxiety on outcomes of disease severity. However, as the adjusted analyses did not control for depression or anxiety, larger associations were found when adjusting for all of the potential confounding variables.

According to the adjusted analyses, depression was significantly associated with increased disease activity (OR 5.12, 95% CI 2.95-8.90), pain (OR 3.36, 95% CI 1.94-5.82) and functional impairment (OR 5.21, 95% CI 2.97-9.12). Similar significant associations were also found with anxiety and increased disease activity (OR 4.44, 95% CI 2.76-7.15), pain (OR 3.17, 95% CI 1.98-5.17) and functional impairment (OR 3.02, 95% CI 1.87-4.88).

Full tables including all of the potential confounders are found in Appendix A.7.

Table 4.5: Associations of increased disease severity on depression and anxiety in patients with ankylosing spondylitis (AS)

	Mood status[a]			
	Depression (HADS-D ≥8) (n=194)		**Anxiety (HADS-A ≥8)** (n=271)	
Independent variable	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**[b]	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**[b]
Disease activity (BASDAI)				
<4 (n=275)	1.00	1.00	1.00	1.00
≥4 (n=337)	6.53 (4.30-9.37)***	5.12 (2.95-8.90)***	4.74 (3.34-6.75)***	4.44 (2.76-7.15)***
Pain (NRS)				
<4 (n=236)	1.00	1.00	1.00	1.00
≥4 (n=376)	4.46 (2.94-6.77)***	3.36 (1.94-5.82)***	3.58 (2.51-5.11)***	3.17 (1.98-5.17)***
Function (BASFI)				
<4 (n=280)	1.00	1.00	1.00	1.00
≥4 (n=332)	6.21 (4.12-9.37)***	5.21 (2.97-9.12)***	3.33 (2.37-4.68)***	3.02 (1.87-4.88)***

Note: BASDAI = Bath AS disease activity index; NRS = numerical rating scale; BASFI = Bath AS functional index; HADS-D = Hospital Anxiety and Depression Scale - depression domain; HADS-A = Hospital Anxiety and Depression Scale - anxiety domain; OR = odds ratio; CI = confidence interval.
* p <0.05, ** p <0.01, *** p<0.001

[a] reference categories: HADS-D ≥8, HADS-A ≥8.

[b] multivariable model controlling for gender, age, symptom duration, marital status, employment, and deprivation.

4.5 Association of mood disturbance on disease severity

A large majority (84.3%) of patients with mixed depression and anxiety also had increased disease activity (Table 4.6). These frequencies were also similar for pain (84.9%) and functional impairment (81.3%). When compared to patients with mixed depression and anxiety, patients with isolated depression or anxiety reported lower frequencies of increased disease activity and pain. However, functional impairment was slightly more common in patients with depression only (81.5%).

Table 4.6: Number and percentage of patients with ankylosing spondylitis (AS) with increased disease severity, according to mood status

n=605	**Disease status**[a]		
Mood status	**Disease activity (BASDAI ≥4)** (n=332)	**Pain (Pain NRS ≥4)** (n=371)	**Function (BASFI ≥4)** (n=328)
Normal mood (HADS-D <8/ HADS-A <8) (n=307)	110 (35.8)	140 (46.6)	116 (37.8)
Depression only (HADS-D ≥8) (n=27)	19 (70.4)	19 (70.4)	22 (81.5)
Anxiety only (HADS-A ≥8) (n=105)	63 (60.0)	69 (65.7)	55 (52.4)
Depression and anxiety (HADS-D ≥8/HADS-A ≥8) (n=166)	140 (84.3)	143 (84.9)	135 (81.3)

Note: BASDAI = Bath AS disease activity index; NRS = numerical rating scale; BASFI = Bath AS functional index; HADS-D = Hospital Anxiety and Depression Scale - depression domain; HADS-A = Hospital Anxiety and Depression Scale - anxiety domain.

Table 4.7 displays the results of the separate logistic regression analyses with outcomes of disease activity, pain and function. The full tables including all of the potential confounding variables are provided in Appendix A.8.

Table 4.7: Association of mood disturbance on increased disease severity in patients with ankylosing spondylitis (AS)

	Disease severity status[a]					
	BASDAI ≥4 (n=337)		**Pain NRS ≥4** (n=376)		**BASFI ≥4** (n=332)	
Independent variable	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**[b]	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)** [b]	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)** [b]
Normal mood (HADS-D <8 and HADS-A <8) (n=307)	1.00	1.00	1.00	1.00	1.00	1.00
Depression only (HADS-D ≥8) (n=27)	4.86 (1.98-11.93)*	4.16 (1.27-13.57)*	2.72 (1.16-6.41)*	2.45 (0.77-7.83)	9.01 (3.03-26.80)**	5.58 (1.49-20.88)*
Anxiety only (HADS-A ≥8) (n=105)	2.75 (1.74-4.35)***	3.17 (1.72-5.83)***	2.20 (1.39-3.49)**	2.39 (1.31-4.38)**	1.84 (1.17-2.88)*	1.78 (0.95-3.32)
Depression and anxiety (HADS-D ≥8 and HADS-A ≥8) (n=166)	9.64 (5.97-15.57)***	7.66 (4.10-14.30)***	6.18 (3.84-9.93)***	4.76 (2.56-8.86)***	7.90 (4.95-12.61)***	5.91 (3.17-10.99)***

Note: OR = odds ratio; CI = confidence interval. BASDAI = Bath AS disease activity index; NRS = numerical rating scale; BASFI = Bath AS functional index; HADS-D = Hospital Anxiety and Depression Scale - depression domain; HADS-A = Hospital Anxiety and Depression Scale - anxiety domain; * p <0.05, ** p <0.01, *** p<0.001

[a] reference categories: BASDAI, BASFI or Pain NRS scores <4.

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation.

Patients with mixed anxiety and depression had over nine times the odds of reporting disease activity scores ≥4 than those patients with normal mood in the unadjusted analysis (OR 9.64, 95% CI 5.97-15.57). This risk was still substantial when adjusting for potential confounders (OR 7.66, 95% CI 4.10-14.30). The odds ratios were attenuated but similar for those patients with anxiety or depression only; suggesting a comparable association between disease activity with both depression and anxiety.

There was a significant, yet slightly lower association of mixed depression and anxiety on pain in the unadjusted (OR 6.18, 95% CI 3.84-9.93) and adjusted (OR 4.76, 95% CI 4.76, 95% CI 2.56-8.86) analyses. As with disease activity, increased pain was equivocally associated with both anxiety and depression. The adjusted odds ratio for depression was statistically non-significant, however, this is likely to be due to the low number of patients with depression only (n=27).

There was a significant unadjusted association of mixed depression and anxiety with poor function (OR 7.90, 95% CI 4.95-12.61). This association remained significant in the adjusted model (OR 5.91, 95% CI 3.17-10.99). Interestingly, there was only a slight overlap with the adjusted confidence intervals for patients with anxiety only (OR 1.78, CI 0.98-3.32) and patients with mixed depression and anxiety; highlighting the unique impact of depression on functional disability. This was also evident by the higher odds ratio for the patients with depression only when compared to those with anxiety only.

4.6 Association of disease severity on mood disturbance

Table 4.8 presents the results from the multinomial logistic regression analyses with mood disturbance as the outcome variable, according to separate analyses with disease activity, pain and function. The full tables including all of the potential confounding variables are provided in Appendix A.9.

Table 4.8: Association of increased disease severity on mood disturbance in patients with ankylosing spondylitis (AS)

	Mood category[a]					
	Depression only (n=27)		**Anxiety only** (n=105)		**Depression and anxiety** (n=166)	
Independent variable	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**[b]	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**[b]	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**[b]
Disease activity (BASDAI)						
<4 (n=275)	1.00	1.00	1.00	1.00	1.00	1.00
≥4 (n=337)	4.86 (1.98-11.93)**	4.39 (1.33-14.55)*	2.75 (1.74-4.35)***	3.15 (1.71-5.78)***	9.64 (5.97-15.57)***	7.60 (4.06-14.22)***
Pain (NRS)						
<4 (n=236)	1.00	1.00	1.00	1.00	1.00	1.00
≥4 (n=376)	2.72 (1.16-6.41)*	2.20 (1.39-3.49)**	6.18 (3.84-9.93)***	2.34 (0.74-7.47)	2.39 (1.31-4.38)**	4.67 (2.51-8.69)***
Function (BASFI)						
<4 (n=280)	1.00	1.00	1.00	1.00	1.00	1.00
≥4 (n=332)	9.01 (3.03-26.80)***	5.42 (1.49-19.77)*	1.81 (1.16-2.83)**	1.78 (0.96-3.31)	7.17 (4.56-11.28)***	6.15 (3.28-11.52)***

[a] reference category: HADS-D and HADS-A scores <8,

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation

* p <0.05
** p <0.01
*** p<0.001

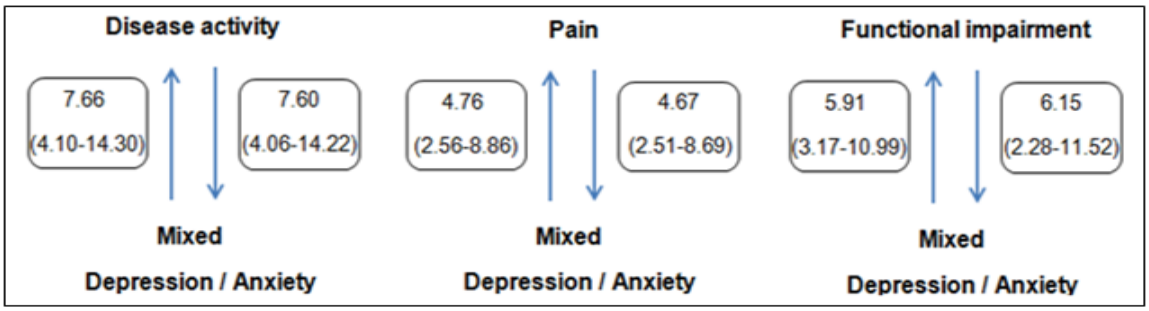
All measures of disease severity were significantly associated with increased odds of mood disturbance. All odds ratios were similar when compared to the previous analyses where mood was the outcome variable. This demonstrated a reciprocal relationship between mood disturbance and disease severity.

4.7 Summary

Depression and anxiety were commonly reported by the baseline survey recipients. Almost half of the sample had some form of mood disturbance (49.3%), according to a cut-off of ≥8 on the HADS scale. The majority of these patients had a co-existence of both depression and anxiety (55.7%). There was also a significant increase in the mean mood scores of patients with mixed depression and anxiety, when compared to those with depression or anxiety only. Depression was specifically found in patients with unemployment/early retirement and increased deprivation, whereas, anxiety was associated with female gender, unemployment/early retirement and unmarried status.

When accounting for all of the potential confounding variables, depression and anxiety were independently associated with outcomes of increased disease activity and pain. However, functional impairment was only associated with depression. In addition, the co-existence of depression and anxiety was associated with all measures of increased disease severity. Conversely, increased disease severity was significantly associated with mixed depression and anxiety (Figure 4.2).

Figure 4.2: Adjusted associations between mood disturbance and disease severity



* Note: Figures represent odds ratios (95% confidence intervals). Arrows point from independent to dependant variables

CHAPTER 5

Results: prospective cohort study

This Chapter provides the follow-up results from a prospective cohort study of AS patients, based on the methods previously described in Chapter three. Firstly, the study is described in relation to the response rates and characteristics of the follow-up responders. This is followed by a presentation of results according to four objectives:

(i) to compare the baseline characteristics of responders and non-responders at follow-up

(ii) to describe the individual variability of clinically significant changes in mood and each measure of disease severity.

(iii) to determine the relationship between baseline depression and anxiety with clinically significant changes in disease severity.

(iv) to determine the relationship between baseline disease severity with clinically significant changes in depression and anxiety.

A summary of principle findings is provided at the end of the Chapter.

5.1 Survey response

From the 612 patients that responded to the baseline questionnaire, 470 (76.8%) patients responded at follow-up. Item response rates for disease activity, pain and function were 469 (99.8%), 467 (99.4%) and 468 (99.6%), respectively. The response rates for mood were similarly high at 462 (98.3%) for both depression and anxiety. Of the 470 responders, 455 (96.8%) provided item responses for all of the mood and disease severity measures. The baseline characteristics of the responders and non-responders at follow-up are presented in table 5.1 below.

Table 5.1: Baseline characteristics of responders and non-responders to six month follow-up study of patients with ankylosing spondylitis (AS)

	Responded to follow-up	Not responded to follow-up	P-value
Total *n* (%)	455 (74.3)	157 (25.7)	
Patient characteristics			
Male gender *n* (%)	326 (72.3)	112 (71.8)	0.907
Mean age (SD)	51.90 (12.07)	47.61 (12.12)	<0.001***
Mean AS symptom duration (SD)	23.21 (12.41)	19.81 (11.90)	0.004**
Mean AS diagnosis duration (SD)	17.77 (11.88)	15.73 (10.92)	0.072
Married/cohabiting *n* (%)	326 (72.4)	120 (77.9)	0.18
Employed/normal retirement *n* (%)	235 (54.4)	96 (68.6)	0.003**
Least deprived *n* (%)	72 (20.7)	21 (17.5)	0.59
Mid deprived *n* (%)	205 (58.9)	77 (64.2)	
Most deprived *n* (%)	71 (20.4)	22 (18.3)	
Patient-reported outcome measures (PROMS)[a]			
Mean HADS-D (SD)	5.70 (4.17)	6.41 (4.34)	0.69
Mean HADS-A (SD)	7.17 (4.40)	8.25 (4.59)	0.009**
Mean BASDAI (SD)	4.46 (2.57)	4.90 (2.55)	0.069
Mean BASFI (SD)	4.66 (2.85)	4.40 (2.87)	0.323
Mean Pain NRS (SD)	4.73 (2.66)	4.98 (2.64)	0.308

[a] HADS-D score 0-21: higher scores indicate greater depression; HADS-A score 0-21: higher scores indicate greater anxiety; BASDAI score 0-10: lower scores indicate less disease activity; BASFI score 0-10: lower scores indicate less functional disability; Pain NRS score 0-10: higher scores indicate more pain. *<0.05, ** <0.01, *** <0.001

Note: SD = standard deviation; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain. BASDAI = Bath AS Disease Activity Index; NRS = numerical rating scale; BASFI = Bath AS Functional Index.

The responders to follow-up were significantly older than the non-responders to follow-up, with longer disease durations and lower rates of employment/normal retirement. In addition, the responders reported lower levels of anxiety at baseline, although there was no significant difference in depressive symptoms.

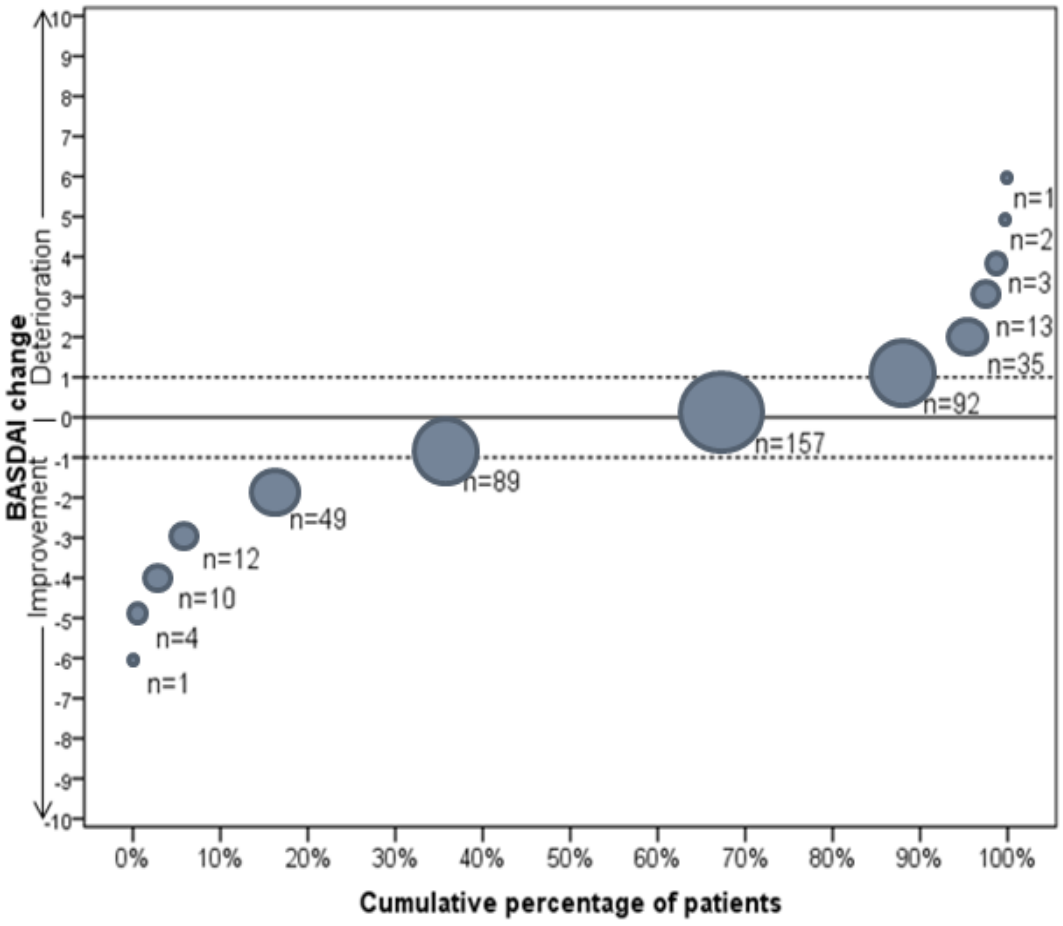
5.2 Variability of change in mood and disease status

Change in mood and disease severity was then measured for each patient, by subtracting baseline scores from follow-up scores. There were no significant mean differences between the depression (mean difference 0.18, 95% CI -0.07 to 0.44) or anxiety (mean difference -0.06, 95% CI -0.33 to 0.21) scores of the baseline and follow-up samples. Disease status was also stable for function (mean difference -0.04, 95% CI -0.15 to 0.07)

and disease activity (mean difference -0.13, 95% CI -0.27 to 0.01) scores. There was, however, a small but significant improvement in pain levels (mean difference -0.20, 95% CI -0.38 to -0.02).

Variability in individual change was explored through cumulative probability plots. The plots for changes in disease activity, pain and depression scores are presented in Figures 5.1, 5.2 and 5.3 respectively. The plots for the other PROMs are provided in Appendix A.10. Each graph has three horizontal lines. The solid horizontal line represents no change according to a difference of zero. The upper and lower dashed horizontal lines represent deterioration and improvement, respectively, according to the MCID for each measure (Pavy et al, 2005; Angst et al, 2008).

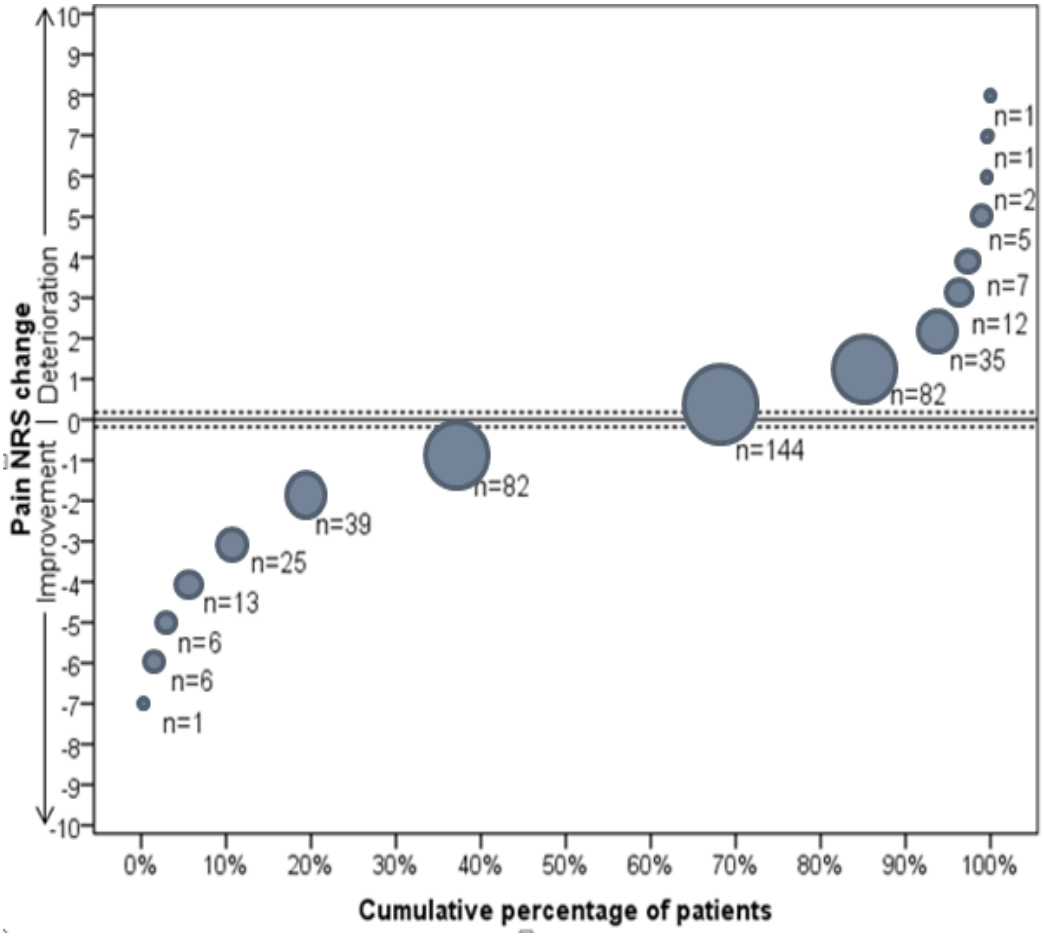
Figure 5.1: Cumulative plot of disease activity (BASDAI) change over six months (n=469)



Note: larger circles represent greater numbers of patients. Change was defined according to a minimal clinically important difference (MCID) of 1.0. The solid horizontal line signifies no change. The upper and lower dashed horizontal lines represent the MCID.

