Understanding the barriers, facilitators and extent of diagnostic delay in axial spondyloarthritis

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"*Beware of the man who works hard to learn something, learns it,*

and finds himself no wiser than before."

-Kurt Vonnegut

Declaration

This PhD was funded by a full-time National Institute for Health and Care Research (NIHR) School for Primary Care (SPCR) studentship from 2018-2021, and was undertaken at Keele University.

The overall program of research was laid out initially by Dr James Prior and Dr Jon Packham, but the design of the constituent studies as they are presented here is my own, as was the collection, interpretation and discussion of the findings of those studies.

Analysis and writing throughout this thesis was undertaken by me, under the supervision of Dr James Prior, Dr Jon Packham, Prof Sarah Ryan and Prof Christian Mallen.

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To my friends, I am sorry to say I shall have to find something else to talk about in the pub from now on, but thank you for listening.

Abstract

Background: Axial spondyloarthritis (axSpA) causes inflammation of the pelvis and spine, resulting in chronic pain, impaired range of movement, fatigue and physical disability. Diagnosis remains challenging and is frequently delayed, resulting in poorer outcomes for patients.

Aim: To ascertain the extent of diagnostic delay for axSpA, to explore patient and healthcare professionals (HCP) perspectives on barriers and facilitators in diagnosing axSpA and to study primary care consultation histories prior to diagnosis.

Method: Mixed-methods design. A systematic review examined the extent of aXSpA diagnostic delay and the role of certain characteristics on delay. A qualitative study explored patient and HCP knowledge and experience of barriers and facilitators in diagnosing axSpA using semi-structured one-to-one interviews and thematic analysis. A case-control study compared the type and frequency of primary care consultations histories of patients with axSpA to those of matched controls.

Results: The systematic review found median diagnostic delay to range from 2-5 years. Gender and family history of axSpA, despite affecting disease presentation, were not associated with delay.

Qualitative study found that patients and HCPs felt that communication, symptoms and behaviour of patients, difficulties in diagnosing axSpA, lack of awareness of axSpA and systemic issues with healthcare impeded diagnosis.

The case-control study found that patients who subsequently are diagnosed with axSpA consult more than those who don't have axSpA. AxSpA patients are more likely

to consult with axial and peripheral symptoms, uveitis, enthesitis, inflammatory bowel disease and psoriasis prior to diagnosis.

Conclusion: Diagnostic delay in axSpA remains extensive and multicausal. This thesis highlights factor currently impeding diagnosis, along with possible solutions including disease education and improving the means and process of communication between patients and HCPs. This thesis suggests several symptoms which can be viewed as indicators of potential axSpA which could reduce diagnostic delay.

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Chapter 1 – Introduction

This chapter outlines the structure and rationale for this thesis, and lays down the aims and objectives, with attendant hypotheses. Specifically, this chapter will describe in general terms axial spondyloarthritis (axSpA) and the concept of diagnostic delay, which will be expanded upon in greater detail in Chapter 2: Background.

1.1 Spondyloarthropathies

Axial spondyloarthritis is a form of spondyloarthropathy, which in turn is a group of inflammatory arthritides. Inflammatory arthritis is arthritis characterised by symptoms and damage related to inflammation rather than directly due to mechanical joint trauma or degeneration. Inflammation is an immune reaction to toxins, pathogens and injury and can present with swelling, heat and pain in the inflamed area, along with redness of the skin (Chen et al., 2017). The spondyloarthropathies also include psoriatic arthritis, reactive arthritis, enteropathic arthritis and enthesitis-related juvenile idiopathic arthritis (Kataria and Brent, 2004).

The prevalence of spondyloarthropathies ranges globally from 0.2% (95% CI 0.00 – 0.66) in South East Asia to 1.61% in North Arctic communities, and has been estimated at 0.54% (0.34 – 0.78) in Europe (Stolwijk et al., 2016). The diseases described under the term spondyloarthropathy share some key characteristics, notably inflammatory back pain, synovitis (inflammation in joints), enthesitis (inflammation of the site of connection between bone and tendon/ligament), and co-morbidities such as psoriasis, uveitis and inflammatory bowel disease (colitis) (Kataria and Brent, 2004).

The spondyloarthropies are also characterised by an association with the biomarker HLA-B27 (Kataria and Brent, 2004). This antigen is present in 6-9% of the general population in Western Europe. Its prevalence is far higher among the spondyloarthropathies. Up to 94% of patients with axSpA are HLA-B27 positive, 40-50% of patients with psoriatic arthritis, 50% of patients with uveitis and 76% of patients with enthesitis related juvenile idiopathic arthritis (Bowness, 2015). Although the cause for this association is not entirely understood, its roles in the immune response and commensurate inflammation have been investigated.

Reactive arthritis is inflammatory arthritis following specific systemic infections (Salmonella, Yersinia, Shigella, Campylobacter, Chlamydia) that then provoke an autoimmune reaction causing joint inflammation (Kataria and Brent, 2004). Psoriatic arthritis (PsA) is inflammatory arthritis occurring alongside psoriasis, affecting up to 42% of patients with that disease. Prevalence is equal between sexes and the disease frequently involves peripheral arthritis along with axial manifestations (Gladman et al., 2005). Enteropathic arthritis occurs alongside inflammatory bowel disease such as ulcerative colitis and Crohn's disease and is reported in between 17 and 39% of patients with IBD. As with PsA, both peripheral and axial involvement occurs in enteropathic arthritis (Peluso et al., 2013). Enthesitis-related juvenile idiopathic arthritis is a form of inflammatory arthritis found in children and adolescents which also presents with peripheral and axial involvement and also involvement of the hips. It is characterised by inflammation of the entheses, the point at which tendons and ligaments attach to bone, and frequently affects the feet, ankles, legs, hips and spine (Ravelli and Martini, 2007).

1.2 Axial Spondyloarthritis

1.2.1 What is axSpA?

Axial spondyloarthritis affects between 0.16% and 1.5% of the UK population (Hamilton et al., 2015; Morgan et al., 2020) and in its modern definition is an umbrella term for all the spondyloarthropathies which affect the axial spine, predominantly radiographic and non-radiographic axSpA. The term "axial spondyloarthritis" was introduced as a specific classification in 2009 (M. Rudwaleit et al., 2009c, 2009a) to group together the two forms of spondyloarthritis; now referred to as radiographic (r-axSpA) and non-radiographic axSpA (nr-axSpA). Prior to this, axial inflammation was generally diagnosed under the term ankylosing spondylitis (Van Der Linden et al., 1984), which is now generally analogous to radiographic axSpA. The primary difference between these two forms of axSpA is that, in radiographic axSpA, the characteristic inflammation of the sacroiliac joints is visible in x-ray imaging, whereas in non-radiographic axSpA, it is characterised by MRI changes in the spine and sacroiliac joints (SIJ) or by specific clinical features in the presence of chronic back pain in individuals with an HLA-B27 positive genetic test. Indeed, AS and ankylosing spondylitis are both still terms frequently used by clinicians when talking about axSpA. As this thesis focuses on both the radiographic and non-radiographic forms of the disease, the terms axSpA and axial spondyloarthritis will be used throughout, apart from in direct quotes.

It is worth noting that any detectable x-ray change of the sacroiliac joints is suggestive that axSpA has been present for some time; symptoms are often present for years before detectable radiographic sacroiliitis (Feldtkeller et al., 2003). In a substantial

proportion of cases, non-radiographic axSpA will eventually develop into radiographic axSpA. One study showed development of non-radiographic to radiographic axSpA in 10% of patients over a two-year follow up (Sampaio-Barros et al., 2001), and another showed 12% nr-axSpA cases developing into the radiographic disease over the same length of time (Poddubnyy et al., 2011). Wang et al found that over a follow-up period of up to 15 years, 26% of non-radiographic axSpA patients developed radiographic axSpA (Wang et al., 2016).

The likelihood of developing the radiographic or non-radiographic form of the disease has also been shown to differ with gender. One study showed patients with the radiographic form of the disease were more likely to be male (64% male) than patients with the non-radiographic form (42.9% male) ($p=<0.001$). This was reinforced by the findings of another study, which showed 70.4% of r-axSpA patients to be male, whereas only 46.5% of nr-axSpA were male (de Winter et al., 2016). With the radiographically visible disease being less prevalent among the female population, MRI imaging is more frequently necessitated for diagnosis, leading to a longer time to diagnosis.

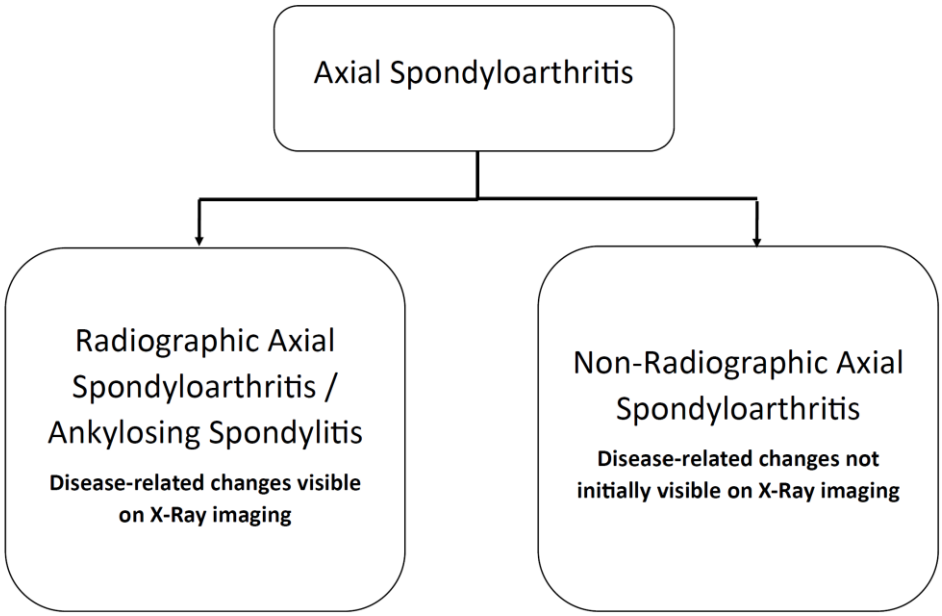


Figure 1.1 The relationship between axial spondyloarthritis, radiographic axSpA (ankylosing spondylitis) and non-radiographic axSpA

1.2.2 Characteristics of axSpA

AxSpA is characterised by inflammation in the SIJ, where the sacrum meets the ilium, and the axial spine. Symptoms most commonly start manifesting in early adulthood, usually in the mid-20s (Boel et al., 2022) and include chronic back pain, stiffness and fatigue (Sieper et al., 2015). Initial presentation of back pain is often described as insidious, i.e., slow to develop, varying in severity over time and affecting different sites in the body. This lowers the likelihood that either patient or clinician recognise that disparate symptoms are connected (Walsh and Magrey, 2021). Many early symptoms are not immediately indicative of inflammatory musculoskeletal disease, such as the aforementioned fatigue, non-specific back pains (common in the general

population) and non-musculoskeletal comorbidities such as uveitis, psoriasis and colitis. As the disease progresses, it can lead to the destruction of bone in the sacroiliac joint and spine, which is replaced by fibrocartilage which itself then ossifies, causing fusion (Walsh and Magrey, 2021). Bony spurs called syndesmophytes can also form along the spine, which can lead to spinal fusion (known as 'bamboo spine'); the process of their formation is not completely understood, but is similar to the processes of early bone formation and fracture healing (Lories and Haroon, 2014).

1.2.3 The Diagnostic Journey of axSpA

While the classification of axSpA is increasingly well defined, it remains difficult to recognise based on presentation of symptoms. A 2006 study found that many of the features most associated with inflammatory back pain, such as morning stiffness, age of onset <45 years, no improvement in pain with rest, night waking due to pain, alternating buttock pain and pain chronicity, were on their own not sufficient to discriminate from mechanical back pain (Rudwaleit et al., 2006), making it extremely difficult to recognise in primary care where mechanical back pain is a very common reason for consultation.

This difficulty of recognition in primary care is problematic as they are the gatekeepers to secondary care, where the majority of diagnosis for axSpA is made. If suspicion is not raised in primary care, it is far less likely patients will consult for their symptoms in secondary care. Research has been undertaken into the experience of patients and healthcare professionals (HCPs, defined throughout this thesis as a professional who provides healthcare treatment and advice based on formal training and experience

("Health professional," 2023)) regarding the process towards diagnosis in primary care, but this is currently very limited and focused on the US (Dube et al., 2021; Kiwalkar et al., 2021; Lapane et al., 2020). Two European studies explore HCP and patient experiences of the diagnostic journey (van Onna et al., 2014) and (Martindale and Goodacre, 2014), respectively, but only the latter reports on the UK. It is widely felt among these studies that awareness of the disease in the general public and in healthcare spheres is problematically low, and that structural issues in healthcare services lead to delayed diagnosis. There is currently a paucity of research into this area however, particularly in the UK, and more is required to create a detailed picture.

1.2.4 Burden of axSpA

Axial spondyloarthritis can be a substantial individual burden for patients, with women reporting greater disease burden and HRQoL impairment compared to men (Bostan et al., 2003; Kotsis et al., 2014; van der Horst-Bruinsma et al., 2013). Additionally, axSpA has a large economic burden, with patients often changing jobs or careers to better suit their ability, retiring early and experiencing work-instability, i.e. their means of employment becoming a bad match for their changing levels of capability (Strand and Singh, 2017). 45% of men with axSpA switch to less demanding jobs as a result of their disease, and 24% retire early, at a mean age of 36 years (Cakar et al., 2009).

Work instability, i.e. continuity in a job for which the patients' capabilities no longer fit well, is also a significant economic burden of axSpA, with it being reported for 40% of patients still in work (Fabreguet et al., 2012).

A recent study estimated the economic burden of axSpA in Spain at an average cost of €11,462.30, over half of which is the direct cost of healthcare, followed by lost labour

costs and non-medical costs (Garrido-Cumbrera et al., 2019a). Research into the economic burden of diagnostic delay in the UK is ongoing, and is currently estimated at a loss of £18.7 billion (National Axial Spondyloarthritis Society [NASS], 2022a; Xydopoulos et al., 2022).

1.2.5 Treatment

While outcomes can frequently be poor for patients with axSpA, current options for management and treatment of the disease are good and continually improving. Physiotherapy and exercise are often initiated and advised, and non-steroidal anti-inflammatory drugs (NSAIDs) such as Naproxen are administered to reduce the symptoms of inflammatory "flares", i.e. the periods during which pain and stiffness caused by the disease becomes acute. These treatments are often effective in the reduction of symptoms, but less so at slowing the rate of disease development, requiring high doses for this effect (Poddubnyy et al., 2012). For greater effect, disease modifying anti-rheumatic drugs (DMARDs) are employed, and these fall under two groups: conventional DMARDs (cDMARDs) and biologic DMARDs (bDMARDs). Conventional DMARDs such as methotrexate and sulfasalazine aim to inhibit radiographic damage (to peripheral joints), whereas biologic DMARDs such as TNF inhibitors and interleukin-17 inhibitors target specific molecules, inhibiting their inflammatory function. While bDMARDs are considerably more expensive than cDMARDs and NSAIDs, their efficacy is comparatively high, they reduce both peripheral joint and axial inflammation, with improved physical function and quality of life scores along with partial remission in up to a third of treated patients (Sieper et al.,

2015). The most positive responses to TNF inhibitors were in patients of younger age and with shorter disease duration (M. Rudwaleit et al., 2004).

1.3 Diagnostic Delay

Diagnostic delay is defined as a situation in which diagnosis of a disease is made over a timeframe which precludes, or at least reduces likelihood of, optimal treatment and management (Seo et al., 2015). Frequently, the actual measure of delay is defined as the time-period between initial onset of the symptoms of disease and final correct diagnosis, but in many cases is broken down into specific periods to assist in understanding which aspects of the diagnostic journey have the most significant effect on diagnostic delay as a whole. Most commonly, these component periods of delay are the delay between: 1) initial symptom onset and initial consultation with an HCP, 2) between first consultation with an HCP and referral to a specialist, 3) first consultation with a specialist and diagnosis. The first period described is often known as “patient delay”, while the subsequent delay is known as “healthcare delay” (Almeida Santos et al., 2021). Additionally, studies will commonly describe “treatment delay”, which is either described as the initial onset of patients’ symptoms to treatment or first consultation/referral to treatment. In some cases the delay between diagnosis and treatment is also described (Salvadorini et al., 2012). Delayed diagnosis for axSpA is common, with around half of patients experiencing some delay (Fallahi and Jamshidi, 2016).

Reducing diagnostic delay has been shown to be an achievable and effective means of improving patient outcomes across a wide spectrum of different diseases. A successful

example of this is in rheumatoid arthritis (RA): In the UK in the 1980s, diagnosis of rheumatoid arthritis (RA) was delayed by a median 100 months (8.3 years); changes in practice reduced this delay to 4 months within a decade. It is of note that 73% of RA patients with diagnostic delay of over 12 months presented with erosive radiographic changes, compared to 35% of patients who encountered 3 or fewer months of delay (Irvine et al., 1999). During this time, it became evident that the most successful method of treatment for slowing disease progression and, in some cases, even reaching a state of remission, was to treat RA aggressively with DMARDs such as methotrexate (Visser and Heijde, 2009). As a result of the changes in treatment approaches and measures taken to reduce diagnostic delay in RA, it is now accepted best practice to aim for diagnosis within a "window of opportunity" of 12 weeks; if diagnosis is achieved within this window, the patient outcomes are considerably improved (Burgers et al., 2019). There is strong evidence that the use of biologic DMARDs such as TNF inhibitors and interleukin 17 inhibitors improve patient outcomes, therefore the potential to define a similar "window of opportunity" for axSpA may be increasing (Agrawal and Machado, 2020).

1.3.1 Impact of diagnostic delay

In 2009, when the classification of axial spondyloarthritis was formalised by ASAS (M. Rudwaleit et al., 2009c, 2009a), there were few treatment options for the disease aside from physiotherapy and NSAIDs. Since that time, the use of bDMARDs such as Adalimumab (TNFα inhibitor), which are considerably more efficacious, has become more common (M. Rudwaleit et al., 2004). The improvement in treatments and the

fact that bDMARDs are shown to be more effective in younger patients with shorter disease duration takes the reduction of delay to diagnosis from being an ideal to an imperative. As described below, earlier diagnosis can avoid many negative disease and lifestyle effects, and now with the increasing use of effective drugs, the push to reduce delay can also reduce the destructive effects of axial spondyloarthritis.

1.3.1.1 Personal Burden

Personal burden of diagnostic delay refers to general health-related quality of life (HRQoL) (physical, mental, emotional and social wellbeing (Yin et al., 2016)), ankylosing spondylitis-related quality of life (ASQoL (Doward et al., 2003)) and levels of disease-related depression (Yi et al., 2020). It also refers to disease activity, mobility, spinal movement, and muted response to treatment.

Disease development is commonly measured using the Bath Ankylosing Spondylitis tools, BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), BASFI (function index) and BASMI (metrology index), and poorer scores in all three have been found in axSpA patients with delayed diagnosis, with an association between diagnostic delay (defined as greater than five years from symptom onset to correct diagnosis) and increased BASMI scores, indicating worsened spinal mobility ($p=<0.001$), along with poorer scores on the remaining Bath indices (Fallahi and Jamshidi, 2016). Additionally, a 2015 study showed delay in diagnosis (defined as a time of greater than eight years having passed between first symptom onset and correct diagnosis) often leads to worse response to drug treatment, with the disease modifying effects of drugs being reduced in patients with delayed diagnosis, despite the length of treatment duration not being significantly increased. The same study also showed increased

radiographically visible changes in the spinal vertebrae associated with delayed diagnosis. Additionally, patients with delayed diagnosis performed worse in day-to-day activity function scores (BASFI, including more difficulty getting out of chairs, worse neck movement, difficulty getting off the floor among other things) and has reduced lumbar spinal range of motion (Seo et al., 2015).

The psychological burden associated with diagnostic delay is also notable, impacting on areas such as quality of life and mood (Yi et al., 2020). One 2017 study showed significantly higher prevalence of depression among patients with diagnostic delay of greater than seven years; 15.5% compared to 9.1% in patients with diagnosis time of less than seven years. Regarding the psychological burden of diagnostic delay, the experience of delay itself has a substantial impact on the patient, being described as "feeling like one is adrift, upsetting, distressing, disheartening, angering and frustrating; time wasted, spent fighting for recognition of a diagnosis and living in confusion and uncertainty" (Martindale and Goodacre, 2014).

1.3.1.2 Economic Burden

Economic burden involves increased likelihood of work absence or unemployment, and also increased cost of healthcare in settings where that is relevant. AxSpA often results in unemployment, with employment rates among patients with axSpA as low as 55% and sick leave of between six to 45 days per year reported (Boonen et al., 2001). Diagnostic delay has also been shown to increase the likelihood of work disability and unemployment in patients with axSpA. A 2014 study found that the risk of work disability, i.e. the inability of an individual to fully perform tasks in their employment

role, increased by 6.6% with every added year of diagnostic delay (Gunasekera et al., 2014). Similarly, a 2009 study found a significant association between length of diagnostic delay and work disability, with patients diagnosed within four years showing no change in employment status, while those with a diagnostic delay of around eight years were significantly more likely to have work disability and permanent disability (Cakar et al., 2009).

1.4 Thesis Rationale

The delay between the onset of axSpA symptoms and the successful diagnosis of the disease remains substantial, causing poorer physical and mental health outcomes for patients through delayed access to treatment and subsequent accelerated disease development. Such impacts also lead to notable micro and macro-economic burdens.

There are increasing numbers of pharmaceutical treatments for axSpA with a high degree of efficacy, and these have greatest effect if introduced as early in disease development as possible, thus reducing burden on both the individual and the system of healthcare. Reductions in time to diagnosis have been achieved in other rheumatological condition, with diagnosis times for RA substantially reduced since the 1980s, resulting in better experiences and outcomes for patients. While this stands as evidence that diagnostic delay can be reduced in other inflammatory conditions, axSpA itself would require a specific approach which takes into account its idiosyncrasies, the experiences of individuals with the disease and the experiences of clinicians managing and diagnosing the disease.

Ascertaining the current global understanding of diagnostic delay (in extent and association) would provide a benchmark against which any future intervention could be gauged. Additionally, understanding characteristics associated with delay is important as it would provide nuance and detail to the wider picture of delay; it could also suggest who to target with interventions to reduce delay.

Exploring the barriers to diagnosis and its possible facilitators from patient and HCP perspectives would provide experiential evidence which could be utilised not only to create a more detailed understanding of the diagnostic journey, but which could also suggest interventions which take into account the lived experience. When diagnostic delay occurs, it frequently occurs prior to referral to secondary care (Deodhar et al., 2016). Exploratory qualitative investigation would give access to data which would not be available at the population level, such as regarding health-seeking behaviours.

Exploration of individuals' experiences and opinions of barriers to, and facilitators of, the diagnosis of axSpA is a powerful avenue of research for many reasons. For instance, while it is invaluable to identify associations with and risks of diagnostic delay, it is also important to explore the circumstances which affect diagnosis time. Exploration of individuals' experiences of receiving a diagnosis of axSpA can enhance understanding of the circumstances and context which contribute to barriers and facilitators of the diagnostic journey.

While qualitative studies have been undertaken into the causes of diagnostic delay, none in the UK have explored the experiences of patients and HCPs in the same study, using the same philosophy and methodology. Exploration into the experiences and understanding of patients and HCPs regarding barriers to and facilitators of diagnosis

of axSpA could lead to novel insights into the diagnostic journey from both perspectives which would not typically be identified using a quantitative approach.

This would be supported by research into consultation patterns prior to diagnosis for axSpA; such research could supply primary care clinicians with evidence-backed means of raising suspicion of possible axSpA and justification for earlier referral. Using primary care electronic health records, a picture of interactions at the start of patients' diagnostic journey can be constructed. Primary care is the gatekeeper to management and diagnosis of axSpA in secondary care; knowing and understanding frequency and character of consultation in primary care could aid in future pattern recognition by GPs, leading to suspicion of inflammatory arthritis being raised earlier.

Together, these three avenues of investigation will generate results to illuminate the current state of the journey to diagnosis for axSpA from three distinct and mutually supporting directions. Knowing the extent of diagnostic delay will create a benchmark against which improvement can be gauged. Knowing more about the barriers and facilitators of diagnosis from patient and HCP perspectives will afford further understanding of the individual experience of the diagnostic process, highlighting important aspects of circumstance and interaction that can be acted upon in future. Knowing more about patterns of consultation in primary care will give greater understanding of what can in future raise suspicion earlier that a patient needs rheumatological referral.

1.5 Aim & Objectives

1.5.1 Aim

The aim of this thesis is to investigate the extent to which diagnosis of axSpA is delayed, the potential reasons for this delay and barriers to diagnosis, and to identify possible methods by which delay can be reduced in the future.

1.5.2 Objectives

1. To systematically review the body of research literature reporting the length of diagnostic delay in axSpA and to synthesise these data.
2. To qualitatively investigate patients' and HCPs' experience and opinion regarding delay during the journey to axSpA diagnosis.
3. To identify and analyse patterns of patients' healthcare consultations prior to their diagnosis of axSpA using a primary care electronic health record database

1.6 Structure of Thesis

This section describes in brief the contents of the subsequent chapters of this thesis, including summarisations of the thesis' constituent studies.

Chapter 2 – Background

This chapter explores in depth the current body of relevant literature regarding axial spondyloarthritis, its characterisation, classification, aetiology, pathophysiology and disease course. Additionally, this chapter will describe further the diagnostic process for axSpA, along with the understanding of its delay prior to this thesis. Finally, this

chapter details current gaps in the existing body of research which require exploration to reach answers to the research questions proposed here.

Chapter 3 – Diagnostic Delay in Axial Spondyloarthritis: A Systematic Review

This systematic review synthesises the current body of literature regarding diagnostic delay in axial spondyloarthritis. In addition to reporting the delay to diagnosis for the disease, this systematic review also reports any factors associated with diagnostic delay.

Chapter 4 – Barriers and Facilitators in Diagnosing Axial Spondyloarthritis: A Qualitative Study

This qualitative study seeks to answer the question: what are HCPs' and patients' experiences and perspectives of barriers to, and facilitators of, diagnosis of axSpA? HCPs and patients were interviewed, and the results of their interviews were thematically analysed to answer this question. This chapter details the method, results, and implications of this study.

Chapter 5 – Primary Care Consultation Patterns Prior to Diagnosis of axSpA: A Case-Control Study

This study utilised patient and matched control data from the Consultations in Primary Care Archive (CiPCA) database, a healthcare records database of several general practices in North Staffordshire. This study shows through comparison with matched controls the strength of association between diagnosis of axSpA and prior frequency of

consultations with primary care. It also shows the strength of association between diagnosis of axSpA and having prior recording in primary care of symptoms known to be suggestive of the disease.

Chapter 6 – Discussion

This chapter discusses the findings of the above studies altogether. It explores their success in answering their respective research questions and as a larger synthesised body of work. Additionally in this chapter the clinical and research implications of the above studies are discussed; how can the results of the above studies be used to justify change in clinical practice to improve diagnosis times, and how do they suggest further research to continue these improvements?

1.7 Summary

AxSpA is chronic and disabling and causes substantial psychological and social stress for the individual. Additionally, due to its presentation so early in life, it causes financial burden not just on healthcare but also due to removing many of its sufferers from work quite early in their life. Despite its severity, the diagnosis of axSpA is still commonly severely delayed, which presents a further burden. Delayed diagnosis is associated with worse disease development, worse response to treatment and significant psychological impact.

This thesis will examine the extent of diagnostic delay in axSpA and factors associated with delay. It will also investigate patient and HCP experience of the diagnostic journey

for axSpA, focusing on barriers and facilitators of diagnosis. Finally, consultation patterns prior to diagnosis of axSpA will be explored. These studies will provide valuable information regarding axSpA and its associated diagnostic journey. This information will add to the body of knowledge on diagnostic delay in axSpA, pointing towards areas for future research and methods by which diagnostic delay can be reduced.

Chapter 2 – Background

This chapter will explore the current body of literature regarding axial spondyloarthritis (axSpA). It will detail the range of symptoms, clinical signs and associated manifestations of axSpA, along with common comorbidities and the course of the disease. Risk factors and aetiology of the disease will then be explored. Following this, the history and rationale of the different diagnostic and classification criteria for axSpA will be detailed, including the current guidelines and diagnostic techniques. Current treatment strategies will then be described, followed by the

methods of measuring disease activity and outcomes of the disease. The chapter will conclude by addressing the issue of delay in the diagnosis of axSpA and the impact on patient outcomes.

2.1 Axial Spondyloarthritis

Axial spondyloarthritis is a painful and often debilitating inflammatory arthritis with a complex, insidious aetiology and a high degree of diagnostic delay. The ache and increasing pain in the lower back and buttocks is caused by the inflammation of the sacroiliac joint, between the sacrum and the ilium, and the pain can radiate in some cases to the groin, abdomen and legs (Sieper et al., 2015). The radiographic changes suggesting inflammation of the sacroiliac joint starts with sclerosis next to the joint, irregularities along the joint-edges and widening of the joint space. This is followed by a narrowing and ankylosing of the joint (Slobodin et al., 2018), a process which starts with excess bone formation known as osteo-proliferation, resulting in fusion of joints (Lories and Haroon, 2014). It is worth noting that any x-ray radiographic changes suggestive of inflammation of the sacroiliac joints is indicative of axSpA at an advanced stage of its development; symptoms can be present for years before radiographic sacroiliitis is detected (Feldtkeller et al., 2003).

2.1.2 Disease Prevalence and Incidence

2.1.2.1 Prevalence

AxSpA is a common inflammatory arthritis, but its prevalence, i.e. the numbers of existing cases within a population, is not uniform globally. Dean et al systematically

reviewed literature detailing prevalence and reported that axSpA is most prevalent in North America with 0.32% people developing it. According to this review, the prevalence in Europe is 0.24%, which can be extrapolated to an estimated 1.3-1.56 million Europeans with the disease (this estimate is pooled from population-based studies from Finland, France, Greece, Hungary, Italy, Lithuania and Turkey). 0.17% have the disease in Asia (estimated 4.63-4.98 million), 0.1 in Latin America and 0.07% have the disease in Africa (Dean et al., 2014).

A recent study estimated the prevalence of axSpA in the UK as 0.16% (Morgan et al., 2020), based on 20,199 confirmed diagnoses between 2003-2017 in the primary care consultation dataset, the Clinical Practice Research Datalink (CPRD). A subsequent 2021 study (data from 1998 to 2018), also based on CPRD, but limiting their search to ankylosing spondylitis (AS) codes, excluding newer axSpA codes, found 12,333 patients in the database with AS, from which they estimated a prevalence in 2017 of 0.18% of the UK population (Crossfield et al., 2021). What is noteworthy and possibly problematic about these latter two studies, whose periods of study substantially overlap, is that they reported very similar prevalence despite the former examining axSpA and the latter examining AS. The possible implications here are that either nr-axSpA is still being coded as AS or that nr-axSpA is being under-recorded, at least in primary care electronic health records databases.

Using the ASAS criteria, Costantino et al found a prevalence in France of 0.43% (Costantino et al., 2015), and examining a Swedish population based on definite diagnoses, Haglund et al. reported prevalence of ankylosing spondylitis in the Swedish population of 0.12%, a considerably lower estimate than found in the estimates based

on European Spondyloarthropathy Study Group (ESSG) criteria (Haglund et al., 2011). A study in the USA showed a prevalence in the American adult population (between the age of 20-69) of 0.9%, using the Amor (1990) criteria (Reveille, 2011). Using the ESSG criteria, the same study found a prevalence in the same population of 1.4% (95% CI 1.0-1.9). Zeng et al (Zeng et al., 2015) found a prevalence in a Chinese population of 0.3% and Julian-Santiago (Julián-Santiago et al., 2016) found a prevalence of 0.09% in a population if indigenous Mexicans. Knowing the variation which can be caused by the criteria by which axSpA is defined is therefore important when examining prevalence estimates. It is important to note here that ESSG and Amor are less specific than mNYC and ASAS, and mNYC and ASAS are far more commonly used, with the NICE Guidelines on spondyloarthropathy referring to the ASAS classification criteria (National Institute for Health and Care Excellence [NICE], 2017).

Table 2.1 Prevalence estimates by year and country

Author	Data Year	Country	Prevalence %
Julián-Santiago et al	2016	Mexico	0.09
Haglund et al	2011	Sweden	0.12
Morgan et al	2003 - 2017	UK	0.16
Crossfield et al	2017	UK	0.18
Zeng et al	2015	China	0.3
Constantino et al	2015	France	0.43
Reveille et al	2011	USA	0.9

2.1.2.1 Incidence

Morgan et al (2020) found the incidence (i.e. the occurrences of new cases of a disease within a defined time-period) of axSpA in the UK population to be 10.8 per 100,000 person-years, based on confirmed diagnoses in the CPRD (Morgan et al., 2020). A US study, using data from all local healthcare providers from the Mayo Clinic, its affiliated hospitals, local nursing homes and private practitioners, found the incidence in a Minnesotan population of 3.1 per 100,000 (Wright et al., 2015) and three Scandinavian studies also showed incidence of 6 or below per 100,000 (6, 6 & 1, (Kaipiainen-Seppänen and Aho, 2000), (Savolainen et al., 2003) & (Söderlin et al., 2002) respectively).

A 2018 systematic review (Bohn et al., 2018) found a wide range of incidence reported globally, from the lowest reported incidence in an Icelandic study reporting 0.44 per 100,000 patient years (Geirsson et al., 2010) to the highest in a Canadian study reporting 15 per 100,000 patient years (Lories and Haroon, 2014). This systematic review did note, however, that reporting of axSpA is currently problematic, based on the studies included in their review; none of the four included studies described axSpA as a whole, for instance, instead reporting ankylosing spondylitis, and different classification criteria were employed for different studies, with two using the modified New York Criteria (Bakland et al., 2005; Koko et al., 2014), one using the New York Criteria (Geirsson et al., 2010) and one using its own bespoke criteria (Lories and Haroon, 2014).

Table 2.2 Incidence estimates by year and country

Author	Data Year	Country	Incidence (per 100,000 PY)
Geirsson et al	2010	Iceland	0.44
Söderlin et al	2002	Scandinavia	1
Wright et al	2015	USA	3.1
Savolainen et al	2003	Scandinavia	6
Morgan et al	2020	UK	10.8
Lories et al	2014	Canada	15

2.1.3 Age, Gender & Geography

A 2022 systematic review found that the first symptoms of axSpA present at a median age of 26 (IQR 20-34), with only small differences globally. In Asia, median age at onset was 24 (20-34), in Europe and North America it was 26 (20-35), Latin America was 27 (21-40) and in the Middle East and North Africa it was 27 (21-35) (Boel et al., 2022). The age of onset is also influenced by other characteristics, as a 2014 study found the average age of onset in axSpA to be 26.3±9.3 years in men and 28.5±10.1 years in women, with non-radiographic disease also shown to manifest at a younger age in male, than in female patients (26.3±9.8 years versus 29.3±11.7 years respectively). However, this research found no significant difference between the age of symptom onset for the radiographic and non-radiographic forms of the disease (Ciurea et al., 2014).

2.1.4 Clinical Presentation

2.1.4.1 Pain & stiffness

Stiffness and pain in the back, hips, chest or neck which abates temporarily through exercise and resuming with inactivity is a defining feature of axSpA (Sieper et al., 2015). Chronic back pain (CBP) of longer than three months is a key characteristic of axSpA but not one that can raise suspicion of axSpA alone, as among the general population, CBP occurs very frequently and axSpA is rarely the cause. Using the ASAS criteria, Hamilton et al estimated that the axSpA prevalence in the population of adults with chronic back pain is 1.3%, meaning the majority of back pain in the general population is due to causes other than axSpA (Hamilton et al., 2015). However, van Hoeven (2014) reported a 24% likelihood of axSpA in a sample with low back pain when symptom onset occurs younger than 45 and pain lasts longer than 3 months, demonstrating the importance of selecting a cohort based on filtering factors (van Hoeven et al., 2014). The majority of chronic back pain symptom onset in axSpA patients occurs in the middle of life; 16.8% starts before the age of 20, 25.3% between the ages of 20 and 29, 31.4% between 30 and 44 and 26.5% after the age of 45. 68% questioned reported their pain was constant (Reveille et al., 2012).

Patients with axSpA commonly experience stiffness after waking up in the morning, lasting 45 minutes or more, and can find themselves woken up with stiffness and pain throughout the second half of the night (Ward, 2013). Approximately 70% of patients describe the back pain associated with axSpA as typically being felt in the lumbar region of the spine and buttocks (Dougados et al., 2011). The back pain is described as a dull ache, becoming more pronounced and persistent over time (Taurog et al., 2016).

Among patients with axSpA, pain and stiffness are also commonly found in the chest, with a study conducted in France demonstrating that 44.6% of patients with symptoms suggestive of axSpA also encounter anterior chest wall pain (Wendling et al., 2013). Pain in the thoracic and cervical spine is less common, but still notable, with 23.3% reporting the former and 11.2% reporting the latter (Dougados et al., 2011).

2.1.4.2 Peripheral arthritis

As with the other spondyloarthropathies, peripheral arthritis is common among patients with axSpA and is experienced by around a third of patients (López-Medina et al., 2019; Winter et al., 2019); its incidence was reported by Lopez-Medina to be 3.7 per 100 patient years among confirmed axSpA patients. Peripheral involvement in axSpA can include inflammation of the joints of the hips, shoulders, hands and knees, with knee involvement reported most frequently (31.7%), and is most frequently reported to manifest after axial symptoms of axSpA, although a fifth of patients do report peripheral symptoms prior to their axial symptoms (López-Medina et al., 2019). Peripheral involvement has been shown to be associated with worsened disease activity and functional impairment (Capelusnik et al., 2021; Winter et al., 2019).

2.1.4.3 Enthesitis

Enthesitis is the inflammation of the insertion site for tendons and ligaments into bone and is very frequently found in patients with axSpA, to the extent it is considered characteristic of the disease (McGonagle et al., 2021). A 2020 study found a quarter of axSpA patients had enthesitis upon entry to the study, with the hip and elbow joints

being the most commonly affected sites (Mease et al., 2020). The same study showed that patients with enthesitis were more likely to be female and to have the non-radiographic form of axSpA and that it was associated with worsened disease activity and physical function.

2.1.4.4 Uveitis

Uveitis is a painful inflammation of the uvea of the eye which can result in blindness (Harthan et al., 2016); it affects between 21 and 33% of patients with axSpA (Rademacher et al., 2020). The prevalence of uveitis increases with axSpA disease duration, from 12% within the first 5 years of disease to 43% after more than 30 years of disease. A 2018 study found the prevalence of axSpA in a population of patients with uveitis to be 20.2% (Sykes et al., 2018).

2.1.4.5 Psoriasis

Psoriasis is an immune-related skin disease causing flaky patches on the skin which can increase in size and number over time and is frequently comorbid with axSpA. It has been found in up to 16.7% of axSpA patients at time of diagnosis, with this number rising to 26.8% over a six-year follow-up. AxSpA patients with comorbid psoriasis experience more swollen joints and peripheral involvement in their disease and are more likely to be treated with either conventional or biological DMARDS (Lucasson et al., 2022).

2.1.4.6 Inflammatory Bowel Disease (ulcerative colitis and Crohn's disease)

Inflammatory bowel disease encompasses two major disorders, ulcerative colitis and Crohn's disease, both of which are inflammatory bowel disorders which cause inflammation and immune disruption in the intestines (Baumgart and Carding, 2007). Prevalence in the UK is estimated as 0.73% of the population seen in primary care, with ulcerative colitis found in 0.4% and Crohn's disease found in 0.28 (Pasvol et al., 2020). It is found in between 6 and 14% of axSpA patients (Fragoulis et al., 2019) and is more frequent in male patients with axSpA and is associated with younger age and higher axSpA disease indicator scores (Van Praet et al., 2013).

2.1.4.7 Sleep Disturbance and Fatigue

Along with the musculoskeletal and inflammatory effects of axSpA, 66% of patients experience fatigue, the causes of which are multi-faceted (Aissaoui et al., 2012). The pain and disturbed sleep caused by the disease both contribute to fatigue, with 46% of patients reporting periods where they "hardly slept" (term from study), resulting in a state of constant tiredness (Kotsis et al., 2014). The unpredictability of axSpA flares and side-effects of medication have also been reported, leaving patients tired and with low mood. It also left them unable to anticipate the presentation behaviour of their disease meaning mitigation for symptoms was often difficult (Davies et al., 2013).

2.1.5 Aetiology

The causes of axSpA are complex, involving the interplay of many environmental, and genetic factors, differing from patient to patient (Zhu et al., 2019). Two factors with a

confirmed association with an increased likelihood of an individual developing axSpA are family history of axSpA and the presence of the human leukocyte antigen B27 (HLA-B27).

2.1.5.1 Genetic

HLA-B27 was first identified in de Blecourt et al (de Blecourt and Polman, 1961) and Caffrey and James (Caffrey and James, 1973) respectively. The prevalence of HLA-B27 in white European populations is between 8 and 10% (Van Der Linden et al., 1984), but <5% of HLA-B27 individuals present with axSpA (Robinson and Brown, 2012).

The majority of axSpA patients are HLA-B27 positive, with its prevalence ranging from 58-95% across different studies. HLA-B27 is a human leukocyte antigen, part of the immune system and responsible for helping the immune system detect problematic particles and molecules; it is possible that HLA-B27 may confer higher levels of viral immunity either through its peptide-binding properties or due to its adjuvant-like effects, which could explain its development and persistence in the population (Bowness, 2015).

A 2014 literature review found between 74-89% of patients with axSpA to be positive (encompassing both radiographic and non-radiographic forms of the disease) (Poddubnyy and Sieper, 2014). A 2012 study found HLA-B27 positivity in 58-75% of non-radiographic axSpA patients and 82-89% of radiographic axSpA patients (Robinson and Brown, 2012). The converse of this association is that, in the whole HLA-B27 positive population, only 1-2% will develop radiographic-axSpA (Reveille et al., 2012), and the absolute risk of spondyloarthropathy in this population is 2-10% (Taurog,

2007), showing that it does have limitations as a biomarker on its own. HLA-B27 positive individuals with a family history of axSpA are significantly more likely to develop axSpA than HLA-B27 positive individuals with no family history; 15-20% likelihood compared to the previously stated 1-2% (Reveille, 2011).

Despite the association between HLA-B27 and axSpA having been known since 1973 (Caffrey and James, 1973), the nature of this association remains unclear (Taurog, 2007). There have, however, been hypotheses regarding the role of HLA-B27 in the pathogenesis of axSpA (Bowness, 2015):

1) HLA-B27 presents arthritogenic peptides, causing inflammatory T cell responses.
2) HLA-B27 may misfold within the endogenous reticulum and trigger cell destruction.
3) HLA-B27 heavy chains may be expressed at cell surfaces, resulting in inflammatory responses.
4) HLA-B27 can influence the gut biome, leading to an inflammatory response.

Defining the risk of axSpA in HLA-B27 positive populations is difficult. For instance, in a German cohort, HLA-B27 was found in 82.2% of patients with radiographic axSpA, and 74.7% of non-radiographic patients; while the percentage remains high in both sub-types, it does range by over ten percent (Martin Rudwaleit et al., 2009). A study of patients with early axSpA showed only 57.3% of patients tested positive for HLA-B27 (Dougados et al., 2011). Furthermore, HLA-B27 positivity is not globally homogenous, and there are many sub-types of the gene. Some of these are regionally specific: HLA-B2704 is predominantly found in the Chinese population, for example, whereas HLA-

B2705 is found in Caucasian populations, HLA-B2707 is found in South Asian and Middle Eastern populations and HLA-B2702 is found in Mediterranean populations, and all of these are associated with axSpA. Some sub-types are not associated with axSpA at all, such as HLA-B2706 and B2709, found in the South of Italy (Khan, 2013). Furthermore, despite its association with disease onset, HLA-B27 has not been found to have a significant association with radiographic change and disease progression (Boonen et al., 2015).

Further to HLA-B27, other genes have been linked to axSpA. HLA-B60 and B61 have shown a degree of association with axSpA, particularly where the disease develops in HLA-B27 negative patients (Wei et al., 2015). Additionally, HLA-B60 found alongside HLA-B27 has been shown to be a strong predictor of axSpA development in a Taiwanese population, with the relative risk (RR) of the disease in HLA-B27+/HLA-B60- patients being 152 (95% CI 91-255), and the RR of HLA-B27+/HLA-B60+ patients being 201 (95% CI 85-475) compared to patients without these genes. HLA-B51 and HLA-DRB1*0103 have also been shown to be a moderate risk for the radiographic disease (Wei et al., 2015).

Further, ERAP1 which provides protein building instructions important to the endoplasmic reticulum is also associated with axSpA, as is MEFV a gene involved in the process of inflammatory response and which is implicated in the pathogenesis of familial Mediterranean fever (Brown et al., 2016).

2.1.5.2 The Gut

Genetics alone do not account entirely for the development of axSpA. The presence of commensal bacteria seems to be a trigger for inflammatory symptoms in HLA-B27 positive transgenic rats (Taurog et al., 1994), and HLA-B27 positive children with enthesitis-related arthritis were found to harbour specific species of bacteria such as *Akkermansia muciniphila and Bacteriodes*, which could contribute to the development of the disease (Stoll *et al.*, 2014). HLA-B27 may be in some ways causative here, as altering the gut biome, leading to a microbial imbalance can lead to inflammation (Rosenbaum and Davey, 2011). This is supported by findings showing that between 57-70% of patients with the radiographic disease have asymptomatic inflammation of the small intestine (Hwang et al., 2021).

The interaction between the gut microbiome remains poorly understood, however, with little consensus between triggering bacterial species found between studies.

2.1.5.3 Mechanical

Another factor implicated in the development of axSpA is mechanical joint stress leading to inflammation of the entheses. This has been demonstrated in transgenic rats, where mechanical joint stress was shown to lead to the development of enthesitis and bone growth (Jacques et al., 2014). It has also been demonstrated in humans, with a possible corollary that this inflammatory reaction is likely associated with the genetic predispositions detailed above. Individuals genetically predisposed to axSpA may show greater reaction to mechanical joint stress, meaning it would be advisable for individuals with axSpA who are in a highly physical career to consider

changing their professional paths to mitigate their disease progression (McGonagle et al., 2001).

2.1.6 Disease Classification

Classification criteria for the diseases encompassed by axSpA have been developed iteratively over the past six decades, starting with the Rome Criteria in 1963 (Kellgren et al., 1963) for ankylosing spondylitis. The Rome Criteria has been superseded in the intervening decades, but elements remain fundamental to subsequent classification criteria. The Assessment of Spondyloarthritis International Society classification criteria (M. Rudwaleit et al., 2009c, 2009a) are the current benchmark criteria for axSpA and the modified New York Criteria (Van Der Linden et al., 1984) is still widely used and has been since the 1980s. Aside from these, other sets of classification criteria have been developed, such as the Amor criteria (Amor et al., 1990) and the European Spondyloarthropathy Study Group (ESSG) (Dougados et al., 1991), but these are not widely used due to the superior sensitivity and specificity of the ASAS criteria.

Table 2.3 History of Classification Criteria

Year	Classification Criteria
1963	Rome Criteria (Kellgren, Jeffrey and Ball, 1963)
1968	New York Criteria (Bennett PH, 1968)
1984	Modified New York Criteria (Van Der Linden, Valkenburg and Cats, 1984)

1990	Amor Criteria (Amor, Dougados and Mijiyawa, 1990)
1991	European Spondyloarthropathy Study Group (ESSG) Criteria (Dougados *et al.*, 1991)
2009	Assessment of SpondyloArthritis International Society (ASAS) Criteria (Rudwaleit, Landewé, *et al.*, 2009; Rudwaleit, Van Der Heijde, *et al.*, 2009)

Box 2.1 Criteria of the Modified New York Criteria for Ankylosing Spondylitis

1) Clinical criteria

a) Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest.

b) Limitation of motion of the lumbar spine in both the sagittal and frontal planes.

c) Limitation of chest expansion relative to normal values corrected for age and sex.

2) Radiologic criterion

Sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3-4 unilaterally

Grading

1) **Definite ankylosing spondylitis if the radiologic criterion is associated with at least 1 clinical criterion.**
2) **Probable ankylosing spondylitis if:**
    a) **Three clinical criteria are present.**
    b) **The radiologic criterion is present without any signs or symptoms satisfying the clinical criteria. (Other causes of sacroiliitis should be considered)**

With the aim of identifying patients with early, pre-radiographic, axial spondyloarthritis, the Assessment of SpondyloArthritis International Society (ASAS) developed an axSpA classification criteria based around "clinical" and "imaging" arms, with the clinical arm requiring the presence of haplotype HLA-B27, plus two spondyloarthritic features whereas the imaging arm (x-ray or MRI) required inflammation of the sacroiliac joints (sacroiliitis) plus one further spondyloarthritic feature to be classed as being diagnosed with axial spondyloarthritis.

The ASAS criteria have higher sensitivity and specificity than other preceding criteria, with a sensitivity of 82.9% and specificity of 84%, compared to 70.7% sensitivity and 63.5% specificity from the ESSG criteria and 69.4% and 78.4% for the Amor criteria (Van Den Berg et al., 2013).

Box 2.2 ASAS classification criteria for axial spondyloarthritis

In patients with ≥3 months back pain and age of onset <45 years:		
Sacroiliitis on imagine AND ≥ 1 spondyloarthritis (SpA) feature	**OR**	**HLA-B27 positive AND ≥ 2 other SpA features**
SpA Features		

	• Inflammatory back pain • Arthritis • Enthesitis (heel) • Uveitis • Dactylitis • Psoriasis • Crohn's/colitis • Good response to NSAIDs • Family history of SpA • HLA-B27 • Elevated CRP
Sacro-iliitis on imaging • Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA • Definite radiographic sacroiliitis according to modified New York Criteria	

2.1.7 Diagnosis

AxSpA diagnosis in the UK involves excluding other similar diseases, or a range of other conditions which present with similar symptoms. There are guidelines for diagnosis, the most prominently used in the UK being the NICE Spondyloarthritis clinical Guidelines for (National Institute for Health and Care Excellence [NICE], 2017).

2.1.7.1 NICE GUIDELINES

In primary care, HCPs in the UK are advised that if a person presents with lower back pain lasting longer than three months, which started before the age of 45, they should be referred to a rheumatologist for a spondyloarthritis assessment if four or more of the following additional criteria are also present:

- Low back pain that started before the age of 35 years (this further increases the likelihood that back pain is due to spondyloarthritis compared with low back pain that started between 35 and 44 years)
- Waking during the second half of the night because of symptoms
- Buttock pain
- Improvement of symptoms with movement
- Improvement within 48 hours of taking non-steroidal anti-inflammatory drugs (NSAIDs)
- A first degree relative with spondyloarthritis
- Current or past arthritis
- Current or past enthesitis
- Current or past psoriasis

If three of these criteria are present, it is advised that a HLA-B27 test be performed; if it is positive, the patient is to be referred to a rheumatologist for assessment. If the criteria are not fully met, but suspicion of axSpA remains, the patient is advised to seek repeat assessment if any new signs, symptoms or risk factors arise (National Institute for Health and Care Excellence [NICE], 2017).

Upon referral to specialist care, rheumatologists will refer to classification criteria such as the ASAS classification criteria (M. Rudwaleit et al., 2009c, 2009a) to aid diagnosis, supported by radiography and MRI to attempt visual proof of axSpA. If inflammation is not visible upon imaging, but suspicion remains, there is the further possibility of diagnosis on clinical grounds, specialist musculoskeletal radiology review, HLA-B27

testing (if not already performed) or follow-up MRI (National Institute for Health and Care Excellence [NICE], 2017).

2.1.7.2 Berlin diagnostic algorithm and the ASAS update to Berlin diagnostic algorithm for diagnosing axSpA

In 2004, Rudwaleit et al designed an algorithm to assist with the accurate diagnosis of axSpA before the development of radiographically visible inflammation and damage (M Rudwaleit et al., 2004). This algorithm used probabilities accumulating through a flowchart to allow a practitioner to reach a quantified estimate of the likelihood of axSpA diagnosis, while also reducing the need for unnecessary interventions and tests. This diagnostic model was also the first time the utility of MRI in diagnosis of axSpA was given a definite diagnostic value. This is shown in the flowchart below, where likelihood of axSpA diagnosis associated with characteristics, is noted as a percentage (Figure 2.1). The likelihood that a patient presenting with chronic back pain will go on to develop axSpA, for instance, is estimated in this study at 5%.

While this algorithm was regarded as a useful means with which to guide HCPs regarding the likelihood of a patient's diagnosis, there were a number of points of underperformance which were later raised by van den Berg et al in 2013 (Van Den Berg et al., 2013). Significantly, the Berlin algorithm included inflammatory back pain as a necessary symptom for axSpA diagnosis, despite this not being found universally in patients with axSpA. Indeed, only 70-80% of axSpA patients initially present with inflammatory back pain, meaning the Berlin algorithm could potentially be excluding 30% of possible patients (Rojas-Vargas et al., 2009). The ASAS modification adjusted

for this by removing inflammatory back pain as a necessity for axSpA diagnosis, instead classing it as an SpA feature and requiring four SpA features rather than three to reach an 80-95% probability of axSpA diagnosis without further investigation (Van Den Berg et al., 2013). When tested on a sample of 685 patients presenting with chronic back pain, the ASAS revision showed greater sensitivity and specificity than the original Berlin algorithm.

Figure 2.1 The Berlin Diagnostic Algorithm (Rudwaleit 2004)

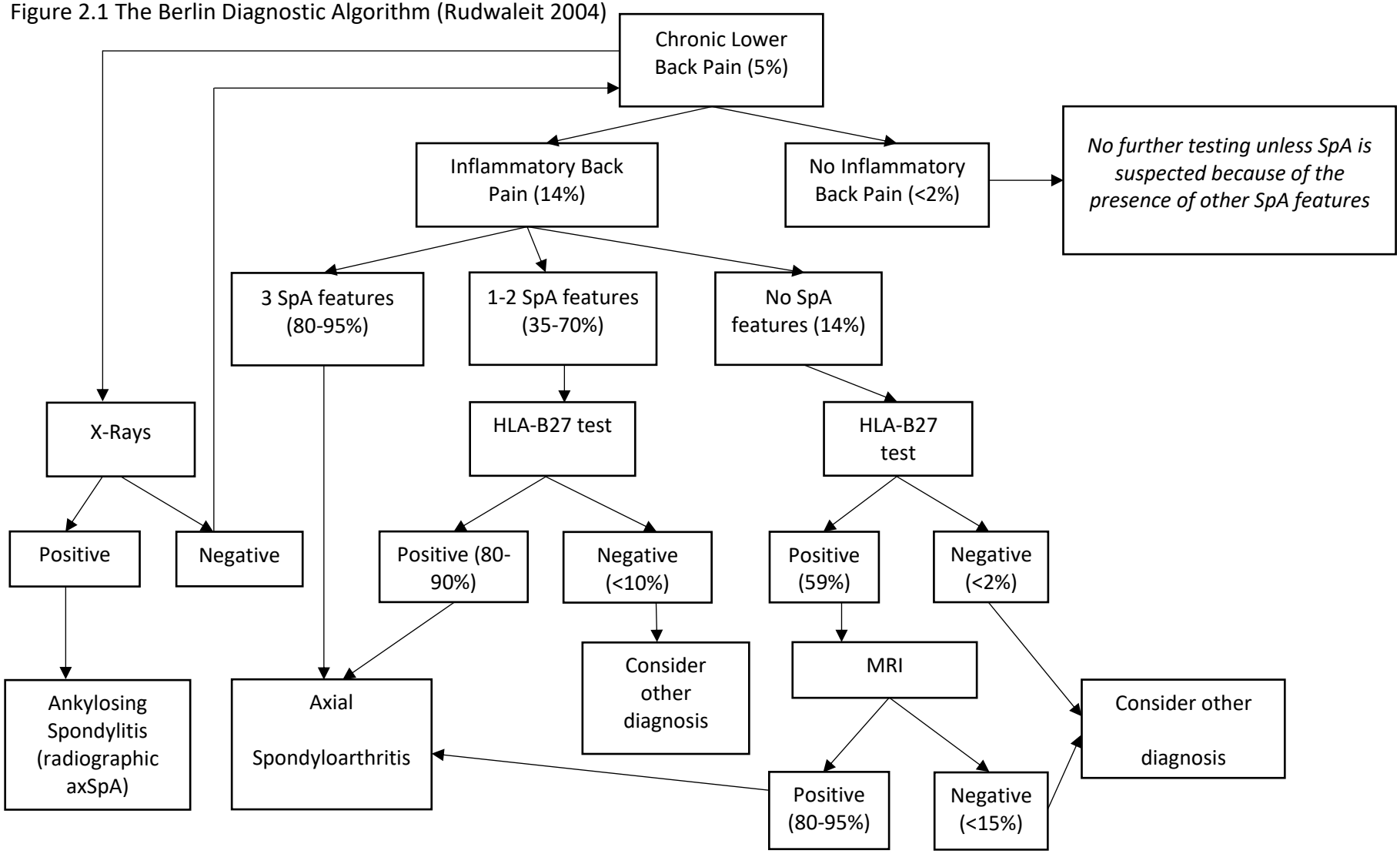
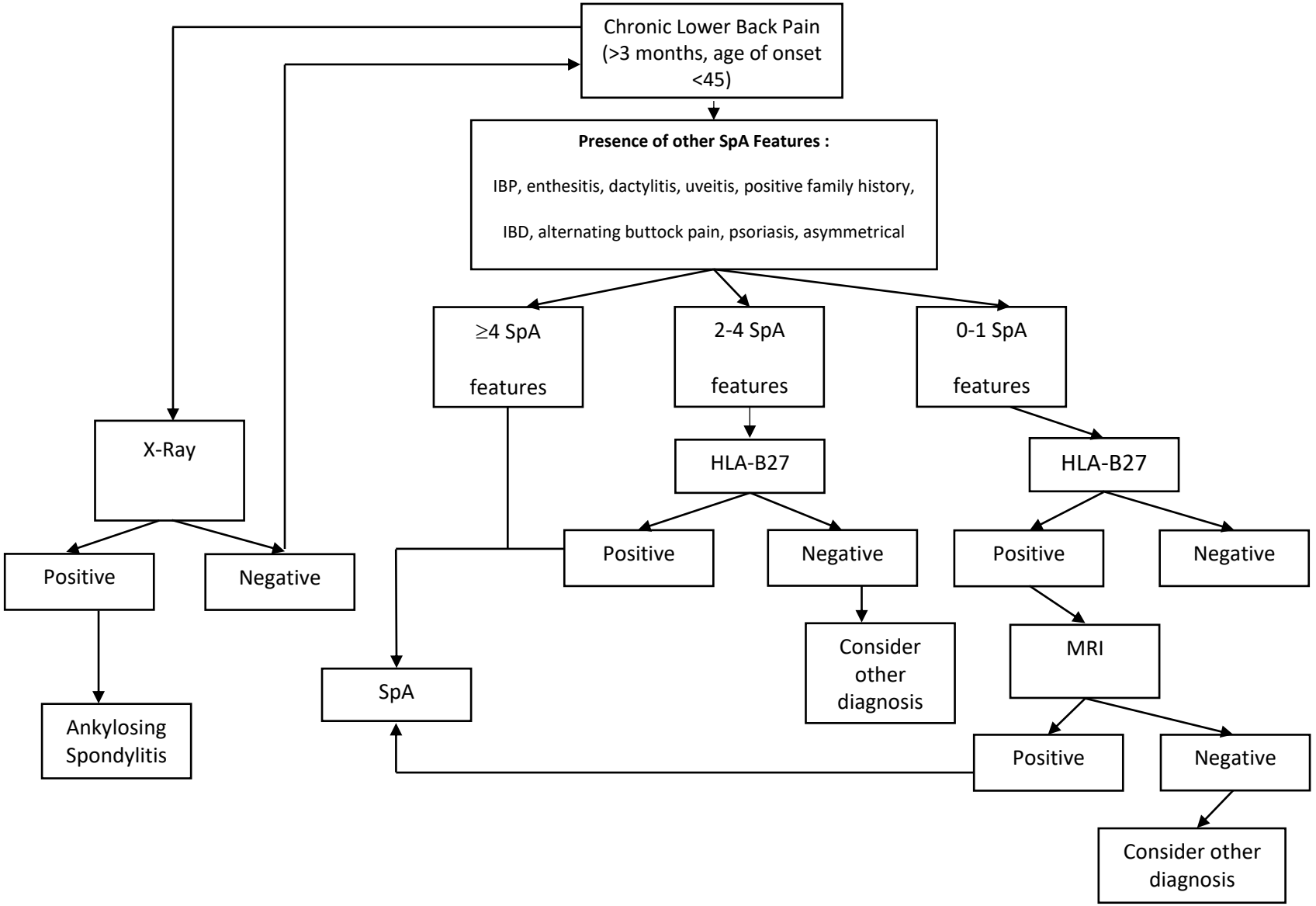


Figure 2.2 ASAS Modification of Berlin Diagnostic Algorithm (van den Berg 2012)



2.1.7.3 Use of radiography in diagnosis

Radiography in the diagnosis of axSpA can show the sacroiliac inflammation and joint erosions characteristic of radiographic axSpA, although compared to other imaging methods, such as magnetic resonance imaging (MRI), it does not achieve high sensitivity or specificity (66 and 67% respectively) (Diekhoff et al., 2022). Radiographic axSpA presents in X-Ray imaging as visible changes along the sacroiliac joint connecting the sacrum to the ilium, including initial widening of the joint before later narrowing, erosions, sclerosis and bony proliferation along the joint sides and, in advanced cases the line of the SI joint can cease to be visible (Wang et al., 2005). When present alongside chronic back pain, radiographically visible inflammation and joint destruction was considered the "gold standard" for diagnosing AS, but these are clinical signs that would only be indicative of axSpA at a relatively advanced stage. By the time axSpA features are radiographically visible, the disease can be quite advanced in its development, and treatment of the disease has been shown to be less effective in cases where diagnosis is delayed (Seo et al., 2015). Radiographic evidence is also inconclusive for axSpA in juvenile patients, as incomplete ossification in these patients can be mistaken for the effects of axSpA (Lukas et al., 2018), and NICE guidance suggests X-Rays aren't used for patients with a skeleton still in development; MRI would be used (National Institute for Health and Care Excellence [NICE], 2017).

Additionally, radiological changes caused by axSpA do not always start with the sacroiliac joint. In around 5% of cases, inflammation, joint destruction and the formation of syndesmophytes can occur prior to, or in exclusion to, radiographically visible sacroiliac inflammation (Machado et al., 2016).

2.1.7.4 Use of Magnetic Resonance Imaging in diagnosis

Where radiography is insufficient to assist in the diagnosis of axSpA, such as in early disease where sacroiliac inflammation may not yet be radiographically visible or in the cases of patients with non-radiographic axSpA, magnetic resonance imaging (MRI) can be a more informative alternative. MRI can be used to detect bone marrow oedema, erosions, sclerosis, synovitis, enthesitis and capsulitis, which are associated with axSpA (Lukas et al., 2018).

Despite its sensitivity relative to X-Ray (Diekhoff et al., 2022), MRI diagnosis is by no means a 'gold standard' diagnostic test for axial inflammation as all inflammation present may not be shown on an MRI scan. Additionally, interpretation of MRI evidence is quite subjective. While in theory, two inflammatory lesions visible in one slice or one lesion visible over two slices should be indicative of inflammatory arthritis, there is a possibility of false positives caused by structural tension or visual artefacts caused by vasculature (Lukas et al., 2018; M. Rudwaleit et al., 2009b). Additionally, sacroiliac bone marrow oedema has also been reported in over a third of athletes included in a 2016 study (Latourte et al., 2018; Weber et al., 2016). MRI, therefore, is not a singular and conclusive diagnostic tool for axSpA, but rather a means by which to reach greater certainty of diagnosis when used alongside a wide array of other methods and observations.

Imaging using radiography or MRI is not, however, the only method of reaching a definite axSpA diagnosis. Where neither radiographic nor MRI evidence is found, but a

high suspicion of axSpA remains, particularly in patients testing positive for HLA-B27, a diagnosis of non-radiographic axSpA can still be reached (Lukas et al., 2018).

2.1.8 Measures of Disease Activity

The disease activity measures below are designed to provide metrics by which to chart the course of the development of axSpA in a patient. There are many varied methods for measuring disease activity, but described below are the most frequently utilised, as described by Taurog et al (Taurog et al., 2016).

2.1.8.1 Bath Ankylosing Spondylitis Disease Activity Index – BASDAI

The most frequently used method of quantifying axSpA disease activity is the Bath Ankylosing Spondylitis Disease Activity Index, introduced in 1994 by a multidisciplinary team to capture the effect of axSpA on a range of patient characteristics. The characteristics examined are severity of fatigue, spinal and peripheral joint pain, localised tenderness and morning stiffness over the previous week. A total score of zero to ten represents the level of disease activity, with a higher score indicating greater disease activity (Garrett et al., 1994).

2.1.8.2 Bath Ankylosing Spondylitis Functional Index – BASFI

The BASFI was developed contemporaneously with the BASDAI. It assesses the patients' level of ability to perform everyday tasks. These are: putting socks on without an aid, bending down at the waist to pick a pen up off the floor, getting up out of an armless chair without using their hands, getting up from the floor from lying on their

back, standing unsupported for ten minutes without discomfort, taking 12-15 steps without a hand rail or walking aid, looking over their shoulder without turning their body, physically demanding activity and a full day's work. Like the BASDAI, the BASFI is also scored out of ten with a higher score indicating poorer physical function (Calin et al., 1994).

