The burden of early axial spondyloarthritis

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Chapter 1

General Introduction

AXIAL SPONDYLOARTHRITIS

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic musculoskeletal disease mainly affecting the sacroiliac joints and spine and usually starts in the second or third decade of life.[1] The predominant symptoms of axSpA are chronic back pain and spinal stiffness. Other additional features are musculoskeletal manifestations (i.e. (peripheral) arthritis, enthesitis, and dactylitis) and extra-articular manifestations (i.e. uveitis, psoriasis, and inflammatory bowel disease (IBD)).[1] The first anatomical descriptions of the disease that we nowadays call axSpA were reported in the 16th and 17th century[2-5] and the clinical characteristics were described for the first time by various physicians in the 19th century.[6-9]

In the mid-1970s the concept of 'spondyloarthritis' was introduced as a group of interrelated disorders[10], see **Figure 1**. The wider spectrum of SpA includes psoriatic arthritis, arthritis associated with IBD, juvenile onset SpA, undifferentiated SpA and ankylosing spondylitis (AS).[11, 12] The subgroups have several clinical and genetic characteristics in common, such as a high prevalence of human leukocyte antigen B27 (HLA-B27). The reported prevalence of SpA varies worldwide from 0.2% in South-Asia to 1.3-1.6% in North America and Northern Arctic communities. In Europe the estimated prevalence is 0.5%.[13] SpA has a heterogenous disease presentation distinguishing patients with predominantly axial complaints, axSpA, and patients with predominantly peripheral complaints, peripheral SpA (pSpA).[14] This distinction is made in order to better characterize axSpA and pSpA according to predominant presenting symptom as both subgroups have different therapeutic approaches.[14, 15]

AxSpA can be further divided into radiographic axSpA (r-axSpA, also known as AS), i.e. patients who have structural damage in the sacroiliac joints that is visible on radiographs, and non-radiographic axSpA (nr-axSpA), i.e. patients who do not have structural damage visible on radiographs.[1] The natural disease course of early axSpA is not completely understood and may vary considerably. Some patients never develop radiographic damage, while others progress from nr-axSpA to r-axSpA over a short period. Varying numbers for the progression from nr-axSpA to r-axSpA are found ranging from a progression rate of 12% in 2 years to 26% in 15 years.[16-18] Recently, in patients with a recent onset of axSpA a net progression of 5.1% over 5 years of follow-up was found.[19] This large variability is due to the cohorts investigated and the way progression is defined. Unfortunately, it is not yet possible to predict which patients will progress to r-axSpA.

Diagnostic delay is common in axSpA. Studies have reported an average delay up to 11 years between symptom onset and diagnosis.[20-23] Timely identification of axSpA is difficult as its hallmark feature is chronic back pain, which is a very common symptom and axSpA

has no single feature that distinguishes the disease from other causes of back pain. The diagnostic delay is even more pronounced in women than in men which could possibly be due the traditional belief that axSpA, especially r-axSpA, predominantly exists in males.[24] Being young at disease onset or having psoriasis are also factors which are related to a longer diagnostic delay in addition to HLA-B27 status and gender.[25]

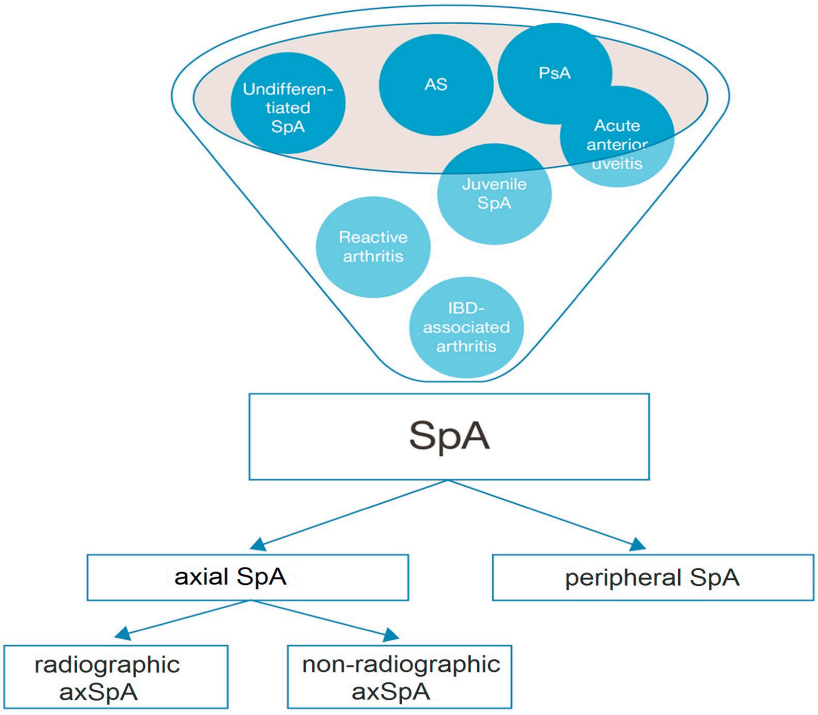

Figure 1. The concept of SpA by Sieper et al (2017).[70] AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; IBD, inflammatory bowel disease; PsA, psoriatic arthritis; SpA, spondyloarthritis.

