The burden of early axial spondyloarthritis

Lunteren, M. van

The burden of early axial spondyloarthritis

Miranda van Lunteren

ISBN: 978-94-6402-127-1

Cover Photo: Jökulsárlón by Remco Joukes
Printing: Gildeprint, Enschede

The printing of this thesis was financially supported by the Dutch Arthritis Foundation (ReumaNederland), Pfizer B.V., UCB Pharma B.V., and Chipsoft B.V. which is gratefully acknowledged.

The burden of early axial spondyloarthritis

Proefschrift

Ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op
dinsdag 22 september 2020
klokke 15:00 uur

door

Miranda van Lunteren
geboren te Naarden
in 1990

Promotores

Prof. dr. D.M.F.M. van der Heijde

Prof. dr. R.B.M. Landewé — Amsterdam UMC, locatie AMC

Co-promotor

Dr. F.A. van Gaalen

Leden promotiecommissie

Prof. dr. A.H.M. van der Helm-van Mil

Dr. D. van der Woude

Prof. dr. A.E.R.C.H. Boonen — Maastricht UMC+

Prof. dr. I.E. van der Horst-Bruinsma — Amsterdam UMC, locatie VUmc

Dr. A.A. den Broeder — Sint Maartenskliniek

Patience attracts happiness; it brings near that which is far.

- Swahili proverb -

CONTENT

Chapter 1	General Introduction	9
Chapter 2	Do ethnicity, degree of family relationship, and the spondyloarthritis subtype in affected relatives influence the association between a positive family history for spondyloarthritis and HLA-B27 carriership? Results from the worldwide ASAS cohort *Arthritis Research & Therapy 2018;20:166*	29
Chapter 3	Is a positive family history of spondyloarthritis relevant for diagnosing axial spondyloarthritis once HLA-B27 status is known? *Rheumatology 2019;58:1649-54*	41
Chapter 4	In early axial spondyloarthritis, increasing disease activity is associated with worsening of health-related quality of life over time *The Journal of Rheumatology 2018;45:779-84*	55
Chapter 5	Disease activity decrease is associated with improvement in work productivity over 1 year in early axial spondyloarthritis (SPondyloArthritis Caught Early cohort) *Rheumatology 2017;56:2222-8*	71
Chapter 6	The impact of illness perceptions and coping on the association between back pain and health outcomes in patients suspected of having axial spondyloarthritis: data from the SPondyloArthritis Caught Early cohort *Arthritis Care & Research 2018;70:1829-39*	93
Chapter 7	Do illness perceptions and coping strategies change over time in patients recently diagnosed with axial spondyloarthritis? A two-year follow-up study in the SPACE cohort *Submitted*	119
Chapter 8	Summary and General Discussion	135
Chapter 9	Nederlandse Samenvatting	151
Appendices	Curriculum Vitae List of publications Dankwoord	165

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]

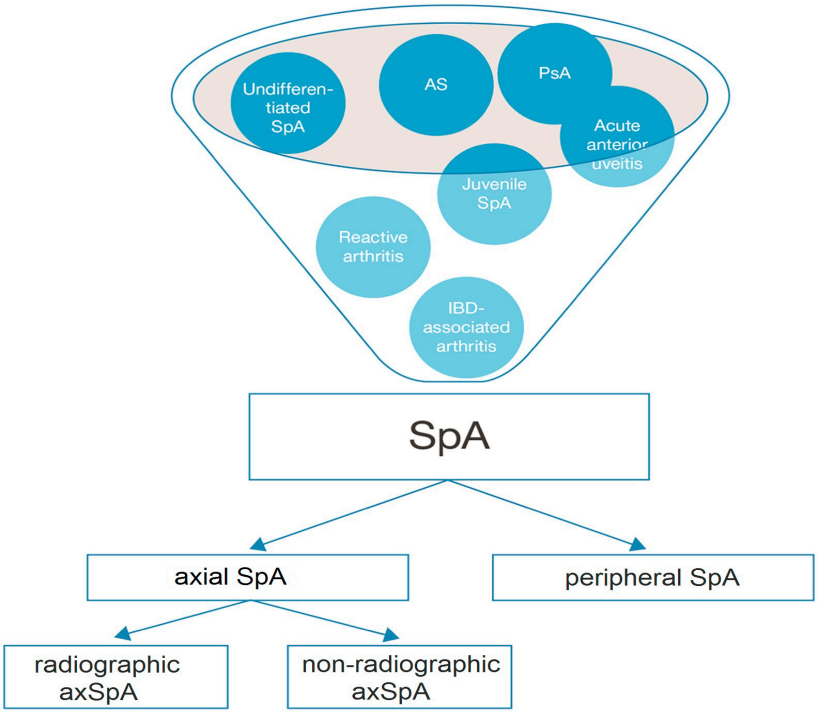

Figure 1. The concept of SpA by Sieper et al (2017).[70] AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; IBD, inflammatory bowel disease; PsA, psoriatic arthritis; SpA, spondyloarthritis.

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.

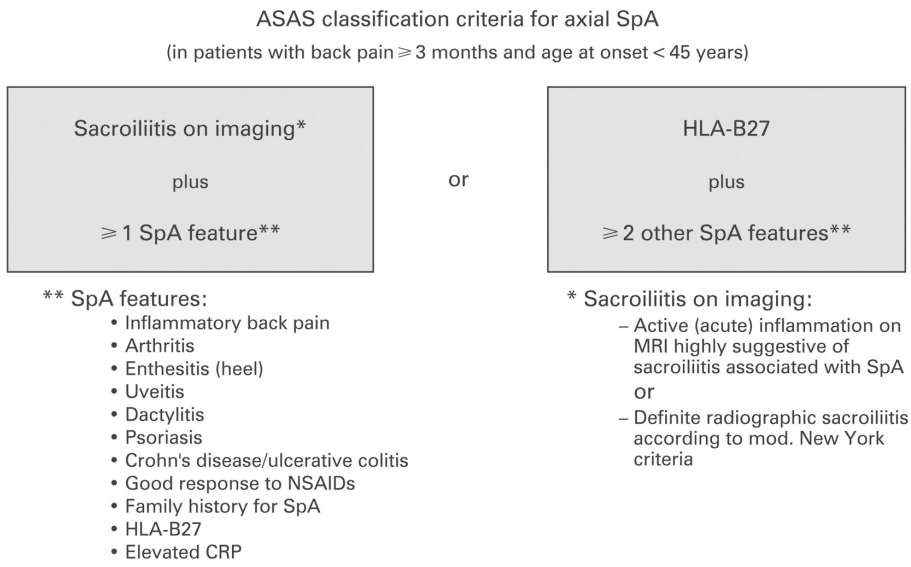

Figure 2. ASAS classification criteria for axial spondyloarthritis by Rudwaleit et al (2009).[32]
ASAS, Assessment in SpondyloArthritis international Society; SpA, spondyloarthritis; NSAIDs, nonsteroidal anti-inflammatory drugs; HLA-B27, human leukocyte antigen B27; CRP, C-reactive protein; MRI, magnetic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

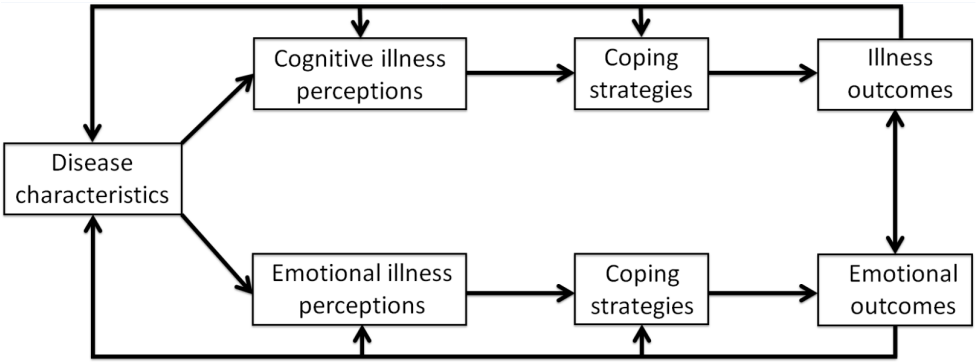

Figure 3. Leventhal's Common Sense model of self-regulation adapted by Daleboudt (2014).[96]

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.