2.1.8.3 Bath Ankylosing Spondylitis Metrology Index – BASMI

Also in 1994, the BASMI was developed to measure the range of movement in patients with axSpA, with the resultant score being indicative of disease activity (Jenkinson et al., 1994). The BASMI measures degrees of neck rotation, the distance between the tragus and the wall while the patient has their back to the wall, sideways flexion of the lumbar spine and the distance between patients' medial malleoli (ankle bones) when the legs are fully separated (usually measured lying down). Additionally, BASMI includes the modified Schober test, which measures the amount of flexion taking place in the lumbar spine as the patient bends forward from the hips to touch their toes.

2.1.8.4 Stoke Ankylosing Spondylitis Spinal Score – mSASSS

The modified Stoke Ankylosing Spondylitis Score is a 2005 update of the Stoke Ankylosing Spondylitis Score (SASSS), which measures disease activity primarily by observing bony changes of the spine (Creemers et al., 2005). It utilises a numerical scoring system for radiographic observations of the lumbar and cervical spine, which is as follows: 0 – no abnormality, 1 – erosion, sclerosis or squaring, 2 – syndesmophyte, 3 – total bony bridging.

2.1.8.5 Ankylosing Spondylitis Disease Activity Score – ASDAS

Published in 2011, is the ASDAS, which was designed to represent the frequently complex presentation of axSpA, not only providing a metric for global disease progression, but also allowing prognostic inference based on regional development (Machado et al., 2011). The foci of this disease activity measure are spinal pain, the duration of morning stiffness, a patient overall global assessment, peripheral arthritis and levels of blood inflammation (CRP) (Taurog et al., 2016).

2.1.9 Treatment and Management

As stated in the 2016 update of the ASAS/EULAR recommendations for the management of axSpA, "*the primary goal of treating the patient with AS is to maximise the long-term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalisation of function and social participation*" (van der Heijde et al., 2017). The full list of ASAS/EULAR management recommendations from 2016 can be found below (Box 2.3).

Box 2.32016 ASAS/EULAR Management Recommendations for axSpA

#	Recommendation
Recommendation 1	The treatment of patients with axSpA should be individualised according to the current signs and symptoms of the disease (axial, peripheral,

	extra-articular manifestations) and the patient characteristics including comorbidities and psychosocial factors
Recommendation 2	Disease monitoring of patients with axSpA should include patient-reported outcomes, clinical findings, laboratory tests and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity and treatment
Recommendation 3	Treatment should be guided according to a predefined treatment target
Recommendation 4	Patients should be educated about axSpA and encouraged to exercise on a regular basis and stop smoking; physical therapy should be considered
Recommendation 5	Patients suffering from pain and stiffness should use an NSAID as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise
Recommendation 6	Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated and/or poorly tolerated
Recommendation 7	Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receiv long-term treatment with systemic glucocorticoids

Recommendation 8	Patients with purely axial disease should normally not be treated with csDMARDs; sulfasalazine may be considered in patients with peripheral arthritis
Recommendation 9	bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with TNFi therapy
Recommendation 10	If TNFi therapy fails, switching to another TNFi or an anti-IL-17 therapy should be considered
Recommendation 11	If a patient is in sustained remission, tapering of a bDMARD can be considered
Recommendation 12	Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age; spinal corrective osteotomy in specialised centres may be considered in patients with severe disabling deformity
Recommendation 13	If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed

2.1.9.1 Non-Pharmacological

As highlighted by Recommendation 3 above, patient education and physiotherapy is recommended for first line treatment (van der Heijde et al., 2017). While specific guidance for physiotherapy, physical activity and lifestyle management are scarce for axSpA management (Martey and Sengupta, 2020), research into the field has reached

encouraging conclusions. Supervised physiotherapy has been shown to reduce disease activity and functional limitation, while increasing spinal mobility. Further to this, self-supervised activity such as Pilates, cardiorespiratory exercise, exercise with videogames and muscle-strengthening exercise all had positive effects on pain, fatigue, swelling and morning stiffness (Gravaldi et al., 2022). In 2013, a set of recommendations for behaviours to improve the living and working environment for patients with axSpA were laid out by Feldtkeller et al, based on a thorough review of literature; a summarised version of these can be found below (Feldtkeller et al., 2013). For greatest efficacy, it is recommended that this advice be provided to patients as early in the course of their disease as possible.

Table 2.3 Behavioural Recommendations for Patients with axSpA

#	Recommendation	Description
1	Basic principle	Maintain a proper posture at work, at leisure and when sleeping
2	Sitting position	Hollow back while sitting
3	Walking	Long steps, well-fitted footwear adapted for axSpA
4	Sleeping	Sleep on back, upper body elevated
5	At work	Change position regularly, maintain posture. Work involving bending, twisting, stretching and vibration are not recommended
6	Exercises	Daily exercise and breathing exercises

7	Sports/recreation	Remain physically active. Sports connected with straight posture and stretching of the trunk especially recommended
8	Diet/lifestyle	Less meat and more vegetarian. No smoking
9	Sexuality/pregnancy	Openness and experimentation for comfortable positioning recommended
10	Membership in patient organisation	AS-specific patient organisations will provide reliable information on disease, education courses, exchange of experiences, physiotherapy, sports, social activity, overcoming social isolation, medical and legal advice

2.1.9.2 Non-Steroidal Anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line treatment for axSpA (Poddubnyy, 2013), as they have been shown to be effective at reducing pain and stiffness and are reported to produce clinically significant improvement in 60% of treated patients (Sieper et al., 2014). NSAIDs operate by suppressing cyclo-oxygenase (COX), reducing the inflammatory response, resulting in symptomatic relief for patients with inflammatory conditions (Ghlichloo and Gerriets, 2022).

NSAIDs are commonly used to treat pain and inflammation and consist of a wide range of oral medications including over-the-counter varieties such as ibuprofen to those taken at a higher dose such as diclofenac and 'traditional' NSAIDs such as naproxen and COX-2 selective/specific NSAIDs such etoricoxib.

Evidence also suggests that, in addition to improving health related quality of life (HRQOL), NSAIDs can also reduce disease activity in axSpA and prevent more radiographic changes than TNF inhibitors in the first 5-7 years of therapy (van der Heijde et al., 2017), with greater efficaciousness reported from COX-2 NSAIDs (Poddubnyy, 2020). Where possible, it is recommended patients with axSpA continue treatment with NSAIDs for as long as feasible. In some cases, this may be the result of gastric mucosal issues and bleeding caused by the inhibition of COX, which mediates gastric mucosa, platelet aggregation and kidney function (Ghlichloo and Gerriets, 2022). In other cases the efficacy of treatment by NSAIDs may no longer have sufficient positive effects for a patient (Poddubnyy, 2013). Where disease activity is not reduced within four weeks despite a therapeutic trial of at least two different NSAIDs, patients may become candidates for the use of disease modifying anti-rheumatic drugs (DMARDs) (van der Heijde et al., 2017).

2.1.9.3 Disease Modifying Anti-Rheumatic Drugs

If patients are intolerant of NSAIDs or if they are no longer efficacious, DMARDs are recommended (Braun and Sieper, 2007; van der Heijde et al., 2017). Conventional synthetic DMARDs (csDMARDs), such as sulfasalazine and methotrexate suppress inflammatory responses, and are commonly used to treat other inflammatory conditions such as rheumatoid arthritis. Their use for axSpA is a source of controversy as they are unlikely to be efficacious in treating axial inflammation (Ganapati et al., 2021), although they do have a role for peripheral synovitis / enthesitis manifestations of axSpA (Poddubnyy, 2013). Ganapati et al's 2021 study does show a degree of

efficacy in treating axSpA, regardless of peripheral involvement, where methotrexate and sulfasalazine are combined. Additionally, csDMARDs may be indicated in cases of a reaction to biologic DMARDs (detailed below) and/or NSAIDs or where cost may be a factor (van der Heijde et al., 2017).

2.1.9.4 Biologic Disease Modifying Anti-Rheumatic Drugs

Biologic DMARDs (bDMARDs) are so called due to their production using biological methods such as monoclonal lines, and target specific aspects of the immune system, in contrast to the more general approach of synthetic DMARDs such as methotrexate and sulfasalazine, the mechanism of action is not well understood (Choi and Fenando, 2022). bDMARDs are indicated when NSAIDs are no longer sufficient in the management of axSpA (van der Heijde et al., 2017); the most frequently used are tumour necrosis factor alpha (TNFα) inhibitors such as adalimumab, which inhibits the action of TNFα, an inflammatory cytokine implicated in the pathogenesis of axSpA. The efficacy of TNFα inhibitors in the treatment of axSpA, particularly the radiographic form of the disease, is high, with 50% of patients reported to respond well over the course of a two-year study, reducing disease activity and improving function (Corbett et al., 2016). Where TNF inhibitors are ineffective, interleukin-17 inhibitors such as secukinumab can be introduced, as can Janus Kinase (JAK) inhibitors such as tofacitinib, upadacitinib, and filgotinib (Toussirot, 2022).

While bDMARD treatments have been shown to be effective in a large number of axSpA cases, the increased financial burden they introduce is considerable. In response to this, measures have been enacted to minimise unnecessary use of

bDMARDs, including tapering anti-TNFα dosage after a patient has achieved sustained remission (van der Heijde et al., 2017).

2.1.10 Comorbidities

The definition of comorbidity used here is any disease and illness present in addition to an index condition, which here is axial spondyloarthritis (Valderas et al., 2009). 61% of patients with axSpA present with comorbidities (Zhao et al., 2019b), with the most frequent being hypertension and fibromyalgia. The above study also reported that patients with comorbidities tend to be older (mean 48.9 years with comorbidities *vs* 40.4 years without) and experience impaired quality of life, more fatigue and more spinal pain.

2.1.10.1 Hypertension

Hypertension is prevalent in approximately 1 in 5 patients with axSpA (Derakhshan et al., 2019; Zhao et al., 2019b), with the risk of diagnosis with hypertension increasing by 13% with every passing five years of disease duration (OR 1.13 (95%CI 1.07-1.19)). The prevalence of comorbid hypertension has also been shown to be more strongly associated with axial disease than with peripheral spondyloarthropathy (1.20 (1.05-1.37) vs 0.90 (0.76-1.07) respectively) (Derakhshan et al., 2019).

2.1.10.2 Fibromyalgia

Fibromyalgia is arguably one of the most impactful and controversial comorbidities of axSpA as not only is it difficult in itself to diagnose, some of its symptoms, such as musculoskeletal pain, global pain and fatigue overlap considerably with those of axSpA (Gau et al., 2021), and it is frequently noted as a misdiagnosis prior to axSpA diagnosis. A pooled estimate of the prevalence of fibromyalgia among patients with axSpA is 16.4% (Jones et al., 2020). This study also found prevalence varied by phenotype, with fibromyalgia seen in 13.8% of patients with radiographic disease, 20.3% in non-radiographic disease and 11.1% in 'clinical disease', i.e., patients presenting with the symptoms of axSpA but with no confirmation by imaging. There is evidence that comorbid fibromyalgia can worsen the effects of axSpA and lower treatment benefits: in a UK study which found 22.1% of patients with axSpA also had co-morbid fibromyalgia, higher disease activity and lower quality of life was reported. Higher fibromyalgia classification criteria scores in patients with axSpA were also associated with less benefit from treatment with TNF inhibitors (Macfarlane et al., 2018).

2.1.11 Further burden of axSpA

2.1.11.1 Personal burden

AxSpA inflicts a considerable personal burden upon patients. Over time, axSpA can cause lifestyle-altering changes to mobility and posture (Strand and Singh, 2017), which in turn have been shown to be linked to psychological struggles. Body image can be negatively impacted, causing depression and anxiety, and has been implicated in a higher degree of relationship and sexual dysfunction than is found in the general

population (Healey et al., 2009). Prevalence of at least moderate depression among patients with axSpA has been reported as between 11 to 64%, dependant upon criteria of classification for depression (Zhao et al., 2018); pooled prevalence in that reporting review was 15%. This depression is multi-causal and often case-specific, but common causes reported are pain, unpredictability of the disease, fatigue and lack of ability to fully contribute to work (Davies et al., 2013). AxSpA can have pronounced negative effects on the patient's continued ability to function physically and psychologically.

Chronic pain, reduced physical function and changes to the physical structures of the body and posture, can lead to body image disturbances, affecting mood (Shen et al., 2014). AxSpA patients are at risk of depression (43%) and anxiety (21%). Rates of depression among patients with axSpA are 80% higher in women and 50% higher in men than they are in the general population described in a Swedish study (Meesters et al., 2014). Another reported 44% of patients with axSpA being at high risk for depression (Kilic et al., 2014). Additionally, sleep disturbance and fatigue, both elements very disruptive to quality of life, have been found to be extremely common among patients with axSpA. Two thirds of patients in a 2012 study experienced fatigue and nearly as many endured sleep disturbance (Aissaoui et al., 2012). Another study found 74% of patients diagnosed with AS reported experiencing fatigue, and 75% of these described it as frequent and severe. Patients with frequent, severe fatigue showed worse scores across health measures than those with less severe or less frequent fatigue (Healey et al., 2013).

A very common consequence of axSpA for patients is anger, irritation and depression. Fatigue, pain and stiffness are common in axSpA and are themselves triggers to

psychological difficulty, but patients report that, further to it being unpleasant to live with fatigue, pain and stiffness, it is the unpredictability which adds to the challenge. It makes social lives, activities, leisure and simple daily activities such as cooking, driving or moving about difficult to take for granted, and can lead to significant changes to a patient's outgoing personality, to the extent that many give up many activities which previously brought them happiness, or a sense of normalcy (Berenbaum et al., 2014; Madsen et al., 2015).

Furthermore, patients often harbour worries about the course and exacerbators of the disease, its heritability, its effects on lifestyle and relationships, and its effect on the patients' psychology. In addition to these personal effects of the disease, fears regarding employment were also reported. There exists the perception that axSpA will cause problems with job-security in the future, due to increasing amounts of time off being required. Patients reported worrying about their physical changes being off-putting in meetings, and some reported bullying and harassment in the workplace environment (Hamilton-West and Quine, 2009).

Self-esteem and self-image can be negatively impacted by the disease too, due to physical changes, fatigue, pain, disease unpredictability and the stress and effects of painkillers (Berenbaum et al., 2014; Raybone et al., 2019). In a study of men with the disease, the effects of axSpA have been described as having a negative effect on the masculine identity and its associated expectations. Not being able to lift their wife or children in their arms and being made to feel vulnerable were described as being a dent to masculinity (Madsen et al., 2015). These impacts on self-esteem can have negative consequences for relationships, even resulting in break-up.

AxSpA can have both positive and negative effects on relationships. In some relationships, the experience of coping with the disease can lead to a feeling of increased mutual support and closeness. Other couples, however, reported difficulties related to axSpA, with various causes from either side of the relationship. Pain-induced irritability of the partner diagnosed with axSpA caused their partner to be less likely to show affection in one relationship, whereas the non-axSpA partner in another relationship was worried about causing their axSpA diagnosed partner pain, resulting in a total cessation of their sex life (Raybone et al., 2019). Sexual dysfunction, such as erectile dysfunction and sexual dissatisfaction have been reported, with 42% of axSpA diagnosed men reporting erectile dysfunction, compared to 18% in the general population (Dhakad et al., 2015). 31% of patients with axSpA report that their sexual relationships have suffered as a result of the disease (Healey et al., 2009).

AxSpA can seem like a constantly present third party in relationships, affecting everything a couple does, from physical activity to leisure to diet. The presence of the disease has been described as making life appear effortful to both partners in a relationship, particularly when comparing their experiences to those couples where neither has the disease. A particular strain on relationships is caused when the non-axSpA partner adopts a “carer role”, taking it upon themselves to ensure the axSpA diagnosed partner is looking after themselves physiologically and psychologically. This can induce guilt in the partner with axSpA, and the feeling of over-reliance and of being a burden. Conversely, for the non-axSpA partner, this role can feel like an imposition, leading to resentment of the disease and their partner. In addition to this straightforward friction, the carer-role can over-rule the partner role, resulting in the carer-partner doing too much and undermining their partner’s feelings of

independence and ability, making them feel “useless” and “not capable” (Raybone et al., 2019).

The effect of the disease on relationships with patients’ children has also been examined. Patients reported worrying about the heritability of the disease, to the extent of feeling guilty about the increased possibility of their children developing it, despite its complex and multi-causal aetiology: “*This is really upsetting to me as I think that perhaps my daughters will get this disease because of me and I will have given it to them”* (Berenbaum et al., 2014). Some patients reported that their interaction with their children was significantly impacted by the disease. Not being able to play with their children or help with homework was described as “the worst part of the disease”, and some found it difficult to communicate their fatigue and pain to their children (Madsen et al., 2015). This difficulty regarding communication is also felt more generally, with patients reporting avoiding talking about their disease for fear of being perceived to be “a cry baby” (Hamilton-West and Quine, 2009).

Fears for the future also focused on the disease course for the patients themselves, with worries about future disability including paralysis and increasing uncertainty inherent to the development of the disease causing psychological strain. These worries were often directly related to the activity of the disease, abating somewhat when disease activity was low, and increasing again with increased disease activity (Berenbaum et al., 2014).

2.1.11.2 Economic burden

There is also a significant economic burden of axSpA on patients. The personal effect on finance of axSpA manifests in its effects on employment. Over 40% of patients with axSpA have been reported to experience work instability, i.e. their disease has made them mis-matched to their work, causing risk to their continued employment (Fabreguet et al., 2012). Poor physical function in axSpA has been shown to be associated with unemployment (OR 3.42 (95% CI 1.90-6.13)), as has longer disease duration (1.03 per year (1.01-1.06)). Additionally, increased disease activity has been shown to be associated with both absenteeism (not being present for work) and presenteeism (being present for work but incapable of performing the role to its potential) (3.24 (1.11-9.48) and 3.97 (1.76-8.98) respectively) (Healey et al., 2011). It has been found that 5% of patients with axSpA leave employment entirely within a year of their diagnosis, 13% have left after 5 years, 21% after 10 years, 23% after 15 years and 31% after 20 years, with patients in manual work being more likely to leave employment. Overall, patients with axSpA have been shown to be 3.1 times more likely than those in the general population to withdraw from work (Boonen et al., 2001), although these numbers may improve with improvements in treatment over recent years.

Recent research is also showing that axSpA and its delay has a great impact on the wider economy. The National Axial Spondyloarthritis Society (NASS) is funding ongoing research into the effect of axSpA and its delay on the UK economy, estimating that delay to axSpA diagnosis costs the UK economy £18.5 billion (based on a patient aged 26 experiencing delay of 8.5 years losing around £187,000, and reduction of this delay saving £167,000 per person). The ongoing research intends to show the full economic

cost, including that imposed through medical productivity loss (National Axial Spondyloarthritis Society [NASS], 2022a; Xydopoulos et al., 2022).

2.2 Diagnostic Delay in Axial Spondyloarthritis

Patients with axSpA experience a long journey to diagnosis, very frequently waiting several years. This delay to diagnosis has considerable implications not just for the treatment and management outcomes for the disease (Seo et al., 2015), but also the more general wellbeing of the patient.

The period between symptom onset and diagnosis has been described as a period of frustration, pain, fatigue, interrupted sleep and discomfort, with final diagnosis sometimes coming as a relief, a point of certainty after a period of unpleasant uncertainty. Additionally, final diagnosis can serve as a means of validation and confirmation that the symptoms were real and not the result of hypochondria (Madsen et al., 2015).

2.2.1 The Extent of Delay

A recent systematic review of diagnostic delay of axSpA reported a pooled global delay from its constituent studies as a mean 6.7 years (Zhao et al., 2021). The median diagnostic delay for the UK is 5 years and the mean is 8.53 years (Sykes et al., 2015).

Diagnostic delay can also be broken down into increments, length of delay related to significant events in the journey to diagnosis. The two major stages of delay prior to diagnosis are patient delay and healthcare delay. Patient delay is the period of delay

between the initial onset of axSpA symptoms and the first consultation with a HCP regarding these symptoms (Raza et al., 2011; Stjepanović et al., 2018). There is often a certain degree of uncertainty regarding absolute timing of initial onset of symptoms due to the unreliability of recall and the uncertainty about what constitutes early symptoms indicative of axSpA. This is sometimes referred to as "presentation delay" in wider literature, but for consistency, will be uniformly referred to as patient delay in this review. Healthcare delay is the delay between the initial visit of a patient to their HCP regarding axSpA symptoms and their correct diagnosis (Stjepanović et al., 2018). It is sometimes broken down into further increments, including:

a. Delay between first HCP visit and referral to a rheumatologist.
b. Delay between referral to a rheumatologist and correct diagnosis.

2.2.2 Causes of Delay

The reasons for diagnostic delay in axSpA are currently unclear, but several factors have been investigated.

2.2.2.1 Clinical presentation

The variation in clinical presentation of axSpA has been shown in some studies to have a significant effect on the length of diagnostic delay, but there is very little consensus over the direction of these effects in many cases. The systematic review by Zhao et al (2021), for example reports disagreement regarding the direction of effect on delay of the presence of peripheral arthritis; two studies reported it to be associated with longer delay (Fallahi and Jamshidi, 2016; Hajialilo et al., 2014) and five reported longer

delay in patients without (Bandinelli et al., 2016; Behar et al., 2017; Nakashima et al., 2016; Seo et al., 2015; Sykes et al., 2015).

Overall, axSpA symptoms tend to have insidious onset; they present slowly over time and are often not obvious. In addition to this, many aspects of axSpA's clinical presentation, such as chronic back pain, are so frequent in the general population that they do not in themselves suggest axSpA. These characteristics make earlier diagnosis difficult and very reliant upon the experience and intuition of the HCP (M Rudwaleit et al., 2004).

2.2.2.2 Misdiagnosis

A recent study found some of the most common reason for misdiagnoses prior to correct axSpA diagnosis to be back problems, psychosomatic issues, anxiety/depression, sciatica, fibromyalgia, orthopaedic problems, osteoarthritis, rheumatoid arthritis and bursitis, with variations in frequency between men and women (Ogdie et al., 2018).

Another common misdiagnosis is lumbar disc herniation (LDH), with one study showing that patients diagnosed with LDH before axSpA experiencing a mean delay of 9.1 years as opposed to the 6.2 years experienced by patients without an LDH diagnosis (Gerdan et al., 2012). Women have historically been under-represented in axSpA research due to the lower likelihood of radiographic presentation of sacroiliitis; this has resulted in axSpA being less readily considered as a diagnostic possibility for female patients (Rusman et al., 2018).

2.2.2.3 Healthcare Professional Knowledge

HCPs' experience of axSpA have also been examined. A Dutch 2014 study found the level of knowledge of axSpA in primary care to be remarkably low. Most GPs were not aware of the specific differences between mechanical and inflammatory back pain, and none stated they would request an HLA-B27 test for patients with suspected axSpA. Some of the typical associated manifestations of axSpA such as enthesitis were unknown to all GPs in the study, but others such as uveitis and inflammatory bowel disease were mentioned. Knowledge of the typical age of onset for the disease was found in all GPs, but all of the GPs were under the misapprehension that axSpA was only found in men (van Onna et al., 2014). While many of the GPs involved in this study stated they would want to know more about the disease, the low level of their existing knowledge provides a clear opportunity for improvement. This problematic lack of awareness of the disease among HCPs was also found in an American qualitative study (Lapane et al., 2020). Due to factors such as the infrequency with which GPs encounter axSpA, outdated education and time constraints in consultation, identification of the disease in primary care is still sub-optimal.

2.2.3 Impact of diagnostic delay of axSpA

The improvements in treatment options in recent years is incentive to improve times to diagnosis for axSpA, as earlier intervention leads to improved efficacy, but an argument for improving diagnosis times is also shown in research reporting worsened clinical outcomes due to delay.

There is still not much written regarding outcomes specific to delay, but what research there is shows that patients with delayed diagnosis experience worse and more common bony changes of the spine and more radiographic changes to the skeleton. Additionally, physical function (BASFI), disease activity (BASDAI) and range of motion (modified Schober score) are all negatively affected. Additionally, measures of radiographic change were not only worse, but deteriorated more year-on-year in patients with delayed diagnosis than in those with more timely diagnosis (Seo et al., 2015). A systematic review from 2020 supported the above; patients with axSpA who experienced delay in their diagnosis tended to have higher disease activity and worse physical function, along with greater degrees of structural damage. Along with these outcomes, quality of life was worsened in patients with delayed diagnosis, as ere economic realities such as higher healthcare costs and higher likelihood of work disabilities. (Yi et al., 2020).

2.3 Evidence gaps

Axial spondyloarthritis is a disease with a persistently long delayed diagnosis time-period, which has considerable subsequent effects on its treatment, treatment outcomes and progression in many patients. Its epidemiology, aetiology and pathogenesis have been researched thoroughly by teams from around the globe. Methods of classifying, diagnosing and defining the disease continue to be iteratively improved with a general trend of increasing understanding of the disease as broad and systemic. However, there remain gaps in the evidence surrounding axSpA and its

diagnostic delay which require research to create a fuller and more detailed base from which further measures can be taken to reduce the delay to diagnosis.

2.3.1 The extent of diagnostic delay in axSpA

It is important to review the existing literature on diagnostic delay to make clear the current extent of delay for axSpA globally and establish a benchmark of known diagnostic delay against which future improvements can be compared. This has already been approached from one direction by Zhao et al (Zhao et al., 2021) in a systematic review and meta-analysis of diagnostic delay in axSpA, but further work is required in this area, primarily as that review focused on pooled mean diagnostic delay. Diagnostic delay population data are not normally distributed; they are positively skewed, with the majority of patients experiencing shorter delay than the mean. Therefore, pooling mean data presents an average value which overestimates delay for the majority of patients.

Median delay gives a more representative average and therefore a clearer understanding of diagnostic delay in axSpA. A better understanding of associated factors and characteristics may allow certain patient groups to be targeted to reduce delay; Zhao et al also studied these, focusing exclusively on mean delay.

2.3.2 Patient & HCP reported barriers and facilitators to axSpA diagnosis

In addition to understanding the extent of diagnostic delay and the role of certain factors in delay, more research is required into the experience of living with the

disease and using healthcare during the process leading to diagnosis. While there are many quantitative studies into diagnostic delay and variables associated with it, there is still little consensus regarding who is vulnerable to delay and how delay can be reduced. Qualitative research is well placed to explore these concerns. Data collected on personal experience can provide more possible signposts to raise clinical suspicion and awareness of axSpA, possibly shortening time to diagnosis. Specifically, barriers and facilitators of diagnostic delay in axSpA are important subjects of inquiry. The more known about the circumstances and hurdles during this diagnostic journey, the more can potentially be done to mitigate those issues. Barriers to delay will not be the same for all patients, but some common barriers may exist, offering possibilities for systemic change and research in the future. There may also be elements along the diagnostic journey which could be improved or made more efficient to speed up diagnosis.

A qualitative approach to the collection of this data is preferable as it provides not just greater levels of detail about experiences, but also highly useful detail on what those individuals providing data *feel* to be important, raising the possibility of targeted action based on patient and HCP priorities in addition to obvious operational factors affecting delay

Five studies have investigated diagnostic delay of axSpA from the patient or HCPperspective. Two of these explored the patient only perspective of diagnostic delay in samples from the UK and US respectively (Dube et al., 2021; Martindale and Goodacre, 2014). Two explored the perspective of HCPs only from the Netherlands

and the USA respectively (Lapane et al., 2020; van Onna et al., 2014) and one explored both perspectives within a US sample (Kiwalkar et al., 2021).

Martindale et al explored ten UK patients' experiences during their diagnostic journey, analysing interviews using interpretive phenomenological analysis (IPA). Included patients met the ASAS classification criteria for axSpA. The central organising theme was "finding my route map", which explores the challenges for patients of living through the diagnostic journey, its uncertainties and their impacts on their life and communication. The two main barriers to timely diagnosis relate to a lack of comprehension and understanding of the disease by patients and HCPs and having to push to get answers about their disease.

Dube et al (2021) investigated diagnostic delay in American patients, using focus groups analysed thematically. This study found communication issues with clinicians, lack of continuity of care and difficulties diagnosing the disease. Also based in the US, Kiwalker et al (2021) investigated 16 rheumatologists' opinions and experiences alongside those of 25 patients using a method based on grounded theory. Their main results showed a difficult-to-diagnose disease and an insufficient level of understanding in the public and healthcare spheres, although it is important to note that these results originate from secondary care clinicians, while the majority of healthcare delay occurs in primary care.

Van Onna et al (2014), also basing their study analysis in grounded theory, found a very low degree of understanding and awareness of axSpA in a sample of ten Dutch GPs. Lapane et al (2020), similarly to Dube et al, Martindale et al (2014) and Kiwalker et al (2021), found that communication issues and the difficulty in diagnosing early

axSpA impeded diagnosis when interviewing primary care clinicians. When discussing these studies comparatively, it is of note that the latter study explores only patient and HCP experiences of diagnostic delay in the non-radiographic disease. All these studies also discussed systematic problems within healthcare which slowed diagnosis.

Out of these five studies, 3 were American, one of which studied the patient perspective of diagnostic delay in axSpA (Dube et al., 2021), one which studied the HCP perspective (Lapane et al., 2020) and one which studied both perspectives in relation to the non-radiographic disease (Kiwalkar et al., 2021). A further study focused on Dutch HCP perspectives (van Onna et al., 2014). Only one took place in the UK (Martindale and Goodacre, 2014). This is noteworthy as social-cultural and geopolitical differences along with differences in the means of seeking and being provided healthcare between countries can have profound effects on the experience of participants. Furthermore, this study only collected data from 10 patients. It is essential to gather data on the experiences and opinions of both patients and HCPs to improve the journey to diagnosis of axSpA in the UK. Facilitating these solutions requires high-quality data regarding the experiences of both patients and HCPs, and both the barriers and facilitators, to ensure success.

2.3.3 Patterns of consultation by patients in UK primary care prior to axSpA diagnosis

There is a large body of knowledge regarding axial spondyloarthritis, but much of this is gathered from populations who already have a diagnosis of axSpA; literature is sparse regarding the time prior to diagnosis. What is necessary, is a quantification of that journey from a population perspective. Where qualitative research can lead to

insight into the intricacies and human perspectives of the journey to diagnosis, quantitative research can show useful associations between factors and diagnosis for the wider population, giving future researchers and HCPs signposts for possible axSpA to be alert for.

There are multiple means by which patient data from prior to diagnosis can be collected. Cross sectional, case-control, inception cohort or retrospective cohort studies using electronic health record (EHR) databases would all be effective ways of gathering quantitative data on the period leading to diagnosis. Using EHR databases would be an efficient way of gathering large quantities of patient data as there are many based on coding of consultations in primary care available, such as CPRD, THIN and CiPCA.

Historically there has been little research into pre-diagnosis consultations specifically regarding axSpA, but this has been changing in recent years. Several studies since 2019 have studied consultation histories of patients with axSpA prior to their diagnosis, including Zhao et al (2019), Deodhar et al (2020), Kennedy et al (2021) and, most recently Sengupta et al (2022) (Deodhar et al., 2020; Kennedy et al., 2021; Sengupta et al., 2022; Zhao et al., 2019a). All four of these studies utilised forms of machine learning to analyse consultation data to attempt to devise a predictive algorithm to assist earlier diagnosis of axSpA. Machine learning is a means of computation in which algorithms mimic the methods of human thinking, i.e. instead of following a rigidly designed process, algorithms based on machine learning can adapt and improve their means of analysis; they improve automatically with experience (Mitchell, 1997).

Zhao et al focused on natural language processing to avoid some of the pitfalls of relying on coding, which can include errors and be incomplete in electronic health record (EHR) databases. All studies reported their models to be capable of achieving some utility regarding predicting an axSpA diagnosis based on consultation data, but as noted by Kennedy et al, the usefulness of models such as these in 'real world' data, is substantially lower, particularly if basing the output of the models on coding in EHR databases. While Zhao et al address this issue somewhat by focusing on natural language processing, they are still reliant upon what has already been coded to produce predictions.

This manner of predictive modelling could conceivably be of use as a support to primary care clinicians and may become increasingly useful as methods become more advanced and nuanced, but currently the most important concern is allowing GPs, the primary gatekeepers in the UK of healthcare, greater access to resources and understanding of the early forms of axSpA to assist early diagnosis.

With greater knowledge of axSpA and better understanding of early signposts to possible diagnosis, GPs can target their questioning and react to changes in consulting behaviour based on stronger evidence which is also practical in a resource-constrained health service. In day-to-day practice, it is not realistic to expect primary care clinicians to augment their pattern recognition with diagnostic frequencies of infrequent but suggestive diagnostic coincidences and symptoms. It is possible machine learning algorithms will be able to provide a substantial predictive boost to this process in the future, but human knowledge and pattern finding will be necessary until then and will remain valuable for validation purposes. Research into consultation frequencies and

behaviours is essential to contextualise consulting behaviour on larger scales, giving insight into the wider picture that may not be readily evident from the ground and undertaking this research using different datasets will provide valuable validation.

2.3.4 Summary

Axial spondyloarthritis is a complex disease with varying presentation, a suite of common comorbidities and substantial personal and economic burden. Adding to this is a considerable and persistent degree of delay to diagnosis which worsens the activity, development and burden of the disease. Much research into axSpA and its delay has been undertaken, with increasing quantity of work in recent years. There are, however, still gaps in our knowledge. To address these, the present thesis will collate the current literature regarding levels of diagnostic delay and any associated circumstances, comorbidities, symptoms and demographic factors. It will also use qualitative research to bring further detail and context to the body of literature, allowing access to experiences and perceptions not reflected in quantitative data. Examination of consultation records prior to diagnosis to assess what is recorded for patients prior to diagnosis. Finally quantitative research will show consultation frequencies and associations prior to diagnosis of axSpA with comorbidities and symptoms frequently found in patients with axSpA. This can signpost possible axSpA earlier in primary care, reducing time to referral and therefore diagnosis.

Chapter 3 – Diagnostic Delay in Axial Spondyloarthritis: A Systematic Review

This chapter describes a systematic review which identified and synthesised the body of research examining the extent of diagnostic delay experienced by patients with axial spondyloarthritis, and the factors which may be associated with such delay. This synthesis of data provides a benchmark of the state of delay in this disease group, against which to measure future attempts to reduce diagnostic delay.

3.1 Introduction

Diagnostic delay in axSpA is widely acknowledged and is a global problem. A recent systematic review and meta-analysis has been undertaken by Zhao et al which addressed many of the above concerns (Zhao et al., 2021). That review examined studies reporting either mean diagnostic delay for axSpA or mean ages of symptom onset and disease diagnosis, from which they imputed diagnostic delay. Their pooled estimate of global mean diagnostic delay was 6.7 years (95% CI 6.2 – 7.2). They found a lack of clear consensus between studies among almost all factors investigated for association with diagnostic delay, including gender, presence of peripheral arthritis and presence of HLA-B27. They found delay to be associated with extra-articular manifestations (uveitis etc), lower patient education levels and younger age at onset. While this review provides a comprehensive investigation of many aspects of diagnostic delay, there are still areas where a better understanding would be helpful. The largest is due to the intentional exclusion by this study of studies presenting medians alone. The rationale for this was that their review aimed to create a pooled

estimate of global delay, and only publications reporting means could be used in the necessary meta-analysis.

To reach an understanding of the current state of diagnostic delay in axSpA and to create a benchmark against which future improvements can be compared, a full exploration is to be undertaken of the literature detailing diagnostic delay, variables associated with it and the extent to which those variables affect diagnostic delay. Benchmarking here can be understood as a means by which evaluation of current practices and identification of causes of shortfall can be used to work towards improved practice and outcomes in future (Ellis, 2006; Ettorchi-Tardy et al., 2012). A full understanding of the current diagnostic delay experienced by patients can be used to evaluate the success of any future interventions or strategies to reduce diagnostic delay.

3.1.2 Aims and Objectives

The aim of this systematic review is to ascertain the extent of, and potential reasons for, diagnostic delay in patients with axSpA. The objectives of this review were:

1) To identify and synthesise existing published literature detailing a reported mean and/or median time-period of delay from symptom onset to final diagnosis in patients with axSpA
2) To examine any variables associated with the extent of diagnostic delay experienced by patients with axSpA.

3.3 Methods

3.3.1 Overview of methods

A systematic review is a method of identifying, appraising, and synthesising all relevant studies on a particular topic. The aim of a systematic review is to present, in as comprehensive and unbiased a way as possible, the body of research for a specified area, and is undertaken in a systematic and repeatable method (Uman, 2011).

A systematic review was conducted with the primary aim of compiling all available research literature examining diagnostic delay in axSpA. A protocol was developed to ensure the study was undertaken in a systematic manner and to act as a framework for the review. This protocol described the aims, timeframe, methods and planned outcomes. It was then submitted to the systematic review team at the School of Medicine, Keele University, for critical evaluation and the finalised information was used as the basis for submission to the National Institute for Health Research (NIHR) supported PROSPERO, a database register of systematic reviews (PROSPERO ID: CRD42019118963, Appendix 3.1). The remit of this systematic review was made more specific after submission of the protocol. The focus became specific to diagnostic delay and associated factors where association was quantified in terms of length of diagnostic delay. This was primarily to control the focus of the review to ensure the ability to present clear results based on planned outcomes. It also ensured the systematic review be undertaken within the available timeframe. Additionally, due to the skewed nature of diagnostic delay data, the proposal to undertake meta-analysis was discarded.

After the literature database search was undertaken, studies were reviewed for eligibility initially by title, then abstract content and then full-text. When it was ascertained which studies were eligible for inclusion, data were extracted in a standardised way. Results from all included studies were then collated into a narrative synthesis, and where results were directly comparable, they were tabulated. The narrative synthesis and tabulation of data were both organised to group together and compare studies with comparable characteristics. Narrative synthesis was ordered by degrees of scope, starting with the presentation of diagnostic delay in populations, followed by more specific points, such as factors associated with delay.

3.3.2 Literature Search

Five medical literature databases were searched for articles from their inception to November 2019: Web of Science, Medline (accessed through Ovid), Excerpta Medica dataBASE (EMBASE) (accessed through Ovid), Allied and Complementary Medicine Database (AMED) (accessed through Ovid) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (accessed through HDAS). These databases were chosen as they cover a significant proportion of global health research publications, and a wide cross-section of experiences in the medical profession and in medical research. The specific strengths of each database are detailed below. Additional to this search strategy, reference lists for existing reviews and studies were reviewed to ensure the capture of any studies which may have been missed in the search strategy.

3.3.2.1 Web of Science

Web of Science, previously Web of Knowledge, is owned by Clarivate Analytics in the USA and provides access to more than 161 million articles dating from 1900 onwards.

Web of Science offers coverage of many subjects beyond medical research, but the search for this systematic review was limited to science and social science domains.

3.3.2.2 Medline

Medline is also a US based literature database, created in 1946 by the US National Library of Medicine. It has access to more than 26 million records from 5,200 journals **(https://www.nlm.nih.gov/bsd/medline.html - Medline about website**).

3.3.2.3 EMBASE

This is a European pharmacological and biomedical database, founded in 1947 and merged with Elsevier in 1972. It has access to more than 32 million records from 8,500 journals from over 95 countries **(https://www.elsevier.com/en-gb/solutions/embase-biomedical-research - Embase about website)**.

3.3.2.4 AMED

The Allied and Complimentary Medicine Database Health Care is a database which covers records for more than 500 journals. It has been run since 1985 by the Information Service of the British Library, covering complementary and alternative health topics such as rehabilitation, physiotherapy and chiropractic care (**https://health.ebsco.com/products/amed-the-allied-and-complementary-medicine-database - AMED about page**).

3.3.2.5 CINAHL

The Cumulative Index to Nursing and Allied Health Literature was created in 1961 and covers material going back to 1937. It is owned by EBSCO in the USA and offers over 6 million indexed records from 5,500 journals

(**https://www.ebscohost.com/nursing/products/cinahl-databases/cinahl-complete CINAHL about page**).

Reference lists of systematic reviews and other studies were also searched. Additionally, authors were contacted for any missing data, where appropriate. Where further data made available by authors, they are presented in this systematic review as being associated with the published material.

3.3.3 Inclusion Criteria

To be considered for inclusion in the review, studies needed to meet defined criteria. Studies needed to report the primary outcome of interest for the systematic review, i.e. average time-period of diagnostic delay for axSpA. However, in addition to studies reporting the delay from initial symptom onset to final diagnosis of axSpA (including studies reporting either non-radiographic or radiographic axSpA, or previously widespread diagnoses such as ankylosing spondylitis), studies which reported delay for specific periods of the entire time between symptom onset and diagnosis were also accepted. Studies were also required to have used human participants. Studies were included which had used a sample of more than 20 patients, as studies of fewer than 20 patients were considered unlikely to be generalisable to the wider population, as such small sample sizes are more prone to bias and any conclusions based on their observation lack statistical power (Whitley and Ball, 2002). The study types to be included were cross-sectional, cohort, case-control and RCT, all of which are capable of recording specific diagnostic delay data. In the case of RCTs, delay data would only have been included in this review if it was recorded prior to any intervention. There

were no restrictions on language, and as no studies lacking an English translation were encountered, translation did not pose a problem.

3.3.4 Exclusion criteria

Editorials and opinion pieces were excluded from the systematic review, as they contain no new study data. Conference abstracts were excluded as there is the possibility that between presentation at a conference and final publication, details of the study may change during the peer-review process prior to publication.

Qualitative studies were also excluded, as the outcomes this systematic review focused on are quantitative measures of diagnostic delay and quantified risk. Case reports/case series were also excluded, as they either focus on a single case or a low number of cases and are therefore rarely generalisable to a population. Finally, systematic reviews were excluded, as they do not present novel data; where systematic reviews were returned by database searches, however, their reference lists were searched to identify any further publications relevant to the present study.

3.3.5 Search Criteria

To search medical literature databases in a systematic way, specific search criteria are required. This differs in form and entry method between databases, so each requires its own suitably different search criteria. Medical Subject Headings (MeSH) terms, or their database-specific equivalents, were searched, along with free-text phrases across all databases. The term "MeSH" is described as a thesaurus; a "*controlled and hierarchically-organized [sic] vocabulary produced by the National Library of Medicine"* (nlm.nih.gov/mesh/meshhome.html) with the National Library of Medicine (NLM) (USA) and is based on subject headings from Medline and NLM databases. These are

used to find relevant articles to the keywords of interest. No time or language limits were applied to the database results.

Search term modifiers are a series of command characters interspersed between different search terms with an aim to ensuring the greatest possible number of relevant results were returned by the database searches. The modifiers used in this search strategy were as follows:

- * - this is a “wildcard” character, used in circumstances where a word may have many relevant endings. For example, in this search, the term “spondyloarthritis” was entered as “spondyloarth*”, which not only covers “spondyloarthritis” but also “spondyloarthritides” and “spondyloarthritic” as possible alternatives, among others.
- ADJ – this is placed between words in a phrase to specify that they should be found next to one another. Adding a number to the end also shows that the words can be within a certain range of each other. For example “spin* (as in “spinal” “spine” adj3 arthr*” ensures that a result will be returned if “spin*” is found within three words of “arthr*”.
- Two letter abbreviations – These were used to denote what part of a journal article the specific term was searched within. For example, “spondyloarth*.ti,ab,kw ” informs the database search that the key terms should be searched for within the title (.ti), the abstract (.ab), or a section on keywords (.kw).

Boolean operators were also used to either increase or reduce the scope of search results. The two Boolean operators used in this search were OR and AND.

- OR – This increases the scope of a search when used to combine two or more search terms by allowing for *any* of the comprising search terms to be included in the search results. For example, all the search terms relating to axial spondyloarthritis were grouped together using OR, creating one large search term which encompassed them all, excluding none. If, however, one of the search terms grouped together by OR returns nothing, this does not affect the final number of search results.
- AND – This decreases the scope of a search by requiring the results of a search to include all the composite search terms. In this database search, the groupings created by using OR to combine all the terms referring to axial spondyloarthritis and all the terms referring to diagnostic delay into two separate sets were finally combined with an AND operator, meaning the final search results only showed studies referring to axial spondyloarthritis AND diagnostic delay.

3.3.5.1 Axial Spondyloarthritis Search Terms

The terminology of Axial Spondyloarthritis has gone through several iterations over time and this was reflected in the search strategy created. These terms were arrived at by exploring the literature regarding axSpA and noting all synonyms and permutations which were encountered. The names considered for this review were as follows:

- Spondyloarthropathies: this term covers the gamut of variants of spondyloarthritis, of which axial spondyloarthritis is one.
- Spondyloarthritis: many studies examining axial spondyloarthritis are covering spondyloarthritis more generally, and might be titled referring to

spondyloarthritis rather than axial spondyloarthritis. It is, therefore, necessary to cast a wider search using this term.

- Spondylitis: similar to the previous point, many studies examining ankylosing spondylitis will refer in title to spondylitis, rather than ankylosing spondylitis.
- Spondylarthritis: this is a permutation of spelling which, while not common, has been used frequently enough to be of use in the search strategy.
- Axial spondyloarthritis: this is the umbrella term under which all of the following pre-exsiting diagnostic terms fall. It breaks down into two sub-types: radiographic axial spondyloarthritis and non-radiographic axial spondyloarthritis.
- Ankylosing spondylitis: before the 2009 definition of axial spondyloarthritis, ankylosing spondylitis was the common diagnostic term used to describe axial inflammation. It is also still frequently used as a synonym for radiographic axSpA.
- Bechterew's Disease: this is a commonly used term for ankylosing spondylitis among German speaking HCPs and researchers.
- Marie-Strümpell Disease: another German/French alternative term for ankylosing spondylitis. This is infrequently used now.
- Bamboo-spine: this is a term which refers to axSpA which has progressed to a point where syndesmophytes merge and join at many levels resulting in continuous extravertebral ossification on plain x-ray
- Sacroiliitis: this is a feature characteristic of axSpA. And refers to inflammation of the sacroiliac joint

3.3.5.2 Diagnostic Delay Search Terms

In addition to the principal term of diagnostic delay, several alternative phrases were included in the search criteria including “diagnostic lag” or “delay interval”. Furthermore, terms for subcategories of delay, such as “late or early referral” and “late or early detection” were used (Prior et al., 2017). Case finding and health seeking behaviours were also represented in the search terms. The complete set of search terms used for this review can be found in Appendix 3.2.

The search strategy for this systematic review was reviewed and assessed by the systematic review team in the School of Medicine at Keele University.

3.3.6 Screening Process

Once the constructed searches were run in their respective literature databases, citations were exported into the reference management software, Endnote X8. This software was used as this allowed all citations to be managed in a single place and in a standardised format. Where duplicate articles were identified, these were deleted, first using the automated de-duplication tool in Endnote and then manually. The reference list was then exported to Rayyan QCRI, an online systematic reviewing tool developed by the Qatar Computing Research Institute at Hamad Bin Khalifa University (rayyan.ai). It is designed to facilitate collaborative work between reviewers, allowing two or more reviewers to view the full list of studies being considered for inclusion. It is also possible to attach Portable Document Formats (PDF) versions of studies to their record within Rayyan QCRI, for the convenience of all reviewers. All reviewers can mark studies to be included or excluded (there is also an option to mark them as

"maybe") and record a reason for exclusion. Additionally, there is a further "Label" field, which can be used for identifying studies by type or leaving notes for the other reviewers, among other things.

Using the inclusion criteria, studies were initially screened by the first reviewer (CH) by title only. Any further de-duplication not achieved by Endnote was undertaken at this stage. After review by title had been completed, a second reviewer (Alexandros Chatzicenitidis, hereon referred to as AC) was invited for the abstract review stage. In Rayyan QCRI, studies which were not excluded in the title review stage were independently reviewed by CH and AC for eligibility by abstract. The studies' abstracts were imported automatically from Endnote, and so were available to view within Rayyan QCRI. Following the abstract review stage, CH and AC both reviewed the remaining studies by full text to ascertain whether they contained eligible delay data. Full texts were then attached within Rayyan QCRI. After each stage of review, both reviewers met in person to discuss any disagreements over which studies to include. Where there were differences in decision, the relevant studies were reviewed again during the meeting, and a collaborative decision was made. In the case of any unresolvable disagreement between reviewer one and two, a third reviewer (JP) arbitrated to reach a final decision.

3.3.7 Data Extraction

Data extraction was undertaken using a spreadsheet in Microsoft Excel 365. The data extraction spreadsheet was designed iteratively, with the initial version of the sheet being tested on fourteen studies, and fields being added as and where they became relevant or necessary. Where new fields were added, studies which had previously

undergone data extraction were revisited to ensure no data was lost. Data extraction was initially validated by a second reviewer (AC) extracting sample studies (50% of all studies). Following this, it was further validated by a third reviewer (JP) who extracted data from a representative group of studies for comparison (again, 50% of all studies). The main fields for extraction can be found in Table 3.1.

Table 3.1 Data extraction fields

Field Name	Field Definition
Year	Year the study was completed
Country	Country of origin of the study
Age	Average age of the patient sample in the study. Where multiple time-points for average age were presented, all were extracted (eg: age at symptom onset, age at diagnosis etc).
Gender	Gender presented as a percentage of the study sample
M:F	The ratio of male to female patients in the study
Ethnicity	Where ethnicity or race were stated, they were noted here
Study period	The period over which the entire study took place
Study follow-up	The period of time over which patients in the study were followed-up
Study setting	Here we specified the specific healthcare setting under which the study took place. This was noted in our data extraction in the same way it was presented in the study; by specific hospital or by primary or secondary care etc.
Study population	The size of the population from which the study sample was sourced
Study sample	The sample size for the study
Disease Definition	Whether the study described ankylosing spondylitis, axial spondyloarthritis (or its sub-types, radiographic and non-radiographic axSpA) or a study-specific definition.
Diagnosis Method	The method or criteria by which axSpA was diagnosed (eg. Modified New York Criteria, physician verified etc)

Symptom Duration	The average length of symptom duration for patients in the study
Delay Period	The reported delay period (e.g. From symptom to diagnosis, from first consultation to diagnosis) or where diagnostic delay has been associated with a characteristic, this characteristic is noted here (eg. HLA-B27 positivity, sex, axSpA type etc). N.B. where a delay-associated characteristic is noted here, it refers to the delay between symptom onset and diagnosis, unless otherwise stated.
Delay Unit	The units of time in which diagnostic delay is reported in a study; weeks, months, years.
Delay Original	The delay as reported in its original units
IQR/SD Original	The interquartile range (for medians) or standard deviation (for means) reported in the study's original units
Range	The range of diagnostic delay values reported
P value	The p value associated with characteristics associated with diagnostic delay measures, where p=>0.025 shows a statistically significant association between said characteristic and an increased or decreased length of diagnostic delay.
Delay Years	Diagnostic delay converted to years using Microsoft Excel formulae
IQR/SD Years	Interquartile range (medians) or standard deviation (means) converted to years using Microsoft Excel formulae
Range Years	The range of diagnostic delay values reported, converted to years using Microsoft Excel formulae
Delay Causes/Associations	The factors examined for association with either longer or shorter diagnostic delay (eg. Presence of uveitis, HLA-B27 positivity etc)
Delay Outcomes/Associations	Reported outcomes of diagnostic delay (eg. More frequent bony growth on the spine, higher BASDAI score etc)

3.3.8 Quality Assessment

Quality assessment was undertaken using the Newcastle-Ottawa tool for case-control, cross-sectional and cohort studies (GA Wells D O'Connell, n.d.) (Appendix 3.3). This tool provides a balance between flexibility to assess a wide range of study designs and specific questions which prompt substantial scrutiny of the study design. For the purposes of this systematic review, the questions were selected from the Newcastle-Ottawa assessments for all study types. Where questions from the Newcastle-Ottawa quality assessment tool are deemed irrelevant, they were discarded, as in Prior et al (Prior et al., 2017). Questions would be deemed irrelevant if they did not address the methodology of the study being assessed, such as "Selection of the non-exposed cohort", as studies examining diagnostic delay are focused on patients with a definite diagnosis, or "Adequacy of follow up of cohorts", as studies examining diagnostic delay select their cohorts based on their already being diagnosed, so follow-up time is not relevant. The full list of questions for quality assessment for cohort studies are listed in Table 3.2, with the justifications for those discarded in this systematic review.

3.3.9 Analysis

3.3.9.1 Narrative Synthesis

The data extracted from the eligible studies was pooled into a narrative synthesis. A narrative synthesis is a means of presenting data from several studies in a systematic and integrated way, but it is not limited to summarising data from across studies by category. It is a method of collating and analysing data from across studies which takes into account similar or differing study characteristics, such as their strengths and

weaknesses, the bases for their data collection/rationale for their study design, their method of data presentation, their methods of recording, their study settings, populations and study samples, among other things (Ryan R, 2013). This level of assessment of studies is essential, as different study characteristics can alter the interpretation of data. Differences in study populations, for instance, can lead to very different outcomes; a limited population based in a small, self-selected group will give different study outcomes to a large population based on a national database. This level of assessment aids the decision as to which data to present and how, with the priority for presentation being that the reader can understand the significance of the data and the conclusions regarding its relevance and veracity.

Table 3.2 Newcastle-Ottawa Scale for Cohort Studies

Selection	
1. **Representativeness of exposed cohort**	**a) Truly representative of the average axSpA patient in the community *** **b) Somewhat representative of the average axSpA patient in the community *** **c) Selected group of users eg nurses, volunteers** **d) No description of the derivation of the cohort**

2. **Selection of non-exposed cohort**	There were no non-exposed cohorts in the studies.
3. **Ascertainment of exposure**	**This question was interpreted for this systematic review as ascertainment of diagnosis of axSpA.** **a) Secure record (eg surgical records) *** **b) Structured interview *** **c) Written self report** **d) No description**
4. **Demonstration that outcome of interest was not present at start of study**	The "outcome of interest" for this review was diagnostic delay, making this question irrelevant.
Comparability	
1. **Comparability of cohorts on the basis of the design or analysis**	The comparison of cohorts was not relevant to the focus of this systematic review.
Outcome	
1. **Assessment of outcome**	**For the purposes of this systematic review, this question was interpreted as assessment of diagnostic delay.** **a) Independent blind assessment ***

		b) Record linkage * **c) Self report** **d) No description**
2.	**Was follow-up long enough for outcomes to occur?**	This question was discarded as with diagnostic delay studies, the "outcome" (diagnostic delay) precedes the "exposure" (axSpA).
3.	**Adequacy of follow-up of cohorts**	This question was discarded for the same reason as the previous question.

(GA Wells_D O'Connell, accessed 2019)

The three questions from the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies which we used for this systematic review were: **Selection** 1) Representativeness of the exposed cohort, 3) Ascertainment of exposure, **Outcome** 1) Assessment of outcome.

3.3.9.2 Standardisation of Delay Measures

After initial data extraction, diagnostic delay data were standardised for ease of comparison and interpretation. Formulae were utilised to standardise all delay into years (to two decimal places) as, due to the typical length of diagnostic delay for axSpA, this was the most descriptive time-period.

- Delays reported in days were converted using the formula "=(Reported Delay/365)".

- Delays reported in weeks were converted using the formula "=(Reported Delay/52)" Delays reported in months were converted using "=(Reported Delay/12)".

3.3.9.3 Average Diagnostic Delay

Data were extracted from all studies which reported an average time-period of diagnostic delay for axSpA, but for the purposes of this systematic review, those studies reporting median diagnostic delay were prioritised due to these being considered a more likely presentation of the average distribution of diagnostic delay. This is due to the reported length of diagnostic delay in populations consistently being non-normally distributed. The majority of patients will report diagnostic delay towards the lower end of the whole range of reported delay; however, as a small sample typically experience extreme delay, these outliers, result in positive skew and are therefore less representative of the majority (Sykes et al., 2015). Sykes et al found that in a UK, over half of axSpA patients experienced delay of less than five years, and a third experienced less than two years delay; consequently, the median diagnostic delay for this study was 5 (IQR 2-12) years, reflecting the experience of the majority of patients, whereas the mean delay in that cohort was 8.53 (SD 9.04) years. As such, calculating a mean from diagnostic delay data does not accurately represent the average experienced by the majority, being more influenced by these extreme delay measures and consequently overestimating the average of delay in the population (Manikandan, 2011).

However, as stated above, mean diagnostic delay was also extracted and is presented in this systematic review. Mean delay data has been included for transparency as this

systematic review aims to present the whole range of research data available regarding diagnostic delay in axSpA. Additionally, including the mean diagnostic delay data allows for direct comparison with median delay data, showing the different impact of these two approaches.

3.3.9.3 Disease Type

Throughout the literature, 'ankylosing spondylitis' and 'axial spondyloarthritis' are generally used interchangeably. Ankylosing spondylitis (Van Der Linden et al., 1984) is now more commonly used as a synonym for radiographic-axSpA. However, historically it has been used to describe the entirety of axSpA and is still occasionally used synonymously with the entire disease spectrum, potentially including those patients with normal x-rays but with MRI changes; this is particularly likely prior to the ASAS classification criteria adoption. To ascertain whether the terminology was related to trends in reported delay, a sensitivity analysis was undertaken. In this sensitivity analysis, diagnostic delays from studies using the diagnosis "AS" were compared with delays from studies using the diagnosis "axSpA".

3.3.9.4 Analysis of Variables of Delay

While our analysis of overall diagnostic delay focused on median data, the reporting of delay associated with specific variables has used a wider definition. Rather than the extent of delay, here the focus of interest was on the statistical difference reported in the delay experienced between those with or without a certain defining variable. Considering this focus on the differences in delay associated with variables, and the strength of any association, mean values were included in the analysis of variable-related delay. Differences in mean delay associated with variables are treated within

this systematic review as being equally informative as differences in median characteristic delay. Mean and median variable-related delay is presented separately to avoid confusion. For clarity, in this systematic review variables examined for association with diagnostic delay were grouped into four categories based on the strength of evidence for association found. These categories are:

1) No association with delay: a variable examined in more than five studies for which no evidence or very weak evidence was found for association with diagnostic delay.
2) Variables for which several studies showed increased delay: shown by more than five studies as being statistically significantly associated with increased diagnostic delay.
3) Mixed results: a variable examined in more than three studies for which evidence of significant association is contradictory across studies.
4) Limited studies: a variable examined by three or fewer studies, judged to be too few to provide meaningful consensus.

3.4 Results

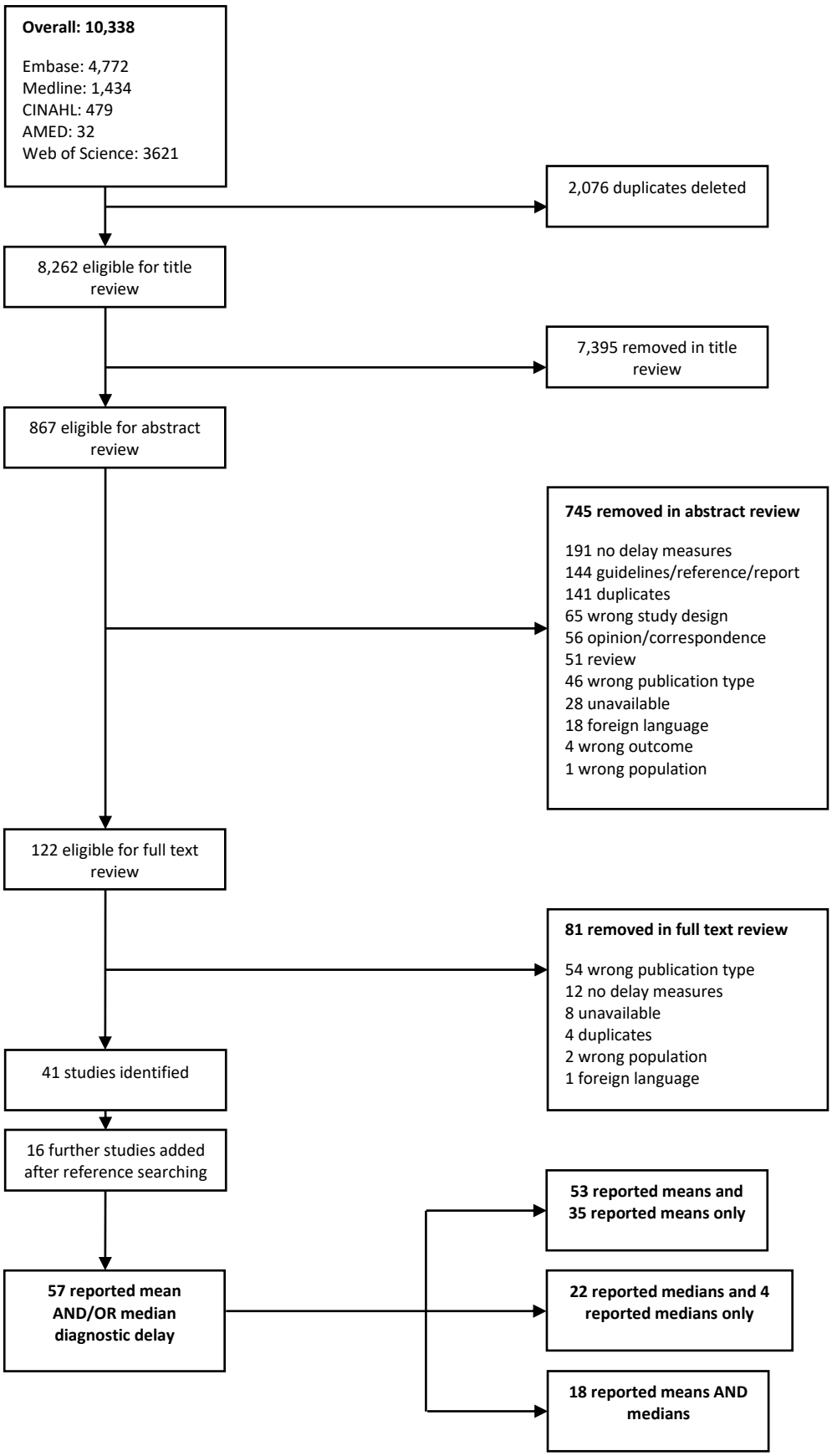
3.4.1 Studies

Collated, the database searches identified 10,338 eligible studies, 2076 of which were duplicates. 8262 titles were reviewed, 867 abstracts were reviewed and 122 full texts were reviewed. Finally, upon searching the references in the eligible studies and in related literature, 16 more studies were found to be eligible for the systematic review, bringing the total number of studies included to 57. Of these, 35 reported diagnostic delay as a mean only, four reported delay as a median only and 18 reported delay as both a mean and median value. Therefore, this resulted in the identification of 35 individual mean values of diagnostic delay and 22 individual median values.

Table 3.3 Total Numbers of Studies by Review Stage

	Total Search
Initial Results Total	10,338
Duplicates Removed	2,076
Title Phase Eligible	8,262
Title Phase Removed	7,395
Abstract Eligible	867
Abstract Removed	745
Full Text Eligible	122
Full Text Removed	81
16 Studies Added from Reference Search	16
Included Studies Means or Medians	57
Included Studies Medians (*medians only*)	22 (*4*)
Included Studies Means (*means only*)	53 (35)
Included Studies Means & Medians	18

Figure 3.1 Flowchart of Overall Search and Review Process



3.4.2 Quality Assessment

The quality of included studies was assessed using the three questions from the Newcastle-Ottawa scale, as specified in the methods.

22 studies in this review achieved 3 stars, one for each question, 27 achieved 2 stars and 8 received one star. For 'representativeness of cohort', 32 studies scored the highest possible A*, 23 scored B*, 2 scored C and none scored D. Regarding 'ascertainment of exposure', 37 scored A*, 12 scored B*, 5 scored C and 2 scored D. For 'assessment of outcome', no studies scored A*, 23 scored B*, 22 scored C and 10 scored D. As such, the highest overall score available among the studies included in this review was A*A*B*, which was achieved by 10 studies. Of the remaining 3-star studies, 3 scored A*B*B*, 2 scored B*B*B* and 7 scored B*A*B*.

Ascertainment of exposure was the criteria most commonly fulfilled to the highest quality (n=37), which required confirmation using clinical records; in the case of the studies in this review, this meant a patient's diagnosis of axSpA was ascertained by their inclusion in a medical/hospital database or medical insurance database. Only two studies gave no details of their ascertainment of the presence of axSpA. Representativeness of the exposed cohort was of a similarly high quality, with 32 studies being graded as having an exposed cohort "truly representative of the average axSpA patient" Assessment of outcome did not in any studies achieve the A* rating, which would have required an independent blind assessment. The most common result for this question was B*, i.e. "record linkage (identified through ICD codes on database records etc), which was achieved by 23 studies, closely followed by C: self-report.

3.4.3 Study Characteristics

3.4.3.1 Country of Origin

Of all the 57 studies included in this systematic review, seven were from the UK, six were from Turkey, five from China, four from Germany, three each from India, Iran and Italy, two each from France, Morocco, Norway, Spain, Ireland and the USA, and a single study from Albania, Australia, Czechia, Denmark, Egypt, Europe (this study was by a Spanish team, but covered data from the whole continent), Iceland, Israel, Japan, Poland, Qatar, Switzerland, Taiwan and South Korea.

Twenty-two studies presented diagnostic delay as a median value. Five of these were from the UK, three came from Turkey, two each were from Germany and China, and one each came from Czech Republic, Italy, France, India, Iran, Norway, Denmark, Spain, South Korea and the USA.

Demographics and disease/diagnosis definitions for studies describing median diagnostic delay are detailed below. Demographic details from all studies are described in Table 3.4.

3.4.3.2 Demographics

3.4.3.2.1 Age

Age (typically mean) was commonly reported by studies in three ways: age at the time of the study, age at symptom onset or age of diagnosis.