As no adequate treatment was available in the past, timely recognition of axSpA was not as important as it is now. Only years ago the availability of therapeutic options were limited but with the introduction of tumour necrosis factor (TNF)-α blockers[26] and more recently IL-17 inhibitors[27] more therapeutic options have become available. This made reducing diagnostic delay more important as timely diagnosis and treatment in an early phase of the disease could possibly influence the course of the disease.[28] Moreover, patients in an early phase of the disease experience similar severity of symptoms as those with longstanding disease.[29]

ASAS Classification criteria

The evaluation of the pattern (the 'Gestalt') of signs and symptoms by an (experienced)

rheumatologist is leading for the diagnosis of axSpA. Diagnostic criteria are lacking, but several classification criteria for axSpA are available. These classification criteria are important for research in order to create groups of patients who have similar characteristics. The classification criteria may only be applied once the diagnosis of axSpA has been made by a rheumatologist to avoid misclassification of patients.[30] On the one hand, classification criteria could miss patients as classification criteria form homogenous groups of patients but may not capture all patients who have the disease due to the heterogeneous character of the disease; on the other hand, and even more importantly, using classification criteria as diagnostic criteria will lead to overdiagnosis of patients who do fulfil the criteria but have other conditions mimicking axSpA.[31]

The Assessment in SpondyloArthritis international Society (ASAS), an international group of experts in the field of SpA, has developed classification criteria for axSpA in 2009 that classify axSpA into an imaging arm, i.e. patients with signs of sacroiliitis on magnetic resonance imaging (MRI) or radiographs, and a clinical arm, i.e. patients without sacroiliitis on imaging, see **Figure 2**.[32] The ASAS criteria were developed to encompass the full spectrum of axSpA including patients with nr-axSpA. The classification criteria can be applied to patients who have back pain almost daily for at least three months that started before the age of 45 years. Patients fulfil the imaging arm if they have sacroiliitis on imaging plus ≥ 1 SpA feature and they fulfil the clinical arm if they are HLA-B27 positive plus have ≥ 2 SpA features. The SpA features are inflammatory back pain, peripheral arthritis, (heel) enthesitis, dactylitis, uveitis, psoriasis, IBD, good response to nonsteroidal anti-inflammatory drugs (NSAIDs), positive family history for SpA, HLA-B27 positivity, and elevated C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR). Patients can also fulfil both arms. It is important that the ASAS criteria for axSpA are interpreted in its entirety, that means considering both arms. However, it is sometimes useful to provide information on which arms are fulfilled to describe the characteristics of the patients.

Treatment

The 2016 ASAS-European League Against Rheumatism (EULAR) recommendations defined the primary treatment goal in axSpA as "*to maximise 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*".[33] The optimal treatment of axSpA should be individualised and involves non-pharmacological and pharmacological treatments. Non-pharmacological treatment options include education, physical therapy, encouragement of physical activity, and smoking cessation. The recommended first-line drug treatment for patients with axSpA suffering from pain and stiffness is NSAIDs.

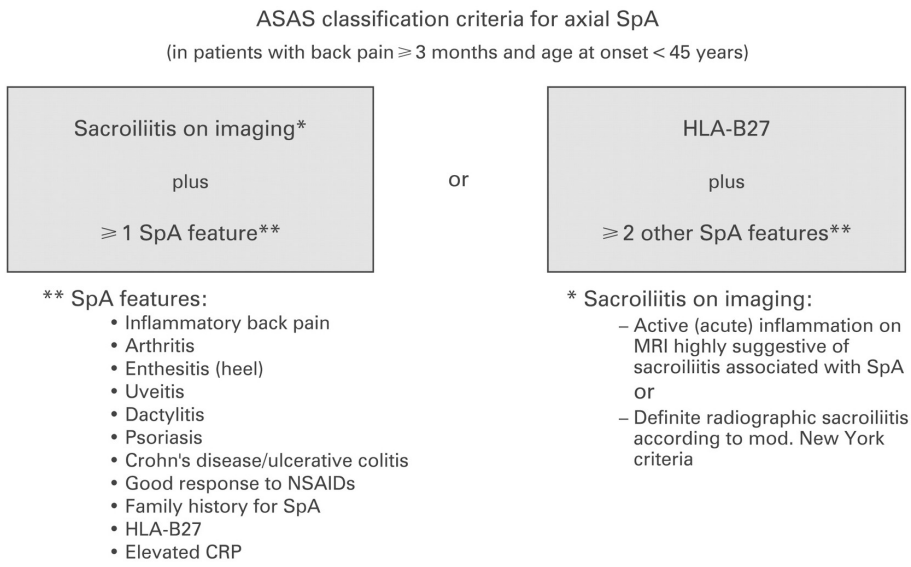

Figure 2. ASAS classification criteria for axial spondyloarthritis by Rudwaleit et al (2009).[32]
ASAS, Assessment in SpondyloArthritis international Society; SpA, spondyloarthritis; NSAIDs, nonsteroidal anti-inflammatory drugs; HLA-B27, human leukocyte antigen B27; CRP, C-reactive protein; MRI, magnetic resonance imaging.

In the past years, effective biological therapies have become available. These therapies became not only available for patients with r-axSpA but also for patients with nr-axSpA, which implies that patients can be treated in an early phase of the disease.[34-36] Biologicals are used by patients who are refractory to NSAIDs. Even though currently available treatment options are efficacious, many patients remain symptomatic and experience an impaired health-related quality of life (HRQoL) and loss of work productivity.[35]

Despite major advances that have been made in diagnosing, classifying, and treating axSpA, there is clearly room for improvement and many questions remain unanswered. For example, the familial aggregation of axSpA show that genetics play an important role in axSpA. This is also reflected in the ASAS classification criteria for axSpA in which both HLAB27 positivity and a positive family history are considered separate SpA features. However, the value of a positive family history of SpA itself or in combination with HLA-B27 in identification of axSpA is hardly investigated. Additionally, the early phase of axSpA has only been studied recently and therefore a knowledge gap exists. Most importantly, the extent of the impact of axSpA on health outcomes is not yet determined in the early phase of the disease. Importantly in this respect, it is known that, in addition to disease-associated factors, certain psychological attributes such as illness perceptions and coping strategies may co-influence health outcomes. In this thesis we will further focus on the relevance of a positive family history in the identification of patients at risk of axSpA, but also investigate several health outcomes in early axSpA, as well as investigating illness

perceptions and the usage of coping strategies and their impact on health outcomes.