1

Chapter 2

Do ethnicity, degree of family relationship, and the spondyloarthritis subtype in affected relatives influence the association between a positive family history for spondyloarthritis and HLA-B27 carriership? Results from the worldwide ASAS cohort

Miranda van Lunteren, Alexandre Sepriano, Robert Landewé, Joachim Sieper, Martin Rudwaleit, Désirée van der Heijde, Floris van Gaalen

Arthritis Research & Therapy 2018;20:166

ABSTRACT

Objective

The Assessment of SpondyloArthritis international Society (ASAS) defines a positive family history (PFH) of spondyloarthritis (SpA) as the presence of ankylosing spondylitis (AS), acute anterior uveitis (AAU), reactive arthritis (ReA), inflammatory bowel disease (IBD), and/or psoriasis in first-degree relatives (FDR) or second-degree relatives (SDR). In two European cohorts, a PFH of AS and AAU, but not other subtypes, was associated with human leukocyte antigen B27 (HLA-B27) carriership in patients suspected of axial SpA (axSpA). Because the importance of ethnicity or degree of family relationship is unknown, we investigated the influence of ethnicity, FDR, or SDR on the association between a PFH and HLA-B27 carriership in patients suspected of axSpA.

Methods

Baseline data from the ASAS cohort of patients suspected of axSpA were analysed. Univariable analyses were performed. Each disease (AS, AAU, psoriasis, IBD, ReA) in a PFH according to the ASAS definition was a determinant in separate models with HLA-B27 carriership as outcome. Analyses were stratified for self-reported ethnicity, FDR, and SDR. Analyses were repeated in multivariable models to investigate independent associations.

Results

A total of 594 patients were analysed (mean ± SD age 33.7 ± 11.7 years; 46% male; 52% HLA-B27+; 59% white, 36% Asian, 5% other). A PFH was associated with HLA-B27 carriership in patients with a white (OR 2.3, 95% CI 1.4–3.9) or Asian ethnicity (OR 3.1, 95% CI 1.6–5.8) and with a PFH in FDR (OR 2.9, 95% CI 1.8–4.5), but not with a PFH in SDR (OR 1.7, 95% CI 0.7–3.8) or in other ethnicities. A PFH of AS was positively associated with HLA-B27 carriership in all subgroups (white OR 7.1, 95% CI 2.9–17.1; Asian OR 5.7, 95% CI 2.5–13.2; FDR OR 7.8, 95% CI 3.8–16.0; SDR OR 3.7, 95% CI 1.2–11.6). A PFH of AAU, ReA, IBD, or psoriasis was never positively associated with HLA-B27 carriership. In the multivariate analysis, similar results were found.

Conclusion

In the ASAS cohort, a PFH of AS, but not of AAU, ReA, IBD, or psoriasis, was associated with HLA-B27 carriership regardless of white or Asian ethnicity or degree of family relationship. This cohort and two European cohorts show that a PFH of AS and possibly a PFH of AAU can be used to identify patients who are more likely to be HLA-B27-positive and therefore may have an increased risk of axSpA.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that causes inflammation mainly in the sacroiliac joints (SI) and spine.[1] In patients with ankylosing spondylitis (AS), also termed radiographic axSpA, susceptibility is thought to be largely genetically determined, and the strongest known genetic risk factor for axSpA is human leukocyte antigen B27 (HLA-B27).[1, 2] Different prevalence rates of axSpA are reported across geographical regions, which have been related to the varying prevalence of HLA-B27 worldwide.[3] A family history of spondyloarthritis (SpA) is common in patients with AS[4], and HLA-B27-positive first-degree relatives of HLA-B27-positive patients with AS are 16 times more likely to develop AS than HLA-B27-positive individuals in the general population.[5] Additionally, several studies have shown that first-degree relatives of a patient with AS have a higher risk of developing AS than second-degree relatives.[6-8] Therefore, a positive family history (PFH) of SpA, and in particular a PFH in first-degree relatives of patients with SpA, is thought to be a risk factor of axSpA in patients with chronic back pain (CBP), and a PFH of SpA is a component of several SpA classification criteria.[9, 10]

The Assessment of SpondyloArthritis international Society (ASAS) defined, by consensus, a PFH of AS, acute anterior uveitis (AAU), reactive arthritis (ReA), inflammatory bowel disease (IBD), and/or psoriasis in first- or second-degree relatives as an SpA feature in the ASAS classification criteria for axSpA.[11] Because a PFH of SpA is thought to increase the risk for axSpA in patients with CBP, it has been incorporated into several referral strategies for patients with CBP suspected of axSpA.[12, 13]

So far, only one study has investigated the performance of the definition of a PFH in identifying patients with an increased risk for axSpA. Ez-Zaitouni et al. reported that in two cohorts predominantly Caucasian CBP patients suspected of axSpA, a PFH for AS and AAU was positively associated with HLA-B27 carriership. A PFH for ReA, IBD, or psoriasis was not associated with HLA-B27 carriership and did not point to HLA-B27 carriership in patients with back pain.[14] Unfortunately, this study did not to distinguish between first- or second-degree relatives, and therefore it was unclear if a distinction in a PFH in first- or second-degree relatives matters. Moreover, because the study was performed in two European cohorts, it was unclear if the authors' findings are relevant to populations outside Europe.

The ASAS cohort provides a unique opportunity to study the performance of the current ASAS definition of a PFH in patients of different ethnicities who have CBP and are suspected of axSpA.[11,15,16] Therefore, we investigated in this international cohort the impact of ethnicity and degree of family relationship on the association between thecurrent ASAS definition of a PFH and the presence of HLA-B27 in patients suspected of axSpA.

METHODS

The ASAS cohort is an international cohort that includes patients with a suspicion of axSpA (> 3 months of back pain, age at onset < 45 years, with or without peripheral symptoms) or peripheral SpA (pSpA; current peripheral arthritis and/or dactylitis and/or enthesitis but without current CBP).[11, 15, 16] Worldwide, 975 patients were included by 29 ASAS centres between November 2005 and January 2009. Patients were included in a consecutive manner, including all eligible patients or every first to third eligible patient per day. Local ethical committees approved the study, and informed consent was obtained from all study participants before inclusion.[11, 15, 16]

Data collection

At baseline, clinical, laboratory, and imaging data were collected from all patients, including HLA-B27 carriership and radiography of the SI. Magnetic resonance imaging of the SI (MRI-SI) was considered obligatory for the first 20 patients of each centre. Patients were diagnosed by the treating rheumatologist, and for each patient, the level of confidence regarding the diagnosis on an 11-point numerical rating scale from 0 (not confident at all) to 10 (very confident) was provided. For the current analysis, only patients with a certain diagnosis of axSpA or no axSpA (confidence level ≥ 6) were analysed.

In addition, patients were asked to report their ethnicity using an open-ended question. Self-reported ethnicities were white, Asian, black, East Indian, Hispanic/Latino, mixed, and Turkish. The self-reported ethnicities were reclassified into white, Asian, and other ethnicities (Hispanic/Latino n=11, black n=7, mixed n=4, Turkish n=3, East Indian n=2, unknown n=5).

The ASAS expert definition was used to assess if patients had a PFH of SpA (ASAS PFH) (i.e., the presence of AS, AAU, psoriasis, IBD, and/or ReA in first- or second-degree relatives).[11] Patients were asked to report if any family history disease was present in a relative and in which relative(s). In the ASAS expert definition, father, mother, sister, brother, daughter, and son are defined as first-degree relatives and grandmother, grandfather, aunt, uncle, niece, and nephew as second-degree relatives.[11] Furthermore, in addition to the ASAS definition, granddaughter, grandson, half-sister, and half-brother were also considered to be second-degree relatives.