There was a large variation between individual changes in disease activity scores (range -6 to 6). However, the majority of patients had stable BASDAI scores (n=275, 58.6%), with a variation in their BASDAI score of <1 (within the limits of MCID). 194 (41.4%) reported a clinically significant change in BASDAI score ≥1. Among those patients who changed, more patients improved (54.6%) than deteriorated (45.4%). BASFI scores were similarly distributed to BASDAI scores (see Appendix A.10).

Figure 5.2: Cumulative plot of pain (NRS) change over six months (n=467)

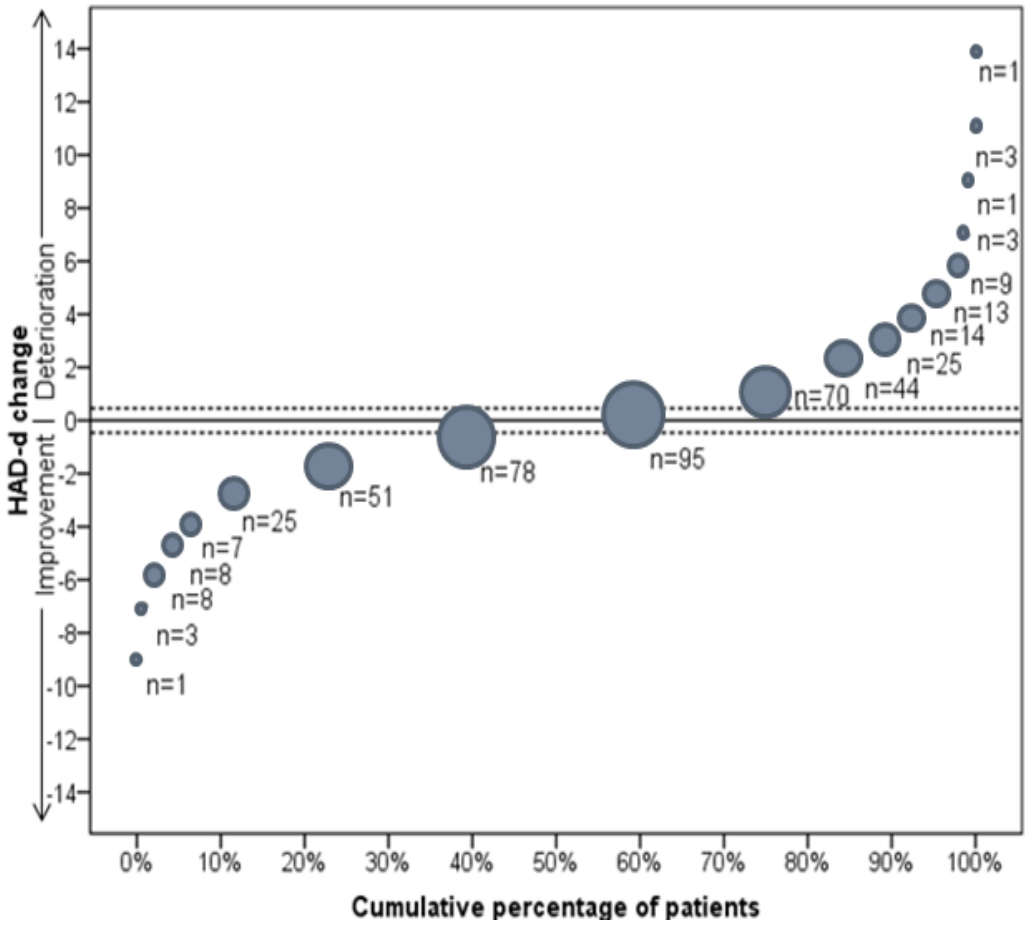


Note: larger circles represent greater numbers of patients. Change was defined according to a minimal clinically important difference (MCID) of 0.18. The solid horizontal line signifies no change. The upper and lower dashed horizontal lines represent the MCID.

A greater variation was seen with the pain NRS scores. Change ranged from -7 to 8. Only 150 (32.1%) patients kept the same pain score according to an MCID or 0.18. The majority of patients changed their pain score ≥0.18 (n=317, 67.8%). Among those patients

with clinically significant change, slightly more improved (54.3%) than deteriorated (45.7%).

Figure 5.3: Cumulative plot of depression (HADS-D) change over six months (n=462)



Note: larger circles represent greater numbers of patients. Change was defined according to a minimal clinically important difference (MCID) of 0.56. The solid horizontal line signifies no change. The upper and lower dashed horizontal lines represent the MCID.

The most variation was seen with the mood PROMs, with change in depression ranging from -9 to 14. Only 95 (21.2%) patients reported stable HADS-D scores, according to an MCID of 0.56. 364 (78.8%) patients demonstrated a clinically significant change of ≥0.56. Among those patients who changed, similar numbers of patients improved (49.7%) and deteriorated (50.3%). Changes in anxiety demonstrated a similar distribution to the HADS-D scores (see Appendix A.10).

5.3 Association of baseline depression and anxiety on changes in disease status

Table 5.2 presents the results from the one-way ANOVA test with linear trend analysis. Mean baseline scores for depression and anxiety are provided for each of the three categories of change in disease status: deterioration, stable and improvement. Changes were defined according to MCIDs.

Table 5.2: Baseline depression and anxiety scores of patients with ankylosing spondylitis according to changes in disease severity over six months

	Change in disease status[ł]			P-value
	Deterioration	Stable	Improvement	
Disease activity (BASDAI)[a]				
n	88	275	106	
Mean depression (HADS-D) score (95% CI)	5.89 (5.01-6.77)	5.60 (5.07-6.13)	6.07 (5.37-6.77)	Overall: 0.596 Linear trend:0.722
Mean anxiety (HADS-A) score (95% CI)	7.30 (6.41-8.20)	7.01 (6.47-7.56)	7.69 (6.82-8.55)	Overall:0.480 Linear trend:0.498
Pain (NRS)[b]				
n	145	150	172	
Mean depression (HADS-D) score (95% CI)	5.55 (4.87-6.23)	5.97 (5.25-6.69)	5.63 (5.03-6.24)	Overall:0.662 Linear trend:0.891
Mean anxiety (HADS-A) score (95% CI)	7.29 (6.58-8.00)	7.13 (6.35-7.92)	7.78 (6.54-7.82)	Overall: 0.954 Linear trend: 0.836
Function (BASFI)[c]				
n	99	243	126	
Mean depression (HADS-D) score (95% CI)	5.70 (4.89-6.51)	5.60 (5.06-6.15)	6.04 (5.31-6.77)	Overall: 0.641 Linear trend: 0.514
Mean anxiety (HADS-A) score (95% CI)	7.42 (6.55-8.29)	7.06 (6.49-7.62)	7.35 (6.52-8.19)	Overall: 0.730 Linear trend: 0.966

[ł] change defined according to minimal important differences (MCIDs) for each measure. [a]MCID 1.00, [b]MCID 0.18, [c]MCID 0.70

Note: HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain. BASDAI = Bath AS Disease Activity Index; NRS = numerical rating scale; BASFI = Bath AS Functional Index.

The results of the one-way ANOVA test showed that there were no significant associations between the baseline mood scores and changes in any of the measures of disease status. When linear trend analysis was applied, there was also no significant trend in mood scores between those patients who deteriorated, remained stable or improved in disease status. Surprisingly, there was a trend for mean mood scores to be higher in those patients who improved their disease status than those patients who deteriorated. However, this difference was not statistically significant.

Tables 5.3a and 5.3b present the results of the unadjusted and adjusted multinomial logistic regression analyses, respectively. Independent variables of depression and anxiety were entered into separate analyses with outcome variables for change in disease activity, function and pain. Changes were defined according to the MCIDs for each of the measures of disease severity. Full tables including all of the potential confounding variables are found in Appendix A.11.

There was no significant unadjusted association between depression or anxiety and changes in any of the measures of disease status. There was, however, a small significant association between increasing anxiety levels and an improvement in disease activity (OR 1.08, 95% CI 1.01-1.16), when adjusting for other potential confounding variables. All of the other analyses remained non-significant.

Table 5.3a: Unadjusted association of baseline depression and anxiety with changes in disease severity of patients with AS over six months

	Change in disease status[ł]					
	Disease activity (BASDAI)[a]		Function (BASFI)[b]		Pain (NRS)[c]	
Independent variable	**Deterioration** (n=88)	**Improvement** (n=106)	**Deterioration** (n=99)	**Improvement** (n=126)	**Deterioration** (n=145)	**Improvement** (n=172)
Depression (HADS-D)	1.02 (0.96-1.08)	1.03 (0.97-1.08)	1.01 (0.95-1.00)	1.03 (0.97-1.08)	0.98 (0.93-1.03)	0.98 (0.93-1.03)
Anxiety (HADS-A)	1.02 (0.96-1.07)	1.03 (0.98-1.09)	1.02 (0.97-1.07)	1.02 (0.97-1.07)	1.01 (0.96-1.06)	1.00 (0.95-1.05)

[ł]change defined according to minimal important differences (MCIDs) for each measure. Reference category: stable. [a]MCID 1.0; [b]MCID 0.70; [c]MCID 0.18

Table 5.3b: Adjusted association of baseline depression and anxiety with changes in disease severity of patients with AS over six months

	Change in disease status[ł]					
	Disease activity (BASDAI)[♦]		Function (BASFI)[♦]		Pain (NRS)[♦]	
Independent variable	**Deterioration** (n=88)	**Improvement** (n=106)	**Deterioration** (n=99)	**Improvement** (n=126)	**Deterioration** (n=145)	**Improvement** (n=172)
Depression (HADS-D)	1.03 (0.95-1.11)	1.05 (0.98-1.14)	1.01 (0.94-1.10)	1.06 (0.98-1.14)	0.96 (0.89-1.04)	0.97 (0.90-1.04)
Anxiety (HADS-A)	1.04 (0.97-1.12)	1.08 (1.01-1.16)*	1.03 (0.96-1.11)	1.04 (0.97-1.11)	0.96 (0.89-1.03)	0.97 (0.91-1.04)

[ł] Reference category: stable. Change defined according to minimal important differences (MCIDs) for each measure. [a]MCID 1.0; [b]MCID 0.70; [c]MCID 0.18
* p=<0.05. [♦] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation

Note: AS=Ankylosing spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain. BASDAI = Bath AS Disease Activity Index; NRS = numerical rating scale; BASFI = Bath AS Functional Index.

5.4 Association of baseline disease severity on changes in depression and anxiety

Table 5.4 presents the results from the one-way ANOVA test with linear trend analysis. Mean baseline scores for BASDAI, BASFI and pain NRS are provided for each of the three categories of change in mood status: deterioration, stable and improvement. Changes were defined according to MCIDs.

Table 5.4: Disease severity scores of patients with ankylosing spondylitis, according to changes in mood status over six months

	Change in mood status[ł]			**P-value**
	Deterioration	**Stable**	**Improvement**	
Depression (HADS-D)[a]				
n	183	98	181	
Mean disease activity (BASDAI) score (95% CI)	4.45 (4.07-4.82)	4.27 (3.72-4.82)	4.61 (4.24-4.98)	Overall:0.571 Linear trend: 0.546
Mean pain (NRS) score (95% CI)	4.62 (4.23-5.00)	4.78 (4.20-5.36)	4.81 (4.42-5.20)	Overall: 0.772 Linear trend: 0.493
Mean function (BASFI) score (95% CI)	4.73 (4.31-5.16)	4.38 (3.79-4.97)	4.80 (4.38-5.20)	Overall: 0.500 Linear trend: 0.841
Anxiety (HADS-A)[b]				
n	186	88	188	
Mean disease activity (BASDAI) score (95% CI)	4.43 (4.06-4.79)	3.96 (3.38-4.54)	4.78 (4.41-5.14)	Overall: 0.045 Linear trend: 0.185
Mean pain (NRS) score (95% CI)	4.62 (4.23-5.01)	4.23 (3.61-4.84)	5.10 (4.73-5.46)	Overall: 0.031 Linear trend: 0.085
Mean function (BASFI) score (95% CI)	4.56 (4.13-4.99)	4.29 (3.67-4.92)	5.00 (4.60-5.40)	Overall: 0.117 Linear trend: 0.135

[ł] change defined according to minimal important differences (MCIDs) for each measure. [a]MCID 0.46, [b]MCID 0.56

Note: HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain. BASDAI = Bath AS Disease Activity Index; NRS = numerical rating scale; BASFI = Bath AS Functional Index.

There were no significant associations between the baseline disease severity scores and changes in mood over six months. When linear trend analysis was applied, there was also no significant trend in disease status scores between those patients who deteriorated, remained stable or improved in mood.

Tables 5.5a and 5.5b present the results of the unadjusted and adjusted multinomial logistic regression analyses, respectively. Independent variables of disease activity, pain and function were entered into separate analyses with outcome variables for change in mood. Changes were defined according to MCIDs for depression and anxiety. Full tables including all of the potential confounding variables are provided in Appendix A.12.

Increased disease severity was significantly associated with improvement in anxiety across all of the disease measures in the unadjusted analyses. When adjusting for other covariates, all associations became non-significant. Similarly, all of the analyses with depression were not significant.

Table 5.5a: Unadjusted association of baseline disease severity with changes in depression and anxiety in patients with AS over six months

	Change in mood status[a]			
	Depression (HADS-D) [a]		**Anxiety (HADS-A)** [b]	
Independent variable	**Deterioration** (n=183)	**Improvement** (n=181)	**Deterioration** (n=186)	**Improvement** (n=188)
Disease activity (BASDAI)	1.03 (0.93-1.13)	1.05 (0.96-1.16)	1.08 (0.97-1.19)	1.13 (1.03-1.25)*
Function (BASFI)	1.04 (0.96-1.14)	1.05 (0.96-1.15)	1.03 (0.95-1.13)	1.09 (1.00-1.19)*
Pain (NRS)	0.98 (0.89-1.07)	1.00 (0.92-1.10)	1.06 (0.96-1.17)	1.13 (1.03-1.25)*

[f]Reference category: stable; Change defined according to minimal important differences (MCIDs) for each measure. [a]MCID 0.46; [b]MCID 0.56.
*=p value <0.05

Table 5.5b: Adjusted association of baseline disease severity with changes in depression and anxiety in patients with AS over six months

	Change in mood status[a]			
	Depression[♦]		**Anxiety**[♦]	
Independent variable	**Deterioration** (n=183)	**Improvement** (n=181)	**Deterioration** (n=186)	**Improvement** (n=188)
Disease activity (BASDAI)	1.01 (0.88-1.15)	1.02 (0.89-1.17)	1.07 (0.93-1.24)	1.08 (0.94-1.25)
Function (BASFI)	1.10 (0.96-1.26)	1.09 (0.95-1.25)	0.98 (0.85-1.12)	1.01 (0.88-1.17)
Pain (NRS)	0.94 (0.83-1.06)	0.94 (0.83-1.07)	1.05 (0.92-1.20)	1.09 (0.95-1.24)

[f]Reference category: stable; Change defined according to minimal important differences (MCIDs) for each measure. [a]MCID 0.46; [b]MCID 0.56. *p value <0.05
[♦] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation

Note: AS = Ankylosing Spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain. BASDAI = Bath AS Disease Activity Index; NRS = numerical rating scale; BASFI = Bath AS Functional Index.

5.5 Summary

Responders to the six month questionnaire were significantly older than the non-responders, with longer disease durations and higher levels of unemployment. Follow-up responders also had significantly lower levels of baseline anxiety than non-responders; however, there was no significant difference in baseline depression scores.

The majority of patients in this study reported stable levels of disease activity (58.6%) and function (51.9%) according to minimal clinically important changes over six months. Pain was more variable, with only one third of patients reporting stable pain scores (32.1%). However, only a minority of patients reported stable depression (21.2%) and anxiety (19.0%) scores.

There was no significant bivariate association between mean baseline mood scores and deterioration or improvement in any of the measures of disease status. Similarly, there was no significant association between mean baseline disease status scores and changes in mood. No linear trend was found in any of the analyses.

This was consistent with the findings of the multinomial logistic regression analyses, where results were mostly non-significant. The only significant adjusted association was found between increasing baseline anxiety scores and improvement in disease activity. Although this result was contradictory to clinical expectations, the association was undoubtedly small (OR 1.08, 95% CI 1.01-1.16) and may also be related to other unmeasured variables.

CHAPTER 6

Discussion and Conclusions

This study has investigated the cross-sectional and prospective relationships of depression and anxiety with disease severity in patients with ankylosing spondylitis (AS). This Chapter presents a review of the aims and principle findings from parts (I) and (II) of this thesis, with a critical appraisal of the strengths and limitations of each chosen methodology. Finally, there is a discussion on the practical implications of these findings, both for clinical practice and future research.

6.1 Part I: literature review

The main aim of the literature review was to summarise the existing evidence on the prevalence of depression and anxiety in patients with AS, and their associations with disease severity.

6.1.1 Principle findings and gaps in current literature

The prevalence of possible or mild depression and anxiety was estimated at 23-36% and 45-57%, respectively. Both depression and anxiety have been shown to demonstrate stable correlations with disease severity over time. However, there are no studies which have examined the reciprocal relationships of mood and disease severity, either cross-sectionally or longitudinally. Existing studies have also considered a limited number of potential predictive variables.

There are currently no studies that have considered the combined impact of depression and anxiety for patients with AS, although studies among the general population highlight the frequent co-existence of both symptoms (Sartorius et al, 1996). Despite estimates for

anxiety being consistently higher than those for depression in AS patients, the majority of existing studies have considered depression only.

6.2 Part II: Cross-sectional and prospective cohort studies

The analyses reported in this thesis were based on a six-month observational study of AS patients. The baseline data from this study was used to determine the unique and combined associations of a) depression and anxiety on disease severity; b) disease severity on depression and anxiety. Follow-up responders were then included in the prospective analysis in order to determine the predictive relationships of a) depression and anxiety on disease severity; b) disease severity on depression and anxiety.

6.2.1 Strengths and limitations of the cross-sectional study

The data for this study was derived from a large secondary care cohort of AS patients. Baseline scores for depression, anxiety and AS severity were comparable to those reported by studies within other specialist UK rheumatology centres (Martindale et al, 2006; Barlow et al, 2010). The multicentre design allowed for inclusion of a wide range of urban and rural settings; providing a good representation of AS patients generally seen in rheumatology clinics across the UK.

This study described the disease status of AS patients in relation to three disease-related constructs: disease activity, pain and function. Most of the existing studies have reported only one or two of these factors (Assassi et al, 2010; Baysal et al, 2011). In addition, this is the only study which has examined the disease severity of AS patients with mixed depression and anxiety, although the co-existence of both symptoms is undoubtedly common. The categorisation of patients into exclusive mood groups allowed for the observation of the unique and combined relationships of depression and anxiety with each measure of disease severity.

The main limitation of this study was the unavailability of clinical data to validate patient-reported outcome measures (PROMs). Clinician administered assessments such as the Bath AS Metrology Index (BASMI) could have provided an objective estimation of AS severity. In addition, depression and anxiety could have been further confirmed by diagnostic interviews such as the DSM-IV and ICD-10.

It should be considered that questionnaires may not be flexible enough for patients to express specific problems they experience and that they would normally report. Patients may also exaggerate or under-report the severity of symptoms such as pain and functional limitation according to their current mood, social circumstances and what they feel is socially or medically desirable. Self-report measures tend to not be completed by those patients who have limited levels of literacy, which may exclude patients with low levels of education. In addition, it is not possible to confirm whether patients have understood each survey item or completed each measure independently.

As this was a large cohort study, clinical data would have been provided by different assessors, which without significant efforts to ensure assessment homogeneity, may have been a less reliable method than selecting outcomes reported consistently by patients. Furthermore, the use of postal questionnaires allowed for the inclusion of a large and geographically diverse selection of patients; thus further increasing the generalisability of the study. Furthermore, all of the PROMs used in this study have been previously validated according to clinical assessment measures.

6.2.2 Principle findings of the cross-sectional study

This thesis has served to illustrate the complexity of the relationship between mood and disease severity in AS patients. Several socio-demographic variables were identified as risk factors for mood disturbance; the principle factors being unemployment and deprivation. Depression was positively associated with increased disease activity, pain and functional impairment, whereas anxiety was associated with increased disease

activity and pain. These relationships were reciprocal, with significant associations found with disease severity on depression and anxiety.

The greatest association was found between mixed depression and anxiety and disease activity. This association was almost twice that observed for pain, even though the measure for disease activity encompassed questions pertaining to pain. This highlighted the association of mood disturbance on the other measured aspects of disease activity, such as stiffness and fatigue. Interestingly, conventional arguments concerning mood disturbance in chronic physical illness have often focussed specifically on the disruptive psychological impact of pain (Bair et al, 2003).