HLA-B27 carriership and positive family history

AxSpA is a multifactorial disease in which genetics are thought to play an important role, with HLA-B27 being the strongest known genetic risk factor for axSpA.[1, 37] HLA-B27 is estimated to contribute up to 20% to the heritability of r-axSpA.[38] HLA-B27 is a major histocompatibility complex class 1 antigen and is important in the initiation and propagation of immune response. Its precise pathogenic role in axSpA is still not completely understood.[39]

The difference in prevalence rates of axSpA worldwide has been related to the varying prevalence of HLA-B27 across geographical regions.[40] One of the highest prevalence rates of HLA-B27 in the general population is found in Scandinavian countries ranging from 10-17%.[41-43] The prevalence rates of HLA-B27 are somewhat lower in Western European and non-Hispanic White American populations ranging from 4% to 13% (11, 44-46) and are relatively low in Arab and Asian countries ranging from ≤ 1% to 5%[47-50], while HLA-B27 is virtually absent in African black populations.[51] The varying HLA-B27 prevalence worldwide is reflected in the prevalence of HLA-B27 positivity among axSpA patients. This ranges from 25% in the Middle East to 90% in Northern Europe in r-axSpA patients.[11] It is difficult to estimate the HLA-B27 prevalence in nr-axSpA patients as most studies include only a selection of patients, frequently fulfilling the ASAS axSpA criteria, or are registry-based studies which often contain no data about HLAB27 carriership. However, the HLA-B27 prevalence in nraxSpA patients seems to be similar or somewhat lower than in r-axSpA patients.[52]

A positive family history of SpA is common in axSpA patients.[53] HLA-B27 positive first-degree relatives of HLA-B27 positive patients with r-axSpA are 16-times more likely to develop r-axSpA than HLA-B27 positive individuals in the general population.[54] Additionally, first-degree relatives of a patient with r-axSpA also have a higher risk of developing r-axSpA than second-degree relatives.[55-57] This is why a positive family history of SpA, in particular a positive family history in first-degree family members, is considered a risk factor of axSpA and forms an integral part of several SpA classification criteria.[58, 59] Based on consensus by experts, ASAS defined a positive family history of SpA far broader by taking into account the wider spectrum of SpA. Therefore, the definition of a positive family history includes the presence of a first- or second-degree family member with not only r-axSpA, both also uveitis, psoriasis, IBD, or reactive arthritis.[32] HLA-B27 positivity seems to be important in this definition as three out of five diseases are associated with HLA-B27 positivity; namely r-axSpA, uveitis, and reactivity arthritis.[60, 61]

Recently, the performance of the ASAS definition of a positive family history was investigated. In European patients with a suspicion of axSpA, a positive family history of raxSpA and a positive family history of uveitis are related to HLA-B27 positivity.[62] This suggests that a positive family history identifies patients who may be HLA-B27 positive and therefore have an increased risk of axSpA. However, a positive family history of reactive arthritis, inflammatory bowel disease, and psoriasis were not related to HLA-B27 status[62] which suggests that the current ASAS definition might be better restricted to a positive family history of axSpA and a positive family history of uveitis.

However, we do not know if a distinction should be made in the presence of a positive family history in either first- or second-degree family members and if the findings are applicable to populations outside Europe. Moreover, it is also important to investigate if a positive family history further contributes to diagnosing axSpA if HLA-B27 status is known since a positive family history clusters with HLA-B27 positivity. In this thesis we have further investigated the contribution of a positive family history for SpA in identifying axSpA in patients with a suspicion thereof.

Health outcomes in (early) axSpA

Inflammation due to axSpA can not only lead to structural damage of the sacroiliac joints and spine, but also to decreased spinal mobility, functional impairment and physical disability, that in turn all contribute to impaired health-related quality of life (HRQoL).[63] The negative impact of r-axSpA on HRQoL is well-described in the literature. The HRQoL of r-axSpA patients is poor compared to the general population and similar to patients with rheumatoid arthritis.[64, 65]

Patients with r-axSpA do not only have impaired HRQoL, but also impaired work productivity. Work productivity does not only pertain to sick leave, i.e. absenteeism, but also to working less efficiently, i.e. presenteeism. It is known that patients with r-axSpA are three times more likely to be work-disabled and withdrawn from labour force than the general population.[64, 66] Especially having extra-articular manifestations, higher age, higher disease activity and more impairment in physical functioning are related to more work disability.[67] This leads to substantial costs to patients and society.[64, 68]

The previously described studies have focused on r-axSpA patients and most of these patients have a long disease duration. Several studies have also investigated HRQoL and work productivity in patients with nr-axSpA. Although r-axSpA and nr-axSpA belong to the same disease entity, axSpA, they are somewhat different. As its name suggests, patients with r-axSpA have radiographic sacroiliitis while nr-axSpA lack any radiographic changes in the sacroiliac joints. Patients with r-axSpA are more often male, while patients with

nraxSpA have a more or less equal gender distribution. Furthermore, nr-axSpA patients on average have lower levels of CRP and inflammation seen on the MRI, which are regarded as objective measures of inflammation.[69-71] Even though r-axSpA and nr-axSpA are not completely similar, the studies in nr-axSpA showed that HRQoL and work productivity are similarly jeopardized in non-radiographic and radiographic disease.[69, 72]

AxSpA often affects patients early in their adult lives. However, all previously mentioned studies did not investigate patients in the first years after the start of symptoms, even though patients can be identified earlier than in the past. Moreover, these studies either investigated patients with radiographic disease or patients with non-radiographic disease while early disease encompasses both patients with radiographic and non-radiographic disease. One of the few cohorts that investigates patients in an early phase of axSpA, regardless having raxSpA or nraxSpA, indicated that HRQoL and work productivity were seriously impacted.[73, 74] For example, 13% of the patients with a persistent high disease activity became work disabled over time. In this cohort the mean symptom duration was less than 2 years, the male-to-female ratio was one to one, and one-third of the patients had radiographic sacroiliitis.

In this thesis we will elaborate on the impact of axSpA on HRQoL and work productivity in patients with recently diagnosed axSpA.