Age at the 'time of study' in studies (n=12) reporting median diagnostic delay ranged across 20.7 years, with the lowest age recorded being 29.5 (SD 10.7), reported by

Bodur et al (Turkey) in 2010 and the highest by Forejtova et al's 2008 Study (Czech Republic) at 50.2 years (SD 10.7) (Bodur et al., 2012; Forejtová et al., 2008).

'Age at symptom onset' in studies reporting median diagnostic delay covered a range of 6.3 years. The lowest average age of symptom onset was recorded by Aggarwal et al (India) in 2009 at 23 years (SD 8.8) and the highest was recorded by Behar et al (France) in 2016 at 29.3 years (SD 12.2) (Aggarwal and Malaviya, 2009; Behar et al., 2017). Seo et al (South Korea, 2014) also recorded an age at symptom onset of 23 years, but this was a median, with interquartile range (IQR) of 17-31 (Seo et al., 2015).

'Age at diagnosis' ranged by 5.8 years. The lowest recorded was by Ozgocmen (Turkey) in 2009 at 30.7 years (SD 9.42) and the highest was by Salvadorini et al (Italy) in 2012 at 36.5 years (SD 12.2) (Ozgocmen et al., 2009; Salvadorini et al., 2012).

3.4.3.2.2 Gender

The distribution of gender was measured either as percentages or ratios, and they varied widely between studies. The highest male percentage was found in Abdul Sattar et al's (Egypt) 2014 study at 94.4%, and the lowest male percentage was 38.6% in Garrido-Cumbrera et al's 2019 study (Europe) (Abdul-Sattar and Abou El Magd, 2017; Garrido-Cumbrera et al., 2019b).

3.4.3.2.3 Presentation of Delay

Diagnostic delay was presented in several different ways across studies. The majority presented the period of time between initial onset of axSpA symptoms and correct diagnosis of axSpA. However, several other periods of delay reported were:

- The delay from first symptom onset to initial consultation with any HCP (n=1) (Li et al., 2019).

- From symptom onset to first consultation with a rheumatologist (n=2) (Deodhar et al., 2016; Salvadorini et al., 2012).
- From symptom onset to first x-ray (n=1) (Salvadorini et al., 2012).
- From rheumatology referral to diagnosis (n=2) (Deodhar et al., 2016; Kidd and Cawley, 1988).

Many of the included studies not only described diagnostic delay across their whole sample, but also specifically for patients exhibiting different characteristics. This allows one to infer associations between patient characteristics and length of diagnostic delay; these "factor delays" are described below.

3.4.3.3 Disease and Diagnosis Definitions

The disease and diagnostic definitions were not standardised throughout the included literature. Fourteen of the studies (25%) examining overall diagnostic delay described their samples as being diagnosed with ankylosing spondylitis (AS)(Aggarwal and Malaviya, 2009; Bakland et al., 2011; Bodur et al., 2012; Chimenti et al., 2020; Deodhar et al., 2016; Fallahi and Jamshidi, 2016; Forejtová et al., 2008; Gerdan et al., 2012; Hamilton et al., 2011; Ozgocmen et al., 2009; Qian et al., 2017; Salvadorini et al., 2012; Sørensen and Hetland, 2015; Zwolak et al., 2019).

All apart from four of these studies classified their patients' AS using the mNYC (Van Der Linden et al., 1984). The remaining four defined AS as follows:

- Deodhar et al 2016 and Sorensen et al 2014 used the International Classification of Diseases (ICD) codes to define AS (versions 9 and 10 respectively).

- AS in Hamilton 2011 was self-reported.
- Zwolak 2019 does not describe the classification method.

In context, it is clear that Chimenti et al are acknowledging the radiographic and non-radiographic form of the disease, differentiated as patients fulfilling mNYC and patients fulfilling ASAS criteria without radiographic inflammation respectively (Chimenti et al., 2020).

Eight studies described their patients as having axSpA (Brandt et al., 2007; Chimenti et al., 2020; Garrido-Cumbrera et al., 2019a, 2019b; Li et al., 2019; Redeker et al., 2019; Seo et al., 2015; Sykes et al., 2015). Three of these (Chimenti et al., 2020; Li et al., 2019; Seo et al., 2015) classified axSpA using the Assessment of Spondyloarthritis International Society criteria (M. Rudwaleit et al., 2009c, 2009a), while Brandt 2007 used the modified New York Criteria, Sykes et al 2015 relied on physician verification, Garrido-Cumbrera et al 2019 relied on self-report for both their studies and Redeker et al 2019 used the ICD version 10 code.

Table 3.4 Demographic details, disease definition and type of average for all studies

				Age			Gender	Disease Definition	Delay Average	
Author	**Year**	**Country**	**Sample Size**	**Age at Study**	**Age at Onset**	**Age at Diagnosis**	**Male %**		**Median**	**Mean**
Coughlan et al	1981	Ireland	78		23.3 (7-50)	27.5 (15-60)	73	AS		X
Calin et al	1988	UK	1500	44.1	23.8			AS	X	X
Kidd et al	1988	UK	125					AS	X	
Brunner et al	2002	Switzerland	1177			32.5	66	AS		X
Feldtkeller et al	2003	Germany/Austria	1044	48.9 (SD 11.8)	25.1 (SD 8.5)	33.8 (SD 9.5)	64	AS		X
Bakland et al	2005	Norway	534		24.2 (SD 8.5)		76	AS		X
Brandt et al	2007	Germany	350	40 (range 16-75)				axSpA (pre-ASAS 2009)	X	X
Dincer et al	2007	Turkey	111	33.58 (SD 11.96)	23.18 (SD 9.58)		92.7	AS		X
Reed et al	2007	Australia	126	44.9 (SD 12.3)			91	AS		X
Feldtkeller et al	2008	Germany	1614					AS		X
Forejtova et al	2008	Czech Rep	1008	50.2 (SD 10.7)	27.3 (SD 8.5)		62	AS	X	X
Aggarwal et al	2009	India	70		23 (SD 8.8)	31.5 (SD 8.7)	83	AS	X	X
Cakar et al	2009	Turkey	121	31.6 (SD 10.6)			100	AS		X
Ozgocmen et al	2009	Turkey	279	36.11 (SD 10.2)	25.63 (SD 7.49)	30.7 (SD 9.42)	73	AS	X	X

Rojas-Vargas et al	2009	Spain	46	39.5 (SD 12.7)	38.1 (SD 12.8)	38.9 (SD 12.7)	72	AS		X
Bodur et al	2010	Turkey	1381	39.5 (SD 10.7)	27.5 (SD 9.8)	32 (SD 10.7)	75.2	AS	X	X
Geirsson et all	2010	Iceland	223		M 23.6 (SD 8.4), F 24.1 (SD 8.9)	M 32.1 (SD 10.2), F 34.2 (SD 10.1)	65	AS		X
Roussou et al	2010	UK	516	47.1 (SD 13.7)			66.6	axSpA	X	X
Ibn Yacoub et al	2010	Morocco	100	38 (SD 13)		32.68 (SD 11.56)	67	AS		X
Slobodin et al	2010	Israel	151			M 35.6 (SD 11.7), F 38.5 (SD 12.3)	52.3	axSpA		X
Bakland et al	2011	Norway	677		23.2 (SD 8.5)		76	AS	X	X
Chung et al	2011	France	654	HLA-B27+ 32.5 (SD 8.4), HLA B27- 35.6 (SD 8.7)	HLA-B27+ 31.0 (SD 8.5), HLA-B27- 34.0 (SD 8.8)		HLA-B27+ 51.2, HLA-B27- 37.4	axSpA		X
Hamilton et al	2011	UK	807				75	AS	X	X
Ibn Yacoub et al	2011	Morocco	130		M 27.9 (SD 11.1) F 28.8 (SD 10.7)		66.9	AS		X
Gerdan et al	2012	Turkey	393	39.3 (SD 10.8)			65.6	AS	X	X
Ma et al	2012	China	234	S 28.6 (SD 9.7), N 28.3 (SD 12.8)	S 20.2 (SD 8), N 22.3 (SD 11.1)		North 81 South 80	AS		X
Salvadorini et al	2012	Italy	135		28.3 (SD 10.2)	26.5 (SD 12.2)	66	axSpA	X	X

Sullivan et al	2013	Ireland	92	46.7 (23-80)			74	AS		X
Abdul-Sattar et al	2014	Egypt	90	37.8 (SD 9.7)			94.4	AS		X
Hajialilo et al	2014	Iran	60			36.4 (SD 4.5)	88.3	AS		X
Jamshidi et al	2014	Iran	230	38 (SD 10)			79.1	AS		X
Jones et al	2014	UK	138	35.2	25.8 (10-48)	31.9 (19-49)		axSpA		X
Koko et al	2014	Albania	54	51.6 (12.7)	29.7 (SD 8.4)		89	AS		X
Seo et al	2015	South Korea	94	40 (IQR 39-49)	23 (IQR 17-30)	35 (IQR 24-43)	78.7	axSpA	X	
Sørensen et al	2014	Denmark	1335	40.8 (SD 12.4)			70.9	AS	X	X
Gaveli et al	2015	India	96		35 (SD 7.07)		91.6	axSpA		X
Hammoudeh et al	2015	Qatar	169		32.3 (SD 9.9)	34.9 (SD 9.8)	59	AS		X
Nakashima et al	2015	Japan	72		25.6 (SD 11.3)	33.3 (SD 13.2)	83	AS		X
Sykes et al	2015	UK	1193					axSpA	X	X
Wright et al	2015	USA	86		28.7 (SD 9.2)	34.9 (SD 9.9)	79	AS		X
Zhao et al	2015	China	256	34 (SD 8.26)	22.99 (SD 5.5)		88.28	AS		X
Bandinelli et al	2016	Italy	135		27.9 (SD 0.89)		67.4	axSpA		X
Behar et al	2016	France	432		29.3 (SD 12.2)	34.2 (SD 12.5)	56.2	AS	X	X
Burgos-Varga et al	2016	Taiwan	757	38.68 (SD 12.02)			64.33	axSpA		X
Deodhar et al	2016	USA	3336			42.9[1], 45.8[2]	50	AS	X	
Duran et al	2016	Turkey	51		41.5		58.8	AS		X

Fallahi et al	2016	Iran	163	37.7 (SD 9.9)	23.4 (SD 7.1)	31.3 (SD 9.7)	79	AS	X	X
Bansal et al	2017	India	254		27.29 (SD 10.13)	32.98 (SD 11.82)	88	axSpA		X
Qian et al	2017	China	1251	36 (SD 12.5)	29.2 (SD 11.4)	33.5 (SD 12.6)	73	AS		X
Quraishi et al	2018	UK	88		28.4 (SD 9.8)	31.9 (SD 9.7)	80.7	AS		X
Nie et al	2018	China	281	31.71 (SD 9.8)			68	AS		X
Chimenti et al	2019	Italy	210					axSpA		X
Garrido-Cumbrera et al	2019	Spain	680	45.7 (SD 10.8)			47.5	axSpA		X
Garrido-Cumbrera et al	2019	Europe	2846	43.9 (SD 12.3)	26.2 (SD 11.1)	33.7 (SD 11.5)	38.6	axSpA	X	X
Li et al	2019	China	208	35.5 (SD 12.8)	28.1 (SD 12.3)		71.6	axSpA	X	X
Redeker et al	2019	Germany	4471	55.9	30.6		54.1	axSpA	X	X
Zwolak et al	2019	Poland	82		30.9 (SD 8.5)	40.7 (SD 10.2)	66	AS		X

3.4.4 Extent of delay in axSpA diagnosis

Eighteen studies described median delay between the initial onset of axSpA symptoms and final diagnosis, with three from Turkey, two from the UK, Germany and China, and one each from South Korea, the Czechia, Norway, Iran, India, Italy, France and Denmark. Garrido-Cumbrera et al (2019) reported overall diagnostic delay for Europe, from 13 countries (Austria, Belgium, France, Germany, Italy, the Netherlands, Norway, Russia, Slovenia, Sweden, Switzerland, the UK and Spain). Across all of these studies, reported diagnostic delay ranged from an average of 0.67 years in Denmark (Sørensen and Hetland, 2015) to 8 years in South Korea (Seo et al., 2015). A third of articles reported median delay to be 2 years, with a further third of articles reporting a median of between 2-5 years of delay, including Garrido-Cumbrera et al who reported a median of 4 years across 13 different European countries, and a final third reported diagnostic delay greater than 5 years. Mean overall diagnostic delay can be found in Appendix 3.4.

3.4.4.1 Median Delay and Disease Type

There appeared to be no relationship between whether axSpA was reported as either AS or axSpA in studies reporting median overall diagnostic delay. Diagnostic delay for axSpA (which includes the radiographic and non-radiographic disease) ranged from 2.1 years (Salvadorini et al., 2012) to 8 years (Seo et al., 2015), while delay for ankylosing spondylitis ranged from 0.7 years (Sørensen and Hetland, 2015) to 7.5 years (Forejtová et al., 2008).

Table 3.5 Overall Median Diagnostic Delay in Years

Author	Year	Country	Sample Size	Diagnostic Delay	IQR	Range	Disease Definition
Seo et al	2014	South Korea	94	8	3-15		axSpA
Forejtova et al	2008	Czechia	1008	7.5	3.5-12.5		AS
Bakland	2011	Norway	877	7			AS
Fallahi et al	2016	Iran	163	6		0-32	AS
Hamilton et al	2011	UK	807	6	2-12		AS
Aggarwal et al	2009	India	70	5.9	3-11		AS
Brandt et al	2007	Germany	350	5		0.1-45	axSpA[1]
Sykes	2015	UK	1193	5	2-12		axSpA
Gerdan et al	2012	Turkey	393	5	11		AS
Garrido-Cumbrera et al	2019	Europe	2846	4			axSpA
Ozgocmen et al	2009	Turkey	279	3			AS
Redeker et al	2019	Germany	4471	2.3		0.1-7.2	axspA
Li et al	2019	China	208	2.1		4-74.8	axSpA
Salvadorini et al	2012	Italy	135	2.1		2-3	AS
Bodur et al	2010	Turkey	1381	2			AS
Masson Behar et al	2016	France	432	2	1-7		axSpA
Qian et al	2017	China	1251	2	0-2		AS
Sorensen et al	2014	Denmark	1335	0.7			AS

[1]Pre-ASAS 2009 criteria definition of axSpA; based on mNYC

Table 3.6 Sensitivity Analysis of Diagnostic Delay by Disease Terminology

Author	Year	AS/axSpA	Delay (years)
Seo at al	2014	AxSpA	8
Brandt et al	2007	AxSpA[1]	5
Sykes et al	2015	AxSpA	5
Garrido-Cumbrera et al	2019	AxSpA	4
Redeker et al	2019	AxSpA	2.3
Li et al	2019	AxSpA	2.1
Salvadorini et al	2012	AxSpA	2.1
Forejtova et al	2008	AS	7.5
Bakland et al	2011	AS	7
Fallahi et al	2016	AS	6
Hamilton et al	2011	AS	6
Aggarwal et al	2009	AS	5.9
Gerdan et al	2012	AS	5
Ozgocmen et al	2009	AS	3
Bodur et al	2010	AS	2
Masson Behar et al	2016	AS	2
Qian et al	2017	AS	2
Sorensen et al	2014	AS	0.7

[1]Pre-ASAS 2009 axSpA definition; based on mNYC

Eighteen studies presented diagnostic delay as both medians and means, illustrating disparity between the two, where means were consistently greater. These differences ranged from 1 year in Aggarwal et al 2009 (India) to 4.58 years in Sorensen et al 2014 (Denmark).

Table 3.7 Results from studies reporting both mean and median diagnostic delay

Author	Year	Country	Diagnostic Delay Median	Diagnostic Delay Mean	Difference in Delay Estimate (Mean-Median)
Forejtova et al	2008	Czech Republic	7.5	9.1	1.7
Bakland et al	2011	Norway	7	9	2
Fallahi et al	2016	Iran	6	7.88	1.88
Hamilton et al	2011	UK	6	8.57	2.57
Aggarwal et al	2009	India	5.9	6.9	1
Brandt et al	2007	Germany	5	7.7	2.7
Gerdan et al	2012	Turkey	5	8.12	3.12
Sykes et al	2015	UK	5	8.53	3.53
Garrido-Cumbrera et al	2019	Europe	4	7.4	3.4
Ozgocmen et al	2009	Turkey	3	5.08	2.08

Redeker et al	2019	Germany	2.3	5.7	3.4
Li et al	2019	China	2.13	4.83	2.7
Behar et al	2016	France	2	4.9	2.9
Bodur et al	2010	Turkey	2	5	3
Sorensen et al	2014	Denmark	0.67	5.25	4.58

3.4.5 Extent of Diagnostic Delay Over Time

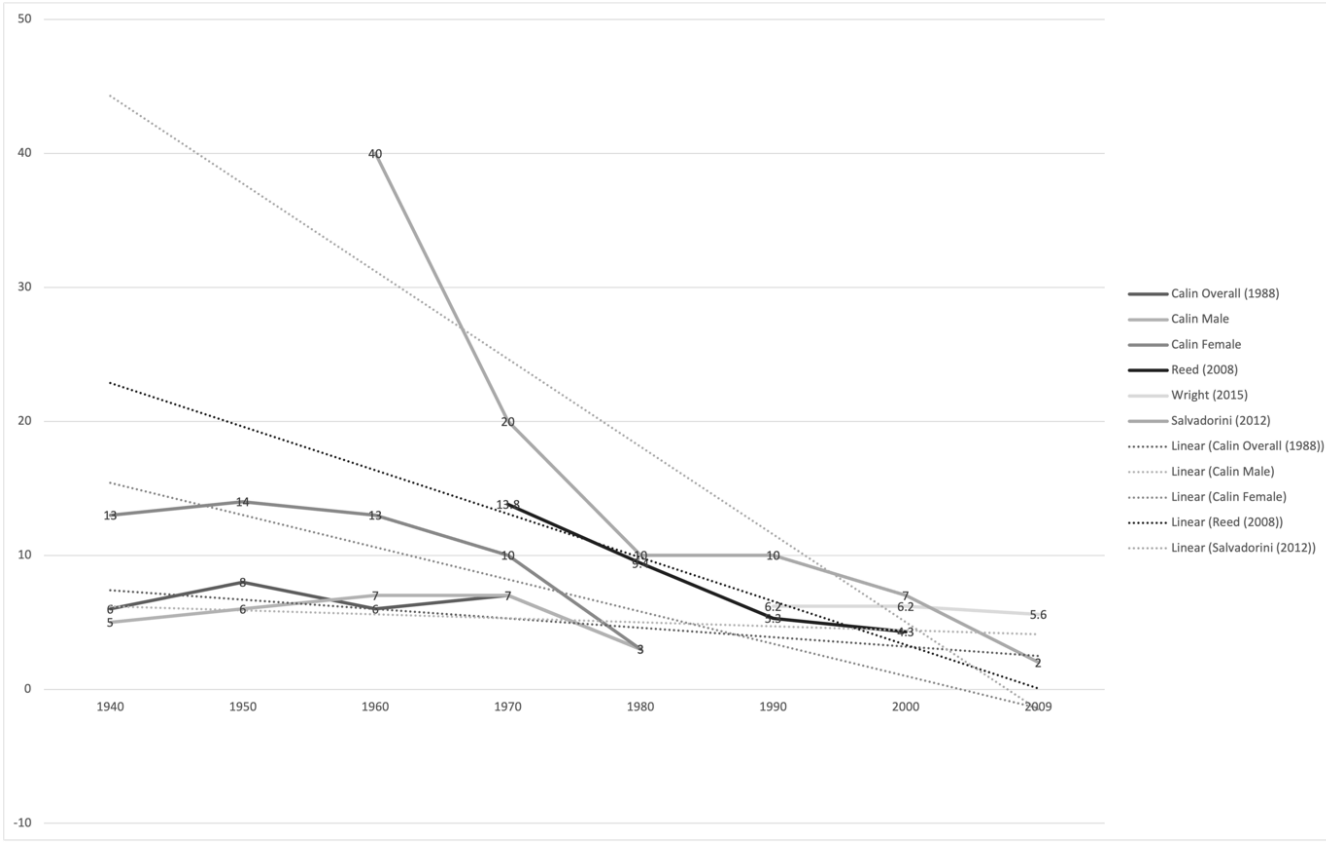
Four studies reported the change in diagnostic delay over time, two of which reported median diagnostic delay (Calin et al., 1988; Salvadorini et al., 2012) and two which reported mean diagnostic delay (Reed et al., 2008; Wright et al., 2015).

Salvadorini et al presented delays over six decades from the 1950s through to 2000 in Italy, showing a reduction in delay, with this halving every decade, apart from the 1970s-80s. Calin et al presented median delay over 15 time-periods in the UK, and also compared male delay with female delay over the same period (Calin et al., 1988; Salvadorini et al., 2012). This study showed reduction in delay throughout the 20th century, although not to the extent found by Salvadorini et al; overall diagnostic delay in the UK in the middle of the century was far shorter than in Italy, according to these data.

Reed et al's Australian study presented diagnostic delay over three decades, from 1978 to 1993, which showed diagnostic delay reducing from an initial 1978 level of 13.8 years, to less than a third of this (4.3 years) by 1993.

Wright et al's USA study presented diagnostic delay from 1980 through to 2009.The delay in 1980 was 6.2 years, which showed little improvement over time, with delay duration between 2000 and 2009 being reported as 5.6 years.

Figure 3.2 Changes in Diagnostic Delay Over Time



3.4.6 Diagnostic Delay Associated with Patient or Circumstantial Characteristics

This section details the results of studies which examined the effects of different factors, whether specific to patients or their healthcare journey on diagnostic delay. While means and medians are both reported here, the results of these two methods of presenting an average have been reported consecutively to avoid confusion resulting from direct comparison of data presented using different methodology.

3.4.6.1 Overview of Characteristic Effects on Delay

The effects of factors examined by more than five studies each are summarised here, grouped into two categories: 1) "Directional impact on delay", which includes factors which were showed to either have a significant effect on the increase or decrease of delay, or which were showed to have no significant effect on delay by five or more studies and 2) "Unclear Impact on Delay", which includes factors which more than three studies examined, but for which the directions of effect were found to be contradictory across studies.

Table 3.8 Characteristic Effects on Delay

	Characteristics	Total no of studies	Decreased Delay	No Difference	Increased Delay
Directional Impact on Delay	**Gender *(male)***	**16**	**0**	**14**	**2**
	Family history of axSpA *(yes)*	**5**	**0**	**5**	**0**
Unclear Impact on Delay	**HLA-B27 *(+)***	**11**	**5**	**5**	**1**
	Peripheral arthritis *(yes)*	**5**	**1**	**3**	**1**
	Uveitis *(yes)*	**5**	**1**	**3**	**1**
	Juvenile onset *(yes)*	**6**	**0**	**3**	**3**
	Radiographic axSpA (*yes*)	**7**	**0**	**4**	**3**

3.4.6.1.1 Study Characteristics

Median - Nine studies examined the following patient or circumstantial characteristics associated with median diagnostic delay: gender, referral process, diagnostician, disease type, patient history, age at symptom onset, symptoms, comorbidities, HLA-B27 positivity, education level and employment status (Bodur et al., 2012; Brandt et al., 2007; Fallahi and Jamshidi, 2016; Forejtová et al., 2008; Kidd and Cawley, 1988; Li et al., 2019; Qian et al., 2017; Roussou and Sultana, 2011; Sykes et al., 2015). The delays associated with these characteristics are tabulated below, and those which were statistically significant are summarised here.

Mean - Thirty studies presented patient or characteristics associated with mean diagnostic delay. The characteristics described were: gender, age at onset/diagnosis, year of onset, race, region (of a country), education level attained, employment, patient history, symptoms, clinical signs, treatment, comorbidities, sleep quality and disease type (Abdul-Sattar and Abou El Magd, 2017; Aggarwal and Malaviya, 2009; Bandinelli et al., 2016; Bodur et al., 2012; Brandt et al., 2007; Burgos-Varga et al., 2016; Cakar et al., 2009; Chimenti et al., 2020; Chung et al., 2011; Coughlan et al., 1981; Dincer et al., 2008; Fallahi and Jamshidi, 2016; Feldtkeller et al., 2003; Forejtová et al., 2008; Gavali et al., 2015; Geirsson et al., 2010; Gerdan et al., 2012; Hajialilo et al., 2014; Ibn Yacoub et al., 2012; Jones et al., 2014; Koko et al., 2014; Ma et al., 2012; Nakashima et al., 2016; Nie et al., 2018; Quraishi et al., 2018; Roussou and Sultana, 2011; Slobodin et al., 2018; Sullivan et al., 2014; Zhao et al., 2019b; Zwolak et al., 2019).

3.4.6.2 No Association with Delay

3.4.6.2.1 Gender

The role of gender on diagnostic delay was the most commonly examined of any factor this review identified, with 17 studies examining delay across males and females, 3 of which statistically examined the difference between median delay in the genders. Two studies found a significant association, one between median delays and one between mean delays (Bandinelli et al., 2016; Li et al., 2019). However, the further 15 studies which reported diagnostic delay associated with gender did not find statistical significance.

Table 3.9 Gender and Diagnostic Delay

Characteristics	Author	Year	Extent of diagnostic delay by characteristic (Years)		P-values
Gender (Median)			Male	Female	
	Fallahi et al	2016	6	6.5	0.68
	Sykes	2015	5	6	N/S
	Li et al	**2019**	**2.92**	**1.04**	**0.014**
	Bodur et al	2010	2	2.3	0.385
	Qian et al	2017	2	2	N/S
Gender (Mean)			*Male*	*Female*	
	Bandinelli et al	**2016**	**9.91**	**6.3**	**0.0023**
	Geirsson et al	2010	8.3	9.6	0.87

	Fallahi et al	2016	7.67	8.71	0.68
	Nakashima et al	2015	6.9	5.5	0.47
	Aggarwal et al	2009	6.5	8.6	0.23
	Hajialilo et al	2014	5.9	8	0.14
	Slobodin et al	2010	5.9	5.7	0.87
	Jones et al	2014	5.56	8.5	-
	Roussou et al	2010	5.56	6.27	-
	Dincer et al	2007	5.32	14.42	0.061
	Bodur et al	2010	4.9	5.3	0.385
	Ibn Yacoub et al	2011	4.6	4.8	0.075
	Coughlan et al	1981	4.6	5	-

			Male North China	*Female North China*	
	Ma et al	2012	4	4.1	NS
			Male South China	*Female South China*	
	Ma et al	2012	6.6	6.2	NS

3.4.6.2.2 Family history of axSpA

Despite being a significant risk factor for developing axSpA, family history was not found to have a significant effect on diagnostic delay in all five studies where this had been examined.

Table 3.10 Family History of axSpA and Diagnostic Delay

Variable	**Author**	**Year**	**Extent of diagnostic delay by** variable **(Years)**		**P-values**
Family History (Median)			*Family history of axSpA*	*No family history of axSpA*	
	Fallahi et al	2016	6.5	6	0.32
	Li et al	2019	1.36	2.38	N/S
Family History (Mean)			*Family History of axSpA*	*No Family History of axSpA*	
	Bandinelli et al	2016	9.48	8.68	0.5561
	Fallahi et al	2016	8.36	7.67	0.32
	Aggarwal et al	2009	7.1	6.6	0.68
	Hajialilo et al	2014	6.5	6	0.64

3.4.6.3 Suggestion of Increased Delay

3.4.6.3.1 Age of Onset and Diagnosis

Three of the eight studies which examined age of onset found it to be significantly associated with diagnostic delay, although the definitions they used varied considerably. Three studies, Aggarwal et al , Ozgocmen et al and Bodur et al described the difference in diagnostic delay between juvenile onset axSpA patients and adult onset axSpA patients, but of the three, only Aggarwal et al specified their definition of juvenile and adult onset (juvenile being <16 years and adult being ≥16 years); Bodur et al referred only to juveniles and adults (Aggarwal and Malaviya, 2009; Bodur et al., 2012; Ozgocmen et al., 2009). Aggarwal et al found diagnostic delay for patients with juvenile onset to be higher, at mean 9.1 years compared to 6.1 for those with onset after the age of 16 (p=0.03). Bodur et al's findings concur, showing juvenile axSpA patients to have mean 7.6 years delay compared to 4.7 years found in adults (p=<0.001), as do those of Ozgocmen et al, who report juvenile onset patients to experience mean 9.21 (SD 5.41) (mean 9) years delay, where adult-onset patients experience mean 5.08 (SD 5.99) (mean 3) years delay. A possible cause for this is the often inconclusive of sacro-iliac joint x-ray imagine in adolescents, and considering the timeframe during which these studies were undertaken, MRI for more sensitive imaging which could have alerted HCPs earlier to inflammation might not have been widely available or affordable.

Three further studies did find longer delays to diagnosis in patients with disease onset before the age of 16, but none of these delays was statistically significant (Cakar et al., 2009; Fallahi and Jamshidi, 2016; Li et al., 2019), and one study found no difference in the length of delay for patients with symptom onset younger than 16 (Qian et al.,

2017). Nakashima et al also found that patients with disease onset younger than 20 also had longer periods of diagnostic delay than those with disease onset after the age of 20, but again, these results did not reach statistical significance.

Zwolak et al examined the difference in delay for those diagnosed before and after the age of 45, finding that those diagnosed after the age of 45 experienced considerably more delay, at mean 18 years compared to 6.2 years for under 45s ($p=<0.0001$). This could be a result of the ASAS criteria defining axSpA as a disease which develops in individuals younger than 45 years; patients older than this might not be being considered as potentially having axSpA.

Table 3.11 Age of onset and diagnosis

Variable	Author	Year	Extent of diagnostic delay by variable (years)		P-values
Age of onset (median)			*<16 yrs*	*>16 yrs*	
	Fallahi et al	2016	5.5	6	0.91
	Qian et al	2017	2	2	N/S
	Li et al	2019	2.17	2.13	N/S
			Juvenile onset	*Adult onset*	
	Ozgocmen et al	**2009**	**9**	**3**	**<0.001**
Age at onset/diagnosis (mean)			*<16 yrs*	*>16 yrs*	
	Dincer et al	2007	8.89	5.51	0.027
	Fallahi et al	2016	7.88	7.8	0.91
	Aggarwal et al	**2009**	**9.1**	**6.1**	**0.03**
			<20 yrs	*>20 yrs*	
	Nakashima et al	2015	7	6.4	0.17
			<45 yrs	*>45 yrs*	
	Zwolak et al	**2019**	**6.2**	**18**	**<0.0001**
			Juvenile onset	*Adult onset*	
	Ozgocmen et al	**2009**	**9.21**	**5.08**	**<0.001**
	Bodur et al	**2010**	**7.6**	**4.7**	**<0.001**

3.4.6.4.2 Disease Type

Seven studies examined the association of axSpA type (radiographic or non-radiographic) with delay. One found radiographic axSpA patients encountered median 3.04 years delay, whereas non-radiographic axSpA patients had only 0.5 years (p=<0.0001) (Li et al., 2019). Two further studies found a significant association with mean delay. Gavali et al showed that radiographic axSpA patients experienced greater mean delay (4.4 years compared to 1.3 years for non-radiographic axSpA patients) (p=<0.0001), and Chimenti et al also showed radiographic patients with greater delay (5.91 years compared to 3.04 years for non-radiographic patients) (p=0.007) (Chimenti et al., 2020; Gavali et al., 2015). This could be due to the fact that radiographic changes can take a longer time to develop, whereas MRI-visible changes are potentially visible from outset, resulting in those patients diagnosed with the non-radiographic disease reporting shorter delay.

Four further studies all showed that diagnostic delay was longer in patients with the radiographic disease, with Kidd et al reporting r-axSpA patients experiencing median 3 years of delay compared to 2.83 in nr-axSpA patients, Brandt et alreporting median 8 years delay for r-axSpA compared with 2 years for nr-axSpA, Burgos-Varga et al reporting mean 6.48 years delay for r-axSpA compared with 5.21 years for nr-axSpA and Dincer et al reporting mean 6.63 years delay for r-axSpA, 5.53 for nr-axSpA (Brandt et al., 2007; Burgos-Varga et al., 2016; Dincer et al., 2008; Kidd and Cawley, 1988). However, none of these in delay were found to be statistically significant.

Table 3.12 Factors for which several studies showed increased delay

Characteristics	**Author**	**Year**	**Extent of Diagnostic Delay by Characteristic (years)**		**P-Values**
Disease type (Median)			*Radiographic axSpA*	*Non-radiographic axSpA*	
	Kidd et al	1988	3	2.83	-
	Brandt et al	2007	8	2	-
	Li et al	**2019**	**3.04**	**0.5**	**<0.0001**
Disease type (Mean)			*Radiographic axSpA*	*Non-radiographic axSpA*	
	Brandt et al	2007	10.7	4.6	-
	Burgos-Varga et al	2016	6.48	5.21	0.747
	Gavali et al	**2015**	**4.4**	**1.3**	**<0.0001**
	Chimenti et al	**2019**	**5.91**	**3.04**	**0.007**
	Dincer et al	2007	6.63	5.53	0.407

3.4.6.4 Unclear Results

3.4.6.4.1 Human Leukocyte Angigen-B27 (HLA-B27) Positivity

Of the eleven studies which examined the relationship of HLA-B27 positivity with delay, six studies found a significant association. Fallahi et al showed HLA-B27 positive patients to have median 5 years delay (mean 7.14), compared to 9 years (mean 10.1) for HLA-B27 negative patients (p=0.013). Four further studies showed HLA-B27 positivity to be associated with shorter mean delay than HLA-B27 negativity: 8.5 years vs 11.4 years (p=<0.001) (Feldtkeller et al., 2003), 5.33 years vs 9.20 years (p=0.037) (Dincer et al., 2008), 4.6 years vs 10.1 years (p=0.0001) (Hajialilo et al., 2014) and 2.7 years vs 3.7 years (p=0.01) (Chung et al., 2011). One study, however, showed the opposite effect: Li et al reported HLA-B27 positive patients encountering median 2.79 years delay whereas negative patients had 0.75 years delay (p=0.009) (Li et al., 2019). Five further studies examined association between the presence of HLA-B27 and diagnostic delay. Qian et al found no difference in median delay between HLA-B27 positive or negative patients. Two further studies identified no difference in mean delay based on HLA-B27 positivity (Aggarwal and Malaviya, 2009; Nakashima et al., 2016) and another two found HLA-B27 negative patients to have longer diagnostic delay, but these results were not statistically significant (Bakland et al., 2011; Bandinelli et al., 2016). While the results suggesting longer delay in patients without HLA-B27 were not significant, they are suggestive and could be explained by the potentially longer process of diagnosing HLA-B27- patients. Diagnosis in line with ASAS criteria would require further MSK changes evident upon imaging to confirm a diagnosis in the absence of HLA-B27 (M. Rudwaleit et al., 2009c, 2009a).

Table 3.13 Presence of HLA-B27

Variable	Author	Year	Extent of diagnostic delay by variable (years)		P-values
HLA-B27 (Median)			*HLA-B27+*	*HLA-B27-*	
	Fallahi et al	**2016**	**5**	**9**	**0.013**
	Qian et al	2017	2	2	N/S
	Li et al	**2019**	**2.79**	**0.5**	**0.009**
HLA-B27 (Mean)			*HLA-B27+*	*HLA-B27-*	
	Feldtkeller et al	**2003**	**8.5**	**11.4**	**<0.001**
	Dincer et al	2007	5.33	9.2	0.037
	Bandinelli et al	**2016**	**8.43**	**10.26**	**0.345**
	Bakland et al	2011	7.9	8.5	0.9
	Fallahi et al	**2016**	**7.14**	**10.1**	**0.013**
	Aggarwal et al	2009	6.9	6.6	0.9
	Nakashima et al	2015	6.6	6	0.84
	Hajialilo et al	**2014**	**4.6**	**10.1**	**0.0001**
	Chung et al	**2011**	**2.7**	**3.7**	**0.01**

3.4.6.4.2 Peripheral Arthritis

Sykes et al found diagnostic delay to be associated with the absence of peripheral arthritis, with median 4 years delay for patients with it and 6 years for those without ($p=0.025$), possibly due to it highlighting the possibility that concurrent low back pain might also be inflammatory. Hajialilo et al, conversely, showed that the presence of peripheral arthritis was associated with greater mean delay, at 11.3 years, than its absence (5.1 years) ($p=0.0001$). While this second result is superficially contradictory to that of Sykes et al, it may be that it reflects that in the Iranian healthcare system, symptomatic treatment of the peripheral symptoms does not lead to further investigation; the improvement of peripheral symptoms could lead to other symptoms being overlooked.

Three further studies examined possible associations between peripheral arthritis and diagnostic delay, and those studies, similarly to those which reported significant associations, showed mixed results. Two showed a non-significant increase in mean diagnostic delay(Aggarwal and Malaviya, 2009; Fallahi and Jamshidi, 2016) while another showed reduced mean delay (Dincer et al., 2008).

Table 3.14 Peripheral arthritis

Characteristics	Author	Year	Extent of Diagnostic Delay by Characteristic (years)		P-Values
Peripheral Arthritis (Median)			Peripheral arthritis	No Peripheral Arthritis	
	Sykes	**2015**	**4**	**6**	**0.025**
	Fallahi et al	2016	6	5	0.086
Peripheral Arthritis (Mean)			*Peripheral arthritis*	*No Peripheral Arthritis*	
	Hajialilo et al	**2014**	**11.3**	**5.1**	**0.0001**
	Fallahi et al	2016	8.92	6.81	0.086
	Aggarwal et al	2009	6.8	6.4	0.8
	Dincer et al	2007	4.78	6.55	0.291

3.4.6.4.3 Uveitis

Sykes et al showed the presence of **uveitis** was associated with median 10 years delay, compared to 5 years for those without it (p=0.005). Hajialilo et al, however, found it to be associated with lower diagnostic delay (mean 2.4 years) than no uveitis (6.4 years) (p=0.02).

There was also no consensus found among the three studies which, in examining the relationship between uveitis and delay, found no significant association. Li et al and Nakashima et al showed an increase in delay in patients with uveitis. Fallahi et al however, presented conflicting results from their own data, with patients with uveitis having lessened median delay but greater mean delay (it is of note that this result was not statistically significant).

Table 3.15 Uveitis

Characteristics	Author	Year	Extent of Diagnostic Delay by Characteristic (years)		P-Values
Uveitis (Median)			*Uveitis*	*No uveitis*	
	Fallahi et al	2016	5	6	0.71
	Li et al	2019	3.61	1.9	N/S
	Sykes	**2015**	**10**	**5**	**0.005**
Uveitis (Mean)			*Uveitis*	*No uveitis*	
	Fallahi et al	2016	7.91	7.88	0.71
	Nakashima et al	2015	7.5	6.5	0.86
	Hajialilo et al	**2014**	**2.4**	**6.4**	**0.02**

3.4.6.5 Variables with Limited Studies

3.4.6.5.1 Patient History

Three aspects of patient history were found to be significantly associated with mean diagnostic delay. Dincer et al showed that having a 1st degree seronegative SpA (as opposed to specifically axSpA/AS, as reported above) diagnosed relative is associated with less delay (mean 4.6 years) compared to 10 years delay experienced by patients with no 1st degree seronegative SpA relatives (p=0.003). Gerdan et al found prior diagnosis of lumbar disc herniation to be associated with more delay than not having this prior diagnosis, likely due to either focus on the present herniation itself causing symptoms rather than axSpA or a total misdiagnosis necessitating further investigation. The former experienced an average mean 9.1 years compared to 6.2 years for the latter (p=0.002).

Patients with a history of smoking had twice the median delay than those without, with the former having 3.04 years of delay compared to 1.58 years for the latter (p=0.043) (Li et al., 2019).

3.4.6.5.2 Healthcare History

The referral journey for patients was also shown by one study to be associated with diagnostic delay; patients whose initial consultation was to a non-rheumatologist reported 2.54 years delay, compared to 0.54 years for those whose initial consultation was to a rheumatologist (p=0.018) (Li et al., 2019).

3.4.6.5.3 Symptoms

Nakashima et al found articular involvement (i.e the presence of extra-spinal symptoms such as coxalgia, knee-pain or enthesitis) in axSpA was associated with less diagnostic delay (mean 5.2 years) than no articular involvement (8.9 years) (p=0.03). Aggarwal et al showed the opposite: extra-articular involvement was associated with 8.7 years delay compared to 5.9 years for a lack of extra-articular involvement (p=0.03).

Two studies showed that patients with no inflammatory back pain (IBP) at disease onset encountered more mean delay than those with IBP: Hajialilo et al found delay for IBP vs no-IBP was mean 4.8 vs 8.7 years (p=0.001) and Dincer et al found mean 3.28 vs 8.57 years (p=0.001). As inflammatory back pain is a characteristic feature of axSpA, its presence will raise suspicion of inflammatory arthritis earlier, leading to earlier referral, hence the delay found in those patients who did not present at outset.

The presence of enthesitis was associated with increased delay: Hajialilo et al found a mean of 13 years compared to 5.9 years for those with no enthesitis (p=0.004), and Fallahi et al showed median 6 years delay (mean 8.8 years) compared to 4 years (mean 6.04 years) for those without enthesitis (p=0.007). This is counter-intuitive, as enthesitis is a characteristic feature of axSpA, and needs further investigation.

Inflammatory bowel disease was shown by Sykes to be associated with 4 years median delay, compared to 6 years without (p=0.024), possibly due to its raising clinician suspicion that any concomitant MSK pain may be inflammatory.

Hajialilo et al also showed morning stiffness to be associated with shorter delay, with mean 4.6 years compared to 10.1 years for those without morning stiffness (p=0.0001). Morning stiffness which improves with movement is associated with

inflammation and would again raise earlier suspicion that MSK symptoms may be inflammatory.

Nie et al showed that increased mean delay was associated with worse sleep quality (PSQI 5); 4.95 years compared to 2.95 years associated with less reduced sleep quality (PSQI <5) (p=<0.001). This is possibly due to sleep quality organically worsening with the length of disease duration as a result of more physical discomfort and commensurate mental health effects.

3.4.6.5.4 AxSpA Clinical Signs

ESR above 30 was shown to be associated with less mean delay (4.8 years) than ESR below 30 (7.9 years) (p=0.0001) by Hajialilo et al. CRP of >6 (5.6 years) was associated with less mean delay than CRP of <6 (7.8 years) (p=0.036), also by Hajialilo et al. Zhao et al showed hip disease severity increasing proportionately to mean diagnostic delay, with minimal hip disease being associated with mean 3.46 years delay, moderate hip disease with 3.68 years and severe hip disease with 4.59 years (p=0.001). The symptoms here are not causal of delay, however; they are worsening due to delayed diagnosis and treatment.

3.4.6.5.5 Demographic Characteristics

Ma et al examined the differences between regions of China regarding patients with axSpA and found that patients from the North of the country experienced significantly less mean delay (3.2 years) than those in the South (7.3 years) (p=<0.0001), suggesting either of two main options: either healthcare in the north of the country is more

effective than that in the south, or after a certain amount of time waiting to be diagnosed, more patients in the north are never diagnosed and are therefore lost to follow-up. Given the South of China is far more urbanised and wealthy than the North, this may be the case.

Of the four studies which examined the association between employment and benefit status and mean diagnostic delay, one found a significant association. Abdul-Sattar et al found patients experiencing work disability (i.e. the inability to work to full capacity due to impaired ability) are less likely to experience diagnostic delay (mean 4 years) than those who experience no work disability (8 years) ($p=<0.001$); this could be due to the former experiencing a more progressive disease with more blatant symptomology, resulting in an easier diagnosis.

Dincer et al showed a statistically significant reduction in diagnostic delay for patients who attended higher education: patients with 14-15 years of education experienced a mean 4.55 years of delay (SD 3.58), compared to 12 years (SD 12.41) experienced by those with 0-8 years education ($p= 0.018$). There are two intermediate educational increments described, 9-11 years and 12-13 years, but the effects these had on diagnostic delay compared to the difference between the lowest and highest level of education were not statistically significant. Trend analysis on these data, which could have offered more context on the relationship between education level and diagnostic delay, was not present.

Table 3.16 Factors with Limited Studies

Characteristics	**Author**	**Year**	**Extent of diagnostic delay by characteristic (Years)**			**P-values**
Race (Mean)			*Arab*	*Caucasian*	*Indian sub-continent*	
	Quraishi et al	2018	2.89	1.87	3.85	0.39
Region (Mean)			*South China*	*North China*		
	Ma et al	**2012**	**7.3**	**3.2**		**<0.0001**
Referral process (Median)			Direct rheumatology referral	1st referral non-rheumatology		
	Kidd et al	1988	3	6		-
			Initial visit non-rheumatologist	*Initial visit rheumatologist*		
	Li et al	**2019**	**2.54**	**0.54**		**0.018**
Diagnostician (Median)			Expert rheumatologist	General rheumatologist	GP	
	Roussou et al	2011	6	10	>15	-
History (Median)			*History of nephrolithiasis*	*No history of nephrolithiasis*		
	Fallahi et al	2016	5	6		0.44
			History of infection prior to disease	*History of infection prior to disease*		

	Fallahi et al	2016	3	6	0.31
			History of smoking	*No history of smoking*	
	Li et al	**2019**	**3.04**	**1.58**	**0.043**
History (Mean)			*1st degree, Sero- SpA relative*	*No 1st degree, Sero- SpA relative*	
	Dincer et al	**2007**	**4.6**	**10**	**0.003**
			History of nephrolithiasis	*No history of nephrolithiasis*	
	Fallahi et al	2016	9.79	0.63	0.44
			History of infection prior to diagnosis	*No history of infection prior to diagnosis*	
	Fallahi et al	2016	6.53	8.2	0.31
			Prior diagnosis of lumbar disc herniation	*No prior diagnosis of lumbar disc herniation*	
	Gerdan et al	**2012**	**9.1**	**6.2**	**0.002**
Year of onset (Mean)			*<1999*	*>2000*	
	Nakashima et al, 2015	2015	**7.5**	**2.6**	**0.02**
Symptoms (Median)			*Enthesitis*	*No enthesitis*	

	Fallahi et al	**2016**	**6**	**4**	**0.007**
Symptoms (Mean)			*Articular involvement*	*No articular involvement*	
	Nakashima et al	**2015**	**5.2**	**8.9**	**0.03**
			Extra-articular involvement	*No extra-articular involvement*	
	Aggarwal et al	**2009**	**8.7**	**5.9**	**0.03**
			Spinal initial symptoms	*Extra-spinal initial symptoms*	
			7	6.4	0.5
			Inflammatory back pain at onset	*No Inflammatory back pain at onset*	
	Aggarwal et al	2009	7.3	5.9	0.3
	Hajialilo et al	**2014**	**4.8**	**8.7**	**0.001**
	Dincer et al	**2007**	**3.28**	**8.57**	**0.001**
			Radiological sacroiliitis at onset	*No Radiological sacroiliitis at onset*	
	Dincer et al	2007	6.63	5.53	0.407
			Sacroiliitis radiological stage 1-2	*Sacroiliitis radiological stage 3-5*	

	Koko et al	2014	1.6	3.3		0.021
			Minimal hip disease	*Moderate hip disease*	*Severe hip disease*	
	Zhao et al	2015	**3.46**	**3.68**	**4.59**	**0.001**
			Enthesitis	*No enthesitis*		
	Hajialilo et al	**2014**	**13**	**5.9**		**0.004**
	Fallahi et al	**2016**	**8.8**	**6.04**		**0.007**
			Buttock pain	*No buttock pain*		
	Hajialilo et al	2014	5.3	7		0.07
			Morning stiffness	*No morning stiffness*		
	Dincer et al	2007	7.29	5.16		0.174
	Hajialilo et al	**2014**	**4.6**	**10.1**		**0.0001**
Comorbidity (Median)			*Inflammatory bowel disease*	*No inflammatory bowel disease*		
	Sykes	**2015**	**4**	**6**		**0.024**
	Fallahi et al	2016	8	6		0.87
Comorbidity (Mean)			*Comorbidity*	*No comorbidity*		
	Nakashima et al	2015	8.3	5.6		0.24
			Psoriasis	*No psoriasis*		

	Nakashima et al	2015	8.3	6.4			0.57
			Inflammatory Bowel Disease	*No inflammatory bowel disease*			
	Fallahi et al	2016	8.36	7.85			0.87
	Nakashima et al	2015	7.9	6.5			0.2
Other Clinical Signs (Mean)			*ESR >30*	*ESR <30*			
	Hajialilo et al	**2014**	**4.8**	**7.9**			**0.0001**
			CRP >6	*CRP <6*			
			5.6	**7.8**			**0.036**
Treatment (Mean)			*Anti-TNF*	*No anti-TNF*			
	Sullivan et al	2013	5.7	5.4			
Sleep Quality			*PSQI ≤5*	*PSQI ≥5*			
	Nie et al	2018	**2.95**	**4.95**			**<0.001**
Education (Median)			*<9 yrs*	*>9 yrs*			
	Li et al	2019	2.92	1.75			N/S
Education (Mean)			*Low*	*Medium*	*High*		
	Bandinelli et al	2016	10.28	8.578	7.253		0.0763
			0-8 years	*9-11*	*12-13*	*14-15*	
	Dincer et al	**2007**	**12**	**6.28**	**4.96**	**4.55**	**0.0018***

Employment (Median)			*Full disability pension*	*No disability pension*		
	Forejtova et al	2012	7.5	7.5		0.021
Employment (Mean)			*Manual*	*Non-manual*		
	Bandinelli et al	2016	10.54	8.275		0.0476
			Full disability pension	*No disability pension*		
	Forejtova et al	2012	9.93	8.39		0.021
			Work disability	*No work disability*		
	Abdul-Sattar et al	**2014**	**4**	**8**		**<0.001**
			Work, no change	*Work-disabled, change in job*	*Work-disabled-permanently disabled*	
	Cakar et al	2009	3.7	7.3	7.8	0.028

* Only the difference between 0-8 years and 14-15 years of education is statistically significant

3.5 Discussion

3.5.1 The extent of diagnostic delay

This systematic review examined all available studies reporting diagnostic delay in patients with axSpA, with particular focus on studies reporting median diagnostic delay. The review found that patients with axSpA, in all countries examined, experienced years of diagnostic delay, ranging from the longest average delay of eight years (Seo et al., 2015) to the shortest average diagnostic delay of 0.67 years (Sørensen and Hetland, 2015); the majority of the studies, however, reported between 2 and 5 years median delay. It is notable that this review also illustrates in depth the extent to which studies reporting mean diagnostic delay are overestimating delay for the majority of patients; in most of the studies which report both mean and median delay, mean delay is between 30 and 50% greater than median delay. Four studies examined changes in diagnostic delay over time and presented a marked reduction over the second half of the 20th century (Calin et al., 1988; Reed et al., 2008, p. 20; Salvadorini et al., 2012; Wright et al., 2015).

While the pooled mean estimate of diagnostic delay presented in Zhao et al's systematic review and meta-analysis on diagnostic delay for axSpA (Zhao et al., 2021) (6.7 years) falls within our presented median range, it is higher than that shown by the majority of our included studies. Additionally, where the present review found reduction in diagnostic delay over several decades, Zhao et al found none due to the non-inclusion of data from Calin et al (1988) and Salvadorini et al (2012); these two studies presented the most persuasive evidence for reduction in delay through the

second half of the 20th century. The data presented by Salvadorini et al showing change over time was presented as medians, leading to its non-inclusion by Zhao et al.

3.5.2 Quality Assessment

The quality of included studies was generally high, with the majority achieving two or more stars out of a possible three, 22 of which achieved three stars. Of those 22, 10 achieved A*A*B*, the highest grading among these studies. Representativeness of the exposed cohorts, apart from in 2 studies, in the top two highest categories, suggesting the results of the included studies and, therefore the results of this systematic review, are highly generalisable. Ascertainment of exposure, i.e. ascertainment of diagnosis of axSpA, was also extremely high for the majority of studies which ensures the diagnostic delay presented in this review is reliably associated with axSpA. The outcome criteria (assessment of outcome, in this case interpreted as confirmation of diagnostic delay) we used from the Newcastle-Ottawa Assessment Scale for Cohort Studies, however, did not achieve A* in any studies. While this superficially would seem to be a concern, it must be noted that the A* rating, "independent blind assessment", is not applicable to an outcome such as diagnostic delay as diagnostic delay is an absolute measure rather than a set of measurements which require assessment and judgement by a diagnostic specialist, for instance. Taking note of this, B* (record linkage) becomes the highest mark of quality available for studies of diagnostic delay, and 40% of included studies achieved this. This possible minor incompatibility between the Newcastle-Ottawa Assessment Scale suggests that a quality assessment scale specific to studies of diagnostic delay would hold merit for future research.

3.5.3 Variables associated with diagnostic delay

The review found 24 variables reported to have significant association with a difference in diagnostic delay, but many of these were reported only by one or two studies, meaning that results were not validated by repetition and cannot be claimed to be supported by consensus. Where the role of a variable had been examined across multiple studies, many of the variables reported to have a significant association with diagnostic delay in contradictory directions of effect. Importantly, the majority of studies which reported diagnostic delay associated with gender and family history of axSpA showed no significant association. This is of particular note, as both of these variables are significantly associated with the development of axSpA (Poddubnyy and Sieper, 2014). It is of note however that ASAS criteria for axSpA classification specify family history of SpA overall rather than specifically axSpA (M. Rudwaleit et al., 2009c, 2009a), and this is the criterion used in the NICE guidelines in the UK (National Institute for Health and Care Excellence [NICE], 2017). When Dincer et al (2008) investigated association between delay and SpA family history, they found patients with SpA family history encountered less delay. This may reflect that 1) SpA, rather than specifically axSpA, includes diseases such as IBD and psoriasis, which relatives may be more aware of than axSpA and 2) as axSpA diagnosis has improved over time, it is possible that is more likely that spondyloarthropathies with less ambiguous and insidious presentations, such as PsA and IBD, were correctly diagnosed in the previous generation. It may be that as axSpA diagnosis improves, so a significant association between axSpA family history and reduced delay might occur in a similar pattern to that found in the other SpAs.

Male gender appears specifically to be associated with the development of the radiographic disease, which was itself reported by several studies to be more delayed in its diagnosis than the non-radiographic disease, although the directionality of this association is important to consider. Patients who have already waited a long time for their diagnosis are also more likely to have developed radiographically visible changes.

3.5.3.1 Variables with no effect on delay

While three quarters of the studies which presented delay by gender superficially appeared to show female patients to encounter longer or equal delay than males, the only two studies which showed a statistically significant difference showed diagnosis time to be shorter in women than men (Bandinelli et al., 2016; Li et al., 2019). This is an important finding regarding the possibility in the future of addressing diagnostic delay, as it implies that outdated presumptions regarding the possibility of a male predominance among the axSpA population is not influencing speed of diagnosis, nor is the different weighting between sexes of the radiographic and non-radiographic disease (Poddubnyy and Sieper, 2014). These findings are concordant with those of Zhao et al, who found no association between gender and delayed diagnosis (Zhao et al., 2021).

Additionally, where five studies examined the relationship between family history of axSpA and diagnostic delay, none found a significant association. Family members having developed axSpA has repeatedly been shown to significantly increase risk of axSpA in an individual (van Lunteren et al., 2018) and spondyloarthropathy (not limited to axSpA) in a patients' family history is a feature supporting classification of axSpA as per the ASAS criteria (M. Rudwaleit et al., 2009c, 2009a). An absence of

family history of SpA in a patient might therefore be presumed to lower their likelihood of timely diagnosis with axSpA. The fact that patients with family history of axSpA experience no more or less delay than patients with no family history of the disease implies (but does not explicitly demonstrate) that this conversation is not occurring for many patients. Furthermore, where the conversation regarding family history is taking place, it may be overly specific in its subject; family history of axSpA defined by the ASAS classification criteria covers not just axSpA but spondyloarthritis more generally (the genetically overlapping conditions of reactive arthritis, PsA and psoriasis, inflammatory bowel disease and uveitis).

What this signifies is unclear, but it could be hypothesised that this is related to the lack of frequency with which axSpA is seen in primary care; the question of family history of the disease is one which would arise only after the HCP being consulted had become suspicious of the disease. It is possible that its being included in a standardised set of questions asked of patients presenting with chronic back pain and other suggestive symptoms could increase the speed by which HCPs suspect symptoms of being indicative of axSpA.

3.5.3.2 Variables with unclear impact on delay

Where there was agreement among studies with statistically significant results that r-axSpA patients encounter a longer delay to diagnosis than nr-axSpA patients (Chimenti et al., 2020; Gavali et al., 2015; Li et al., 2019), more studies found that there was no difference in effect between the radiographic and non-radiographic disease, so no clear conclusion can be reached from this pooled data. While studies showing longer

delay in the radiographic disease were outnumbered by those showing no effect, a possible effect is still worth discussion here. While it might initially seem counter-intuitive, with nr-axSpA being the more challenging diagnosis, explanations have been suggested. Gavali et al suggest that as the radiographic disease is by definition quite far advanced, so patients diagnosed at the point at which their disease can be described radiographically will very often have longer disease duration and therefore diagnostic delay than non-radiographic patients (Gavali et al., 2015). This explanation does not, however, describe *why* r-axSpA have such delayed diagnosis. More typical axial features of r-axSpA, such as chronic lower back pain, are commonly misinterpreted in primary care, being mistaken for mechanical back pain or other possible diagnoses (Tant et al., 2017), or with the pain being misattributed to other causes such as lumbar disc herniation (Caetano et al., 2021).

While three studies showed significant increase in delay for r-axSpA patients over nr-axSpA patients, four showed no significant difference (Brandt et al., 2007; Burgos-Varga et al., 2016; Dincer et al., 2008; Kidd and Cawley, 1988). The studies which found a significant difference were Chinese (Li et al., 2019), Italian (Chimenti et al., 2020) and Indian (Gavali et al., 2015), while those which found no difference were Turkish (Dincer et al., 2008), German (Brandt et al., 2007), British (Kidd and Cawley, 1988) and finally, Burgos-Varga et al examined patient data from Latin-America, Africa, Europe and Asia (Burgos-Varga et al., 2016). It is possible that this points to differences in medical capabilities between countries which should be examined at greater length in future. It has been reported by Aggarwal et al, for instance, that there is a high instance of initial misdiagnosis of axSpA in India, which could hypothetically be exacerbated in the less-obvious diagnostic process of the non-

radiographic disease (Aggarwal and Malaviya, 2009). The equivocal nature of the pooled data in this review on this subject shows this requires further research.

Juvenile age of symptom onset was shown by some studies to be associated with increased length of delay with all three studies presenting significant results finding adult-onset patients to experience three years less delay than juvenile onset patients (Aggarwal and Malaviya, 2009; Bodur et al., 2012; Ozgocmen et al., 2009). These studies were, however, outnumbered by studies which found no effect so as a pooled set of data, these results should not be regarded as conclusive in any direction. Regarding those studies which found a directional effect, however, discussion is warranted. Aggarwal et al point out that misdiagnosis was present in a quarter of the young patients in their study, and that misdiagnosis is extremely common for axSpA patients prior to their correct diagnosis; as stated by the authors, there is a strong implication that education regarding the disease is too low among the involved professional cohort, leading to delay. Additionally it has been shown that juvenile onset axSpA patients have less severe radiographic axial involvement (Gensler et al., 2008) and more frequent peripheral involvement (O'Shea et al., 2009), and Ozgocmen et al point out that they found juvenile-onset axSpA patients to have greater peripheral disease involvement and less axial involvement than adult-onset patients, which could lead to less immediate suspicion of axSpA (Ozgocmen et al., 2009). Regarding juvenile-onset patients, suspicion of future axSpA development would be difficult to justify as development of the former into the latter is by no means guaranteed. Again, it could be supposed that this situation could be improved by greater education regarding the non-axial presentations of the disease and the degree to which axSpA presents comorbidity alongside other spondyloarthropathies;

development of axSpA following juvenile inflammatory symptoms may not be a demonstration of contiguity in a single disease but presentation of comorbid spondyloarthropathy requiring a wider focus of management. Briefly: delay in axSpA patients who report their symptoms as having juvenile onset must be considered thoroughly and their early symptoms cannot always be thought of as "predictive". This is a valuable example of delay being a *post hoc* qualifier in the case of developing symptomology in patients, and one which may in many cases be resultant not of systemic failure but in the truly insidious and unclear nature of early axSpA.

It is important to note that a greater number of studies presented no significant difference in diagnostic delay period between patients whose symptoms became apparent before or after the age of 16 (Dincer et al., 2008; Fallahi and Jamshidi, 2016; Li et al., 2019; Qian et al., 2017) or, in the case of Nakashima et al 2015, before or after the age of 20. Further multi-national research using standardised methods is needed to form any persuasive conclusions regarding the differences in results between these studies; it may be a study, cohort or even temporally specific effect.

The effects on diagnostic delay of three further major variables were not agreed upon across studies: the effect of HLA-B27 positivity, the effect of the presence of peripheral arthritis and that of uveitis. Of the 11 studies which examined possible association between diagnostic delay and HLA-B27 positivity, 5 showed a reduction (Chung et al., 2011; Dincer et al., 2008; Fallahi and Jamshidi, 2016; Feldtkeller et al., 2003; Hajialilo et al., 2014), 5 showed no effect (Aggarwal and Malaviya, 2009; Bakland et al., 2011; Bandinelli et al., 2016; Nakashima et al., 2016; Qian et al., 2017) and 1 showed an

associated increase in delay (Li et al., 2019). There is little explanation from the latter as to why HLA-B27 positivity might be associated with increased diagnostic delay.

The difference in results between Sykes and Hajialilo et al regarding the delay associated with peripheral arthritis at onset could be due to the very small number of patients in Hajialilo's study who presented initially with peripheral arthritis (n=10) (Hajialilo et al., 2014; Sykes et al., 2015). It is not possible to make a direct comparison here with Sykes' study, as they did not report their number of patients with peripheral arthritis, but 10 is well below a number generally seen as being necessary for reliable statistical power (Whitley and Ball, 2002). The contradictory results here could imply that the effect of peripheral arthritis on delay is specific to the study samples. This supposition is supported in Sykes' study, in which it is suggested that the shorter length to delay in patients with peripheral arthritis might be due to the introduction of the Early Arthritis Initiative, intended to speed referral for rheumatoid arthritis by frequently reminding primary care HCPs to refer swiftly patients presenting with swollen joints (National Institute for Health and Care Excellence [NICE], 2017). Further supporting that point, Hajialilo et al suggest in their study that peripheral arthritis being associated with longer delay is due to Iranian primary care physicians and non-rheumatologists not considering axSpA in differential diagnosis of peripheral symptoms (Hajialilo et al., 2014). Also of note, is that while 2 studies showed a significant effect, 3 did not (Aggarwal and Malaviya, 2009; Dincer et al., 2008; Fallahi and Jamshidi, 2016). These three studies statistically analysed the difference in delay between patients with and without peripheral arthritis showed no difference; as with the two studies showing significant effects, however, it is impossible to reach conclusions regarding the implications of these results. It is clear that, as there are

only five studies found here which examine the relationship between the presence of peripheral arthritis and diagnostic delay, more research is required to form any further conclusions. As was the case regarding gender, these results showing a lack of consensus for the association of diagnostic delay with the presence of peripheral arthritis and HLA-B27 are also concordant with Zhao et al (2021).

The case of disagreement regarding the effect of uveitis on diagnostic delay might not be as significant as it initially seems. Sykes et al reports patients with uveitis encountering twice as much median diagnostic delay as those without (10 years vs 5 years) (p=0.005), but continues to show that the difference in delay is at its most at the mid-range of the survival distribution, i.e. the difference in delay between patients with or without uveitis is significant over the middle of the range of delay found in this sample; the level of delay found in patients with or without uveitis converges again toward to lower and top end of the range (Sykes et al., 2015). The difference between the entire samples was not statistically significant (p=0.073). Conversely to the increase in delay showed by Sykes et al, Hajialilo et al showed patients with uveitis to experience less than half the diagnostic delay than patients without uveitis (median 2.4 years vs 6.4), which is attributed to uveitis being a symptom which would suggest spondyloarthropathies to ophthalmologists (Hajialilo et al., 2014). While there superficially seems to be a stark disagreement between these two studies, the truth is more subtle. The difference found in Sykes et al's study may not be as significant as it seems at first glance (based on the above demonstration of significance only in the middle of the delay range), and Hajialilo et al's study is less a proof that patients with uveitis encounter less delay, and more that other characteristics which in the UK may be picked up as characteristic of an inflammatory arthritis are commonly misdiagnosed

or misattributed in Iranian primary care, leaving the association between uveitis and delay seeming exaggerated by comparison. Additionally, three further studies (Fallahi and Jamshidi, 2016; Li et al., 2019; Nakashima et al., 2016) found no significant effect of uveitis on diagnostic delay, further suggesting that the apparent significance of the effect shown by Sykes et al and Hajialilo et al may not be generalisable. Alternatively, the historically higher prevalence of Behçet's disease in the East-Mediteranean, Middle-East and Asia compared to Western European populations may have an effect on studies from those areas; Behçet's disease causes uveitis, so either uveitis in those countries with higher prevalence might be less likely to be caused by spondyloarthropathy or it could be less likely to cause suspicion of spondyloarthropathy (Nair and Moots, 2017). Uveitis has been shown to be an important variable to consider in association to axSpA. The research surrounding the Dublin Uveitis Evaluation Tool (DUET) illustrates that patients with uveitis are also quite likely to also have undiagnosed spondyloarthropathy and specifically axSpA. In a cohort of patients with uveitis, 40% were subsequently diagnosed with SpA, 96.5% of whom were specifically diagnosed with axSpA (Haroon et al., 2015). This shows clearly that, while the relationship between the presence of uveitis and diagnostic delay lacks clarity, further links between ophthalmology and rheumatology in the cases of uveitis patients may well shorten the time to diagnosis for a proportion of patients with axSpA.