The cross-sectional association between mood disturbance and functional impairment was somewhat different that than observed with disease activity and pain; where the association was found to be specifically with depression. This might be explained by both depression and functional impairment being slow evolving symptoms, with limited short-term fluctuation. Furthermore symptoms of depression, such as low mood and anhedonia, may prevent patients from keeping active: an important component to maintaining good physical function.

When considering the results for patients with mixed depression and anxiety, it is clinically important to consider that the patients within this group had higher mean scores than those patients with depression or anxiety only. Therefore, increased disease severity in these patients may be due to the co-existence of mood symptoms; an increased severity of mood symptoms; or a combination of both.

6.2.3 Strengths and limitations of the prospective cohort study

A limited number of studies have examined the predictive relationships between depression and anxiety with AS severity. In order to thoroughly explore these relationships, this study adopted a twofold approach to the analysis. Firstly, the effect of

baseline depression and anxiety on changes in disease severity was analysed. Secondly, the effect of baseline disease severity on changes in depression and anxiety was examined. Previous studies have focussed on the former association only (Baysal et al, 2009).

The main limitation of the prospective cohort study was that it re-assessed mood at only one further time point. Additional information concerning the cause and effect of changes in mood and disease status may have been gained from a longer follow-up period containing measurements at multiple time points. However, as no other such studies have been reported, the results from this study will be useful for informing the planning and implementation of future prospective studies in this area.

It must also be considered that follow-up responders were significantly older; had longer disease durations and higher levels of unemployment than non-responders. In addition, follow-up responders had significantly lower levels of baseline anxiety than non-responders; suggesting that the full impact of anxiety on AS severity may not have been captured. However, there was no significant difference in the baseline depression scores of responders and non-responders.

6.2.4 Principle findings of the prospective cohort study

Disease activity and function were stable for the majority of AS patients over a period of six months. This was consistent with the findings of Robertson and Davis (2004) who reported a non-significant mean change in disease activity and a slow decline in function over five years. Brophy et al (2006) also reported detectable radiographic changes in AS patients only after two years, with slow disease progression over a ten year period. Pain, depression and anxiety, on the other hand, were more variable; with only a minority of patients reporting stable scores over six months.

Despite clinically significant changes for some patients, there was no longitudinal association between changes in depression and anxiety and any of the measures of disease severity. Although perplexing, there are several logical explanations for this. Firstly, the causal relationships between mood and disease severity may take longer than six months to become evident. Secondly, other unmeasured modifying factors, such as coping mechanisms, may play a role. Finally, it must be considered that a predictive association between mood and disease status may not exist. However, this latter explanation appears unlikely due to the strong independent associations found between all of the measures of mood and disease severity at baseline.

6.3 Clinical implications of findings

Cross-sectional findings suggest that patients with depression or anxiety have increased disease severity. The co-occurrence of depression and anxiety not only increases this likelihood, but also increases the risk of having more severe mood disturbance. Therefore, management for both physical AS-related and mood-related symptoms should be considered. Potential contributors to disease severity are important to target in AS patients, as disease activity and functional impairment have been significantly associated with increased personal and societal costs (Rafia et al, 2012).

Both anxiety and depression should be considered in patients with increased disease activity and pain. However, symptoms specific to depression are likely to be of more importance in patients with predominantly functional impairment. Previous studies have reported significant associations between depression and non-adherence (Grenard et al, 2011). This may be particularly relevant in AS patients, where participation in physical therapy is essential to preventing further functional deterioration. In addition, clinicians should account for the socio-demographic status of each patient, in order to effectively target individuals at increased risk, e.g. unemployed patients.

As no longitudinal association between mood and disease severity was found, the evidence from this study suggests that symptoms relating to mood and AS-severity should be treated independently if the aim of treatment is to achieve an improvement in both over a period of six months.

6.4 Recommendations for future research

Future studies should consider longer follow-up periods in order to further explore the temporal relationships between mood and AS severity. Whenever possible, other moderating factors, such as social class and employment, should be considered. In order for significant mean changes in both disease activity and function to develop, a five year study period may be required. Otherwise, interventional studies of physiotherapy or pharmacological interventions may provide a practical means of eliciting change in disease status within a shorter period of time.

6.5 Summary

This study has shown that there is a high prevalence and frequent co-existence of depression and anxiety in patients with AS. Both depression and anxiety have been found to demonstrate significant independent associations with increased disease activity, pain and functional impairment. Findings suggest that patients with mixed depression and anxiety have worse disease outcomes, although this may, in part, reflect the increased severity of mood disturbance when the conditions co-exist.

This research highlights the importance of treating symptoms of both AS and mood disturbance in clinical practice. Although mixed depression and anxiety carries the majority of clinical impact, patients with isolated severe anxiety or depression still need to be identified and treated. Further research to determine which variables play a causative role in mood disturbance over time will be crucial in targeting care.

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Appendix A.1

Systematic review protocol

Title of the review	What are the rates of Anxiety and Depression in patients with ankylosing spondylitis (AS)?
First reviewer	Nicola Cooper-Moss (NCM)
Team of reviewers	Dr. Jon Packham (JP) Dr. Vicky Strauss (VS)
Supervisors	Dr. J. Packham Dr. V. Strauss
Project title	The cause and effect of mood disturbance in patients with ankylosing spondylitis.

Background to review
Anxiety and depression are common features of other inflammatory disorders such as Rheumatoid Arthritis (RA). The evidence for depression and anxiety in AS is less robust than RA, although the same clinical factors exist in both disease. Currently there are no published completed or on-going systematic reviews in this area. There is the need to review the existing literature in order to summarise the prevalence of depression and anxiety in patients with AS. Furthermore, the review will aim to identify gaps in the current research, in order to inform secondary analysis of a large postal survey of AS patients at baseline and six months.

Research questions
What is the risk of depression and anxiety associated with AS? How is the prevalence of depression and anxiety in AS affected by how mood is defined and measured? How does the prevalence of depression and anxiety in AS differ between clinical settings? What are the associations of depression and anxiety with patient- and disease- characteristics?

Criteria for including studies in the review	
Population, or participants and conditions of interest	Patients with ankylosing spondylitis or spondylarthropathy
Interventions or exposures	Anxiety and/or Depression.
Comparisons groups	General Population. Patients with RA.
Outcomes of interest	Understanding of prevalence of depression and anxiety in patients with AS.
Settings	Primary, secondary and tertiary Care. General population. Any geographical location
Study designs	Cohort, case-control, cross-sectional and trials
Languages	All papers with English Abstracts; relevant papers to be considered for translation (Translation of German performed by N.C.M)
Dates of publication	All dates from 1950 to present accepted

Criteria for excluding studies not covered in inclusion criteria
(i) Non-human (ii) Inappropriate study design (reviews and editorials) (iii) Children and adolescents (Age < 16) (iv) Studies only reporting outcomes on personality disorders (v) Patients selected based on disease severity or functional limitation (vi) Patients exposed to surgical intervention as a result of complications related to AS

Search methods	
Electronic databases	**NHS interface:** • MEDLINE • PsycINFO • Cinahl • British Nursing Index (BNI) • Embase **Web of Science:** • Citation Index • Conference proceedings
Other methods used for identifying relevant research	• Contacting experts – initial contact by J.P if required • Reference checking • To check for hard copies of papers not available electronically at Health library (UHNS), Haywood site and Keele University campus library
Journals hand searched	All relevant journals should be picked up by the databases above

Methods of review	
Details of methods	To perform each search individually for separate databases, download onto RefWorks and exclude duplicated articles. Record numbers of relevant titles, abstracts and papers. J.P to second review all included and unsure abstracts, with random sample of included titles. Sort relevant abstracts into 'include, unsure and exclude categories' Searches saved on NHS database systems with second copy of search strategies in word, managed in RefWorks
Quality assessment	Pilot CASP, Newcastle Ottawa and QUIPs tools

Data extraction	Excel/ word to be used **Information to be extracted:** study title, author(s), journal, Pub. Date, source, study group (AS/SpA), patients recruited, number of completers, gender ratios, disease duration, AS diagnostic criteria, inclusion/exclusion criteria of study, recruitment method, location, 1°/2°/3° care, Trial (Y/N), anxiety/depression scale, defined clinical anxiety/depression score, number of patients clinically depressed/anxious, linked studies Reviewed by J. Packham – random sample to be blindly extracted and compared for inaccuracy
Narrative synthesis	**Initial theories** • AS Vs General population: AS is a chronic painful disease and is likely to result in higher rates of anxiety and depression • AS Vs SpA: lower rates of anxiety and depression in SpA due to general diagnosis/ early unspecific symptoms • Primary Vs Secondary/Tertiary care: milder disease in community therefore lower rates of anxiety and depression in community • Trials Vs epidemiological studies: likely to be more severe disease in trials (due to inclusion criteria), therefore greater rates of anxiety and depression **Preliminary Synthesis** • To develop a descriptive paragraph on each relevant study, from data extracted in Excel/word. • Group according to AS/SpA, clinical setting, mood assessment tool, defined cut-off for depression/anxiety. • Tabulate results, with summaries of patient characteristics and any potential bias • Identify similar/linked studies **Exploring relationships** • Frequency distributions according to mood assessment tools and clinical settings **Accessing robustness** • Reflection on discrepancies and uncertainties identified • Contact of authors for interpretation of findings if necessary
Meta-analysis (if feasible)	Meta-analysis to be performed if: • number of relevant studies found and presence of sufficient data, such as sample size • Studies report the means and standard deviations for depression/anxiety scores, with degree of significance reported if studies compare groups
Grading evidence	Evidence to be graded based on the quality appraisal and the following characteristics: Studies with AS higher value than generalised SpA papers Specific anxiety and depression scores higher value than generalised scores Higher value given to increased sample size

Appendix A.2

Full search strategies and results

EMBASE search results

Search number	Search terms	Number of hits
1	(Ankylosing ADJ Spondyl*).ti.ab	10059
2	ANKYLOSING SPONDYLITIS/	14533
3	Spondyloarth*.ti,ab	3456
4	Spondylarth*.ti,ab	1917
5	Spondylitis.ti,ab	12040
6	Exp SPONDYLARTHRITIS/	428
7	SPONDYLARTHROPATHIES/	3267
8	SPONDYLITIS/	3846
9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8	23741
10	Depress*.ti,ab	306268
11	Exp DEPRESSION/	247814
12	Affective.ti,ab	37865
13	(Affect* ADJ disorder*).ti,ab	14365
14	Exp AFFECT/	34263
15	Mood*.ti,ab	47815
16	Exp MOOD/	17748
17	Exp MOOD DISORDER/	269976
18	Exp MOOD DISORDERS/	269976
19	Exp MOOD DISTURBANCE/	269976
20	Neurotic*.ti,ab	11378
21	Neurosis.ti,ab	4265
22	Neuroses.ti,ab	2380
23	Exp NEUROSIS/	46959
24	Anxiet*.ti,ab	109980
25	Anxious*.ti,ab	11466
26	Exp ANXIETY/	86032
27	Exp ANXIETY DISORDER/	112381
28	Exp ANXIETY NEUROSIS/	8414
29	Emotion*.ti,ab	106659
30	Exp EMOTION/	269229
31	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30	761072
32	9 AND 31	401

Medline search results

Search number	Search terms	Number of hits
1	(Ankylosing ADJ Spondyl*).ti.ab	8401
2	ANKYLOSING SPONDYLITIS/	10548
3	Spondyloarth*.ti,ab	2727
4	Spondylarth*.ti,ab	1560
5	Spondylitis.ti,ab	10178
6	SPONDYLARTHRITIS/	474
7	SPONDYLARTHROPATHIES/	604
8	SPONDYLITIS/	2890
9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8	18009
10	Depress*.ti,ab	270601
11	Exp DEPRESSION/	62543
12	Exp DEPRESSIVE DISORDER/	71152
13	Affective.ti,ab	32178
14	(Affect* ADJ disorder*).ti,ab	12093
15	Exp AFFECT/	22409
16	AFFECTIVE SYMPTOMS/	9946
17	Mood*.ti,ab	39069
18	Exp MOOD DISORDERS/	101142
19	Neurotic*.ti,ab	10048
20	Neurosis.ti,ab	3813
21	Neuroses.ti,ab	2375
22	NEUROTIC DISORDERS/	14962
23	Anxiet*.ti,ab	89579
24	Anxious*.ti,ab	9385
25	Exp ANXIETY/	46878
26	Exp ANXIETY DISORDERS/	57864
27	Emotion*.ti,ab	90272
28	Exp EMOTIONS/	142467
29	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29	573034
30	9 AND 30	167

CINAHL search results

Search number	Search terms	Number of hits
1	(Ankylosing ADJ Spondyl*).ti.ab	727
2	ANKYLOSING SPONDYLITIS/	847
3	Spondyloarth*.ti,ab	277
4	Spondylarth*.ti,ab	95
5	Spondylitis.ti,ab	793
6	Exp SPONDYLARTHRITIS/	1433
7	SPONDYLARTHROPATHIES/	62
8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	1678
9	Depress*.ti,ab	38739
10	Exp DEPRESSION/	35399
11	Affective.ti,ab	4324
12	(Affect* ADJ disorder*).ti,ab	1277
13	AFFECT/	3495
14	Exp AFFECTIVE DISORDERS/	37324
15	AFFECTIVE SYMPTOMS/	878
16	Mood*.ti,ab	7379
17	Neurotic*.ti,ab	694
18	Neurosis.ti,ab	179
19	Neuroses.ti,ab	30
20	NEUROTIC DISORDERS/	280
21	Anxiet*.ti,ab	19334
22	Anxious*.ti,ab	1654
23	Exp ANXIETY/	12221
24	Exp ANXIETY DISORDERS/	12491
25	Emotion*.ti,ab	26031
26	Exp EMOTIONS/	39087
27	9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26	118443
28	8 AND 27	37

PsychINFO search results

Search number	Search terms	Number of hits
1	(Ankylosing ADJ Spondyl*).ti.ab	67
2	Spondyloarth*.ti,ab	7
3	Spondylarth*.ti,ab	10
4	Spondylitis.ti,ab	77
5	1 OR 2 OR 3 OR 4	89
6	Depress*.ti,ab	177587
7	Exp “DEPRESSION (EMOTION)”/	20095
8	Exp MAJOR DEPRESSION/	76533
9	Affective.ti,ab	55257
10	(Affect* ADJ disorder*).ti,ab	12780
11	Exp AFFECTIVE DISORDERS/	99862
12	Mood*.ti,ab	43713
13	Neurotic*.ti,ab	23668
14	Neurosis.ti,ab	7778
15	Neuroses.ti,ab	4798
16	Exp NEUROSIS/	7145
17	Exp NEUROTICISM/	3579
18	Anxiet*.ti,ab	114252
19	Anxious*.ti,ab	13418
20	Exp ANXIETY/	43370
21	Exp ANXIETY DISORDERS/	51451
22	Emotion*.ti,ab	178136
23	Exp EMOTIONAL STATES/	173084
24	6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23	448234
25	5 AND 24	21

British Nursing Index (BNI) search results

Search number	Search terms	Number of hits
1	(Ankylosing ADJ Spondyl*).ti.ab	23
2	Spondyloarth*.ti,ab	3
3	Spondylarth*.ti,ab	0
4	Spondylitis.ti,ab	22
5	1 OR 2 OR 3 OR 4	26
6	Depress*.ti,ab	4181
7	Exp DEPRESSION/	2829
8	Affective.ti,ab	193
9	(Affect* ADJ disorder*).ti,ab	99
10	Mood*.ti,ab	387
11	Neurotic*.ti,ab	26
12	Neurosis.ti,ab	11
13	Neuroses.ti,ab	4
14	Exp “NEUROSES AND PHOBIAS”/	210
15	Anxiet*.ti,ab	2135
16	Anxious*.ti,ab	54
17	Emotion*.ti,ab	2625
18	Exp EMOTIONS/	1816
19	6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20	10179
20	5 AND 21	1

Appendix A.3

Guidance for quality appraisal of full-text articles

Question	Guidance for marking
1	The population is adequately described if the following participant characteristics are provided: age, disease duration, gender proportions and diagnostic criteria (e.g. MNY criteria). If one or two of these are absent mark as 'partly'. If three or more are absent mark as 'no'.
2	The sampling frame and recruitment are adequately described if the study provides the following details: setting for recruitment (e.g. clinic), method of study invitation (e.g. letter) and method of sampling (e.g. simple randomisation). If one or two of these are absent mark as 'partly'. If all are absent mark as 'no'.
3	If details are only given for either the exclusion or inclusion criteria mark as 'partly'. If neither are described mark as 'no'.
4	The outcome of interest is adequately described if there is a clear description of the depression/anxiety tool used (e.g. 18-item tool) and reference to what is being assessed (e.g. current somatic and cognitive symptoms). If only one is provided mark as 'partly'. If neither is provided, mark as 'no'.
5	The outcome measure is valid if there is evidence of other studies which have analysed the psychometric properties of the measure on patients with physical illness or chronic pain. If the measure has only been validated within a single study, mark as 'partly'. All studies should be marked as 'Yes' or 'partly', as studies containing invalid measures should have already been excluded.
6	The clinical significance is adequately described if a definition of possible or clinical depression/anxiety is given, with a clear cut-off score. This also applies to 'severe', 'moderate' and 'mild' classifications. If only a definition or cut-off score is provided, mark as 'partly' If neither are provided, mark as 'no'.
7	The important confounders include: disease activity/functional limitation, social deprivation, a history of previous depression or anxiety, another co-existing chronic illness, and current medication. Mark as 'yes' if three are considered. Mark as 'partly' if two are considered. Mark as 'no' if one or less considered.
8	If one of the clinical confounders is found within the exclusion criteria mark as 'partly'. If two or more of the clinical confounders are excluded mark as 'no'.
9	Presentation of data is sufficient if: 1) Average scores are reported with an appropriate measure of dispersion. 2) The sample size is indicated for analysed data. 3) Numbers and proportions of depressed or anxious participants are provided. If one of these is absent, mark as 'partly'. All studies should be marked a 'Yes' or 'Partly', as studies which do not adequately report depression or anxiety outcomes should have already been excluded.
10	If results are presented separately for different groups of interest (eg. intervention groups) with sufficient data to combine results, mark as 'partly'. If there is not sufficient data to combine results, mark as 'no'.