Illness perceptions and coping strategies

As described in the previous paragraphs, patients with axSpA in general have impaired health outcomes. Health outcomes are affected by biomedical factors associated with the disease as well as other contextual factors such as socio-economic status, education, or the perception of and coping with the illness.[75] The Leventhal's Common Sense Model of self-regulation (CSM) is a theoretical model which describes the process of a patient becoming aware of his/her illness, developing perceptions about this illness, establishing coping strategies to manage this illness, and the impact of these actions on health outcomes, see **Figure 3**.[76] It is important to make a distinction between illness and disease. Illness can be seen as impaired health from the patient's perspective, while disease is a condition diagnosed by a physician or another health care professional.[77] The CSM postulates that the patient considers his or her health as their normal state and the onset of an illness and its characteristics are considered as a health threat; a problem which needs to be solved in order to re-establish their normal state, their healthy state.[76]

Patients respond to their illness by generating illness perceptions. Illness perceptions are beliefs formulated by the patient about his/her illness which may help them in better understanding their illness but it also represents the emotional state of a patient. Illness

perceptions guide the patient in coping with the illness. Illness perceptions could be, for example, beliefs of severe consequences such as serious financial consequences due to a patient's illness or negative emotions such as fear and angriness towards the illness.[76] It is even claimed that illness perceptions might contribute more to HRQoL than disease activity.[78] The impact of a particular illness perception on health outcomes could be negative, positive, or mixed depending on the coping strategies that were used.[79]

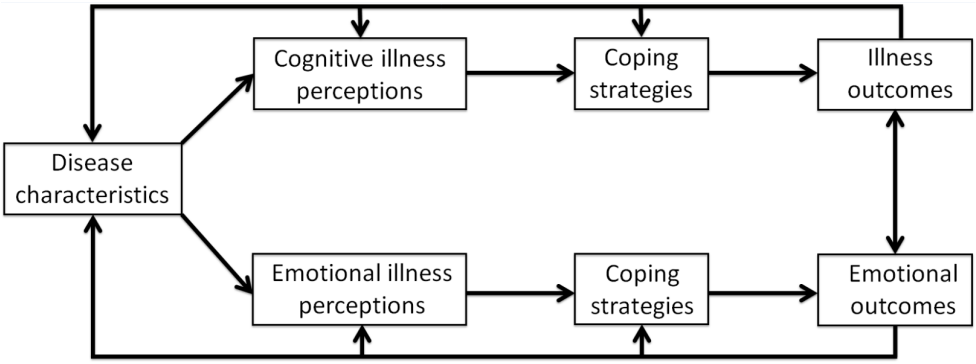

Figure 3. Leventhal's Common Sense model of self-regulation adapted by Daleboudt (2014).[96]

Illness perceptions can be assessed by the Revised Illness Perceptions Questionnaire (IPQ-R).[80, 81] The IPQ-R covers 8 dimensions which are explained in **Table 1**. Illness perceptions are hardly investigated in patients with axSpA. The only study among axSpA patients showed that having more concerns about the illness (not described in Table 1 as the described study used the brief version of the questionnaire) was associated with decreased physical HRQoL.[82] The interpretation of a single illness perception or coping strategy is difficult, as the combinations of illness perceptions and coping strategies are numerous. According to the CSM, it is thought that strong beliefs in severe '*consequences*' of the illness, attributing many experienced symptoms to the illness ('*illness identity*'), strong beliefs that the disease is chronic ('*timeline acute/chronic*'), and having negative emotions such as fear or angriness towards the illness ('*emotional representation*') are associated with worse health outcomes. In contrast, feeling a lot of control over the illness (both *'personal control'* and '*treatment control*') and better understanding of the illness ('*illness coherence*') are considered to be associated with better health outcomes.[83]

Patients develop coping strategies as a response to illness perceptions, based on the their illness beliefs and emotional state. Coping strategies are cognitive and behavioural strategies and help patients to manage stress associated with having to live with their illness (e.g. decreasing activities or adapting the level of physical activity in response to pain and limitations).[76] A questionnaire to assess coping strategies is the Coping with

Rheumatic Stressors (CORS) questionnaire.[84, 85] The CORS addresses the most important stressors of rheumatic diseases; pain, limitations and dependence, see **Table 2**.

Table 1. Overview of illness perceptions measured by the Revised Illness Perception Questionnaire (IPQ-R)[80, 81]

Label/Dimension	Explanation	Example
Illness perceptions		
Identity	The totality of experienced symptoms that the patient attributes to his/her illness	*Symptoms as "pain" or "fatigue"*
Consequences	Perceived impact of the illness on the patient's life	*"My illness has major consequences on my life"*
Acute/chronic timeline	Perceived likeliness of chronicity of the illness	*"My illness is likely to be permanent/chronic rather than temporary"*
Personal control	Perceived personal control over the illness	*"There is a lot which I can do to control my symptoms"*
Treatment control	Perceived efficacy of treatment	*"My treatment will be effective in curing my illness"*
Illness coherence	Extent to which the patient feels he/she understand the illness	*"My illness is a mystery to me"*
Cyclical timeline	Patient's perceptions of variability of the illness	*"My symptoms come and go in cycles"*
Emotional representation	Experienced negative emotions due to the illness	*"When I think about my illness I get upset/angry/afraid"*
Illness perceptions (causative)		
Psychological attributions	Believing that psychological attributions are a possible cause for the illness	*"Stress/worry or my mental attitude e.g. thinking about life negatively "*
Risk factors	Believing that risk factors are a possible cause for the illness	*"Hereditary – it runs in my family"*
Immunity	Believing that immunity is a possible cause for the illness	*"A germ or virus"*
Accident	Believing that accident is a possible cause for the illness	*"Accident or injury"*
Chance	Believing that chance is a possible cause for the illness	*"Chance or bad luck"*

Table 2. Overview of coping strategies measured by the Coping with Rheumatic Stressors (CORS) questionnaire[84, 85]