Data analysis

Baseline data were analysed. Continuous variables were presented as mean ± SD and categorical variables as frequencies (proportions). Univariable logistic models, stratified by self-reported ethnicity or degree of family relationship (a PFH in first- or only second-

degree relatives), were used to assess the association between each disease (AS, AAU, ReA, IBD, psoriasis) in a PFH and HLA-B27 carriership. The analyses were repeated in multivariable logistic models to investigate if each family history disease was associated, independently of other PFH subtypes, with HLA-B27 carriership. Patients with a PFH in both first- and second-degree relatives were classified into the group of patients with PFH in a first-degree relative (n=11) for both the univariable and multivariable analyses. STATA SE version 14 software (StataCorp, College Station, TX, USA) was used to perform data analyses.

RESULTS

In the ASAS cohort, 642 patients were diagnosed with a confidence level ≥ 6 as axSpA or no axSpA. Patients were excluded from the analysis if the family history was missing (n=48). For the current analysis, 594 patients were used. Patients had a mean age ± SD of 33.7 ± 11.7 years, and 46% were male. Mean symptom duration was 7.1 ± 9.0 years, and a mean of 2.4 ± 1.6 SpA features, excluding HLA-B27 and imaging, were present. Of the sample, 52% were HLA-B27-positive, 20% had radiographic sacroiliitis, and 45% had active inflammation by MRI-SI (**Table 1**). Sixty-two percent of the patients were diagnosed as axSpA.

In total, 59% of patients reported to be white, 36% to be Asian, and 5% reported another ethnicity (**Table 1**). An ASAS PFH was reported by 23% of the patients; a PFH of AS was the most frequently reported family history, with 15% (64% of all PFH), and a PFH of AAU was the least often reported, with 1% (5% of all PFH), among all patients (**Table 1**). An ASAS PFH in first-degree relatives only was reported in 17% of patients, in second-degree relatives in 4%, and in both first- and second-degree relatives in 2% of the patients.

An ASAS PFH and a PFH of AS were positively associated with HLA-B27 in all patients suspected of axSpA (ASAS PFH OR 2.6, 95% CI 1.7–3.9; PFH of AS OR 6.5, 95% CI 3.5–12.1). When these patients were stratified according to ethnicity and degree of family relationship, positive associations were found between an ASAS PFH and HLA-B27 carriership in patients with a self-reported white (OR 2.3, 95% CI 1.4–3.9) or Asian ethnicity (OR 3.1, 95% CI 1.6–5.8) and with a PFH in first-degree relatives (OR 2.9, 95% CI 1.8–4.5), but not in second-degree relatives (OR 1.7, 95% CI 0.7–3.8) (**Table 2**). A PFH of AS was positively associated with HLA-B27 carriership in all subgroups (white OR 7.1, 95% CI 2.9–17.1; Asian OR 5.7, 95% CI 2.5–13.2; first-degree relatives OR 7.8, 95% CI 3.8–16.0; second-degree relatives OR 3.7, 95% CI 1.2–11.6). A PFH of AAU, ReA, IBD, or psoriasis was not positively associated with HLA-B27 carriership in patients suspected of axSpA, regardless of the degree of family relationship or ethnicity (**Table 2**). In the multivariable

analysis, similar results were found (data not shown).

Table 1. Baseline characteristics of chronic back pain patients suspected of axSpA included in the ASAS cohort

Characteristics	n=594
Age (years) at baseline, mean ± SD	33.7 ± 11.7
Male	276 (46%)
Duration of back pain (years)[a], mean ± SD	7.1 ± 9.0
Self-reported ethnicity	
White	348 (59%)
Asian	214 (36%)
Other[b]	32 (5%)
Inflammatory back pain (according to experts definition)	301/532 (57%)
Good response to NSAIDs[c]	274 (46%)
Peripheral arthritis[d]	197 (33%)
Enthesitis[d]	241 (41%)
Acute anterior uveitis[d]	53 (9%)
Dactylitis[d]	23 (4%)
Psoriasis[d]	22 (4%)
Inflammatory bowel disease[d]	8 (1%)
Positive family history according to ASAS definition	135 (23%)
Positive family history of ankylosing spondylitis	87 (15%)
Positive family history of acute anterior uveitis	7 (1%)
Positive family history of reactive arthritis	8 (1%)
Positive family history of inflammatory bowel disease	12 (2%)
Positive family history of psoriasis	36 (6%)
Total number of SpA related diseases in first- or second-degree relatives	
Number of patients with 1 disease	120 (20%)
Number of patients with 2 diseases	15 (3%)
Total number of family members with SpA related diseases	
Number of patients with 1 relative	102 (17%)
Number of patients with 2 relatives	30 (5%)
Number of patients with 3 relatives	3 (1%)
Total number of patients with positive family history in	
First degree only	100 (17%)
Second degree only	25 (4%)
Both first and second degree	10 (2%)
HLA-B27 positivity	310 (52%)
Elevated CRP / ESR level	185 (31%)
Definite radiographic sacroiliitis[e]	119/593 (20%)
Presence of active inflammation on MRI-SI	189/424 (45%)
Number of SpA features[f,g], mean ± SD	2.4 ± 1.6
Clinical diagnosis of axSpA[h]	368 (62%)

Results are presented as n (%) unless specified otherwise.
ASAS, Assessment of SpondyloArthritis international Society; (ax)SpA, (axial) spondyloarthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leucocyte antigen B27; MRI-SI, magnetic resonance imaging of the sacroiliac (SI) joints; NSAID, non-steroidal anti-inflammatory drug.
[a] <5% missing values. [b] Self-reported ethnicity was missing for five patients, who are included in this category, and other self-reported ethnicities are Black, East-Indian, Hispanic/Latino, mixed, or Turkish. [c] Back pain not present anymore or is much better 24-48 hours after a full dose of NSAID. [d] Past or present condition. [e] Grade ≥ 2 bilateral or grade ≥ 3 unilateral. [f] Excluding HLA-B27 carriership and imaging. [g] <20% missing values. [h] Level of confidence regarding the diagnosis is ≥ 6.

Table 2. Univariable associations between a positive family history and HLA-B27 carriership in axSpA suspected patients (n=594)

	HLA-B27+ (n=310)	HLA-B27- (n=284)	OR (95% CI)	p-value
Positive family history according to ASAS definition				
Stratified by self-reported ethnicity				
White	**54**	**26**	**2.3 (1.4-3.9)**	**0.001**
Asian	**38**	**14**	**3.1 (1.6-5.8)**	**0.001**
Other ethnicities[a]	2	1	2.3 (0.2-25.0)	0.509
Stratified by degree of family relationship				
First-degree relatives	**79**	**31**	**2.9 (1.8-4.5)**	**<0.001**
Only second-degree relatives	15	10	1.7 (0.7-3.8)	0.212
Positive family history of ankylosing spondylitis				
Stratified by self-reported ethnicity				
White	**37**	**6**	**7.1 (2.9-17.1)**	**<0.001**
Asian	**35**	**7**	**5.7 (2.5-13.2)**	**<0.001**
Other ethnicities[a]	2	0	n.a.	n.a.
Stratified by degree of family relationship				
First-degree relatives	**61**	**9**	**7.8 (3.8-16.0)**	**<0.001**
Only second-degree relatives	**13**	**4**	**3.7 (1.2-11.6)**	**0.023**
Positive family history of acute anterior uveitis				
Stratified by self-reported ethnicity				
White	4	0	n.a.	n.a.
Asian	2	1	1.9 (0.2-20.7)	0.613
Other ethnicities[a]	0	0	n.a.	n.a.
Stratified by degree of family relationship				
First-degree relatives	5	1	4.7 (0.5-40.1)	0.162
Only second-degree relatives	1	0	n.a.	n.a.
Positive family history of reactive arthritis				
Stratified by self-reported ethnicity				
White	2	2	0.9 (0.1-6.5)	0.924
Asian	1	3	0.3 (0.03-2.9)	0.302
Other ethnicities[a]	0	0	n.a.	n.a.
Stratified by degree of family relationship				
First-degree relatives	3	2	1.4 (0.2-8.2)	0.735
Only second-degree relatives	0	3	n.a	n.a
Positive family history of inflammatory bowel disease				
Stratified by self-reported ethnicity				
White	2	7	0.3 (0.05-1.2)	0.089
Asian	0	2	n.a.	n.a.
Other ethnicities[a]	0	1	n.a.	n.a.
Stratified by degree of family relationship				
First-degree relatives	1	7	0.1 (0.02-1.0)	0.054
Only second-degree relatives	1	3	0.3 (0.03-2.9)	0.294