3.5.3.3 Limited Studies

Due to the low numbers of comparable studies pooled in this systematic review in this category, showing the value of further research in all its comprising variables. Of particular interest is the association between first consultations and referrals (Kidd and Cawley, 1988; Li et al., 2019; Roussou and Sultana, 2011), as quantitative data on this area would be of potential use in the reduction of diagnostic delay. To an extent, this question is also handled qualitatively in the following chapter.

In 2021, a systematic review with a very similar scope to this one was published in Rheumatology by Zhao et al, titled Diagnostic Delay in Axial Spondyloarthritis: A Systematic-Review and Meta-analysis (Zhao et al., 2021). As with the current review, the aims were to describe the extent of diagnostic delay in axSpA globally, and to describe any variables associated with delay and the extent of that association.

There were, however, notable differences between that systematic review and this which result in the two being complementary and giving the current review methodological benefits in some important areas. The most major unique difference between Zhao et al and the present systematic review is the focus here on median delay, where Zhao et al focused on mean delay. Additionally, Zhao et al compared the diagnostic delay found in axSpA with that of other spondyloarthropathies, which is outside the remit of this thesis. Also included in that review were conference abstracts presenting diagnostic delay, (excluded from this study due to lack of peer review for many conference abstracts) and diagnostic delays imputed from studies which provided date of symptom onset and date of diagnosis. Our own study did not do this as it is not possible to estimate medians by imputation.

Zhao et al focused on diagnostic delay reported recently, as their study aimed to pool diagnostic delay data using meta-analysis and therefore intended this pooled result to be a "current snapshot" for benchmarking purposes. Without this restriction, the review presented here includes studies reporting diagnostic delay back into the middle of the previous century and have thus been able to present a useful picture of a declining trend in diagnostic delay times in many countries.

The most significant methodological difference between Zhao et al and the present review, however, is the decision regarding presentation of average diagnostic delay. As has been described previously in this thesis, the decision was made to present median diagnostic delays in this systematic review as the primary representative measure for a population, rather than mean delay. This is due to the positively skewed nature of distribution of extent of diagnostic delay in a population; the majority of patients experience delay of around five years, but there are still patients who experience multiples of this. This results in a non-normal distribution, most appropriately described by a median. Zhao et al presented mean diagnostic delay to allow for meta-analysis of delay across studies, leading to a single mean measure of diagnostic delay for their review.

These methodological differences present an unusual boon for the area of research: these two systematic reviews complement each other closely, capitalising on differing and specific methodology to show a large and complex body of research in different lights.

3.5.4 Strengths and limitations

This is the first systematic review to synthesise the median delay data globally to provide a benchmark range, giving the most representative understanding of diagnostic delay for axial spondyloarthritis. This is reinforced by the direct comparison of means to medians, showing the difference in estimates resulting from the two methods. Additionally, this systematic review details and compares many characteristics and circumstances of patients which are associated with diagnostic delay, which may suggest new avenues for future research. Of note, this study pools a large amount of data on the effects of gender and family history on diagnostic delay, showing that neither are associated with increased delay. The study also compares studies presenting changes in diagnostic delay for over half a century, showing an encouraging improvement in the duration of delay.

A limitation of this systematic review includes the parameters set by the initial search strategy. While this search strategy was very effective at identifying studies explicitly naming diagnostic delay in their titles and abstracts, it was less sensitive to studies which examined diagnostic delay as a secondary outcome. This was remedied by an extremely detailed manual reference search of a wide array of literature examining axSpA; many studies which examined demographic characteristics in axSpA patients, the effects of axSpA on quality of life, employment and economies, and smaller-scale studies showing the lived experience of the disease reference studies which note diagnostic delay as a secondary outcome.

Some of the included studies were published in the 1980s and it is therefore questionable how comparable these are with current data (Calin et al., 1988; Coughlan

et al., 1981; Kidd and Cawley, 1988). Of those studies published since 2000, eight were published before the introduction of ASAS classification criteria, again bringing into question direct comparability with current studies (Bakland et al., 2005; Brandt et al., 2007; Brunner et al., 2002; Dincer et al., 2008; Feldtkeller et al., 2003; Feldtkeller and Erlendsson, 2008; Forejtová et al., 2008; Reed et al., 2008). Additionally, MRI scans were not widely used to assess inflammation prior to the 2000s, meaning the patient samples discussed in those earlier studies will not cover the same diversity of demographic and disease presentation as more recent studies.

3.6 Conclusions

There is still considerable diagnostic delay experienced by patients with axial spondyloarthritis, despite marked improvement over the last few decades. This study shows the most common range for diagnostic delay is a median of between 2 and 5 years (study n=9, median=3). Patient gender and family history do not appear to influence diagnostic delay, and while studies examining other characteristics were numerous, evidence of associations between patient characteristics and diagnostic delay remain mixed or limited. The current study provides a benchmark against which future developments and strategies to reduce diagnosis delay in axSpA can be compared. Further research with large sample sizes which involve broad spectrum of patients will further elucidate the details of diagnostic delay for axSpA, its causes and methods for its reduction.

Chapter 4 – Barriers and Facilitators in the Diagnosis of Axial Spondyloarthritis: A Qualitative Study

This chapter presents a qualitative study examining patients and HCP experiences and perspectives regarding barriers to and facilitators of the timely and accurate diagnosis of axSpA. The introduction to the chapter outlines the current state of understanding regarding barriers and facilitators in the diagnosis of axSpA, along with an overview of qualitative research already undertaken in this field. The methods section describes the sampling strategy, data collection, analysis and theoretical underpinnings for the study. The results are structured to identify the themes relating to barriers or facilitators of diagnosis from the patient and professional perspective. Finally, the discussion examines the significance of these results, how they add to and compare with the current body of literature on the subject, and what the results imply regarding future research and clinical practice.

4.1 Introduction

As reported in the previous chapter, the diagnosis of axial spondyloarthritis (axSpA) is typically delayed by between 2 and 5 years globally (Hay et al., 2022) and can result in poorer clinical outcomes and reduced response to treatment (Seo et al., 2015). The time between symptom onset and diagnosis has been the subject of many population-level studies which highlight variation in diagnostic delay between geographic areas, along with results which suggest causes for diagnostic delay, or at least characteristics associated with delay.

To understand the impact of diagnostic delay and the experience of the individual, it is not enough to know what factors and characteristics are, on average, associated with delay. It is necessary to understand the perspective of all those affected, as this not only provides a rich and further contextualised understanding of the situation.

4.2.1 Aims and Objectives

This study aimed to explore the experiences and opinions of patients and HCPs regarding the barriers to and facilitators of timely diagnosis of axSpA.

The objectives are as follows:

1) To explore barriers to diagnosis of axSpA from patient and HCP perspectives.
2) To explore facilitators of diagnosis of axSpA from patient and HCP perspectives.

4.2 Methods

4.2.1 Design overview

Semi-structured interviews were undertaken via telephone and Microsoft Teams. The content of these interviews was then thematically analysed using the process outlined by Braun and Clarke (2006)(Braun and Clarke, 2006). The primary outcome was to further understand the elements of the journey to diagnosis which continues to cause delay and how this can be mitigated.

4.2.2 Theoretical Foundation

4.2.2.1 Phenomenology

The theoretical framework underpinning this work is descriptive phenomenology. Phenomenology is concerned with the nature by which things (objects, events, people

etc) are experientially received by observers; i.e. objective measures such as the size and colour of a thing in themselves are not a useful measure of effect on an individual. Moreso, a person's reported reaction and experience of the thing are the closest one can get to understanding this effect and to apprehend the existence of said thing from personal perspectives. Fundamentally, apprehending, comprehending and reporting this effect and this nature of a thing requires that the phenomenological researcher reports the experience as communicated; a fact in itself (Zahavi, 2019). In this study this relates to the experience of diagnostic delay. Phenomenological research seeks to present the object of a study's enquiry through the lens of individual perspective, rather than seeking a generalised or objective presentation (Sundler et al., 2019).

Phenomenology has its roots in the philosophy of Edmund Husserl in the first half of the 20th century. It was his assertion that the world and objects within it cannot be fully understood as objective entities; our perception and comprehension of the world is unavoidably subjective, and the universe primarily exists to those within it as viewed from a subjective point of view. While not denying objective existence of the world, he stated that objects within the world only become "real" in a human sense when one becomes conscious of them. Events, objects, and circumstances in the world described thus, from an unavoidably intentional (intentional here referring to being the object of observation) perspective, are named "phenomena" by Husserl. Phenomena, due to their existence in this philosophical context being intrinsically linked to human perspective, are therefore to be interpreted keeping in mind the internal life of the observer, such as their biases, motivations and presumptions (Moran, 2000).

It has also been noted that phenomenology, with its underpinning philosophy regarding human reality being illuminated through exploring experience, is particularly useful in understanding under-researched phenomena (Peat et al., 2019), as with patient and HCP experience of diagnostic delay in axSpA.

There are other philosophies and methodologies of qualitative enquiry which would also arguably have been suited to this research question, namely interpretative phenomenological analysis (IPA) and grounded theory. These are briefly described below, with a rationale as to why they were not considered for this study.

4.2.2.1.1 Interpretative Phenomenological Analysis (IPA)

Beyond the aforementioned philosophy of phenomenology, IPA also integrates the concepts of hermeneutics and ideography (Smith et al., 2009). Hermeneutics originally intended to understand the meanings and intentions of the creator of text, whether they be author or interviewee. IPA also employs a methodological concept known as ideography, a focus on detail, and depth of analysis. It is a focus on systematic analysis of experience, whether individually embodied or shared and relational, to reach more precise and well-defined conclusions.

While these concepts inevitably influence any study employing phenomenology in its analysis, their formal inclusion into the process of analysis here goes beyond the research question. This study sought to explore patient and HCP experiences and perspectives regarding barriers to, and facilitators of, diagnosis of axSpA. While it is of interest to consider the reasons patients and HCPs interpret their circumstances in

certain ways, and while the relationship between creation of narrative and its interpretation is integral to the reflexive analysis espoused by phenomenology, it does not add any greater depth to the answers gained through thematic analysis underpinned by phenomenology.

4.2.2.1.2 Grounded Theory

Grounded theory seeks to generate theory, which is then fed back into an iterative and cyclical process of theory-directed sampling, data collection and testing and re-testing of emerging theories (Corbin and Strauss, 2014).

In this study, iteration was built into the process of analysis. Coding was based predominantly on aspects that emerged from the data. However, using the phenomenological paradigm as a foundation for thematic analysis of reported experiences and perspectives avoided the need to generate new explanatory theory. This study is exploratory, not explanatory, and consequently ground theory was not used in this study.

4.2.2.1.3 Application of Theoretical Underpinning to this study

In this study, the testimonies of patients and HCPs were taken and analysed on their own terms, in the context in which they were given. Even in cases where reported barriers and facilitators were clear conjecture, they were treated as entirely valid; the fact that the situation was perceived as such was treated as significant in its own right. Additionally, the participant perspective was treated as intrinsic and inextricable from their perspective. Where their emotional reactions to their circumstances and outlook

were clear, even stated, this was not discounted and again treated as valid. This can be characterised in practice with the ontological/epistemological position of critical realism, which is in this thesis defined as the ontological underpinning of realism mediated by the epistemological position of relativism (Braun and Clarke, 2019). That is to say: the researcher assumes an immutable and concrete nature to events being communicated, but also that it is impossible for the absolute nature of these events to be communicated due to imperfections in language and the fundamental impossibility of being able to receive communication without bias, unintentional misinterpretation or incomplete apprehension/comprehension.

The decision to approach data in this way was due to the nature of the subject matter. Patients and HCPs alike were reporting on episodic events and their reactions to them; critical realism allowed appraisal of recounts and opinion using the same analytical philosophical position.

Similarly, when approaching coding, a the approach taken was broadly semantic. Coding focused on the received meaning of statements rather than on conceptual or abstracted implications (Braun and Clarke, 2019).

In focusing on the patient and HCP perspectives and their recounting of experiences, this study gives access to rich new data regarding the lived experience of the diagnostic journey, barriers to diagnosis and how delay could be improved.

4.2.3 Study Sample

Two groups were included in this study: patients with axSpA and HCPs with experience of diagnosing and managing axSpA. Patients of 18 years and older from across the UK were invited for an interview if they had a current diagnosis of axial spondyloarthritis. For this study, diagnosis was self-reported. HCPs working in the UK who had experience in the management of patients with axSpA were sourced opportunistically through a snowball sampling technique (Parker et al., 2019) beginning with known contacts within Keele University and the Haywood Hospital in the West Midlands.

4.2.4 Recruitment

4.2.4.1 Patients

Patients with a self-reported diagnosis of axSpA were recruited from across the UK to be interviewed for this study. To ensure their inclusion into this study was appropriate, they were sampled to conform to the following criteria.

Box 4.1 Inclusion Criteria

Criteria	Rationale
Had a diagnosis of axial spondyloarthritis since 2009, to minimise recall bias and aid memory recall of the current state of axSpA management.	In 2009 the Assessment of Spondyloarthritis International Society (ASAS) published their classification criteria for axial spondyloarthritis *(Rudwaleit et al., 2009a, 2009b)*.
Had greater than a year's delay to diagnosis	This is to ensure the patients recruited for the study did actually experience what can be described as "delayed" diagnosis as per Act on Axial Spa - www.actonaxialspa.com.
Be 18 years or older	Before adulthood, formal diagnosis of axSpA is problematic; it could for instance more readily characterised as enthesitis related juvenile idiopathic arthritis (JIA), which while sometimes following a contiguous disease course with later-diagnosed axSpA, is not a guaranteed pro-drome.

Box 4.2 Exclusion Criteria

Criteria	Rationale
If the patient possessed cognitive impairments which would preclude the level of conversational involvement required by this study	• Informed consent from the patient for inclusion into the study would be undermined • Greater possibility the testimony given by patients would be incomplete or

	impossible to interpret/easier to misinterpret • Their experience with their cognitive impairments could complicate or overshadow their experiences with axSpA diagnosis
If the patient did not possess a level of comprehension and use of the English language	• Patient might not be able to sufficiently understand the participant information sheet and consent forms • Lack of understanding of interview questions could lead to unhelpful or inappropriate responses • Answers might be difficult to interpret or impossible to understand

4.2.4.2 HCPs

HCPs from across the UK were recruited primarily from the West Midlands to be interviewed for this study. To ensure eligibility, they were sampled to conform to the criteria listed below.

Box 4.3 Inclusion Criteria

Criteria	Rationale
Currently or have previously in their career been involved in the diagnosis, management or treatment of axSpA in the NHS	To be able to discuss barriers to and facilitators of diagnosis of axSpA

Box 4.4 Exclusion Criteria

Criteria	Rationale
Were unavailable within the study period	The study was constrained to a timeframe dictated by the course of the PhD

4.2.4.3 Sampling

The intended sample size was 15-20 patients with axSpA and 15-20 HCPs who had experience of patients with axSpA. This sample size was based on the following criteria:

1) Studies have historically suggested that sample sizes between 5 and 25 being sufficient for phenomenological studies to achieve data saturation *(Morse, 1995)*. A recent more empirical approach found that a sample size of 12 is sufficient to reach a high degree of data saturation in qualitative studies *(Guest et al., 2020)*.
2) The sample size chosen was deemed a manageable size to handle to a good degree of depth considering the limited timescale of a PhD. Any fewer risked paucity of data and a lack of data saturation, anything greater risked diminishing returns regarding depth of analysis. Large quantities of data can lead to heavily triangulated but nonetheless superficial analysis of themes.

Male/female parity was sought across the sample. Many historical studies have under-represented female patients, which is problematic as women and men experience the disease and its diagnostic journey differently (Rusman et al., 2018).

Patient sampling for this study was purposive. Qualitative studies are by nature frequently based on small sample-sizes as in depth exploration of the experiences of individuals is sought. This contrasts with methods of sampling used in quantitative research, such as randomisation, which are intended to ensure a study's resultant data are generalisable to wider populations with minimum bias (Palinkas et al., 2015).

Purposive sampling allows for the identification of potential participants who are able to share their experiences of the phenomenon being explored. The purposive characteristics that informed the sampling strategy are detailed in table 4.1 below. When patients contacted the research team, they were asked basic questions about the length of their diagnostic delay and the approximate date of their diagnosis or duration of their disease, which was expressed either as a year or as a period of time having elapsed since.

Table 4.1 Purposive characteristics for patient participants

Criteria	**Rationale**
A range of disease durations among participants	Represents different manifestations and disease courses in patients with axSpA.
Representation of both male and female patients	Female and male patients often experience axSpA differently *(Rusman et al., 2018)* it is important to represent this in the current study.

The sampling strategy for HCPs was also purposive, as the inclusion criteria sought HCPs with clinical experience of patients with axSpA. However, due to the limited

availability at Keele University of HCPs who met the inclusion criteria, a "snowball" sampling method was also used. Snowball sampling has been recorded in use since at least the 1960s (Becker, 1963) and is used as means of recruiting through existing networks related to the area of study (Parker et al., 2019). In practice for the present study, this involved contacting HCPs working at the Haywood Hospital via email who were reported to have clinical experience with patients with axSpA by the initial contacts at Keele University stated above. Upon their responding to our communications, potential participants were then asked if they knew of further HCPs who would be suitable. Additional to the requirement that clinicians have experience of axSpA, HCPs were also purposively sampled to provide a range of different professional disciplines. This ensured distinct clinical perspectives were included, increasing the scope of analysis, including the comprehensiveness of available data, which increases the level of detail and depth of said data (Morse, 1995).

Emails were sent to prospective participants, stating who had recommended them for inclusion and asking whether they would be interested in involvement in the study.

Table 4.2 Purposive characteristics of HCP participants

Criteria	**Rationale**
Health professionals who had clinical experience of patients with axSpA (GP, rheumatologist, physiotherapist, nurse)	This was intended to ensure a wider range of experiences and perspectives among the HCP sample. Additionally, recruiting HCPs from different health related professions allowed access to experiences from different points on the

	patients' diagnostic journey and showed different priorities regarding management of and interaction with patients.

4.2.4.4 Sample Identification

4.2.4.4.1 Recruitment of Patients

Patients were recruited for this study through one of three different avenues including clinic lists from the Haywood hospital, the social media platform Twitter and the patient charity, the National Axial Spondyloarthritis Society.

1) Patients were recruited from the Haywood hospital in Stoke-on-Trent in Staffordshire which has a specialist rheumatology department. The patients' computerised clinical record was searched by a Midlands Partnership NHS Foundation Trust (MPFT) research nurse, to identify axSpA patients who meet the inclusion criteria. Once identified, the nurse emailed an invitation letter to potential patients. Following a patient contacting the study team with an expression of interest in the study, a study information pack (containing a patient information sheet (PIS), a consent form and self addressed envelope) was posted to them. Within two weeks, the patient was then contacted by the study co-ordinator to confirm their eligibility for the study (see section 4.2.3 for full inclusion and exclusion criteria) and where eligible, an interview was arranged.
2) Patient recruitment via the National Axial Spondyloarthritis Society (NASS). NASS is a UK-based charity which provides advice, support and information to patients with axSpA (https://www.nass.co.uk). It operates at national and regional levels

and encourages online communication and advocacy among, and for patients with axSpA. Patients recruited through NASS were initially informed of the study in either of two ways:

a. Details of the study were included in the NASS monthly email, which is sent to the full United Kingdom membership list. Details included a brief description of the study and the contact details for the study team. NASS members diagnosed with axSpA registered their interest by contacting the study co-ordinator directly, at which point, if they were eligible for inclusion, they were mailed/emailed a formal invitation, consent form and a PIS. NASS members were also informed via email of recruitment messages broadcast on Twitter (detailed in point 3) and these messages were re-tweeted to reach a wider audience.

b. The NASS groups local to Keele University, in Crewe and Stoke-on-Trent, also contacted their membership through their social media presence on Facebook and/or Twitter, again providing the contact details for the study co-ordinator. As above, potential participants, if eligible, were provided with full study documentation.

3) The intent and required participant characteristics of the study were broadcast on Twitter; these tweets were then often “re-tweeted” (a form of referenced republication which directs conversation back toward the author of the original “tweet”) by Keele University, NASS and professional colleagues also using the platform; this ensured the original “tweets” reached a wider audience. Potential participants were asked to “direct message” CAH rather than directly

reply to the broadcasted tweet; this ensured they did not publicly announce their intention to join the study which would undermine their confidentiality. Patients who registered interest via social media were sent study invitations, a patient/participant information sheet (PIS) and consent forms via email after a process of assessment of their eligibility for the study involving a brief email exchange or exchange on Twitter's direct message function.

4.2.4.4.2 Recruitment of HCPs

HCPs were recruited from several sources, including Keele University (both from within the School of Medicine and the wider University), the Haywood Hospital and GP practices / rheumatology services within the West Midlands area. HCPs were contacted through their existing links with the study team or publicly available email or telephone numbers. After contacting HCPs, the study co-ordinator ascertained whether the inclusion criteria were met see (section 4.3.2.2). When further HCP participants were still required after this first recruitment wave, then recruited HCP participants were asked for recommendations of other HCPs who may will be willing to take part in the study. This process continued until sufficient HCP participants have been contacted.

4.2.5 Patient and Public Involvement and Engagement

Patient and Public Involvement and Engagement was sourced by the Research User Group (RUG) from the Keele School of Medicine. A group of patients with a diagnosis of axSpA were invited from the local National Axial Spondyloarthritis patients' group to

assist in the development of the interview topic guides, along with other patient facing documentation, such as information leaflets and consent forms.

Due to the Covid19 pandemic and subsequent lockdowns, only one PPIE group took place on the 22nd January 2020. This meeting lasted 3 hours, and was attended by myself, Dr James Prior, Keele University Medical School's PPIE Project Coordinator, and six PPIE members. The study was described to the patients, who were then asked if they had any questions or concerns from the outset. After a round of conversation regarding the study itself, the patients were handed print outs of the topic guide and patient information sheets. A round-table discussion was held where elements of the documents and concerns were brought up on a part-by-part basis, i.e., the documents were not discussed as a whole, but split up into sections to make conversation more straightforward.

This resulted in alterations including making the language more suitable for its intended audience. The importance of defining "axSpA" and "axial spondyloarthritis" was raised as a universal concern, as many still refer to the condition as ankylosing spondylitis or AS. It was advised that the topic guide should request patients to describe the type and order of symptom presentation. Importantly, the group advised that more was added to the introductory section of the interview, noting that it was necessary to help people feel relaxed with the conversation. Questions about their general wellbeing were advised. It was also felt appropriate that questions regarding the potential impact on mental health associated with diagnostic delay was a useful avenue of enquiry.

The HCP topic guide underwent some re-structuring due to suggestions of the PPIE group. At the outset, the questions regarding which symptoms the HCP associates with axSpA and how frequently they encounter axSpA were swapped around. It was advised that HCPs be asked whether they would consider axSpA initially as a possible diagnosis given a set of suggestive symptoms. It was also suggested that the HCPs be asked what they thought would help them specifically make an earlier diagnosis, and what aspects of the diagnostic process patients most frequently wanted to talk about.

4.2.6 Ethics

Prior to the study beginning, NHS Health Research Authority (HRA) approval was sought, due to the inclusion of patients in the study. NHS HRA ethical approval requires the provision of a participant information sheet (PIS) (Appendices 4.3, 4.4), participant consent forms (Appendices 4.5, 4.6), a provisional topic guide (Appendices 4.7, 4.8), a letter from the study sponsor and from the study funder, a schedule of events, and CVs for both student and supervisor.

4.2.7 Data Collection and Management

4.2.7.1 Interviews

This study utilised semi-structured interviews as its method of data collection, which can be defined as interviews which do not require rigid structure (Ritchie et al., 2013). Semi-structured interviews help keep the conversation relevant and ensures that many topics can be explored; additionally, they use open-ended questions which do not constrain the interviewee; but define an area to be explored and within

reasonable bounds allow the participant free rein over how they answer. Either interviewee or interviewer can diverge to explore ideas in greater detail (Pope and Mays, 2006). Semi-structured interviews are the most commonly used form of interviews in qualitative health services research (DeJonckheere and Vaughn, 2019), due in large part to the versatility and exploratory scope which enables the conversation with the interviewee to follow organic off-shoots of the "set" questions. This leads to a greater depth and detail in data emerging from the interview. The interviews were undertaken by the author, who is male.

4.2.7.2 Patient Interviews

Semi-structured interviews were undertaken over the telephone with patients diagnosed with axSpA. The duration of the interviews lasted between 45 and 60 minutes and were structured using a topic guide (appendix 4.7) which was designed with the input of a Patient and Public Involvement and Engagement (PPIE) group comprised of six patients with axSpA (see section 4.2.5).

Patients were asked about their experiences and opinions of the diagnostic journey for axSpA, including factors which they felt impeded or facilitated their diagnosis. To ensure patient participants felt comfortable in the interview, patients were engaged conversationally, and limited tangential discourse was pursued. When discourse did become disconnected from the main themes under study, conversation was explicitly guided back towards the research question. Further detail can be found below in the Field Notes section.

4.2.7.3 Healthcare Professional interviews

HCPs participated in semi-structured telephone and MS Teams interviews informed by a topic guide (appendix 4.8), which were designed to take an hour. HCPs were asked about their opinions regarding barriers to axSpA diagnosis and their experiences of the process of referral and diagnosis.

4.2.7.4 Topic Guides

Interviews were based on two topic guides, each designed specifically for its intended sample, either patient or HCP. Topic guides are a schedule of questions and subjects which are intended to be raised during interview to ensure sufficient data is generated to usefully answer the research question of a study (Ritchie et al., 2013). Two considerations while designing a topic guide are the importance of avoiding repetition in interviews and the importance of avoiding "scope-creep". The former becomes an issue when it negatively impacts the flow of an interview, which can in turn result in an inadequate ability for exploration of subjects in an interview, lessening the quality and quantity of data. The latter, scope-creep, refers to the temptation to include too many subjects in a topic guide, to try to explore too much in the allotted time, resulting again in too little detail and scope for exploration (Ritchie et al 2013). Where this becomes apparent during topic guide design, it is often necessary to return to the research question to refine the guide and ensure what is being approached in interviews is relevant. Also, they can be used as later contextual reference for readers of a study and other interested parties who were not members of the research team (Ritchie et al 2013).

The content and structure of the topic guides for this study was designed taking the following factors into account, as per Ritchie et al (2013),

1) **Contextual information**: at this stage, information for later use in the interview is collected. In the case of this study, this was regarding levels of knowledge of the disease, lengths of diagnostic delay and, in the case of HCPs, it involved the organisation they worked in and position within it.
2) **Opening topics:** This area continued organically from the above, involving further questions which introduced the interviewees to the topics of the interview. With patients it was further conversation regarding their diagnostic journey and with HCPs, the level of interaction the interviewee typically had with the disease. This stage is designed to provide insight into motivators and attitudes of the interviewee.
3) **Clarifying meanings and definitions from outset:** It was made clear that the terms “axial spondyloarthritis”, “axSpA” were umbrella terms encompassing ankylosing spondylitis, AS, and any other terms patients and HCPs might habitually use.
4) **Ensuring sufficient space and time for the main substantive research questions:** The majority of the topic guide was devoted to discussion of the diagnostic process for axSpA, what impedes it and what aspects lead to prompt diagnosis.
5) **Winding down and finishing on a positive note:** In addition to thanking participants for their time, all were informed of future intentions for the research and asked if they would like to be informed upon publication and dissemination.

6) **Summarising and checking key issues:** ensuring that the participant doesn't have anything further they would like to add and also that they are still comfortable with the way the interview was run.

The topic guides were designed in collaboration with the research team and input of a PPIE group. The HCP topic guide was piloted in one practice interview, resulting in minimal changes in the structure. Due to the changes required to recruitment and data collection due to the COVID19 pandemic, it was not clear how many patient participants would be available for the study. Additionally, the patient topic guide was reviewed and altered as a result of PPIE involvement. Initially, it was not obvious how large a response from the patient community would be expected from the patient community, so the topic guide was not formally piloted; instead, in keeping with the planned iterative approach to the topic guide, the first interview was treated as a provisional pilot interview. If it resulted that substantial revisions were required to the topic guide, this interview would not have been included in the study for analysis. This was not the case, however, and that interview was included in this study. Through an iterative process of drafting and acting on suggested edits and comments from the research team, the first version of the topic guides for patient and HCP participants were constructed. The full topic guides can be found in (appendices 4.7, 4.8).

4.2.7.5 Consent

4.2.7.5.1 Patients

Once a patient was deemed eligible for inclusion (see section 4.2.3.1 for criteria) a patient information sheet (PIS) and consent form were emailed to the patient participants.

The PIS (appendix 4.3) detailed the aims and objectives of the study, what would be required of patients and the data they would provide during the study. It also explained their rights per General Data Protection Regulation (GDPR) 2018 ("Data protection," accessed 2022) and any future use of their data. Potential participants who wanted to take part in the study signed and emailed the consent form back to the researcher. Upon receipt of this, the interview was scheduled with the patient via email.

4.2.7.5.2 Health Care Professionals

A similar process took place to obtain written consent from HCPs prior to their interviews, which again involved the participant information sheet and consent forms being emailed to the participant if they met the inclusion criteria (see section 4.2.3.2).

Prior to the commencement of the telephone interview, the interviewer asked the participant to reiterate that they had understood the consent form and still agreed to consent to all the points on the form. In the circumstance where a participant had answered at that stage in the negative, the interview would have been terminated; this eventuality did not occur in any case.

4.2.8 Analysis

The audio recording files were transferred for transcription to 'The Transcription Company' via their proprietary secure online portal. Receipt of files was then sent to CAH via email.

Data analysis took place using a home computer using a VPN link to the university. Electronic data was to be stored and analysed on a password protected university computer and any paper documentation and data will be stored in a locked filing room also on the grounds of Keele University. The study files were stored on and accessed from Keele University's secure servers remotely. No data were moved using USB drives and no sensitive or identifying information was transferred over the internet, aside from the aforementioned audio recordings which were only sent via The Transcription Company's secure online portal.

Data were thematically analysed by CAH. For the purposes of validation, Professor Sarah Ryan (SR) coded six interview transcripts (3 patient, 3 HCP). Beyond validation, this second instance of coding offered CAH the ability to recognise to an extent a wider perspective on the data, so as to further avoid biases as per phenomenological methodology. Thematic analysis was used as an exploratory construct by which patient and HCP reports of their experiences and perceptions of the diagnostic journey were understood.

Personal data was stored for one year after the study has ended. Research data will be retained for ten years after the study has ended, in accordance with Keele University policy. The data custodian is Dr James Prior.

4.2.8.1 Computer-Assisted Analysis in NVivo 12

The thematic analysis was undertaken primarily using NVivo 12, which is a form of software known as Computer-Assisted Qualitative Data Analysis Software (CAQDAS). NVivo is developed by QSR International, (https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/about/nvivo). It is designed to facilitate analysis of semi-structured or unstructured qualitative data, but its utility is not restricted to this. It allows for import of the texts which comprise a study's data (in the case of this study, pseudo-anonymised interview transcripts), and the creation of codes; within NVivo these are referred to as nodes. These "nodes" can be nested to separate themes, and into directories, which is used as a means to denote categories. Within NVivo 12, thematic analysis was structured as follows:

- **Category (e.g. Barriers to Diagnosis)**
    - **Theme, or category (eg. "axSpA Difficult to Diagnose")**
        - **Code, or sub-theme (eg. "Difficult to Define or Differentiate")**

4.2.8.2 Phenomenological Thematic Analysis

Thematic analysis was employed as the main method of analysing the study data, based upon a phenomenological framework. The process of thematic analysis used in this study, was based on the steps described by Braun and Clarke (2006) as follows:

1) **Familiarisation with data: transcription of interviews, repeated reading and noting of initial codes**

   Familiarisation began prior to the transcription process, during the interviews. This did not extend to formal coding but involved exploratory thoughts and

hypotheses regarding the content of the interview. Turns of phrase were noted. Further salient details were also noted for context.

Six interviews (3 patients, 3 HCPs) were transcribed by myself, which provided another layer of familiarisation. Interviews were read over several times before what could be considered early, non-formalised coding was undertaken using highlighter and annotations on paper printouts and pdfs interacted with on an iPad.

2) **Generation of initial codes: coding interesting and relevant features from the interviews**

The transcripts were imported into NVivo 12 and coding began using this software. Coding at this stage was exhaustive and not only limited to direct discussion of barriers to and facilitators of axSpA diagnosis. All information regarded as salient was coded, along with more ancillary information regarding lived experiences; this was due to the suspicion that on further exploration, the more outlying information would at the very least provide further context for the "main" narrative, i.e., that regarding barriers and facilitators in diagnosis.

3) **Identifying themes: examining the coded data to identify specific patterns of meaning**

At this stage, within NVivo, the codes identified in the previous stage were collated into hierarchies, based on how closely related they were.

4) **Review of themes: checking that the themes represent the data and address the research question, along with the generation of a thematic map**

The identified themes were then reviewed in two phases. The first phase involved reviewing the codes collated into themes to see whether the codes

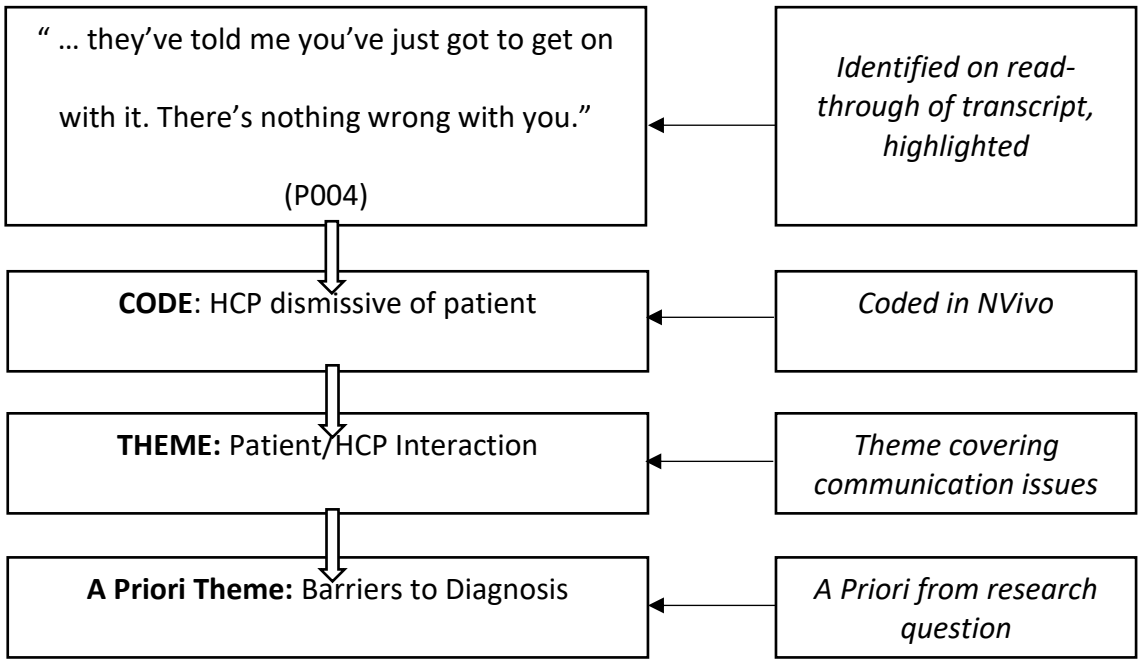
contained within themes belonged there and reached a level of coherence with each other sufficient to be considered genuinely relevant to each other. If this was not the case, codes were removed from the theme and placed elsewhere. In the second phase themes were reviewed to ensure they contributed to answering the research question and whether they could justify their existence as discrete themes. Some themes were amalgamated into each other, as they overlapped to such an extent that their boundaries were arbitrary. Some themes were split into two, and some were renamed to better represent their constituent codes and to relate more closely to the research questions.

5) **Defining and naming themes: refining the specifics of each theme. Clear names for themes were derived**

   This stage involved formalising the themes, ensuring they contributed to answering the research question and the names of themes were self-explanatory and descriptive of constituent codes.

6) **Writing up: final analysis of data, discussion of analysis and full writing up of study**

Figure 4.1 The process of coding and creating themes



4.2.8.3 Data Management

Transcription was undertaken by myself (six interviews, three patient and three HCP) and The Transcription Company. The interviews were pseudo-anonymised during the transcription process, with names being replaced with unique identifiers. The unique identifier consists of three components: 1) participant type – patient (p), HCP (h); 2) a number assigned sequentially (01,02,03…12); 3) the session that was participated in – interview (i).

The link between participant name and their unique identifier was recorded in 2 locations: 1) on their consent form (stored securely: digital copies kept on Keele servers, accessed through a secure VPN software (Cisco AnyConnect), paper copies scanned, the file sent to Keele servers, original destroyed), 2) on an excel sheet on an encrypted, password protected University computer. Only the core research team had access to this information. Access to participants' personal data was restricted to the research team.

All data related to this study was kept on-site at Keele University on secure servers. As the COVID19 pandemic precluded the research team from accessing the university campus, these data were accessed using secure virtual private network (VPN) software, for which licensing and guidance was provided by Keele University.

4.2.8.4 Field Notes

Throughout the course of data collection and analysis, field notes were kept, mostly in hand-written form. Particularly during interviews, taking hand-written notes interrupts conversation far less than typing notes, and is entirely silent on audio recordings.

The field notes taken during and after interviews performed several purposes. Salient contents of the interview were noted to ensure the interviewer was able to recall important details throughout the conversation and to help contextualise transcripts at the analysis stage. Much of these notes taken focussed on details of the participant's story, such as the length of delay, previous diagnoses and history of consultations, taken for use in conversation.

In interviews with HCPs, these notes informed the tone and content of questioning at certain stages of the interview, as they would include the stage in the patients' diagnostic journey at which the participant would encounter a patient. Questions regarding actually making the diagnosis were, for instance, most relevant to rheumatologists, whereas GPs, occupational therapists and physiotherapists would be more likely to share opinions regarding appropriateness of referrals.

Another application of these brief field notes during interviews was this: if the participant mentioned something while in full conversational flow which was deemed of sufficient interest or importance that further detail was required, instead of interrupting the participant and risking losing detail and conversational comfort, these details were brought up for further exploration when the participant had concluded what they were saying.

Notes were made immediately after interviews to describe the nature and content of the conversation. These notes detailed the mood of the participant, the atmosphere of the conversation, personal inferences from what was said by participants and aspects of the interview which I felt at that point either gone well or had aspects that could have been improved upon.

4.2.8.5 Data Saturation/Information Power

In quantitative research, there are means of calculating a requisite sample size to produce results of useful statistical power, i.e. results that are reflective of real effects (or lack thereof), and not due to random variation within a sample. The same is not true of qualitative research. As qualitative research does not output specific comparable values, the concept of statistical power becomes moot, and it is therefore less obvious how to calculate sample sizes and how to assess their effect on the quality of research. There has been lengthy academic discussion on this subject, leading to the concepts of "data saturation" and, more recently, "information power". Information power has been proposed as a concept to supersede and replace data saturation.

The definitions of data saturation vary but consensus defines data saturation as the point at which the themes arising from analysis are sufficiently understood and would not be benefited by the addition of further data (Fusch and Ness, 2015; Morse, 2015).

The concept of data saturation has implications for many aspects of research design, as was explored by Saunders et al (2018), who in reviewing literature on the subject, arrived at the following breakdown of major concepts of saturation (Saunders et al., 2018):

Box 4.2 Major concepts of data saturation

#	Model	Description	Principal focus
1	Theoretical saturation	Relates to the development of theoretical categories; related to grounded theory methodology	Sampling
2	Inductive (ground up, supported by data from present	Relates to the emergence of new codes of themes	Analysis

	study) thematic saturation		
3	*A priori* (top down, based on existing theory and study) thematic saturation	Relates to the degree to which identified codes or themes are exemplified in the data	Sampling
4	Data saturation	Relates to the degree to which new data repeat what was expressed in previous data	Data collection

However, the concept of data saturation has in recent years been re-appraised and an additional concept has been proposed: the concept of "information power" (Malterud et al., 2016). As Braun & Clarke state, "there is no simple way to take all data related elements – such as data depth, richness, complexity – and determine the *right* size of dataset for a particular project" (Braun and Clarke, 2019). Exploratory research does not aim for total description of the entirety of studied phenomena; qualitative research cannot aim for a "total" amount of facts regarding a subject (Malterud et al., 2016). Based on these considerations, the concept of information power is proposed, which considers the effect of five different aspects on necessary sample size for recruitment:

1) Study aim – narrow or broad?

   A broad study aim requires a larger sample than a narrow aim to offer sufficient information power.

2) Sample specificity – dense or sparse?

   Information power is related to the specificity of experiences, knowledge, or properties among the participants included in the sample.

3) Established theory – applied or not?

   The more theoretical grounding research has, the more information power it will have, requiring less support from a larger sample size.

4) Quality of dialogue – strong or weak?

   Higher quality dialogue in interview leads to greater information power.

5) Analysis strategy – case or cross-case?

   Studies comparing data between participants require a larger sample size.

(Malterud et al., 2016)

The present study has a specific and defined study aim, a specific sample (patients with axSpA, HCPs with experience and/or clinical interest in axSpA), it is not grounded in specific developed behavioural or sociological theory aside from the phenomenological paradigm, the quality of dialogue based on PPIE and peer-reviewed topic guides is high, and the data analysis is cross-case. While the concept of information power does not attempt to indicate specific numbers for sampling, it does give some suggestion. Based on the above characteristics of the present study, and comparing with recent studies with similar aims but undertaken by more experienced research teams which interviewed ten patients (Martindale and Goodacre, 2014) and ten GPs (van Onna et al., 2014), the aimed-for sample sizes of this current study are appropriate in aiming for credible information power.

4.3 Results

Participant characteristics will be described initially, followed by the results of the interviews, arranged as follows.

Two main *a priori* High Level Themes structure the main results:

1) Barriers to Diagnosis: these are characteristics, circumstances and events which patients and HCPs felt were detrimental to the process of diagnosis.
2) Facilitators of Diagnosis: these are characteristics, circumstances and events which were felt to assist, speed up and initiate a definite process toward diagnosis. The discussion of facilitators was not limited to experiences of patients and HCPs; it also encompassed other diseases and areas of healthcare, and opinion.

Results from the analysis of patient and HCP interviews are presented separately.

4.3.1 Patient Characteristics

Of the 14 patient participants, ten were female and four were male. In all participants, axSpA status was self-reported. Median age was 43yrs and median age of onset of first symptoms was 20yrs. Median age of diagnosis was 39.5yrs. The length of delay to diagnosis ranged from one year to greater than 20 years, with a median delay of 15.5 years reported. 6 out of the 8 patients with known HLA-B27 results reported testing positive for HLA-B27 and 12 patients were diagnosed by a rheumatologist. Family history of axSpA was reported in 4 patients. Patient participants were distributed throughout the UK.

Table 4.3 Individual Patient Characteristics[1]

ID	Gender	Year of Diagnosis	Age at Interview	Age at Symptom onset[2]	Age at Diagnosis	Diagnostic Delay
P002	F	2016	54	25	50	25
P003	M	2017	42	27	39	12
P004	M	2011	43	20	34	14
P010	F	2011	40	15	32	17
P015	F	2017	43	20	40	20
P018	F	2019	51	30	50	10
P021	F	2018	29	20	27	7
P024	F	2020	-	-	-	13
P025	F	2013	47	12	40	20
P030	F	2019	54	30	53	21
P032	F	2010	30	11	20	9
P033	F	-	-	-	-	20
P035	M	2016	24	19	20	1
P035	M	2006	59	25	45	20

[1] Patient characteristics reported here are based on information voluntarily provided by patients. Where it was not voluntarily supplied, it was not sought. [2] Initial symptoms are patient reported and based on patient interpretations of their disease history.

4.3.1.1 Initial Symptoms and Provisional Diagnoses

The commonest initial symptom reported by patients was lower back pain (n=9), followed by neck pain (n=3), leg pain (n=2), hip pain (n=2), sciatica (n=2), foot pain (n=2), headaches (n=1), a swollen ankle (n=1) and peripheral joint pain (n=1). The most common provisional diagnosis prior to the diagnosis of axSpA were fibromyalgia (n=3) and Achilles tendonitis (n=3). Two of the four patients who reported symptom onset occurring when they were teenagers had their symptoms explained by HCPs as growing pains, and this explanation was reported by a third patient who suspected their symptoms originated in their teens but whose symptoms became more bothersome in their 30s and onwards. Sciatica, scoliosis, psoriasis, psoriatic arthritis, plantar fasciitis, and osteoarthritis diagnoses were all reported by two patients each. In one case, a patient had a prior diagnosis of AS, which was subsequently disregarded, before the patient was re-diagnosed with axSpA at a later date.

4.3.1.2 Management

Pharmacological management prior to a diagnosis of axSpA included analgesia (n=7), non-steroidal anti-inflammatory drugs (n=5), steroid injections (n=5) and DMARDs (n=2). Non-pharmacological treatment included physiotherapy (n=4) and alternative therapy/homeopathy (n=4). Lifestyle adjustment was reported by three patients, which included: home modifications, exercise regimens and dietary control, some introduced by the patient themselves and some advocated by their HCPs. Massage therapy, input from chiropractors, and recreational substances (alcohol and marijuana) were used by two patients each.

4.3.2 Healthcare Professional Characteristics

The 14 HCP participants comprised physiotherapists (n=5), GPs (n=4), rheumatologists (n=3), a nurse and an occupational therapist. All HCPs were based in the West Midlands or the North West region of the UK. The frequency with which HCPs interacted with patients then knew or suspected to have axSpA ranged widely between six or seven per week to two or three per year.

Table 4.4 Frequency of Contact with Patients with Suspected axSpA

ID	Gender	Specialism	Frequency of seeing patient with suspected axSpA
H071	F	Musculoskeletal extended scope physiotherapist	"… you're probably looking at one every couple of months. So a handful a year…"
H072	M	Rheumatologist	Wasn't able to specify
H074	M	Rheumatologist	Wasn't able to specify
H075	M	Rheumatologist	"I would probably say six or seven [per week]… incidence is a bit less… ten [new patients] in six months…"
H076	M	Physiotherapist	"… I definitely say monthly… I would usually have some AS patients on my caseload…"
H077	M	GP	"… in the past 12 months… maybe 2 or 3 who've been formally diagnosed with axSpA…"
H078	M	GP	"Very infrequently… I would suspect it no more than a couple of times a year…"
H079	M	GP	"I'm sure there should be somebody at least once a month or a couple of times a month…"
H080	F	Physiotherapist	"… probably there's going to be about 2 or 3 a month…"
H082	F	Spinal service physiotherapist	"… about 5% [of patients presenting with back pain]."
H083	F	Spinal service physiotherapist	"… up to a dozen a year…"

H085	F	Specialist nurse	"… it's probably about 40% of our biologic patients…"
H089	F	GP	"… I could probably think of three times in the past couple of years or so…"
H091	F	Occupational therapist	"… it's hard to come up with a sensible number really."

4.3.3 Barriers to Diagnosis: Patient Perspective

4.3.3.1 Overview of themes relating to barriers to diagnosis of people with axSpA

Five major themes emerged from people living with axSpA regarding barriers to diagnosis:

4.3.3.2 Patient/HCP Interaction

Interactions between patients and their healthcare providers were described as the main barrier to diagnosis. The sub-themes identified in this area can be characterised as communication issues originating from the patient or from the HCP but reported by the patient.

4.3.3.2.1 Sub-theme - Patient Communication

Patients felt that if they had been more assertive in their consultation, they would have been reviewed and possibly referred quicker. This perceived lack of assertiveness often led to feelings of self-directed anger:

> "I'm angry at myself for not having made more of a fuss…" "I'm kicking myself at the moment because the AS has got worse over the last couple of years and I'm thinking, 'Why didn't I say something six months ago or a year ago?'" (P010)

> "… so I've got this pain that I've had for a few years in the lower back in the lower back and now I've hurt my upper back as well… so for three years before then I already knew I'd had it… I've never complained profusely enough to the GP to get it looked at if you know what I mean." (P033)

> "I've since felt annoyed, partly at myself for not pushing further earlier… This is going back over a decade of saying, 'it hurts'." (P024)

4.3.3.2.2 Sub-theme - HCP Communication

Participants living with axSpA experienced disinterest in their symptoms from HCPs, which often resulted in being dismissed from the consultation:

> "… I was referred to a physio. I walked into the room, she took one look at me and said, 'you've got bad posture. Leave.' That was the extent of it. She didn't examine me or anything." (P010)

"… it's awful and I felt as if every time I was going, people were just ignoring me…" "I've never experienced pain like that and they were like, 'no, just go home and see how you are. If it's any worse, come back.'" (P018).

"… I was being completely dismissed and made to feel like I was overreacting… I just felt disbelief… like you're banging your head against a brick wall." (P021)

In other cases, patients reported that, while HCPs acknowledged their pain, they did not seem to take it seriously:

"Everyone just went on face value, 'you've got a sore back. Well, that's a shame'…" (P025)

"I think it honks like a duck, talks like a duck, it probably is a duck, don't discount it. And I think GPs do." (P002)

Many people living with axSpa felt that the only treatment they were offered was medication without any explanation as to what was causing the symptoms

"Nobody was believing the fact that I was in pain or something. I just couldn't figure out why nobody was saying, 'right, what's going on with this girl's body? Why is she in so much pain?', rather than just fobbing me off with ibuprofen." (P025)

"And it was y'know paracetamol and when paracetamol didn't work, it was ibuprofen. And it was ibuprofen for everything… it was like, 'oh it's you again, have some ibuprofen!'" (P032)

"Just back to my GP and you know he just kept throwing pills at it…" (P015)

The attitude people living with axSpA encountered from health professionals was interpreted as belittling, undermining or distrusting, which negatively affected their attitude towards healthcare:

"It was very much a, 'go away. What more do you want us to do?...'" (P004)

"… we think you're just trying to get drugs out of us… it's all in your head, you're just imagining it now, you obviously like being ill…" (P015)

4.3.3.3 axSpA is Difficult to Diagnose

People living with axSpA identified missed opportunities for diagnosis, including the unpredictable nature of their symptoms or having pre-existing conditions.

4.3.3.3.1 Sub-theme - Not Presenting in the Classical Way/Unclear and Inconsistent Symptoms

"Something that… was also a massive delay, was how my arthritis presented itself in that it was just a limp… so I can understand why people wouldn't initially jump to arthritis…" (P035)

"I suppose that it didn't help that I didn't probably present in the classic way with I've gone in with a bad back that's lasted three months… it's with it starting higher up… because my joints are kind of more affected in the beginning. With my knee first up… I think that was probably all against me when it came to diagnosis." (P002)

"It would come and it would go. You know pain would return and I would think, 'oh that's weird, I don't think I did anything to make that pain come back', and then it would disappear again." (P032)

"They'd say, 'oh that's good movement. You've obviously not got AS.' I think. Having the hypermobility masked it…" (P021)

4.3.3.3.2 Sub-theme - Alternative Explanations for Symptoms

Both people living with axSpA and HCPs provided alternative explanations for their symptoms. People living with axSpA often related their symptoms to their lifestyle or occupation:

"I was very, very sporty and so I did have various aches and pains, but I always put it down to playing rugby or whatever… I was a bit obsessive, so I figured I'd damaged myself." (P010)

"I was always on my feet, 14, 16 hour shifts… and doing that with always sort of back pain and neck pain and just thought, ' oh it's just the job I'm doing…' I kept getting these blinding headaches and a couple of times I would pass out and I thought, 'oh it's just all the extra hours…'" (P018)

"… I just put it down to my lifestyle of not really ever stopping… put back pain down to just getting older and lifestyle being a bit chaotic…" (P033)

People living with axSpA were often informed by HCPs that their symptoms could be attributed to 'growing pains', pregnancy or menopause:

"… I'd be crying myself to sleep, they were that painful… but I'd been to the doctor so many times about it and it was literally just, 'it's growing pains, take paracetamol…'" (P025)

"I was screaming in pain with pains in my legs – and I was told I had growing pains…" (P030)

"… when I was about 25, it was the first bout of really bad back pain I had when I was pregnant and… of course it was blamed on the pregnancy… basically that was it. 'You're pregnant, it's sciatica, baby's laying…'"

"… it was like, 'oh you're menopausal. It's the menopause'…" (P018)

Some people living with axSpA had back pain attributed to leisure activities or trauma by HCPs:

> "I did do a lot of gymnastics… and every time they were just saying it was my gymnastics and told me to give up my gymnastics because it was hurting my spine." (P025)

> "GP told me that I'd sprained my ankle, even though I hadn't… They said, 'you must have done it without realising it.'" (P021)

A number of people living with axSpA were told that their pain was influenced by their mental state and somatisation:

> "… you know I remember him saying to me one day, 'are you sure this isn't all in your head?' …" (P033)

> "… so I was just getting told it was in my head for about 12 years…" (P015)

> "But there were several times where it was kind of suggested to me that it might be in my head or that it might be because I was anxious…" (P032)

People living with axSpA felt their symptoms were often attributed to other conditions including fibromyalgia, sciatica and rheumatoid arthritis:

"I think everywhere I went, every GP or doctor or whatever I went to see, it was fibromyalgia and then it was the physio that was saying sciatica in my legs." (P018)

"… you've got fibro, off you pop, just deal with it sort of thing, and I was like, no, I've not got fibro and I'm not popping more pills I don't need…" (P015)

"You've got a frozen shoulder. You've got plantar fasciitis, but there was nothing to explain everything, do you know what I mean? Because it got diagnosed, 'oh you've got sciatica'. There was just diagnosis of the small things…" (P025)

"… he said, 'right, you've got rheumatoid arthritis. I'm going to start you on this medication… I think [I was living with RA diagnosis] for two years and was on steroids and oral methotrexate for two years." (P021)

Some patients' back pain was described as a normal aspect of osteoarthritis:

"This time round with the x-rays they said, 'oh there is some arthritic change, a little wear and tear… general back pain is what they'd put it down to. General lower back pain…" (P004)

"… they kept just saying, 'oh it's just wear and tear.'" (P018)

4.3.3.3.3 Sub-theme - HCPs missed symptoms strongly suggestive of axSpA

Many people living with axSpA felt HCPs missed clinical indicators for their axSpA, extending the delay of diagnosis:

"… manifested into different things, which again are pointers to AS and again nobody picked it up… nothing was flagged with it or anything…" (P025)

"… my MRIs lit up like a Christmas tree with inflammation but nothing on the x-rays, no, you know, evidence of bone-fusing, so that was what was delaying everything…" (P035)

"… nobody ever questioned that, it was just, 'oh you've got scoliosis, you've got sclerosis, that's why you're getting this upper and lower back pain.' And that was it, so I was just kind of left to get on with it." (P002)

4.3.3.3.4 Sub-theme - Missed Opportunities for Diagnosis

People living with axSpA identified missed opportunities for earlier diagnosis:

"… [my rheumatologist] looked through the notes and said, 'to be honest, I don't think there's much point me doing anything else… I can see your entire history and I can't believe you've not made it here before.'" (P004)

"… if they'd just scanned that little bit lower, they'd have seen I had scoliosis further down and sclerosis… which is one of the first major obvious things in AS I believe." (P002)

4.3.3.4 Patient Behaviour

Two aspects of patient behaviour which influenced the delay in diagnosis were acceptance of symptoms, and low confidence in healthcare services to effectively manage their condition.

4.3.3.4.1 Sub-theme - Patients' Acceptance of Their Symptoms

Patients often accepted their symptoms and only sought medical intervention when their symptoms became more frequent:

> "I mean at the time I just put it down to it was just one of those things that happens to people but yeah, you've just got to get on with life, I suppose." (P004)

> "I've always been in pain for years and years and you just get on with it, don't you? You have to. You've got a family. You've got things you need to try and do" (P018)

> "I used to get a bit worn down by it and just accept what was happening." (P024)

> "When it flares up, you know and I know for sure it's happened many times before I went to the GP definitely." (P003)

For one patient repeated consultations with the GP were influenced by their psychological wellbeing:

"… things were very bad… but I didn't go back to the GP. My mental health wasn't good and I think I just found it very difficult to face it." (P010)

4.3.3.4.2 Sub-theme - Low Confidence in Healthcare

Several people living with axSpA referred to a lack of confidence in the healthcare system which influenced their consulting behaviour. The initial response from their general practitioner focused on prescribing medications when patients were often seeking explanations for their symptoms

"… they didn't have a clue, or they were giving the impression that I was some sort of medical mystery... I think I'd just written off healthcare as a whole…" (P032)

"I just gave up on it… I'd go to the GP, my back was still hurting, so they'd send me for more steroids, they never looked at why my back was hurting… I just thought there's no point in complaining any more…" (P033)

"I'm not going to bother with the GP because all they do is give me painkillers. I could have gone back earlier. In my mindset, I think I closed off the GP route." (P024)

4.3.3.5 Lack of Awareness of axSpA

The lack of awareness of axSpA in the public and amongst health professionals was attributed as one factor that could influence the delay in diagnosis.

4.3.3.5.1 Sub-theme - Patient and Public Lack of Awareness

Several people living with axSpA described a lack of awareness of the condition and its associations which extended to, their friends and their family.

> "… before I got diagnosed I'd never even heard of AS… I mean I speak to friends and family, who are intelligent people, have good jobs, and not one of them had heard of AS." (P018)

> "When I got diagnosed, I had no idea what it was. My family hadn't heard about it. My friends had no idea what it was." (P025)

> "[By the time I was diagnosed] all my joints had swollen up, my hands, my feet… I couldn't believe all my joint pains were related to this bad back I'd had for years…" (P002)

4.3.3.5.2 Sub-theme - HCP Lack of Awareness

Some people living with axSpA described HCPs as having a limited awareness of the condition which often led to axSpA not being considered as a potential diagnosis.

> "I mean I'm sure my first doctor had probably never even heard of it…" (P015)

> "I think it's because they don't realise how common it is and they don't realise how much you need to be aware of it and screening for it. I think awareness of how common it is and then having the right knowledge about it would be really helpful." (P021)

"They don't think about it. Maybe they obviously know about it but don't think about it." (P018)

"I don't think it ever occurred to any GP even when I hit 50 and all me joints had swollen up I don't think it ever occurred to them." (P002)

There was also an apparent lack of understanding of the gender distribution of axSpA:

"the head GP at my practice, said to me "oh you can't have AS, women don't get AS" (P002)

"it wasn't long after my dad had been diagnosed [with axSpA] and I asked is there any chance that this could be what I'm suffering from because the symptoms sound the same… no, only men suffer from that so we are not going to do the test…" (P015)

"… the idea that it's a male disease, cos that was still at the time that I was diagnosed, that was still what was being said…" (P032)

4.3.3.6 Sub-optimal Practice in Healthcare

Barriers to diagnosis often related to the configuration of health care services, including being referred to many different health professionals, with no one

professional co-ordinating their care, causing a lack of continuity. Patients also identified not being referred to a rheumatologist at an early stage in their condition.

4.3.3.6.1 Sub-theme - Lack of defined referral pathway

"I went to the doctors. They sent me for some X-rays. They sent me to physio. I just never really went anywhere with that…" (P004)

"…20 years' worth of back and forwarding…" (P015)

"I certainly did get a couple of X-rays… There was never any comeback to any of those. There was never a follow-up appointment to see what the X-ray said." (P025)

"… then be referred quicker to rheumatology and not discount it or fob it off…" (P002)

"I think there needs to be more access to.. the referral to a rheumatologist… it can take somebody years just to get that referral because there are a lot of GP's who are reluctant to do so…" (P033)

4.3.3.6.2 Sub-theme - Lack of co-ordination/communication between different healthcare services

People living with axSpA identified a lack a co-ordination between difference sectors of the healthcare service impacting on diagnostic delay.

> “There doesn’t seem to be an umbrella department that says the eye people should talk to the rheumatology should talk to the GP… There’s nothing, no branch connecting all these things and yet all of the symptoms are connected as far as I can see.” (P003)

> “it's that line of questioning which I know can be an issue between primary and secondary care. It's about saying, 'I've got this patient who has X, Y, Z. Would you see them?' rather than a combative approach. It's obvious if somebody has got raging CRP and that they should probably be seen if they've got joint pains but what if they haven't? Isn't there a middle ground where they can at least put in a request and that there's a bit more consultation, even if it's via email? To just block that route doesn't seem a necessarily good thing…” (P024)

A lack of continuity of care undermined the process of diagnosis.

> “I think it would have been easier for them if it was the same doctor, they would be picking it up ‘cause I don’t think doctors have got time to sit and read through everybody’s history before that patient walks through the door.” (P025)

4.3.3.6.3 Sub-theme - Insufficient consultation time

Finally, many people living with axSpA found the short duration of their consultations made it difficult to communicate a meaningful amount of information:

> "… they were very short appointments and, yeah, it didn't feel like they wanted to listen. They wanted to get you in and out the door as quick as they could." (P004)

> "… a 10-minute visit if you're lucky and it's a mad rush in and back out again. You trying to remember everything you say and you come back and you forget half of what you wanted to say..." (P018)

> "… I don't think your quick five minutes or ten minutes they allocated are enough to go over everything you need... Because we're so used to hiding our pain, getting to talk about it and to say exactly what's going on takes time sometimes." (P002)

4.3.4 Barriers to Diagnosis: The HCP Perspective

4.3.4.1 Overview of themes relating to barriers to diagnosis: The HCP Perspective

Analysis of the HCP interviews identified five major themes relating to barriers to diagnosis which, while discrete, still had significant overlap with each other:

4.3.4.2 AxSpA is Difficult to Diagnose

The difficulty of diagnosing axSpA was identified by all HCP participants as a major reason for the delay in diagnosis. HCPs acknowledged that axSpA is a challenging disease to define, particularly in its early stages. As many symptoms are similar to other, common conditions, this can reduce suspicion of axSpA. Also, the insidious onset and presentation can make it difficult to differentiate:

> "… if you go out on the street and ask ten people, nine of them will say, 'yes I do have low back pain from time to time, so what?'" (h079)

> "The onset is quite insidious and so even patients, quite often, cannot really put their finger on when the symptoms have started. That's definitely one of the reasons why we delay the diagnosis of it." (h079)

4.3.4.2.1 Sub-theme - Difficult to Define and Differentiate

The high general population prevalence of non-inflammatory back pain was a major factor that delayed the diagnosis of axSpA. On the spectrum of probabilities for a patient presenting with back pain, axSpA is hardly considered:

> "I think it is just a tricky condition because there isn't one single diagnostic test, it's more forming the picture through a collection of signs, symptoms and your investigation results so it isn't just any one thing." (H080)

> "back pain is such a common presenting feature for GPs that they would not be thinking about SpA when it comes to them" (H075).

> "… back pain is two things. It's either a medical emergency… or at the other end of the spectrum… it's mechanical back pain and it's just common and you don't really have to do anything about it…" (H077).

> "… lot of patients are picked up a bit late so it's not uncommon to see people in their forties presenting with it. And I find that's a more challenging group to tease out symptomology and I think the reasons for that might be because they have a mixed mechanical and inflammatory problem usually by that time" (H075).

The frequency of back pain appears to condition HCPs into not considering it to be anything other than either a transient issue or standard "wear and tear":

> "Because back pain is so common… there's going to be a large number of people where it gets minimised, they get told it's mechanical, there's not really anything that can be done, it's wear and tear" (H078).

The vagueness, ephemerality and similarity to symptoms of other conditions can also cause difficulties in diagnosis:

> "… it's not rocket science, but the problem is I think… is that a lot of things that people present with are quite subtle… [it] might take years before they get the back pain that used to get better with anti-inflammatories, but now it's persistent" (H077).

Not only does this make it less likely that early symptoms will raise suspicion, but it also leads to a hesitant approach to suspicion:

> "… after seeing somebody with symptoms for six months and after a second presentation you send them to a rheumatologist saying, 'Doctor, is it possible that he might have ankylosing spondylitis?' … The rheumatologist says, 'it's probably not. Let's just wait and see.' There we go. That's probably another couple of years or so later on" (H079).

Additionally, many HCPs mentioned how the unclear nature of axSpA symptomology can lead to mis-attribution of symptoms, or even misdiagnosis, with many patients treated for mechanical back pain:

> "… again, it just looks like mechanical back pain, so it's kind of let's see how you go…" (H076)

> "… if they've been to primary care, they tend to think osteoarthritis, ask them to manage it with paracetamol, that doesn't necessarily help…" (H089).

> "… the ones with back pain are probably going to be the ones that are not so quickly managed because of that difficulty distinguishing between inflammatory and mechanical back pain…" (H080).

Often symptoms, shared with HCPs were attributed by patients to their occupation which may act as a barrier to the HCP considering other causes:

> "… they've attributed it to that heavy work and then it's left alone as mechanical back pain because it's attributed to something that the patient's done…" (H076)

> "'… oh well I've done a bit too much gardening so that's what's set my back off', so a lot of people don't present at the GP and go and seek medical attention for just niggly, fairly manageable back pain" (H080).

It was also noted that many patients, particularly women, had previously had their symptoms attributed to fibromyalgia by HCPs, although it is difficult, to state whether this counted as misdiagnosis or simply concurrent diagnosis with complicating symptomology:

> "… many of those patients are possibly labelled initially with non-specific back pain, clinical back pains, some with fibromyalgia, and eventually they end up having the diagnosis… maybe three years down the line" (H074)

> "… most women with AS tend to be misdiagnosed with fibromyalgia…" (H091)

> "A large proportion of our patients have coexistent fibromyalgia as well, which makes it very tricky to diagnose SpA" (H075)

> "I mean we see it a lot with conditions such as fibromyalgia. So, a lot of patients can also have that diagnosed alongside and that really does tend to muddy the waters" (H085).