Label/Dimension	Explanation	Example
Coping with pain		
Comforting cognitions	Coping with pain by putting pain in perspective	*"I think the pain will decrease in time"*
Decreasing activities	Coping with pain by decreasing activities	*"I stop my activities"*
Diverting attention	Coping with pain by thinking about/ focusing on something else	*"I think of pleasant things"*
Coping with limitations		
Optimism	Coping with limitations by being optimistic	*"I try to be optimistic"*
Pacing	Coping with limitations by adapting/ lowering the level of activity	*"I take more time for my activities"*
Creative solution seeking	Coping with limitations by searching for creative solutions to cope with limitations in daily life	*"I try to find new ways of getting things done"*
Coping with dependence		
Accepting	Coping with dependence by making efforts to accept the level of dependence	*"I accept my dependence on other people"*
Showing consideration	Coping with dependence by considering other people's feelings	*"I try not to ask too much from any one person"*

The coping strategies '*Comforting cognitions*', '*decreasing activities*', and '*diverting attention*' reflect coping with pain, '*Optimism*', '*pacing*', and '*creative solution seeking*' reflect coping with limitations, and '*accepting*' and '*showing consideration*' reflect coping with dependence. Coping strategies are also hardly investigated and the interpretation of a particular coping strategy is difficult but it seems that frequent use of coping strategies that decreasing ('*decreasing activities*') or adapting the level of activities ('*pacing*') in order to cope with pain and limitations have been related to worse health outcomes and were more likely to lead to withdrawal from work among patients with rheumatic musculoskeletal diseases.[66, 86, 87] Thus far, no other coping strategies described by the CORS were found to be related to health outcomes in rheumatic musculoskeletal diseases in other studies.

According to the CSM, illness perceptions and the use of particular coping strategies can be adjusted as feedback loops are connecting health outcomes to illness perceptions and coping strategies.[76, 79] For example, when a coping strategy results in an unsuccessful outcome of health, illness perceptions might be altered and as a result coping strategies might be revised by these feedback loops. It is difficult to predict the impact of a single illness perception or coping strategy due to these feedback loops and due to the numerous

combinations of illness perceptions and coping strategies.

It is important to further investigate illness perception and coping strategies. One of the reasons is that illness perceptions and coping strategies could impact health outcomes. Relatively little is known about illness perceptions and coping strategies in patients with axSpA and these studies either investigated illness perceptions or coping strategies. As illness perceptions determine coping strategies but are also adapted based on the outcome of coping strategies, according to the CSM, it is important to explore them jointly.

Another reason to investigate illness perceptions and coping strategies is the hypothesis that influencing illness perceptions and interfering coping strategies might be used to improve health outcomes further in addition to the existing treatment. A first step in this hypothesis is to assess if illness perceptions and coping strategies change over time and if a change in illness perceptions or coping strategies is related to a change in disease activity. Studies in other rheumatic musculoskeletal diseases report conflicting results about the stability or change in illness perceptions over time.[88-90] Only one study has investigated patients with r-axSpA and found slight changes in coping strategies over 4 years but these changes were not related to changes in physical functioning or pain.[91]

In conclusion, more knowledge and understanding of illness perceptions and coping strategies might be valuable to better understand the impact of these factors on health outcomes. In this thesis we will explore illness perceptions and coping strategies in patients with axSpA or a suspicion thereof.

AIMS AND OUTLINE OF THIS THESIS

Research databases

The questions that have been addressed in this thesis have been answered using data from three independent cohorts in which patients with axSpA or a suspicion thereof were included.

ASAS

The ASAS cohort is a worldwide longitudinal cohort and has included 975 patients from 29 centres. Consecutive patients who first presented for a diagnostic workup were included by rheumatologists from November 2005 to January 2009. The 'axial population' comprised patients suspected of axSpA (> 3 months back pain, onset < 45 years, with or without peripheral symptoms). Patients were assessed at baseline and at one follow-up visit and had a mean follow-up time of approximately 4 years.[32, 92, 93] Data from the ASAS cohort is used in **Chapters 2** and **3**.

DESIR

The DEvenir des Spondyloarthropathies Indifférenciées Récentes (DESIR) cohort is an ongoing longitudinal study and consists of 708 patients from 25 French centres included between October 2007 and April 2010. Patients were eligible if their age was between 18 and 50 years, they had inflammatory back pain persisting ≥ 3 months but < 3 years fulfilling either the Calin or Berlin criteria for inflammatory back pain, and symptoms were suggestive of axSpA according to the local investigator. Patients had bi-annual visits and imaging was performed at 1, 2, and 5 years of follow-up.[94] Data from the DESIR cohort is used in **Chapter 3**.

SPACE

The SPondyloArthritis Caught Early (SPACE) cohort is an ongoing international inception cohort that was established in January 2009. Patients aged ≥ 16 years with chronic back pain, persisting ≥ 3 months but ≤ 2 years, and onset of back pain < 45 years were included in the SPACE cohort. Dutch, Norwegian, Italian, and Swedish outpatient clinics participated in the SPACE study.[95] Data from the SPACE cohort is used in **Chapters 3, 4, 5, 6,** and **7**.

Aims of this thesis

The main rationale behind the different chapters described in this thesis is centered around the value of a positive family history in identifying patients suspected of axSpA and investigating health outcomes, illness perceptions, and coping strategies in axSpA patients (or a suspicion thereof). Therefore, the following research aims were elucidated in this thesis:

1. To investigate the value of different aspects of a positive family history in identifying patients who are HLA-B27 positive and in diagnosing patients with suspected of axSpA.
2. To study the impact of patient-reported disease activity on health outcomes in patients with recently diagnosed axSpA.
3. To increase knowledge about the use of illness perceptions and coping strategies, to learn if illness perceptions and coping strategies change over time and investigate their impact on health outcomes in patients with axSpA or a suspicion thereof.