Table 2. Continued

	HLA-B27+ (n=310)	HLA-B27- (n=284)	OR (95% CI)	p-value
Positive family history of psoriasis				
Stratified by self-reported ethnicity				
White	16	15	1.0 (0.5-2.0)	0.938
Asian	2	2	0.9 (0.1-6.5)	0.926
Other ethnicities[a]	0	1	n.a.	n.a.
Stratified by degree of family relationship				
First-degree relatives	15	14	1.0 (0.5-2.1)	0.949
Only second-degree relatives	3	4	0.7 (0.2-3.1)	0.620

Statistically significant results are printed in bold. CI, confidence interval; HLA-B27, human leucocyte antigen B27; n.a., not applicable; OR, odds ratio.[a] Self-reported ethnicities was missing for five patients, who are included in this category, and other ethnicities are black, East-Indian, Hispanic/ Latino, mixed, or Turkish.

DISCUSSION

In patients suspected of axSpA in the worldwide ASAS cohort, a PFH of AS was the predominant PFH subtype and was associated, independently of other PFH subtypes, with HLA-B27 carriership, regardless of self-reported ethnicity or degree of family relationship. No positive associations were found between a PFH of AAU, ReA, IBD, or psoriasis and HLA-B27 carriership. However, it should be noted that in patients with CBP suspected of axSpA, a PFH of AAU, ReA, and IBD was less common than a PFH of AS, which is in line with previous studies. Somewhat stronger associations were found for patients with white ethnicity and for patients with a PFH in first-degree relatives. Nonetheless, a PFH of AS was strongly associated with HLA-B27 carriership in both white and Asian patients and in both first- and second-degree relatives.

Our study is in line with the study of Ez-Zaitouni et al. in two European cohorts because they reported that a PFH of AS is associated with HLA-B27 carriership, but a PFH of ReA, IBD, or psoriasis was not.[14] In this study, a PFH of ReA, IBD, and AAU was also less common than a PHF of AS. However, in contrast to our findings, Ez-Zaitouni et al.[14] also found that a PFH of AAU contributed to the identification of axSpA because this was associated with HLA-B27 carriership in patients with CBP. In our study, a PFH of AAU was rarely reported (1%), as compared with 5–6% in the study of Ez-Zaitouni et al., which may limit detecting a possible association with HLA-B27 carriership owing to sample size. We have no proper explanation why a PFH of AAU was less common in our study. It may be attributed to differences in ethnicity (European cohorts vs. worldwide cohort in our study). However, the frequency of a PFH of AAU was similarly low in white and Asian patients in our cohort (0.7% vs. 0.5%). Moreover, the frequency of AAU in patients suspected of axSpA was

similar in our cohort (9% overall; 10% in white and 6% in Asian patients) as compared with 8% in the study by Ez-Zaitouni et al.

In a general practice setting or other low SpA prevalence settings, a PFH of AS could be used for identifying HLA-B27-positive patients among patients suspected of axSpA. The RADAR study showed that HLA-B27 is a good referral tool for identifying patients with axSpA, because HLA-B27 has a higher sensitivity than an ASAS PFH.[17] Therefore, it is recommended that a PFH of AS should be used as a criterion for referral to secondary care only when HLA-B27 testing is not feasible.

The current study investigated patients with axial symptoms (i.e., patients with CBP suspected of axSpA) of the ASAS cohort, and therefore it is important to emphasize that the results are not applicable to patients with predominantly peripheral symptoms. In patients with predominantly peripheral symptoms, a PFH of, for example, psoriasis could be important and relevant for identifying patients with an increased risk of pSpA.[15]

An important strength of this study is that the ASAS study is a worldwide cohort, which enabled us to investigate different self-reported ethnicities. Another strength is the availability of extensive information on family history, which allowed us to investigate the role of first- and second-degree relatives for each manifestation of a PFH. A major limitation is the self-reported family history by patients. This could lead either to an underestimation if a patient forgets or is unaware that a relative has an SpA-related disease or to an overestimation if a patient is confused or mistaken in the type of disease of a relative. Nevertheless, in a clinical setting, the physician usually has to depend on patient-reported family history. Another limitation is the small percentage of patients with self-reported ethnicity other than being white or Asian. Only 5% of the patients reported to be Hispanic/Latino, black, mixed, Turkish, East Indian, or unknown ethnicity. Therefore, the results are applicable only to white or Asian populations, which corresponds to the largest population with axSpA worldwide.[18] Preferably, future research into the value of a PFH for identifying HLA-B27 carriership should be conducted in patients with other ethnicities. In this study, we focused on the use of a PFH of SpA for identifying patients with CBP who are at an increased risk of HLA-B27 carriership, but we did not investigate the potential added value of a PFH in diagnosing patients with axSpA. We are currently analysing data from three independent axSpA cohorts to address this issue.

Our data, in combination with data from two European cohorts, show that a PFH of AS and possibly also a PFH of AAU, regardless of ethnicity (white or Asian) or degree of family relationship, is valuable for identifying patients with CBP who could be HLA-B27-positive and consequently have an increased risk of axSpA.

REFERENCES

1. Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet* 2017;390:73-84.
2. 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.
3. 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.
4. Bedendo A, Glorioso S, Venturi Pasini C, et al. A family study of ankylosing spondylitis. *Rheumatol Int* 1984;5:29-32.
5. 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.
6. Brown MA, Laval SH, Brophy S, Calin A. Recurrence risk modelling of the genetic susceptibility to ankylosing spondylitis. *Ann Rheum Dis* 2000;59:883-6.
7. 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.
8. Geirsson AJ, Kristjansson K, Gudbjornsson B. A strong familiality of ankylosing spondylitis through several generations. *Ann Rheum Dis* 2010;69:1346-8.
9. Amor B, Dougados M, Mijiyawa M. [Criteria of the classification of spondylarthropathies]. *Rev Rhum Mal Osteoartic* 1990;57:85-9.
10. Dougados M, van der Linden S, Juhlin R, et al. The European Spondylarthropathy study group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991;34:1218-27.
11. 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. A*nn Rheum Dis* 2009;68:777-83.
12. Poddubnyy D, van Tubergen A, Landewé R, et al. Assessment of SpondyloArthritis international Society (ASAS). Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis. *Ann Rheum Dis* 2015;74:1483-7.
13. Abawi O, van den Berg R, van der Heijde D, van Gaalen FA. Evaluation of multiple referral strategies for axial spondyloarthritis in the SPondyloArthritis Caught Early (SPACE) cohort. *RMD Open* 2017;3:e000389.
14. 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.
15. Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis international Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011;70:25-31.
16. Sepriano A, Landewé R, van der Heijde D, et al. Predictive validity of the ASAS classification criteria for axial and peripheral spondyloarthritis after followup in the ASAS cohort: a final analysis. *Ann Rheum Dis* 2016;75:1034-42.
17. Sieper J, Srinivasan S, Zamani O, et al. Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing spondylitis Reliably (RADAR) study. *Ann Rheum Dis* 2013;72:1621-7.
18. Dean LE, Jones GT, MacDonald AG, et al. Global prevalence of ankylosing spondylitis. *Rheumatology* 2014;53:650-7.

Chapter 3

Is a positive family history of spondyloarthritis relevant for diagnosing axial spondyloarthritis once HLA-B27 status is known?