Additionally, it was noted that pregnancy could act as a barrier to diagnosis:

> "… [a] young female patient with subsequent pregnancies, that makes the symptoms more obscured" (H074).

Many HCPs also spoke about the disease's insidious and seemingly random and inconsistent early presentation making early identification extremely difficult, and even retrospective association is problematic:

> "… I've seen patients who come in with things like fatigue and then three years down the line say, 'I knew there was something wrong. I've been diagnosed with such and such', Maybe that's just a very early presenting feature of X, Y or Z', but who knows?" (P077)

> "The onset is quite insidious and so even patients, quite often, cannot really put their finger on when the symptoms have started. That's definitely one of the reasons why we delay the diagnosis of it"

> "… it's such slow progress and unless you see radiographic evidence, then it's a tricky thing to do. That's the delay" (H079).

The variable nature of axSpA symptoms were described by several HCPs as causing a delay in diagnosis:

> "… too infrequent for the pattern to be picked out unless you're deliberately looking for it" (H076).

In some cases, patients might not always present with active symptoms:

> "… obviously they have periods where the symptoms flare, periods where the symptoms are a bit more quiet. And I suppose having investigations and things when the symptoms might be a bit more quiet, then it may not show up some of the inflammation with the bloods or on an MRI scan. And therefore they kind of have to wait…" (H071).

In some instances, it might be that the "quieter" periods of the disease might give the patient and HCP a false sense of security, delaying the need for a diagnosis:

> "…people will have a flare up of symptoms, and then actually it will settle back down again… they don't push or the GP doesn't push to look at it any further because things do settle in between" (H082).

4.3.4.2.2 Sub-theme - Investigations with Uncertain Outcomes

Even when axSpA is suspected, diagnosis is not a quick process due to the inconclusive nature of clinical symptoms or investigations.

> "Especially the ones on the borderline of being diagnosed, but there's not enough sort of from an investigation point of view to formally, formally diagnose them but you've got every clinical suspicion" (H071),

> "… one of the challenges certainly I think is in rheumatology, the diagnostic uncertainty that we can have… You know they're in limbo aren't they?" (H072).

> "… the symptoms are not really easy to spot and only when you have somebody that's been diagnosed, you can then look retrospectively and say, 'yes, of course,' with the benefit of hindsight" (H079).

Early in the disease, testing and imaging might not aid diagnosis:

> "… in the early phase they have no bone damage, the x-ray is not picking up or there have been changes that are so premature that MRIs are not picking them up… somebody has got inflammatory back pain, but the diagnosis cannot be made because the symptoms are not matching the rheumatological investigations" (H074).

Even in later disease, imaging is not guaranteed to give a definite diagnosis:

"… when you see a patient, you can't just clinically say, this is axial spondyloarthritis', you have to do imaging to confirm. That imaging can take time and sometimes you get equivocal imaging and then you have to repeat the imaging after a period of time and see how things evolve" (H072)

"… quite often an MRI scan might come back with a result that quite frankly I don't quite know what to do. Because none of them ever seem normal. You never get a radiologists saying, 'yeah perfectly normal MRI of back'. There's always something that's a bit out of alignment…" (H078).

The following experience of one HCP highlights the different stages that can be involved in trying to reach a diagnosis. Imaging and testing may also have to occur repeatedly over time before signs of axSpA become more apparent:

"… a diagnosis is not a one-stop shop. So, they have bloods then they have x-rays. X-rays come back to clinicians… It's discussed in x-ray meetings, then it could be an MRI scan and that MRI is four or five months down the line already. Then the MRI is done, there's waiting around then, it's reported six weeks later… sometimes that is not enough… you might have to, clinicians might consider wanting to re-image in a few months again or a year… So a year, year and a half, you could sometimes be thinking do they have it, do they not have it…" (H075).

There is sometimes the misapprehension that axSpA diagnosis requires a HLA-B27 positive result from a blood test for a patient to be diagnosed with axSpA:

> "… there's the risk from a GP's point of view they go, 'oh the blood test's negative,' and then, 'ooh they got better, so they haven't got it."

Similarly, a lack of raised inflammatory markers in the blood can mistakenly erase suspicion of axSpA:

> "I tend to see a lot of GPs referring for CRP and ESR and it's not really showing anything… so they'll sort of say… there's nothing there, off you go…" (H083).

Other HCPs acknowledged that the results of blood tests can be influenced by other illnesses:

- "The false negatives and false positives… the specificity of those tests is very poor actually. You see those tests and he's got inflammatory markers, but he had a chest infection a couple of weeks ago…" (H079).

Finally, even with clinical suspicion of axSpA, the absence of a specific symptoms might preclude immediate further testing:

> "… I saw this patient the other day who came in because he'd got uveitis and… the ophthalmologist who had sorted that out, 'oh he's got this. He's young. You might want to exclude axSpA'. Then it's like, 'have you ever had back pain?' 'No.' 'Oh,

okay.' You think, well, if someone's got no musculoskeletal problems, how far do you then pursue that?" (H077).

4.3.4.3 Lack of Awareness of axSpA

4.3.4.3.1 Sub-theme - Patient Lack of Awareness

A lack of awareness of axSpA in patients and the general public was noted by several HCPs as a possible reason for delay in their seeking consultation for their symptoms, meaning on presentation to healthcare, patients are less likely to frame their symptoms as inflammatory and more likely to focus on other explanations:

"… when we say… 'spondyloarthritis', people don't know what it is…" (P091)

"… patients themselves lack awareness of inflammatory causes of back pain… They don't know something like this exists, they just think it's back pain, muscle strain, mechanical back pain, that sort of thing so that will often have delayed them seeking help" (H075).

"… it's not a common presentation, unless you've got someone in the family… I don't think even Google brings up inflammatory back pain… they don't usually come up with, 'I think I've got axSpA.'" (H083)

4.3.4.3.2 Sub-theme - HCP Lack of Awareness

More frequently, it was the lack of awareness of axSpA among HCPs which was described.

> "I think GPs, community physios aren't necessarily all well versed on all of the symptoms that might be involved with diagnosing somebody with AS. So, I think there might be a delay from that point of view…" (H071).

> "I think physiotherapists may not understand the relationship between back pain and the other associated sort of things that come along with spondyloarthropathy, so things like psoriasis, enthesitis, uveitis, inflammatory bowel disease…" (H083),

> "… they don't know as much about back pain and spondyloarthropathies, they wouldn't necessarily know which test to ask for" (H082).

It is worth noting that this lack of awareness is not addressed as implication of ignorance; it is an observation that, "GP's can't know everything of course…" (H071)

4.3.4.4 Sub-optimal Practice in Healthcare

Issues within the healthcare system were identified by many HCPs as delaying the process of diagnosis for axSpA. The main problems identified included insufficient time for consultations, a lack of guidance and resources, and problems relating to referral and the 'revolving door' nature of healthcare.

4.3.4.4.1 Sub-theme - Time

The time available to GPs and other HCPs was generally felt to be insufficient to fully explore symptoms. Shorter consultations led to less exploratory interactions, and limited lines of questioning from the HCP which did not address the likelihood of axSpA:

> "GPs just need to be aware that they're referring into the right service at the right time for the patient. And that's a bit difficult if you've only got 5 or 10 minutes with somebody isn't it…" (H071),

> "GPs and physicians in primary care… don't have much time…" (H083),

> "…clinicians don't have enough time to spend with the patient, or consultants who make this diagnosis, or GPs who refer them or you know suspect the patient has AS, don't have enough time to actually sort of look into those nuances to make a differential diagnosis" (H091).

4.3.4.4.2 Sub-theme - Clinical Guidance

It was felt that current clinical guidance tends to steer HCPs away from the possibility of inflammatory disease:

> "… it ends up that there's quite a strong guidance to manage everything essentially as mechanical. … understandably it's playing to the incidence and prevalence

numbers and to this whole public health aspect that we don't want to be overly irradiating people unnecessarily…" (H078).

4.3.4.4.3 Sub-theme - Referral Issues

Problems with referral was identified by many HCPs as being a cause of diagnostic delay.

The time taken for referral between primary and secondary care was not of great concern among some HCPs (aside from the notable issues caused by the 2020-21 COVID19 pandemic), but there was an acceptance that it was extra time taken in an already meandering process:

> "… it probably took close on twelve months from first presentation to secondary care referral and then of course there's some additional delay after referral to first consultant appointment" (H078).

However, other HCPs felt it was a point of significant delay and consternation:

> "… then the GP goes, 'right I'm going to refer you', and then it's just like, 'brilliant I'm going to get this sorted', and then they get their appointment and it's in 12 months' time" (H077).

Additionally, some HCPs reported a referral delay due to the demand of hospital services:

> "Then you've got the delay in rheumatology seeing the patient. A lot of services are very stretched" (H072),
>
> "… it feels like they're probably quite crowded out with people with mechanical back pain…" (H078).

Of greater concern was the lack of clarity in the referral process:

> "If somebody has got joint swellings, stiffness and pain. I think there's no clear guidance on that for primary care… there's a bit of a lack of clarity on that in the pathway… That's definitely something that can be improved" (H074).

Some HCPs also reported systemic disincentives to refer:

> "… we are aggressively told not to refer to specialist care. Our CCG will regularly audit. … for example, our practice is one of the highest referrers to the musculoskeletal clinic in the area and they say, 'we want you to audit this and find out why your referring is so high and what can you do to reduce these referrals" (H077).

Others, however, state that the cause for lack of, or slow, referrals, can be due to the HCP:

> "Some patients have said that GPs have been reluctant to refer on, even though they keep going back with the same pains" (H085).

4.3.4.4.4 Sub-theme - “A Bit of a Revolving Door”

Many HCPs talked about the “revolving door” problem in healthcare, and of patients being “bounced around”, significantly delaying diagnosis:

> “… they might have been seen by a service like ours before, been investigated, nothing maybe’s shown up at that point in time, so they’ve been discharged. And then it may be that they come back round or there’s been a bit of a revolving door until things are maybe a bit more clear with their symptoms” (H071),

> “… then we’re into potentially quite long primary care delay is going round that loop potentially a number of times…” (H078).

4.3.4.4.5 Sub-theme - Communication Between HCPs

Many HCPs remarked that communication between HCPs could contribute towards diagnostic delay due to the complexity involved in making a diagnosis.

> “… interestingly, there have been times when there are split opinions between rheumatology colleagues. Some might think this is inflammatory, some might think it is not, so once again, that’s another complication involved in the process of diagnosis…” (H074).

Also, the desire by some managers to adhere to protocols rather than support the clinical autonomy of the practitioner might contribute to diagnostic delay:

> "… my direct line manager…. was traumatised when she found out I'd been emailing backwards and forwards with a consultant saying this is misdiagnosed. She said to me the protocol was that I had to go back to the GP, write to the GP for the GP to then question the diagnosis to my consultant, that was the standard operating procedure… I said, I'm not doing that, I don't care what standard operating procedures, it's ridiculous…" (H091).

4.3.4.5 Patient Behaviours and Characteristics

Patient attributes were also identified by HCPs as causes for a delay in diagnosis, including people's propensity to simply cope with pain and discomfort rather than get it investigated. Presentation behaviour and gender were also identified as sources of diagnostic delay.

4.3.4.5.1 Sub-theme - Presenting to Healthcare

Many HCPs observed that many patients delayed presenting with their symptoms.

> "Well firstly I think people have got to present with it, so you know if they think oh I'm 20 but I've just got some back pain and it goes away when I take ibuprofen, it might settle for a while and then flare again and you treat it, and you are not really aware of this as an issue then you are not going to present and if people don't present then we can't do anything for them…" (H089).

Some patients cause further delay by not following up on prior consultations:

"… even if you're deliberately looking for it, and think, 'okay, I'll keep an eye on that patient', and then they don't reconsult within a couple of years, it's kind of gone, and you might not see the same GP at that point anyway…" (H076).

A major rationale for patients not presenting to healthcare was that many patients attempt to live with their condition rather than investigate it, or attribute their symptoms to their occupation.

"Sometimes patients… just put it down to their work and have not sought any medical attention initially… this will be one of the factors that delays the things" (H074),

"'Oh, I can live with my back pain at the moment…" (H077),

"… they just sort of say you know, just everyone gets back pain, it's common, I didn't go to my doctor I just sort of… it didn't really stop me from doing anything…" (H083).

Other patients, rather than ignoring the pain, will attempt self-management, including keeping active, for extended periods of time before seeking healthcare consultation:

"… it depends on severity doesn't it and how badly it's affecting them and whether you know they are self-treating because it could be that they've realised they've got pain, they've got stiffness, it's not getting better, it might be getting worse, it

might be waking them up at night time, but they can take some ibuprofen and… get relief from it so self-treatment might go on for a little while…" (H089)

"… people who are active, physically more active or employed physically active and do not have any sort of depression, anxiety… I think they tend to just get on with it. And the more active you are, you can manage your symptoms a bit better, and I suspect that triggers them not presenting soon enough to the GPs or seeking medical attention" (H075).

4.3.4.5.2 Sub-theme - Gender

Many HCPs referred to the influence of gender on diagnosis. Women were felt to present sooner than men, possibly due to their more frequent use of healthcare overall:

"…male patients present a bit later compared to female patients and I think in female patients often life events like childbirth etc which would sometimes strain the back triggers investigations sooner" (H075),

"… I think women will present sooner than men. Whether it's because as a working population women tend to work part time more than men and whether they've got more availability to be able to get to a GP" (H082).

Despite women being considered to present earlier than men, however, it was felt by several HCPs that men were diagnosed faster after presentation and the raising of suspicion of axSpA:

> "… there's also gender bias I find, you know men tend to get diagnosed with AS quicker than females" (H091),

4.3.4.6 Patient/HCP Interactions

Interactions between HCPs and their patients were identified by several HCPs as a barrier to diagnosis.

The major challenge in patient/HCP communication identified by HCPs was that firstly patients often struggle to communicate their symptoms adequately, and secondly patients were not always listened to as they shared their symptoms or their symptoms were misinterpreted.

HCPs felt patients may find it difficult to articulate their symptoms especially if they had a mixture of mechanical and inflammatory problems:

> "I think probably 2 out of 10 might struggle to clearly differentiate and understand what stiffness is" (H075)

> "I find patients really struggle to answer stiffness questions and how you ask if something is stiff, it doesn't really make sense to them, you might ask about night pain but actually not clarify well when is it in the night…" (H083),

Related to this, some symptoms might not be mentioned by patients unless explicitly asked about, as they might not regard it as diagnostically important, or they may simply view it as normal for life:

> "It's rare that somebody would actually say, "I'm really stiff first thing in the morning", it wouldn't necessarily be something that they would complain about." (H082).

Some patients may find specifying important symptoms difficult, instead exhaustively listing everything they feel is wrong:

> "…especially if they don't really have good psychological health, [people] tend to concentrate on their symptoms and then will analyse and identify every single small pain and ache" (H079).

The second challenging area of communication between patients and HCPs is the issue of patients not being listened to or their symptoms being misinterpreted.

"…some health professionals I think stop hearing what they're saying when they're saying the same complaints over and over again" (H091).

"… early doors [patients would] not necessarily be convinced that clinicians understand what they're experiencing and perhaps feel that their symptoms are being mischaracterised or minimised…" (H078),

"… if you've got a teenager that turns up I think quite often things are dismissed as growing pains, or you're playing on your Xbox too much…" (H082)

4.3.5 Facilitators of Diagnosis: The Patient Perspective

4.3.5.1 Overview of themes relating to facilitators of diagnosis: The patient perspective

Factors that may facilitate diagnosis were identified by patients in the following 5 themes:

Patient behaviour and advocacy	(4.3.5.2)
Patient characteristics	(4.3.5.3)
Good practice in healthcare	(4.3.5.4)
Education and awareness	(4.3.5.5)
Luck	(4.3.5.6)

4.3.5.2 Patient Behaviour and Advocacy

Patients spoke about the impact of their own behaviour and advocacy facilitating a diagnosis.

> "… I thought, 'Do you know what? I'm not going to home'… eventually I get admitted into the surgical ward. Got a CT scan the next day… and this young consultant, 'I know what's wrong with you'. I went, 'Oh, don't tell me it's a kidney stone', and he went, 'No', and he called it, he went, 'It's called sacroiliitis'" (P018)

Other patients described less dramatic, but nonetheless effective moments of advocating for themselves:

> "… the rheumatologist that I went to see first tried to say I had fibromyalgia… we disputed that and luckily the junior doctor agreed with me and we went for a second opinion and then I actually finally got diagnosed." (P015)

> "… they said it's fibromyalgia and I thought there's absolutely no way this is fibromyalgia… So I pushed to get a referral to rheumatology which they finally did…" (P002)

One patient, aware of having a family history of axSpA, was sceptical when told their eye symptoms were cataracts:

> "I did some reading up around uveitis I just walked into the eye hospital… and insisted on an appointment. They had a look and said, 'Oh yes, it's uveitis' … went back in and said, 'This is not good enough. I want moving to a different hospital' so I was transferred to a different hospital.… At that point, somebody said, 'Why don't you get a blood test?' So I had a blood test for the HLA-B27 marker which I was positive for." (P010)

Some patients felt their diagnosis was facilitated by their relatives taking on the role of advocate

> "… my mother and father were fighting to get people to just find an answer and they contacted my GP about it and that's how I first got involved with [HCP] at the [Hospital] and that's how I got my diagnosis." (P035)

> "… one of my aunties is a physio occupational therapist… and she wrote a letter to my GP and the GPs were very dismissive of it but did run the blood test HLA-B27… then I got a phone call… from the GP, saying that the result come back positive and I'd get an appointment with the Rheumatology department at the hospital through the post… (P004).

Patients referred to the positive impact of taking somebody with them to their consultation

> "… if [patients] take someone, then not only does it give them the confidence to take their time and go through everything, but they feel they're listened to a bit more as well." (P021)

One patient discussed the need to take on an active role in the consultation

> "… what I say to everybody is you have to partner with your healthcare provider to work it out together because I think if you don't question and you don't ask and you don't push and you don't negotiate… I think you literally only get what you fight for…" (P030)

4.3.5.3 Patients, Symptoms and Consultation

Two main sub-themes arose under the theme of "patients, symptoms and consultation" as facilitators of diagnosis. This theme describes the symptoms and circumstances surrounding patients which 1) triggered health seeking behaviour and 2) started indicating to the patients that their symptoms were signs of something quite serious.

4.3.5.3.1 Sub-Theme - Triggers to consultation

Many patients stated that their reason for visiting their GP was due to unbearable pain and the increasing impact on normal life of their symptoms.

> "I was in agony, absolute agony. So that was probably the main turning point for me… obviously went to the doctors about that…" (P002)

"… I was constantly waking up at 2am and watching TV because I couldn't sleep because my back was hurting… I was thinking this is crazy because it shouldn't be impeding your life that much. So I went to the GP and I guess that's the point at which you would say the journey to diagnosis had started…" (P003)

"It was the pain." (P010)

Others, however, were encouraged to see a doctor by people around them who had become increasingly concerned:

"… and my movement was severely hampered, and it was actually come of the women at work who bullied me into going back to the doctors." (P004)

"My tutors at university said, 'you need blood tests or something', because I was still hobbling into university." (P021)

"… [the out of hours doctor] said, 'you have to promise me after your exams you're going to go straight to your GP at uni and get referred…" (P032)

4.3.5.3.2 Sub-theme - Point at which patients realised their symptoms were something severe

Many people living with axSpA reported becoming aware that what they were experiencing could be quite serious. While pain and immobility were frequent triggers to consultation, they were by no means the first symptoms patients encountered.:

> "I'd been complaining to my partner that my vision was a bit blurry in one of my eyes and when we were out at the weekend for a walk and thick fog and mist rolled in… I said to him, 'that's what my eye looks like.' He looked at me and said, 'that's not right.'" (P010)

> "I just noticed my energy level was going down and down and my mood was going down and down and I thought, 'there's something not right here…" (P018)

> "… I began to think, 'this isn't right. Why is my back sore? Why do I have these spells? Why does my shoulder freeze?" (P024)

> "No, this isn't in my head. My back's sore, sitting in this chair…" (P025)

4.3.5.4 Good Practice in Healthcare

Many patients could identify specific factors that they felt facilitated their diagnosis. These included having investigations, being listened to by the clinician and being referred to the appropriate service.

> "So it went from years and years of nothing and no one listening and no one willing to do anything about it to a whirlwind week of, 'We're getting you an MRI. Right, you're diagnosed. That's what it is. Let's go, treatment'." (P025)

> "…if I hadn't have had that HLA-B27 test, I never would have got that MRI… and I'd probably still be searching now…" (P002)

Several patients described the importance of being listened to by the clinician

> "He was really good. He was very respectful and wanted to listen. He reflected back what I was saying and was just open to the idea that this was something that they needed to be looking at." (P024)

> "…in the hospital my experience was great, when my history was being taken it felt like the first time I'd properly been listened to… when she diagnosed and said I'm going to hand you to my colleague who specialises in this… I was part of this well-oiled machine…" (P030)

Patients recognised the importance of being referred to the appropriate service by other clinicians:

> "… I got sent to the pain clinic at the hospital … he was looking at my records saying no-one has said what is wrong with you, no-one has said why this pain is

happening so I think you have to see someone in rheumatology and so he referred me to rheumatology…" (P030)

"[My GP] referred me to rheumatology. Whether she thought it was AS, I don't know at that stage. But she knew that it was a problem that could be identified at rheumatology or investigated." (P003)

The importance of recognising different symptoms and a family history to arrive at a diagnosis was also acknowledged:

"… somebody to spot that there was a link between all these things, every symptom I've complained about, and said, 'Hang on a minute, how many times have you actually complained about this? What else have you had that's to do with your bones that could relate to one another? Let's have a look here back at your history. Is there something we're missing here?'" (P025)

"…the first thing you would do would be to go through family history, wouldn't it? And if the family history looks promising for it then do the [HLA-B27] test…" (P015)

Specific areas patients wanted to see improvement in were continuity of care and to be guided through the consultation:

"… it would have been easier for them if it was the same doctor, … because I don't think doctors have got time to sit and read through everybody's history …I think having the same doctor over and over that actually got to know you, they wouldn't have to have that issue…" (P025)

"I'm not particularly good in the consultation. Probably need more time and probably need more help drawing that out to say because I'd say "oh yeah this hurts". I never really get it across enough." (P002)

4.3.5.5 Education and Awareness

4.3.5.5.1 Sub-theme - HCP education and awareness

It was felt that education about axSpA and a greater level of awareness and understanding of the disease in the medical community would be of great benefit to the diagnostic process.

"I think [what is desperately needed is] undergraduate training. There needs to be some way of auditing the training that's going on to make sure it's up to date for GPs, rheumatologists and AHPs as well." (P021)

"I'd want to make sure medical professionals were educated in all the symptoms and how it can present itself, so arthritis is at least put on the table sooner as a possibility of someone's condition." (P035)

"GPs need to have more understanding of it. They need to be aware that it's something, particularly for women, because I think blokes tend to get a better deal out of it with diagnosis." (P002)

4.3.5.5.2 Sub-theme - Patient and public awareness

Patients also felt that increasing the public visibility of axSpA would increase the likelihood of patients either presenting with symptoms in healthcare or of people being more likely to recognise symptoms in people around them.

"… I think just raising awareness of it in terms of the public as well, so the public are going in and saying, 'could I have [axSpA]?'" (P021)

"… someone put up a BBC article today about a singer who has got it and I put that on my Facebook page… and I said you might know someone who's got long term back pain, who feels worse in the morning, who feels better with exercise, who might have bowel or bladder problems or eye problems. Have a think about it… because there's a campaign to impose diagnosis times…" (P030)

4.3.5.6 Luck

A number of patients attributed their diagnosis to a single, seemingly arbitrary occurrence or coincidence.

"… it was only right at the end that I got the diagnosis, and that was through luck more than anything…" (P004)

After a long time living with axSpA symptoms, P004 was only prompted that it might be something inflammatory during a meal with family, one of whom was a physiotherapist:

> "… it was my aunty who was sat at the dinner table with Christmas... There's me moving my entire body to speak to somebody and she was like, 'What on earth have you done?... Right, I want you to come into my clinic and I want to check you out'… checking my neck and the movement and making me do this, that and the other and it was her that said after seeing me twice, 'It could be [axSpA].'" (P004)

Another patient was diagnosed after admission to A&E with a suspected kidney stone:

> "My diagnosis was a total fluke… just one day of your life and after all those years then you turn up and somebody does a scan…" (P018)

A further patient remarked that their diagnosis was driven forward by an HCP whose knowledge of and interest in axSpA was due to their personal circumstances more than it was by formal training:

> "The only reason that she got the ball rolling is because her dad has got ankylosing spondylitis… she just went, 'I think you've got a thing called AS. My dad's got that. Let me send you off for an MRI', and she was the first person to know that there was a link to all this stuff and actually to check it out." (P025)

4.3.6 Facilitators of Diagnosis: The HCP Perspective

4.3.6.1 Overview of themes relating to facilitators of diagnosis: The HCP perspective

Factors that may facilitate diagnosis were identified by HCPs in the following 4 themes:

Promoting awareness of axSpA	(4.3.6.2)
Raising suspicion of axSpA	(4.3.6.3)
Improving practice in healthcare	(4.3.6.4)
Improving HCP/patient interactions	(4.3.6.5)

4.3.6.2 Promoting Awareness of axSpA

HCPs identified the different ways that awareness of symptoms, related to axSpA, could be promoted including via national charities, in hospital waiting rooms, in GP surgeries and through public campaigns.

> "… if we come up with something like [RA patient campaign] for axSpA through NASS or any other platform or charitable organisation…" (H075)

> "… we do have a patient group [in hospital] we are looking at getting televisions on the walls so we can start using promotional information on there around our service… in waiting areas when people are sitting there…" (H083)

> "… there could be a poster type of campaign, there would be a place for it in GP practices, in waiting areas… to identify the kind of differences between inflammatory back pain and mechanical back pain… do you have psoriasis or is

there a family history of psoriasis, do you have back pain that is strongly associated with stiffness, just pointing out some of these features just to mention this to your GP…" (H080)

"… presenting three symptoms which in combination might raise concern and then suggesting talking to your doctor… so you see it on the back of buses… I suppose it would certainly trigger a patient's concern… I'm sure you can place somebody in Coronation Street with it… that often for the short term triggers people to consult about their symptoms, if they've seen somebody else with them on telly or in the media…" (H089)

HCPs felt prompting awareness could also occur online, which would relate to the typical age of initial axSpA presentation:

"… it's generally going to be a younger population isn't it? So I think digital medium would be appropriate and I think social media obviously… some kind of catchy social media campaign…" (H072)

"Everything is at a stroke of a keyboard isn't it? We're talking about really young people and people that are IT literate." (H079)

While it was acknowledged that increasing awareness of axSpA through public campaigns would reduce patient delay, it would also increase the workload for HCPs.

> "That is tricky because there's a lot of back pain out in society I think if we did a drive of it we would be inundated with referrals…" (H085)

> "if you start promoting these three symptoms of low back pain, stiffness and fatigue… my surgery would be absolutely full all the time… actually it might be counterproductive because that will then delay people with genuine symptoms…" (H079)

4.3.6.2.1 Sub theme - Promoting awareness in primary care

While it was felt that improved awareness of axSpA would help with diagnosis. In primary care there was recognition of the need to improve the education of GPs and AHPs and provide consultation tools to aid diagnosis.

> "Definitely there's a big educational need for GPs because this is a very small part of what they see on a day-to-day basis. So, if we could have simple questionnaires for GPs… which would prompt GPs to start thinking about this…" (H075)

> "… it's got to fundamentally come down to GP awareness because that's the patient's first port of call… so it's an educational role, I suppose to GPs and to primary care physiotherapists…" (H080)

"… I think it's important to educate the primary care practitioners and they know what questions to ask, if somebody came with back pain, you ask, this question, if that then refer… we want to make their life easier don't we?" (H091)

4.3.6.2.2 Sub theme - Education delivery

Methods of education and raising awareness, included workshops, events, communications and being familiar with current guidelines:

"I think there could be initiatives linking in with primary care clinicians, education and workshops to discuss more and improve knowledge and competence around diagnosing axial SpA…" (H072)

"I think educational events maybe… we used to do little inserts [on the bottom of letters], we'd put an insert about exercise, an insert about a charity an insert about a key message… and one month it was around a new guideline… or new evidence…" (H083)

"I make sure I stay up to date by regularly checking the NICE guidelines because often things can change. I also try and intermittently review the EULAR guidelines to make sure nothing has changed…" (H072)

"… it is that training need and not necessarily just a one off training need, but that refresher maybe every couple of years just to keep it fresh in the minds of those in primary care so they don't forget some of the things that they maybe learned earlier in their career." (H071)

4.3.6.3 Raising Suspicion of axSpA

All HCPs listed symptoms and characteristics of patients that would indicate a clinical suspicion of axSpA and therefore instigate the process towards diagnosis.

The most frequently mentioned symptom likely to raise suspicion was lower back pain (n=13). Early morning stiffness was the second most frequently mentioned characteristic (n=9), followed by symptom onset younger than 45 years (n=7), stiffness in the back (n=6), family history of axSpA or SpA (n=6), personal history of inflammatory bowel disease (n=6), psoriasis (n=6), peripheral arthritis (n=6) and buttock pain (n=5). Four HCPs mentioned that a family history of psoriasis, symptoms responding to anti-inflammatories, and symptoms improving with exercise and movement would also raise their suspicion.

"I would look at lower back pain, inflammatory in nature so we're talking about waking in the night usually the second part of the night, pain that's worse in static conditions." (H071)

"… lower back pain, buttock pain, which is less of feature of kind of mechanical back pain I think." (H072)

"…sometimes in particular people, young people have got a very classical inflammatory back pain history, they normally give you very classical history of the early morning stiffness more than half hour, in particular night-time symptoms, trouble sleeping because of the pain." (H074)

"Their age and symptoms starting from an early age and with non specific mechanisms of onset of symptoms, so no injury, no trauma. Alternating buttock pain is another one that would make me think…" (H082)

"…maybe it's to do with the way it ebbs and flows early on in the course and its only when those episodes start to get longer, or they start to get more frequent, that people start to say, okay so what maybe going on here." (H076)

4.3.6.4 Improving Practice in Healthcare

HCPs identified a range of practices in healthcare that could be improved to avoid delays in diagnosis, including improvements to the referral process and patients' first contact with healthcare, and identifying clinical symptoms.

4.3.6.4.1 Sub-theme - The Referral Process

Speeding up, clarifying, and improving the referral process were all felt to be important aspects of reducing diagnostic delay.

"… optimising the referral pathways for patients so that we have a streamlined process where patients with axial SpA are seen in a timely fashion, they get scans and diagnostic testing in a timely fashion." (H072)

"… it would be helpful… having fast track pathways where there's a dedicated clinic for the patients who are not coming to a general pool. And if we can segregate that pool of patients who are waiting to be diagnosed, whether they've got axial spondyloarthritis, then direct them into a particular clinic, we can segregate the patients into different categories, for ones who have definitely not got axSpA can be discharged, category B has definitely got the disease…" (H074)

Whereas other HCPs detailed more specific solutions, such as the ability to refer directly in different areas of healthcare and having a defined referral pathway:

"… community physiotherapists looking after back-pain patients… they might have more time compared to GPs or medics to go through things with patients. I think them being able to refer patients straight on to rheumatology services, would certainly make a difference and reduce the time delay." (H075)

"Referral to a specialist centre earlier on to break this revolving door really of GP to physio to GP to physio…" (H083)

"I would like to see something along the lines of what we have now with rheumatoid arthritis… When I have a reasonable clinical suspicion… I would send the patient to a clinic that can reasonably rule in or rule this out…" (H079)

The importance of keeping patients in the system when axSpA might be a clinical possibility was also advocated to improve the likelihood of a diagnosis:

> "… for the ones that maybe don't show up on any investigations, but they've got that clinical suspicion... I know our service tends to keep them on and we tend to sort of monitor them and review them every now and again… keeping them in the system so that they don't get lost in the system, hopefully at some point they will get a diagnosis and hopefully quicker than if they were discharged and then had to find their way back in again…" (H071)

4.3.6.4.2 Sub-theme - Improvements to First Contact

Several HCPs felt that the availability of first contact physiotherapists at the beginning of clinical presentation might reduce diagnostic delay by allowing for a more detailed and productive consultation.

> "…it will be interesting to see, as Physiotherapists become first contact practitioners in primary care if this becomes a watershed moment in time and in 10 years' time we can look back and say diagnostic delay was improved because of that…indexing needed
>
> … so that these people can walk into their practice and go straight to a Physio who can then administer their treatment pathway…" (H076)

"… first-contact physiotherapists or other, working as an integral part of a primary care team in the same way that midwives and district nurses do, so that referrals from the GP to the physio could happen with reasonable rapidity…" (H078)

"… as physio's we're maybe best placed because we've got a bit more luxury of time sometimes, especially in community physio settings where they get brought in for initial assessments." (H071)

4.3.6.4.3 Sub-theme - Enhancing consultations

Several HCPs felt that having a simple, focused sets of exploratory questions could be employed when there is a clinical suspicion of axSpA:

"… you ask a patient, you know under 45, under 35, if they're waking in the middle of the night feeling painful, stiff symptoms in their back, if they get on and off back pain, if it improves in movement, there's a few other symptoms you can look for… so in a normal GP consultation for example, I think it could be ascertained quite quickly…" (H076)

HCPs identified how diagnosis could be improved with the use of computer programs and pop-ups:

"… I think you would need that alert that then takes you to a kind of diagnostic process that the GP then does. So it says, 'they're under 45 and they've got back pain and they've had it twice in the last six months, so you should be thinking

about screening for axSpA', and then you click in something and it goes, 'Right', and this is like a standard set of investigations almost that can already be predetermined and you just click, 'Okay'. Print off the piece of paper and off it goes and then they get called in for whatever it is. I mean all that can be automated…" (H077)

"… you could, within the search that causes that pop up to trigger, put in things like age and consultation patterns and high NSAID use or associated stiffness, have you considered this as a possibility and consider a referral to a rheumatologist…" (H089)

Finally, HCPs revisiting diagnoses and investigations in patients with persistent or less straightforward symptoms was seen as a means of ensuring a diagnosis of axSpa had not been overlooked:

"I think acknowledging that we don't get it right all the time and being willing to acknowledge that the first call wasn't necessarily the right one… promoting awareness amongst clinicians to at least be willing to review their diagnosis could be good…" (H078)

4.3.6.5 Improving Patient/HCP Interactions

Interactions between patients and HCPs were seen to have scope to facilitate faster diagnosis of axSpA. Being open to patient input regarding their own symptoms and

possible diagnosis was raised, as they could be more informed than may perhaps be presumed:

> "… people have quite often got good ideas as to what's wrong with them and you've got to listen to those ideas because quite often they're right, because they've had time to reflect on those symptoms and have a read around and have a chat and if there is a family history with HLA-B27 links then it's quite likely that they'll be concerned that this might happen to them and if they get symptoms…" (H089)

> "… you've got to tailor the management to the individual and obviously it's got to be a shared decision with the individual patients and focusing on the area they want addressing." (H072)

One HCP advocated using a lateral, conversational approach to address patient unwillingness to directly approach their symptoms and symptomatic history:

> "I would tend to ask what you were like growing up, were you sporty and they go oh yeah I didn't have any problems then, what about college, uni, work, that sort of thing… I kind of ask through their phases of life… I don't think people actually tend to give that kind of information freely…" (H083)

Another HCP suggested the following solution to communication breakdown with patients:

> "If there really is an antipathy then there's a communication failure. Occasionally clinicians are unreasonable, occasionally patients are unreasonable but in general if there's a sense of antipathy, it's a sign the consultation needs to begin again. … I think there would be some patients and clinicians who would be willing to almost literally do that, to start the consultation again. Sometimes it means the patient will go off and see another clinician…" (H078)

4.3.7 Summary of identified themes relating to barriers and facilitators of axSpA diagnosis

Box 4.5 Barriers to Diagnosis

Patient Perspective		
Theme	**Brief Description**	**Sub-themes**
Patient/HCP interaction	Barriers caused by issues with the interaction between patients and the HCPs with whom they consult	1) Patient communication 2) HCP communication
axSpA is difficult to diagnose	Barriers caused by the complexity of axSpA diagnosis	1) Not presenting in the classical way/unclear and inconsistent symptoms 2) Alternative explanations for symptoms 3) HCPs missed symptoms suggestive of axSpA 4) Missed opportunities for diagnosis
Patient behaviour	Patient behaviour and personality traits slowing down journey to axSpA diagnosis	1) Patients' acceptance of their symptoms 2) Low confidence in healthcare
Lack of awareness of axSpA	Awareness of axSpA in healthcare and general public spheres reduces likelihood of suspicion of inflammatory arthritis being raised by symptoms	1) Patient and public lack of awareness 2) Lack of awareness in healthcare
Sub-optimal practice in healthcare	Configuration of, and practice within, healthcare services slowing down journey to diagnosis	1) Lack of defined referral pathway 2) Lack of communication/co-ordination between different healthcare services 3) Insufficient consultation time
Healthcare Professional Perspective		

	axSpA is difficult to diagnose	Barriers caused by the complexity of axSpA diagnosis	1) Difficult to define and differentiate 2) Investigations with uncertain outcomes
	Lack of awareness of axSpA	Awareness of axSpA in healthcare and general public spheres reduces likelihood of suspicion of inflammatory arthritis being raised by symptoms	1) Patient and public lack of awareness 2) Lack of awareness in healthcare
	Sub-optimal practice in healthcare	Configuration of, and practice within, healthcare services slowing down journey to diagnosis	1) Time 2) Clinical guidance 3) Referral issues 4) "A bit of a revolving door" 5) Communication between HCPs
	Patient behaviour and characteristics	Patient behaviour and personality traits slowing down journey to axSpA diagnosis	1) Presenting to healthcare 2) Gender
	Patient/HCP interaction	Barriers caused by issues with the interaction between patients and the HCPs with whom they consult	

Box 4.6 Facilitators of Diagnosis

Patient Perspective		
Theme	**Brief Description**	**Sub-themes**
Patient behaviour and advocacy	Aspects of patient behaviour and advocacy of patients that speed up diagnosis	
Patient characteristics	Patient behaviour and personality traits speeding up journey to axSpA diagnosis	1) Triggers to consultation 2) Point at which patients realised their symptoms were something severe

Good practice in healthcare	Instances where patients' healthcare experiences sped their journey to diagnosis/aspects of healthcare that can be improved	
Education and awareness	Means of educating and raising awareness of axSpA	1) HCP awareness and education 2) Patient and public awareness
Luck	A number of patients attributed their diagnosis to a single, seemingly arbitrary, circumstance or coincidence	
Healthcare Professional Perspective		
Promoting awareness	Different means of raising awareness to speed up diagnosis times	1) Promoting awareness in primary care 2) Education delivery
Raising suspicion	Symptoms and characteristics that could raise clinical suspicion of axSpA	
Improving practice in healthcare	Aspects of healthcare that could be improved to speed diagnosis	1) The referral process 2) Improvements to first contact 3) Enhancing consultations
Patient/HCP interactions	How communication and interaction between HCPs and patients could be improved to speed diagnosis	

4.4 Discussion

This study has explored barriers and facilitators to the diagnosis of axSpA from the perspectives of both patients and HCP. The themes which arose had significant overlap between the patient and the HCP samples. Some of the key barriers identified related to the general difficulty of diagnosing axSpA, the lack of education and awareness regarding the condition and the erroneous belief of axSpA being a 'male-only' condition. Facilitators included improvements to communications, advocacy for patients and education regarding axSpA. While the prioritisation of these aspects was different between the two participant groups, the fact there was such a large degree of agreement is important and encouraging, as it shows that there is common ground between patients and HCPs with potential for better communication to result in an improvements in patients' and HCPs' experiences. It also shows that despite patients' negative experiences of healthcare, HCPs do largely share their concerns.

4.4.1 Challenges with diagnosing axSpA

Both people living with axSpA and HCPs were aware of the difficulty of differentiating between axSpA and other conditions causing similar symptoms, such as osteoarthritis and fibromyalgia. Many different reasons for symptoms were offered to patients prior to diagnosis, such as growing pains, pregnancy, sciatica, "wear and tear", viral infection, somatisation of anxiety and simply "a bad back." Similar explanations have been reported in other studies (Dube et al., 2021; Martindale and Goodacre, 2014) with patients being told by their HCP that their symptoms were due to sports injuries, groin strain, flat feet, asymmetric legs, sciatica, pinched nerves, dehydration or a

miscarriage.

People living with axSpA recognised that their unusual initial presentations may have slowed their diagnosis and many HCPs also reported that one of the main causes of delay was insidious or atypical symptom onset along with the somewhat unpredictable nature of flares, i.e., the acute onset of symptoms. This awareness has previously been identified with early symptoms being described in terms of "unusual gait", fatigue, various manifestations of pain and changes in posture (Dube et al., 2021); as with the sample in the present study, these early symptoms were feasibly the first manifestations of axSpA, but weren't in themselves "diagnosable". An American study by Lapane et al (2020) also reported the intermittent and slow initial onset of the disease as a cause of delay (Lapane et al., 2020). In Dube et al 2021, delayed diagnosis wasn't only associated with particularly unusual presentation. Simply not falling into the widely accepted category of being male, in their 30s and with predominantly axial skeletal symptoms was seen as sufficient to slow down diagnosis. This observation complements the findings in the present study that female patients were being told they were unlikely to have the disease due to their being female, which is discussed below in section ***4.4.1.3.***

A further issue with diagnosing axSpA reported by HCPs in this study was that chronic back pain, a characteristic symptom of axSpA, is extremely common in the general population. In the majority of patients, back pain is mechanical in nature and treated as such, meaning that in many patients with axSpA patients, by the time suspicion of axSpA has been raised, they have been living with worsening disease for some time. This situation was also described in Lapane et al (2020), with one HCP stating, "*… I'm*

not sure if I'm missing it because I'm not looking for it or is it just relatively rare…", a sentiment reflected by many HCPs in the present study.

HCPs commonly described: chronic back pain, night waking, stiffness in the morning, improvements to symptoms and physical function with exercise, age at symptom onset, history of psoriasis, buttock pain and family history as factors which would raise suspicion of axSpA. Several HCPs voiced the opinion that a simple set of questions based on the presence of these factors would be a very useful diagnostic tool, and this is supported by Braun et al (2013) and Baraliakos et al 2020) who demonstrated the impact of using a short series of questions in discerning the likelihood of axSpA in patients (Baraliakos et al., 2020; Braun et al., 2013). The first of these two studies showed that a short series of questions based around the presence of specific related factors was a good filter to raise axSpA suspicion and also reduce the amount of arbitrary HLA-B27 testing. In the case of this study, the presence of buttock pain on both sides, improvement with movement and history of psoriasis were found to be of high utility in diagnosing axSpA; where two or more of these factors were present, referral to a rheumatologist was recommended, and if fewer were positive, HLA-B27 testing was recommended, with a positive HLA-B27 test resulting in a referral. The later study investigated the efficacy of other questions being asked and found the highest sensitivity and specificity with "good response to NSAIDs", "morning stiffness longer than 30 minutes" and "elevated CRP". Encouragingly, many HCPs, both general and specialist, in the present study identified these, although it is noteworthy that Braun et al and Baraliakos et al, when considering back pain as a symptom of axSpA to raise suspicion, it was buttock pain which raised the likelihood of differentiation from

other arthritic conditions; back pain alone did not discriminate meaningfully from arthritis with mechanical causes (Baraliakos et al., 2020; Braun et al., 2013).

Sets of questions are therefore available that can help raise suspicion of axSpA and expedite an appropriate referral, and most HCPs included in this study were able to list many of the features which would raise suspicion of inflammatory arthritis and axSpA; why then is there still delay? The answer may be suggested by the results of van Onna et al (2014). Unlike the present study, van Onna et al chose a sample of GPs who did not have a specific clinical interest in axSpA, and they found a very low level of awareness and understanding of the disease.

4.4.2 Insufficient education and awareness of axSpA

The lack of education and awareness of axSpA was also widely observed by patients and HCPs, to the extent that patients are not even aware of the possibility of pain being caused by joint inflammation. Diagnostic delay was in part caused by many patients "just getting on with it", treating or managing, or even ignoring their symptoms themselves for extended periods of time with no suspicion or even knowledge of axSpA, before seeking medical attention as symptoms became worse. Similar behaviour was also shown by Martindale et al (2014), where patients reported feeling resigned about their pain, not suspecting for a long time that it was a sign of something worse than they imagined (Martindale and Goodacre, 2014). As with the sample included in our study, many patients in Martindale's study initially suspected their symptoms to be caused by something circumstantial and inconsequential; it was only the recurrence and worsening of these symptoms which led them to suspect

something more severe. As has been shown by this study, the irregular nature of flares and the insidious nature of symptom development make recognition of these patterns difficult. In both this study and Martindale et al, by the point a great number of patients realised their symptoms were suggesting something quite severe, their disease had become quite advanced; more widespread knowledge of axSpA and its earlier symptoms may reduce diagnostic delay

Many patients stated their GPs and, family and friends were unfamiliar with the condition. This caused confusion and consternation among patients as many other diseases of similar or even lower prevalence were more widely known. This is brought sharply into focus by the 2014 study by van Onna et al, which explored the level of knowledge and experience of Dutch GPs with axSpA. GPs in The Netherlands act in a very similar faculty to those in the UK; they are a gatekeeper to further consultation and management within healthcare. Furthermore, health insurance is mandatory in The Netherlands, so as with the UK, there are no transactive financial boundaries to healthcare. These factors suggest van Onna et al's study is, superficially and within reason, generalisable to the UK and Western Europe. It found that the level of understanding of the disease, its signs and symptoms, its associated risks and appropriate management, were extremely low in primary care (van Onna et al., 2014). The ability to differentiate between inflammatory and mechanical back pain was poor and several HCPs felt they probably missed quite a large number of cases. None reported they would order an HLA-B27 test when presented with chronic back pain and most would order a spinal X-Ray for chronic back pain.

Both groups recognised the importance of information campaigns in the media and online, and awareness of axSpA being raised by public figures such as television personalities and pop musicians. Social media and the internet were seen as a highly potent tool for the spread of information by participants in our study, although the downsides of that were also commented upon, such as the specific nature of audiences using different services. A strength mentioned, however, is that social media is heavily used by younger audiences, in whom raised awareness of axSpA and its earlier symptoms could have a bigger impact. This suspicion is supported by evidence in a 2019 NIHR study into mass-media public health campaigns, which shows some evidence that the greatest impact with regards to behavioural change in the public was in young people (National Institute for Health and Care Excellence [NICE], accessed 2022).

Inundation of information and the possibility of a wave of self-diagnosis was raised as an issue that could result in capacity for referral being undermined. This concern was also raised in a 2014 study (Stack et al., 2014), in which GPs were asked their opinions on campaigns to promote rapid health-seeking behaviour with early symptoms of rheumatoid arthritis (RA). Like axSpA, patients with RA frequently experience delayed diagnosis. The main concerns raised were, as stated above, that a poorly designed awareness campaign could vastly increase workload and strain upon healthcare resources, as early symptoms of RA are quite non-specific; many GPs in that study felt that there was a possibility of an influx of individuals without RA rushing to primary care for consultation, overloading the system. Additionally, concern was raised that

referral pathways could be saturated unnecessarily with new patients if the specifics of early RA symptoms were not sufficiently well communicated. Related to this was the concern that early inflammatory arthritis symptoms were so variable, non-specific and ill-understood that it would be very difficult to focus a campaign such as this one. A poorly designed campaign could end up being irrelevant or unhelpful to individuals with more advanced symptoms and insufficiently informative to those who genuinely have early symptoms of the disease.

These concerns are directly transferrable to any such campaign for axSpA; early symptoms are irregular, non-disease-specific and seemingly unconnected. These concerns do raise possibilities of logical points in the disease course to raise in a campaign. In patients, the two most frequent triggers to consultation were the point at which symptoms, became unbearable or when somebody in their life encouraged them to seek healthcare for their symptoms. Pain was not the first symptom which caused concern for patient. A range of symptoms, such as blurred vision, fatigue, low mood, peripheral pain and reduced mobility were all reported as points at which either the patient or someone close to them felt, “that’s not right”. This period of time between initial rising consciousness of symptoms and patients’ circumstances becoming so unpleasant they seek healthcare would probably be a very beneficial point towards which a campaign’s message could be focused. While such a campaign could never be claimed to be aiming towards a total capture of early undiagnosed axSpA, it would avoid the pitfalls of targeting early symptoms which were so non-specific as to cause the aforementioned consultation deluge in primary care and the potential of overwhelming referral pathways, along with that of targeting patients who already have significant diagnostic delay. While axSpA patients with advanced

disease do obviously require diagnosis and care, targeting them with a campaign such as this would not be a pragmatic approach as the benefit compared to cost outlay of such a campaign would be less than that of a campaign aimed at individuals who have not lived with the disease for long. The previous statement does not, however, dismiss the utility of the method; some patients' diagnosis would still be relatively expedited.

The participants of Stack et al's study gave opinions on what they considered to be, helpful and poor public health campaigns. Features of good campaigns, such as FAST (campaign to raise awareness of signs of stroke) and the CPR awareness campaign is that they used simple, memorable messages and, in the case of FAST, there was a focus on very strong and unmistakable signs. Frustration was raised about a campaign to raise RA awareness, as it lacked specificity regarding location and threshold of symptoms. A campaign held in particularly poor regard was one raising awareness of risk of lung cancer which advised the public to seek a chest X-Ray if they had experienced three weeks continuous cough; the issue held here was that the campaign did not specify the cough had to be of unknown cause. Again, these insights can be integrated into any future planning regarding public health campaigning to raise awareness of early axSpA with the possibility of reducing delay. The findings of Braun et al (2013) and Baraliakos et al (2020) could be implemented here; a public health campaign which raises the public awareness that buttock pain, psoriasis, prolonged stiffness in the morning and family history of axSpA, for instance, as these signs and symptoms have been shown to be efficacious as markers for referral (Baraliakos et al., 2020).

There are currently campaigns to increase the awareness of early axSpA. NASS's 'Act on axial SpA' campaign utilises the acronym "SPINE" as a means of quickly conveying core concepts of axSpA: Symptoms starting slowly, Pain in the lower back, Improves with movement, Night time waking, Early onset (National Axial Spondyloarthritis Society [NASS], accessed 2022). However, as remarked upon in the Stack et al study, they might currently be too non-specific. Many of these concepts are not specific to axSpA however, and in particular the symptom of pain in the lower back which has been shown by Braun et al (2013) to be insufficient to discriminate between early axSpA and back pain from other causes. Future campaigns could take the ethos of this public health campaign, i.e. simple, bold and memorable messaging, while also taking into account the findings of Braun et al and Stack et al. However effectively designed a campaign is, a persistent challenge remains to encourage engagement with the campaign's website for further education and consolidation of understanding. QR codes embedded in printed material is one method which is increasingly used, although it is difficult to project the level of further engagement this leads to (S. Tiwari, 2016). A further challenge is that axSpA awareness may be difficult to justify economically for a public health campaign when extremely common diseases such as stroke and covid or disease with profound personal or population consequences (stroke, HIV respectively) will be given priority.

Aside from simply raising public awareness of the disease, specific education programs were discussed by patients and HCPs, aimed at improving knowledge and competence regarding the diagnosis of axSpA, the timeline of its referral and to whom patients with possible axSpA should be referred. While patients felt HCPs should have their clinical knowledge assessed and education increased, HCPs favoured regular top-up

courses to ensure their knowledge was updated. In-depth education on axSpA in primary care would, however, be logistically unfeasible and produce low benefit for cost; rather, the introduction of simple sets of clinical screening questions that could lead to higher levels of certainty for referral, such as those detailed in Braun et al and Barialikos et al could possibly lead to lowering of diagnosis times for axSpA (Baraliakos et al., 2020; Braun et al., 2013). While this is already suggested by NICE guidelines for the management of SpA, it is only actionable if sufficient clinical suspicion has arisen in the HCP to think to refer to these questions, and as was repeatedly stated by participants of this study, the low level of awareness in the general public and in healthcare of axSpA is a significant issue and cause of delay.

4.4.3 Gender and its effects, both perceived and observed, on delay

Even in cases where axSpA was known to practitioners, many patients described barriers caused by a lack of full understanding of axSpA, its symptoms, development, and associations. In particular many female patients were told it was not possible for them to have axSpA due to their gender. Despite the incidence of axSpA being roughly equal between the sexes, its presentation can be quite divergent; a higher percentage of male patients experiences radiologically visible effects and a higher percentage of female patients experiences the non-radiological disease (Rusman et al., 2018).

Additionally, some HCPs were under the impression that female patients experience longer delay than male patients with axSpA. Though similar beliefs were identified in HCPs from the Netherlands (van Onna et al., 2014), this was not supported by the systematic review within this thesis, which for the most part showed no statistically

significant difference in diagnostic delay between men and women with axSpA. This area of study is by no means settled, however, and while the majority of studies in Chapter 3 showed no statistically significant relationship between gender and diagnostic delay, a recent meta-analysis reports the converse, that men are diagnosed globally 7 months earlier than women (Jovaní et al., 2017). The persistence of this uncertainty supports both further research and education, such as that that suggested by Marzo-Ortega et al in their 2022 paper (Marzo-Ortega et al., 2022). This paper gives a tripartite approach of education, improvement of understanding of differences between genders and the undertaking of gender-stratified trials. Together these methods reduce uncertainty and support a more targeted approach in healthcare. Importantly, they can also be used as the foundation of more standardised and generalisable high quality research; Jovaní et al stated that of the studies included in their meta-analysis, only 40% were of high quality, and as has been shown by the systematic review in this thesis, there is still a high degree of ambiguity regarding the differences between the experiences of male and female patients with axSpA.

4.4.4 Enhancing communications

Improvements to the manner and quality of communication between patients and HCPs were suggested in a number of forms. Advocacy for patients was held to be an important aspect of improving a patient's journey through healthcare; several patients described the benefits of having taken friends and family to their consultations to provide emotional support and also assist with communication with HCPs. The people who accompanied these patients were able to act as a calming influence in the consultation, less effected by the emotional impact of what was being said and its implications. Additionally, they bolstered the patient when they were not feeling

sufficiently assertive. Self-advocacy was strongly espoused by some patients who, through their journeys to diagnosis, came to reject the role of patient as someone taking advice from HCPs and took on an attitude of "not taking no for an answer". They felt their diagnosis was something they fought for personally, and that they had to fight against dismissal, disinterest, and perceived systemic issues in the NHS. Finally, some patients discussed the potential of professional patient advocates being made available within the healthcare setting, who could explain complex medical concepts to patients, explain referral processes and pathways, and keep patients informed of their ability to self-refer or change HCP if that was found to be necessary and appropriate. In addition to ensuring the patient maintains a good grasp of their circumstances and the information on their diagnostic process, a professional advocate could, based on conversations had before their HCP consultation, help the patient describe their symptoms in a way that more precisely informs their HCP of their condition. Such services do already exist and are suggested through the NHS' website, although importantly the services recommended are independent. Such services as The Advocacy People (The Advocacy People, accessed 2022) and VoiceAbility (VoiceAbility, accessed 2022) are not specifically aimed at any patient population, offering services which aid comprehension of healthcare processes, aid communication between patient and HCP and help appeal against decisions with which patients disagree, among other things.

Despite a feeling by many patients in this study that there was very little will in healthcare to appreciate the perspective and insight of patients, many HCPs voiced the opinion that they should and do attempt to as much as possible advocate for and act in the best interests of patients. Davoodvand et al found that the concept of advocacy

also included understanding the patient's condition, showing compassion, taking care of the patient and commitment to completing the care period, all of which were also brought up by both patients and HCPs in our study (Davoodvand et al., 2016).

While not explicitly framed in terms of advocacy, many patients and HCPs spoke of how important it was for HCPs to actively advocate for their patients. Many patients noted that the HCPs who were the most helpful were often the ones who were willing to acknowledge when they had reached the bounds of their knowledge and would seek further opinions or refer the patient. HCPs who didn't underestimate the patients' symptoms or those who displayed a pro-active attitude to problem solving were described in positive terms by patients. It may be that these characteristics are found to be conducive to more useful and in-depth initial enquiry into patients' symptoms. Some HCPs mentioned that ensuring patients' concerns were listened to and that they were well informed through the process of diagnosis was important to them, and several patients spoke in very positive terms about HCPs they encountered who were perceived to have shown particular interest in the patient's diagnosis and being transparent when they had reached the limits of their understanding, necessitating referral. While it appears that the process of diagnosis for axSpA may involve many different HCPs, it was often these HCPs who were felt to actively advocate for their patients which patients associated most with their correct diagnosis and a positive period in their diagnostic journey. A great deal of frustration in the diagnostic process is caused by issues with communication, and this is also reflected in the samples examined by Dube et al and Martindale et al, so focus on professional advocacy could be an area in which considerable tangeable improvements could be made (Dube et al., 2021; Martindale and Goodacre, 2014). With so many patients in

this study reporting difficulties in healthcare due to communication issues, professional advocacy, whether supported by the NHS or by charities, and a promotion of informal advocacy, could be of enormous assistance in reducing delay.

A number of patients expressed a conviction that self-advocacy was a very valuable force in the process towards diagnosis. This was expressed in the positive and negative; some patients recounted how their "not taking no for an answer" led to their being diagnosed while others lamented that their overly deferential behaviour and lack of self-advocacy slowed down their journey to diagnosis. Self-advocacy was strongly encouraged by patients in an American sample described by Dube et al (2021). Tenacity and determination of either the patient or people close to them is attributed to the success of their search for explanations for their symptoms. Similarly in Martindale et al (2014), patients described the challenges involved in being listened to and the struggle they underwent to convey their situation and reach useful results.

4.4.5 The Healthcare System

All participants agreed that there were many issues with the current structure and provision of healthcare which hindered the process to diagnosis. Lack of navigable referral pathways was described by many participants, leading to seemingly aimless journeys through healthcare for the patient, often involving repeated interactions through primary and secondary care which left many frustrated and demoralised.

This problem was exacerbated by issues shared by HCPs, several of whom felt communications were not read when they were passed on, leading to a discontinuous, stuttering, and repetitive process for the patient. The length of time taken for referrals

to be undertaken was raised by HCPs in van Onna et al, in which not only is the suspicion that referrals take too long to be made, but also the admission that this length of time is not known (van Onna et al., 2014). Patients in Martindale et al's study described how this lack of continuity of care during their diagnostic journey led them to have to repeat their symptoms over and over to different HCPs, resulting in reduced motivation to continue their search for a diagnosis (Martindale and Goodacre, 2014). Additionally, the short duration of clinical consultations to adequately explore their problems also precluded the formation of a useful continuous relationship. The requirement to repeat their clinical history in every consultation, was also raised as a concern in Lapane et al (Lapane et al., 2020). In that study, American HCPs remarked that a 30-minute consultation with patients would make a constructive difference to the quality of care given. HCPs in the same study also noted that commensurate diagnostic delay could also arise due to a propensity towards symptomatic treatment rather than a willingness to arrange more complex investigations. This is likely caused in part by the lack of awareness noted previously, along with a reliance on heuristics and personal experience in the process of diagnosis (Mishra et al., 2017). From the patient perspective, being passed between different HCPs and primary and secondary care, along with different, sometimes unhelpful specialisms, resulted in a significant delay on their diagnostic process. Patients described that their GPs would sometimes be resistant to referral and ordering further investigations, which was also found by Martindale et al (2014), where patients described gaining referrals and further investigations as a fight.

4.4.6 Luck

A particularly serendipitous facilitator of diagnosis, stated by several patients, was that of "luck", i.e. the patient's diagnosis being precipitated by a chance meeting of a person or an event. There have been attempts to define luck in medical settings in a quantified way, such as by Prasad (2019); to this author, for an event or outcome to be considered to be either good or bad luck in medical settings, it had to meet three criteria: 1) the occurrence has to be beyond the control of the person to whom it occurred. Actions by the affected individual could not have influenced the way the occurrence took place; 2) the concerned event results from chance or accident; 3) the event has to have been perceived as significant by the individual to whom it occurred (Prasad, 2020).

That many of the patients in this study credited the success of their diagnosis to luck is indicative of four things, which are not mutually exclusive. The first is that as this study recruited the majority of its patient participants through social media and respondents to NASS newsletter advertisements, there may be a self-selection bias towards individuals with more dramatic stories, such as those which involve a high degree of diagnostic delay and an interesting, well rehearsed story. The second implication is that luck is either an extremely common facilitator of final diagnosis in axSpA or that by sheer chance, the participants in this study show unrepresentatively high frequencies of luck being involved. The third possibility is that luck is a narrative tent-pole, and in reality, it played less of a part in their diagnosis than more straightforward process such as gradual understanding and awareness of symptoms followed by a sometimes serpentine route through healthcare. This does not discount the possibility that luck is indeed an important factor in some people's diagnostic journey, but it does

highlight the reality of recalled experience, in that patients in repeating, and to an extent, rehearsing their diagnostic story, might highlight the more entertaining aspects. The fourth possibility is that patients who experience more delay are comparatively more likely to experience chance encounters/circumstances; the more time lived, the greater the likelihood of experiencing serendipitous events.

4.4.7 Misdiagnosis

A number of patients in recalling their diagnostic journey noted that the diagnosis of fibromyalgia complicated their path to axSpA diagnosis, characterising it as a misdiagnosis. While this might be true for some patients, it is not always the case. The overlap in symptomology and the relative frequency of fibromyalgia's comorbidity with axSpA means it is not always a misdiagnosis or misattribution, but sometimes a reflection of the complexity of the condition contributing to the difficulty of its successful diagnosis (López-Medina et al., 2019). The comorbidity of fibromyalgia and axSpA is high, with a recently reporting prevalent comorbidity with the radiographic form of axSpA of 13.8% and 20.3% in the non-radiographic form (Jones et al., 2020). The same review (Jones et al., 2020) reported 1 in 6 axSpA patients met the classification criteria for fibromyalgia.

While fibromyalgia is a complex case and its diagnosis often difficult to extricate from that of axSpA, misdiagnosis is a genuine issue during the diagnosis of axSpA, with Jin et al reporting a third of patients with the radiographic disease experiencing misdiagnosis and two thirds of those with the non-radiographic disease (Jin et al., 2013). Another study found 77% of patients to have received a wrong diagnosis prior to their

diagnosis with AS, with the most frequent being non-specific back pain, degenerative disc disease, rheumatoid arthritis and tuberculosis (Aggarwal and Malaviya, 2009). Seo et al (2015) reported 59% of patients with SpA having received prior diagnoses to their final one, with diseases characterised by mechanical back pain being the most frequent, despite over 90% of their patient sample having inflammatory back pain. While these figures, in addition to the patient reported misdiagnosis, do point towards a need to raise awareness and improve education about axSpA, it is important to note that many of the above diagnoses may not be entirely erroneous. It is feasible that in many cases they are occurring simultaneously with axSpA, which raises the importance of continuing to investigate beyond an initial diagnosis if treatment is not as effective as might be expected.

4.4.8 The Diagnostic Journey and Mental Health

In addition to the data provided directly regarding barriers and facilitators in the diagnosis of axSpA, other concepts arose from the interviews which suggest the need for future research and reinforce the importance of qualitative research into diagnostic delay in axSpA.

Concerns which initially seem ancillary are of critical importance here: the effect of diagnostic delay on mental health. Many patients in this study reported a negative effect on their mental health of diagnostic uncertainty, a feeling of not being taken seriously by HCPs and the length of time taken to reach any conclusion regarding their symptoms. The data from this study suggests diagnostic delay causes psychological distress to the extent of suicidal ideation. Negative effects on mental health by the

symptomology of axSpA and the extended period of uncertainty and frustration prior to diagnosis is clearly the subject of conversations of a vital nature. Not only is the intrinsic danger of negative mental health effects of symptoms and healthcare shortfalls obviously something which needs addressing in healthcare and wider society, there is the more specific possibility that it is creating feedback mechanisms that could worsen the situations causing diagnostic delay and worsening disease presentation and coping mechanisms. It is here only addressed obliquely as the discussion of mental health is not within the remit of the research question, which focused specifically on barriers and facilitators in diagnosing axSpA. While the possibility remains that it is a causal or at least compounding factor in diagnostic delay, to make this point would require rational extrapolation bordering on assumption, which I was not willing to make.

This is of high relevance and is supported by patient voices from Martindale et al (2014), describing depression, annoyance and feelings of social stigma resultant of attitudes of HCPs, a lack of progress towards useful answers and a feeling that the system was not a caring one. Patients participating in Dube et al (2021) also described frustration and mental suffering during their journey towards a diagnosis.

Not only is this negative effect on mental health of concern in its own right, it could be a cause for further delay in some patients. Psychological effects such as anxiety and depression could lead to patients not consulting with their symptoms. Additionally, they could undermine capacity for trust, a phenomenon explicitly communicated by patients in the present study; some described having had enough of being dismissed. Patients reported being led to doubt themselves and some experienced a degree of

depression that caused them to lose the motivation to seek further help until their physical symptoms worsened, sometimes catastrophically. This undermining of motivation to obtain a diagnosis is present in Martindale et al (2014) and could conceivably be not simply an impediment to further consultation, but also to willingness or even ability to take in positive messaging and advice from any planned public health campaigns designed to alert possible axSpA patients to their condition.