Outline of this thesis

To answer the first research aim, **Chapter 2** evaluates the role of ethnicity, degree of family relationship, and each SpA subtype in a positive family history for identifying patients who are HLA-B27 positive and therefore have an increased risk of axSpA. **Chapter 3** provides more insight into the value of a positive family history in diagnosing patients with axSpA when HLA-B27 status is known.

Chapters 4 and **5** address the second research aim: **Chapter 4** investigates the association between disease activity and HRQoL over time in patients with early axSpA. **Chapter 5** explores the association between disease activity and work productivity over time in these patients.

The third research aim is addressed in **Chapters 6** and **7**: **Chapter 6** analyses existing illness perceptions and applied coping strategies in patients with axSpA or a suspicion thereof. The (modifying) effect of illness perceptions and usage of coping strategies on the relationship between chronic back pain and health outcomes is also investigated. **Chapter 7** explores which illness perceptions patients with recently diagnosed axSpA have and which coping strategies they use over time. **Chapter 7** also investigates if illness perceptions are susceptible to changes in disease activity or if illness perception and coping strategies are rather independent of variation in disease activity.

The last two chapters of this thesis, **Chapter 8** and **Chapter 9**, provide a summary and general discussion on the findings of this thesis in English and Dutch, respectively.

REFERENCES

1. Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet* 2017;390:73-84.
2. Connor B. Lettre écrite à Monsieur le chevalier Guillaume de Waldegrave, premier medicin de sa Majeste Britannique. Paris, France. 1693;17.
3. Connor B. Dissertationnes medico-physicae. Sheldonian Theatre. Oxford, England. *NY Acad Med and Royal Soc* 1695.
4. Connor B. An extract from a letter to Sir Charles Walgrave, published in French at Paris: Giving an account of a extraordinary humane skeleton, whose vertebrae of the back, the ribs and several bones down to the os sacrum, were firmly united into one solid bone, without jointing or cartilage. P*hilos Trans* 1695;19:21-7.
5. Colombo MR. De Re Anatomica. Venice, Austria. 1559.
6. Arnett FC. Ankylosing spondylitis 1992: from Connor to transgenes. *J Ir Coll Physicians Surg* 1993;22:207-11.
7. Bechterew, W. Steifigkeit der Wirbelsaule und ihre Verkrummung als besondere Erkrankungsform. *Neurol Centralbl.* 1893;12:426-34.
8. Strümpell A. Bemerkungen über chronisch-ankylosierende Entzündung der Wirbelsoule und der Huftergelenks 1897. *Deutsch Nervenheilk* 1897;11:338-42.
9. Marie P. Sur la spondylose rhizomelique. *Rev Med* 1898;18:285-315.
10. Moll JM, Haslock I, Macrae IF, Wright V. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. *Medicine* 1974;53:343-64
11. Stolwijk C, Boonen A, van Tubergen A, Reveille JD. Epidemiology of spondyloarthritis. *Rheum Dis Clin North Am* 2012;38:441-76.
12. Bakland G, Nossent HC. Epidemiology of spondyloarthritis: a review. C*urr Rheumatol Rep* 2013;15:351.
13. Stolwijk C, van Onna M, Boonen A, van Tubergen A. Global Prevalence of Spondyloarthritis: A Systematic Review and Meta-Regression Analysis. *Arthritis Care Res* 2016;68:1320-31.
14. Rudwaleit M. New approaches to diagnosis and classification of axial and peripheral spondyloarthritis. *Curr Opin Rheumatol* 2010;22:375-80.
15. Smolen JS, Schols M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis* 2018;77:3-17.
16. Poddubnyy D, Rudwaleit M, Haibel H, et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011;70:1369-74.
17. Sampaio-Barros PD, Bortoluzzo AB, Conde RA, et al. Undifferentiated spondyloarthritis: a longterm followup. *J Rheumatol* 2010;37:1195-9.
18. Wang R, Gabriel SE, Ward MM. Progression of Nonradiographic Axial Spondyloarthritis to Ankylosing Spondylitis: A Population-Based Cohort Study. *Arthritis Rheumatol* 2016;68:1415-21.
19. Dougados M, Sepriano A, Molto A, et al. Sacroiliac radiographic progression in recent onset axial spondyloarthritis: the 5-year data of the DESIR cohort. *Ann Rheum Dis* 2017;76:1823-8.
20. Feldtkeller E, Khan MA, van der Heijde D, et al. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int* 2003;23:61-6.
21. Masson Behar V, Dougados M, Etcheto A, et al. Diagnostic delay in axial spondyloarthritis: A cross-sectional study of 432 patients. *Joint Bone Spine* 2017;84:467-71.
22. Lubrano E, De Socio A, Perrotta FM. Unmet Needs in Axial Spondyloarthritis. *Clin Rev Allergy Immunol* 2018;55:332-9.
23. Sykes MP, Doll H, Sengupta R, Gaffney K. Delay to diagnosis in axial spondyloarthritis: are we improving in the UK? *Rheumatology* 2015;54:2283-4.
24. Navarro-Compan V. An Update on Diagnosis and Classification of Axial Spondyloarthritis. *Curr Rheumatol Rep* 2019;21:39.
25. Redeker I, Callhoff J, Hoffmann F, et al. Determinants of diagnostic delay in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data. *Rheumatology* 2019;58:1634-8.
26. Braun J, van der Heijde D. Novel approaches in the treatment of ankylosing spondylitis and other spondyloarthritides. E*xpert Opin*