Miranda van Lunteren, Désirée van der Heijde, Alexandre Sepriano, Inger Jorid Berg, Maxime Dougados, Laure Gossec, Lennart Jacobsson, Roberta Ramonda, Martin Rudwaleit, Joachim Sieper, Robert Landewé, Floris van Gaalen

Rheumatology 2019;58:1649-54

ABSTRACT

Objective

A positive family history (PFH) of spondyloarthritis, in particular a PFH of ankylosing spondylitis (AS) or acute anterior uveitis(AAU), is associated with human leukocyte antigen B27 (HLA-B27) carriership in chronic back pain patients. As it is unknown, the study aimed to investigate if a PFH contributes to diagnosing axial spondyloarthritis (axSpA) once HLA-B27 status is known.

Methods

In axSpA suspected patients from the Assessment of SpondyloArthritis international Society (ASAS), DEvenir des Spondyloarthropathies Indifférenciéés Récentes (DESIR), and SPondyloArthritis Caught Early (SPACE) cohorts logistic regression analyses were performed with HLA-B27 status and PFH according to the ASAS definition (ASAS-PFH) as determinants and clinical axSpA diagnosis as outcome at baseline. Analyses were repeated with a PFH of AS or AAU.

Results

In total, 1818 patients suspected of axSpA were analysed (ASAS n=594, DESIR n=647, and SPACE n=577). In patients from the ASAS, DESIR, and SPACE cohorts, respectively 23%, 39%, and 38% had an ASAS-PFH, 52%, 58%, and 43% were HLA-B27 positive, and 62%, 47%, and 54% were diagnosed with axSpA. HLA-B27 was independently associated with an axSpA diagnosis in each cohort but an ASAS-PFH was not (ASAS cohort: HLA-B27 odds ratio (OR) 6.9 (95% CI 4.7–10.2), ASAS-PFH OR 0.9 (95% CI 0.6–1.4); DESIR: HLA-B27 OR 2.1 (95% CI 1.5–2.9), ASAS-PFH OR 1.0 (95% CI 0.7–1.3); SPACE: HLA-B27 OR 10.4 (95% CI 6.9–15.7), ASAS-PFH OR 1.0 (95% CI 0.7–1.5)). Similar negative results were found for PFH of AS and AAU.

Conclusion

In three independent cohorts with different ethnical backgrounds, ASAS, DESIR, and SPACE, a PFH was not associated independently of HLA-B27 with a diagnosis of axSpA. This indicates that in the vast majority of patients presenting with back pain, a PFH does not contribute to the likelihood of an axSpA diagnosis if HLA-B27 status is known.

INTRODUCTION

Susceptibility for axial spondyloarthritis (axSpA) is thought to be largely genetically determined with human leukocyte antigen B27 (HLA-B27) as the strongest known risk factor for axSpA.[1, 2] With several studies showing an increased prevalence of this disease in relatives of axSpA patients, a positive family history (PFH) of spondyloarthritis (SpA) is thought to be a risk factor for axSpA in patients with chronic back pain.[3, 4] Currently, a PFH of SpA is defined, based on consensus, by the Assessment of SpondyloArthritis international Society (ASAS) as a PFH of ankylosing spondylitis (AS), acute anterior uveitis (AAU), reactive arthritis (ReA), inflammatory bowel disease (IBD), and/or psoriasis in first- or second-degree relatives.[5] A PFH is a SpA feature in the ASAS classification criteria for axSpA and may contribute to classification independently of HLA-B27 status.[5, 6]

We found in two European cohorts of chronic back pain patients suspected of axSpA that a PFH of AS and a PFH of AAU were positively associated with HLA-B27 carriership. However, such an association was not found for a PFH of ReA, IBD, or psoriasis.[7] Moreover, another study in a worldwide population of patients suspected of axSpA showed that only a PFH of AS had an association with HLA-B27 carriership irrespective of ethnicity or degree of family relationship.[8]

Hence, these two studies show that a PFH according to ASAS (ASAS-PFH), but in particular a PFH of AS, clusters with HLA-B27 positivity in chronic back pain patients.[7, 8] While a PFH can be useful in identifying chronic back pain patients who are more likely to be HLA-B27 positive and therefore may have an increased risk of axSpA, it is currently unknown if a PFH contributes to diagnosing axSpA when HLA-B27 status is known.

In the present study, we combined data of the above mentioned three cohorts of patients suspected of axSpA: the worldwide ASAS cohort, the French DEvenir des Spondyloarthropathies Indifférenciéés Récentes (DESIR), and the European SPondyloArthritis Caught Early (SPACE) cohort. The main objective of this study was to investigate if an ASAS-PFH, a PFH of AS, or a PFH of AAU contributed to a diagnosis of axSpA in an ethnically diverse group of patients with known HLA-B27 status.

METHODS

The ASAS study is a longitudinal cohort in 29 centres worldwide and has included patients with a suspicion of axSpA (> 3 months' back pain, onset < 45 years, with or without peripheral symptoms) or peripheral SpA (current peripheral arthritis and/or dactylitis and/or enthesitis but without current chronic back pain).[5, 9, 10] Only patients suspected of axSpA

were included in the analysis for this study. The DESIR study (NCT01648907, datalock: April 2015) is a longitudinal cohort study in 25 French centres that included patients aged 18–50 years with inflammatory back pain for ≥ 3 months and < 3 years.[11] The SPACE study is an ongoing inception cohort and includes patients aged ≥ 16 years with chronic back pain (≥ 3 months, ≤ 2 years, onset ≤ 45 years) from rheumatology outpatient clinics in the Netherlands, Italy, Norway, and Sweden.[12] All three studies were approved by local ethical committees and informed consent was obtained before inclusion from all patients. A detailed description of all cohorts is provided elsewhere.[5, 9-12]

All patients underwent a full diagnostic work-up in which clinical, laboratory, and imaging data were collected at baseline, including HLA-B27 testing and radiography of the sacroiliac joints (X-SI). Magnetic resonance imaging of the SI (MRI-SI) was performed in all DESIR and SPACE patients, but in the ASAS cohort the MRI-SI was considered obligatory only for the first 20 patients for each centre. For each patient the clinical diagnosis of axSpA was established by the treating rheumatologist based on the information obtained from the full diagnostic work-up.

The ASAS expert definition of PFH is the presence of AS, AAU, psoriasis, IBD, or ReA in first- or second-degree relatives. Father, mother, sister, brother, daughter, and son are first-degree relatives and grandmother, grandfather, aunt, uncle, niece, and nephew are second-degree relatives in this definition.[5] In the ASAS cohort, information was available concerning which relatives had a SpA-related disease. Therefore, granddaughter, grandson, half-sister, and half-brother were also considered to be second-degree relatives in addition to the ASAS definition.

Data analysis

Baseline data of patients suspected of axSpA in the ASAS, DESIR, and SPACE cohorts were analysed. Descriptive statistics were used to present demographic and clinical characteristics for each cohort. In each cohort, univariable logistic regression models were performed with HLA-B27 status and ASAS-PFH as determinants and a clinical axSpA diagnosis as outcome. The analyses were repeated in multivariable models with both determinants. All analyses were repeated with a PFH of AS and a PFH of AAU. Interactions were tested between HLA-B27 status and each PFH. Interaction terms with $P<0.10$ were considered to be statistically significantly. Age and gender were tested for confounding. Results were stratified for age, gender, and ethnicity in order to test whether results differed between subgroups. Data analyses were performed with Stata SE v.14 software (StataCorp, College Station, TX, USA).