Appendix A.4

Study characteristics and mood assessment tools used in 36 original studies included in the systematic review

Reference, first author (year)	AS/SpA Criteria	Study Population	Inclusion (I)/ Exclusion (E) criteria	Sample Size (n)	% male	Age, years ± SD if reported	Disease duration, years ± SD if reported	Depression tool	Anxiety Tool
Analay et al (2003)	Amor	Outpatient clinics, Istanbul, Turkey	I - age 18-55, no regular exercise in 3 month E - systemic disease, reduced hip/knee movement, DMARDS	45	84	mean 35.99	Not reported	BDI	Not reported
Assassi et al (2009, 2010, 2011)	MNY	Outpatient clinics, self-help group, internet advert, USA	I – age ≥18 E – not reported	294	67	mean 45.1 ± 14.40	mean 21.2 ± 13.85	PHQ-9	Not reported
Barlow et al (1993, 1994)	ACR	Outpatient clinics, self- help groups, AS symposium,UK	I - not reported E - not reported	177	73	mean 43.79	mean 19.15	CES-D	Not reported
Barlow et al (2001)	ACR + clinical	NAAS, outpatient clinics	I - age 16-65 E -diagnosis > age 40	133	73	mean 49	mean 28	HADS-D	HADS-A
Barlow et al (2010)	Criteria not reported	Outpatient clinics, Coventry and Warickshire UK	I - not reported E -not reported	29	86	mean 47.9 ± 11.8	Not reported	HADS-D	HADS-A
Basler and Rehfisch (1989, 1991)	clinical diagnosis	Rheumatism league self-help group members, Germany	I – not reported E- not reported	39	56	mean 44.5	mean 14.98	Von Zerssen	STAI
Baysal et al (2011)	MNY	5 hospital outpatient clinics east Turkey	I – not reported E - other serious illness	243	86	mean 34.65 ± 10.36	mean 6.02 ± 6.60	HADS-D	HADS-A

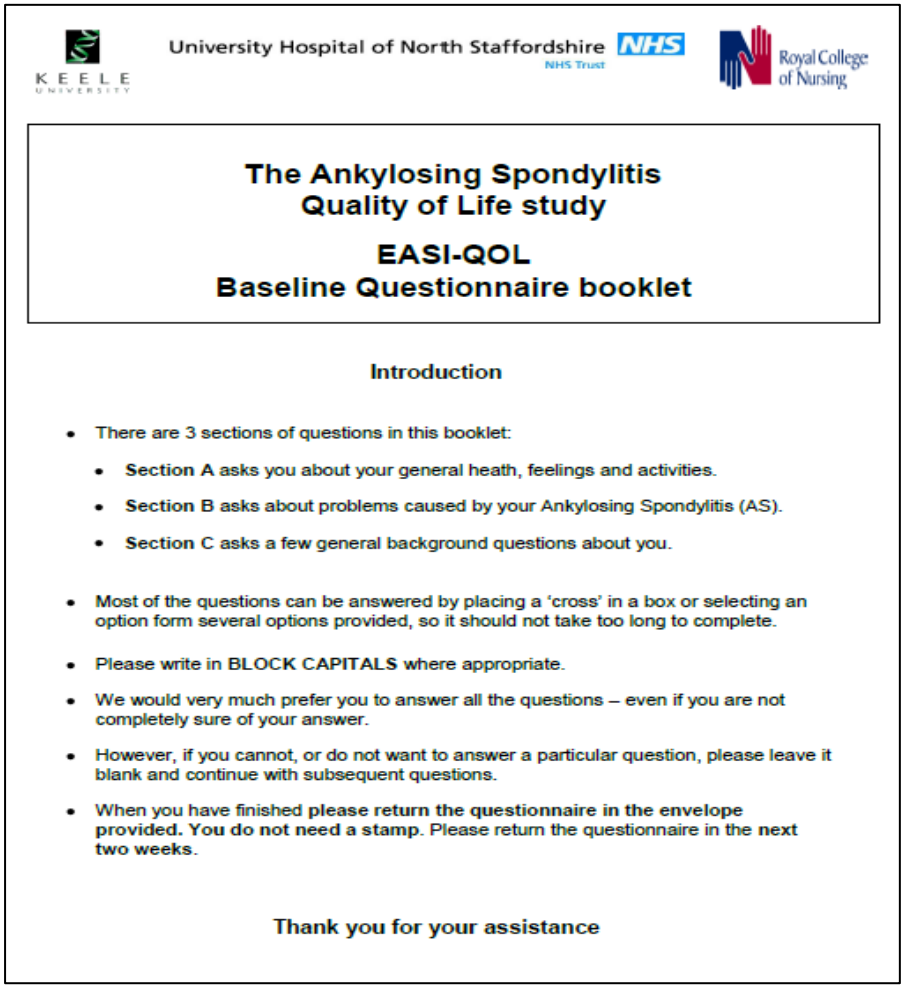
Continued									
Bodur et al (2011)	MNY	Outpatient clinics Ankara, Turkey	I - age 16-65 E - diagnosis > age 40	54	80	mean 35.9 ± 9.2	mean 10.5 ± 7.7	BDI	Not reported
Bradna et al (2004)	Criteria not reported	Czech Republic, Clinical setting not reported	I – not reported E – not reported	33	Not reported	Mean 46.7	Mean 19	Zung	Not reported
Cagliyan et al (2007)	MNY	Outpatient clinics Turkey	I - tolerate exercise E - lumbar disc herniation pain, co-morbidity, systemic disease/infection	46	83	mean 36.04 ± 8.62	mean 7.54	BDI	Not reported
Cakar et al (2007)	MNY	Military medicine academy, Turkey	I - sexually active, age ≥ 18 E - Systemic locomotor disorder, co-morbidity	53	100	mean 35.85 ± 12.11	mean 9.09 ± 7.36	BDI	Not reported
Cakar et al (2009)	MNY	Military medicine academy, Turkey	I - military service E- not reported	121	100	mean 31.6 ± 10.5	mean 9.1 ± 6.9	BDI	Not reported
Cay et al (2011)	ESSG	Outpatient clinics, Antalya, Turkey	I - live in Antalya, comprehend E - learning disability, psychotropic drugs, renal/hepatic impairment	15	Not reported	mean 43.5 ± 10.8	mean 10.3 ± 9.6	BDI	Not reported
Da Costa et al (2009, 2011)	ESSG	Outpatient and satellite community clinics, Canada	I - age ≥18 E - inability to comprehend English/French, pregnancy	125	46	mean 46.5 ± 12.5	mean 12.7 ± 11.6	CESD-AR	Not reported
Dincer et al (2007)	MNY	Outpatient clinics, Turkey	I - sexually active E - systemic disease, hip OA, psychiatric disorder	68	100	mean 32.9 ± 11.0	Not reported	BDI	Not reported
Durmus et al (2009)	MNY	Turkey, clinical setting not reported	I - no regular exercise in 6 month E – systemic disease, a-TNF	43	81	mean 39.42	mean 9.55	BDI	Not reported
Guenther et al (2010)	AS – criteria not reported	Spa santorium, Austrian AS association, Austria	I – not reported E – not reported	56	55	median 52.50 (IQR 41.25-60.00)	median 25 (IQR 17.00-32.75)	Von Zerssen	Not reported
Gunaydin et al (2009)	MNY	Outpatient clinics, Turkey	I - not reported E - fibromyalgia, cancer/other chronic illness	62	84	mean 39.6 ± 10.3	median 8 (IQR 1-35)	Zung	Not reported

Continued									
Hamilton-West and Quine(2007)	AS - clinical	NASS and outpatient clinics	I - daily pain, age ≥18, E - not reported	68	66	mean 52	mean 16	HADS-D	HADS-A
Healey et al (2006, 2009, 2010, 2011)	MNY	Postal survey 10 UK specialist outpatient centres	I – understand English E - learning disability, pregnancy	612	72	mean 50.8 ± 12.2	mean 17.3 ± 11.7	HADS-D	HADS-A
Hider et al (2002)	criteria not reported	NASS and outpatient clinics Cannock, UK	I - not reported E -not reported	40	73	mean 48	mean 13.2	HADS-D	HADS-A
Juanola-Roura et al (2005)	MNY	Single outpatients Spain	I – not reported E – not reported	160	not reported	not reported	not reported	BDI	Not reported
Karapolat et al (2008)	MNY	Outpatient clinics Turkey	I - age 18-75 E - systemic disease, severe co-morbidity, regular exercise in 6 month	38	68	mean 47.12	mean 19.3	BDI	Not reported
Karapolat et al (2009)	MNY	Outpatient clinics, Turkey	I - age 18-75, able to swim/exercise E - systemic disease, regular exercise, active peripheral arthritis, a-TNF	37	73	mean 48.54	mean 18.94	BDI	Not reported
Karatay et al (2004)	MNY	Turkey Clinical setting not reported	I – not reported E – not reported	27	81	mean 36.51 ± 7.05	mean 7.3 ± 4.9	BDI	Not reported
Kobayashi-Gutierrez et al (2009)	ACR	Outpatient clinics Mexico	I –age ≥ 18 E - ≥2 diagnoses, cancer, pregnancy, substance abuse, AntiD use, neuropathic pain	18	not reported	not reported	not reported	CES-Dr	Not reported
Lim et al (2005)	Criteria not reported	Bulletin advert at exercise program, outpatients, korea	I – no regular exercise in 6 months E - systemic disease	50	78	mean 28.45	mean 8.9	BDI	Not reported
Marengo et al (2008)	MNY	Tertiary centre, Argentina	I – age ≥16 E - housewives, students	64	89	median 43 (IQR33-52)	not reported	CES-D	Not reported

Continued									
Martindale et al (2006, 2010)	MNY	Single hospital review group, Lancashire, UK	I - booked appointment E - other serious illness, pregnancy	89	83	median 50 (IQR 38.5-55.5)	median 18 (IQR 13-27)	HADS-D	HADS-A
Ortancil et al (2010)	MNY	Outpatient clinics, Turkey	I – not reported E – other systemic diseases, psychiatric disorder	29	69	mean 42.0 ± 1.8	mean 9.4 ± 7.7	SCL-90-R	SCL-90-R
Pirildar et al (2004)	MNY	Outpatient clinics, Turkey	I - age 26-50, living with partner E - penile defects, co-morbid physical/ psychiatric disorder	65	100	mean 36 ± 8.1	mean 12.2 ± 6.4	BDI	Not reported
Pritchard et al (2010)	Not reported	Outpatient clinics, UK	I – not reported E- not reported	73	89	Median 49 (IQR 42-57)	Not reported	HADS-D	HADS-A
Rau et al (2008)	Not reported	Rehabilitation clinic outpatients, Germany	I - pain duration >3m, E – poor German	27	Not reported	Not reported	Not reported	HADS-D	HADS-A
Roussou et al (1997)	criteria not reported	NASS, Outpatients from the royal national hospital, UK	I – age ≤55 E- not reported	100	100	mean 43.25	mean 21.35	AIMS	AIMS
Ward (1999)	MNY	Outpatient clinics and community advertisement, USA	I – age ≥18 E- IBD	175	68	mean 51.1 ± 14.0	mean 23.7 ± 14.3	Question-naire	Question-naire
Yang et al (2010)	Criteria not reported	Clinical setting not reported, China	I - not reported E – not reported	1224	Not reported	Not reported	Not reported	Zung	Zung

Note: AS = ankylosing spondylitis; NAAS = national ankylosing spondylitis society; SD=standard deviation; IQR = interquartile range, MNY = modified New York, ESSG=European SpA study group; ACR: American College of Rheumatology.

Appendix A.5



KEELE UNIVERSITY

University Hospital of North Staffordshire NHS Trust

Royal College of Nursing

The Ankylosing Spondylitis Quality of Life study

EASI-QOL
Baseline Questionnaire booklet

Introduction

- There are 3 sections of questions in this booklet:
  - **Section A** asks you about your general heath, feelings and activities.
  - **Section B** asks about problems caused by your Ankylosing Spondylitis (AS).
  - **Section C** asks a few general background questions about you.
- Most of the questions can be answered by placing a 'cross' in a box or selecting an option form several options provided, so it should not take too long to complete.
- Please write in **BLOCK CAPITALS** where appropriate.
- We would very much prefer you to answer all the questions – even if you are not completely sure of your answer.
- However, if you cannot, or do not want to answer a particular question, please leave it blank and continue with subsequent questions.
- When you have finished **please return the questionnaire in the envelope provided. You do not need a stamp.** Please return the questionnaire in the **next two weeks.**

Thank you for your assistance

KEELE UNIVERSITY

University Hospital of North Staffordshire NHS Trust

Royal College of Nursing

EASI-QOL:

The Ankylosing Spondylitis Quality of Life study
Consent Form Version 4 dated 30/04/07

If you feel able to take part in this research study, please complete your name and address below, before returning this form with the completed questionnaire.

Name:.....**Date of birth:** ...../...../.....

Address:.....

.....

Post Code:.....**Telephone Number:** .....

- I fully and freely consent to participate in the study: 'The Ankylosing Spondylitis Quality of Life Study'
- I understand and acknowledge that the study is designed to improve medical understanding of the way in which people with AS are affected by the disease, and how this can be measured.
- I note that I may withdraw my consent to take part at any stage in the study.
- I have received a written explanation (information sheet Version 4, 31st January 2007) of the study and understand the requirements of my participation.

Signed: ..... **Date:** .....

Many thanks for your assistance.
The information that you provide will be very helpful to us.

If you *do not* wish to take part in the study please return the blank questionnaire booklet in the pre-paid envelope.

Many thanks for your time and consideration.

SECTION A – YOUR GENERAL HEALTH

This section is made up of questions about your health, the activities you do, and some of the ways in which people do things in everyday life.

Please answer each set of questions as the instructions ask you to.

Part 1

Your overall health

The following questions ask you for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer each question by marking a cross in the box that best describes your answer.

1. In general, would you say your health is:
(Please put a cross in one box only)

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

2. **Compared to one year ago,** how would you rate your health in general **now**?
(Please put a cross in one box only)

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐	☐	☐	☐	☐

3. The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?
(Please put a cross in one box on each line)

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a)	**Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b)	**Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
c)	Lifting or carrying groceries	☐	☐	☐
d)	Climbing **several** flights of stairs	☐	☐	☐
e)	Climbing **one** flight of stairs	☐	☐	☐
f)	Bending, kneeling or stooping	☐	☐	☐
g)	Walking **more than a mile**	☐	☐	☐
h)	Walking **several hundred yards**	☐	☐	☐
i)	Walking one hundred yards	☐	☐	☐
j)	Bathing and dressing yourself	☐	☐	☐

4. During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?
(Please put a cross in one box on each line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐
d) Had **difficulty** performing the work or other activities (for example, it took extra effort)	☐	☐	☐	☐	☐

5. During the **past 4 weeks**, how much time have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?
(Please put a cross in one box on each line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Did work or other activities **less carefully** as usual	☐	☐	☐	☐	☐

6. During the **past 4 weeks**, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?
(Please put a cross in one box only)

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

7. How much **bodily** pain have you had during the **past 4 weeks**?
(Please put a cross in one box only)

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?
(Please put a cross in one box only)

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.
(Please put a cross in one box on each line)

How much of the time during the **past 4 weeks**...	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Did you feel full of life?	☐	☐	☐	☐	☐
b) Have you been very nervous?	☐	☐	☐	☐	☐
c) Have felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐
d) Have you felt calm and peaceful?	☐	☐	☐	☐	☐
e) Did you have a lot of energy?	☐	☐	☐	☐	☐
f) Have you felt downhearted and low?	☐	☐	☐	☐	☐
g) Did you feel worn out?	☐	☐	☐	☐	☐
h) Have you been happy?	☐	☐	☐	☐	☐
i) Did you feel tired?	☐	☐	☐	☐	☐

10. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?
(Please put a cross in one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

11. How TRUE or FALSE is **each** of the following statements for you?
(Please put a cross in one box on each line)

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get ill more easily than other people	☐	☐	☐	☐	☐
b) I am as healthy as anybody I know	☐	☐	☐	☐	☐
c) I expect my health to get worse	☐	☐	☐	☐	☐
d) My health is excellent	☐	☐	☐	☐	☐

Part 2

By placing a cross [X] in one box in each group, please indicate which statements best describe your own health state **today**.

Mobility
- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-care
- I have no problems with self-care ☐
- I have some problems washing and dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities *(e.g. work, study, housework, family or leisure activities)*
- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort
- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/depression
- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

Part 3

This section of the questionnaire will help you let us know how you are. Read each item and put a cross in the box, which comes closest to how you have been feeling in the **past week.**

Don't take too long over your replies; your immediate reaction will probably be more accurate than a long thought out response.

1. I feel tense or wound up:
- Most of the time ☐
- A lot of the time ☐
- From time to time, occasionally ☐
- Not at all ☐

2. I still enjoy the things I used to enjoy:
- Definitely as much ☐
- Not quite so much ☐
- Only a little ☐
- Hardly at all ☐

3. I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly ☐
- Yes, but not too badly ☐
- A little, but it doesn't worry me ☐
- Not at all ☐

4. I can laugh and see the funny side of things:
- As much as I always could ☐
- Not quite so much now ☐
- Definitely not so much now ☐
- Not at all ☐

5. Worrying thoughts go through my mind:
- A great deal of the time ☐
- A lot of the time ☐
- From time to time but not too often ☐
- Only occasionally ☐

6. I feel cheerful
- Not at all ☐
- Not often ☐
- Sometimes ☐
- Most of the time ☐

7. I can sit at ease and feel relaxed:
- Definitely ☐
- Usually ☐
- Not often ☐
- Not at all ☐

8. I feel as if I am slowed down:
- Nearly all the time ☐
- Very often ☐
- Sometimes ☐
- Not at all ☐

9. I get a sort of frightened feeling like "butterflies" in the stomach:
- Not at all ☐
- Occasionally ☐
- Quite often ☐
- Very often ☐

10. I have lost interest in my appearance:
- Definitely ☐
- I don't take so much care as I should ☐
- I may not take quite as much care ☐
- I take just as much care as ever ☐

11. I feel restless as if I have to be on the move:
- Very much indeed ☐
- Quite a lot ☐
- Not very much ☐
- Not at all ☐

12. I look forward with enjoyment to things:
- As much as I ever did ☐
- Rather less than I used to ☐
- Definitely less than I used to ☐
- Hardly at all ☐

13. I get sudden feelings of panic:
- Very often indeed ☐
- Quite often ☐
- Not very often ☐
- Not at all ☐

14. I can enjoy a good book or radio or TV programme:
- Often ☐
- Sometimes ☐
- Not often ☐
- Very seldom ☐

SECTION B – YOU AND YOUR ANKYLOSING SPONDYLITIS

This section asks you for some details about your Ankylosing Spondylitis (AS) and some of the problems caused by your AS.

Please answer each set of questions as the instructions ask you to.

Part 1

1. Please write down the year you were first **diagnosed** with Ankylosing Spondylitis

☐☐☐☐ e.g. 1998

2. Please write down the number of years that you have had **symptoms** from the Ankylosing Spondylitis

☐☐ years

3. Have you been hospitalised in the previous **3 months** for your Ankylosing Spondylitis?

No ☐ Yes ☐ If '**YES**', how many days were you in the hospital: ☐☐ days

4. Have you made any visits to a Doctor for your Ankylosing Spondylitis (not including study visits or hospitalisations) during the previous **3 months**?

No ☐ Yes ☐ If '**YES**' how many times? ☐☐☐

5. Have you visited a physiotherapist for your Ankylosing Spondylitis (not including hydrotherapy sessions) in the previous **3 months**?

No ☐ Yes ☐

			Number of visits
If '**YES**' was the visit:	NHS	☐	☐☐☐
	Private	☐	☐☐☐
	NASS	☐	☐☐☐

6. Have you attended a hydrotherapy session for your Ankylosing Spondylitis in the previous **3 months**?

No ☐ Yes ☐

			Number of visits
If '**YES**' was the visit:	NHS	☐	☐☐☐
	Private	☐	☐☐☐
	NASS	☐	☐☐☐

7. Are you currently prescribed any of the following medications for your AS? *(Please put a cross in each box that applies)*

Sulphasalazine / Salazopyrin	☐
Methotrexate	☐
Influximab / Remicade	☐
Etanercept / Enbrel	☐
Adalumimab / Humira	☐

Part 2

LIMITATIONS DUE TO YOUR ANKYLOSING SPONDYLITIS

The following questions ask about the problems that your **Ankylosing Spondylitis** has caused you. Please answer every question with a cross.
If you are unsure about how to answer a question, please give the best answer you can.

These questions ask about activities you might do during a typical day.
Does your **Ankylosing Spondylitis** limit you in these activities **today**? If so, how much?
For each question, please cross the **one** response that **applies to you today**.

Please cross one box on each line

	Not limited at all	A little limited	Moderately limited	Very limited	Totally limited / unable to do
1. Lifting a child or **heavy objects** such as shopping or furniture	☐	☐	☐	☐	☐
2. Walking **one mile**	☐	☐	☐	☐	☐
3. Walking **one hundred metres**	☐	☐	☐	☐	☐
4. **Going up or down** one flight of stairs	☐	☐	☐	☐	☐
5. Standing for **30 minutes**	☐	☐	☐	☐	☐
6. Standing for **five minutes**	☐	☐	☐	☐	☐
7. Staying seated for **two hours**	☐	☐	☐	☐	☐
8. Staying seated for **15 minutes**	☐	☐	☐	☐	☐
9. **Lying down** in bed	☐	☐	☐	☐	☐
10. **Changing position** in bed	☐	☐	☐	☐	☐
11. **Getting up** from a sitting position	☐	☐	☐	☐	☐

Does your **Ankylosing Spondylitis** limit you in these activities **today**? If so, how much?
For each question, please cross the **one** response that **applies to you today**.

Please cross one box on each line

	Not limited at all	A little limited	Moderately limited	Very limited	Totally limited / unable to do
12. Finding a **comfortable** position in which you can relax	☐	☐	☐	☐	☐
13. **Drinking** from a small glass or can	☐	☐	☐	☐	☐
14. **Bending down** to pick something up from the floor	☐	☐	☐	☐	☐
15. Wiping yourself after using the **toilet**	☐	☐	☐	☐	☐
16. **Washing** yourself including your hair	☐	☐	☐	☐	☐
17. **Dressing or undressing** yourself	☐	☐	☐	☐	☐

We would now like to ask you questions about the ***past week***. We understand that your Ankylosing Spondylitis may have changed from day to day but we would like you to give a response that shows how you have been ***feeling on average*** over the ***past week***.

Please answer every question with a cross. If you are unsure about how to answer a question, please give the best answer you can.

18. During the **past week**, how much of the time has your Ankylosing Spondylitis interfered with your normal work (including work both outside the home and housework)?

☐ **None of the time** ☐ **A little of the time** ☐ **Some of the time** ☐ **Most of the time** ☐ **All of the time**

19. During the **past week**, how much of the time has your Ankylosing Spondylitis interfered with your hobbies, pastimes or sporting activities?

☐ **None of the time** ☐ **A little of the time** ☐ **Some of the time** ☐ **Most of the time** ☐ **All of the time**

Please answer every question with a cross. If you are unsure about how to answer a question, please give the best answer you can.

20. During the **past week**, how much did your Ankylosing Spondylitis interfere with social activities (like visiting friends, eating out, or going to the cinema or theatre)?

☐ **Not at all** ☐ **A little bit** ☐ **Moderately** ☐ **Quite a bit** ☐ **Extremely**

21. During the **past week**, how much did your Ankylosing Spondylitis interfere with family life or friendships?

☐ **Not at all** ☐ **A little bit** ☐ **Moderately** ☐ **Quite a bit** ☐ **Extremely**

22. During the **past week**, how much of the time have you felt embarrassed or self-conscious because of your Ankylosing Spondylitis?

☐ **None of the time** ☐ **A little of the time** ☐ **Some of the time** ☐ **Most of the time** ☐ **All of the time**

23. During the **past week**, how much did your Ankylosing Spondylitis affect your intimate or sexual relationships? *Please cross one box if applicable*

☐ **Not at all** ☐ **A little bit** ☐ **Moderately** ☐ **Quite a bit** ☐ **Extremely**

24. During the **past week**, how much did your Ankylosing Spondylitis interfere with traveling either by car or public transport (including buses or trains)?

☐ **Not at all** ☐ **A little bit** ☐ **Moderately** ☐ **Quite a bit** ☐ **Extremely**

25. During the **past week**, how much of the time did you feel that your Ankylosing Spondylitis was slowing you down in your daily activities?