*Investig Drugs 2*003;12:1097-109.
27. Torgutalp M, Poddubnyy D. IL-17 inhibition in axial spondyloarthritis: current and future perspectives. *Expert Opin Biol Ther* 2019;19:631-41.
28. Rudwaleit M, Claudepierre P, Wordsworth P, et al. Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. *J Rheumatol* 2009;36:801-8.
29. Rudwaleit M, Haibel H, Baraliakos X, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum* 2009;60:717-27.
30. Landewé RB, van der Heijde DM. Why CAPS criteria are not diagnostic criteria? *Ann Rheum Dis* 2017;76:e7.
31. Aggarwal R, Ringold S, Khanna D, et al. Distinctions between diagnostic and classification criteria? *Arthritis Care Res* 2015;67:891-7.
32. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-83.
33. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017;76:978-91.
34. Callhoff J, Sieper J, Weiss A, et al. Efficacy of TNFalpha blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. *Ann Rheum Dis* 2015;74:1241-8.
35. Strand V, Singh JA. Patient Burden of Axial Spondyloarthritis. *J Clin Rheumatol* 2017;23:383-91.
36. Jones A, Ciurtin C, Ismajli M, et al. Biologics for treating axial spondyloarthritis. *Expert Opin Biol Ther* 2018;18:641-52.
37. Brown MA, Kennedy LG, MacGregor AJ, et al. Susceptibility to ankylosing spondylitis in twins: the role of genes, HLA, and the environment. *Arthritis Rheum* 1997;40:1823-8.
38. Cortes A, Hadler J, Pointon JP, et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. *Nat Genet* 2013;45:730-8.
39. Bowness P. HLA-B27. *Annu Rev Immunol* 2015;33:29-48.
40. Mathieu A, Paladini F, Vacca A, et al. The interplay between the geographic distribution of HLA-B27 alleles and their role in infectious and autoimmune diseases: a unifying hypothesis. Autoimmun Rev 2009;8:420-5.
41. Geirsson AJ, Eyjolfsdottir H, Bjornsdottir G, et al. Prevalence and clinical characteristics of ankylosing spondylitis in Iceland - a nationwide study. *Clin Exp Rheumatol* 2010;28:333-40.
42. Gran JT, Mellby AS, Husby G. The prevalence of HLA-B27 in Northern Norway. *Scand J Rheumatol* 1984;13:173-6.
43. Bjelle A, Cedergren B, Dahlqvist SR. HLA B27 in the population of northern Sweden. *Scand J Rheumatol* 1982;11:23-6.
44. Costantino F, Talpin A, Said-Nahal R, et al. Prevalence of spondyloarthritis in reference to HLA-B27 in the French population: results of the GAZEL cohort. *Ann Rheum Dis* 2015;74:689-93.
45. Khan MA. Epidemiology of HLA-B27 and Arthritis. *Clinical Rheumatol* 1996;15 Suppl 1:10-2.
46. Reveille JD, Hirsch R, Dillon CF, et al. The prevalence of HLA-B27 in the US: data from the US National Health and Nutrition Examination Survey, 2009. *Arthritis Rheum* 2012;64:1407-11.
47. Hukuda S, Minami M, Saito T, et al. Spondyloarthropathies in Japan: nationwide questionnaire survey performed by the Japan Ankylosing Spondylitis Society. *J Rheumatol* 2001;28:554-9.
48. Liu X, Li YR, Hu LH, et al. High frequencies of HLA-B27 in Chinese patients with suspected of ankylosing spondylitis. *Rheumatol Int* 2010;30:1305-9.
49. Mou Y, Wu Z, Gu J, et al. HLA-B27 polymorphism in patients with juvenile and adult-onset ankylosing spondylitis in Southern China. *Tissue Antigens* 2010;75:56-60.
50. Mustafa KN, Hammoudeh M, Khan MA. HLA-B27 Prevalence in Arab Populations and Among Patients with Ankylosing Spondylitis. *J Rheumatol* 2012;39:1675-7.
51. Khan MA. HLA-B27 and its subtypes in world populations. *Curr Opin Rheumatol* 1995;7:263-9.
52. Lockwood MM, Gensler LS. Nonradiographic axial spondyloarthritis. *Best Pract Res Clin Rheumatol* 2017;31:816-29.
53. Bedendo A, Glorioso S, Venturi Pasini C, et al. A family study of ankylosing spondylitis. *Rheumatology Int* 1984;5:29-32.