4.4.9 A Note on Transferability

While a substantial portion of the themes which arose from this study are specific to axSpA, such as the complexity of axSpA as a diagnosis and the lack of regularity in its presentation, there are elements which reflect problems in health-care and management of lifelong and invisible diseases on a wider scale. Of particular note are the issues of communication and the issues raised with regards to referral and the time available for consultation in primary care. The problems of healthcare provision in the UK are well appreciated and as of 2023 entirely pervasive; 1 in 5 patients surveyed reported that after being referred to specialist care by GP, they were "bounced back" to primary care (Healthwatch.co.uk, 2023), and time spent in consultation with GPs is too short to elaborate on more complex symptomologies (Salisbury, 2019). This has already been discussed to an extent in this chapter.

Of further note, however, is the similarity of accounts of patients with axSpA of their interactions with primary healthcare and those of others with so-called "invisible diseases", i.e. diseases which show little outwardly obvious presentation but which nonetheless have a profound effect on the life of the patient. The struggle to be taken seriously or even to be listened to experienced by axSpA patients echoes the situations

described by patients with other diseases such as chronic fatigue syndrome and long covid. As with patients with axSpA, people with these conditions face a range of reactions through from mild scepticism or incredulity all the way through to suspicion and accusatory behaviour (cambridgechildrens.org.uk, 2022; Ireson et al., 2022; Pilkington et al., 2020). While the commonness of these complaints could be seen negatively, it is also a signpost to a positive possibility. Many of the approaches suggested in this study for improving the process of diagnosis for axSpA could be applied more widely and could help a greater number of people beyond axSpA. A reasonable extrapolation from the theme raised in this study of raising awareness of axSpA would be raising awareness of invisible disability and invisible diseases; while Occam's Razor must tend to apply, a heightened societal understanding that people's experiences may, and often do, stretch beyond the immediately obvious will lead to more exploratory and less dismissive mindsets becoming normalised in and outside of healthcare.

4.4.10 Study Strengths and Limitations

4.4.10.1 Strengths

The main strength and novelty of this study is that it is the first qualitative study in the UK to collect data from both patients and HCPs regarding barriers and facilitators in diagnosing axSpA. The data presented here show there is a great degree of agreement between patients and HCPs on the issue. This study also goes further than the majority of qualitative reporting on the subject of the diagnostic journey, not only focusing on barriers to diagnosis, but also asking of patients and HCPs what, from their perspective, can be improved based on their experiences. Working within the

phenomenological paradigm, focusing on the personal perspectives of patients and HCPs, led to some potentially useful insights which suggest further exploration.

Regarding the recruitment of HCPs for the study, the majority of those included were representative of clinical areas most commonly involved in the management of individuals with axSpA, resulting in rich and useful data. Regarding patient recruitment, the patient sample was not geographically limited; recruitment covered the whole UK, widening the potential for regional representation and lowering the possibility that results were characterised by geographical idiosyncrasies.

4.4.10.2 Limitations

4.4.10.2.1 Covid19

The most substantial possible limitation of this study is the change in recruitment and data collection methods due to the COVID19 pandemic. Due to the necessity for social distancing in 2020, the initial plan for focus groups held with patients was replaced with telephone interviews, and all planned in-person interviews with HCPs were replaced with telephone interviews and interviews held over MS Teams. Additionally, the recruitment method for the study was altered to more heavily rely on patient self-selection via social media, where originally it was intended that the majority of patients would be selected by rheumatologists at the Haywood Hospital during consultation. While it is impossible to reach concrete conclusions about what differences these changes to method had on the results of the study, some suppositions can be made.

The change from focus groups to interviews for patient participants altered the means by which data was collected from patients in this study, which likely had a limited

impact. Having had opportunity to discuss this with researchers and PPIE representatives, on balance the change does not seem likely to be a limitation. Focus groups might help patients "open up" about their experience as the conversation progresses, resulting in more, rich data from quiet participants. When raised with a PPIE representative however, this was strongly refuted; while focus groups certainly do encourage discussion, it can become performative, practiced, exclusionary and unavoidably each participant has less time to speak than during a one-to-one interview. The aforementioned PPIE representative stated they believed interviews allow for the participant to take more time in "opening up", potentially in a safer and less judgemental environment which can be improved by the development of interviewer/interviewee rapport.

Edley and Litosseliti (2010) describes how focus groups, along with the above criticism, can also be influenced by the emergent group dynamic, with participants becoming deferential toward more dominant personalities, possibly even to the extent of changing their outlook (Litosseliti, 2010). If members of the focus group know each other, this can also have effects; familiarity can both undermine or exaggerate self-expression. The same authors do suggest positives of focus groups, however, such as the possibility of very dynamic conversation taking place, leading to unpredictable and unique insights. This aspect of focus groups does point to another of note: that the interviewer themselves may lose some control over the narrative and research focus of the data collection (Litosseliti, 2010). While this might seem to suggest that semi-structured interviews are preferable for conversations regarding personal experiences about which specific beliefs and knowledge are sought, it is important to note a further note of caution. While focus groups may reduce an interviewer's control over

the narrative and research focus of the interview, so a semi-structured interview, if not handled correctly, may result in overly directed data collection and analysis(Pope and Mays, 2006). In the context of the present study, while the choice of either focus group or semi-structured interview would inevitably have altered the output data, when handled in a considered way and with focus on the possible role of the interviewer, neither would have negatively affected the output.

Easier to describe are the possible outcomes of the changes to recruitment strategy, where some outcomes are actually implied in the characteristics of patients. It is possible the recruitment being altered from being led by HCPs at the Haywood Hospital to focusing on advertising through the NASS newsletter and through posts on social media led to a change in the demographic of participants for the study, and this has some important possible commensurate effects. Recruiting this way may have resulted in a sample of participants who are younger and more IT literate than if recruitment had taken place through Hospital clinic lists, which will have had an effect on the data collected in this study; this may have been slightly mitigated however by diagnosis post-2009 being an eligibility criterion.

It is noteworthy that the diagnostic delay found in this patient sample is significantly longer than found in the wider population, which suggest two possible interacting causes. Firstly, it is possible that, as the reliance on social media and advertising through NASS' newsletter led to a far greater degree of self-selection for this study, this then resulted in a bias in this study towards patients who had experienced a worse than average experience. It could also simply be a result of a small sample coincidentally comprised of outliers, but a counterargument to this possibility is that Dube et al (2021) and Martindale et al (2014) both reported longer than average

diagnostic delay in their samples (12 years and 10.1 years respectively); this implies it is a selection bias of smaller qualitative studies. As this issue is not specific to the situation caused by COVID19; however, it will be continued in the following section on recruitment.

4.4.10.2.2 Recruitment Strategy

The mode of patient recruitment for this study relied predominantly upon self-selection, which can lead to a sample bias. Of note is that patients with longer diagnostic delays and more negative experiences of the diagnostic journey could be more likely to self-select for involvement in studies. This is described by the negativity bias, whereby negative experiences more significantly influence one's recollection and therefore sway more people with negative experiences towards public comment. In a systematic review of reasons for participation in studies, altruism was found to be the second most likely cause for participation (after perceived personal gain) (Sheridan et al., 2020). It is therefore feasible that while negative experiences increase likelihood of self-selection, the underlying motivation for participation could be altruistic, in that. participants want to avoid their experiences occurring for others, and this sentiment was voiced by several patient participations among the opening and closing sections of their interviews.

Another issue arising from the level of self-selection for this study is it created issues regarding certainty of information power. While the themes identified in this study were well populated with data from participants, with many conversational points being repeated by many different participants, it is possible that subjects were missed

or among underserved populations such as those not typically well represented in qualitative research such as those of low socioeconomic status or less well represented minorities. This is, however, a possibility with all qualitative research, and indeed all research in general; it is impossible to know whether the point at which recruitment is completed is excluding participants who could have instigated whole new areas of investigation. However, the repetition of themes provides confidence that this study reached a good level of information power.

Another possible limitation of the recruitment strategy for this study was the larger prevalence of female participants. When it became apparent that female participants outweighed male participants, a second round of patient recruitment was undertaken, with some limited success. The disparity between male and female patients in the study is unfortunate, as greater equality would have been desirable, but considering the large historic focus on male patients with axSpA, there is benefit to be able to present a female perspective.

4.4.10.2.3 Conceptual Limitations

Also worth considering is the concept of "initial symptoms", their presence as the beginning of diagnostic delay and implications regarding their time of occurrence along a patient's life-course. From the patient perspective it was challenging to define the point at which earliest disease was recognisable. While many had working theories as to a trigger event, these were frequently offered up with the disclaimer that it was not possible to be sure. There is also the possibility of recall bias effecting the accuracy of self-reported initial symptoms. Recall bias is possible inaccuracy in data caused by

vague or inaccurate participant recall of the subject of study, and it increases with elapsed time (Althubaiti, 2016).

These observation is not intended to critically undermine the widely accepted definition of diagnostic delay being the time between reported symptom onset and diagnosis with axSpA; more so it is a caveat which must be taken into account when interpreting data and studies on diagnostic delay, and one which puts particular significance on the means by which the first instance of symptoms is recalled and reported. The period of "patient delay" is unavoidably far vaguer than periods of healthcare delay, i.e. the delay between first consultation and referral to secondary care, or the period between referral to secondary care to diagnosis and/or treatment, but this does not lessen its significance. It does, however, suggest that where possible, quantitative studies into diagnostic delay should break down the delay reported by patients into patient and healthcare delay as: 1) this ensures a portion of delay is quantifiably accounted for, i.e. the healthcare delay, 2) it lessens possible vagueness regarding the actual length of diagnostic delay, particularly in demographically and geographically diverse samples and 3) the degree of patient delay, and associations with demographic and clinical characteristics are of interest and import. Obtaining more data on this area would help determine where the extent of delay lies and would help show when and where improvements have been made.

Additionally, many of the patient participants' earliest identified symptoms were in their teenage years, at which point the diagnosis of axSpA would possibly be problematic and treated more accurately as enthesitis related juvenile idiopathic arthritis (JIA) or something similar at the time, with no full guarantee upon that

diagnosis that development into axSpA was inevitable (Colbert, 2010). However, as the patient experienced symptoms in their adolescence that seem contiguous with those which resulted in an adult axSpA diagnosis, there is an argument to be made that this does count towards the lifespan of their disease. Although they would not have been given a diagnosis of axSpA as adolescents, it is entirely possible that investigations for spinal inflammation (MRI) would have been positive in some patients if undertaken even at this developmental stage. It would not then be accurate to simply "start the clock" on their diagnostic delay at age 18, as this would be wilfully ignoring prior and possibly related symptoms. As with the patient delay issue detailed above, this issue does not fully undermine the narrative of diagnostic delay stretching backward into adolescents, but it does suggest that at the very least this is a concern which must be explicitly stated in cases where these patient circumstances are presented.

4.5 Conclusion

This study demonstrates that there are considerable communicative, systematic and educational barriers to the timely diagnosis of axSpA, and also presents means by which these areas can be improved and other ideas for interventions which could possibly reduce diagnostic delay. On barriers to diagnosis, there was a notable level of concordance between the experience and opinions patients and HCPs, despite their differing modes of communication. Encouragingly, there was also a considerable amount in common between patients and HCPs when discussing facilitators of diagnosis.

This study shows that building on and diversifying the work already in progress to improve education about axSpA and raising awareness of the disease is an approach with enthusiastic support among the patient and healthcare communities. Further work and research in these areas could work well towards alleviating the current state where patients are waiting too long to receive diagnosis of axSpA.

Chapter 5 – Consultation Patterns Prior to Diagnosis with Axial Spondyloarthritis: A Case-Control Study

This chapter reports a case-control study examining differences in consultation types and frequencies between patients diagnosed with axial spondyloarthritis and matched controls without the diagnosis. All patients were registered with North Staffordshire general practices. The clinical and research implications of these results are then discussed.

5.1 Introduction

The systematic review in Chapter 3 found that the extent of diagnostic delay in axial spondyloarthritis (axSpA) remains prolonged, at between 2 and 5 years for the majority of people. Though many of the studies included in the systematic review reported associations between specific patient- or healthcare-related factors and diagnostic delay of the disease, there was an insufficient number of repeated studies for the majority of factors to clearly determine their role in any subsequent diagnostic delay. Additionally, most of the included studies were unable to determine when factors affecting the time of diagnosis occurred.

Of further note is that the data reported in the systematic review was mainly representative of secondary care, where the majority of management of diagnosed axSpA takes place. However, primary care is the main gatekeeper of referral to secondary care and specialised services, and it is the period between symptom onset and referral from primary to secondary care which comprises the vast majority of the

period of diagnostic delay; pre-referral delay has been reported as ten times longer than the period between referral and diagnosis (median 307 vs 28 days, respectively)(Deodhar et al., 2016).

The qualitative component of this thesis (Chapter 4) then presented further evidence of the experiences of patients prior to diagnosis, including reasons for consultation prior to diagnosis, such as chronic and acute pain, eye problems and fatigue. These new data, along with the above points regarding the systematic review highlight a need to examine this pre-diagnosis period of patients' healthcare journey to gather data which can be used to expediate diagnosis by providing further information to raise axSpA suspicion in primary care and speed up appropriate referrals.

Various conditions have been shown to precede a diagnosis of axSpA in patients, such as uveitis, psoriasis, enthesitis and inflammatory bowel disease (Sieper *et al.*, 2015). AxSpA diagnosis has also been reported to be preceded by several common misdiagnoses, such as osteoarthritis, rheumatoid arthritis and lumbar disc herniation. It is worth noting these are classed as misdiagnosis when the original diagnosis is superseded by a diagnosis of axSpA; co-existence of these diagnoses is possible (Aggarwal and Malaviya, 2009). The results of Chapter 4 reveal that patients experience their symptoms being described in a myriad of different ways on their route to diagnosis, such as growing pains, pregnancy, menopause, sciatica, fibromyalgia and wear-and-tear.

Whilst previous studies show overall associations of these factors with axSpA, more clarity would aid signposting for future practice and research aiming to improve the diagnostic journey. This can be achieved by collecting data on consultation types

(observations, diagnoses) and rates in the primary care setting prior to diagnosis. As shown in Chapter 4, patients have to repeatedly consult their GP, and sometimes several GPs, before being referred to secondary care and finally specialist rheumatology care. Many HCPs spoke candidly about how difficult axSpA is to distinguish amongst the far larger population of patients presenting with symptoms such as back pain and fatigue due to other reasons. Examining primary care consultation data will give insight into what factors may be associated with the suspicion of axSpA in primary care, facilitating earlier and more reliable referrals for diagnosis.

Research has been undertaken into "prodromes" (symptoms prior to diagnosis that are indicative of, or associated with, the diagnosis in question (e.g. Muller *et al.*, 2019)) of other inflammatory conditions. For Rheumatoid Arthritis (RA), data from the Clinical Practice Research Datalink (CPRD) was used to examine the extent of associations between consultations for particular symptoms and subsequent diagnosis of RA, providing signposts for primary care HCPs and indicating whether a patient should be referred to a rheumatologist. Such signposts would be invaluable for potential patients with axSpA, as currently their journey to diagnosis are being slowed down by misdiagnosis, lack of awareness in primary care and lack of clarity regarding symptoms and development in axSpA (Ogdie et al., 2019).

Several studies have examined consultations prior to diagnosis of axSpA which utilise large electronic health record (EHR) databases (Deodhar et al., 2020; Kennedy et al., 2021; Sengupta et al., 2022; Zhao et al., 2019a). These studies investigate means of prediction of possible axSpA using machine learning to help analyse primary care data

and report several features and variables which could be of use for primary care HCPs. Further understanding of consultation frequencies and associations prior to diagnosis variables which are associated with the established disease can bring a further appreciation of the journey to diagnosis. It can aid the pattern recognition of HCPs and show whether commonly associated comorbidities and symptoms are evident prior to diagnosis.

Case-control studies using EHR databases such as this can show associations between clinical presentations, consultation frequencies and diagnosis with axSpA, as has been achieved by Muller et al (2019) in a study of prodromes of rheumatoid arthritis, which used CPRD (Muller et al., 2019). Results of this type of study can act as useful signposts for clinicians to raise their suspicion that a patient may have axSpA.

In brief, understanding the symptoms with which patients present to primary care prior to having an axSpA diagnosis, along with patients' frequency of consultation, may present opportunities to identify patients earlier in the disease course. Further research is therefore required to determine the patient factors and health-seeking behaviours that occur in primary care prior to a diagnosis of axSpA in well-defined and generalisable population using high quality, validated data, as held in the electronic health record (EHR) database, the Consultations in Primary Care Archive.

5.1.1 Aims and Objectives

The aim of this study was to investigate whether primary care consultation history differs between people subsequently diagnosed with axSpA and demographically similar people who do not receive this diagnosis.

The objectives were:

1) to examine the reasons for primary care consultation using the Read codes recorded for patient consultations in the time prior to their axSpA diagnosis, compared to those with no axSpA diagnosis.
2) to compare rates of consultations prior to diagnosis to ascertain whether they change over time compared to consultation rates of control patients.

5.2 Method

5.2.1 Study design

This was a case-control study which ascertained consultation rates of patients with axSpA compared to matched, non-axSpA patients. The study also investigated associations between specific health conditions and symptoms with a subsequent diagnosis of axSpA.

5.2.2 Study Population

Patients with axSpA were identified within the Consultations in Primary Care Archive (CiPCA), an EHR database of consultation records from 14 general practices in North Staffordshire, with a dataset spanning from 2000 to 2016. Consultation data in this context are data recorded by primary care clinicians, predominantly GPs, on characteristics and reasons for a patient's consultation, such as their symptoms or diagnoses, but also administrative details pertinent to their consultation, and results of examinations and tests they might have required.

The data are of a high quality; involved practices are annually assessed and trained in morbidity coding and an estimated 93% of doctor contacts at these practices are given a diagnosis code or a symptom code (Porcheret et al., 2004). Prevalence figures for musculoskeletal conditions in CiPCA are comparable with those found in larger national databases such as the Royal College of General Practitioners Weekly Returns Service (RCGP WRS) (Jordan et al., 2007). Observations in CiPCA are coded as Read codes, hierarchically arranged alphanumeric codes which can be used to supply a variety of information about patients including, most importantly for this study,

diagnoses, symptoms and test results (Booth, 1994). Read codes were adopted in 1988 by the RCGP and the British Medical Association (BMA). The hierarchy of the ankylosing spondylitis Read code operates as so:

- N…. – Musculoskeletal and connective tissue diseases
    - N100. – ankylosing spondylitis

Read codes were retired from widespread use in primary care in 2018 and replaced by SNOMED codes, but this does not affect their use here, as CiPCA data ranges from 2000 to 2016 and is held at Keele University. The data is pseudo-anonymised.

5.2.3 Clinical outcome

As patients who meet the current ASAS criteria for axSpA (M. Rudwaleit et al., 2009c, 2009a) are likely, historically, to have received alternative diagnostic labels to indicate axial inflammation, this study incorporated a number of Read codes to define axSpA; this list is based on previous research at Keele University using CiPCA (Ahmed et al., 2016), Keele University's Medical Record Data Research website (Keele University, accessed 2021) along with conversations with clinicians with a clinical interest in axSpA. The list is as follows:

- Axial spondyloarthritis (N11F)
- Ankylosing spondylitis/Marie-Strumpell spondylitis (N100)
- Inflammatory spondlyoarthropathis (N10)
- Sacro-iliitis (N102)
- Reactive arthropathy of the sacro-iliac joint (N01wA)
- Other specified inflammatory spondylopathies (N10y)

- Other inflammatory spondylopathies NOS (N10y0)
- Other inflammatory spondylopathies NOS (N10yz)
- Spondylitis NOS (N10z)

To address the objectives of this project, a case-control study was conducted within the CiPCA database. A case-control design allows examination of associations between exposures and outcome by comparison between a group of individuals selected for a specific outcome, described as cases, and a matched group of individuals who do not have the outcome, the controls. For this study, the outcome is the diagnosis of axial spondyloarthritis. The exposures can be symptoms, other diagnoses, and test results which have been shown in prior studies to be associated with axSpA. This study examined whether these exposures were significantly more likely to occur in patients who were subsequently diagnosed with axSpA than those without axSpA. Using the same data, the association between frequency of consulting healthcare and diagnosis with axSpA was also investigated compared to those with axSpA.

The case-control study design is ideal for retrospective observational studies as, unlike with prospective cohort studies, the presence of individuals having experienced the outcome in the population has already occurred. This means no data collection is necessary so data can be accessed promptly, study costs are therefore reduced, and the sample size is clear at the outset of the study, allowing for close matching. There is also no risk of loss to follow up, which could occur for cohort studies. A retrospective cohort study could solve the latter problem, but not the first; without a matched

control group, the only calculation for association are between presence or lack of covariates, a limitation also of cross-sectional studies.

5.2.4 Clinical Exposures

Below are the groups of clinical exposures included in this study for analysis (Appendix 5.1). These exposures were based on other studies into axSpA and conversations with axSpA-interested clinicians.

- Axial features: Axial features included all axSpA-related symptoms which involved the spine (cervical, thoracic, and lumbar), sacrum and buttocks.
- Peripheral features: Peripheral features were all those associated with axSpA which affected joints and areas not focused on the axial skeleton. This included the shoulders, hips, legs, hands, and feet.
- Enthesitis: This group included enthesitis, bursitis, tendonitis, and synovitis.
- Sleeping problems: All relevant sleep problems were included in this group.
- HLA-B27: This included the codes for HLA-B27 positivity and negativity, as well as those for the HLA-B27 test.
- Uveitis: This included the codes for uveitis and iritis.
- Psoriasis: This group included psoriasis and psoriatic arthritis.
- Fibromyalgia: This group included the code for fibromyalgia, and a collection of related codes for related fatigue.
- Fatigue: This group encompassed several codes for fatigue

- Inflammatory bowel disease: This group was made up of three codes; one for IBD overall, then ulcerative colitis and Crohn's disease.
- Cramps: Cramps are often experienced with axSpA. This was a small group of three Read codes related to cramps.
- Mobility: This group listed measures of mobility through to chronic disability.
- Raynauds: Raynaud's phenomenon is often associated with inflammatory arthritis and presents as blanching of the skin of the hands.

5.2.5 Study sample

Cases were defined as individuals in CiPCA over the age of 18 and with one or more of the above outcome codes in their record. Cases were matched to controls by age within a five- year band (30-35, 36-40 etc), gender, and GP practice in a 4:1 ratio, as per recommend practice (Coggon et al., 2003), as matching cases with greater than four controls confers very little increase in statistical power. Both cases and controls needed to have consulted their GP between the years of 2000 and 2016, i.e. between the time of the earliest data in CiPCA and the most recent data extraction. The date of a patient's first axSpA code was defined as the index date and their matched controls were assigned the same index date. Cases and controls needed to have at least one year's worth of available data, one year before index date, so diagnosis of axSpA was actually included from 2001 onwards.

5.2.6 Data Request

A request for data was sent to the data manager for CiPCA at Keele University, Mr James Bailey, who reviewed it and advised upon changes required; it also underwent an internal peer review process. The data request was also reviewed by Dr James Prior, Prof Sarah Ryan, Dr Jon Packham and Prof Christian Mallen.

5.2.7 Data and Database Construction

Data were returned as .txt documents containing tab-delimited formatting, compatible with Stata 17.0, a statistics software package developed by StataCorp. The data were split into six files, three specific to the study cases, two specific to controls and one showing data of controls matched with their associated cases:

- Case patient data, which detailed the demographic and diagnostic details for the cases
- Case consultation data, which detailed the consultations prior to diagnosis for patients, and their reasons
- Case referral data, which detailed cases' onwards referral
- Case and control data, which detailed demographic data for the controls and the cases to whom they were matched
- Control consultation data
- Control referral data

Prior to analysis, the data received from the data manager were organised such as they were appropriate for analysis. The process of data cleaning, after importing the data into STATA 17, involved the following major steps:

- All variables were standardised across datasets. For example, unique patient identifiers across case and control patient data and their consultation data were all standardised as 'patid'.
- All dates contained within the data were converted from 'string' format (free text) to STATA's date format.
- Index dates were created to correspond with the diagnosis dates of the cases to which controls were matched.
- Any consultations which were erroneously entered as occurring before date of registration or after index date were removed.
- Case and control patient data were merged, and the variable "case" was created, which noted "0" for control and "1" for a case.
- Case and control consultation data was imported, appended together and all but the following variables were dropped.
    - Patid (patient identifier)
    - Readcode (observation Read code)
    - Effectivedatetime (observation date)
    - Event_type (type of observation. Only three types were allowed into the analysis due to their relevance: observation, test result and NULL, which was frequently found to be an observation).
- Patient data was merged with consultation data.

- Variables were created for consultations across all time and consultations within a year of index/diagnosis date.
    - These variables were binary, i.e. 1 to indicate a consultation and 0 showing the lack thereof.
- Read code data split into groups related to the ASAS classification criteria were merged into the dataset, creating a wide dataset which facilitated analysis.

5.2.8 Frequency of Consultations Prior to axSpA Diagnosis

In addition to searching for associations between reasons for consultation and axSpA diagnosis, this study also aimed to examine whether consultation frequency, regardless of the nature of consultation, was associated with diagnosis of axSpA. A notable difference between frequency of consultations in cases and controls would give primary care clinicians another feature on which to base suspicion of the possibility of axSpA in a patient. Consultations were counted in two ways. Firstly, average number of consultations in cases and controls were calculated for all available time and within a year of index date, giving a number which within this study sample was directly comparable, but not generalisable beyond this study. Secondly, consultation rates were calculated for the cases and controls to give a number which could be generalised to the wider population and compared to other studies using comparable methods but with different time periods and population sizes. The larger rate was divided by the smaller rate to provide a rate ratio describing the difference in consultation rates between cases and controls. The length of time of one year was

chosen as this is seen as the length of time beyond which a diagnosis of axSpA can be considered delayed, based on the current definition held by the National Axial Spondyloarthritis Society (National Axial Spondyloarthritis Society [NASS], accessed 2022).

5.2.9 Analysis

Analysis took place in STATA 17, software which allows for statistical analysis and visual representation of data (https://www.stata.com/). Frequencies were calculated for consultations, defined in this study as "observation" (in which diagnosis or presenting characteristic were noted), "test result" (which showed the occurrence of a clinical test) and "NULL" (undefined, very frequently contained observation and test result data); for each individual, only one consultation was considered per day, as it was their attendance to healthcare that was of interest at this stage of analysis, rather than the specific circumstances. This stage of analysis aimed to show whether patients who were diagnosed with axSpA consulted with greater frequency over their whole time registered prior to diagnosis, and also whether their frequency of consultation increased prior to diagnosis. Initially, averages of the counts of consultations for cases and controls were calculated to give directly comparable numbers within this study. These averages were calculated over all registered time and within a year of index date.

To ensure useful comparability between different individuals who all had varying lengths of registered time prior to index date, and to give a measure which could be generalised to the wider population and compared with other studies on other populations and differing time-periods but similar methods, consultation rates were

calculated. This first required calculation of patient years for all patients, which is the sum of the time between earliest date and index date divided by a year. Using patient years, rates of consultations were calculated for cases and controls over all time and within a year of index, with confidence intervals also calculated to quantify accuracy of estimates. This comparison between all time and a year was chosen in favour of several time-periods due to the small sample size of this study. Rate ratios between cases and controls were then calculated by dividing the case incident rate by the control incident rate to show the comparison between cases and controls. Again, 95% confidence intervals were calculated.

To calculate the association between types of consultation (observations as grouped above; axial, peripheral etc) and diagnosis of axSpA, conditional logistic regression (CLR) was used. Conditional logistic regression is of use when a study matches cases with controls and quantifies the association between exposure and an outcome (Breslow et al., 1978). CLR was used to show association between consultation types over a patient's whole recorded time prior to index date, and in the five years prior to index date. Analysis over all time and in one-year increments over five years was undertaken due to the inclusion of a large number of variables; despite the small sample size, it was considered prudent to explore back from index until no change was consistently evident. In the case of this study, this occurred at four years and five years prior to index. Results are presented as odds ratios with 95% confidence intervals.

Sub-group analysis was also undertaken to calculate association between types of consultation and diagnosis of axSpA by sex, over all time and within a year of index. Additionally, sub-group analysis was undertaken to show the rate ratio between male

and female cases, and cases and controls by sex. Rate ratio between sexes was also calculated for controls alone, as a comparator.

5.3 Results

5.3.1 Descriptive Characteristics

289 patients diagnosed with axSpA were identified in the CiPCA database, 56% of whom (n=162) were male and who had a mean age of 50.9 years (SD 16.3). These were matched to 1156 controls. Due to matching, 56% of these were also male (n=648) and the average age was the same as the cases, at 50.9 years. The age category with the highest percentage of the sample was 36-40, making up 12.5% of both cases and controls (cases n=36, controls n=144), while the lowest was 81-85 comprising 2.4% of the sample (cases n=7, controls n=28).

Table 5.1 Patient Characteristics

	Cases (n=289)	**Controls (n=1156)**
Age (mean)[1]	50.9 (SD 16.3)	50.9 (SD 16.6)
Age (range) *n (%)*[1]		
18-25	14 (4.84)	56 (4.84)
26-30	15 (5.19)	60 (5.19)
31-35	21 (7.27)	84 (7.27)
36-40	36 (12.46)	144 (12.46)

41-45	30 (10.38)	120 (10.38)
46-50	33 (11.42)	132 (11.42)
51-55	33 (11.42)	132 (11.42)
56-60	32 (11.07)	128 (11.07)
61-65	23 (7.96)	92 (7.96
66-70	14 (4.84)	56 (4.84)
71-75	11 (3.81)	44 (3.81)
76-80	11 (3.81)	44 (3.81)
81-85	7 (2.42)	28 (2.42)
>86	9 (3.11)	36 (3.11)
Gender (m)	162 (56%)	648 (56%)

1 Age at patient diagnosis date for cases and index date for controls

5.3.2 Consultation Frequency

5.3.2.1 All Cases and Controls

Consultation frequencies were calculated for both cases and controls, showing cases to have consulted on average 45.3 times across their registered time prior to diagnosis with axSpA and controls to have consulted on average 35.6 times before index date. Calculated consultation rates were 10.3 per 100 patient years for cases and 9.9 for controls. The ratio between these two consultation rates was 1.04, with a 95%

confidence interval of 1.02-1.06, showing the consultation rate of cases was 4% higher than that of controls, with this difference reaching statistical significance.

In the year prior to index date, cases consulted an average of 11.31 times (consultation rate 2.6, 2.5-2.7) and controls consulted an average of 7.3 times (consultation rate 2.04 per 100 patient years, 95% CI 1.9-2.08). The rate ratio for the year prior to index was 1.27 (95% 1.22-1.32), showing a greater disparity between consultation rates of cases and controls than over all recorded time, which consultation rates for cases 27% higher than controls (Tables 5.2 & 5.3).

Table 5.2 Average consultation numbers for cases and controls

	Mean consultations (SD)	
	Cases	Controls
Full EHR record	45.3 (60.1)	35.6 (50.7)
1 year prior to index date	11.31 (9.11)	7.3 (8.31)

Table 5.3 Consultation Rates for Cases and Controls[1]

	Consultations rate per 100 py (95% CI)		**RR (95% CI**
	Cases	Controls	
Full record	10.3 (10.15-10.51)	9.9 (9.85-10.04)	**1.04 (1.02-1.06)**
1 year prior to index date	2.6 (2.5-2.7)	2.04 (1.9-2.08)	**1.27 (1.22-1.32)**

5.3.2.2 Sub-group Analysis: Female and Male

Sub-group analysis showed significant differences in the consultation behaviours of male and female patients. Average mean consultations for male cases in the year prior to index were 1.8 times higher than those of male controls, while in the same time period, female cases had only 1.3 times as many consultations.

Table 5.4 Average consultation numbers for female cases and controls

	Mean consultations (SD)	
	Cases	Controls
Full EHR record	66.61 (73.51)	53.25 (58.83)
1 year prior to index date	12.62 (9.45)	9.41 (9.05)

Table 5.5 Average consultation numbers for male cases and controls

	Mean consultations (SD)	
	Cases	Controls
Full EHR record	28.08 (39.23)	21.84 (37.93)
1 year prior to index date	10.26 (8.72)	5.65 (7.27)

Over all time, male cases consulted 18% less than female cases, and in the year prior to index, male patients consulted 58% less than female cases. Male controls consulted less than female controls, but not by the same amount as found in cases (15% over all time, 43% in the year prior to index).

Table 5.6 Rate Ratios Between Female and Male Cases

	Consultations rate per 100 py (95% CI)		**RR (95% CI)**
	Female	Male	
Full record	9.69 (9.69-9.89)	11.81 (11.47-12.17)	**0.82 (0.79-0.85)**
1 year prior to index date	1.83 (1.74-1.92)	4.32 (4.11-4.53)	**0.42 (0.39-0.45)**

Table 5.7 Rate Ratios Between Female and Male Controls

	Consultations rate per 100 py (95% CI)		**RR (95% CI)**
	Female	Male	
Full record	9.42 (9.31-9.53)	11.11 (10.93-11.30)	**0.85 (0.83-0.87)**
1 year prior to index date	1.66 (1.62-1.71)	2.87 (2.78-2.97)	**0.57 (0.56-0.61)**

When cases and controls were compared within sexes, the increase in rate ratio in the year prior to index was more substantial in male cases than in female cases.

Table 5.8 Rate Ratios Between Female Cases and Controls

	Consultations rate per 100 py (95% CI)		**RR (95% CI)**
	Cases	Controls	
Full record	9.69 (9.5-9.9)	9.42 (9.31-9.53)	**1.03 (1.00-1.05)**
1 year prior to index date	1.83 (1.04-1.16)	1.66 (1.62-1.71)	**1.09 (1.04-1.16)**

Table 5.9 Rate Ratios Between Male Cases and Controls

	Consultations rate per 100 py (95% CI)		**RR (95% CI)**
	Cases	Controls	
Full record	11.81 (11.47-12.17)	11.11 (10.93-11.29)	**1.06 (1.03-1.09)**
1 year prior to index date	4.32 (4.11-4.53)	2.87 (2.78-2.97)	**1.5 (1.42-1.59)**

5.3.3 Associations between consultation types and diagnosis of axSpA

5.3.3.1 Overall time

Overall time, a diagnostic code of inflammatory bowel disease (IBD) in the consultation records was shown to be significantly associated with a subsequent axSpA diagnosis (Odds Ratio (OR) 4.00 (95% CI 1.00-15.99)) compared to those with an IBD code but without axSpA. This was also the case for psoriasis, including psoriatic arthritis (3.35 (1.59-7.06)) and uveitis (5.33 (1.19-23.83)). The groups of axial, and peripheral symptoms were shown to be significantly associated with axSpA diagnosis, with an OR of 1.95 (1.5-2.6) for axial symptoms and 1.57 (1.17-2.11) for peripheral symptoms. This shows patients diagnosed with axSpA are more likely to have consulted with axial symptoms or peripheral symptoms at anytime prior to this diagnosis than those without a diagnosis of axSpA.

Overall recorded time, cramps, enthesitis, fatigue, fibromyalgia, mobility and sleep problems were not found to be associated with axSpA diagnosis, while Raynaud's symptoms and HLA-B27 codes were not present in sufficient individuals to calculate an OR (Table 5.4).

5.3.3.2 Over the year prior to index date

In the year prior to the index date, the ORs for axial and peripheral symptoms increased to 3.36 (2.31-4.89) and 2.06 (1.38-3.08) respectively compared to overall time. Within a year of diagnosis, enthesitis became significantly associated, with an OR of 3.52 (1.13-10.97), while the confidence interval for uveitis widened beyond statistical significance, probably due to lack of power caused by low numbers (1 case, 3 controls) (1.02 (0.1-10.02)). Similarly, the confidence interval for psoriasis including psoriatic arthritis expanded below 1, with an OR of 3.10 (0.92-10.51). Sufficient data were not available to determine the level of association between axSpA diagnosis and IBD coding in this time-period.

In the year prior to index date, cramps, fatigue, fibromyalgia, mobility and uveitis did not reach statistically significant association. HLA-B27 status, IBD, Raynaud's symptoms and sleep problems were not present in sufficient individuals to calculate an OR (Table 5.5**)**.

Table 5.10 Associations with axSpA diagnosis over all recorded time

Symptom	Controls n=1156 (%)	Cases n=289 (%)	OR 95% CI	P value
Axial	**274 (23.7)**	**105 (36.71)**	**1.95 (1.5-2.6)**	**<0.001**
Peripheral	**303 (26.21)**	**100 (34.97)**	**1.57 (1.17-2.11)**	**0.002**
Cramps	9 (0.78)	3 (1.05)	1.35 (0.35-5.17)	0.66
Enthesitis	41 (3.55)	15 (5.24)	1.53 (0.82-2.86)	0.19
Fatigue	74 (6.4)	18 (6.29)	0.97 (0.56-1.68)	0.91
Fibromyalgia	0	4 (1.4)	-	-
HLA-B27	0 (0)	3 (1.05)	-	-
Inflammatory Bowel Disease	**4 (0.35)**	**4 (1.40)**	**4 (1-15.99)**	**0.05**
Mobility	9 (0.78)	2 (0.7)	0.88 (0.18-4.23)	0.88
Psoriasis	**17 (1.47)**	**13 (4.55)**	**3.35 (1.59-7.06)**	**0.001**
Raynaud's Symptoms	3 (0.26)	0 (0)	-	-
Sleep Problems	11 (0.95)	2 (0.7)	0.73 (0.16-3.28)	0.68
Uveitis	**3 (0.26)**	**4 (1.4)**	**5.33 (1.19-23.83)**	**0.03**

Table 5.11 Associations with axSpA diagnosis in year prior to index

Symptom	Controls n=1156 (%)	Cases n=289 (%)	OR 95% CI	P value
Axial	**69 (7.23)**	**62 (21.68)**	**3.36 (2.31-4.89)**	**<0.0001**
Peripheral	**84 (8.8)**	**45 (15.73)**	**2.06 (1.38-3.08)**	**<0.0001**
Cramps	3 (0.31)	1 (0.35)	1.15 (0.12-11.09)	0.905
Enthesitis	**6 (0.63)**	**6 (2.10**	**3.52 (1.13-10.97)**	**0.03**
Fatigue	12 (1.26)	3 (1.05)	0.79 (0.22-2.85)	0.73
Fibromyalgia	0	1 (0.35)	-	-
HLA-B27	0	3 (1.05)	-	-
Inflammatory Bowel Disease	2 (0.21)	0	-	-
Mobility	1 (0.1)	1 (0.35)	2.83 (0.17-47.15)	0.47
Psoriasis	6 (0.63)	6 (2.10)	3.10 (0.92-10.51)	0.069
Raynaud's Symptoms	0	0	-	-
Sleep Problems	1 (0.1)	0	-	-
Uveitis	3 (0.31)	1 (0.35)	1.02 (0.10-10.02))	

5.3.3.3 The second year prior to index date

In the second year prior to index date, only IBD was significantly associated with diagnosis of axSpA (11.21 (1.16-108.11), the notably wide confidence interval

reflecting the low numbers of cases and controls at this stage (3 and 1 respectively). Although there was a suggested positive association, axial and peripheral symptoms were not significantly associated with axSpA diagnosis in the second year prior to index. Enthesitis nor fatigue did not appear to be associated (Table 5.6).

Table 5.12 Association in second year prior to diagnosis

Symptom	Controls n=1156 (%)	Cases n=289 (%)	OR 95% CI	P value
Axial	57 (6.57)	23 (10.70)	1.58 (0.94-2.63)	0.083
Peripheral	78 (9)	30 (13.95)	1.52 (0.96-2.39)	0.07
Cramps	0	0	-	-
Enthesitis	10 (1.15)	3 (1.4)	1.26 (0.03-4.77)	0.74
Fatigue	13 (1.5)	2 (0.93)	0.58 (0.12-2.71)	0.49
Fibromyalgia	0	3 (1.4)	-	-
HLA-B27	0	0	-	-
Inflammatory Bowel Disease	**1 (0.12)**	**3 (1.4)**	**11.21 (1.16-108.11)**	**0.037**
Mobility	3 (0.35)	0	-	-
Psoriasis	9 (1.04)	6 (2.79)	2.51 (0.78-8.13)	0.12
Raynaud's Symptoms	1 (0.12)	0	-	-
Sleep Problems	0	2 (0.93)	-	-
Uveitis	0	2 (0.93)	-	-

5.3.3.4 The third year prior to index date

In the third year prior to index, only axial symptoms were significantly associated with axSpA diagnosis (3.03 (1.82-5.1). Peripheral symptoms, cramps, enthesitis, fatigue and psoriasis were not significantly associated (Table 5.7).

Table 5.13 Association in third year prior to diagnosis

Symptom	Controls n=1156 (%)	Cases n=289 (%)	OR 95% CI	P value
Axial	**57 (7.93)**	**32 (18.93)**	**3.03 (1.82-5.1)**	**<0.001**
Peripheral	62 (8.62)	21 (12.43)	1.19 (0.68-2.09)	0.54
Cramps	2 (0.28)	1 (0.59)	2 (0.18-22.06)	0.571
Enthesitis	6 (0.83)	1 (1.59)	0.86 (0.09-8.39)	0.89
Fatigue	9 (1.25)	5 (2.96)	2.22 (0.69-7.09)	0.18
Fibromyalgia	0	0	-	-
HLA-B27	0	0	-	-
Inflammatory Bowel Disease	1 (0.14)	3 (1.78)	-	-
Mobility	0	1 (0.59)	-	-
Psoriasis	5 (0.7)	1 (0.59)	0.72 (0.08-6.52)	0.77
Raynaud's Symptoms	1 (0.14)	0	-	-
Sleep Problems	1 (0.14)	0	-	-
Uveitis	0	0	-	-

5.3.3.5 The fourth and fifth years prior to index date

No symptoms were statistically significantly associated with axSpA diagnosis four and five years prior to index, possibly due to the small sample size of this study (Tables 5.8 & 5.9).

Table 5.14 Association in fourth year prior to diagnosis

Symptom	**Controls n=1156 (%)**	**Cases n=289 (%)**	**OR 95% CI**	**P value**
Axial	47 (7.68)	21 (14.29)	1.59 (0.89-2.81)	0.12
Peripheral	60 (9.8)	12 (8.16)	0.72 (0.36-1.45)	0.357
Cramps	0	0	-	-
Enthesitis	4 (0.65)	1 (0.68)	0.84 (0.08-8.38)	0.88
Fatigue	12 (1.96)	0	-	-
Fibromyalgia	0	2 (1.36)	-	-
HLA-B27	0	0	-	-
Inflammatory Bowel Disease	2 (0.33)	2 (1.36)	2.23 (0.29-16.85)	0.439
Mobility	1 (0.16)	0	-	-
Psoriasis	2 (0.33)	1 (0.68)	2.45 (0.15-39.72)	0.53
Raynaud's Symptoms	0	0	-	-

Sleep Problems	2 (0.33)	0	-	-
Uveitis	0	0	-	-

Table 5.15 Association in fifth year prior to diagnosis

Symptom	Controls n=1156 (%)	Cases n=289 (%)	OR 95% CI	P value
Axial	30 (5.36)	14 (10.69)	1.96 (0.9-4.24)	0.087
Peripheral	54 (9.64)	15 (11.45)	1.62 (0.84-3.13)	0.152
Cramps	1 (0.18)	1 (0.76)	-	-
Enthesitis	2 (0.36)	1 (0.76)	1.56 (0.14-17.75)	0.72
Fatigue	11 (1.96)	0	-	-
Fibromyalgia	0	2 (1.53)	-	-
HLA-B27	0	0	-	-
Inflammatory Bowel Disease	1 (0.18)	3 (2.29)	-	-
Mobility	1 (0.18)	0	-	-
Psoriasis	1 (.018)	5 (3.82)	-	-
Raynaud's Symptoms	0	0	-	-
Sleep Problems	1 (0.18)	0	-	-
Uveitis	0	0	-	-

5.3.3.6 Sub-group analysis: Female and Male

Associations between variables and diagnosis of axSpA were also calculated for male and female patients over all time and within a year of index.

Over all time, axial symptoms were significantly associated with axSpA diagnosis in male and female patients, as were psoriatic symptoms. However, peripheral symptoms were only significantly associated in female patients, as was inflammatory bowel disease. Uveitis was only significantly associated in male patients over this timeframe.

Table 5.16 Associations between variables and diagnosis of axSpA over all time by sex

	Female OR (95% CI)	**Male OR (95% CI)**
Axial	**2.01 (1.31-3.11)**	**1.87 (1.26-2.76)**
Peripheral	**1.83 (1.19-2.79)**	1.43 (0.95-2.16)
Cramps	1.67 (0.29-9.39)	2 (0.18-22.06)
Enthesitis	1.44 (0.58-3.56)	1.42 (0.62-3.25)
Fatigue	1.18 (0.63-2.19)	0.69 (0.23-2.02)
Fibromyalgia	-	-
HLA-B27	-	-
Inflammatory Bowel Disease	**6 (1.35-35.91)**	2 (0.18-22.06)

Mobility	-	-
Psoriasis	**5 (1.34-18.62)**	**3.29 (1.18-9.12)**
Sleep Problems	0.89 (0.19-4.11)	1 (0.11-8.95)
Uveitis	-	**5.33 (1.19-23.83)**

In the year prior to index, axial symptoms were still associated with diagnosis of axSpA in both sexes. Peripheral symptoms remained associated only in female patients. Consultation for enthesitis in the year prior to index is significantly associated with axSpA diagnosis for men but not women (insufficient numbers led to no result being available for women). Similarly for fatigue. In the year prior to index, psoriasis is only significantly associated with diagnosis of axSpA in men.

Table 5.17 Associations between variables and diagnosis of axSpA in the year prior to index by sex

	Female OR (95% CI)	**Male OR (95% CI)**
Axial	**3.28 (1.85-5.85)**	**4.02 (2.45-6.61)**
Peripheral	**2.97 (1.76-4.99)**	1.27 (0.66-2.45)
Cramps	2 (0.18-22)	-
Enthesitis	-	**5 (1.34-18.62)**
Fatigue	-	**6 (1-35.91)**
Fibromyalgia	-	-
HLA-B27	-	-
Inflammatory Bowel Disease	-	-
Mobility	2 (0.18-22.06)	-

Psoriasis	4 (0.25-63.95)	**4.7 (1.03-21.39)**
Sleep Problems	-	-
Uveitis	-	1.33 (0.14-12.82)

5.4 Discussion

This study shows that patients who go on to receive diagnosis of axSpA consult more than matched controls over all recorded time and within the last year prior to index, with the strength of association increasing in the final year. This study also found that patients with axSpA in North Staffordshire consulted primary care with several axSpA-related symptoms more frequently than matched patients without an axSpA diagnosis. The frequency of consultation for these factors was typically greater in the 12-months prior to diagnosis. Symptoms more frequently consulted for included the presence of axial and peripheral joint problems and pain, enthesitis and inflammatory bowel disease. Analysing consultations over the five years prior to index date showed an increase in association for several variables in the last three years. Axial and peripheral symptoms being significantly associated in the final year prior to diagnosis, as was enthesitis. IBD was associated in the second year (data from the final year was too sparse to show an association) and axial symptoms were associated in the third year prior.

5.4.1 Patient Characteristics

The patient sample of this study had some notable characteristics worth comment. At inclusion, the mean age of patients was 50.9 years, five years older than the age specified as an upper boundary for classification of new axSpA diagnosis (M. Rudwaleit et al., 2009c, 2009a). 59.9% (n=173) of patients in this study were older than 45 at the time of study, 26% were over 60, 13.2% were over 70 and a further 5.5% were over 80. While feasibly many of those at the younger end of this spectrum do not cause any issue as they may have been diagnosed younger than 45, the older end of the age

ranges does present questions. It is extremely unlikely these patients were newly diagnosed with axSpA, leaving the possibilities of them being new transfers from other GPs or mis-classified individuals. Newly transferred or incorrectly diagnosed patients may have resulted in a paucity of salient consultation data prior to index.

5.4.2 Discussion of Significant Associations

The current study supports previous findings in research, such as those by Braun et al (2013) and Baraliakos et al (2020) that show variables that have a high degree of success in helping predict likelihood of axSpA diagnosis and are therefore of use to primary care clinicians as a quick tool to speed up appropriate referral (Braun *et al.*, 2013; Baraliakos *et al.*, 2020). Specifically, having uveitis, IBD or psoriasis were important indicators of future axSpA. Furthermore, factors such as family history, pain in thoracic spine and alternating buttock pain, were also significantly associated with axSpA. Additionally, the results here are in concordance with those found in studies of other EHR datasets, which showed comparatively more frequent pain coding and uveitis coding to be associated with diagnosis of axSpA (vs healthy controls) (Kennedy et al., 2021; Sengupta et al., 2022; Zhao et al., 2019a).

5.4.2.1 Axial and peripheral symptoms

The strength of association between axial and peripheral symptoms and diagnosis of axSpA increased in the year leading to index date, doubling for axial symptoms compared to over all available time. This suggests that frequency of consultations for these symptoms increases in the year prior to diagnosis; again, this increase in

frequency can be seen as a possible signpost to alert clinicians that the patient in question is experiencing something more complex than they might perhaps be presuming.

In the second year prior to index, axial and peripheral symptoms were not significantly associated with diagnosis, while in the third year prior to index, they were significantly associated with diagnosis of axSpA. It is unclear why these symptoms should be associated in the third year prior to index, non-significant in the second year prior to index, then significant again in the year prior to diagnosis. It is possible that a higher-powered study would show association across all three years; the odds ratio for year 2 prior to index is suggestive of a positive association. Similarly, particularly in year 2 prior to index, while not significant, the odds ratio for peripheral symptoms is suggestive of an association and could possibly become significant in a study with a larger cohort.

Studies using other EHR have also shown musculoskeletal symptoms and diagnoses to be predictive of diagnosis of axSpA, and this had been explored in different ways. One study, using the SAIL (secure anonymised information linkage) database, found not only that codes associated with MSK diagnoses prior to axSpA are predictive of an eventual diagnosis with axSpA, but also that this is particularly true for younger patients (15-20). Additionally, female patients tended to have received more MSK diagnoses than men prior to axSpA diagnosis. This was interpreted as indicating a more complex route to diagnosis of axSpA (Kennedy et al., 2021). Another study, using CPRD, showed that the number of low back pain symptoms prior to axSpA diagnosis was a predictive factor (Sengupta et al., 2022).

5.4.2.2 Inflammatory bowel disease

There were exposures which, while significantly associated with diagnosis over all time, were not found to be associated within a year of index date. Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD) was significantly associated with axSpA diagnosis over all time. An OR was not possible to calculate within a year of index, as no IBD codes were available among the case sample.

A significant association was found in the second year prior to index with IBD with seemingly an extremely high odds ratio of 11.21. The dramatic confidence interval however (1.16-108.11) belies the very low numbers of cases and controls (1, 3 respectively) it represents. A study with a larger cohort would bring further clarity to these results; it may be that IBD was significantly associated with diagnosis of axSpA in the final year prior to diagnosis but the sample size was too small to show this.

5.4.2.3 Uveitis

Uveitis was strongly associated with diagnosis of axSpA over all time, but again this was not significant in the year prior to diagnosis, potentially due to a small sample. In this study, the number of uveitis exposures was very low in the year prior to index date, with 3 (0.31%) being found among controls and 1 in cases (0.35%).

In other research, Kennedy et al found uveitis was specifically predictive for male patients and not female patients (Kennedy et al., 2021) in data from the SAIL database.

Zhao et al also found uveitis to be significantly more prevalent among patients who went on to be diagnosed with axSpA compared to those who didn't (24% vs 5%, p<0.001) (Zhao et al., 2019) and a 2016 study found uveitis in approximately 1 in 10 patients with ankylosing spondylitis (9.7%) (Sun et al., 2016). These studies demonstrates that despite a lower prevalence of patients with uveitis in our sample, some association was retained.

5.4.2.4 Psoriasis/psoriatic arthritis

The odds ratio for the association between a previous diagnosis of psoriasis and psoriatic arthritis and a subsequent diagnosis with axSpA was high in the final year prior to diagnosis, although the confidence interval overlaps 1, meaning this association is not considered significant. Psoriasis is present in a quarter to a third of established axSpA patients (Lucasson et al., 2022; Solmaz et al., 2020). Noting psoriasis early would not only act as an important signpost for possible axSpA though; it has been shown to be associated with higher levels of synovitis and enthesitis and a higher requirement for methotrexate and biologic DMARDs in patients with axSpA, a further incentive to diagnose and begin appropriate management sooner than is often currently occurring (Lucasson et al., 2022).

5.4.2.5 Enthesitis

Enthesitis was not significantly associated with axSpA diagnosis over all time, but it was within a year of index date. The fact of its increase in association in the year prior to diagnosis suggests that this could be a symptom which starts to significantly affect

likelihood of health-seeking, resulting in greater frequency of consultation. Its increase in association with diagnosis compared to non-axSpA patients within a year of diagnosis also implies that this is a symptom which raises suspicion of something more complex with GPs and triggers referral to rheumatology.

Enthesitis was not significantly associated with diagnosis in the second year prior to index, suggesting that, as with axial and peripheral symptoms, its frequency of presentation increased towards index date. This finding should be treated with caution, however, as unlike axial and peripheral symptoms, the numbers of cases and controls presenting with enthesitis in each individual year prior to diagnosis are very low (6 each in the year prior, 3 cases and 10 controls in the second year prior).

No significant associations between variables and diagnosis of axSpA were found in years four or five prior to index date.

5.4.3 Findings with no association

5.4.3.1 Fibromyalgia

Across the full timescale, there were insufficient consultations for fibromyalgia to examine it's association with axSpA diagnosis. However, it is noteworthy that no fibromyalgia was found among the control sample. In studies elsewhere, fibromyalgia has been shown to be commonly comorbid with axSpA, with a prevalence of 1 case of fibromyalgia in every 6 axSpA cases reported in a 2020 meta-analysis based on 16 studies from around the globe (Jones et al., 2020). Concurrence with this result is found in Gau et al's 2021 cohort study, which showed AS patients as having a higher risk than individuals without AS for developing fibromyalgia (HR1.32 (95%CI 1.12-1.55)

(Gau et al., 2021). The order of presentation of axSpA/fibromyalgia is not readily evident in the above studies, but due to the high degree of comorbidity between the fibromyalgia and axSpA and the frequency with which early axSpA is mis-diagnosed as fibromyalgia alone (Aggarwal and Malaviya, 2009), a diagnosis of fibromyalgia could justifiably be cause for suspicion of axSpA. As with uveitis, far fewer cases of fibromyalgia were found among the cases in the present study than might be expected considering the points raised above; a possible cause for this is that fibromyalgia is infrequently formalised as a diagnosis prior to diagnosis of axSpA and therefore is not of utility as a predictive variable for axSpA.

5.4.3.2 HLA-B27

HLA-B27 status did not return sufficient data from which to calculate an OR, but it was consistently higher in cases than controls. Additionally, while too few patients had codes for HLA-B27 to be conclusive, it could be worth noting that HLA-B27 codes were only present in the year prior to diagnosis. Considering HLA-B27 tests are unlikely to be requested for reasons other than suspicion of axSpA, this is what would be expected. Additionally, it is possibly not entirely classifiable as a variable occurring prior to diagnosis, as HLA-B27 testing would likely be requested to confirm suspicion of an axSpA diagnosis, which would then be formalised on confirmation of HLA-B27; the coding of HLA-B27 and diagnosis are effectively simultaneous.

5.4.3.3 Sleep Problems

Sleep problems did not return sufficient data from which to calculate an OR within a year of index. Sleep disorders are an impactful feature of axSpA and are found in 55% of patients with axSpA (Deodhar et al., 2019; Günaydin et al., 2009), but may not be of use as a means of raising early suspicion of axSpA due to frequency in the general population (nearly a quarter of adults (van de Straat and Bracke, 2015) and the frequency with which it is presented in primary care _.

5.4.4 Sub-group analysis: consultation behaviours by sex

Analysing the data by sex showed some significant differences between male and female patients which are suggestive not only of different presentations of axSpA between the sexes but also different consulting behaviour between the sexes. While some symptoms were significantly associated with axSpA diagnosis across the sexes, such as axial symptoms, others were sex-specific. When viewed over all time, for instance, uveitis was only significantly associated with axSpA diagnosis in male patients, whereas IBD and peripheral arthritis were significantly associated only in female patients. In the year prior to diagnosis, the significant association between peripheral arthritis and axSpA diagnosis remained only in female patients. Psoriatic symptoms remain significantly associated only in men. Enthesitis at this stage in the diagnostic journey has already been shown to be significantly associated with diagnosis, and sub-group analysis shows this is only the case for male patients. These differences approximately conform to previous differences between the sexes in presentation of the disease (Wright et al., 2020), but some caveats need to be addressed. Firstly, what is reported here is not an exhaustive representation of symptom presentation in patients; only what is being reported in primary care and

then coded for in CiPCA. Secondly, in the case of enthesitis, the number of instances available in this last year prior to index is very low, and none at all are available for female patients, resulting in no association being calculated for women. While superficially this suggests a higher frequency of enthesitis among male patients than female, the available numbers are not high enough to rule out chance.

The differences in consultation rates and rate ratios between men and women are also quite suggestive. While average number of consultations raises for both sexes in the final year prior to diagnosis compared to all time, the increase is more substantial in men than women. Men, however, consult far less than women, so their consultation rates were still significantly lower. One way of interpreting these data is that women might tend towards a more stable consultation behaviour overall, with their frequency of consultation not rising as much (although the rise in the year prior to index is significant) as it does in men; male patients may be more likely to seek healthcare when their symptoms are far advanced, still requiring fewer consultations than female patients due to more obvious symptomology. It is possible to interpret these results as reflecting not just the more stable consultation history of female patients, but also the different presentation of the disease in men and women; the non-radiographic form of the disease is more common in women than in men, for instance (Wright et al., 2020).

5.4.5 Clinical relevance

The main implication of these results is that there are several symptoms being consulted for prior to diagnosis of axSpA that are not being acted upon promptly enough to achieve timely diagnosis. The findings also show an increase in frequency of consultation of any kind in the year prior to diagnosis, which can act as an important

signpost for a GP to realise a patients' condition may be worsening or becoming more complex, prompting further questioning and encouragement of the patient to communicate their general situation beyond the symptom for which they are consulting on the day. This is shown in literature, which shows that GP consultations only cover an average of 2.1 exposures (Stuart et al., 2019).

Along with being cued into further and more nuanced questioning by the increase in consultation frequencies, there are exposures shown here as highly associated with diagnosis which could, in the presence of greater education and understanding, be used as signposts for possible axSpA. While axial symptoms are associated with diagnosis of axSpA, these are difficult to discriminate in primary care due to the high number of patients presenting with back problems of any causes (M Rudwaleit et al., 2004). Pragmatically, this means non-axial symptoms might be more useful as a means of raising clinical suspicion of axSpA. Psoriasis, peripheral arthritis and inflammatory bowel disease were all significantly associated with diagnosis of axSpA in this study, and are distinctive enough that they could be used as clinical signposts for axSpA, particularly in combination with increasing consultation frequency. As mentioned above, the fact that enthesitis coding within a year of diagnosis shows a stronger, statistically significant association with diagnosis than over all time implies the possibility that this is also a symptom which is distinct enough to raise awareness and cue referral to rheumatology. Enthesitis is a common feature of axSpA, reported in a third of patients with the disease (29% in patients with the radiographic disease, nearly half of patients with the non-radiographic disease)(Mease et al., 2020), so the present study showing association with axSpA diagnosis is to be expected; the temporality of such a significantly associated feature, however, is worth pursuing.

5.4.6 Strengths and Limitations

This study shows statistically significant associations between axial, peripheral and psoriatic symptoms, inflammatory bowel disease and enthesitis, and subsequent diagnosis of axSpA, along with a significantly higher frequency of consultations prior to diagnosis, at least in patients seen in primary care practices in North Staffordshire. Considering CiPCA has been shown to produce MSK prevalence results comparable to larger national databases such as RCGP WRS (Jordan et al., 2007), this could suggest the same can be stated for the UK as a whole.

Conversely, CiPCA's relatively small size as a database and the low number of axSpA cases found within it result in relatively low statistical power. Strength of association could not be calculated over all time for fibromyalgia (code only), HLA-B27 status and Raynaud's sign. Similarly, associations could not be examined for the year preceding diagnosis for fibromyalgia (code only), HLA-B27 status, IBD, Raynaud's and sleep problems. This is a problem which could be solved by a larger population size, such as in the case of using database such as CPRD.

Another limitation is one of EHR databases generally, which is the possibility that GPs are not recording all salient details from consultations and simply focusing on the main point of consultation. While coding for test results or definite symptoms such as back pain could be presumed to almost always take place due to its clinical importance, other more loosely defined exposures such as fatigue and sleep disturbance may not. Whether this is due to lack of clear communication, dismissal of its importance or prioritisation of recording codes of perceived greater importance due to time constraints, this will result in under-representation of some symptoms in databases.

This supposition is supported by Salisbury et al (2013) who show that while 72% of consultations were regarding multiple conditions, only 37% of conditions were coded as such (Salisbury et al., 2013). CiPCA data is regularly quality checked, which has been shown to improve levels and detail of consultation coding; ideally this somewhat mitigates the issue of coding incompleteness (Porcheret et al., 2004).

5.5 Conclusion

This study shows that among the patients of practices registered with CiPCA, those who go on to receive a diagnosis of axSpA consult more frequently than those without the diagnosis. In addition to this, axSpA diagnosis is significantly associated with presentation in primary care with axial, peripheral and psoriatic arthritis as well as inflammatory bowel disease, uveitis and enthesitis prior to their diagnosis. Of note, this association between enthesitis and diagnosis of axSpA only becomes apparent in the year prior to index while not being significantly associated over all time or in the 2nd, 3rd, 4th and 5th years prior to index, suggesting it is a signposting diagnosis for axSpA. Similarly, inflammatory bowel disease is significantly associated two years prior to diagnosis and may also be considered a signpost for diagnosis; while this association may well survive into the final year prior to diagnosis, numbers were too sparse to make a computation. Further research into the utility of this association is indicated.

Considering the extent to which these conditions are associated with axSpA, the utility of automated systems to flag up patients for further examination or referral to rheumatology (such as that described in NASS' Gold Standard for Diagnosis program) becomes apparent. Additionally, further research into the strength of these

associations prior to diagnosis, such as through retrospective cohort studies, can further validate these results and those derived from CPRD and other EHR databases, and may help address any reportage issues intrinsic to EHR databases.

Chapter 6 – Discussion

This chapter will discuss the findings of the studies detailed in chapters 3, 4 & 5 in the context of the existing wider body of research and current clinical practice regarding axial spondyloarthritis. This thesis is of an exploratory sequential mixed-methods design, and as such the studies comprising it can be viewed separately but also as elements of a larger piece of research which inform one another in context and analysis (Creswell and Plano Clark, 2018). Following this, the implications for future research and clinical practice will be discussed. The strengths and limitations of the thesis as a whole will be addressed, followed by conclusions to be drawn from this body of research.

6.1 Summary of interactions and findings of thesis studies

This thesis aimed to examine the extent of diagnostic delay of axSpA, its causes and possible means by which diagnosis times could be shortened. The systematic review of Chapter 3 established that diagnostic delay is a considerable concern globally, with the majority (11 of 18) of studies showed median diagnostic delay of between 2 and 5 years (a third of studies reported 2-2.3 years delay) which should be used as the benchmark against which future improvement is judged and against which future research can compare their results. The role of gender and family history on diagnostic delay had been sufficiently examined across included studies and found the majority of studies reported no significant association between these factors and delay experienced.

The systematic review's results informed the qualitative study detailed in Chapter 4 in several important ways, notably in the areas of recruitment and study design, and the analysis phase. Having a well-defined range for diagnostic delay from the systematic review served the design for recruitment of patients; the majority of median diagnostic delay is between 2 and 5 years, so >1 year was chosen as our definition of diagnostic delay. The lack of consensus on associations found between different factors and diagnostic delay strengthened the rationale for the qualitative study; the experiences of patients with axSpA and HCPs with interest in axSpA could potentially suggest relationships between causes and effects that are not readily evident in population-level data.

This study established what were perceived to be the most substantial barriers to diagnosis of axSpA. While there was overlap between the findings from patients and HCPs, the order of importance of barriers was different. Patients felt patient/HCP interactions were most important, followed by the difficulty of axSpA to diagnose, patient behaviour, lack of public and clinical awareness of axSpA and sub-optimal practice in healthcare. HCPs most commonly considered the biggest barrier to prompt diagnosis to be the difficulty of diagnose, followed by lack of awareness of axSpA, sub-optimal clinical practice, patient behaviour and patient/HCP interaction.

The behavioural issues raised as barriers to diagnosis lead organically to the two other main areas viewed by patients and HCPs as barriers to diagnosis: systemic issues within healthcare and lack of awareness and education of axSpA. Regarding axSpA, these problems are arguably two sides of the same coin. If there was greater public and healthcare awareness of axSpA, there would not be such confusion regarding

referral, communication between specialisms or lack of clear guidelines regarding its symptomatic management in primary care (it is worth noting however that there would be a commensurate increase in people presenting to primary care; this would require mitigatory action). As implied by one GP: there was systematic pressure to treat back pain as mechanical, with analgesics, a perspective which closely aligned with the experiences of many patients interviewed. Following from this, the NICE guidelines for managing lower back pain and sciatica explicitly discourage use of imaging as a means of assessment, meaning it is unlikely that the characteristic radiographic changes of r-axSpA will be picked up while a patient is being managed in non-specialist care. There is guidance to be alert to possible inflammation but the means of doing this is not explicitly outlined (National Institute for Health and Care Excellence [NICE], 2020).