RESULTS

In total, 1818 patients suspected of axSpA and with complete data on family history at baseline were analysed (ASAS n=594, DESIR n=647, SPACE n=577) (**Table 1**). MRI-SI results were available for 424/594 (71%) ASAS patients, 636/647 (98%) DESIR patients, and 565/577 (98%) SPACE patients. ASAS, DESIR, and SPACE patients, respectively, had a mean ± SD symptom duration of 85.7 ± 108.4, 18.2 ± 10.5, and 13.3 ± 7.1 months; 46%, 47%, and 38% were male; 59%, 89%, and 94% were Caucasian; 52%, 58%, and 43% were HLA-B27 positive; 62%, 47%, and 54% received a clinical diagnosis of axSpA. An ASAS-PFH was reported in 23% of ASAS patients, 39% of DESIR patients, and 38% of SPACE patients. A PFH of AS and a PFH of AAU were reported in 15% and 1% of ASAS patients, 20% and 4% of DESIR patients, and 18% and 6% of SPACE patients, respectively.

In the univariable analysis, HLA-B27 status was significantly associated with an axSpA diagnosis in all three cohorts (**Table 2**). An ASAS-PFH (**Table 2**) and a PFH of AAU (**Supplementary Table S2**) were univariately associated with an axSpA diagnosis in the SPACE cohort, but not in ASAS and DESIR cohorts. A PFH of AS was associated with diagnosis of axSpA in the ASAS cohort, but not in the DESIR and SPACE cohorts (**Supplementary Table S1**).

In the multivariable models, HLA-B27 status was independently and positively associated with a diagnosis of axSpA but such an independent positive association was not found for ASAS-PFH in any cohort (ASAS cohort: HLA-B27 odds ratio (OR) 6.9, 95% CI 4.7–10.2; ASAS-PFH OR 0.9, 95% CI 0.6–1.4; DESIR cohort: HLA-B27 OR 2.1, 95% CI 1.5–2.9; ASAS-PFH OR 1.0, 95% CI 0.7–1.3; SPACE cohort: HLA-B27 OR 10.4, 95% CI 6.9–15.7; ASAS-PFH OR 1.0, 95% CI 0.7–1.5) (**Table 2**). Similar results were found for the multivariable models with a PFH of AS or a PFH of AAU in the ASAS, DESIR, and SPACE cohorts (**Supplementary Tables S1 and S2**) although in the SPACE cohort only a PFH of AS was negatively associated with an axSpA diagnosis.

Statistical interactions between HLA-B27 status and a PFH were tested for each association. No statistically significant interactions were found, except the interaction between HLA-B27 status and a PFH in the SPACE cohort (P=0.016). Compared with the HLA-B27 negative/PFH negative subgroup (n=234) as reference (OR=1), the HLA-B27 negative/PFH positive (n=97) subgroup had an OR of 1.4 (95% CI 0.9–2.3) on a diagnosis of axSpA, the HLA-B27 positive/PFH negative subgroup (n=125) had an OR of 16.8 (95% CI 9.2–30.9), and the HLA-B27 positive/PFH positive subgroup (n=121) had an OR of 8.4 (95% CI 5.0–14.0). This illustrates that PFH does not contribute to a diagnosis of axSpA, not even in the absence of HLA-B27 positivity.

Table 1. Baseline characteristics of the patients suspected of axSpA in the ASAS, DESIR, and SPACE cohort

Characteristics	ASAS (n=594)	DESIR (n=647)	SPACE (n=577)
Age (years) at baseline, mean ± SD	33.7 ± 11.7	33.6 ± 8.6	30.8 ± 8.1
Male	276 (46%)	305 (47%)	221 (38%)
Caucasian	348 (59%)	577 (89%)	454/484 (94%)
Duration of back pain (months), mean ± SD	85.7 ± 108.4[a]	18.2 ± 10.6[a]	13.3 ± 7.1
IBP	301/532 (57%)	647 (100%)[b]	396/576 (69%)
Good response to NSAIDs[c]	274 (46%)	515/644 (80%)	263/563 (47%)
Peripheral arthritis	197 (33%)	363 (56%)	97/575 (17%)
Enthesitis	241 (41%)	312 (48%)	121 (21%)
Dactylitis	23 (4%)	83 (13%)	35 (6%)
AAU	53 (9%)	51 (8%)	47 (8%)
Psoriasis	22 (4%)	97 (15%)	77 (13%)
IBD	8 (1%)	23 (4%)	38 (7%)
Positive family history according to ASAS definition	135 (23%)	249 (39%)	218 (38%)
A positive family history of			
AS	87 (15%)	127 (20%)	104 (18%)
AAU	7 (1%)	29 (4%)	34 (6%)
ReA	8 (1%)	6 (1%)	19/563 (3%)
IBD	12 (2%)	32 (5%)	32/570 (6%)
Psoriasis	36 (6%)	129 (20%)	95/571 (17%)
HLA-B27 positivity	310 (52%)	376/646 (58%)	246 (43%)
Elevated CRP / ESR	185 (31%)	254 (39%)	188 (33%)
Radiographic sacroiliitis[d]	119/593 (20%)	172 (27%)	80/570 (14%)
Sacroiliitis on MRI[d]	189/424 (45%)	207/636 (33%)	207/565 (37%)
Clinical diagnosis of axSpA[e]	368 (62%)	302 (47%)	313 (54%)

Results are presented as n (%) unless specified otherwise. [a] <5% missing values. [b] Inclusion criterion. [c] Back pain not present anymore or is much better 24-48 hours after a full dose of NSAID. [d] Imaging based on local reading of the sacroiliac joints. [e] Level of confidence regarding the diagnosis is ≥ 6 in ASAS and SPACE, ≥ 8 in DESIR. AAU; acute anterior uveitis; AS; Ankylosing Spondylitis; ASAS, Assessment of SpondyloArthritis international Society; (ax)SpA, (axial) spondyloarthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leucocyte antigen B27; IBD, inflammatory bowel disease; IBP, inflammatory back pain; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drug; ReA; Reactive Arthritis.

Table 2. Results of the contribution of a PFH and HLA-B27 to a clinical diagnosis of axSpA

	axSpA+	axSpA-	OR (95% CI)	P-value
ASAS cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**254 (43%)**	**56 (9%)**	**6.7 (4.7-9.8)**	**<0.001**
HLA-B27-	114 (19%)	170 (29%)	1.0 (ref)	(ref)
Univariable analysis: ASAS-PFH				
ASAS-PFH+	91 (15%)	44 (7%)	1.4 (0.9-2.0)	0.138
ASAS-PFH-	277 (47%)	182 (31%)	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and ASAS-PFH				
HLA-B27+	**254 (43%)**	**56 (9%)**	**6.9 (4.7-10.2)**	**<0.001**
ASAS-PFH+	91 (15%)	44 (7%)	0.9 (0.6-1.4)	0.561
DESIR cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**204 (32%)**	**172 (27%)**	**2.1 (1.5-2.9)**	**<0.001**
HLA-B27-	98 (15%)	172 (27%)	1.0 (ref)	(ref)
Univariable analysis: ASAS-PFH				
ASAS-PFH+	117 (18%)	132 (20%)	1.0 (0.7-1.4)	0.900
ASAS-PFH-	185 (29%)	213 (33%)	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and ASAS-PFH				
HLA-B27+	**204 (32%)**	**172 (27%)**	**2.1 (1.5-2.9)**	**<0.001**
ASAS-PFH+	117 (18%)	132 (20%)	1.0 (0.7-1.3)	0.772
SPACE cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**205 (36%)**	**41 (7%)**	**10.3 (6.9-15.5)**	**<0.001**
HLA-B27-	108 (19%)	223 (39%)	1.0 (ref)	(ref)
Univariable analysis: ASAS-PFH				
ASAS-PFH+	**132 (23%)**	**86 (15%)**	**1.5 (1.1-2.1)**	**0.018**
ASAS-PFH-	181 (31%)	178 (31%)	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and ASAS-PFH				
HLA-B27+	**205 (36%)**	**41 (7%)**	**10.4 (6.9-15.7)**	**<0.001**
ASAS-PFH+	132 (23%)	86 (15%)	1.0 (0.7-1.5)	0.921

Statistically significant associations are printed in bold. ASAS, Assessment of SpondyloArthritis international Society; (ax)SpA, (axial) spondyloarthritis; CI, confidence interval; HLA-B27, human leucocyte antigen B27; OR, odds ratio; PFH, positive family history.