☐ **None of the time** ☐ **A little of the time** ☐ **Some of the time** ☐ **Most of the time** ☐ **All of the time**

Please answer every question with a cross. If you are unsure about how to answer a question, please give the best answer you can.

26. During the **past week**, how much of the time do you feel that *you had control* over your Ankylosing Spondylitis?

☐ **All of the time** ☐ **Most of the time** ☐ **Some of the time** ☐ **A little of the time** ☐ **None of the time**

27. During the **past week**, how much of the time has your Ankylosing Spondylitis caused you to worry about the future (including work, caring for others, your social life and staying active)?

☐ **None of the time** ☐ **A little of the time** ☐ **Some of the time** ☐ **Most of the time** ☐ **All of the time**

28. During the **past week**, how much pain or discomfort did your Ankylosing Spondylitis cause you?

☐ **None** ☐ **A little bit** ☐ **Moderately** ☐ **Quite a bit** ☐ **Extreme**

29. During the **past week**, how much of the time have you experienced pain or discomfort because of your Ankylosing Spondylitis?

☐ **None of the time** ☐ **A little of the time** ☐ **Some of the time** ☐ **Most of the time** ☐ **All of the time**

30. During the **past week**, how much did your Ankylosing Spondylitis interfere with your sleep?

☐ **Not at all** ☐ **A little bit** ☐ **Moderately** ☐ **Quite a bit** ☐ **Extremely**

31. During the **past week**, how much of the time have you felt tired or lacking in energy because of your Ankylosing Spondylitis?

☐ **None of the time** ☐ **A little of the time** ☐ **Some of the time** ☐ **Most of the time** ☐ **All of the time**

Please answer every question with a cross. If you are unsure about how to answer a question, please give the best answer you can.

32. During the **past week**, how much did your Ankylosing Spondylitis interfere with your ability to concentrate (including reading, listening to someone talking or watching the television)?

☐ **Not at all** ☐ **A little bit** ☐ **Moderately** ☐ **Quite a bit** ☐ **Extremely**

33. During the **past week**, how much of the time have you lacked drive or motivation because of your Ankylosing Spondylitis?

☐ **None of the time** ☐ **A little of the time** ☐ **Some of the time** ☐ **Most of the time** ☐ **All of the time**

34. During the **past week**, how much morning stiffness did your Ankylosing Spondylitis cause you?

☐ **None at all** ☐ **A little bit** ☐ **Moderately** ☐ **Quite a bit** ☐ **Extreme**

35. During the **past week**, how much did your Ankylosing Spondylitis interfere with doing errands (like shopping, or going to the post office or bank)?

☐ **Not at all** ☐ **A little bit** ☐ **Moderately** ☐ **Quite a bit** ☐ **Extremely**

36. During the **past week**, how much did your Ankylosing Spondylitis interfere with your ability to do jobs around the home including housework or do-it-yourself?

☐ **Not at all** ☐ **A little bit** ☐ **Moderately** ☐ **Quite a bit** ☐ **Extremely**

37. During the **past week**, how much did your Ankylosing Spondylitis interfere with your ability to keep physically active?

☐ **Not at all** ☐ **A little bit** ☐ **Moderately** ☐ **Quite a bit** ☐ **Extremely**

Please answer every question with a cross. If you are unsure about how to answer a question, please give the best answer you can.

38. During the **past week**, how much of the time have you felt frustrated because of your Ankylosing Spondylitis?

☐ **None of the time** ☐ **A little of the time** ☐ **Some of the time** ☐ **Most of the time** ☐ **All of the time**

39. During the **past week**, how embarrassed or self-conscious have you been because of your Ankylosing Spondylitis?

☐ **Not at all** ☐ **A little bit** ☐ **Moderately** ☐ **Quite a bit** ☐ **Extremely**

40. During the **past week**, how much of the time have you felt downhearted or low because of your Ankylosing Spondylitis?

☐ **None of the time** ☐ **A little of the time** ☐ **Some of the time** ☐ **Most of the time** ☐ **All of the time**

41. During the **past week**, have you been concerned about the medication you take for your Ankylosing Spondylitis?

☐ **Not at all** ☐ **A little bit** ☐ **Moderately** ☐ **Quite a bit** ☐ **Extremely**

42. During the **past week**, how much of the time did you feel that your Ankylosing Spondylitis was interfering with the quality of your life?

☐ **None of the time** ☐ **A little of the time** ☐ **Some of the time** ☐ **Most of the time** ☐ **All of the time**

Part 3

On the following pages you will find some statements, which have been made by people who have Ankylosing Spondylitis.

Please read each statement carefully. We would like you to place a cross in the **'Yes'** box if you feel the statement applies to you. And a cross in the **'No'** box if it does not

Please read each item carefully and place a cross in the ***one*** response that applies best to you ***at the moment***

1. My condition limits the places I can go — Yes ☐ No ☐
2. I sometimes feel like crying — Yes ☐ No ☐
3. I have difficulty dressing — Yes ☐ No ☐
4. I struggle to do jobs around the house — Yes ☐ No ☐
5. It's impossible to sleep — Yes ☐ No ☐
6. I am unable to join in activities with my friends/family — Yes ☐ No ☐
7. I am tired all the time — Yes ☐ No ☐
8. I have to keep stopping what I am doing to rest — Yes ☐ No ☐
9. I have unbearable pain — Yes ☐ No ☐
10. It takes a long time to get going in the morning — Yes ☐ No ☐

11. I am unable to do jobs around the house — Yes ☐ No ☐
12. I get tired easily — Yes ☐ No ☐
13. I often get frustrated — Yes ☐ No ☐
14. The pain is always there — Yes ☐ No ☐
15. I feel I miss out on a lot — Yes ☐ No ☐
16. I find it difficult to wash my hair — Yes ☐ No ☐
17. My condition gets me down — Yes ☐ No ☐
18. I worry about letting people down — Yes ☐ No ☐

Part 4

All questions refer to **last week**: *(Please put a cross in one box only)*
(i.e. ☒)

1. How much **pain** have you had because of your Ankylosing Spondylitis during the **last week**?

0	1	2	3	4	5	6	7	8	9	10

no pain — most severe pain

2. How much **pain** at night have you had because of your Ankylosing Spondylitis during the **last week**?

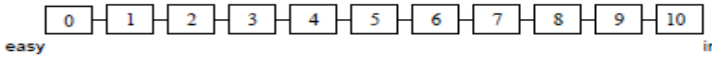
0	1	2	3	4	5	6	7	8	9	10

no pain — most severe pain

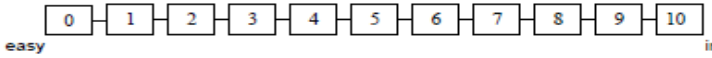
Part 5

Please indicate by placing a cross in the box your level of ability with each of the following activities during **the last week**. *(Please put a cross in one box only)*
(An aid is a piece of equipment, which helps you to perform an action or movement)

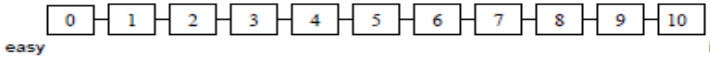
1. Putting on your socks or tights without help or aids (e.g. sock aid).



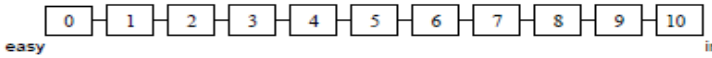
2. Bending forward from the waist to pick up a pen from the floor without an aid.



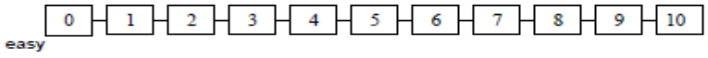
3. Reaching up to a high shelf without help or aids (e.g. helping hand).



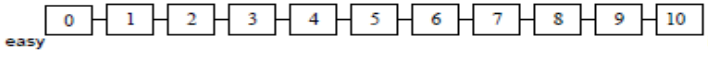
4. Getting up out of an armless dining room chair without using your hands or any other help.



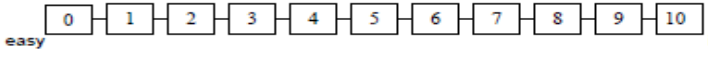
5. Getting up off the floor without help from lying on your back.



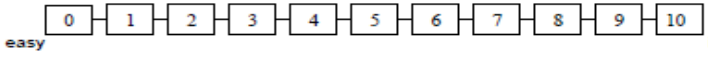
6. Standing unsupported for 10 minutes without discomfort.



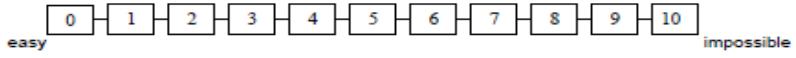
7. Climbing 12-15 steps without using a handrail or walking aid. **One foot at each step**.



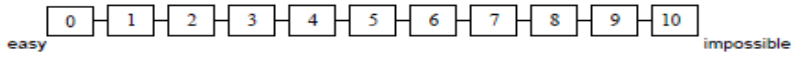
8. Looking over your shoulder without turning your body.



9. Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports).



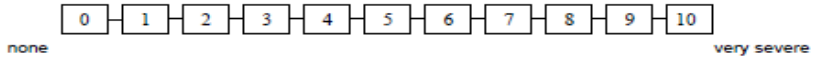
10. Doing a full days activities, whether it be at home or at work.



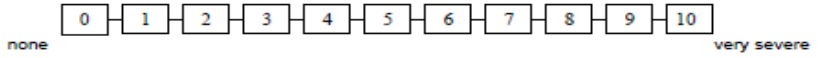
Part 6

All questions refer to **last week**: *(Please put a cross in one box only)*

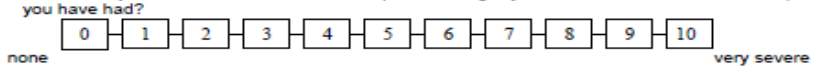
1. How would you describe the overall level of fatigue/tiredness you have experienced?



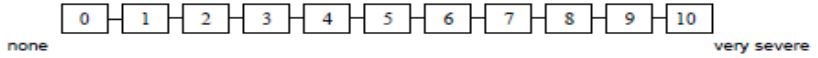
2. How would you describe the overall level of AS **neck, back or hip** pain you have had?



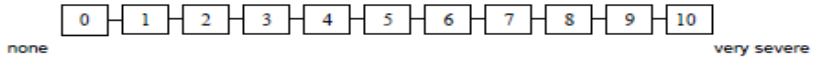
3. How would you describe the overall level of pain/swelling in joints **other than** neck, back or hips you have had?



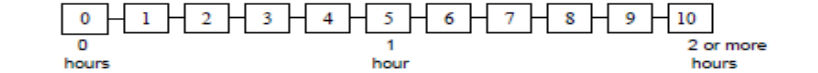
4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?



5. How would you describe the overall level of morning stiffness you have had from the time you wake up?



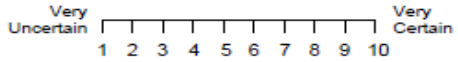
6. How long does your morning stiffness last from the time you wake up?



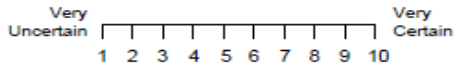
Part 7

For each of the following questions, **please circle** the number that corresponds to how certain you are that you can do the following tasks regularly **at the present time**.

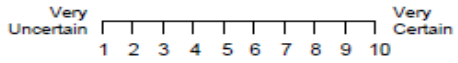
1. How certain are you that you can decrease your pain quite a bit?



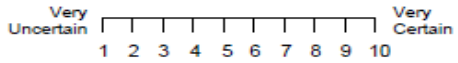
2. How certain are you that you can keep the pain from your Ankylosing Spondylitis from interfering with your sleep?



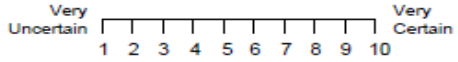
3. How certain are you that you can keep the pain from your Ankylosing Spondylitis from interfering with the things you want to do?



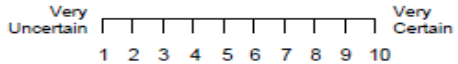
4. How certain are you that you can regulate your activity so as to be active without aggravating your Ankylosing Spondylitis?



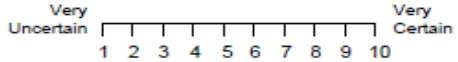
5. How certain are you that you can keep the fatigue caused by your Ankylosing Spondylitis from interfering with the things you want to do?



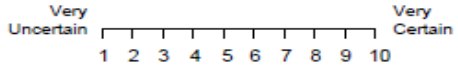
6. How certain are you that you can do something to help yourself feel better if you are feeling downhearted and low?



7. As compared with other people with Ankylosing Spondylitis like yours, how certain are you that you can manage pain during your daily activities?



8. How certain are you that you can deal with the frustration of Ankylosing Spondylitis?



SECTION C – ABOUT YOU

This section is made up of some general demographic questions, as it will help us to understand your previous answers better if we have a little background information from everyone.

Please answer each set of questions as the instructions ask you to.

7. What is your current marital status?
(Please place a cross in the one box that most closely approximates to your current situation).

Single ☐ Divorced/Separated ☐

Widow/Widower ☐ Married/cohabiting ☐

If you have a partner please answer the following questions: (if you don't have a partner please go to **Part 2**)

(a) *If your partner is employed:*

Please write below their job title and area of work. (*Please write in BLOCK CAPITALS their job title and the area of work. For example, machinist making bags in a leather factory or clerical officer for local government).*

.....

Or if they are not employed or are retired:

Please write below their job title and area of work of their last job:

.....

(b) Do you think your partners employment been affected by your AS?
(Please place a cross in one box)

Not at all	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
☐	☐	☐	☐	☐

Part 2

1. What is **your** current work status?
(Please place a cross in the one box that most closely approximates to your current situation).

Unemployed/seeking work	☐	Not working due to ill health	☐
Retired	☐	Retired due to ill health	☐
Housewife/husband	☐	In full/part time education	☐
Employed	☐	Other	☐

Part 1

1. What is your Date of Birth? ☐☐/☐☐/☐☐ *(For example – if you were born on the 5th of June 1946, this would be entered as 05 / 06 / 46).*

2. Are you: Female ☐ Male ☐

3. What is your ethnic origin? *(Please place a cross in one box only)*

White	☐	Afro Caribbean	☐	Chinese	☐
Asian	☐	African	☐	Other	☐ (Please specify).....

4. What is your smoking status?

Non-smoker ☐

Current smoker ☐
(a) At what age did you start smoking? ☐☐
(b) How many do you smoke per day? ☐☐

Ex-smoker ☐
(a) At what age did you start smoking? ☐☐
(b) At what age did you stop smoking? ☐☐
(c) How many did you use to smoke per day? ☐☐

5. How old were you when you left full-time education? ☐☐ years old

6. Thinking about the cost of living as it affects you, which of these descriptions best describes your situation: *(Please place a cross in one box only)*

Find it a strain to get by from week to week	☐	Have to be careful with money	☐
Able to manage without much difficulty	☐	Quite comfortably off	☐

2. Has **your** work status changed during the past **3 months**?

No ☐

Yes ☐ If '**YES**', which alternative best describes your changed working status? (*Please cross one box below).*

- ☐ I have changed from being a part-time employee to a full-time employee.
- ☐ I have changed from being a full-time employee to a part-time employee.
- ☐ I have changed from being **unemployed**, housewife/husband or studying to being employed.
- ☐ I have changed from being **employed** to being unemployed, housewife/husband or studying.
- ☐ I have changed from being on early retirement to being employed.
- ☐ I have changed from being employed to being on early retirement.
- ☐ Other. Please briefly describe how:

.....

(a) **If you are not currently employed** please write below the job title and area of work of your last job (if applicable): *(Please write in BLOCK CAPITALS your job title and the area of work. For example, machinist making bags in a leather factory or clerical officer for local government)*

.....

(b) At what age were **you** last employed? ☐☐ years

If not currently employed please go to Page 27

(c) **If employed** please write below your job title and area of work:

.....

(d) **If currently employed** how many hours do you work per week? ☐☐ hours

(e) What is your annual employment income?

☐ < £10k ☐ £10k- £15k ☐ £15k - £20k

☐ £20k - £30k ☐ £30k - £40k ☐ > £40k

(f) How many days have you had off sick due to your Ankylosing Spondylitis in the **last 3 months**?

☐☐ days

(g) Has your choice of work changed due to your AS? No ☐ Yes ☐

If 'YES' please briefly describe how:

.....

3. In the **past 4 weeks**, how much of the time did your Ankylosing Spondylitis make it difficult to do the following aspects of your job? For each question please place a cross in the box that best describes your response. If the activity described is not part of your job, check the box below NOT PART OF MY JOB and go to the next item.

	DIFFICULT ALL THE TIME (100%)	DIFFICULT MOST OF THE TIME	DIFFICULT SOME OF THE TIME	DIFFICULT A SLIGHT BIT OF THE TIME	DIFFICULT NONE OF THE TIME	NOT PART OF MY JOB
1. Sticking to your work routine or schedule.	☐	☐	☐	☐	☐	☐
2. Working without extra breaks or rests (for example, because you were uncomfortable).	☐	☐	☐	☐	☐	☐
3. Lifting, carrying or moving objects at work.	☐	☐	☐	☐	☐	☐
4. Bending, twisting or reaching.	☐	☐	☐	☐	☐	☐
5. Using hand operated tools or equipment (for example, pen, drill, sander, keyboard or computer mouse).	☐	☐	☐	☐	☐	☐
6. Keeping your body in one position longer than 30 minutes at a time.	☐	☐	☐	☐	☐	☐
7. Keeping track of more than one task or project at the same time.	☐	☐	☐	☐	☐	☐
8. Concentrating on your work.	☐	☐	☐	☐	☐	☐
9. Remembering things having to do with your work.	☐	☐	☐	☐	☐	☐
10. Talking with people in person, in meetings or on the phone.	☐	☐	☐	☐	☐	☐
11. Helping others to get work done.	☐	☐	☐	☐	☐	☐
12. Controlling irritability or anger toward people when working.	☐	☐	☐	☐	☐	☐
13. Doing your work without making mistakes.	☐	☐	☐	☐	☐	☐
14. Satisfying those people who judge your work.	☐	☐	☐	☐	☐	☐
15. Finishing all you work.	☐	☐	☐	☐	☐	☐
16. Feeling a sense of accomplishment.	☐	☐	☐	☐	☐	☐

Appendix A.6

Association of depression and anxiety on increased disease activity in patients with ankylosing spondylitis (AS)

	BASDAI ≥4[a] (n=337)		
Independent variable	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**[b]	**Adjusted OR (95% CI)**[c]
Depression			
normal	1.00	1.00	1.00
possible depression	6.53 (4.30-9.92)***	3.79 (2.36-6.09)***	2.83 (1.51-5.29)***
Anxiety			
normal	1.00	1.00	1.00
possible anxiety	4.74 (3.34-6.75)***	2.60 (1.73-3.90)***	2.84 (1.66-4.87)***
Gender			
male	1.00	-	1.00
female	1.36 (0.95-1.96)	-	1.25 (0.74-2.12)
Age			
20-39 years	1.00	-	1.00
40-49 years	1.67 (1.04-2.69)	-	0.76 (0.38-1.53)
50-59 years	1.26 (0.79-2.01)	-	0.57 (0.27-1.21)
>60 years	1.67 (1.04-2.69)*	-	0.73 (0.32-1.63)
Symptom duration			
< 10 years	1.00	-	1.00
10-19 years	2.24 (1.32-3.79)*	-	1.49 (0.72-3.06)
20-29 years	2.38 (1.36-4.16)*	-	2.66 (1.18-6.02)*
>30 years	2.24 (1.32-3.79)**	-	2.19 (0.94-5.09)
Marital status			
married/cohabiting	1.00	-	1.00
unmarried	1.22 (0.84-1.76)	-	1.06 (0.61-1.83)
Employment			
employed/normal retired	1.00	-	1.00
unemployed/early retired	4.46 (3.10-6.42***	-	2.87 (1.67-4.90)***
Deprivation			
least	1.00	-	1.00
middle	2.24 (1.38-3.64)***	-	1.97 (1.10-3.53)*
most	3.64 (1.99-6.68)***	-	2.35 (1.10-5.01)*

Note: BASDAI = Bath AS disease activity index; OR = odds ratio; CI = confidence interval. * p <0.05, ** p <0.01, *** p<0.00. [a] reference category: BASDAI score <4. [b] controlling for mood variables presented. [c] multivariable model controlling for gender, age, symptom duration, marital status, employment, deprivation and mood variables presented.