Suggested solutions to these issues centre around the need for more education on axSpA, heightened levels of awareness of the disease, combined with greater degrees of formal and informal patient advocacy to alleviate communication issues and ensure a more productive interaction between patient and HCPs and services. In addition, HCPs identified a need for a greater use of physiotherapists in primary care to assist with earlier effective management, more appropriate referral and therefore earlier diagnosis.

Physiotherapy in primary care may also help signpost physical management through self-care, utilising exercise and lifestyle alterations, as indicated in the NICE guidelines (National Institute for Health and Care Excellence [NICE], 2017) and recommended by NASS (National Axial Spondyloarthritis Society [NASS], accessed 2022). Involvement of

other HCPs in early consultation and management does come with the caveat that they would need training and education to reach a requisite level of awareness of inflammatory diseases including axSpA. Without this step, the problems of communication and complex referral pathways could be exacerbated rather than alleviated.

Greater involvement of different specialisms in primary care may help to address another recognised problem: appointments in primary care are shorter than many feel ideal due to increasing clinical demand and national guidance on appointment length and tend to only allow for conversation on one presenting symptom, which is not conducive towards the 'joined-up-thinking' that many espouse. Several HCPs and patients reasoned that, due to the diverse and superficially unconnected nature of axSpA symptoms, a more protracted and in-depth conversation accompanied by an open-minded attitude to associations between disparate symptoms could aid faster diagnosis of axSpA.

Having explored the personal experience of the events leading to diagnosis of axSpA, resulting in valuable granular insight, the final study of this thesis aimed to present a quantified, population-level description of ways in which people consult primary care in the time prior to diagnosis. Where the qualitative study provides illumination and detail of the journey to diagnosis, along with powerful insights into personal perspectives on it, the case-control study of Chapter 5 sought to find aspects of the process which are quantified as counts, rates and odds ratios, which could be generalised. Consultation Patterns Prior to Diagnosis with axSpA: A Case-Control Study showed that in a North Staffordshire population, frequency of all consultations

increases in the final year prior to diagnosis of axSpA when compared to matched patients with no diagnosis of axSpA. This data also showed that presentation with axial symptoms, peripheral symptoms, psoriatic symptoms, inflammatory bowel disease, enthesitis and uveitis in primary care were associated with a future diagnosis of axSpA. The strength of association between axSpA diagnosis and prior consultations increased in the case of axial, peripheral and psoriatic symptoms between being measured over all recorded time and in the year prior to diagnosis. In the second year prior to diagnosis, inflammatory bowel disease was significantly associated with diagnosis although the numbers available for this are low and the confidence interval was commensurately extremely wide, so this finding would benefit from being re-investigated using a larger dataset. The smaller size and low number of axSpA cases in CiPCA may lead to it being underpowered for detection of significant differences in less common comorbidities. The result regarding enthesitis could be useful; over all recorded time there was no significant association between enthesitis and diagnosis of axSpA, but this changed in the year prior to diagnosis. Enthesitis is present in a third of patients with axSpA, so the possibility of using it as a signpost for diagnosis could make appreciable difference for a large number of patients (McGonagle et al., 2021).

Box 6.1 Summary of key findings from each study

<table>
<tr><th>Study</th><th colspan="2">Key Findings</th></tr>
<tr><td>Diagnostic Delay in axSpA: A Systematic Review</td><td colspan="2">• Diagnosis of axSpA is delayed by median 0.67 to 8 years globally
○ 2/3rds of studies reported 2-5 years delay
○ 1/3rd of studies reported 2-2.3 years delay
• Though the role of many factors on delay have been examined previously, findings are inconsistent or limited
• However, gender and family history of axSpA are not associated with delayed diagnosis of axSpA
• Mean diagnostic delay is consistently higher than median delay due to positively skewed data</td></tr>
<tr><td rowspan="5">Barriers and Facilitators in Diagnosing axSpA: A Qualitative Study</td><td colspan="2">Barriers to Diagnosis: Both patients and HCPs noted communication issues, low awareness of axSpA in healthcare and public spheres and the current operation of healthcare services were barriers to timely diagnosis.</td></tr>
<tr><td>Patient Perspective
1. Patient/HCP interactions
2. axSpA is difficult to diagnose
3. Patient behaviour
4. Lack of awareness of axSpA
5. Sub-optimal practice in healthcare</td><td>HCP Perspective
1. axSpA is difficult to diagnose
2. Lack of awareness of axSpA
3. Sub-optimal practice in healthcare
4. Patient behaviour and characteristics
5. Patient/HCP Interactions</td></tr>
<tr><td colspan="2">Facilitators of Diagnosis: Results regarding facilitators of diagnosis were more diverse between patients and HCPs, but there were still overlaps.</td></tr>
<tr><td>Patient Perspective
1. Patient advocacy
2. Patient characteristics
3. Good practice in healthcare
4. Education and awareness
5. Luck</td><td>HCP Perspective
1. Education and awareness
2. Observations that raise HCP suspicion of axSpA
3. Improving practice in healthcare
4. Patient/HCP interactions</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Consultation Patterns Prior to Diagnosis with axSpA: A Case-Control Study</td><td colspan="2">• Patients diagnosed with axSpA consult their GP more frequently in primary care prior to diagnosis compared to matched patients not diagnosed with axSpA
• Over all available time, patients diagnosed with axSpA report axial, peripheral and psoriatic symptoms more frequently than those not diagnosed with axSpA. This was also the case for uveitis.
• Association with diagnosis of axSpA strengthens in final three years prior to diagnosis for axial and peripheral symptoms, enthesitis and inflammatory bowel disease.</td></tr>
</table>

6.2 Themes of this Thesis

Together these three studies present a body of new information and provide substantial contextualisation for the journey to axSpA diagnosis from an individual and population perspective. Across these different studies, overlapping themes with regards to the diagnosis of axSpA in the UK healthcare system are present. Aside from the individual studies providing different perspectives on the journey to diagnosis, the combination of the three studies in this thesis also shows the value of exploring different perspectives to give useful and actionable context to each other.

6.2.1 Patient Behaviour and Communication

6.2.1.1 Communication

Communication between patients and HCPs was frequently seen to be unsatisfactory at best. Poor communication was viewed as at worst, problematic, demoralising and obstructive with regards to seeking diagnosis. In addition to the effect this has on the patient/HCP relationship, this behaviour also points towards possible issues with the level of detail recorded for patients by their clinicians. Salisbury et al (2013) showed that only 2.5 issues were discussed per-consultation, with the implication being that this is primarily due to short consultation times, but the evidence of this thesis also suggests this may be due in part to the quality of communication. Possible further evidence for this supposition is in the pattern of consultations shown in chapter 5: frequency of consultations for axial symptoms increases in the three years prior to diagnosis, with other issues such as IBD, enthesitis and peripheral symptoms becoming more frequent in subsequent years. This suggests a more complex profile of different

symptoms prior to diagnosis, and the causation is not clear from the figures alone. With the insight from chapter 4, however, the possibility arises that this pattern could be interpreted as back pain symptoms being present for an extended period of time and not being communicated about sufficiently by either party to lead to a rheumatology referral; it is only with the addition of further suggestive codes such as those above that this conversation starts to occur. This interpretation must be treated with the caveat that axial symptoms were far more numerous in the data than were IBD and enthesitis codes, meaning this course of events would only explain a fraction of included patients. Peripheral symptoms were, however, comparatively numerous, so it may be that even the development or recognition of peripheral symptoms is enough to change the nature of conversation and lead to referral.

6.2.1.2 Stoicism

Another important aspect of patient behaviour which was felt to have slowed down diagnosis was that of 'just getting on with it'. Patients were aware there was something amiss with their general health but effectively ignored it until it became severe enough to acutely impinge upon their lifestyle or employment. HCPs agreed that there was a significant lag between symptoms becoming apparent to many patients and their seeking healthcare advice on them. Both patients and HCPs noted that there would often be large gaps in patient attendance to healthcare with symptoms, although the reasons for this were more nuanced than 'just getting on with it'.

This may be suggested by the results of Chapter 5. Frequency of consultations for axial symptoms was significantly higher for three years prior to index in patients who go on to receive axSpA diagnoses than those who don't. In the final two years prior to diagnosis, enthesitis, IBD and peripheral arthritis become significantly associated, which may be the point at which overall suspicion was sufficiently raised in patients to want to attend their GP more, hastening their journey to diagnosis.

6.2.2 Type of symptom presentation

6.2.2.1 Expected vs observed

There are noteworthy convergences between the qualitative study of chapter 4 and the case-control study of chapter 5, regarding what was reported by patients (aside from the very prominent axial symptoms), such as enthesitis and uveitis being strongly associated with diagnosis of axSpA. An important point about these two exposures is that while the association agreed with data provided by participants in the qualitative study, they are only present in the primary care CiPCA data in extremely low numbers; qualitative data is hereby contextualised by the quantitative data. While uveitis and enthesitis are undoubtedly associated with axSpA (Mease et al., 2020; Rademacher et al., 2020), and Chapter 5 showed enthesitis to be significantly associated with diagnosis of axSpA in the final year prior to diagnosis. While it is not common in the wider population, its presence could therefore be used as a signpost to referral, particularly as it is present in around a third of patients with axSpA(McGonagle et al., 2021).

There were also instances where the qualitative data are not corroborated in the quantitative data. Many patients reported fatigue and sleep problems as symptoms of their axSpA, and HCPs interviewed in that study also regularly noted these as symptoms, but the results from Chapter 5 did not find either to be associated with diagnosis of axSpA, although again this could be due to low numbers. Another explanation could be that sleep problems either don't get separately coded for, instead being included in free-text, or are not discussed at all in consultation. Mobility exposures (poor mobility, immobility, impossibility of exercise) and cramps, both reported by patients in interview, were similarly not associated and only found in very low numbers in the data, highlighting the need for larger studies. Hypothetically, it may be that these variables simply aren't associated prior to diagnosis of axSpA; they increase in prevalence with increased disease duration and may become characteristic of the disease past the point at which a patient's diagnosis could be considered delayed. They may not be useful as "signpost" symptoms in the way that enthesitis could possibly be.

6.2.2.2 Association with delay

The studies comprising this thesis did not show conclusive evidence of symptoms associated with diagnostic delay. Many variables considered characteristic of axSpA such as enthesitis, buttock pain, morning stiffness, psoriasis and IBD were investigated by too few studies to reach any comparative conclusion in the synthesis. A clue to this conclusion may be offered by the results of chapters 4 & 5. Much delay was ascribed by participants in Chapter 4 to what they thought were atypical symptoms disease or

confusing and variable symptoms at disease onset, which was perceived to make the route to diagnosis more winding as it lowered the likelihood of suspicion of axSpA. This manner of "problematic" symptomology is difficult to capture quantitatively as its characterisation is unavoidably nebulous. There is no means of ensuring patients reporting non-typical onset are reporting the same thing. Furthermore, Chapter 5 found that many variables considered characteristic of axSpA were not significantly associated (in GP records) prior to diagnosis, such as fatigue, sleep problems and cramps. CiPCA may have underreported the prevalence of these symptoms or alternatively it could be proposed that these symptoms are genuinely not associated with the disease early in its course. What is more likely is that an association does exist here and the numbers of axSpA patients in CiPCA and concurrently the number of variables result in low statistical power; underpowered data has led to a type 2 error, a false negative.

6.2.3 The point at which delay occurs in the patient journey

This thesis provides further evidence regarding the points along the patient journey which can be seen to be causing delay. These points were widely perceived to occur between the patient's symptom onset and the event of successful referral from primary care to specialist care, broken down into two stages: 1) the initial presentation of symptoms to consultation with a GP, and 2) missed opportunities for referral once the patient had been seen by a GP.

6.2.3.1 Patient Delay

Patient delay has been defined as the time-period between initial symptom onset and first healthcare consultation for those symptoms (Santos et al 2021), but reality is more complex. While differentiating between patient delay (first symptoms to first healthcare contact) and healthcare delay (first contact to diagnosis) is a convenient way of managing data that allows for quantification of spans of delay, it does not address the issue of attribution. As was noted in chapter 4, it is the case that some delay post-first contact is attributable to the behaviour of the patient. The studies in this thesis illustrate that this is an important aspect in the larger problem of diagnostic delay. It is difficult to define specific points during the patient delay period as it is a period defined by the personality of the individual and their circumstances, personal and professional. HCPs noted the fact that patients often don't present with symptoms until they are quite severe, and this is also stated by patients. Much of the time when they presented with symptoms to primary care, it was due to their symptoms having become unmanageably severe to the extent they were impacting their work and personal life. Even upon having consulted, inconsistency in consulting behaviour by patients causes further delay. This could also be suggested in the results of chapter 5 with the increasing frequency of coding for axial, peripheral and psoriatic symptoms, along with enthesitis and IBD; many patients in chapter 4 reported not consulting much until their disease symptoms became intense, complex and unignorable. Axial symptoms were significantly associated with diagnosis up to three years prior to index date, whereas the other symptoms detailed above only became associated closer to index. This could be interpreted as patients coping with back pain and only consulting more when further symptoms presented. To reiterate the earlier point: while this

hypothetical does occur after first consultation, it is due to patient behaviour as suggested by patients in chapter 4.

6.2.3.2 Healthcare Delay

Primary care is a difficult gateway to get through for many individuals with axSpA. Difficulties of communication, recognition of the disease and lack of clarity regarding onward referral mean that as with the patient delay period, the time spent being managed in primary care can last years and is often recalled with a great degree of negative sentiment. These issues are inextricable from the methods by which they can be improved and will be discussed in section 6.3

6.3 Implications for Future Research and Practice

6.3.1 Future Practice

A major point where there is consensus in the literature and supported by this thesis is that the journey to diagnosis and management of axSpA can be expedited and made a less negative experience through improved referral, better use of consultation time, greater continuity of care and improved communication. While elements such as education and raising awareness of the disease through media will be approached in the next section, this section will focus on practical, logistical and cultural changes within healthcare which could speed up the process of diagnosis.

6.3.1.1 Improvements to referral

After the initial challenge of gaining a referral from their GP, there was a frequently reported problem of 'the revolving door' of referral whereby the patient is referred between several different specialties or managed in several different ways which do not lead to diagnosis and appropriate management. A 2022 study demonstrated the extent to which referral issues occurred for patients in two major healthcare centres (the Royal Free NHS Foundation Trust and Salford Care Organisation), showing that 32% of patients diagnosed with axSpA saw one further HCP prior to their diagnosis, 18% saw 2, 9% saw 3, 7% saw 4 and 2.7% saw 5 (Gregory et al., 2022). Among these other HCPs were GPs, physiotherapists, osteopaths, chiropractors, orthopaedic surgeons and pain consultants. Their data suggest problems being referred onwards from primary care, with 23% seeing their GP 5-10 times prior to referral and 14% seeing their GP more than 10 times. 14% also saw physiotherapists more than 10 times, 20% between 5 and 10 times and nearly a third between 1 and 5. While it must be taken into account the differences in character and function of consultations with GPs and physiotherapists, these findings do suggest the educational need exists in both areas to raise likelihood of raised suspicion of something more complex happening with a patient and therefore speeding the process toward referral.

A further possibility to consider is that beyond being 'bounced' between areas of healthcare repeatedly, there is the possibility of patients being seen in rheumatology but not diagnosed with axSpA for a long time, if at all. There is historical precedent for this: until the latter third of the 20th century, axSpA was widely regarded as a male-only disease, leaving women permanently without diagnosis or living with misdiagnosis and inappropriate management (Rusman et al., 2018; van der Horst-

Bruinsma et al., 2013). Gender-based mis-perception persists, as evidenced by van Onna and the results of Chapter 4 (van Onna et al., 2014). Again, there is an educational need among healthcare which could work towards alleviating these issues.

General Practice is the gateway through which patients access healthcare, and General Practice clinicians are the gatekeepers. If realistic and practical methods of speeding and smoothing a patient's progress through this stage to referral are developed, time to diagnosis of axSpA can be reduced.

6.3.1.2 Awareness and understanding of axSpA

The studies of this thesis provided perspective and detail regarding the level of awareness and understanding of axSpA. It was widely perceived that among healthcare and the wider public that knowledge even of the existence of axSpA was low, as was knowledge and understanding of its risks, management and prognoses. Many solutions were suggested to this, including mass-media campaigns and repeat scheduled education for clinicians. While these solutions may well improve awareness of the disease, it may be difficult to justify them on the basis of cost-benefit analyses. While axSpA is not uncommon (between 0.15 and 1% (Dean et al., 2014; Hamilton et al., 2015)), it is by no means evenly distributed and the risks are not uniform throughout the population, being heavily genetically predicated (Bowness, 2015). Nationwide campaigns will be discussed in greater depth later in the chapter, as will education methods and outlets.

Regarding changes to practices within healthcare to promote awareness of the disease, computer-assisted referral was espoused by several HCPs; the computer

systems used in primary care could flag up the possibility of a patient's pain being inflammatory in nature based on presence of a collection of suggestive codes, leading to their being referred to rheumatology (Ramanayake and Basnayake, 2018). This would serve the dual purpose of possibly speeding up time in primary care before referral and raising awareness of the possibility of inflammatory disease for clinicians.

6.3.1.3 Communication with Patients

It became evident through interviews with patients that interactions with primary care clinicians had a large impact on a patient's outlook and the speed and straightforwardness of their journey to diagnosis. As has been described above, attitudes of GPs to a patient's clinical condition very often undermine effective communication and lower a patient's likelihood of timely diagnosis. This is also suggested by data from studies in Chapter 3. While data is limited (only two recent included studies examined diagnosis times relating to referral journey, and of these only one reported whether their results were statistically significant), the strong suggestion is that faster referral to rheumatology results in faster diagnosis (Li et al., 2019; Roussou and Sultana, 2011).

The amount of time spent being seen and symptomatically managed in primary care was linked to three main problems: communication, which has been addressed above, lack of awareness of axSpA, and GPs not recognising signs of axSpA as distinct/higher risk than the symptoms/signs routinely experienced by the much larger numbers of mechanical back pain patients. While the latter two points are fundamentally related, they are distinct. Overlooking clinical symptoms and signs is not necessarily due to lack

of awareness of the disease; it could also be due to the fact that GPs often do not have the time to assess more than one or two of a patient's issues in one consultation. Additionally, many of the symptoms patients are consulting for could be suggestive of other, more common conditions.

6.3.1.4 Time

The feasibility of a solution to a paucity of available time is currently questionable as the NHS is in the midst of a historically intense period of pressure due to a compounding set of circumstances, raising workloads and fewer full time GPs (Hobbs et al., 2016), and these conditions have only worsened due to the Covid19 pandemic (Flynn et al., 2020; Murphy et al., 2020). However, it was widely agreed upon by both patients and HCPs in Chapter 4 that the amount of time available during primary care consultations is not sufficient to fully allow communication of a patient's circumstances and symptoms. This is reflected in the wider population; a 2019 publication by the Royal College of General Practitioners (RCGP) reports that 68% of GPs feel they don't have enough time to assess and treat patients during appointments, 64% feel they don't have enough time to develop relationships with their patients and 65% believe these circumstances undermine patient safety (RCGP, 2019). It has been acknowledged that, while longer consultations of fifteen minutes, rather than the current average of 9.2 minutes would improve patients' healthcare experiences and afford primary care clinicians a better chance at addressing complex issues, it would unavoidably have effects on waiting times (Salisbury, 2019). The above RCGP report posits that development of primary care multidisciplinary teams,

flexibility of consultation types (in person, via video link etc), and improvements to back-end administration could help mitigate any further issues caused by longer consultations.

A further and potentially very significant improvement to this situation is outlined in the GP five-year contract framework (NHS England, 2019). This aims to support recruitment of, and to financially support, up to 20,000 additional staff working in primary care teams; this would include pharmacists, physician associates, physiotherapists, community paramedics and social workers. Theoretically these would spread the workload in primary care and allow for more specialised management. Additionally, and of relevance here, many of these would be able to give patients more time for consultation and discussion for management, potentially leading to a better, earlier understanding of a patient's condition, more effective management and earlier appropriate referral. There is a notable caveat here; however, that with new staff comes new educational need; otherwise it is possible that mis-management of additional care in primary care could lead to further complications at the first gateway to healthcare for patients. Additionally, it has been reported that while introduction of a wider range of clinicians in primary care including pharmacists, while reducing the number of GP appointments, it does increase the use of primary care overall, which needs to be taken into account (Hayhoe et al., 2019).

In addition to this, there are possibilities of the currently available time being used more efficiently, suggested by aforementioned solutions such as raising of awareness of axSpA and the ways in which it presents and improvements in the patient/HCP relationship through improved communication.

6.3.1.5 'Joined-up-thinking' and Continuity of Care

A lack of time in consultations, lack of understanding of axSpA and lack of communication leads to a lack of diagnostic detail arising which is insufficiently descriptive and complex to raise suspicion of axSpA. Many patients in Chapter 4 reported that they felt their diagnosis was delayed due to GPs only wanting to talk about one thing at a time. Whereas axSpA diagnosis is frequently the combination of a complex mix of symptoms, comorbidities, family/personal medical history and investigations. Commonly reported lack of the 'joined-up-thinking' required to diagnose a systemic condition such as axSpA is not simply a cognitive or logistical error; it is a side-effect of consultations only being long enough to cover on average 2.5 problems (Salisbury et al., 2013). Additionally to this, Salisbury et al also noted that while 81% of problems mentioned were recorded in notes, only 37% were recorded as electronic health record database codes; this reflects what was stated by patients interviewed in Chapter 4 that HCPs were not communicating with each other enough about their conditions. The detail required for this communication might commonly not be available. This also leads to clear issue that this brings to the use of primary care health data in analysis such as found in Chapter 5. While the discussion for that chapter proposed the small numbers a lack of association found between diagnosis of axSpA and prior coding for several commonly associated factors (cramps, fibromyalgia, sleep disturbance etc) was due to its lack of pre-diagnosis association, the alternative solution is that these variables are not discussed until axSpA is suspected, at which point they are discussed in the context of disease activity and function index scores.

This issue can at least in part be alleviated through communicative improvements and an increased level of awareness, as suggested above.

Improved awareness of axSpA would also improve the other side of the 'joined-up-thinking' problem. Clinicians are reportedly not connecting the dots between the sometimes disparate-seeming symptoms of axSpA and potentially related comorbidities, instead managing symptoms separately and not considering that they might all be aspects of the same condition.

6.3.2 Future Research

6.3.2.1 Research into Diagnostic Delay

Chapter 3 showed that in studies which report both mean and median diagnostic delay, mean delay measures are consistently higher by around a third than medians. To create a more accurate picture of diagnostic delay in axSpA, more studies need to be undertaken using medians as their primary outcome measure, as this more appropriately represents the skew nature of diagnostic delay data in populations. Studies of diagnostic delay in populations should also more commonly address delay in a less monolithic, more period-based way. Treating delay as a single block of time between symptom onset and diagnosis misses the opportunity to gain more nuanced insight into what variables are more likely to affect delay at what stage. The qualitative study of Chapter 4 showed that the reasons for delay are complex, context specific and of importance with regards to planning an intervention.

6.3.2.2 Specificity regarding symptom onset

Greater clarity regarding 'symptom onset' in population studies seems necessary to raise the accuracy of diagnostic delay measures. The majority of studies do not specify what they mean by symptom onset. A more specific approach here such as, in the case of studies utilising patient self-report, asking *what* their perceived initial symptoms were, would help presentation and usefulness of data in manifold ways. It would initially allow for avoidance of direct comparison between less-comparable samples, such as those who would describe their initial symptoms as fatigue and those who describe their initial symptoms as chronic back pain. It would be a means of quantifying 1) which initial onset symptoms are related to diagnostic delay, 2) what initial symptoms are associated with other important factors, such as gender, age of onset, which are of clinical importance as it would affect the set of circumstances which would raise suspicion of the disease, 3) what initial symptoms are associated with disease progression and response to management, allowing for a targeted and more case-specific approach to education and means of raising awareness, which is discussed below.

Following from this, there needs to be further research into the earliest points after symptom onset that diagnosis is feasible. This would need to be considered in tandem with further research into the earliest points at which reasonable suspicion of inflammatory arthritis could be raised for further and repeated investigation, and under what circumstances to maintain suspicion and regular investigation even if initial imaging and tests are inconclusive. A better definition and set of defined behaviours surrounding these concepts and earliest points of reasonable suspicion could aid earlier diagnosis.

6.3.2.3 Associations between axSpA diagnosis and variables

An inception cohort study could be a possibility to observe associations between variables and axSpA, as in the upcoming BAxSIC study (The Leeds Teaching Hospitals NHS Trust, 2023). Recruitment could occur at the point of diagnosis and patients' symptoms and developing comorbidities would be observed over time; this would be able to show association between variables and axSpA in general and also proportionate increase (or theoretically decrease) in frequency and prevalence over time. This study could also retrospectively investigate which symptoms precede diagnosis, which could be supported by reference to medical records, although given the aforementioned incompleteness of said records, these may not provide enough detailed confirmatory evidence. Although recall bias would not be completely accounted for, this would be minimised as recruitment to a referral cohort would be at diagnosis. Theoretically, an inception cohort study could be undertaken from the point of clinical suspicion of inflammatory arthritis, with patients eventually diagnosed with axSpA being recorded onwards following diagnosis. The main issue with this design would be that suspicion of pain being of inflammatory causes remains low, meaning this recruitment method would most likely be biased towards patients with severe "tell-tale" signs. This could be ameliorated by the use of referral strategies such as detailed by Braun et al (2013) and Baraliakos et al (2020), where likelihood of correct classification is raised by considering signs and symptoms are considered in combination.

6.3.3 Education and Raising Awareness of axSpA

An awareness of axSpA and the ability to recognise the disease needs increasing throughout healthcare, and communication between primary/secondary care and between specialisms needs improving. Additionally, primary care consultations would be improved if they could identify more relevant information on patients. None of these changes are possible, however, without a concerted effort to raise awareness of axSpA in healthcare and for the general public.

Focusing on raising awareness on education in primary care alone will not suffice to eradicate delay, as a very large portion of the delay experienced prior to referral to rheumatology is due to many patients not approaching their GP until their disease is quite developed to the point where it is affecting quality of life. In addition to this, as was reported in Chapter 4, GPs are only aware of seeing a limited number of patients annually with likely axSpA, a finding supported in another interview study with GPs (van Onna et al., 2014). This is despite a relatively high percentage (24%) of patients in primary care with chronic low back pain having undiagnosed axSpA (van Hoeven et al., 2014), illustrating how many patients are being missed. Considering the large caseloads of a GP, combined with the fact that many of axSpA primary characteristics are more commonly seen in other conditions, one possibility is that education and the raising of awareness regarding axSpA could be aimed at mass audiences.

Healthcare campaigns need to take several things into account to attempt to ensure a measurable amount of positive impact:

1) A level of public understanding cannot be presumed. Many patients in Chapter 4 spoke of not only not knowing of the specific disease, axSpA, before their

diagnosis, but also of their lack of appreciation that inflammatory arthritis can also be a systemic problem potentially affecting many organ systems.

2) While characteristic symptoms such as back pain are a necessary focus of an awareness campaign, the surrounding symptoms (alternating buttock pain, stiffness in the morning etc) and important factors which raise likelihood of axSpA (family history of spondyloarthritis for instance) need to be included.
3) A campaign needs to avoid being so general in its message that it overwhelms health services, causing inefficiencies in referral pathways. Some HCPs when asked about messaging strategies in Chapter 4 stated concern that an overly generalised media campaign could lead to a large influx of patients worried that their joint pains were signs of something more complex and severe, overwhelming GPs. Connected to this, if GPs feel pressured to lower their suspicion of inflammatory arthritis based on very common symptoms, referral pathways and secondary care services could be overloaded, leading to a negative effect for patients, rather than a positive.

While an appeal to a national audience would certainly raise awareness of axSpA, the cost-benefit ratio of this approach would not be in its favour. As has previously stated in this thesis, axSpA has a strong genetic predication and as such it is not a risk distributed throughout the population unlike heart attacks, stroke, covid and HIV. Therefore, more practical are awareness campaigns such as the "Act on Axial SpA" campaign run by the National Axial Spondyloarthritis Society (National Axial Spondyloarthritis Society [NASS], accessed 2022) and material in GP surgery waiting rooms where people with symptoms are likely to go.

The “Act on Axial SpA” campaign provides easily understandable and well-presented information on axSpA for the general public and those working in healthcare, a symptom checker on their website to give people a straightforward insight into the likelihood their symptoms are inflammatory, and a roadmap to improving diagnosis times. NASS are also very active through social media, podcasting and through their membership and meetings. Additionally, they have been actively working with government to increase the profile of axSpA through an APPG, the All Party Parliamentary Group for Axial Spondyloarthritis (National Axial Spondyloarthritis Society [NASS], 2022b), which campaigns to raise awareness of the disease in government and to which evidence presented in this thesis has contributed. Versus Arthritis also provides information on axSpA (among other arthritides) to provide support for patients (Versus Arthritis, 2022).

Organisations and methods such as these have high potential for impact on diagnostic delay, which will hopefully become apparent over coming years. This thesis can be considered as additional evidence to lend support to current guidelines and campaigns and on which to base future interventions such as those undertaken by NASS (with little empirical basis), and further evidence to support guidelines such as those promoted by NICE (National Institute for Health and Care Excellence [NICE], 2017)

Based on the findings of this thesis, campaigns and guidelines focused on minimising diagnostic delay in axSpA should consider including the following messages. Some are already present and supported in current guidelines and literature; the intent here is not to supersede current literature but to support it:

1) Of paramount importance is educating primary care clinicians of the need to discuss more than one symptom in consultations. Patients reported short, terse conversations with GPs focused on a single symptom (often pain), which was responded to using analgesics with no further investigation. This is supported by literature showing that the average GP consultation lasts 9.2 minutes and only 2.5 problems were discussed (Salisbury, 2019). Encouraging HCPs in consultation with patients presenting with pain to ask two or three exploratory questions could be greatly beneficial. To facilitate this, an awareness or education campaign could extoll the importance of a more conversational and open attitude to their patients to ensure patients feel their reportage of symptoms is validated. This has the double benefit of providing more information to the HCP and increasing the likelihood the patient will retain confidence in healthcare and attend more frequently. Both of these benefits could feasibly lead to faster diagnosis.
2) Don't ignore pain in the back and joints in younger adults if its cause is not obvious (below 45 years as per NICE guidelines). Several patients in Chapter 4 felt their pain was minimised due to a triggering factor such as a car crash or childbirth and as such lived with it for a time before becoming more concerned. This points to a lowering of the threshold of suspicion regarding chronic relapsing and remitting pain
3) Don't ignore eye pain, particularly if it presents alongside other symptoms. Uveitis was shown in Chapter 5 to be significantly associated with axSpA diagnosis and was reported as a symptom by several of the patient participants in Chapter 4. Up to 40% of uveitis patients could have undiagnosed SpA, the majority of whom are

axSpA, stressing the need for contact and referral between ophthalmology and rheumatology (Haroon et al., 2015).

4) Psoriasis should also raise suspicion. Psoriasis is commonly comorbid with axSpA (Lucasson et al., 2022) and among patients with psoriasis, dependent upon the severity of skin psoriasis within the studied cohort, up to 42% have inflammatory arthritis (Gladman et al., 2005). This thesis reports an association between psoriasis (Chapter 5). It is also associated with more synovitis and enthesitis in studies comparing patients with axSpA; it is also associated with greater use of methotrexate and biologic DMARDs, so not only is it highly suggestive of axSpA, it is also suggestive of a disease presentation which should acted on quickly.
5) Inflammatory bowel disease is also associated with axSpA and should raise suspicion of possible axSpA if encountered. The results of chapter five showed an association between IBD in the last two years prior to diagnosis with axSpA, increasing later than axial pain (associated within three years prior to diagnosis). This raises the possibility that patients with IBD might already be experiencing axial symptoms which are not being considered as inflammatory.
6) Debilitating fatigue and sleep problems need to be taken more seriously by patients and GPs alike. While association with axSpA diagnosis was not shown in Chapter 5, this may be due to issues of EHR coding rather than actual lack of occurrence. Patients interviewed in Chapter 4 frequently described fatigue and sleep problems as disruptive factors to their quality of life caused by their disease, but these were not often described by HCPs when asked what patients wanted to talk about in consultation. Many HCPs when asked stated patients most frequently

discussed their pain and mobility and didn't go into less physically substantive or quantifiable subjects such as sleep and fatigue.

7) If an individual has family history of inflammatory spondyloarthritis, suspicion of symptoms should be heightened. Several patients in Chapter 4 had family history of axSpA and the association between family history and development of axSpA was acknowledged by several participating HCPs. Family history of SpA has been shown in 1/3rds of patients with axSpA (van Lunteren et al., 2018) and is one of ASAS' classification criteria (van der Heijde et al., 2017) and in combination with other features has been shown to be predictive of axSpA diagnosis (Baraliakos et al., 2020). While the systematic review in chapter 3 did not find conclusive evidence that family history of axSpA affected diagnostic delay, this may indicate it is not being sufficiently discussed and reported rather than its presence or absence not having an effect.
8) If an individual is consulting more frequently with any of the above than they usually do, this should not be dismissed. As shown in Chapter 5, an increase in consultation frequency in itself is associated with axSpA diagnosis.
9) Where consultations regarding axial and peripheral symptoms, psoriasis, IBD, enthesitis or uveitis, suspicion of axSpA should be raised. Pragmatically, IBD, psoriasis, enthesitis and uveitis could be focused on as, due to their distinctiveness from other symptoms which could be mistaken for mechanical or transient issues, these comorbidities and symptoms could more easily be noted and perhaps be the focus for campaign messaging. As psoriasis and enthesitis are experienced by at least a quarter of patients with axSpA (Mease et al., 2020), even highlighting the link between them and axSpA could aid earlier identification.

10) Advocacy is important. As shown in the previous section, many patients espoused the benefits of being accompanied by family or friends, and the possibilities of formalised advocacy and self-advocacy (not taking no for an answer). Many patients interviewed for Chapter 4 felt their journey to diagnosis was delayed substantially due to a lack of confidence in their interactions with HCPs, and strongly espoused self-advocacy (described by some as 'not taking no for an answer') and also involving friends and family in communication with HCPs to provide emotional and communicative support. Regarding self-advocacy: this can be greatly aided with access to online advice and information seeking using resources such as the NASS "Act on Axial Spa" website (National Axial Spondyloarthritis Society [NASS], accessed 2022) or literature produced by VERSUS arthritis (Versus Arthritis, accessed 2022). It is also imperative that the focus on advocacy must be seen in tandem with the focus on improvements in communication. The most effective outcome will come at a confluence of informed patient advocacy and constructive and collaborative communication between patients and HCPs.

6.4 Strengths and limitations of the Thesis

Using a mixed methods approach, this thesis explores the extent of diagnostic delay in axSpA, its risks and causes and areas to be addressed in order to achieve a more prompt diagnosis. The systematic review presents an update on the current extent of diagnostic delay in axSpA from the global literature, providing a benchmark range of median diagnostic delay against which to compare future improvements in diagnosis

time. The qualitative study, informed and supported by the findings of the systematic review, shows problematic areas of the diagnostic journey and possibilities for improvement from both a patient and health care professional perspective; this is the first time this has been undertaken with a UK-based participant sample. These findings are further supported by the case-control study of Chapter 5, which presents associations between certain consultation coding and diagnosis of axSpA, providing further evidence of symptoms which should raise clinicians' suspicion of possible axSpA. These three studies not only further contextualise each others' results; in combination they suggest valuable avenues of future research and clinical practice.

While the three studies of this thesis present a continuum of data describing extent of delay, associations with delay, barriers and facilitators in diagnosis and prodromes to diagnosis, the nature of the data explored in these studies led to only partial cross-over of types of data. Crucially, measures of 'patient delay' are not as straightforward as presented in quantitative data due to a point made repeatedly among patients; many were unsure when their symptoms began. While some could put an absolute start on their symptoms and were aware from a very early stage that something was amiss, many described uncertainty until very late in their pre-diagnosis disease progression; their reckoning of symptom onset was only made retrospectively. This suggests limitations in the definition of diagnostic delay, but these are not by any means insurmountable, and these limitations do not negatively affect the utility of results regarding delay, when interpreted within their context.

6.4.1 Reflection on COVID19

As with society at large, the Covid19 pandemic beginning in 2020 had a disruptive effect on this PhD and the undertaking of its constituent studies. While the systematic review was largely complete by the start of 2020, the impact on the studies of Chapters 4 and 5 was considerable, particularly in the case of the former. Methodologically, the lockdowns imposed throughout 2020 and 2021 meant that face-to-face focus groups had to be replaced by remote interviews, recruitment was almost exclusively undertaken online and no 'in-person' contact with any participants could take place. These facts may have impacted upon the outcomes of the study; whether results of interviews were more or less detailed and salient and whether the content provided by participants was different due to the change in data collection format, but this cannot be determined. It is evident however, that the outlook and experience of patients during the pandemic was greatly affected. A lack of easy contact with HCPs along with social isolation exacerbated by their condition, in addition to fear and anxiety due to many of them being on immune-suppressing treatments, unavoidably influenced the study, and possibly altered the emotional resonance of recall for patients. It is also possible the considerable added stresses of operating under covid altered the outlook of HCPs interviewed. While I believe the results of Chapter 4 are representative of the experiences of those interviewed, it is essential they be viewed in the context under which they were collected.

The impact on the case-control study of Chapter 5 was less fundamental but nonetheless noteworthy. This researcher has had limited experience of statistical analysis and as such this was an educational necessity for the undertaking of this PhD. Unfortunately, it was not possible for large stretches of time during my PhD to be in in-

situ contact with colleagues. When I was eventually able to see these colleagues and discuss issues in person, education and skills development were rapid and productive.

6.5 Conclusion

Diagnostic delay of axial spondyloarthritis is global, extensive and associated with many factors. This thesis shows diagnostic delay for axSpA is currently still ranging, for the majority, from a median of 2-5 years globally. It also explores causes and means of working towards reducing it, presenting perspectives from patient and healthcare communities supporting improvements in communication, education and the provision and logistics of healthcare as means of improving diagnostic time. Consultations in primary care prior to diagnosis were also examined, showing that frequency of consultation increased closer to the time of diagnosis, and that consultations for axial, peripheral and psoriatic symptoms all increased in frequency closer to diagnosis, as do those for IBD and enthesitis.

The results presented in this thesis suggest increases in education and awareness of axSpA, combined with improvements to communication and clearer referral pathways could reduce time to diagnosis for axial spondyloarthritis. Data on the increase in consultation frequency and variables associated with axSpA support the body of evidence working towards finding factors which can be used as predictors of axSpA and signposts to raise suspicion earlier in a patient's diagnostic journey.

Qualitative research can continue to provide individual insight into the personal and wider developing landscape navigated through the diagnostic journey. Education and awareness campaigns and improvements to consultations in primary care, referrals

and communications will at the very least improve the experience for patients and at best reduce time to diagnosis.

This thesis adds to a rapidly developing body of knowledge on axial spondyloarthritis and its persistently delayed diagnosis. It details the extent of the problem, the understanding and perceptions of the problem and many details of the problem. Importantly, it also suggests means and methods of improving the journey to diagnosis for future patients with axial spondyloarthritis.

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Appendices

Appendix 1 Published work relating to this thesis

Hay, C.A., Packham, J., Ryan, S. *et al.* **Diagnostic delay in axial spondyloarthritis: a systematic review**. *Clin Rheumatol* **41**, 1939–1950 (2022)

Charles A Hay, Sarah Ryan, Jon Packham, Christian D Mallen, James A Prior, **P275 The extent and characteristics of diagnostic delay in axSpA: a systematic review**, *Rheumatology*, **59**, Issue Supplement_2 (2020)

Appendix 2 Presentations relating to this thesis

- Results for the systematic review chapter were presented to the NIHR SPCR Trainee Conference at the University of Oxford in October 2019
- Results for the systematic review chapter were presented to the UK Research in Musculoskeletal Epidemiology (UK-RiME) conference in at the University of East Anglia in 2019
- Results of the systematic review chapter were presented by Dr James Prior to the All-Party Parliamentary Group for Axial Spondyloarthritis in January 2020
- I won the Brit-SpA clinical abstract competition in 2021 for the abstract detailing preliminary results of the qualitative study, and this work was presented at the Brit-SpA ASM that year
- A poster detailing the results of the qualitative study was presented at a NASS event adjacent to BSR Glasgow in 2022

Appendix 3.1 Systematic review protocol

Title of the review	Diagnostic Delay for Axial Spondyloarthritis: A Systematic Review and Meta-analysis
First reviewer	Charles Hay
Other reviewers (with role/contribution in the review)	James Prior, Jon Packham, Sarah Ryan
Clinical Portfolio Group	N/A
Funding source	NIHR SPCR Studentship
PROSPERO registration number	

Amendments to the protocol	

Background to review

Brief introduction to the subject of the review, including rationale for undertaking the review and overall aim

Axial spondyloarthritis (axSpA) is an autoinflammatory disease, affecting between 0.1 and 1% of the population. The majority of new cases of axSpA occur before the age of 45 and are characterised by inflammation of the sacroiliac joints, back pain, the formation of bony spurs on the vertebrae and, in cases of advanced disease, fusion of sections of the spine. There are two main types of axSpA: radiographic and non-radiographic axSpA. Radiographic axSpA has historically been called ankylosing spondylitis (AS) and sacroiliitis in this case is often identifiable using radiography. Non-radiographic axSpA precedes radiographic axSpA, but does not always develop into it. Additionally, non-radiographic axSpA is not identifiable using radiography, but often becomes evident under MRI.

Diagnosis of axSpA is complex and problematic, due to a low level of awareness of the disease and the fact that several diagnostic characteristics, such as sacroiliitis, occur late in its development. Additionally, misdiagnosis, lack of sensitivity in imaging techniques and comorbidity can delay diagnosis. Estimates of average delay range between 5-10 years after initial onset of symptoms, but these numbers vary greatly depending on the source, leading to a high degree of uncertainty.

It is important to reduce diagnostic delay because uncontrolled and unattended axSpA can lead to painful and life-changing disability, affecting career choices, mental health, lifestyle and interpersonal relationships. Pharmacological and non-pharmacological interventions have been shown

to improve physical and psychosocial states in patients with axSpA, and should be initiated as soon as possible.

This systematic review aims to ascertain the extent of delay in receiving a diagnosis of axSpA from the available literature. Where possible, the review will also ascertain characteristics associated with these time-periods of delay and examine delay in discrete categories to evaluate the delay risk of different factors and at different stages of the diagnostic journey. Additionally, it will be necessary to consider the different classifications of axSpA that have been used, such as ankylosing spondylitis/radiographic axSpA and non-radiographic axSpA. This review will also take into account diagnostic definitions, such as the New York assessment criteria or the ASAS criteria among others. The systematic review will include a narrative synthesis to compare studies and, if possible, a meta-analysis to pool time-periods of diagnostic delay to produce a benchmark value of delay.

2. Specific objectives/questions the review will address

These lists are not exhaustive, nor are they exclusive. If these categories are found in studies returned in our search, they will be included in analysis. If individual categories are absent, this will not be considered as a means for exclusion of the study.

To explore the extent of diagnostic delay for Axial Spondyloarthritis between these possible categories (categories subject to alteration and addition where necessary);

Symptom onset and treatment

Symptom onset to first consultation

Symptom onset to first diagnosis

First consultation to definitive diagnosis

Definitive diagnosis to treatment

To examine whether the extent of diagnostic delay for axial spondyloarthritis is associated with (categories subject to alteration and addition where necessary);

Comorbidities

Lifestyle

Demographics

Family history Outcome measure Clinical knowledge Referral pathways Reasons for initial consultation Prognosis

3. a) Eligibility Criteria for including studies in the review If the PICOS format does not fit the research question of interest, please split up the question into separate concepts and put one under each heading	
Population, or participants and conditions of interest	**Axial Spondyloarthritis**
Interventions/Exposure/item of interest	**N/A**
Comparisons or control groups, if any	**N/A**
Outcomes of interest	**Time-period of diagnostic delay**

Setting	**Primary and secondary care**
Study designs	**All studies**

3. b) Criteria for excluding studies not covered in inclusion criteria Any specific populations excluded, date range, language, whether abstracts or full text available, etc
Exclusions: Those with a population of <18 year olds There will be no restriction on language, but those which can't be translated won't be included in the final paper Studies which do not use humans participants Systematic reviews

4. Search methods

Electronic databases & websites Please list all databases that are to be searched and include the interface (eg NHS HDAS, EBSCO, OVID etc) and date ranges searched for each. **NB All search strategies should be reviewed by Jo Jordan or Nadia Corp BEFORE searching begins**	Embase (Ovid), Medline (Ovid), CINAHL (HDAS), Web of Science, AHMED. Search will not be limited by date ranges.

Other methods used for identifying relevant research ie contacting experts and reference checking, citation tracking	Reference checking
Journals hand searched If any are to be hand searched, please list which journals and date searched from, including a rationale.	N/A

5. Methods of review	
How will search results be managed & documented? ie which reference management software, how duplicates dealt with	Results will be exported to Endnote. In Endnote, exact duplicates will be deleted and close duplicates will be searched for and looked through by eye. Any duplicates found will then be deleted.

Selection process Number of reviewers, how agreements to be reached and disagreements dealt with, etc.	Using the selection criteria, articles will be initially screened by the first reviewer (CH) by title only, with any duplicates and clearly inappropriate articles being removed. The first & second reviewer (AC) will then screen the remaining articles by their abstract. From this list of selected papers, the two reviewers (CH & AC) will then independently select papers for inclusion based on their full content. Where arbitration is necessary on study inclusion or exclusion, a third reviewer (JP) will take the final decision. CH & AC will independently extract the relevant information from the studies to include in the review.
Quality assessment Tools or checklists used with references or URLs, was this piloted? Is it to be carried out at same time as data extraction?	Select questions from the Newcastle-Ottowa tool will be used as a quality assessment tool.

How is data to be extracted? What information is to be collected on each included study? If databases or forms on Word or Excel are used, were these piloted and how is this recorded and by how many reviewers?	Any reported time-period of diagnostic delay (potential time-period sub-categories listed in objectives) Method of axSpA diagnosis used Year of study Demographic characteristics (age and gender) Sample size Sampling period (time-period over which participants were recruited) Country Study setting (general population, primary care, secondary care) How “delay” was quantified (i.e. delay in diagnosis was classed as the period of time between initial symptoms and final diagnosis, delay in treatment was classed as the period of time between initial symptoms and initial treatment etc) Any axSpA-specific characteristic examined for an association with diagnostic delay (potential characteristics listed in objectives)

Outcomes to be extracted & hierarchy/priority of measures ie which measure is preferred and if that is not available which is next in order of preference?	Mean/median (SD/IQR) time period of delay in receiving a axSpA diagnosis
Narrative synthesis Details of what methods, how synthesis will be done and by whom. Is the Narrative Synthesis Framework to be used?	An analytical description of each article's characteristics and reported diagnostic delays.

Meta-analysis Details of what and how analysis and testing will be done. If no meta-analysis is to be conducted, please give reason.	If the search strategy returns enough papers, a random-effects meta-analysis model will be used to pool reported time-periods of diagnostic delay. Meta-analysis will not be conducted if fewer than three comparable papers are obtained. Where different methods of noting diagnostic delay after symptom onset are used, separate meta-analyses will be used.
Will the overall strength of evidence be assessed? If so, how? ie GRADE?	N/A

6. Presentation of results	
Outputs from review Papers and target journals, conference presentations, reports, etc	Paper: Annals of Internal Medicine, Annals of the Rheumatic Diseases; BMC Medicine BSR conference abstract

7. Timeline for review – when do you aim to complete each stage of the review	
Protocol	November
Literature searching	November-December
Quality appraisal	January
Data extraction	January-February
Synthesis	March-April
Writing up	May-July

Support – please state if advice/training or personnel required at each stage	
SR overview	Advice
Protocol development	Advice
Literature searching	Advice
Quality appraisal	N/A
Data Extraction	N/A
Synthesis	N/A
Writing up	N/A

Please send your completed protocol to Opeyemi (see email below) as we would like to put examples on the Intranet.

The systematic review team are available to answer any queries or give advice on completing your review. Systematic review workshops are run at least once a year, or can be arranged on an ad hoc basis if needed by a group. Presentations from previous workshops can be found on the Centre's Intranet.

Opeyemi Babatunde – o.babatunde@keele.ac.uk

Jo Jordan – j.jordan@cphc.keele.ac.uk

Appendix 3.1 PROSPERO registration

Diagnostic delay for axial spondyloarthritis: a systematic review and meta-analysis

Citation

Charles Hay, James Prior, Jon Packham, Sarah Ryan, Alexandros Chatzixenitidis. Diagnostic delay for axial spondyloarthritis: a systematic review and meta-analysis. PROSPERO 2019 CRD42019118963 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019118963

Review question

These lists are not exhaustive, nor are they exclusive. If these categories are found in studies returned in our search, they will be included in analysis. If individual categories are absent, this will not be considered as a means for exclusion of the study.

To explore the extent of diagnostic delay for Axial Spondyloarthritis between these possible categories (categories subject to alteration and addition where necessary);

Symptom onset and treatment

Symptom onset to first consultation

Symptom onset to first diagnosis

First consultation to definitive diagnosis

Definitive diagnosis to treatment

To examine whether the extent of diagnostic delay for axial spondyloarthritis is associated with (categories subject to alteration and addition where necessary);

Comorbidities

Lifestyle

Demographics

Family history

Outcome measure

Clinical knowledge

Referral pathways

Reasons for initial consultation

Prognosis

Searches

Embase (Ovid), MEDLINE (Ovid), CINAHL (HDAS), Web of Science, AMED. Search will not be limited by date

ranges.

Exclusions:

Those with a population of <18 year olds

There will be no restriction on language, but those which can't be translated won't be included in the final paper

Studies which do not use humans participants

Editorials

Qualitative studies

Case reports/case series

Studies with cohorts of fewer than 20 patients

Systematic reviews

Opinion pieces

Types of study to be included

All study types will be considered, with the exclusion of systematic reviews.

Condition or domain being studied

Diagnostic delay in axial spondyloarthritis.

Participants/population

Patients diagnosed with axial spondyloarthritis over the age of 18 years.

Intervention(s), exposure(s)

The main exposure addressed in this systematic review will be delayed diagnosis.

Comparator(s)/control [1 change]

If the data are available, results of patients diagnosed and treated early or in a timely fashion will be compared to those who are diagnosed and treated after a delay.

Main outcome(s)

The main outcomes this systematic review will study will be those regarding changes and progression of disease activity, effects on quality of life, disability and pain, and involvement and development of comorbidities in patients with axial spondyloarthritis diagnosed and treated after a longer time period than is recommended.

Measures of effect

Median and mean diagnostic and treatment delays will be recorded. Where associations with causes of delay, hypothetical or quantified, have been included in studies, these will be included in our systematic review.

Additional outcome(s)

None.

Data extraction (selection and coding)

Any reported time-period of diagnostic delay (potential time-period sub-categories listed in objectives)

Method of axSpA diagnosis used

Year of study

Demographic characteristics (age and gender)

Sample size

Sampling period (time-period over which participants were recruited)

Country

Study setting (general population, primary care, secondary care)

How “delay” was quantified (i.e. delay in diagnosis was classed as the period of time between initial symptoms and final diagnosis, delay in treatment was classed as the period of time between initial symptoms and initial treatment etc)

Any axSpA-specific characteristic examined for an association with diagnostic delay (potential characteristics listed in objectives).

Risk of bias (quality) assessment

Selected questions from the Newcastle-Ottowa tool will be used as a quality assessment tool.

Strategy for data synthesis [1 change]

Aggregated, anonymised patient data will be extracted from the studies returned by our database search after the review process using Endnote for organisation of papers and Rayyan for comparative review. The content of these studies will then be used to construct syntheses, both narrative and quantitative.

If the database search returns more than three studies with comparable diagnostic-delay data, this will then be included in a meta-analysis which will use a random effects model to pool reported time-periods of delay. Where different methods of noting delay are used, different meta-analyses will be created. This will be achieved using STATA.

The meta-analysis will focus specifically on time-periods of delay, whereas the narrative synthesis will expand on this, including, where available, reasons for and outcomes of diagnostic and treatment delay. Data regarding reasons for and outcomes of diagnostic delay are highly heterogeneous between studies and populations and are therefore more appropriate for presentation in a narrative synthesis.

Analysis of subgroups or subsets

If delay is broken down into sub-groups, these will be recorded. For example, previous systematic reviews into diagnostic delay have recorded delay between initial symptom onset to first consultation in primary care, delay from first consultation for diagnosis et cetera.

Similarly, if there are seperate demographics reported in studies which have differing recorded delays, this will also be recorded in our systematic review. The variation found in delay between countries is considerable, meaning that recording this wherever possible is a high priority.

Contact details for further information

Charles A Hay

c.hay@keele.ac.uk

Organisational affiliation of the review

Keele University keele.ac.uk

Review team members and their organisational affiliations

Mr Charles Hay. Keele University Dr James Prior. Keele University Dr Jon Packham. Keele University

Professor Sarah Ryan. Keele University

Mr Alexandros Chatzixenitidis. Keele University

Type and method of review

Diagnostic, Epidemiologic, Intervention, Meta-analysis, Narrative synthesis, Systematic review

Anticipated or actual start date

10 December 2018

Anticipated completion date

31 July 2019

Funding sources/sponsors

NIHR SPCR Studentship

Conflicts of interest Language

English

Country

England

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Delayed Diagnosis; Humans; Spondylarthritis; Spondylitis, Ankylosing

Date of registration in PROSPERO

03 January 2019

Date of first submission

13 December 2018

Stage of review at time of this submission

The review has not started

Stage	**Started**	**Completed**
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

03 January 2019

Appendix 3.2 Systematic search terms

1	Ankylosing ADJ spondyl*.ti,ab,kw	
2	Spondylitis, ankylosing (MeSH)	
3	Spondyloarth*.ti,ab,kw	
4	Spondylarth*.ti,ab,kw	
5	Spondylitis.ti,ab,kw	
6	Spondylarthritis (MeSH)	
7	Spondylarthropathies (MeSH)	
8	Spondylitis (MeSH)	
9	Bechtere*.ti,ab,kw	
10	Marie-str*.ti,ab,kw	
11	(Bamboo ADJ spine).ti,ab,kw	
12	(Spin* ADJ3 Arthr*).ti,ab,kw	
13	Sacroil*.ti,ab,kw	
14	Sacroiliitis (MeSH)	
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	
16	Delayed Diagnosis (MeSH)	
17	Early Diagnosis (MeSH)	
18	((late* or earl*) ADJ3 diagnos*).ti,ab,kw	
19	((late* or earl*) ADJ3 treat*).ti,ab,kw	
20	((late* or earl*) ADJ3 consult*).ti,ab,kw	
21	((late* or earl*) ADJ3 refer*).ti,ab,kw	
22	((late* or earl*) ADJ3 detect*).ti,ab,kw	
23	(diagnos* ADJ3 delay*).ti,ab,kw	
24	(diagnos* ADJ3 lag*).ti,ab,kw	
25	(diagnos* ADJ3 interval*).ti,ab,kw	
26	(treatment* ADJ3 delay*).ti,ab,kw	
27	(case* ADJ3 find*) .ti,ab,kw	
28	(case* ADJ3 seek*).ti,ab,kw	
29	(health* ADJ3 seek*) .ti,ab,kw	
30	(care ADJ3 seek*) .ti,ab,kw	
31	(delay* adj3 consult*).ti,ab,kw	
32	(delay* adj3 detect*).ti,ab,kw	
33	(delay* adj3 interval*).ti,ab,kw	
34	(Delay* adj3 refer*).ti,ab,kw	
35	(delay* adj3 seek*).ti,ab,kw	

36	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 or 31 or 32 or 33 or 34 or 35	
37	15 and 36	

Appendix 3.3 Newcastle-Ottawa quality assessment tool

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and
Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
    a) truly representative of the average _____ (describe) in the community ¯
    b) somewhat representative of the average _____ in the community ¯
    c) selected group of users eg nurses, volunteers
    d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
    a) drawn from the same community as the exposed cohort ¯
    b) drawn from a different source
    c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
    a) secure record (eg surgical records) ¯
    b) structured interview ¯
    c) written self report
    d) no description
4) Demonstration that outcome of interest was not present at start of study
    a) yes ¯
    b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
    a) study controls for _____ (select the most important factor) ¯
    b) study controls for any additional factor ¯ (This criteria could be modified to indicate specific
    control for a second important factor.)

Outcome

1) Assessment of outcome
    a) independent blind assessment ¯
    b) record linkage ¯
    c) self report
    d) no description
2) Was follow-up long enough for outcomes to occur
    a) yes (select an adequate follow up period for outcome of interest) ¯
    b) no
3) Adequacy of follow up of cohorts
    a) complete follow up - all subjects accounted for ¯
    b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an
    adequate %) follow up, or description provided of those lost) ¯
    c) follow up rate < ____% (select an adequate %) and no description of those lost
    d) no statement

Appendix 3.4 Table: overall mean diagnostic delay

Table 2: Mean diagnostic delay for Axial Spondyloarthritis

Author	Year	Country	Setting	Sample	Mean DD	SD
Zwolak., et al	2019	Poland	Lublin 2000-2019	axSpA	9.75	9.5
Feldtkeller., et al	2008	Germany	DVMB & ÖVMB 1996-2005	2005	9.7	
Bakland., et al	2011	Norway	Trømso, 1978-2009	AS	9	
Bandinelli., et al	2016	Italy	Universities of Pisa and Florence 1950-2008	AS	8.7	
Hamilton., et al	2011	UK			8.57	
Sykes., et al	2015	UK	Bath and Norwich, 2009-2013	axSpA	8.5	9.04
Garrido-Cumbrera., et al	2019	Spain	CEADE 2000-2017	axSpA	8.5	7.7
Gerdan., et al	2012	Turkey	5 Cities in Turkey	AS	8.12	8.57
Brunner., et al	2002	Switzerland	Swiss Association of AS Patients	AS	8.1	
Fallahi., et al	2016	Iran	Tehran University of Medical Sciences 2010-2011	AS	7.88	7.17
Brandt et al	2007	Germany	Charité University Medicine, Berlin 2004-2005	axSpA	7.7	
Garrido-Cumbrera., et al	2019	Europe	Aus, Bel, Fra, Ger, Ita, Neth, Nor Rus, Slov, Swe, Swi, UK & Spa 2017/18	axSpA	7.4	8.4
Sorensen., et al	2014	Denmark	DANBIO 2000-2011	AS	7.33	6.58
Aggarwal., et al	2009	India	Rheumatology Clinic, Indian Spinal Injury Centre Hospital, New Delhi	AS	6.9	5.2
Nakashima., et al	2015	Japan	Kyushu University, Fukuoka 1990-2012	AS	6.7	5.6

Redeker., et al	2019	Germany	PROCLAIR database, 1996-2015	axSpA	6.3	
Hajialilo., et al	2014	Iran	Emam Reza Hospital, Tabriz	AS	6.2	3.5
Dincer., et al	2007	Turkey	Istanbul	axSpA overall	6.05	5.08
Roussou., et al	2011	UK	Rheumatology Outpatients, London	AS	6.02	7.49
Bansal., et al	2017	India	Rheumatology Outpatients, Sir Ganga Ram Institute, New Delhi	AS	5.71	5.21
Ozgocmen., et al	2009	Turkey	Tertiary care, 5 university hospitals, East Turkey	AS	5.08	5.99
Masson Behar., et al	2017	France	Tertiary, secondary and primary care, Paris 2009-2013	axSpA	4.9	6.3
Hammoudeh., et al	2015	Qatar	Egypt, Kuwait, Qatar & Saudi Arabia 2013	AS	4.9	5.1
Chimenti., et al	2019	Italy	Tertiary care in 7 referral centres, Lazio region 2010-2018	axSpA	4.83	7.08
Li., et al	2019	China	Rheumatology Department, Shanghai 2014-2016	axSpA	4.825	6.75
Ibn Yacoub., et al	2010	Morocco	Rheumatology Dept, El Ayachi Hospital, Uni of Rabat-Sale 2008-2009	AS	4.12	3.99
Rojas-Vargas., et al	2009	Spain	REGISPONSER	axSpA	0.8	0.6

Appendix 3.5 PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P98
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	N/A
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pp98-99
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P99
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pp102-103
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pp101-102
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Pp104-109
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pp107-109
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pp109-111
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pp110-111
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P112
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pp110-111
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pp112-115
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data	P115

Section and Topic	Item #	Checklist item	Location where item is reported
		conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pp116-118
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pp112-115
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pp112-118
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P112-118
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P120
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P120
Study characteristics	17	Cite each included study and present its characteristics.	Pp126-129
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	P121
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P122 onward
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P122 onward
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	P121

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P167
	23b	Discuss any limitations of the evidence included in the review.	Pp180-181
	23c	Discuss any limitations of the review processes used.	Pp180-181
	23d	Discuss implications of the results for practice, policy, and future research.	Pp169-179
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	P442
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	P442
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	pIII
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Appendix 4.1 Qualitative study protocol

FULL/LONG TITLE OF THE STUDY

Exploring patients' and clinicians' perspectives and experiences regarding barriers and facilitators in diagnosing Axial Spondyloarthritis: A qualitative study.

SHORT STUDY TITLE / ACRONYM

Barriers and Facilitators in Diagnosing Axial Spondyloarthritis

PROTOCOL VERSION NUMBER AND DATE

Version 2.0 11/08/2020

RESEARCH REFERENCE NUMBERS

IRAS Number:	262371
SPONSORS Number:	RG-0306-20
FUNDERS Number:	Generated by the funder. Enter if applicable

SIGNATURE PAGE

For Keele University sponsored studies, the sponsor will confirm approval of the protocol by signing the IRAS form and therefore a signature on the protocol is not required. The sponsor must be notified of all amendments to the protocol, both substantial and non-substantial. Review of amendments by the sponsor will act as the confirmation that the sponsor confirms approval of the amended protocol.

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: .  .....

Date:

20/11/2019

Name: (please print): Dr James A Prior

Contents

KEY STUDY CONTACTS

Chief Investigator	Dr James A Prior, 01782734847, j.a.prior@keele.ac.uk
Study Co-ordinator	Mr Charles Hay, 01782 734986, c.a.hay@keele.ac.uk
Sponsor	Dr Tracy Nevatte, Head of Project Assurance, David Weatherall Building, Keele University, Staffordshire ST5 5NH. Email: research.governance@keele.ac.uk Tel:01782 732975
Funder(s)	NIHR School for Primary Care Research
Key Protocol Contributors	Charles A Hay: c.hay@keele.ac.uk, Dr James A Prior: j.a.prior@keele.ac.uk: Prof Sarah Ryan, Sarah.Ryan2@mpft.nhs.uk, Prof Christian Mallen: c.d.mallen@keele.ac.uk, Dr Jon Packham: Jon.Packham@mpft.nhs.uk | jonathan.packham@nottingham.ac.uk

STUDY SUMMARY

Study Title	Exploring patients' and clinicians' perspectives and experiences regarding barriers and facilitators in diagnosing Axial Spondyloarthritis: A qualitative study.
Internal ref. no. (or short title)	Barriers and facilitators in diagnosing Axial Spondyloarthritis

Study Design	Qualitative (phenomenology) interviews with patients and individual interviews with clinicians.
Study Participants	Male and female patients with axSpA over the age of 18 who have experienced a delay in their diagnosis. Healthcare professionals (HCPs) who have current or previous experience of providing health care for patients with Axial Spondyloarthritis (axSpA). HCPs will include: rheumatologists, general practitioners (GP), general practice nurses and allied health professionals.
Planned Size of Sample (if applicable)	15-20 HCPs 15-20 Patients
Follow up duration (if applicable)	N/A
Planned Study Period	01/01/2020 – 31/05/2021
Research Question/Aim(s)	What are the opinions and experiences of axSpA patients and HCPs regarding the barriers to, and facilitators of, diagnosis of axSpA?

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
NIHR School for Primary Care Research	SPCR Studentship

ROLE OF STUDY SPONSOR AND FUNDER

Sponsor

Keele University is the sponsor for the study and will act as the data controller for the study. The sponsor has the final decisions regarding how data is collected, used, transcribed, analysed, deleted and stored.

Funder

This study is part of a PhD funded by the National Institute for Health Research (NIHR) School for Primary Care Research (SPCR).

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

PPIE: A Patient Participation, Involvement and Engagement (PPIE) group will be involved in the design and dissemination of this study. Members of this group will be identified and recruited with assistance from the Research User Group (RUG) at the School of Primary, Community and Social Care at Keele University.

Study design: The PPIE group will assist with the design of the topic guides for the interviews involving axSpA patients and the interviews with HCPs along with other patient facing documentation, such as information leaflets and consent forms. A preliminary version of the topic guide will be presented to the PPIE group; the design and content will be discussed so as not to miss any important areas of interest.

Dissemination: Advice will be taken from the PPIE group regarding direction and wording of the dissemination of results from this study, in additional to traditional publication in a peer-reviewed journal and through NASS, such as in its quarterly newsletter. Where appropriate, publications will include a PPIE member as a co-author.

Study Steering Group: This group will consist of Charles Hay, James Prior, Sarah Ryan and Christian Mallen and will meet monthly to oversee and review the progress of the project.