No confounding by age or gender was found and similar results were found when data were stratified for mean age or gender (data not shown). Results were also stratified for Caucasian vs non-Caucasian patients and we found similar results for Caucasian and non-Caucasian patients (data not shown).

DISCUSSION

In all three cohorts with different ethnical backgrounds, HLA-B27 carriership was associated with a clinical diagnosis of axSpA whereas conflicting results were found in the association between a PFH and an axSpA diagnosis in univariable analyses, irrespective of the definitions tested. In multivariable analyses, HLA-B27 was independently associated with an axSpA diagnosis in each cohort but an ASAS-PFH, a PFH of AS, and a PFH of AAU were not (positively) associated with an axSpA diagnosis.

In the multivariable analysis, in the SPACE cohort but not in the ASAS or DESIR cohort, a PFH of AS had a negative association with an axSpA diagnosis after adding HLA-B27 positivity. This is likely a spurious finding as only positive associations (statistically significant or not) with an axSpA diagnosis were found in all three cohorts. Moreover, no interaction was found between HLA-B27 status and a PFH of AS in any of the three cohorts.

A PFH had, at best, only a modest association with a clinical diagnosis of axSpA before adjustment of HLA-B27 and only in the SPACE cohort was this association statistically significant. It was previously shown that HLA-B27 and imaging are key elements for making a diagnosis of axSpA, with other SpA features, including a PFH, playing a more modest role.[13] This can explain the modest association between a PFH and the clinical diagnosis, although a PFH is related to HLA-B27 positivity.[7, 8]

We have repeatedly demonstrated that a PFH of SpA helps in identifying chronic back pain patients at increased risk of axSpA as a PFH of SpA is positively associated with HLA-B27 carriership.[7, 8] However, the effect of this positive association is apparently entirely taken over by a positive test for HLA-B27. Although in all three cohorts a few patients who were HLA-B27 negative but had a PFH were considered to have axSpA, our data show at group level that when knowledge about HLA-B27 status is available, a positive PFH does not have further influence on a diagnosis in an ethnically diverse group of patients. Thus, this finding casts doubt about the relative weight of PFH in the classification criteria for axSpA, in which PFH and HLA-B27 have independent contributions.

Nevertheless, our findings are in line with previous studies in which a PFH is a feature of HLA-B27 positive but not of HLA-B27 negative axSpA.[14, 15] In literature HLA-B27 negative

familial axSpA was found in only a few cases suggesting that HLA-B27 negative familial axSpA may exist. However, these patients were typed using currently obsolete methods with higher risks of mistypings.[16, 17]

Given the potential implications for clinical practice it is important to stress several limitations. The DESIR cohort had inflammatory back pain as an inclusion criterion, while the ASAS and SPACE cohorts included patients with chronic back pain. Nevertheless, similar results were found in all three cohorts. Although data of three cohorts were analysed, there was an under-representation of patients with for instance an African or South American ethnicity. The ASAS cohort included predominantly patients with a Caucasian or Asian ethnicity and the DESIR and SPACE cohorts included predominantly Caucasian patients, which corresponds to the two largest populations of axSpA patients worldwide.[18] Another limitation is the self-reported family history by patients and this could have led to an over- or underestimation of the investigated effects. Nevertheless, this is similar in most clinical settings where the physician usually has to depend on patient-reported information about the family history. Further, HLA-B27 status was known for each patient in each cohort, just as in the clinical setting, and thereby a similar amount of bias was present in each case.

It is important to emphasize that the current study investigated only patients with chronic back pain suspected of axSpA. Therefore, the results are not applicable to patients with predominantly peripheral symptoms. In these patients a PFH of other SpA-related diseases, such as psoriasis, could be valuable in diagnosing patients with peripheral SpA.[9]

Furthermore, we have investigated the association between a PFH and a diagnosis of axSpA when the HLA-B27 status is known. However, rheumatologists or other clinicians might have limited access to HLA-B27 testing. In this case, we would like to recommend assessing the presence of a PFH, especially a PFH of AS. A PFH of AS is associated with HLA-B27 positivity and could therefore be used to identify patients with an increased risk of axSpA.[7, 8]

In conclusion, in three independent cohorts including one worldwide cohort, a PFH was not associated independently of HLA-B27 with a diagnosis of axSpA in patients suspected of axSpA. These results may have implications for diagnosis and classification.

REFERENCES

1. 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.
2. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet 2017;390:73-84.
3. Bedendo A, Glorioso S, Venturi Pasini C, et al. A family study of ankylosing spondylitis. *Rheumatol Int* 1984;5:29-32.
4. 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.
5. 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.
6. 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.
7. 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.
8. van Lunteren M, Sepriano A, Landewé R, et al. Do ethnicity, degree of family relationship, and spondyloarthritis subtype in affected relatives influence the association between a positive family history for spondyloarthritis and HLA-B27 carriership? Results from the worldwide ASAS cohort. *Arthritis Res Ther* 2018;77:335-6.
9. Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011;70:25-31.
10. 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.
11. 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.
12. 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.
13. Ez-Zaitouni Z, Bakker PAC, van Lunteren M, et al. Presence of multiple spondyloarthritis (SpA) features is important but not sufficient for a diagnosis of axial spondyloarthritis: data from the SPondyloArthritis Caught Early (SPACE) cohort. *Ann Rheum Dis* 2017;76:1086-92.
14. Linssen A, Feltkamp TEW. B27 positive diseases versus B27 negative diseases. *Ann Rheum Dis* 1988;47:431-9.
15. Akkoç N, Yarkan H, Kenar G, Khan MA. Ankylosing spondylitis: HLA-B*27-positive versus HLA-B*27-negative disease. *Curr Rheumatol Rep* 2017;19:26.
16. Calin A, Marder A, Becks E, Burns T. Genetic differences between B27 positive patients with ankylosing spondylitis and B27 positive healthy controls. *Arthritis Rheum* 1983;26:1460-4.
17. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. *Arthritis Rheum* 1984;27:361-8.
18. Dean LE, Jones GT, MacDonald AG, et al. Global prevalence of ankylosing spondylitis. *Rheumatology* 2014;53:650-7.

3

SUPPLEMENTARY MATERIAL

Supplementary Table S1. Results of the contribution of a PFH for AS and HLA-B27 to an axSpA diagnosis

	axSpA+	axSpA-	OR (95% CI)	P-value
ASAS cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**254**	**56**	**6.7 (4.7-9.8)**	**<0.001**
HLA-B27-	114	170	1.0 (ref)	(ref)
Univariable analysis: PFH of AS				
PFH of AS+	**65**	**22**	**2.0 (1.2-3.3)**	**0.009**
PFH of AS-	303	204	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and PFH of AS				
HLA-B27+	**254**	**56**	**6.9 (4.6-10.2)**	**<0.001**
PFH of AS+	65	22	0.9 (0.5-1.7)	0.800
DESIR cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**204**	**172**	**2.1 (1.5-2.9)**	**<0.001**
HLA-B27-	98	172	1.0 (ref)	(ref)
Univariable analysis: PFH of AS				
PFH of AS+	63	64	1.2 (0.8-1.7)	0.461
PFH of AS-	239	281	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and PFH of AS				
HLA-B27+	**204**	**172**	**2.1 (1.5-2.9)**	**<0.001**
PFH of AS+	63	64	1.0 (0.6-1.4)	0.829
SPACE cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**205**	**41**	**10.3 (6.9-15.5)**	**<0.001**
HLA-B27-	108	223	1.0 (ref)	(ref)
Univariable analysis: PFH of AS				
PFH of AS+	63	41	1.4 (0.9-2.1)	0.153
PFH of AS-	250	223	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and PFH of AS				
HLA-B27+	**205**	**41**	**13.4 (8.4-21.4)**	**<0.001**
PFH of AS+	**63**	**41**	**0.4 (0.2-0.8)**	**0.004**

Statistically significant associations are printed in bold. AS, Ankylosing Spondylitis; ASAS, Assessment of SpondyloArthritis international Society; (ax)SpA, (axial) spondyloarthritis; CI, confidence interval; HLA-B27, human leucocyte antigen B27; OR, odds ratio; PFH, positive family history.