Association of depression and anxiety on increased pain in patients with ankylosing spondylitis (AS)

	Pain NRS ≥4 (n=376)		
Independent variable	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)[b]**	**Adjusted OR (95% CI)[c]**
Depression			
normal	1.00	1.00	1.00
possible depression	4.46 (2.94-6.77)***	2.78 (1.72-4.50)***	2.12 (1.12-3.99)*
Anxiety			
normal	1.00	1.00	1.00
possible anxiety	3.58 (2.51-5.11)***	2.21 (1.46-3.34)***	2.30 (1.34-3.93)**
Gender			
male	1.00	-	1.00
female	1.02 (0.71-1.46)	-	0.77 (0.46-1.29)
Age			
20-39 years	1.00	-	1.00
40-49 years	1.09 (0.67-1.79)	-	0.92 (0.47-1.79)
50-59 years	1.18 (0.73-1.90)	-	0.57 (0.28-1.16)
>60 years	1.14 (0.71-1.84)	-	0.68 (0.36-1.48)
Symptom duration			
< 10 years	1.00	-	1.00
10-19 years	1.66 (0.99-2.80)	-	1.48 (0.75-2.92)
20-29 years	1.72 (0.99-2.99)	-	1.61 (0.75-3.45)
>30 years	2.01 (1.19-3.41)**	-	2.09 (0.94-4.64)
Marital status			
married/cohabiting	1.00	-	1.00
unmarried	1.02 (0.70-1.48)	-	1.05 (0.62-1.77)
Employment			
employed/normal retirement	1.00	-	1.00
unemployed/early retirement	3.17 (2.20-4.58)***	-	2.34 (1.37-4.01)**
Deprivation			
least	1.00	-	1.00
middle	1.54 (0.96-2.47)	-	1.35 (0.79-2.31)
most	2.31 (1.26-4.25)**	-	1.66 (0.80-3.46)

Note: NRS = numerical rating scale; OR = odds ratio; CI = confidence interval.
* p <0.05, ** p <0.01, *** p<0.001. [a] reference category: Pain NRS score <4. [b] controlling for mood variables presented. [c] multivariable model controlling for gender, age, symptom duration, marital status, employment, deprivation and mood variables presented.

Association of depression and anxiety on increased functional impairment in patients with ankylosing spondylitis (AS)

	BASFI ≥4 (n=332)		
Independent variable	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)[b]**	**Adjusted OR (95% CI)[c]**
Depression			
normal	1.00	1.00	1.00
possible depression	6.21 (4.12-9.37)***	4.62 (2.89-7.39)***	3.77 (1.99-7.15)***
Anxiety			
normal	1.00	1.00	1.00
possible anxiety	3.33 (2.37-4.68)***	1.64 (1.09-2.45)*	1.62 (0.93-2.83)
Gender			
male	1.00	-	1.00
female	1.12 (0.78-1.60)	-	0.97 (0.56-1.68)
Age			
20-39 years	1.00	-	1.00
40-49 years	1.75 (1.07-2.87)*	-	1.32 (0.64-2.73)
50-59 years	2.47 (1.53-4.00)***	-	1.48 (0.69-3.17)
>60 years	3.07 (1.89-5.00)***	-	1.31 (0.57-3.01)
Symptom duration			
< 10 years	1.00	-	1.00
10-19 years	1.89 (1.10-3.25)*	-	1.54 (0.73-3.26)
20-29 years	2.63 (1.49-4.65)**	-	2.41 (1.05-5.52)*
>30 years	3.66 (2.12-6.32)***	-	3.02 (1.27-7.15)*
Marital status			
married/cohabiting	1.00	-	1.00
unmarried	1.14 (0.79-1.64)	-	0.94 (0.54-1.66)
Employment			
employed/normal retirement	1.00	-	1.00
unemployed/early retirement	6.91 (4.71-10.13)***	-	4.01 (2.35-6.86)***
Deprivation			
least	1.00	-	1.00
middle	1.94 (1.20-3.15)**	-	1.65 (0.91-3.01)
most	4.24 (2.29-7.85)***	-	2.88 (1.30-6.39)**

Note: BASFI = Bath AS functional index; OR = odds ratio; CI = confidence interval.
* p <0.05, ** p <0.01, *** p<0.001. [a] reference category: BASFI score <4. [b] controlling for mood variables presented. [c] multivariable model controlling for gender, age, symptom duration, marital status, employment, deprivation and mood variables presented.

Appendix A.7

Association of increased disease activity on depression and anxiety in patients with AS

	Mood status[a]			
	Depression (HADS-D ≥8) (n=194)		**Anxiety (HADS-A ≥8)** (n=271)	
Independent variable	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**[b]	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)** [b]
Disease activity				
<4	1.00	1.00	1.00	1.00
≥4	6.53 (4.30-9.37)***	5.12 (2.95-8.90)***	4.74 (3.34-6.75)***	4.44 (2.76-7.15)***
Gender				
male	1.00	1.00	1.00	1.00
female	1.13 (0.77-1.65)	1.19 (0.68-2.06)	1.69 (1.18-2.43)**	1.95 (1.18-3.17)*
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	0.63 (0.40-0.99)*	0.64 (0.34-1.22)	0.71 (0.46-1.09)	0.57 (0.31-1.05)
50-59 years	0.84 (0.52-1.36)	0.93 (0.44-1.96)	0.74 (0.47-1.15)	0.52 (0.26-1.04)
>60 years	1.01 (0.60-1.71)	1.36 (0.58-3.18)	0.86 (0.54-1.39)	0.76 (0.35-1.67)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	0.69 (0.43-1.12)	0.61 (0.30-125)	0.91 (0.58-1.43)	1.02 (0.53-1.97)
20-29 years	0.94 (0.60-1.48)	0.44 (0.22-0.90)*	0.94 (0.62-1.42)	0.54 (0.28-1.04)
>30 years	0.97 (0.55-1.71)	0.30 (0.12-0.72)**	1.17 (0.69-1.97)	0.53 (0.24-1.20)
Marital status				
married/cohabiting	1.00	1.00	1.00	1.00
unmarried	1.36 (0.92-1.99)	1.10 (0.64-1.89)	1.51 (1.04-2.18)*	1.55 (0.93-2.58)
Employment				
employed/normal retirement	1.00	1.00	1.00	1.00
unemployed/early retirement	3.62 (2.50-5.24)***	2.54 (1.48-4.36)**	2.51 (1.78-3.53)***	2.12 (1.26-3.57)**
Deprivation				
least	1.00	1.00	1.00	1.00
middle	2.23 (1.37-3.63)**	1.85 (1.01-3.39)*	1.56 (0.97-2.50)	1.47 (0.82-2.66)
most	2.67 (1.43-4.99)**	1.23 (0.57-2.66)	1.94 (1.08-3.50)*	1.07 (0.52-2.20)

Note: HADS-D = Hospital Anxiety and Depression Scale - depression domain; HADS-A = Hospital Anxiety and Depression Scale - anxiety domain; OR = odds ratio; CI = confidence interval. * p <0.05, ** p <0.01, *** p<0.001

[a] reference categories: HADS-D ≥8, HADS-A ≥8. [b] multivariable model controlling for gender, age, symptom duration, marital status, employment, and deprivation

Association of increased pain on depression and anxiety in patients with AS

	Mood status[a]			
	Depression (HADS-D ≥8) (n=194)		**Anxiety (HADS-A ≥8)** (n=271)	
Independent variable	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**[b]	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)** [b]
Pain				
<4	1.00	1.00		1.00
≥4	4.46 (2.94-6.77)***	3.36 (1.94-5.82)***	3.58 (2.51-5.11)***	3.17 (1.98-5.17)***
Gender				
male	1.00	1.00	1.00	1.00
female	1.13 (0.77-1.65)	1.35 (0.79-2.33)	1.69 (1.18-2.43)**	1.93 (1.17-3.19)*
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	0.63 (0.40-0.99)*	0.64 (0.34-1.22)	0.71 (0.46-1.09)	0.58 (0.32-1.07)
50-59 years	0.84 (0.52-1.36)	0.94 (0.44-1.91)	0.74 (0.47-1.15)	0.55 (0.28-1.09)
>60 years	1.01 (0.60-1.71)	1.28 (0.56-2.94)	0.86 (0.54-1.39)	0.77 (0.35-1.66)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	0.69 (0.43-1.12)	0.56 (0.28-1.12)	0.91 (0.58-1.43)	0.89 (0.46-1.71)
20-29 years	0.94 (0.60-1.48)	0.46 (0.23-0.91)*	0.94 (0.62-1.42)	0.56 (0.29-1.05)
>30 years	0.97 (0.55-1.71)	0.32 (0.14-0.75)**	1.17 (0.69-1.97)	0.55 (0.25-1.21)
Marital status				
married/cohabiting	1.00	1.00	1.00	1.00
unmarried	1.36 (0.92-1.99)	1.08 (0.64-1.85)	1.51 (1.04-2.18)*	1.55 (0.94-2.55)
Employment				
employed/normal retirement	1.00	1.00	1.00	1.00
unemployed/early retirement	3.62 (2.50-5.24)***	3.07 (1.80-5.22)***	2.51 (1.78-3.53)***	2.50 (1.51-4.15)***
Deprivation				
least	1.00	1.00	1.00	1.00
middle	2.23 (1.37-3.63)**	1.83 (1.01-3.32)*	1.56 (0.97-2.50)	1.50 (0.84-2.68)
most	2.67 (1.43-4.99)**	1.45 (0.69-3.06)	1.94 (1.08-3.50)*	1.25 (0.62-2.54)

Note: HADS-D = Hospital Anxiety and Depression Scale - depression domain; HADS-A = Hospital Anxiety and Depression Scale - anxiety domain; OR = odds ratio; CI = confidence interval. * p <0.05, ** p <0.01, *** p<0.001

[a] reference categories: HADS-D ≥8, HADS-A ≥8. [b] multivariable model controlling for gender, age, symptom duration, marital status, employment, and deprivation

Association of functional impairment on depression and anxiety in patients with AS

	Mood status[a]			
	Depression (HADS-D ≥8) (n=194)		**Anxiety (HADS-A ≥8)** (n=271)	
Independent variable	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**[b]	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)** [b]
BASFI				
<4	1.00	1.00	1.00	1.00
≥4	6.21 (4.12-9.37)***	5.21 (2.97-9.12)***	3.33 (2.37-4.68)***	3.02 (1.87-4.88)***
Gender				
male	1.00	1.00	1.00	1.00
female	1.13 (0.77-1.65)	1.30 (0.75-2.26)	1.69 (1.18-2.43)**	1.82 (1.11-2.99)*
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	0.63 (0.40-0.99)*	0.67 (0.35-1.29)	0.71 (0.46-1.09)	0.61 (0.33-1.12)
50-59 years	0.84 (0.52-1.36)	0.86 (0.41-1.83)	0.74 (0.47-1.15)	0.50 (0.25-1.01)
>60 years	1.01 (0.60-1.71)	1.05 (0.45-2.46)	0.86 (0.54-1.39)	0.63 (0.29-1.37)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	0.69 (0.43-1.12)	0.55 (0.27-1.12)	0.91 (0.58-1.43)	0.91 (0.47-1.74)
20-29 years	0.94 (0.60-1.48)	0.40 (0.19-0.80)*	0.94 (0.62-1.42)	0.52 (0.28-0.99)
>30 years	0.97 (0.55-1.71)	0.26 (0.11-0.64)**	1.17 (0.69-1.97)	0.53 (0.24-1.17)
Marital status				
married/cohabiting	1.00	1.00	1.00	1.00
unmarried	1.36 (0.92-1.99)	1.16 (0.67-2.00)	1.51 (1.04-2.18)*	1.60 (0.97-2.63)
Employment				
employed/normal retirement	1.00	1.00	1.00	1.00
unemployed/early retirement	3.62 (2.50-5.24)***	2.43 (1.40-4.21)**	2.51 (1.78-3.53)***	2.21 (1.32-3.71)**
Deprivation				
least	1.00	1.00	1.00	1.00
middle	2.23 (1.37-3.63)**	1.68 (0.92-3.08)	1.56 (0.97-2.50)	1.41 (0.79-2.50)
most	2.67 (1.43-4.99)**	1.19 (0.55-2.56)	1.94 (1.08-3.50)*	1.13 (0.56-2.27)

Note: HADS-D = Hospital Anxiety and Depression Scale - depression domain; HADS-A = Hospital Anxiety and Depression Scale - anxiety domain; OR = odds ratio; CI = confidence interval. * p <0.05, ** p <0.01, *** p<0.001

[a] reference categories: HADS-D ≥8, HADS-A ≥8. [b] multivariable model controlling for gender, age, symptom duration, marital status, employment, and deprivation

Appendix A.8

Association of mood disturbance on increased disease activity in patients with ankylosing spondylitis (AS)

Variable	BASDAI ≥4[a] unadjusted OR (95% CI)	BASDAI ≥4 [a,b] adjusted OR (95% CI)
Mood		
Normal	1.00	1.00
Anxiety only	2.75 (1.74-4.35)***	3.17 (1.72-5.83)***
Depression only	4.86 (1.98-11.93)*	4.16 (1.27-13.57)*
Both anxiety and depression	9.64 (5.97-15.57)***	7.66 (4.10-14.30)***
Employment		
Employed/normal retirement	1.00	1.00
unemployed	4.46 (3.10-6.42)***	2.85 (1.67-4.88)***
Deprivation		
least	1.00	1.00
middle	2.24 (1.38-3.64)**	1.97 (1.10-3.53)*
most	3.64 (1.99-6.68)***	2.35 (1.10-5.02)*
Marital status		
married	1.00	1.00
unmarried	1.21 (0.84-1.75)	1.04 (0.60-1.80)
Symptom duration		
< 10 years	1.00	1.00
10-19 years	1.71 (1.01-2.89)*	1.51 (0.73-3.11)
20-29 years	2.42 (1.38-4.25)**	2.73 (1.20-6.21)*
>30 years	2.27 (1.33-3.85)**	2.24 (0.96-5.23)
Age		
20-39 years	1.00	1.00
40-49 years	1.17 (0.72-1.91)	0.76 (0.38-1.52)
50-59 years	1.27 (0.80-2.04)	0.56 (0.26-1.19)
>60 years	1.67 (1.04-2.69)*	0.72 (0.32-1.61)
Gender		
male	1.00	1.00
female	1.39 (0.96-1.99)	1.22 (0.72-2.09)

Note: OR = odds ratio; CI = confidence interval. BASDAI = Bath AS disease activity index.
* p <0.05, ** p <0.01, *** p<0.001

[a] reference category: BASDAI score <4.

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation.

Association of mood disturbance on increased pain in patients with ankylosing spondylitis (AS)

Variable	Pain NRS ≥4 unadjusted OR (95% CI)[a]	Pain NRS ≥4 adjusted OR (95% CI)[a,b]
Mood		
Normal	1.00	1.00
Anxiety only	2.20 (1.39-3.49)**	2.39 (1.31-4.38)**
Depression only	2.72 (1.16-6.41)*	2.45 (0.77-7.83)
Both anxiety and depression	6.18 (3.84-9.93)***	4.76 (2.56-8.86)***
Employment		
Employed/normal retirement	1.00	1.00
unemployed	3.17 (2.20-4.58)***	2.34 (1.37-4.00)**
Gender		
male	1.00	1.00
female	1.02 (0.71-1.46)	0.77 (0.46-1.28)
Deprivation		
least	1.00	1.00
middle	1.54 (0.96-2.47)	1.35 (0.78-2.31)
most	2.31 (1.26-4.25)**	1.66 (0.80-3.46)
Symptom duration		
< 10 years	1.00	1.00
10-19 years	1.66 (0.99-2.80)	1.49 (0.76-2.94)
20-29 years	1.72 (0.99-2.99)	1.62 (0.75-3.49)
>30 years	2.01 (1.19-3.41)**	2.11 (0.95-4.69)
Age		
20-39 years	1.00	1.00
40-49 years	1.09 (0.67-1.79)	0.92 (0.47-1.79)
50-59 years	1.18 (0.73-1.90)	0.57 (0.28-1.15)
>60 years	1.14 (0.71-1.84)	0.68 (0.31-1.47)
Marital status		
married	1.00	1.00
unmarried	1.02 (0.70-1.48)	1.04 (0.61-1.76)

Note: OR = odds ratio; CI = confidence interval. NRS = numerical rating scale.
* p <0.05, ** p <0.01, *** p<0.001

[a] reference category: Pain NRS score <4.

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation.

Association of mood disturbance on increased functional impairment in patients with ankylosing spondylitis (AS)

Variable	BASFI ≥4[a] unadjusted OR (95% CI)	BASFI ≥4[a,b] adjusted OR (95% CI)
Mood		
Normal	1.00	1.00
Anxiety only	1.84 (1.17-2.88)*	1.78 (0.95-3.32)
Depression only	9.01 (3.03-26.80)**	5.58 (1.49-20.88)*
Both anxiety and depression	7.90 (4.95-12.61)***	5.91 (3.17-10.99)***
AS symptom duration		
< 10 years	1.00	1.00
10-19 years	1.91 (1.12-3.28)*	1.57 (0.74-3.34)
20-29 years	2.78 (1.57-4.93)***	2.49 (1.08-5.75)*
>30 years	3.71 (2.15-6.42)***	3.11 (1.30-7.43)*
Employment		
Employed/normal retirement	1.00	1.00
unemployed	6.91 (4.71-10.13)***	4.00 (2.34-6.83)***
Deprivation		
least	1.00	1.00
middle	1.97 (1.22-3.20)**	1.65 (0.91-3.02)
most	4.24 (2.29-7.85)***	2.90 (1.31-6.46)**
Marital status		
married	1.00	1.00
unmarried	1.13 (0.78-1.63)	0.93 (0.53-1.64)
Age		
20-39 years	1.00	1.00
40-49 years	1.75 (1.07-2.87)*	1.31 (0.64-2.71)
50-59 years	2.58 (1.59-4.19)***	1.45 (0.67-3.11)
>60 years	3.18 (1.95-5.18)***	1.30 (0.57-2.98)
Gender		
male	1.00	1.00
female	1.11 (0.78-1.59)	0.95 (0.55-1.65)

Note: OR = odds ratio; CI = confidence interval. BASFI = Bath AS Functional Index
* p <0.05, ** p <0.01, *** p<0.001

[a] reference category: BASFI score <4.

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation.

Appendix A.9

Unadjusted association of increased disease activity on mood disturbance in patients with ankylosing spondylitis (AS)

Variable	Depression only[a] unadjusted OR (95% CI)	anxiety only [a] unadjusted OR (95% CI)	Depression and anxiety [a] unadjusted OR (95% CI)
BASDAI			
<4	1.00	1.00	1.00
≥4	4.86 (1.98-11.93)**	2.75 (1.74-4.35)***	9.64 (5.97-15.57)***
Employment			
employed	1.00	1.00	1.00
unemployed	3.82 (1.61-9.06)**	1.53 (0.95-2.47)	4.13 (2.73-6.37)***
Marital status			
married	1.00	1.00	1.00
unmarried	1.95 (0.83-4.57)	1.69 (1.03-2.76)*	1.55 (1.00-2.39)*
Deprivation			
least	1.00	1.00	1.00
middle	1.34 (0.36-5.00)	1.34 (0.69-2.60)	1.23 (0.68-2.21)
most	3.57 (0.87-14.63)	1.42 (0.60-3.37)	2.75 (1.38-5.48)**
Symptom duration			
< 10 years	1.00	1.00	1.00
10-19 years	1.21 (0.64-2.29)	1.23 (0.60-2.52)	1.21 (0.64-2.29)
20-29 years	1.50 (0.78-2.89)	1.02 (0.47-2.23)	1.50 (0.78-2.89)
>30 years	1.10 (0.58-2.08)	1.22 (0.60-2.50)	1.10 (0.58-2.08)
Age			
20-39 years	1.00	1.00	1.00
40-49 years	3.29 (0.66-16.45)	1.41 (0.73-2.73)	1.15 (0.64-2.07)
50-59 years	3.69 (0.77-17.70)	1.07 (0.55-2.09)	1.48 (0.86-2.57)
>60 years	2.72 (0.56-13.25)	0.95 (0.50-1.84)	0.88 (0.50-1.55)
Gender			
male	1.00	1.00	1.00
female	1.01 (0.39-2.62)	2.08 (1.29-3.40)**	1.48 (0.97-2.27)

Note: OR = odds ratio. CI = confidence interval. BASDAI = Bath AS Disease Activity Index.

[a] reference category: HADS-D/HADS-A scores <8.

* p <0.05
** p <0.01
*** p<0.001

Adjusted association of increased disease activity on mood disturbance in patients with ankylosing spondylitis (AS)

Variable	Depression only [a,b] adjusted OR (95% CI)	anxiety only [a,b] adjusted OR (95% CI)	Depression and anxiety [a,b] adjusted OR (95% CI) [a,b]
BASDAI			
<4	1.00	1.00	1.00
≥4	4.39 (1.33-14.55)*	3.15 (1.71-5.78)***	7.60 (4.06-14.22)***
Employment			
employed	1.00	1.00	1.00
unemployed	2.92 (0.89-9.56)	1.65 (0.83-3.28)	3.13 (1.68-5.85)***
Marital status			
married	1.00	1.00	1.00
unmarried	1.82 (0.60-5.59)	2.07 (1.10-3.88)*	1.40 (0.75-2.62)
Deprivation			
least	1.00	1.00	1.00
middle	0.64 (0.15-2.71)	0.82 (0.39-1.72)	0.60 (0.29-1.22)
most	1.34 (0.26-6.90)	1.03 (0.39-2.68)	1.19 (0.50-2.83)
Symptom duration			
< 10 years		1.00	1.00
10-19 years	0.32 (0.07-1.54)	0.94 (0.40-2.24)	0.84 (0.36-1.98)
20-29 years	0.25 (0.05-1.31)	0.43 (0.16-1.21)	0.46 (0.17-1.20)
>30 years	0.14 (0.03-0.77)	0.64 (0.23-1.82)	0.32 (0.12-0.89)
Age			
20-39 years	1.00	1.00	1.00
40-49 years	1.43 (0.17-11.80)	1.47 (0.60-3.42)	1.52 (0.65-3.56)
50-59 years	5.56 (0.89-34.86)	1.28 (0.50-3.25)	1.87 (0.76-4.61)
>60 years	3.16 (0.47-21.24)	0.69 (0.25-1.95)	0.97 (0.37-2.53)
Gender			
male	1.00	1.00	1.00
female	1.81 (0.57-5.78)	2.14 (1.14-4.03)**	1.54 (0.82-2.90)

[a] reference category: HADS-D/HADS-A scores <8,

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation.