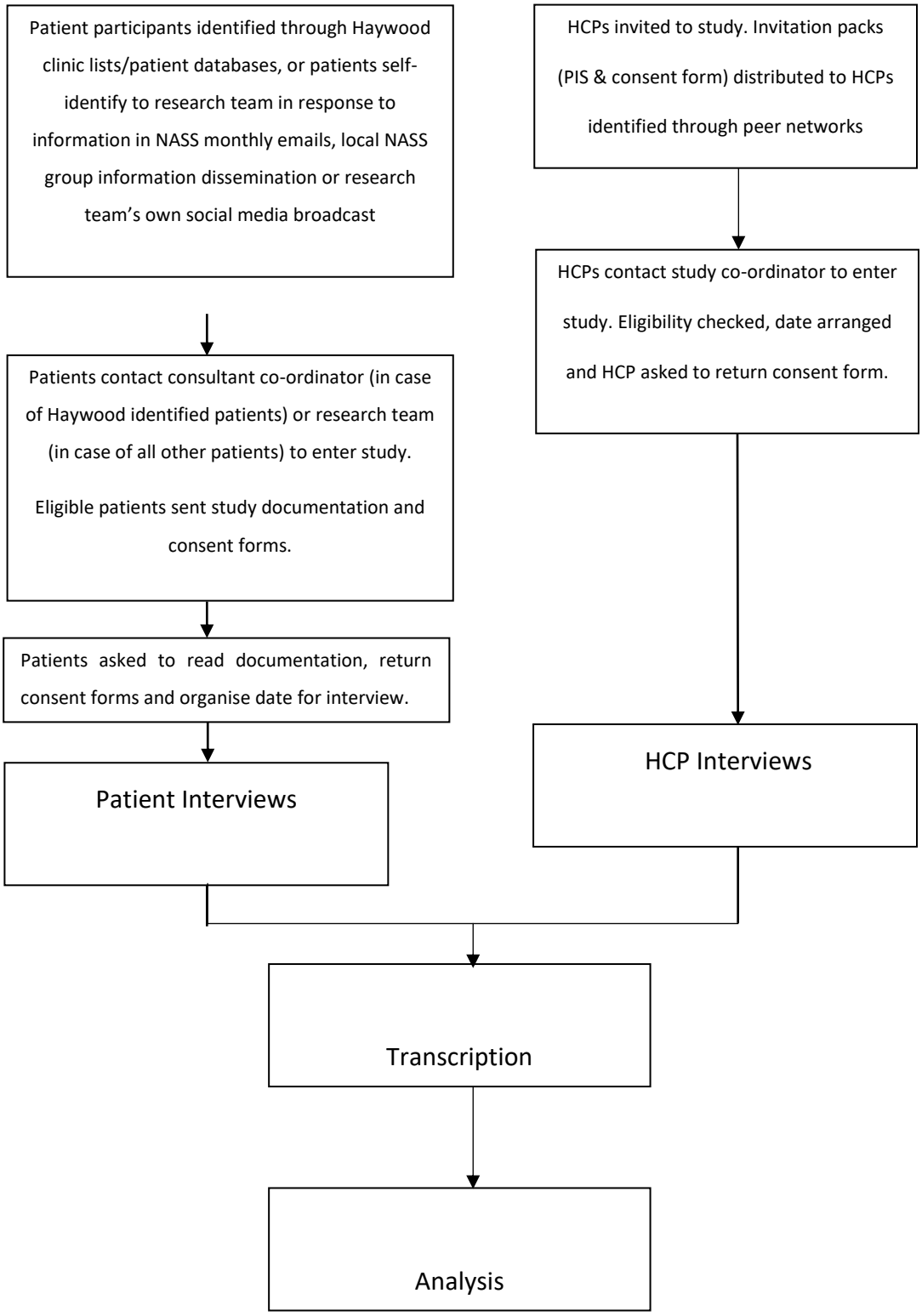
PROTOCOL CONTRIBUTORS

The main contributors to this protocol were Mr Charles Hay, Dr James Prior, Prof Sarah Ryan, Prof Christian Mallen and Dr Jon Packham. All have been involved in study design and will be involved with conducting, analysing and interpreting data, as well as, manuscript writing and dissemination of results.

A PPIE group comprising patients with axSpA will be involved in the design and dissemination of the study, but not this protocol.

KEY WORDS: Axial Spondyloarthritis, Diagnostic Delay, Patient Experience, HCP Experience, Focus Groups, Interviews

STUDY FLOW CHART



STUDY PROTOCOL

Barriers and Facilitators in Diagnosing Axial Spondyloarthritis: A Qualitative Study

1 BACKGROUND

Axial spondyloarthritis (axSpA) is an inflammatory arthritis with a prevalence in the adult UK population of 0.3% (Hamilton et al., 2015, Braun et al., 1998). AxSpA is an umbrella term encompassing two main forms of spondyloarthropathy: radiographic and non-radiographic axSpA. The classification 'ankylosing spondylitis' (AS) continues to be widely used as an overarching term for these, but now should only be used to describe radiographic axSpA.

AxSpA is highly associated with the gene HLA-B27, with >83% of axSpA patients presenting with it (Londono et al., 2015). Symptoms commonly manifest in early adulthood, with the average age of onset being 25.1 years of age (Feldtkeller et al., 2003) and the majority of axSpA symptoms starting before 45 (Sieper et al., 2009). These symptoms can include back pain, stiffness and fatigue (Sieper et al., 2002) and there is also a considerable comorbidity burden associated with axSpA, which can include inflammatory bowel disease, uveitis, psoriasis (Sieper et al., 2015), hypertension and depression (Zhao et al., 2019). Such comorbidity can further reduce quality of life and contribute to a higher degree of disease activity.

The onset of axSpA is typically insidious, and as such, patients can live for many years with this condition before more advanced disease progression occurs. As the disease progresses, it can lead to the destruction of bone in the sacroiliac joint and spine,

which is replaced by fibrocartilage which itself then ossifies, causing bony spurs and fusion along the spine, the extreme form of which is referred to as “bamboo spine” (Sieper et al., 2002) and is highly. Disease progression does not always lead to ossification of the spine, however; inflammation with ossification can be equally painful and debilitating (Sieper et al., 2015). All forms of the disease can result in an inability to work, with employment rates among patients with axSpA as low as 55% and sick leave of between six to 45 days per year reported (Boonen et al., 2001).

The primary treatment for axSpA is non-steroidal anti-inflammatory drugs (NSAIDs), which can bring symptomatic relief by reducing pain and stiffness. They can also have disease-modifying effects, slowing down structural damage to the spine (Poddubnyy, 2013). However, treatment outcomes are negatively affected by delay to diagnosis, with such patients presenting with more spinal bone-growth and fusion, limiting the disease-modifying ability of NSAIDs (Seo et al., 2015).

The National Institute for Health and Care Excellence (NICE) guidelines for diagnosis recommends referral from non-specialist care to a rheumatologist and an HLA-B27 test be performed if a patient presents with lower back pain lasting longer than three months, alongside the presence of three or more additional criteria (Forster et al., 2018, Braun et al., 2011).:

Despite these recommendations, delayed diagnosis of axSpA remains common, with average delays of between eight and 12 years (Seo et al., 2015, Salvadorini et al., 2012). However, prompt diagnosis of axSpA is important as diagnostic delay is associated with poorer outcomes in disease activity, function, spinal mobility and radiographic damage and poorer responses to drug treatments (Seo et al., 2015).

While a large body of research has been dedicated to detailing the extent of diagnostic delay in axSpA, far less has examined the patient and HCP perspective regarding what barriers and facilitators they perceive around axSpA diagnosis. Opinions of patients and practitioners are of central importance regarding the recognition, diagnosis and treatment of axSpA. Erroneous practitioner opinion can lead to underestimation of the probability of axSpA due to mistaken presumptions, as has been the case with female patients with axSpA and the assumption that this is a "male disease" (Rusman et al., 2018). Furthermore, patients' own opinions regarding urgency of the need for consultation for pain, or ease of access to healthcare can also impact on delays to diagnosis.

Avenues for research into the diagnostic journey of axSpA are suggested by a small existing body of qualitative research on the subject. Several studies have explored patient and HCP experiences, knowledge and opinion regarding the effects of living with axSpA, the experience of the process of diagnosis, the level of knowledge regarding axSpA and its diagnosis and the priorities of patients regarding their disease and its management. One Dutch qualitative study of GP experiences of axSpA showed a large gap in knowledge exists, hindering the likelihood of diagnosis or even appropriate referral in primary care. All interviewed GPs were under the misapprehension that ankylosing spondylitis was an exclusively male condition, many significantly underestimated the level of associated diagnostic delay, most associated clinical manifestations were unknown and none of the interviewed GPs would order an HLA-B27 test when a patient presented with back pain (van Onna et al., 2014).

Two UK qualitative studies focusing on the patient experience detailed instances of living with the disease, providing opinions and experiences on its course, its treatment and its effect on personal life, but not factors relating to diagnostic delay (Berenbaum et al., 2014, Raybone et al., 2019). One Danish study, in examining the experiences of the process between symptom onset and diagnosis, did find an overriding theme: "a difficult diagnosis". Several of the participants interviewed in this study describing living for years with significant pain before being diagnosed, with HCPs unable to identify the cause for their pain (Primholdt et al., 2017). Another study described the physical, mental and social effects of AS before diagnosis, describing it as "glum, long, uncomfortable and frustrating" (Madsen et al., 2015).

A pan-European study including patients and HCPs used round table discussions between patients and rheumatologists in which the main priorities for patients and unmet needs were explored. The key recommendations from these discussions were the improvement of patient-physician communication, focusing on patients' priorities for treatment goals, increasing patient and physician disease awareness and reducing time to diagnosis (Garrido-Cumbrera et al., 2017). Related to this theme, a UK-based qualitative study focused on the patient journey to diagnosis reported that many patients perceived communication issues with their HCPs regarding their symptoms, and some even reported HCP reticence regarding the possibility of referral or more in-depth investigation (Martindale and Goodacre, 2014).

While previous qualitative research has been undertaken into the patient and HCP experience of axSpA, there is none yet that focuses specifically on experiences and

opinions from both sides of the patient/HCP relationship regarding barriers to, and facilitators, of axSpA diagnosis.

2 RATIONALE

The National Institute for Health and Care Excellence (NICE) has published guidelines for the referral, diagnosis and management of axSpA to achieve a prompt diagnosis (Forster et al., 2018). Despite this, substantial diagnostic delay remains common and leads to a range of poorer outcomes for patients. The reasons for this disconnect between conceived clinical guidance and actual clinical practice, be it related to the patients or HCP, remains unclear. Therefore, our study aims to garner the opinion and experiences of axSpA patients and HCPs managing patients with axSpA to gain insight into the diagnostic journey and barriers and facilitation in achieving a diagnosis of axSpA. The data gathered during this study will give greater depth to the sum knowledge of the diagnostic process for axSpA and may consequently assist in formulating methods of reducing diagnostic delay for future patients.

3 THEORETICAL FRAMEWORK

The theoretical framework of this study will be phenomenology. The aim of phenomenology is to uncover what a lived experience means to an individual through a process of reflective inquiry (Smith et al., 2009). This approach enables the participants, in this case patients with axSpA and HCPs managing patients with axSpA, to share as full an account as possible of their experience of the journey to axSpA

diagnosis. Phenomenology is particularly useful in understanding under-researched phenomena (Peat et al., 2019), as with the subject of patient and HCP experience of diagnostic delay in axSpA. To date, qualitative research into this field has been limited and focused on experience of the disease itself as opposed to a primary focus on diagnostic delay. Undertaking research using a phenomenological framework will allow researchers to construct insightful, interpretative accounts of patients' and HCPs' experiences, knowledge and opinions regarding facilitators of, and barriers, to timely axSpA diagnosis.

4 RESEARCH QUESTION/AIM(S)

Based on patient and HCP experiences and opinions, what are the main barriers to, and facilitators, of prompt diagnosis of axSpA?

4.1 Objectives

Patients

To explore patients' experiences' of the diagnostic pathway from the period of time between onset of symptoms and diagnosis of axSpA

To explore patients' views on perceived barriers and facilitators to receiving a diagnosis and factors which influence diagnostic delay.

To ascertain perceived outcomes of delay from the patient perspective

HCPs

To explore the HCP experience of the axSpA diagnostic process and the period of time between onset of symptoms and diagnosis of axSpA.

To explore HCP views on perceived barriers and facilitators to diagnosing axSpA and factors which influence diagnostic delay.

To ascertain perceived outcomes of delay .

4.2 Outcome

The primary outcomes of this study are the generation of a greater level of understanding of the patient and HCP experience of the diagnostic pathway of axSpA.

This information will lend insight into the causes behind the persistent delay found in the diagnosis of axSpA and may identify potential avenues to reduce diagnostic delay.

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

This study will use interviews to ascertain patient and HCP opinions on barriers and facilitators in the diagnosis of axSpA. Data collection from patients and HCPs will be conducted separately. The interviews will be facilitated by Charles Hay, supervised by Professor Sarah Ryan.

Interviews for Patients

Interviews will be held with patients diagnosed with axSpA. These interviews will be based on a semi-structured topic guide (Appendix 3) and conducted over the telephone. Interviews will last between 30-60 minutes and will be held at a pre-arranged time convenient for the interviewee. Patients will be asked about their experiences and opinions of the diagnostic journey for axSpA, including factors which impeded or facilitated their diagnosis. This conversation will be structured with the aid of a topic guide.

Healthcare Professional interviews

Telephone interviews will be held with HCPs involved in the diagnosis, management and treatment of axSpA, including (but not limited to) GPs, rheumatologists, general practice nurse and allied health professionals. A range of different areas of professional focus will be represented in these interviews to provide a wider scope of perspective. These interviews will be based on a semi-structured topic guide (Appendix 4).

Interviews will last between 30-60 minutes and will be held at a pre-arranged time convenient with the interviewee. HCPs will be asked about their opinions regarding barriers to axSpA diagnosis and their experiences of the process of referral and diagnosis, this conversation will be structured with the aid of a topic guide.

Data analysis

The interviews will be audio-recorded and anonymised during the transcription process, with names being replaced with unique identifiers. The unique identifier consists of 3 components; 1) participant type – patient (p), healthcare professional (h) or researcher (r); 2) a number assigned sequentially (01,02,03…12); 3) the session that was participated in – interview (i). Approximately 10% of the interviews will be transcribed by Charles Hay (supported by Prof Sarah Ryan), with the majority being transcribed by an external company regularly used by Keele University (The Transcription Company UK). Following transcription, the data from the interviews and focus groups will be analysed in NVivo 12.

Thematic analysis will be employed as the main method of analysing the study data and, as described above, the thematic analysis used here will be based upon a phenomenological framework. The process of thematic analysis can be described thus (Braun and Clarke, 2006):

1 – Familiarisation with data: transcription of interviews , repeated reading and noting of initial codes.

2 – Generation of initial codes: coding interesting and relevant features from the interviews and .

3 – Identifying themes: examining the coded data to identify specific patterns of meaning.

4 – Review of themes: checking that the themes represent the data and address the research question. Generation of a thematic map.

5 – Defining and naming themes: refining the specifics of each theme. Clear names for themes defined.

6 – Writing up: final analysis of data, discussion of analysis and full writing up of study.

This theoretical framework will allow for close examination and interpretation of the patient and HCP experience of the diagnostic journey for axSpA as it aims to explore themes found in individual and compared experiences across participants. It allows for an approach which will avoid the loss of personal experiences and opinions while also facilitating thematic comparison and contrast between individuals and groups. Considering the design of this study incorporates the differing experiences and

opinions of patients and HCPs this multi-level analysis will be of paramount importance.

Data storage

Digital data will be stored on password secured servers at Keele University, and physical data will be stored in a specialised locked storage room in the School of Primary, Community and Social Care at Keele University. Access to these data will require a password in the case of digital records and provision of a key and supervised access by the appropriate staff-member in the case of physical records.

The digital recording of interviews will be transferred via cable to the password protected university computer, then, once it is certain the transfer is successful, it will be deleted from the digital audio recorder.

This data will be transferred to the transcriber in person on a password-protected USB drive, or by secured, recorded delivery on a password-protected USB drive.

The digital file system for this study, to be stored on a password protected university computer, will be planned in advance. Specific file types and information will be kept in pre-agreed location so as to avoid any mis-filing or duplication which could cause problems during the process of deletion.

6 STUDY SETTING

Patients will be identified through four different routes:

AxSpA clinic lists from the Haywood Community Hospital will be reviewed by Dr Jon Packham (Consultant Rheumatologist), to identify patients who meet the inclusion criteria. Only the patients' clinical care team will have access to the patients' medical records and identifiable data. Patients interested in involvement in the study will be provided with information on the study and invited to contact the research team.

At the Haywood Community Hospital, a Midlands Partnership Foundation Trust (MPFT) nurse will search the iPortal/DIAMOND database to identify patients with a current diagnosis of axSpA. The nurse will then arrange for mailing of the study invitation pack to the patient. Patients subsequently wishing to take part will then contact the study team to enter into the study.

The National Axial Spondyloarthritis Society (NASS) will communicate details of the study to their membership through two avenues:

Patient participants will be invited from the local NASS groups in Stoke-on-Trent and Crewe. They will be self-selected from the local NASS patient group, after information regarding the study has been disseminated to that group by the chairman of their group via email.

Details of the study will be included in the national monthly membership email by NASS, along with contact details for the study team.

Patients with axSpA will be invited to join the study, if they meet the inclusion criteria, via an online social media campaign.The study and its intentions will be announced on social media, with an invitation to contact our research team if a patient is interested in joining. Upon contact, further information regarding the study will be sent to the

patient. If the patient is still interested in joining the study, they will be sent a patient information sheet and consent form for completion and return.

The central NASS office will be informed via email of all recruitment communications being made through social media platforms. They will then re-tweet these messages to their followers on Twitter, who can then contact the study team directly with enquiries and/or intention to participate.

The patient and HCP interviews will take place over the telephone. Patient interviews will be organised to take place whenever is most suitable for the participant, including evenings or the weekend to ensure greater representation from working-aged patients with axSpA.

Healthcare professionals (HCPs) will be recruited from within the School for Primary, Social and Community Care at Keele University and through networks linked to this organisation and it's staff. After contacting appropriate HCPs known personally by the research team, the team will ascertain further HCPs for inclusion through these initial contacts. The second wave of HCPs interested in being involved in the study will then be asked for further HCPs to contact. This process will be continued until sufficient HCP participants have been contacted. Healthcare professionals' interviews will take place over the telephone

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

7.1.1 Inclusion criteria

Patients

Patients recruited for this study's will:

Have been diagnosed with axial spondyloarthritis since 2009, to minimise recall bias and better reflect the current state of axSpA management.

In 2009 the Assessment of Spondyloarthritis International Society (ASAS) published their classification criteria for axial spondyloarthritis. These new criteria aimed for greater sensitivity and specificity than previous classification criteria and so acts the current internationally accepted standard for disease definition.

Greater than a year's delay to diagnosis

Be above the age of 18

HCPs

HCPs will be recruited if they:

Are currently or have previously been involved in the diagnosis, management or treatment of axial spondyloarthritis.

7.1.2 Exclusion criteria

Patients

Patients will be excluded if they:

Have a terminal illness

Have cognitive impairments

Possess an insufficient grasp of the English language

HCPs

HCPs will be excluded if they:

Are unavailable within the study period

7.2 Sampling

7.2.1 Size of sample

The patient sample will be 15-20. If possible, equality between male and female patients will be sought, as male and female patients often have different experiences with axSpA and ideally this should be represented by this study.

The HCP sample will be between 15 and 20 to allow for representation of general practitioners, practice nurses, rheumatologists and allied health professionals, while also giving access to multiple perspectives within individual professional areas.

If, after completion of the interviews, it is decided that data saturation has not been reached, further recruitment will be considered. Data saturation is here defined as reaching the stage at which themes arising in conversation are mostly repeated from earlier in the same conversation or from previous interviews .

7.2.2 Sampling technique

Sampling for this study will be purposive; the purposive characteristics detailed in 7.3.1 are: a diagnosis of axSpA from 2009 onwards, delayed diagnosis, different ages, different disease durations, and parity between male and female patients. These characteristics will ensure access to a wide range of experiences to ensure an in-depth exploration of patients experiences.

Patients will be identified through either the clinic lists (by a consultant rheumatologist) or patient databases (by a nurse specialist) at the Haywood Community Hospital or from patients responding to calls for participation through social media or through NASS mailing lists. Patients who meet the inclusion criteria will be invited to participate in the study.

HCPs will be identified through a mix of snowball and convenience sampling, whereby a group of known West Midlands HCPs with interactions with axSpA are contacted and, when being asked for their inclusion into the study, are also asked to give details of other useful contacts. This process will continue until between 15 and 20 HCPs have been recruited.

7.3 Recruitment

7.3.1 Sample identification

Patients

Patients will be recruited for this study on a voluntary basis through one of five different avenues, via three different sources. Patients recruited through all these avenues will be given details to contact the study co-ordinator, at which point they will be asked whether they have a confirmed axSpA diagnosis, when they were diagnosed and whether their diagnosis was delayed to confirm their eligibility for the study.

Patients recruited from the Haywood Community hospital will be recruited in two ways.

Patients recruited through the Haywood Hospital will be made aware of the study by their HCP upon consultation. Upon indication of interest in the study they will be given an invitation letter, patient information sheet and contact details with which to communicate with the research team to signify their willingness to join the study. The HCP will have been informed of the nature of the study, its methods and its outcomes so they are able to give their patients detailed information about the study.

The iPortal/DIAMOND databases will be searched by an MPFT research nurse for current axSpA patients who were diagnosed post-2009. Once identified, the nurse will mail an invitation letter to patients, to which patients can respond either by telephone or email. After a patient contacts the study team with an expression of interest in the study, a study information pack (a patient

information sheet, and a consent form) will be sent to the patient, along with a self-addressed envelope. Using this self-addressed envelope, the patient can send their completed consent form to the study-coordinator. The patient will then contact the study co-ordinator who will establish how long they experienced diagnostic delay (and if eligible), recruit them into the study and arrange an appropriate future date for their telephone interview.

Patients recruited through NASS will initially be informed of the study in either of two ways:

Details of the study will be included in the NASS monthly email, which is sent to their full UK membership list. This message will include a brief description of the study and the contact details for the study team. NASS members diagnosed with axSpA can register their interest by contacting the study co-ordinator directly, at which point, if they are eligible for inclusion, they will be mailed/emailed a formal invitation, consent form and a participant information sheet.

NASS will also be informed via email of recruitment messages broadcast on Twitter (detailed in point 3.) and will then re-tweet these messages, allowing them to reach a far wider audience.

The NASS groups local to Keele University, in Crewe and Stoke-on-Trent, will also contact their membership through their social media presence on Facebook and/or Twitter, again providing the contact details for the study co-ordinator. As above, potential participants, if eligible, will then be provided full study documentation.

Patients who register interest via social media will be sent invitations, PIS and consent forms via mail after a process of assessment of their eligibility for the study, i.e confirmation they fit the inclusion criteria for the study.

In the interest of representing the breadth of experience with the diagnostic journey of axSpA, the following characteristics will be sought:

Patients diagnosed after the 2009 concordance with the ASAS criteria for assessing spondyloarthritis.

A range of ages of patients will help with representation of the experiences of patients with onset of the disease at different points in life. Similarly, a range of disease durations, if possible, would also allow representation of lots of differing experiences with axSpA. Equal numbers of male and female patients will be sought, as the experience of axSpA differs between sexes.

Healthcare professionals

HCPs will be recruited from several sources, including Keele University (both from within the School of Primary, Community and Social Care and the wider University), the Haywood Hospital and GP practices / rheumatology services within the West Midlands area. HCPs will initially be contacted through their existing links with the study team or publicly available email or telephone numbers.. After contacting HCPs the study co-ordinator will ascertain whether the inclusion criteria are met i.e. that they have previous clinical experience of axSpA. If further HCP participants are still

required after this first recruitment wave, then recruited HCP participants will be asked for recommendations of other HCPs who may will be willing to take part in the study. This process will be continued until sufficient HCP participants have been contacted.

7.3.2 Consent

Once a patient has been deemed eligible for inclusion, patients will be mailed or provided with a patient information sheet (PIS) and consent form. The PIS will detail the aims and objectives of the study, the nature of their involvement and data they will be providing, their own rights regarding that data as per General Data Protection Regulation (GDPR) 2018 and the intended further use of their data. If they agree to take part, they will then sign the consent form and post this back to the study coordinator in a freepost envelope. Upon receipt of this, participants will be telephoned to arrange a convenient date for the focus group. Written informed consent will be obtained from either by email or post from HCPs prior to their interviews. Prior to the commencement of the telephone interview, the interviewer will read through the questions in the consent form to ensure the participant is fully aware of the process.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and management of risk

We do not foresee any direct benefit or risk for the participants as a result of participating in this research. However, there is the potential that the subject matter being discussed could prove distressing to some people. Therefore, if a participant becomes distressed, the session will be stopped and recording equipment paused. Participants will be offered contact details of mental health telephone helpline services relevant and, where necessary, local to them if additional support is required to address their distress.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Prior to the study beginning, NHS Health Research Authority (HRA) approval will be sought. NHS HRA ethical approval requires the completion of a participant information sheet (PIS), participant consent forms, a provisional topic guide and interview schedule, a letter from the study sponsor and from the study funder, a schedule of events, and CVs for both student and supervisor.

Before the start of the study a favourable opinion will be sought from a REC.

For NHS REC reviewed research

All correspondence with the REC will be retained.

It is the Chief Investigator's (JP) responsibility to produce the annual reports as required.

The Chief Investigator (JP) will notify the REC of the end of the study.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

If the study is ended prematurely, the Chief Investigator (JP) will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator (JP) will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

Before any site can enrol patients into the study, Chief Investigator (JP) will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the study the Chief Investigator (JP), in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator (JP) will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Amendments

Any amendments that are required to the study will be submitted to the REC.

The CI (JP) will be responsible for the decision to amend the protocol and for deciding whether an amendment is substantial or non-substantial.

The funding body and R&D will be notified in writing if any substantive changes are required.

Any amendments approved by the REC will be added to an updated version of the research protocol.

Guidance on the categorisation of amendments for studies involving the NHS will be sought from the HRA website. http://www.hra.nhs.uk/resources/after-you-apply/amendments/.

8.3 Peer review

This study protocol and the design of this study have been overseen internally by Dr. James Prior, Prof. Sarah Ryan, Prof Christian Mallen and Dr Jon Packham.

8.4 Patient & Public Involvement

Patient and Public Involvement and Engagement will be sourced with the involvement of the Research User Group (RUG) from the School of Primary, Community and Social Care at Keele University. A group of patients with a previous diagnosis of axSpA will be invited to assist in the development of the interview topic guides, along with other patient facing documentation, such as information leaflets and consent forms. The form of interviews will also be discussed. This will cover aspects such as, the amount of time devoted to certain topics, the form of language employed when cueing conversation and considerations to take into account regarding the effects of experience on likelihood of patients responding to lines of questioning.

This PPIE group will also be invited to assist at the dissemination phase of the study, ensuring the outcomes of the study are presented publicly in formats and language which are readily accessible and understandable to those who are affected by axSpA

and its diagnostic process. Any PPIE member involved in dissemination of published literature will be named as authors.

8.5 Protocol compliance

The investigation team will meet monthly to discuss progress of the study and compliance with the protocol. Any minor non-compliance will be reported at these interviews and their severity ascertained and noted. Any major deviation from the protocol will be immediately reported to the CI and, if the deviation is determined to be a total breach of protocol, the study will be halted or, in the case of a total breach of protocol during a focus group, that focus group would be abandoned and re-run with different participants.

Deviation from the protocol will also be reported to the study sponsor in accordance with sponsor policy.

8.6 Data protection and patient confidentiality

All data collected from interviews will be psuedonymised during the transcription process. Patients and HCPs involved in the study will have their rights regarding their data, as per GDPR 2018 made clear to them in their participant information sheets. The participant information sheets will also inform the patients precisely which data are being supplied by their HCP. All data related to this study will be kept on-site at Keele University on secure servers.

The study will adhere to the GDPR 2018. Participant names will not be used; instead unique identifiers will be assigned as outlined in section 5. Consent forms with identifiers will be stored separately to a participant's research data. The link between participant name and their unique identifier will be recorded in 2 locations: 1) on their consent form (which will be stored securely); 2) on an excel sheet on an encrypted, password protected University computer. Only the core research team will have access to this information and it will not be disclosed to anyone else. Access to participants' personal data will be restricted to only those individuals directly involved in the study.

The digital recording of interviews will be transferred via cable to the password protected university computer, then, one it is certain the transfer is successful, it will be deleted from the digital audio recorder.

This data will be transferred to the transcriber in person on a password-protected USB drive, or by secured, recorded delivery on a password-protected USB drive.

The digital file system for this study, to be stored on a password protected university computer, will be planned in advance. Specific file types and information will be kept in pre-agreed location so as to avoid any mis-filing or duplication which could cause problems during the process of deletion.

Data analysis will take place entirely on the grounds of Keele University in the School of Primary, Community and Social Care by a study team member. Electronic data will be stored and analysed on a password protected university computer and any paper documentation and data will be stored in a locked filing room also on the grounds of Keele University. Personal data will be stored for one year after the study has ended.

Research data will be retained for ten years after the study has ended, in accordance with Keele University policy. The data custodian will be Dr James Prior.

8.7 Indemnity

Keele University has in place a broad clinical trials insurance cover that applies equally to CTIMPs and Non CTIMPs and device trials. This includes no fault compensation for all trials.

8.8 Access to the final study dataset

Access to the study dataset will be given primarily to Mr Charles Hay, Dr James Prior, Prof Sarah Ryan, Prof Christian Mallen and Dr Jon Packham. Following this study, the dataset will not be used for any further research.

9 DISSEMINATION POLICY

9.1 Dissemination policy

This study will be presented at local and national conferences and articles published in open access journals. The results of the study will be presented to the PPIE group and involved participants. An article summarising the study and its outcomes will be written for the National Axial Spondyloarthritis Society website and the study will also be presented at the soonest subsequent regional NASS meeting.

Participants in this study will be informed of the results via specifically designed lay language pamphlets, given out at the above-mentioned presentations and posted to

participants who can't attend. The method and form of this dissemination will be designed in conjuntion with the PPIE group.

9.2 Authorship eligibility guidelines

All the named protocol contributors will be granted authorship on the final study article. One lay member from the PPIE group will be a named author on the final study article if a volunteer wishes to be involved.

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11. APPENDICIES

11.1 Appendix 1- Required documentation

Research Passport

Research Protocol

CV of all investigators

Participant Information Sheets (PIS)

Participant consent form

Letters of invitation to participant

GP/consultation information sheets or letters

Interview schedules or topic guides for participants

Flowchart of protocol in non-technical language

Copies of advertisement materials for research participants

Organisation Information document

Letter from sponsor

Letter from funder

Schedule of events

11.2 Appendix 2 – Schedule of Procedures (Example)

Procedures					
	Nov-Dec 2019	Jan-Feb 2020	March-April 2020	May-June 2020	July-October 2020
PPIE involvement: topic guide	X				
Initial contact		X			
Recruitment		X			
Consent attained		X			
Focus Group			X		
Interview			X		
Transcription			X		
Analysis				X	X
Study Writing					X

PPIE involvement: dissemination					X

13.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

Appendix 4.2 Ethical approval

Mr Charles Hay

School for Primary, Community and Social Care Keele University

Staffordshire

ST5 5BG

Email: approvals@hra.nhs.uk

HCRW.approvals@wales.nhs.uk

18 June 2020

Dear Mr Hay

HRA and Health and Care Research Wales (HCRW)

Study title: **Exploring patients' and clinicians' perspectives and experiences regarding barriers and facilitators in diagnosing Axial Spondyloarthritis: A qualitative study**

IRAS project ID:	**262371**
Protocol number:	**RG-0306-20**
REC reference:	**20/LO/0592**
Sponsor	**Keele University**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation.

The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?

HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

Registration of research

Notifying amendments

Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?

Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **262371**. Please quote this on all correspondence. Yours sincerely,

Nicole Curtis Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Dr Tracy Nevatte*

Appendix 4.3 Patient participant information sheet

Patient Information Sheet

Study Title: Barriers and Facilitators in Diagnosing Axial Spondyloarthritis: A Qualitative Study

You are being invited to take part in a new research study examining the diagnostic process for Axial Spondyloarthritis (you may know it as Ankylosing Spondylitis) and why delays in diagnosis occur.

Before you decide whether to take part, it is important for you to understand why this research is being done and what it will involve. Please take the time to read this information sheet carefully and please ask us if there is anything that is unclear or if you would like more information.

What is the purpose of this study?

We are carrying out research into diagnostic delay in axial spondyloarthritis. Diagnostic delay in axial spondyloarthritis is considerable and can cause more severe joint destruction and disease development and poorer response to treatments, therefore it is important that axSpA is diagnosed as quickly as possible after initial onset of symptoms.

This research forms part of a PhD studying diagnostic delay in axSpA at the School for Primary, Social and Community Care at Keele University.

Why have I been invited?

You have been selected because you have previously been diagnosed with axial spondyloarthritis (axSpA) or ankylosing spondylitis (AS) and have been identified to us as being very well suited for inclusion in this study.

Do I have to take part?

No. The decision about whether to take part is up to you and if at any point you don't want to carry on with the study, simply inform any representatives of the research team and you can leave the study. A decision to withdraw, or a decision not to take part, will not affect your right to access health services at your practice or elsewhere.

What would taking part involve?

If you decide to take part in this study, you will be agreeing to take part in a single telephone interview, lasting about half an hour. You will be one of between sixteen and twenty patients interviewed for this study.

The interview will be audio recorded and the audio recording will be converted to text for study. During the transcription process, all participants details will be anonymised, meaning your name and any other identifiable information will be removed from the conversation. It will be ensured that identification of patients through conversation transcripts is impossible.

What are the possible benefits of taking part?

There is unlikely to be any direct benefit for you. However, we hope this research will benefit patients in the future.

What are the possible disadvantages and risks of taking part?

There are no foreseeable disadvantages to taking part in this study. All the answers given in the interview will be anonymised and no sensitive information will be necessary for the study.

How will we use information about you?

Keele University is the sponsor for this study based in the UK, and will act as the data controller for this study. From here on, "we" will refer to the sponsor, i.e. Keele University.
We will be using information from you in order to undertake this study and will act as data controller for this study. This means we are responsible for looking after your information and using it properly. Keele University will keep identifiable information about you for 10 years after the study has finished.

This information will include your name, contact details, relevant diagnosis and avenue of recruitment. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

A third-party transcription service will be used for the transcription of some of the recordings, and a confidentiality agreement will be in place between the research team and the transcription service to ensure confidentiality of all our participants.

We will keep all information about you safe and secure.

You can find out more about how we use your information here

https://www.keele.ac.uk/privacynotices/privacynotice-researchparticipants/

Future contact

In the future, we may contact you again to ask you to be involved in other related studies. We will ask for your permission to contact you again at the end of your interview. If you agree to be contacted again, this does not mean that you must take

part in future; you are only agreeing to be contacted again.

What will happen if I don't want to carry on with this study?

You can withdraw from this study at any stage by contacting **Charles Hay**. Withdrawing means that we would no longer contact you directly, but we would still keep and use the information you have provided up to the point of your withdrawal. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

What will happen to the results of the research study?

The results for this study will be presented at relevant conferences and submitted for publication in medical journals. They will also be disseminated to participating patients where interest is registered. The results will also be written up as part of a student project.

Who is funding and organising the research?

The study is being organised by a research team based at Keele University and the Haywood Hospital and is being funded by the National Institute for Health Research, School for Primary Care Research.

Who has reviewed the study?

The NHS Health Research Authority has reviewed this study (IRAS Project ID 262371).

Contact for further information

For further information, you can contact Charles Hay by telephone on 01782 734986 or via email: c.hay@keele.ac.uk.

If you have any general questions or concerns about taking part in research, you can also contact the Patient Advice and Liaison Service (PALS). You can ask your GP surgery, hospital or phone NHS 111 for details of your nearest PALS; further information about PALS is also available at the NHS Choices website (website link: http://www.nhs.uk/chq/Pages/1082.aspx?CategoryID=68&SubCategoryID=153).

Thank you for taking the time to read this information sheet.

Appendix 4.4 HCP participant information sheet

Healthcare Professional (HCP) Participant Information Sheet

Study Title: Barriers and Facilitators in Diagnosing Axial Spondyloarthritis: A Qualitative Study

You are being invited to take part in a new research study examining the diagnostic process for Axial Spondyloarthritis (you may know it as Ankylosing Spondylitis) and why delays in diagnosis occur.

Before you decide whether to take part, it is important for you to understand why this research is being done and what it will involve. Please take the time to read this information sheet carefully and please ask us if there is anything that is unclear or if you would like more information.

What is the purpose of this study?

We are carrying out research into diagnostic delay in axial spondyloarthritis(axSpA). Diagnostic delay in axSpA is considerable and can cause more severe joint destruction and disease development and poorer response to treatments, therefore it is important that axSpA is diagnosed as quickly as possible after initial onset of symptoms.

This research forms part of a PhD studying diagnostic delay in axSpA at the School for Primary, Social and Community Care at Keele University.

Why have I been invited?

You have been selected because you manage or encounter patients with axial spondyloarthritis.

Do I have to take part?

No. The decision about whether to take part is up to you.

What would taking part involve?

If you decide to take part in this study, you will be agreeing to take part in a single interview held in mid 2020, taking place either at your own practice or via telephone, dictated by your own convenience. This interview will be last 30 minutes and will be semi-structured, based around a pre-set collection of subjects, but open to elaboration or deviation where relevant. This will ensure that important aspects of study are not missed or explored in too little detail.

The interview will be audio recorded and the audio recording will be transcribed for study. During the transcription process, all participants will be anonymised, meaning their names will be removed from conversation, replaced with numbers. It will be ensured that identification of HCPs through conversation transcripts is impossible.

What are the possible benefits of taking part?

There is unlikely to be any direct benefit for you. However, we hope this research will benefit patients in the future.

What are the possible disadvantages and risks of taking part?

There are no foreseeable disadvantages to taking part in this study. All the answers given in the interview will be anonymised and no sensitive information will be necessary for the study.

How will we use information about you?

Keele University is the sponsor for this study based in the UK, and will act as the data controller for this study. From here on, “we” will refer to the sponsor, i.e. Keele University.

We will need to use information from you for this research project. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. This information will include your name and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly.

We will keep all information about you safe and secure.

Keele University will keep relevant study data for 10 years after the study has finished.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

A third-party transcription service will be used for the transcription of some of the recordings, and a confidentiality agreement will be in place between the research team and the transcription service to ensure confidentiality of all our participants.

Consent for this use of your data will be recorded and kept on file at Keele University.

Future contact

In the future, we may contact you again to ask you to be involved in other related studies. We will ask for your permission to contact you again at the end of your interview. If you agree to be contacted again, this does not mean that you must take part in future; you are only agreeing to be contacted again.

What will happen to the results of the research study?

The results for this study will be presented at relevant conferences and submitted for publication in medical journals. They will also be disseminated to participating patients

and HCPs where interest is registered. The results will also be written up as part of a PhD thesis.

Who is funding and organising the research?

The study is being organised by a research team based at Keele University and the Haywood Hospital and is being funded by the National Institute for Health Research, School for Primary Care Research.

Who has reviewed the study?

The NHS Health Research Authority has reviewed this study (IRAS Project ID 262371).

Contact for further information

For further information, you can contact Charles Hay by telephone on 01782 734986/07816 949551 or via email: c.hay@keele.ac.uk.

Thank you for taking the time to read this information sheet.

Appendix 4.5 Patient consent form

IRAS ID: **262371**

Centre Number: N/A

Study Number:

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: **Understanding barriers and facilitators in diagnosing Axial Spondyloarthritis: A qualitative study.**

Name of Researcher: Mr Charles Hay

	Please initial box
1. I confirm that I have read the information sheet dated 11/08/2020 (version 2.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3. (If appropriate) I understand that data collected during the study, may be looked at by individuals from Keele University, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my study data.	☐
4. (If appropriate) I understand that the information held and maintained by Keele University and the Haywood Community Hospital may be used to help contact me to arrange the focus group and provide the results of the study.	☐
5. I agree to take part in the above study.	☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix 4.6 HCP consent form

IRAS ID: **262371**

Centre Number: 1

Study Number:

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: **Understanding barriers and facilitators in diagnosing Axial Spondyloarthritis: A qualitative study.**

Name of Researcher: Charles Hay

	Please initial box
6. I confirm that I have read the information sheet dated 10/06/2020 (version 1.1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
7. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected.	☐
8. (If appropriate) I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.	☐
9. I agree to take part in the above study.	☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix 4.7 Patient topic guide

Topic Guide Interview, 30-60 minutes

Interview Objectives

Primary Aim: To gain understanding of the barriers to and facilitators of diagnosis of axial spondyloarthritis (axSpA).

OR

Understanding reasons for diagnostic delay in axSpA

Sample

Between 15 and 20 patients will be interviewed over the telephone for this study. The patients will be recruited from 1) the membership of the National Ankylosing Spondylitis Society or 3) axSpA patients answering an announcement made on social media.

Selection criteria

- English speaking
- Cognitively capable of participating in and emotionally coping with the interview
- Diagnosed with axial spondyloarthritis
- Subject to diagnostic delay of greater than 12 months

Introductions, consent

- Introductions. I am a PhD student and don't have a clinical background.
- Inform patient that the session is to be recorded and remind them that their testimonial will be anonymised during the transcription process.
- Confirmation that the patient has read and become acquainted with the patient information sheet (PIS) and consents to take part in the study.
- Inform patient that the interview will take up to an hour and what the structure of the interview will be.
    - Background information
    - Exploration of patient's understanding of axSpA and diagnostic delay
    - Patient's experience of axSpA and diagnostic delay
    - Exploration of patient's opinions regarding axSpA and diagnostic delay
- Reiteration of the content of the PIS to ensure understanding.

Background Information, introducing research

- Description of axSpA: Axial spondyloarthritis, previously and also known as ankylosing spondylitis
        - For the most part I'll call it axial spondyloarthitis and axSpA
    - an inflammatory arthritis found in around 1 in 200 people.
    - Primarily affects the lower back, causing chronic back pain and changes in the spine which can lead to reduced range of ability.
    - Patients still suffer between two and eight years diagnostic delay, sometimes far more.
- **This research is part of a three part project looking to assist in the reduction of diagnostic delay**
    - The first part is a review of all research into diagnostic delay to find out global levels of delay
    - After this current study, another will be run looking at the relevant medical histories of patients leading up to their diagnosis of axSpA

- This interview based study aims to find out about patient and HCP experience of the axSpA journey to diagnosis
- We want to know more about what holds up diagnosis and where possible, what speeds it up.
- Do you have some questions at this stage?

Understanding of axSpA and diagnostic delay

- Knowledge of axSpA, its delay, the outcomes of its delay
    - Before what I just told you, what would you have thought the amount of delay was for the disease?
    - Are you aware of the outcomes of delayed diagnosis?

Experience

- How long did it take to reach your diagnosis of axSpA?
    - Are you aware of what was identified as your "initial symptom of onset"?
    - Do you agree with that assessment?
- What symptoms did you first present with and to whom?
- What did you think was causing these symptoms?

Motivators for and Experience of First Consultation

- What motivated you to go and see your GP?
    - How long had you had your symptoms before you went to see your GP?
    - Were you motivated by the experiences or opinions of other patients with axSpA?
- What were you hoping the GP would do (expectations of the consultation)?
- Can you recall what happened when you went to see your GP?
- Did your GP suggest to you what might have caused your symptoms?
- What did your GP advocate trying to help with your symptoms?

Referral and Process of Diagnosis

- Did you have to go for any investigation?
- How long had you had your symptoms before you were given a diagnosis?
- How did it feel when diagnosis was reached?

Barriers/Facilitators

- Did you encounter any setbacks to diagnosis?
    - Uncertainty regarding cause of symptoms
    - Mis-diagnosis
    - Personal circumstances
    - Referral delays
- Did you encounter anything which notably sped up your diagnosis?
    - Suspicion based on experience
    - Obvious set of circumstances Immediate or fast referral
    - Which stages of medical care did you feel were the quickest and most efficient?
- Any knowledge of the experiences of other axSpA patients?

Opinions

- On the road to receiving your diagnosis, what processes could have been improved?
    - This includes your own experience prior to consultation with any healthcare professional regarding your arthritis
    - Process of referral
    - Certainty of diagnosis
- What ideas do you have for how diagnostic delay could be reduced for axial spondyloarthritis?
    - What elements of the diagnostic process do you find the most important?
    - What would you respond to most readily (advertising, press, warnings in GPs surgery etc)?

- What could be altered on the HCP side to better facilitate timely diagnosis?
- How would this apply to yourself?
- How would this apply to the wider population?

That brings us to the end of the interview! Thank you so much for your time, it's very much appreciated. Your input and insights have been very valuable and will make up part of a study which should hopefully prove helpful to lots of people either diagnosed with or managing axSpA in the future.

If you want, I'll keep you appraised of the results of this study and the ways in which these results will be used in the future.

Do you have some final questions?

Appendix 4.8 HCP topic guide

Topic Guide Healthcare Professionals Interview, 30 minutes

Interview Objectives

Primary Aim: To gain understanding of the barriers and facilitators of diagnosis of axial spondyloarthritis (axSpA).

Sample

Healthcare professionals (HCPs) of different specialities will be recruited for interview (rheumatologists, GPs, general practice nurses, physiotherapists, other allied health professionals). Recruitment of HCPs is purposive, with HCPs managing axSpA being targeted for inclusion.

Selection Criteria

English speaking

Currently or previously Managing axSpA

Operating within the West Midlands area

Introductions, consent

Introductions. I am a PhD student and don't have a clinical background.

Inform interviewee that the interview is being recorded and that they will not be identifiable after transcription.

Confirmation that the participant has read and become acquainted with the participant information sheet (PIS) and consents to take part in the study.

Inform interviewee that the interview will take between 30 minutes and an hour, confirm that this time is currently available.

This study makes up part of my PhD, which also involves a systematic review and a case-control study

This interview based study aims to find out about patient and HCP experience of the axSpA journey to diagnosis

We want to know more about what holds up diagnosis and where possible, what speeds it up.

Outline structure and timing of interview

The interview is designed to last between half an hour to an hour

Structure

Background information

Information about the interviewee and their knowledge of axSpA

Experience of managing axSpA

Experience and perception of axSpA patient experience

Conversation on how to help reduce delay

Background Information, introducing research (time – no more than a minute)

I have a brief section to catch anyone who needs it up on axSpA – do you need a run through on prevalence, characteristic and diagnostic delay, or shall we skip straight to the interview?

Apologies to those who already know this, perhaps cut altogether if they already have good grounding:

Axial spondyloarthritis, previously and also known as ankylosing spondylitis

For the most part I'll call it axial spondyloarthitis and axSpA

an inflammatory arthritis found in around 1 in 200 people.

Primarily affects the lower back, causing chronic back pain and changes in the spine which can lead to reduced range of ability.

Patients still suffer between two and eight years diagnostic delay, sometimes far more.

Do you have some questions?

Participant Introduction

Now I've been introduced, along with the study, I'd like to hear a bit about yourself.

We'll talk at greater length about your experiences with axSpA, but briefly could you outline your specialty and work within it, and how this brings you into contact with axSpA?

Experience of managing axSpA

What symptoms do you associate with axSpA?

Can you imagine what you'd see in a patient to make you suspect axSpA?

How frequently do you encounter patients with symptoms suggestive of axSpA?

When did you last see a patient you thought might have axSpA?

What were they in for?

Characteristics of patients

Where referred from?

Where referred to?

Can you think of a "typical" experience of the diagnostic process from HCP perspective?

What can you say about a typical referral process?

How long has often passed between a patient getting symptoms and going to their doctor?

How long do referrals take?

How are these prioritised?

If you manage or treat axSpA, how would you treat/manage a patient who you suspected of having axSpA?

What is your awareness of other HCP and AHP experiences of the axSpA management?

Are there any resources or experts you call upon when assessing a patient with axSpA?

Guidelines?

Colleagues?

Experts?

Personal experience?

Social media?

If you do use guidelines, how useful do you find these in real-world axSpA cases?

What we know so far is that this condition generally takes 8 years to be diagnosed

Why do you think that might be?

Patient behaviours

Unusual presentation

Complex morbidity

HCP related issues

Imaging

Can you think of anything that would be in your power to assist in earlier diagnosis?

Experience and Perception of patient experience of axSpA

Generally, how do you think patients experience the diagnostic journey for axSpA?

Have you seen patient experiences differing based on their referral journey?

Have you seen patient experiences differing based on their reasons for first seeking help?

Up until the point of diagnosis, what do patients on the diagnostic journey want to talk about the most?

Do patients get enough time to discuss their symptoms in enough depth to suggest a less obvious diagnosis such as axSpA?

Process things?

Symptom things?

Access?

IF NOT COVERED EARLIER:

Experience of personal and observed levels of guideline implementation

Awareness of NICE guidelines?

To what extent do you feel NICE guidelines are adhered to?

Is adherence to NICE guidelines all the time realistic?

Are alternative routes sometimes necessary?

If aware of ASAS assessment criteria: have things improved since their introduction?

If unaware of ASAS assessment criteria: do you perceive the process of diagnosis to have improved in recent years?

Opinions regarding what could help with diagnostic delay

Generally, how could things be improved in the diagnostic process?

What has been enacted in other areas which has improved diagnosis times?

What do you think regarding the feasibility of a campaign similar to that of stroke and heart attacks which gave people a more standardised vocabulary with which to communicate symptoms with their HCP?

Interview End

Thank you so much for your involvement today, your input and insight has been extremely helpful and enlightening.

I understand your time is very precious and I'm very grateful for you being able to fit this in. I'll be in touch if you want to know the outcomes of the study.

Appendix 4.9 COREQ checklist

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	P198
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	P1
Occupation	3	What was their occupation at the time of the study?	P1
Gender	4	Was the researcher male or female?	P198
Experience and training	5	What experience or training did the researcher have?	N/A
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	Pp193-195
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	N/A

Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	N/A
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Pp183-187
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Pp190-195
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	Pp193-195
Sample size	12	How many participants were in the study?	P214
Non-participation	13	How many people refused to participate or dropped out? Reasons?	N/A
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	Pp197-199
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	N/A
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	Pp203-206
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Pp199-201
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	N/A
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	Pp198-199
Field notes	20	Were field notes made during and/or after the inter view or focus group?	Pp208-209
Duration	21	What was the duration of the inter views or focus group?	Pp198-199
Data saturation	22	Was data saturation discussed?	Pp210-213
Transcripts returned	23	Were transcripts returned to participants for comment and/or	N/A

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	P203
Description of the coding tree	25	Did authors provide a description of the coding tree?	P207
Derivation of themes	26	Were themes identified in advance or derived from the data?	Pp204-206
Software	27	What software, if applicable, was used to manage the data?	P204
Participant checking	28	Did participants provide feedback on the findings?	N/A
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Pp220-277
Data and findings consistent	30	Was there consistency between the data presented and the findings?	Pp220-277
Clarity of major themes	31	Were major themes clearly presented in the findings?	Pp278-280
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	Pp278-280

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. International Journal for Quality in Health Care. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

Appendix 5.1 Full list of clinical exposures

Read Code Lists

Axial Problems

N131.00	Cervicalgia - pain in neck	N131
N125.00	Cervical disc degeneration	N125
N120.00	Cervical disc displacement without myelopathy	N120
N12zH00	Cervical disc disorder with radiculopathy	N12zH
N13z.00	Cervical and neck disorders NOS	N13z
N120.12	Cervical disc displacement	N120-2
N110.12	Osteoarthritis cervical spine	N110-2
N11D000	Osteoarthritis of cervical spine	N11D0
N138.00	Cervicalgia	N138
N131.11	Pain in cervical spine	N131-1
N131.00	Cervicalgia - pain in neck	N131
16AZ.00	Stiff neck symptom NOS	16AZ
N373.00	Kyphoscoliosis and scoliosis	N373
N373000	Idiopathic scoliosis	N3730
N371.00	Acquired kyphosis	N371

N373600	Postural scoliosis	N3736
N141.00	Pain in thoracic spine	N141
N12z800	Thoracic discitis	N12z8
N141.11	Acute back pain – thoracic	N141-1
N374X00	Other and unspecified kyphosis	N374X
N142.11	Low back pain	N142-1
N12..00	Intervertebral disc disorders	N12
N122.11	Prolapsed lumbar intervertebral disc	N122-1
N114.12	Lumbar spondylosis	N114-2
N114.11	Degeneration of lumbar spine	N114-1
N142.00	Pain in lumbar spine	N142
N122.00	Lumbar disc displacement	N122
N12D.00	Narrowing intervertebral disc space	N12D
N142.14	Lumbago	N142-4
N1...00	Vertebral column syndromes	N1
N331.12	Collapse of vertebra NOS	N331-2
N23yE00	Spasm of back muscles	N23yE
N142.13	Acute back pain – lumbar	N142-3
N143.11	Acute back pain with sciatica	N143-1

N149.00	Back stiffness	N149
N123.11	Intervertebral disc prolapse NOS	N123-1
N148C00	Lumbar spine instability	N148C
N142000	Lumbago with sciatica	N1420
N142.12	Lumbalgia	N142-2
N146311	Lumbosacral strain	N1463-1
N12zC00	Lumbar discitis	N12zC
N11D200	Osteoarthritis of lumbar spine	N11D2
N12z300	Other lumbar disc disorders	N12z3
N14y.00	Other back symptoms	N14y
N12C300	Lumbar disc prolapse with cauda equina compression	N12C3
N331111	Collapse of lumbar vertebra	N3311-1
N146600	Sacroiliac disorder	N1466
N146z11	Sacroiliac strain	N146z-1
N33A000	Bony pelvic pain	N33A0
N094L00	Arthralgia of sacro-iliac joint	N094L
N094500	Arthralgia of the pelvic region and thigh	N0945
N146400	Sacroiliac instability	N1464

N095L00	Stiff sacro-iliac joint NEC	N095L
N146500	Sacral instability NOS	N1465
N245.	Pain in buttock	N245-9
N145.11	Acute back pain – unspecified	N145-1
N14z.00	Back disorders NOS	N14z
N145.12	Back pain, unspecified	N145-2
N118.00	Traumatic spondylopathy	N118

Peripheral Involvement

N245.17	Shoulder pain	N245-7
N210.12	Frozen shoulder	N210-2
N245700	Shoulder pain	N2457
N095111	Shoulder stiff	N0951-1
N094100	Arthralgia of the shoulder region	N0941
N05z100	Osteoarthritis NOS, of shoulder region	N05z1
N094111	Shoulder joint pain	N0941-1
N05z900	Osteoarthritis NOS, of shoulder	N05z9

N094A00	Arthralgia of shoulder	N094A
N06z111	Shoulder arthritis NOS	N06z1-1
N212000	Periarthritis of shoulder	N2120
N095100	Stiff joint NEC, of the shoulder region	N0951
N06z100	Arthropathy NOS, of the shoulder region	N06z1
N094K12	Hip pain	N094K-2
N094512	Hip joint pain	N0945-2
N053512	Hip osteoarthitis NOS	N0535-2
N220S00	Synovitis of hip	N220S
N095511	Hip stiff	N0955-1
N143.	Sciatica	N143
N36y000	Acquired unequal leg length	N36y0
N096611	Knee gives way	N0966-1
N06z611	Knee arthritis NOS	N06z6-1
N224A11	Baker's cyst	N224A-1
N05z500	Osteoarthritis NOS, pelvic region/thigh	N05z5
N094M00	Arthralgia of knee	N094M
N07yH00	Locking knee	N07yH
N094W00	Anterior knee pain	N094W

1M10.	Knee pain	1M10
N0946	Knee joint pain	N0946-1
	Leg pain	N245-6
	Pain in leg	N2452
N05zJ00	Osteoarthritis NOS, of hip	N05zJ
N215800	Snapping hip	N2158
N06z511	Hip arthritis NOS	N06z5-1
N215100	Bursitis of hip	N2151
N064K11	Irritable hip	N064K-1
N224A11	Baker's cyst	N224A-1
N065z11	Polyarthritis	N065z-1
N38..	Other acquired deformity	N38
N090Y00	Acute joint effusion	N090Y
N094.11	Ache in joint	N094-1
N097.00	Difficulty in walking	N097
N097z00	Difficulty in walking NOS	N097z
N095.00	Joint stiffness NEC	N095
N09..00	Other and unspecified joint disorders	N09
N096.12	Musculoskeletal pain – joints	N096-2

N061.00	Traumatic arthropathy	N061
N21z311	Bone spur NOS	N21z3-1
N14z.12	Spinal disorder NOS	N14z-2
N095900	Multiple stiff joints	N0959
N310z00	Paget's disease NOS	N310z
N095711	Ankle stiff	N0957-1
N096711	Unstable ankle	N0967-1
1M13.	Ankle pain	N245-1
N245.	Ankle pain	N245-1
N224800	Ganglion of ankle	N2248
N245.13	Foot pain	N245-3
1M11.00	Foot pain	1M11
N245100	Foot pain	N2451
N094700	Arthralgia of the ankle and foot	N0947
16J7.00	Swollen foot	16J7
N053700	Localised osteoarthritis, unspecified, of the ankle and foot	N0537
N05z700	Osteoarthritis NOS, of ankle and foot	N05z7
N05z712	Foot osteoarthritis NOS	N05z7-2

N051700	Localised, primary osteoarthritis of the ankle and foot	N0517
N06z712	Foot arthritis NOS	N06z7-2
N06z700	Arthropathy NOS, of the ankle and foot	N06z7
N023700	Gouty arthritis of the ankle and foot	N0237
N097300	Walking difficulty due to ankle and foot	N0973
1D17.00	Morning stiffness - joint	1D17
F13z200	Restless legs syndrome	F13z2
N241012	Muscle pain	N2410-2
1DCC.00	Aching muscles	1DCC
N240200	Muscular rheumatism	N2402
N241000	Myalgia unspecified	N2410
N241011	Intercostal myalgia	N2410-1
N241z00	Myalgia or myositis NOS	N241z
N241.00	Myalgia and myositis unspecified	N241
	Arthralgia of multiple joints	N0949
	Osteoarthritis NOS	N05zz
	Pain in upper limb	1M0
	Ankle swelling	1832

	Hand pain	N245-4

Enthesitis

N212500	Shoulder tendonitis	N2125
N210.11	Bursitis - shoulder	N210-1
N211800	Bursitis of shoulder	N2118
N215100	Bursitis of hip	N2151
N2157	Trochanteric bursitis	N2157
N217400	Achilles tendinitis	N2174
N220700	Tenosynovitis of foot	N2207
N2179	Plantar fasciitis	N2179
N223.00	Bursitis NOS	N223
N21z200	Tendinitis NOS	N21z2
N21z.00	Enthesopathy NOS	N21z

N2157	Trochanteric bursitis	N2157
N21z200	Tendinitis NOS	N21z2
N21z.00	Enthesopathy NOS	N21z
N220700	Tenosynovitis of foot	N2207
N212500	Shoulder tendonitis	N2125
N223.00	Bursitis NOS	N223
N2179	Plantar fasciitis	N2179
N210.11	Bursitis - shoulder	N210-1
N217400	Achilles tendinitis	N2174
N220700	Tenosynovitis of foot	N2207
N211800	Bursitis of shoulder	N2118
N2131	Medial epicondylitis – elbow	N2131
N2132	Lateral epicondylitis – elbow	N2132

Uveitis

F4431	Iritis	F4431
F441.	Chronic Iritis	F441
F443.	Uveitis	F443
F4430	Anterior Uveitis	F4430

F4322	Posterior uveitis NOS	F4322
F4412	Chronic anterior uveitis	F4412

Psoriasis

38Gg.	Psoriasis area severity index	38Gg
M16..	Psoriasis and similar disord.	M16
M1600	Psoriasis spondylitica	M1600
M161.	Other psoriasis	M161
M1610	Psoriasis unspecified	M1610
M1611	Psoriasis annularis	M1611
M1612	Psoriasis circinate	M1612
M1613	Psoriasis diffusa	M1613
M1614	Psoriasis discoidea	M1614
M1615	Psoriasis geographica	M1615
M1616	Guttate psoriasis	M1616
M1617	Psoriasis gyrate	M1617
M1618	Psoriasis inveterate	M1618
M1619	Psoriasis ostracea	M1619
M161A	Psoriasis palmaris	M161A

M161B	Psoriasis plantaris	M161B
M161C	Psoriasis punctata	M161C
M161E	Psoriasis universalis	M161E
M161F	Psoriasis vulgaris	M161F
M161H	Erythrodermic psoriasis	M161H
M161J	Flexural psoriasis	M161J
M161z	Psoriasis NOS	M161z
M16y.	Other psoriasis/similar disord	M16y
M16y0	Scalp psoriasis	M16y0
M16z.	Psoriasis/similar disord.NOS	M16z
N0452	Juv arthritis in psoriasis	N0452
Nyu13	[X]Oth psoriatic arthropathies	Nyu13

IBD

8Cc5.	Inflammatory Bowel Disease	8Cc5
J40..	Crohn's Disease	J40
J4101	Ulcerative colitis	J4101

Fibromyalgia

N239.00	Fibromyalgia	N239
1682	Fatigue	1682
168..11	Fatigue - symptom	168-1
8HkW.00	Referral to chronic fatigue syndrome specialist team	8HkW
8HlL.00	Referral for chronic fatigue syndrome activity management	8HlL
8Q1..00	Activity management for chronic fatigue syndrome	8Q1
Eu46011	[X]Fatigue syndrome	Eu460-1
F286.00	Chronic fatigue syndrome	F286
F286.11	CFS - Chronic fatigue syndrome	F286-1
F286000	Mild chronic fatigue syndrome	F2860
F286100	Moderate chronic fatigue syndrome	F2861
F286200	Severe chronic fatigue syndrome	F2862
R007.00	[D]Malaise and fatigue	R007
R007100	[D]Fatigue	R0071
R007z00	[D]Malaise and fatigue NOS	R007z
1684	Malaise/lethargy	1684
1684.11	C/O - debility - malaise	1684-1

168..13	Malaise - symptom	168-3
R007.00	[D]Malaise and fatigue	R007
R007000	[D]Malaise	R0070
R007z00	[D]Malaise and fatigue NOS	R007z
R007300	[D]Lethargy	R0073
168..12	Lethargy - symptom	168-2
1684	Malaise/lethargy	1684
1688	Exhaustion	1688
1683	Tired all the time	1683
1683.11	C/O - 'tired all the time'	1683-1
168..00	Tiredness symptom	168
168Z.00	Tiredness symptom NOS	168Z
E205.12	Tired all the time	E205-2
R007500	[D]Tiredness	R0075
R2y3.00	[D]Debility, unspecified	R2y3
1684.11	C/O - debility - malaise	1684-1

1B1B.00	Cannot sleep - insomnia	1B1B
1B1Q.00	Poor sleep pattern	1B1Q
1BX..00	Sleep observations	1BX
38D0.00	Pittsburgh sleep quality index	38D0
7065A00	Sleep studies NEC	7065A
8HTn.00	Referral to sleep clinic	8HTn
8Q0..00	Sleep management	8Q0
9b9Y.00	Sleep studies - specialty	9b9Y
9Nk0.00	Seen in sleep clinic	9Nk0
E274.00	Non-organic sleep disorders	E274
E274.12	Insomnia due to nonorganic sleep disorder	E274-2
E274000	Unspecified non-organic sleep disorder	E2740
E274C00	Other sleep stage or arousal dysfunction	E274C
E274D00	Repetitive intrusions of sleep	E274D
E274D11	Restless sleep	E274D-1
E274E00	'Short-sleeper'	E274E
E274y00	Other non-organic sleep disorder	E274y
E274z00	Non-organic sleep disorder NOS	E274z
Eu51.00	[X]Nonorganic sleep disorders	Eu51

Eu51200	[X]Nonorganic disorder of the sleep-wake schedule	Eu512
Eu51y00	[X]Other nonorganic sleep disorders	Eu51y
Eu51z00	[X]Nonorganic sleep disorder, unspecified	Eu51z
Fy0..00	Sleep disorders	Fy0
Fy02.00	Disorders of the sleep-wake schedule	Fy02
Fyu5800	[X]Other sleep disorders	Fyu58
R005.00	[D]Sleep disturbances	R005
R005.12	[D]Sleep rhythm problems	R005-2
R005000	[D]Sleep disturbance, unspecified	R0050
R005600	[D]Sleep rhythm irregular	R0056
R005800	[D]Sleep dysfunction with sleep stage disturbance	R0058
R005z00	[D]Sleep dysfunction NOS	R005z
Z1M..00	Sleep and rest interventions	Z1M
Z1M1.00	Disturbing sleep	Z1M1

Reynaud's Phenomenon

G730.00	Raynaud's syndrome	G730

Cramps

		CiPCA read code
N247100	Leg cramps	N2471
N247111	Night cramps	N2471-1
N247200	Cramp	N2472

Physical Function

13CD.00	Mobility very poor	13CD
13CE.00	Mobility poor	13CE
13CP.00	Impaired mobility	13CP
13CZ.00	Mobility NOS	13CZ
N233100	Immobility syndrome	N2331
R00A.00	[D] Poor mobility	R00A
R00C.00	[D]Immobility	R00C
Ryu3200	[X]Other and unspecified abnormalities of gait and mobility	Ryu32
ZO51.00	Impaired mobility	ZO51
ZV4L000	[V]Reduced mobility	ZV4L0
ZV4L011	[V] Poor mobility	ZV4L0-1
ZV4L300	[V]Need for assistance due to reduced mobility	ZV4L3
1381	Exercise physically impossible	1381

6665	Physical handicap problem	6665
13VC300	Chronic physical disability	13VC3
13VM.00	Physical disability	13VM
R034400	[D]Physical retardation	R0344

HLA-B27

43c5.	HLA-B27 antigen screening test	43c5
43cG.	HLA-B27 positive	43cG
4cH.	HLA-B27 negative	4cH
4KB1.	HLA-B27 antigen screen	4KB1