54. van der Linden SM, Valkenburg HA, de Jongh BM, Cats A. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. *Arthritis Rheum* 1984;27:241-9.
55. Brown MA, Laval SH, Brophy S, Calin A. Recurrence risk modelling of the genetic susceptibility to ankylosing spondylitis. *Ann Rheum Dis* 2000;59(11):883-6.
56. Kim HW, Choe HR, Lee SB, et al. Phenotype difference between familial and sporadic ankylosing spondylitis in Korean patients. *J Korean Med Sci* 2014;29:782-7.
57. Geirsson AJ, Kristjansson K, Gudbjornsson B. A strong familiality of ankylosing spondylitis through several generations. *Ann Rheum Dis* 2010;69:1346-8.
58. Amor B, Dougados M, Mijiyawa M. [Criteria of the classification of spondylarthropathies]. *Rev Rhum Mal Osteoartic* 1990;57:85-9.
59. Dougados M, van der Linden S, Juhlin R, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. A*rthritis Rheum* 1991;34:1218-27.
60. Reveille JD. Genetics of spondyloarthritis--beyond the MHC. *Nat Rev Rheumatol* 2012;8:296-304.
61. Sheehan NJ. HLA-B27: what's new? *Rheumatology* 2010;49:621-31.
62. Ez-Zaitouni Z, Hilkens A, Gossec L, et al. Is the current ASAS expert definition of a positive family history useful in identifying axial spondyloarthritis? Results from the SPACE and DESIR cohorts. *Arthritis Res Ther* 2017;19:118.
63. Braun J, Sieper J. Ankylosing spondylitis. *Lancet* 2007;369:1379-90.
64. Boonen A, van der Linden SM. The burden of ankylosing spondylitis. *J Rheum Suppl* 2006;78:4-11.
65. Yang X, Fan D, Xia Q, et al. The health-related quality of life of ankylosing spondylitis patients assessed by SF-36: a systematic review and meta-analysis. *Qual Life Res* 2016;25:2711-23.
66. Boonen A, Chorus A, Miedema H, et al. Withdrawal from labour force due to work disability in patients with ankylosing spondylitis. *Ann Rheum Dis* 2001;60:1033-9.
67. Castillo-Ortiz JD, Ramiro S, Landewé R, et al. Work Outcome in Patients With Ankylosing Spondylitis: Results From a 12-Year Followup of an International Study. *Arthritis Care Res* 2016;68:544-52.
68. van der Weijden MA, Boonen A, van der Horst-Bruinsma IE. Problems in work participation and resource use should not be underestimated in patients with early spondyloarthritis. *J Rheumatol* 2014;41:2413-20.
69. Boonen A, Sieper J, van der Heijde D, et al. The burden of non-radiographic axial spondyloarthritis. *Semin Arthritis Rheum* 2015;44:556-62.
70. Sieper J, Hu X, Black CM, et al. Systematic review of clinical, humanistic, and economic outcome comparisons between radiographic and non-radiographic axial spondyloarthritis. *Semin Arthritis Rheum* 2017;46:746-53.
71. Sieper J, van der Heijde D. Review: Nonradiographic axial spondyloarthritis: new definition of an old disease? *Arthritis Rheum* 2013;65:543-51.
72. van der Heijde D, Joshi A, Pangan AL, et al. ASAS40 and ASDAS clinical responses in the ABILITY-1 clinical trial translate to meaningful improvements in physical function, health-related quality of life and work productivity in patients with non-radiographic axial spondyloarthritis. *Rheumatology* 2016;55:80-8.
73. Molto A, Tezenas du Montcel S, Wendling D, et al. Disease activity trajectories in early axial spondyloarthritis: results from the DESIR cohort. *Ann Rheum Dis* 2017;76:1036-41.
74. Chung HY, Machado P, van der Heijde D, et al. Smokers in early axial spondyloarthritis have earlier disease onset, more disease activity, inflammation and damage, and poorer function and health-related quality of life: results from the DESIR cohort. *Ann Rheum Dis* 2012;71:809-16.
75. Arat S, De Cock D, Moons P, et al. Modifiable correlates of illness perceptions in adults with chronic somatic conditions: A systematic review. Res Nurs Health. 2018;41:173-84.
76. Leventhal H, Phillips LA, Burns E. The Common-Sense Model of Self-Regulation (CSM): a dynamic framework for understanding illness self-management. *J Behav Med* 2016;39:935-46.
77. Wikman A, Marklund S, Alexanderson K. Illness, disease, and sickness absence: an empirical test of differences between concepts of ill health. *J Epidemiol Community Health* 2005;59:450-4.
78. Arat S, Verschueren P, De Langhe E, et al. The association of illness perceptions with physical and mental health in systemic

sclerosis patients: an exploratory study. *Musculoskeletal Care* 2012;10:18-28.
79. Hagger MS, Koch S, Chatzisarantis NLD, Orbell S. The common sense model of self-regulation: Meta-analysis and test of a process model. *Psychol Bull* 2017;143:1117-54.
80. Weinman J, Petrie KJ, Moss-Morris R, Horne R. The Illness Perception Questionnaire: A new method for assessing illness perceptions. *Psychol Health* 1996;11:431-46.
81. Moss-Morris R, Weinman J, Petrie KJ, et al. The Revised Illness Perception Questionnaire (IPQ-R). *Psychol Health* 2002;17:1-16.
82. Hyphantis T, Kotsis K, Tsifetaki N, et al. The relationship between depressive symptoms, illness perceptions and quality of life in ankylosing spondylitis in comparison to rheumatoid arthritis. *Clin Rheumatol* 2013;32:635-44.
83. Hagger MS, Orbell S. A meta-analytical review of the common-sense model of illness representations. *Psychol Health* 2003;18:141-84.
84. van Lankveld W, Näring G, van der Staak C, et al. De ontwikkeling van de CORS: Coping met reuma stressoren. *Gedrag Gezond* 1993;21:40-8.
85. van Lankveld W, van't Pad Bosch P, van de Putte L, et al. Disease-specific stressors in rheumatoid arthritis: coping and well-being. *Br J Rheumatol* 1994;33:1067-73.
86. Chorus AM, Miedema HS, Wevers CW, van der Linden S. Work factors and behavioural coping in relation to withdrawal from the labour force in patients with rheumatoid arthritis. *Ann Rheum Dis* 2001;60:1025-32.
87. Liu R, Damman W, Kaptein AA, et al. Coping styles and disability in patients with hand osteoarthritis. *Rheumatology* 2016;55:411-8.
88. Gafvels C, Hagerstrom M, Rane K, et al. Coping strategies among patients newly diagnosed with diabetes or rheumatoid arthritis at baseline and after 24 months. *J Health Psychol* 2018;23:1273-86.
89. Bijsterbosch J, Scharloo M, Visser AW, et al. Illness perceptions in patients with osteoarthritis: change over time and association with disability. *Arthritis Rheum* 2009;61:1054-61.
90. Damman W, Liu R, Kaptein AA, et al. Illness perceptions and their association with 2 year functional status and change in patients with hand osteoarthritis. *Rheumatology* 2018;57:2190-9.
91. Boonen A, van der Heijde D, Landewé R, et al. Is avoidant coping independent of disease status and stable over time in patients with ankylosing spondylitis? *Ann Rheum Dis* 2004;63:1264-8.
92. Sepriano A, Landewé R, van der Heijde D, et al. Predictive validity of the ASAS classification criteria for axial and peripheral spondyloarthritis after follow-up in the ASAS cohort: a final analysis. *Ann Rheum Dis* 2016;75:1034-42.
93. Rudwaleit M, Landewé R, van der Heijde D, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009;68:770-6.
94. Dougados M, d'Agostino MA, Benessiano J, et al. The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. *Joint Bone Spine* 2011;78:598-603.
95. van den Berg R, de Hooge M, van Gaalen F, et al. Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. *Rheumatology* 2013;52:1492-9.
96. Daleboudt GMN. Systemic lupus erythematosus: a behavioural medicine perspective. Ridderkerk, the Netherlands. Ridderprint 2014.

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