* p <0.05
** p <0.01
*** p<0.001

Unadjusted association of increased pain on mood disturbance in patients with ankylosing spondylitis (AS)

Variable	Depression only[a] unadjusted OR (95% CI)	anxiety only[a] unadjusted OR (95% CI)	Depression and anxiety[a] unadjusted OR (95% CI)
Pain NRS			
<4	1.00	1.00	1.00
≥4	2.72 (1.16-6.41)*	2.20 (1.39-3.49)**	6.18 (3.84-9.93)***
Employment			
employed	1.00	1.00	1.00
unemployed	3.82 (1.61-9.06)**	1.53 (0.95-2.47)	4.13 (2.73-6.37)***
Gender			
male	1.00	1.00	1.00
female	1.01 (0.39-2.62)	2.08 (1.29-3.40)**	1.48 (0.97-2.27)
Deprivation			
least	1.00	1.00	1.00
middle	1.34 (0.36-5.00)	1.34 (0.69-2.60)	1.23 (0.68-2.21)
most	3.57 (0.87-14.63)	1.42 (0.60-3.37)	2.75 (1.38-5.48)**
Symptom duration			
< 10 years	1.00	1.00	1.00
10-19 years	1.21 (0.64-2.29)	1.23 (0.60-2.52)	1.21 (0.64-2.29)
20-29 years	1.50 (0.78-2.89)	1.02 (0.47-2.23)	1.50 (0.78-2.89)
>30 years	1.10 (0.58-2.08)	1.22 (0.60-2.50)	1.10 (0.58-2.08)
Age			
20-39 years	1.00	1.00	1.00
40-49 years	3.29 (0.66-16.45)	1.41 (0.73-2.73)	1.15 (0.64-2.07)
50-59 years	3.69 (0.77-17.70)	1.07 (0.55-2.09)	1.48 (0.86-2.57)
>60 years	2.72 (0.56-13.25)	0.95 (0.50-1.84)	0.88 (0.50-1.55)
Marital status			
married	1.00	1.00	1.00
unmarried	1.95 (0.83-4.57)	1.69 (1.03-2.76)*	1.55 (1.00-2.39)*

Note: OR = odds ratio. CI = confidence interval. NRS = numerical rating scale.

[a] reference category: HADS-D/HADS-A scores <8.

* p <0.05
** p <0.01
*** p<0.001

Adjusted association of increased pain on mood disturbance in patients with ankylosing spondylitis (AS)

Variable	Depression only[a,b] adjusted OR (95% CI)	anxiety only[a,b] adjusted OR (95% CI)	Depression and anxiety[a,b] adjusted OR (95% CI)
Pain NRS			
<4	1.00	1.00	1.00
≥4	2.34 (0.74-7.47)	2.39 (1.31-4.38)**	4.67 (2.51-8.69)***
Employment			
employed	1.00	1.00	1.00
unemployed	3.49 (1.07-11.39)*	1.83 (0.93-3.58)	3.86 (2.10-7.08)***
Gender			
male	1.00	1.00	1.00
female	2.04 (0.64-6.51)	2.43 (1.30-4.55)**	1.82 (0.98-3.39)
Deprivation			
least	1.00	1.00	1.00
middle	0.74 (0.18-3.07)	0.91 (0.44-1.88)	0.73 (0.37-1.47)
most	1.62 (0.32-8.19)	1.16 (0.45-3.02)	1.47 (0.63-3.43)
Symptom duration			
< 10 years	1.00	1.00	1.00
10-19 years	0.34 (0.07-1.62)	0.95 (0.40-2.25)	0.87 (0.38-1.99)
20-29 years	0.32 (0.06-1.65)	0.51 (0.19-1.40)	0.58 (0.23-1.46)
>30 years	0.16 (0.03-0.87)	0.67 (0.24-1.87)	0.35 (0.13-0.93)
Age			
20-39 years	1.00	1.00	1.00
40-49 years	1.30 (0.16-10.50)	1.41 (0.61-3.24)	1.42 (0.63-3.23)
50-59 years	5.01 (0.83-30.31)	1.26 (0.50-3.16)	1.77 (0.75-4.22)
>60 years	2.97 (0.45-19.67)	0.72 (0.26-2.00)	0.95 (0.37-2.41)
Marital status			
married	1.00	1.00	1.00
unmarried	1.81 (0.59-5.52)	2.10 (1.12-3.92)*	1.38 (0.74-2.55)

Note: OR = odds ratio. CI = confidence interval. NRS = numerical rating scale.

[a] reference category: HADS-D/HADS-A scores <8.

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation.

* p <0.05
** p <0.01
*** p<0.001

Unadjusted association of increased functional impairment on mood disturbance in patients with ankylosing spondylitis (AS)

Variable	Depression only[a] unadjusted OR (95% CI)	Anxiety only[a] unadjusted OR (95% CI)	Depression and anxiety[a] unadjusted OR (95% CI)
BASFI			
<4	1.00	1.00	1.00
≥4	9.01 (3.03-26.80)***	1.81 (1.16-2.83)**	7.17 (4.56-11.28)***
Marital status			
married	1.00	1.00	1.00
unmarried	1.95 (0.83-4.57)	1.69 (1.03-2.76)*	1.55 (1.00-2.39)*
Employment			
employed	1.00	1.00	1.00
unemployed	3.82 (1.61-9.06)**	1.53 (0.95-2.47)	4.13 (2.73-6.24)***
Deprivation			
least	1.00	1.00	1.00
middle	1.34 (0.36-5.00)	1.34 (0.69-2.60)	1.23 (0.68-2.21)
most	3.57 (0.87-14.63)	1.42 (0.60-3.37)	2.75 (1.38-5.48)**
Symptom duration			
< 10 years	1.00	1.00	1.00
10-19 years	1.21 (0.64-2.29)	1.23 (0.60-2.52)	1.21 (0.64-2.29)
20-29 years	1.50 (0.78-2.89)	1.02 (0.47-2.23)	1.50 (0.78-2.89)
>30 years	1.10 (0.58-2.08)	1.22 (0.60-2.50)	1.10 (0.58-2.08)
Age			
20-39 years	1.00	1.00	1.00
40-49 years	3.29 (0.66-16.45)	1.41 (0.73-2.73)	1.15 (0.64-2.07)
50-59 years	3.69 (0.77-17.70)	1.07 (0.55-2.09)	1.48 (0.86-2.57)
>60 years	2.72 (0.56-13.25)	0.95 (0.50-1.84)	0.88 (0.50-1.55)
Gender			
male	1.00	1.00	1.00
female	1.01 (0.39-2.62)	2.08 (1.29-3.34)**	1.48 (0.97-2.27)

Note: OR = odds ratio. CI = confidence interval. BASFI = Bath AS Functional Index.

[a] reference category: HADS-D/HADS-A scores <8.

* p <0.05
** p <0.01
*** p<0.001

Adjusted association of increased functional impairment on mood disturbance in patients with ankylosing spondylitis (AS)

Variable	Depression only[a,b] adjusted OR (95% CI)	Anxiety only [a,b] adjusted OR (95% CI)	Depression and anxiety [a,b] adjusted OR (95% CI)
BASFI			
<4	1.00	1.00	1.00
≥4	5.42 (1.49-19.77)*	1.78 (0.96-3.31)	6.15 (3.28-11.52)***
Marital status			
married	1.00	1.00	1.00
unmarried	1.94 (0.63-5.95)	2.13 (1.15-3.96)	1.47 (0.79-2.74)
Employment			
employed	1.00	1.00	1.00
unemployed	2.66 (0.81-8.73)	1.77 (0.89-3.53)	3.01 (1.61-5.63)**
Deprivation			
least	1.00	1.00	1.00
middle	0.69 (0.17-2.91)	0.91 (0.44-1.87)	0.65 (0.32-1.32)
most	1.24 (0.24-6.40)	1.10 (0.43-2.84)	1.18 (0.50-2.77)
Symptom duration			
< 10 years	1.00	1.00	1.00
10-19 years	0.30 (0.06-1.49)	1.00 (0.43-2.35)	0.85 (0.37-1.97)
20-29 years	0.24 (0.04-1.30)	0.52 (0.19-1.42)	0.49 (0.19-1.27)
>30 years	0.12 (0.02-0.67)	0.69 (0.25-1.93)	0.29 (0.11-0.80)
Age			
20-39 years	1.00	1.00	1.00
40-49 years	1.20 (0.15-9.85)	1.31 (0.58-2.99)	1.21 (0.53-2.80)
50-59 years	4.18 (0.67-26.01)	1.05 (0.42-2.61)	1.29 (0.53-3.13)
>60 years	2.64 (0.39-17.67)	0.63 (0.23-1.75)	0.73 (0.28-1.90)
Gender			
male	1.00	1.00	1.00
female	1.96 (0.61-6.35)	2.31 (1.24-4.28)**	1.71 (0.92-3.20)

Note: OR = odds ratio. CI = confidence interval. BASFI = Bath AS Functional Index.

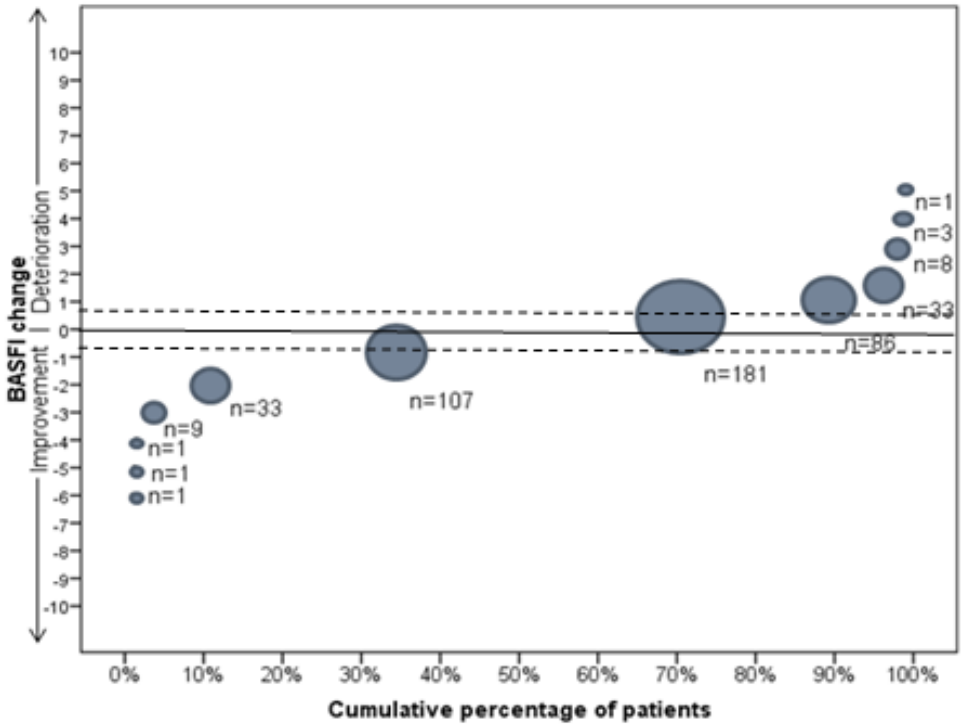
[a] reference category: HADS-D/HADS-A scores <8.

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation.

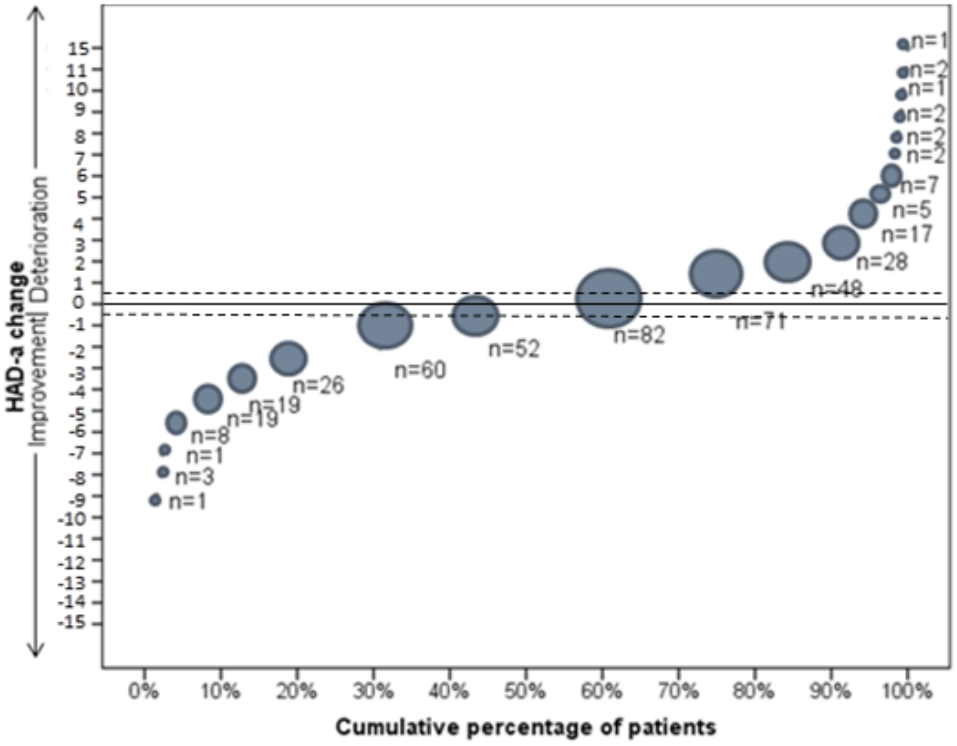
* p <0.05
** p <0.01
*** p<0.001

Appendix A.10

Cumulative plot of function (BASFI) change over six months



Cumulative plot of anxiety (HADS-A) change over six months



Appendix A.11

Association of baseline depression with changes in disease activity (BASDAI)[a] of patients with AS over six months

	Unadjusted BASDAI		Adjusted BASDAI[b]	
Independent variable	**Deterioration** (n=88)	**Improvement** (n=106)	**Deterioration** (n=88)	**Improvement** (n=106)
Depression (HADS-D)	1.02 (0.96-1.08)	1.03 (0.97-1.08)	1.03 (0.95-1.11)	1.05 (0.98-1.14)
Gender				
Male	1.00	1.00	1.00	1.00
Female	1.23 (0.73-2.08)	1.01 (0.61-1.68)	1.36 (0.69-2.69)	1.00 (0.51-1.97)
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	0.74 (0.34-1.63)	1.21 (0.59-2.49)	0.84 (0.33-2.15)	1.34 (0.54-3.32)
50-59 years	0.96 (0.46-1.98)	1.03 (0.50-2.12)	0.97 (0.37-2.56)	1.00 (0.37-2.66)
>60 years	1.19 (0.59-2.39)	1.42 (0.71-2.81)	1.12 (0.40-3.12)	2.07 (0.76-5.64)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	0.41 (0.19-0.88)*	1.38 (0.57-3.32)	0.33 (0.13-0.83)*	1.03 (0.39-2.72)
20-29 years	0.45 (0.20-1.01)	1.31 (0.52-3.28)	0.49 (0.19-1.31)	0.86 (0.30-2.49)
>30 years	0.65 (0.32-1.35)	1.81 (0.76-4.30)	0.73 (0.27-2.04)	1.03 (0.39-2.72)
Marital status				
married	1.00	1.00	1.00	1.00
unmarried	1.10 (0.65-1.86)	0.75 (0.44-1.26)	1.32 (0.68-2.56)	0.81 (0.41-1.61)
Employment				
employed	1.00	1.00	1.00	1.00
unemployed	0.83 (0.51-1.36)	0.68 (0.42-1.08)	0.70 (0.34-1.42)	0.37 (0.18-0.75)**
Deprivation				
least	1.00	1.00	1.00	1.00
middle	0.92 (0.46-1.84)	0.90 (0.48-1.69)	0.83 (0.39-1.75)	0.92 (0.46-1.81)
most	0.58 (0.24-1.41)	0.48 (0.21-1.09)	0.57 (0.21-1.55)	0.50 (0.19-1.33)

Note: AS=Ankylosing spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain. BASDAI = Bath AS Disease Activity Index.

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation * p <0.05, ** p <0.01, *** p<0.001

Association of baseline anxiety with changes in disease activity (BASDAI)[a] of patients with AS over six months

	Unadjusted BASDAI		Adjusted BASDAI[b]	
Independent variable	**Deterioration** (n=88)	**Improvement** (n=106)	**Deterioration** (n=88)	**Improvement** (n=106)
Anxiety (HADS-A)	1.02 (0.96-1.07)	1.03 (0.98-1.09)	1.04 (0.97-1.12)	1.08 (1.01-1.16)*
Gender				
Male	1.00	1.00	1.00	1.00
Female	1.23 (0.73-2.08)	1.01 (0.61-1.68)	1.35 (0.68-2.68)	0.93 (0.47-1.85)
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	0.74 (0.34-1.63)	1.21 (0.59-2.49)	0.74 (0.28-1.94)	1.33 (0.53-3.32)
50-59 years	0.96 (0.46-1.98)	1.03 (0.50-2.12)	0.90 (0.34-2.36)	0.95 (0.35-2.54)
>60 years	1.19 (0.59-2.39)	1.42 (0.71-2.81)	1.08 (0.39-3.02)	2.12 (0.77-5.83)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	0.41 (0.19-0.88)*	1.38 (0.57-3.32)	0.37 (0.15-0.95)*	1.04 (0.39-2.76)
20-29 years	0.45 (0.20-1.01)	1.31 (0.52-3.28)	0.57 (0.21-1.52)	0.89 (0.31-2.61)
>30 years	0.65 (0.32-1.35)	1.81 (0.76-4.30)	0.84 (0.30-2.36)	1.84 (0.62-5.45)
Marital status				
Married	1.00	1.00	1.00	1.00
unmarried	1.10 (0.65-1.86)	0.75 (0.44-1.26)	1.39 (0.71-2.72)	0.81 (0.41-1.63)
Employment				
Employed	1.00	1.00	1.00	1.00
unemployed	0.83 (0.51-1.36)	0.68 (0.42-1.08)		0.35 (0.17-0.69)
Deprivation				
Least	1.00	1.00	1.00	1.00
middle	0.92 (0.46-1.84)	0.90 (0.48-1.69)	0.78 (0.37-1.65)	0.91 (0.49-1.81)
most	0.58 (0.24-1.41)	0.48 (0.21-1.09)	0.55 (0.20-1.49)	0.50 (0.19-1.32)

Note: AS=Ankylosing spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain. BASDAI = Bath AS Disease Activity Index.

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation * p <0.05, ** p <0.01, *** p<0.001

Association of baseline depression with changes in pain (pain NRS)[a] of patients with AS over six months

	Unadjusted pain NRS		Adjusted pain NRS[b]	
Independent variable	**Deterioration**	**Improvement**	**Deterioration**	**Improvement**
Depression (HADS-D)	0.98 (0.93-1.03)	0.98 (0.93-1.03)	0.96 (0.89-1.04)	0.97 (0.90-1.04)
Gender				
Male	1.00	1.00	1.00	1.00
Female	1.40 (0.85-2.33)	0.94 (0.57-1.57)	1.58 (0.80-3.12)	1.15 (0.59-2.27)
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	1.00 (0.48-2.09)	1.08 (0.53-2.20)	1.47 (0.59-3.66)	1.81 (0.75-4.40)
50-59 years	0.73 (0.36-1.47)	0.84 (0.43-1.65)	0.88 (0.35-2.23)	0.76 (0.31-1.91)
>60 years	0.85 (0.43-1.69)	0.88 (0.46-1.72)	1.20 (0.45-3.20)	1.25 (0.47-3.29)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	0.71 (0.34-1.51)	2.01 (0.89-4.50)	0.78 (0.32-1.93)	2.16 (0.84-5.54)
20-29 years	0.76 (0.35-1.64)	1.26 (0.54-2.96)	0.69 (0.26-1.81)	1.23 (0.44-3.41)
>30 years	0.86 (0.41-1.80)	1.99 (0.89-4.46)	0.89 (0.32-2.49)	2.54 (0.88-7.35)
Marital status				
married	1.00	1.00	1.00	1.00
unmarried	1.00 (0.60-1.68)	1.03 (0.63-1.69)	0.94 (0.48-1.84)	1.02 (0.54-1.95)
Employment				
employed	1.00	1.00	1.00	1.00
unemployed	1.11 (0.69-1.77)	0.81 (0.51-1.27)	1.26 (0.63-2.53)	0.79 (0.40-1.56)
Deprivation				
least	1.00	1.00	1.00	1.00
middle	0.73 (0.37-1.44)	0.73 (0.38-1.40)	0.56 (0.27-1.18)	0.65 (0.32-1.35)
most	0.83 (0.36-1.95)	0.95 (0.43-2.12)	0.71 (0.27-1.89)	1.16 (0.45-2.94)

Note: AS=Ankylosing spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain. NRS = numerical rating scale.

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation. * p <0.05, ** p <0.01, *** p<0.001

Association of baseline anxiety with changes in pain (pain NRS)[a] of patients with AS over six months

	Unadjusted pain NRS		Adjusted pain NRS[b]	
Independent variable	**Deterioration**	**Improvement**	**Deterioration**	**Improvement**
Anxiety (HADS-A)	1.01 (0.96-1.06)	1.00 (0.95-1.05)	0.96 (0.89-1.03)	0.97 (0.91-1.04)
Gender				
Male	1.00	1.00	1.00	1.00
Female	1.40 (0.85-2.33)	0.94 (0.57-1.57)	1.65 (0.83-3.26)	1.15 (0.58-2.29)
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	1.00 (0.48-2.09)	1.08 (0.53-2.20)	1.34 (0.53-3.37)	1.86 (0.76-4.53)
50-59 years	0.73 (0.36-1.47)	0.84 (0.43-1.65)	0.85 (0.33-2.15)	0.80 (0.32-2.02)
>60 years	0.85 (0.43-1.69)	0.88 (0.46-1.72)	1.12 (0.42-3.01)	1.28 (0.48-3.39)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	0.71 (0.34-1.51)	2.01 (0.89-4.50)	0.85 (0.34-2.13)	2.08 (0.81-5.37)
20-29 years	0.76 (0.35-1.64)	1.26 (0.54-2.96)	0.73 (0.28-1.93)	1.17 (0.42-3.27)
>30 years	0.86 (0.41-1.80)	1.99 (0.89-4.46)	0.96 (0.34-2.69)	2.46 (0.85-7.12)
Marital status				
married	1.00	1.00	1.00	1.00
unmarried	1.00 (0.60-1.68)	1.03 (0.63-1.69)	0.98 (0.50-1.93)	0.99 (0.52-1.89)
Employment				
employed	1.00	1.00	1.00	1.00
unemployed	1.11 (0.69-1.77)	0.81 (0.51-1.27)	1.27 (0.64-2.52)	0.77 (0.40-1.50)
Deprivation				
least	1.00	1.00	1.00	1.00
middle	0.73 (0.37-1.44)	0.73 (0.38-1.40)	0.54 (0.25-1.13)	0.68 (0.33-1.41)
most	0.83 (0.36-1.95)	0.95 (0.43-2.12)	0.67 (0.25-1.79)	1.17 (0.46-2.97)

Note: AS=Ankylosing spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain. NRS = numerical rating scale. * p <0.05, ** p <0.01, *** p<0.001

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation.

Association of baseline depression with changes in function (BASFI)[a] of patients with AS over six months

	Unadjusted BASFI		Adjusted BASFI[b]	
Independent variable	**Deterioration**	**Improvement**	**Deterioration**	**Improvement**
Depression (HADS-D)	1.01 (0.95-1.00)	1.03 (0.97-1.08)	1.01 (0.94-1.10)	1.06 (0.98-1.14)
Gender				
Male	1.00	1.00	1.00	1.00
Female	1.72 (1.03-2.86)*	1.31 (0.80-2.13)	2.30 (1.16-4.57)*	1.78 (0.93-3.43)
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	0.86 (0.40-1.83)	1.01 (0.51-2.00)	1.05 (0.42-2.66)	1.23 (0.50-3.01)
50-59 years	1.11 (0.54-2.26)	1.09 (0.56-2.12)	1.82 (0.70-4.74)	1.26 (0.49-3.28)
>60 years	1.03 (0.51-2.08)	1.11 (0.58-2.11)	1.60 (0.58-4.37)	1.41 (0.53-3.78)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	0.36 (0.17-0.76)**	0.69 (0.31-1.56)	0.25 (0.10-0.62)**	0.58 (0.22-1.56)
20-29 years	0.43 (0.19-0.95)*	1.17 (0.51-2.67)	0.36 (0.14-0.96)*	0.82 (0.29-2.32)
>30 years	0.41 (0.20-0.86)*	1.08 (0.49-2.38)	0.19 (0.06-0.55)**	1.09 (0.37-3.19)
Marital status				
married	1.00	1.00	1.00	1.00
unmarried	1.14 (0.68-1.90)	0.80 (0.49-1.32)	1.20 (0.62-2.33)	0.67 (0.34-1.32)
Employment				
employed	1.00	1.00	1.00	1.00
unemployed	0.82 (0.51-1.33)	0.73 (0.46-1.14)	0.93 (0.45-1.91)	0.73 (0.38-1.40)
Deprivation				
least	1.00	1.00	1.00	1.00
middle	1.05 (0.53-2.08)	1.03 (0.56-1.92)	0.94 (0.44-2.00)	1.06 (0.54-2.09)
most	0.65 (0.28-1.52)	0.51 (0.23-1.13)	0.50 (0.18-1.36)	0.40 (0.15-1.06)

Note: AS=Ankylosing spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain. BASFI = Bath AS Functional Index. * p <0.05, ** p <0.01, *** p<0.001

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation.

Association of baseline anxiety with changes in function (BASFI)[a] of patients with AS over six months

	Unadjusted BASFI		Adjusted BASFI[b]	
Independent variable	**Deterioration**	**Improvement**	**Deterioration**	**Improvement**
Anxiety (HADS-A)	1.02 (0.97-1.07)	1.02 (0.97-1.07)	1.03 (0.96-1.11)	1.04 (0.97-1.11)
Gender				
Male	1.00	1.00	1.00	1.00
Female	1.72 (1.03-2.86)*	1.31 (0.80-2.13)	2.28 (1.14-4.55)*	1.76 (0.91-3.40)
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	0.86 (0.40-1.83)	1.01 (0.51-2.00)	1.07 (0.42-2.74)	1.26 (0.51-3.10)
50-59 years	1.11 (0.54-2.26)	1.09 (0.56-2.12)	1.78 (0.68-4.66)	1.25 (0.48-3.26)
>60 years	1.03 (0.51-2.08)	1.11 (0.58-2.11)	1.62 (0.59-4.49)	1.42 (0.53-3.83)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	0.36 (0.17-0.76)**	0.69 (0.31-1.56)	0.24 (0.10-0.60)**	0.55 (0.20-1.47)
20-29 years	0.43 (0.19-0.95)*	1.17 (0.51-2.67)	0.35 (0.13-0.93)*	0.78 (0.27-2.24)
>30 years	0.41 (0.20-0.86)*	1.08 (0.49-2.38)	0.18 (0.06-0.54)**	1.00 (0.34-2.96)
Marital status				
Married	1.00	1.00	1.00	1.00
unmarried	1.14 (0.68-1.90)	0.80 (0.49-1.32)	1.21 (0.62-2.36)	0.70 (0.36-1.37)
Employment				
Employed	1.00	1.00	1.00	1.00
unemployed	0.82 (0.51-1.33)	0.73 (0.46-1.14)	0.88 (0.43-1.78)	0.78 (0.41-1.48)
Deprivation				
Least	1.00	1.00	1.00	1.00
middle	1.05 (0.53-2.08)	1.03 (0.56-1.92)	0.93 (0.43-1.99)	1.06 (0.54-2.09)
most	0.65 (0.28-1.52)	0.51 (0.23-1.13)	0.48 (0.17-1.31)	0.42 (0.16-1.10)

Note: AS=Ankylosing spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain. BASFI = Bath AS Functional Index. * p <0.05, ** p <0.01, *** p<0.001

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation.

Appendix A.12

Association of baseline disease activity with changes in depression (HADS-D)[a] of patients with AS over six months

	Unadjusted HADS-D		Adjusted HADS-D[b]	
Independent variable	**Deterioration**	**Improvement**	**Deterioration**	**Improvement**
Disease activity	1.03 (0.93-1.13)	1.05 (0.96-1.16)	1.01 (0.88-1.15)	1.02 (0.89-1.17)
Gender				
Male	1.00	1.00	1.00	1.00
Female	1.78 (0.98-3.22)	1.61 (0.89-2.93)	2.23 (1.02-4.90)*	1.49 (0.67-3.33)
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	1.27 (0.52-3.11)	1.07 (0.44-2.58)	1.99 (0.68-5.84)	1.20 (0.43-3.37)
50-59 years	0.60 (0.27-1.34)	0.50 (0.23-1.11)	1.11 (0.38-3.22)	0.67 (0.24-1.87)
>60 years	0.55 (0.25-1.19)	0.42 (0.19-0.90)*	1.11 (0.36-3.38)	0.71 (0.24-2.09)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	0.76 (0.31-1.87)	0.93 (0.38-2.32)	0.78 (0.26-2.31)	0.79 (0.28-2.28)
20-29 years	0.77 (0.30-2.00)	1.13 (0.43-2.93)	0.99 (0.30-3.23)	0.88 (0.27-2.84)
>30 years	0.54 (0.23-1.29)	0.56 (0.23-1.37)	0.72 (0.22-2.39)	0.69 (0.21-2.26)
Marital status				
married	1.00	1.00	1.00	1.00
unmarried	1.34 (0.77-2.34)	1.17 (0.67-2.06)	0.81 (0.40-1.65)	0.75 (0.37-1.53)
Employment				
employed	1.00	1.00	1.00	1.00
unemployed	0.89 (0.54-1.47)	0.72 (0.43-1.19)	1.24 (0.59-2.62)	0.76 (0.36-1.61)
Deprivation				
least	1.00	1.00	1.00	1.00
middle	0.99 (0.47-2.08)	0.81 (0.39-1.68)	1.20 (0.41-3.48)	1.41 (0.50-4.01)
most	1.30 (0.51-3.29)	1.09 (0.43-2.75)	0.95 (0.43-2.09)	0.88 (0.40-1.91)

Note: AS=Ankylosing spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain.

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation * p <0.05, ** p <0.01, *** p<0.001

Association of baseline pain with changes in depression (HADS-D)[a] of patients with AS over six months

	Unadjusted HADS-D		Adjusted HADS-D[b]	
Independent variable	**Deterioration**	**Improvement**	**Deterioration**	**Improvement**
Pain	0.98 (0.89-1.07)	1.00 (0.92-1.10)	0.94 (0.83-1.06)	0.94 (0.83-1.07)
Gender				
Male	1.00	1.00	1.00	1.00
Female	1.78 (0.98-3.22)	1.61 (0.89-2.93)	2.33 (1.06-5.13)*	1.51 (0.68-3.37)
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	1.27 (0.52-3.11)	1.07 (0.44-2.58)	2.03 (0.69-5.98)	1.22 (0.43-3.44)
50-59 years	0.60 (0.27-1.34)	0.50 (0.23-1.11)	0.99 (0.34-2.88)	0.65 (0.23-1.82)
>60 years	0.55 (0.25-1.19)	0.42 (0.19-0.90)*	1.04 (0.34-3.19)	0.71 (0.24-2.09)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	0.76 (0.31-1.87)	0.93 (0.38-2.32)	0.80 (0.27-2.40)	0.84 (0.29-2.44)
20-29 years	0.77 (0.30-2.00)	1.13 (0.43-2.93)	1.07 (0.32-3.52)	0.96 (0.30-3.10)
>30 years	0.54 (0.23-1.29)	0.56 (0.23-1.37)	0.83 (0.25-2.75)	0.74 (0.23-2.43)
Marital status				
married	1.00	1.00	1.00	1.00
unmarried	1.34 (0.77-2.34)	1.17 (0.67-2.06)	0.83 (0.41-1.70)	0.74 (0.36-1.52)
Employment				
employed	1.00	1.00	1.00	1.00
unemployed	0.89 (0.54-1.47)	0.72 (0.43-1.19)	1.36 (0.66-2.82)	0.87 (0.42-1.80)
Deprivation				
least	1.00	1.00	1.00	1.00
middle	0.99 (0.47-2.08)	0.81 (0.39-1.68)	0.93 (0.42-2.05)	0.90 (0.42-1.97)
most	1.30 (0.51-3.29)	1.09 (0.43-2.75)	1.30 (0.45-3.76)	1.53 (0.54-4.34)

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation * p <0.05, ** p <0.01, *** p<0.001

Note: AS=Ankylosing spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain.

Association of baseline function with changes in depression (HADS-D)[a] of patients with AS over six months

	Unadjusted HADS-D		Adjusted HADS-D[b]	
Independent variable	**Deterioration**	**Improvement**	**Deterioration**	**Improvement**
Function	1.04 (0.96-1.14)	1.05 (0.96-1.15)	1.10 (0.96-1.26)	1.09 (0.95-1.25)
Gender				
Male	1.00	1.00	1.00	1.00
Female	1.78 (0.98-3.22)	1.61 (0.89-2.93)	2.32 (1.05-5.10)*	1.51 (0.68-3.38)
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	1.27 (0.52-3.11)	1.07 (0.44-2.58)	1.96 (0.66-5.77)	1.18 (0.42-3.32)
50-59 years	0.60 (0.27-1.34)	0.50 (0.23-1.11)	0.99 (0.34-2.89)	0.63 (0.22-1.76)
>60 years	0.55 (0.25-1.19)	0.42 (0.19-0.90)*	1.00 (0.33-3.09)	0.68 (0.23-2.03)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	0.76 (0.31-1.87)	0.93 (0.38-2.32)	0.72 (0.24-2.16)	0.76 (0.26-2.20)
20-29 years	0.77 (0.30-2.00)	1.13 (0.43-2.93)	0.90 (0.27-2.95)	0.83 (0.26-2.69)
>30 years	0.54 (0.23-1.29)	0.56 (0.23-1.37)	0.69 (0.21-2.29)	0.64 (0.20-2.11)
Marital status				
married	1.00	1.00	1.00	1.00
unmarried	1.34 (0.77-2.34)	1.17 (0.67-2.06)	0.83 (0.41-1.70)	0.75 (0.37-1.54)
Employment				
employed	1.00	1.00	1.00	1.00
unemployed	0.89 (0.54-1.47)	0.72 (0.43-1.19)	0.96 (0.43-2.14)	0.62 (0.28-1.38)
Deprivation				
least	1.00	1.00	1.00	1.00
middle	0.99 (0.47-2.08)	0.81 (0.39-1.68)	1.07 (0.37-3.13)	0.85 (0.39-1.85)
most	1.30 (0.51-3.29)	1.09 (0.43-2.75)	0.88 (0.40-1.93)	1.30 (0.46-3.72)

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation * p <0.05, ** p <0.01, *** p<0.001

Note: AS=Ankylosing spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain.

Association of baseline disease activity with changes in anxiety (HADS-A)[a] of patients with AS over six months

	Unadjusted HADS-A		Adjusted HADS-A[b]	
Independent variable	**Deterioration**	**Improvement**	**Deterioration**	**Improvement**
Disease activity	1.08 (0.97-1.19)	1.13 (1.03-1.25)*	1.07 (0.93-1.24)	1.08 (0.94-1.25)
Gender				
Male	1.00	1.00	1.00	1.00
Female	0.97 (0.55-1.69)	0.82 (0.46-1.44)	0.75 (0.36-1.55)	0.49 (0.23-1.03)
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	1.16 (0.49-2.76)	0.84 (0.35-2.02)	1.18 (0.40-3.46)	0.83 (0.27-2.52)
50-59 years	0.47 (0.21-1.04)	0.60 (0.27-1.31)	0.32 (0.11-0.96)*	0.56 (0.19-1.65)
>60 years	0.83 (0.37-1.85)	0.83 (0.37-1.85)	0.47 (0.15-1.49)	0.59 (0.19-1.87)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	1.07 (0.44-2.61)	0.77 (0.32-1.85)	0.93 (0.30-2.88)	0.53 (0.18-1.56)
20-29 years	1.41 (0.54-3.68)	1.07 (0.42-2.73)	2.32 (0.64-8.41)	1.09 (0.31-3.80)
>30 years	1.05 (0.44-2.54)	0.83 (0.35-1.97)	1.60 (0.45-5.73)	0.92 (0.28-3.08)
Marital status				
married	1.00	1.00	1.00	1.00
unmarried	1.16 (0.65-2.08)	1.18 (0.66-2.10)	1.22 (0.56-2.65)	1.36 (0.63-2.92)
Employment				
employed	1.00	1.00	1.00	1.00
unemployed	1.07 (0.64-1.81)	1.30 (0.77-2.19)	1.22 (0.55-2.71)	1.08 (0.49-2.37)
Deprivation				
least	1.00	1.00	1.00	1.00
middle	0.50 (0.22-1.13)	0.67 (0.29-1.54)	0.41 (0.17-0.99)	0.70 (0.28-1.70)
most	0.61 (0.22-1.68)	0.99 (0.36-2.74)	0.49 (0.16-1.55)	0.89 (0.28-2.79)

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation * p <0.05, ** p <0.01, *** p<0.001

Note: AS=Ankylosing spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain.

Association of baseline pain with changes in anxiety (HADS-A)[a] of patients with AS over six months

	Unadjusted HADS-A		Adjusted HADS-A[b]	
Independent variable	**Deterioration**	**Improvement**	**Deterioration**	**Improvement**
Pain	1.06 (0.96-1.17)	1.13 (1.03-1.25)*	1.05 (0.92-1.20)	1.09 (0.95-1.24)
Gender				
Male	1.00	1.00	1.00	1.00
Female	0.97 (0.55-1.69)	0.82 (0.46-1.44)	0.79 (0.38-1.65)	0.51 (0.24-1.08)
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	1.16 (0.49-2.76)	0.84 (0.35-2.02)	1.18 (0.40-3.49)	0.83 (0.27-2.52)
50-59 years	0.47 (0.21-1.04)	0.60 (0.27-1.31)	0.30 (0.10-0.91)*	0.55 (0.19-1.62)
>60 years	0.83 (0.37-1.85)	0.83 (0.37-1.85)	0.44 (0.14-1.41)	0.58 (0.18-1.85)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	1.07 (0.44-2.61)	0.77 (0.32-1.85)	0.90 (0.29-2.80)	0.49 (0.17-1.47)
20-29 years	1.41 (0.54-3.68)	1.07 (0.42-2.73)	2.36 (0.65-8.63)	1.11 (0.32-3.87)
>30 years	1.05 (0.44-2.54)	0.83 (0.35-1.97)	1.71 (0.47-6.13)	0.93 (0.28-3.13)
Marital status				
married	1.00	1.00	1.00	1.00
unmarried	1.16 (0.65-2.08)	1.18 (0.66-2.10)	1.25 (0.57-2.73)	1.38 (0.64-2.96)
Employment				
employed	1.00	1.00	1.00	1.00
unemployed	1.07 (0.64-1.81)	1.30 (0.77-2.19)	1.26 (0.58-2.75)	1.06 (0.49-2.27)
Deprivation				
least	1.00	1.00	1.00	1.00
middle	0.50 (0.22-1.13)	0.67 (0.29-1.54)	0.40 (0.17-0.97)*	0.69 (0.28-1.69)
most	0.61 (0.22-1.68)	0.99 (0.36-2.74)	0.52 (0.17-1.62)	0.93 (0.30-2.88)

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation * p <0.05, ** p <0.01, *** p<0.001

Note: AS=Ankylosing spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain.

Association of baseline function with changes in anxiety (HADS-A)[a] of patients with AS over six months

	Unadjusted HADS-A		Adjusted HADS-A[b]	
Independent variable	**Deterioration**	**Improvement**	**Deterioration**	**Improvement**
Function	1.03 (0.95-1.13)	1.09 (1.00-1.19)*	0.98 (0.85-1.12)	1.01 (0.88-1.17)
Gender				
Male	1.00	1.00	1.00	1.00
Female	0.97 (0.55-1.69)	0.82 (0.46-1.44)	0.79 (0.38-1.63)	0.51 (0.24-1.08)
Age				
20-39 years	1.00	1.00	1.00	1.00
40-49 years	1.16 (0.49-2.76)	0.84 (0.35-2.02)	1.22 (0.42-3.61)	0.85 (0.28-2.57)
50-59 years	0.47 (0.21-1.04)	0.60 (0.27-1.31)	0.33 (0.11-0.98)*	0.54 (0.18-1.60)
>60 years	0.83 (0.37-1.85)	0.83 (0.37-1.85)	0.46 (0.14-1.46)	0.59 (0.19-1.87)
Symptom duration				
< 10 years	1.00	1.00	1.00	1.00
10-19 years	1.07 (0.44-2.61)	0.77 (0.32-1.85)	0.98 (0.32-3.02)	0.54 (0.18-1.59)
20-29 years	1.41 (0.54-3.68)	1.07 (0.42-2.73)	2.44 (0.67-8.84)	1.17 (0.33-4.11)
>30 years	1.05 (0.44-2.54)	0.83 (0.35-1.97)	1.73 (0.48-6.24)	0.97 (0.29-3.29)
Marital status				
married	1.00	1.00	1.00	1.00
unmarried	1.16 (0.65-2.08)	1.18 (0.66-2.10)	1.21 (0.56-2.64)	1.35 (0.63-2.90)
Employment				
employed	1.00	1.00	1.00	1.00
unemployed	1.07 (0.64-1.81)	1.30 (0.77-2.19)	1.53 (0.65-3.59)	1.18 (0.51-2.73)
Deprivation				
least	1.00	1.00	1.00	1.00
middle	0.50 (0.22-1.13)	0.67 (0.29-1.54)	0.43 (0.18-1.02)	0.71 (0.29-1.73)
most	0.61 (0.22-1.68)	0.99 (0.36-2.74)	0.56 (0.18-1.75)	0.98 (0.31-3.09)

[b] odds ratios were adjusted for gender, age, symptom duration, marital status, employment and deprivation * p <0.05, ** p <0.01, *** p<0.001

Note: AS=Ankylosing spondylitis; HADS-D = Hospital Anxiety and Depression scale-depression domain. HADS-A = Hospital Anxiety and Depression scale-anxiety domain.