Supplementary Table S2. Results of the contribution of a PFH for AAU and HLA-B27 to an axSpA diagnosis

	axSpA+	axSpA-	OR (95% CI)	P-value
ASAS cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**254**	**56**	**6.7 (4.7-9.8)**	**<0.001**
HLA-B27-	114	170	1.0 (ref)	(ref)
Univariable analysis: PFH of AAU				
PFH of AAU+	4	3	0.8 (0.2-3.7)	0.792
PFH of AAU-	364	223	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and PFH of AAU				
HLA-B27+	**254**	**56**	**6.9 (4.7-10.1)**	**<0.001**
PFH of AAU+	4	3	0.4 (0.08-1.8)	0.224
DESIR cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**204**	**172**	**2.1 (1.5-2.9)**	**<0.001**
HLA-B27-	98	172	1.0 (ref)	(ref)
Univariable analysis: PFH of AAU				
PFH of AAU+	16	13	1.4 (0.7-3.0)	0.350
PFH of AAU-	286	332	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and PFH of AAU				
HLA-B27+	**204**	**172**	**2.1 (1.5-2.9)**	**<0.001**
PFH of AAU+	16	13	1.1 (0.5-2.3)	0.863
SPACE cohort				
Univariable analysis: HLA-B27				
HLA-B27+	**205**	**41**	**10.3 (6.9-15.5)**	**<0.001**
HLA-B27-	108	223	1.0 (ref)	(ref)
Univariable analysis: PFH of AAU				
PFH of AAU+	**25**	**9**	**2.5 (1.1-5.4)**	**0.024**
PFH of AAU-	288	255	1.0 (ref)	(ref)
Multivariable analysis: HLA-B27 and PFH of AAU				
HLA-B27+	**205**	**41**	**10.7 (7.0-16.3)**	**<0.001**
PFH of AAU+	25	9	0.8 (0.3-1.8)	0.540

Statistically significant associations are printed in bold. AAU, acute anterior uveitis; ASAS, Assessment of SpondyloArthritis international Society; (ax)SpA, (axial) spondyloarthritis; CI, confidence interval; HLA-B27, human leucocyte antigen B27; OR, odds ratio; PFH, positive family history.

Chapter 4

In early axial spondyloarthritis, increasing disease activity is associated with worsening of health-related quality of life over time

Miranda van Lunteren, Zineb Ez-Zaitouni, Anoek de Koning, Hanne Dagfinrud, Roberta Ramonda, Lennart Jacobsson, Robert Landewé, Désirée van der Heijde, Floris van Gaalen

The Journal of Rheumatology 2018;45:779-84

ABSTRACT

Objective

In early axial spondyloarthritis (axSpA), data are lacking about the relationship between disease activity and health-related quality of life (HRQoL). We assessed and quantified the association between change in Ankylosing Spondylitis Disease Activity Score (ASDAS) and HRQoL over time in early axSpA.

Methods

Baseline and 1-year data of patients with axSpA fulfilling the Assessment of Spondyloarthritis international Society (ASAS) classification criteria from the SPondyloArthritis Caught Early (SPACE) cohort were analysed. Associations between change in ASDAS and in physical (PCS) or mental component summary (MCS) of the Medical Outcomes Study Short Form-36 were tested by linear regression models. Age, sex, ASAS criteria arm, and blue- versus white-collar work were tested for effect modification. Subsequently, these factors and medication were tested for confounding.

Results

There were 161 patients with axSpA (53% male, mean ± SD age 29.7 ± 7.5 years, symptom duration 13.6 ± 7.2 months, HLA-B27-positive 91%, radiographic sacroiliitis 22%) who had ASDAS of 2.5 ± 1.0 and 2.0 ± 0.8, PCS of 28.4 ± 14.3 and 36.9 ± 13.1, and MCS of 48.2 ± 13.8 and 49.3 ± 12.0 at baseline and 1 year, respectively. Per unit increase in ASDAS between baseline and 1 year, PCS worsened by 9.5 points. The same level of disease activity had fewer adverse effects on physical HRQoL in women and white-collar workers.

Conclusion

To our knowledge, our data are the first to show that in a broad group of patients with early axSpA, increasing ASDAS is associated with worsening of physical HRQoL, but not mental HRQoL, over time.

INTRODUCTION

A task force of international experts recently published recommendations for treat-to-target (T2T) in axial spondyloarthritis (axSpA) and formulated the primary goal of T2T as maximizing long term health-related quality of life (HRQoL) and social participation.[1] To achieve these outcomes, the proposed treatment target is inactive disease, or alternatively, low disease activity by Ankylosing Spondylitis Disease Activity Score (ASDAS).[1]

Ankylosing spondylitis (AS, radiographic axSpA) has a substantial effect on HRQoL, and increased disease activity influences HRQoL adversely.[2-4] Similar data of patients with early axSpA are lacking.

Data from patients with AS cannot be extrapolated to patients with early axSpA. For instance, most patients with early axSpA do not have radiographic sacroiliitis, and sex distribution is similar, whereas patients with severe AS are more often male.[5, 6]

Also in early axSpA, patient changes in disease activity over time seem to be associated with changes in HRQoL. In the ABILITY-1 trial in patients with non-radiographic axSpA, an improvement in disease activity as measured by ASDAS was associated with an improvement in HRQoL.[7] However, patients in the ABILITY-1 trial had a relatively long symptom duration (8-10 years), had exclusively non-radiographic axSpA, and a high level of disease activity necessitating treatment with a tumor necrosis factor inhibitor.

It is rational to assume that the association between changes in disease activity and changes in HRQoL found in AS also extends to patients with early axSpA. However, it is unclear whether this association is of similar magnitude in relevant subgroups of axSpA. The association may, for instance, be different in males and females, or in those with sedentary jobs versus physically demanding ones. For example, physically demanding jobs are associated with greater functional limitations in patients with AS and have been reported to reduce HRQoL.[8, 9] Further, women have higher disease activity and worse physical functioning compared to men.[10]

To implement T2T strategies in patients with early axSpA, more information is needed about the association between disease activity and HRQoL in these patients and relevant subgroups in daily clinical practice. Therefore, the objective of our study was to assess and quantify the association between the change in disease activity and in HRQoL in a broad patient population with early axSpA, and in relevant subgroups over time.

METHODS

Baseline and 1-year data were analysed from the SPondyloArthritis Caught Early (SPACE) cohort, which has been described in detail previously.[5] In brief, the SPACE cohort is an ongoing inception cohort that includes patients > 16 years of age with chronic back pain (persisting ≥ 3 months and ≤ 2 years, and onset < 45 years). For our current study, the database was locked on March 31, 2017. Patients were recruited from multiple European sites in the Netherlands, Norway, Italy, and Sweden. The SPACE cohort has been approved by the medical ethical committee of the Leiden University Medical Center (P08.105). Informed consent forms from all study participants had been obtained beforehand.

All study participants underwent a full examination as part of the study protocol at baseline and 1 year, consisting of medical history, physical examination, laboratory assessments (C-reactive protein (CRP), erythrocyte sedimentation rate), and questionnaires. At baseline, HLA-B27 was tested, and magnetic resonance imaging (MRI) and radiography of the sacroiliac joints and spine were obtained. The treating rheumatologist provided the diagnosis using local reading of imaging and indicated the level of confidence regarding the diagnosis on a numerical scale (0, not confident at all; 10, very confident). For classification, central reading was performed by 3 readers per imaging modality. Images were considered to be positive for sacroiliitis when ≥ 2 readers agreed using the modified New York criteria for radiographs[11] and Assessment of Spondyloarthritis international Society (ASAS) definition for a positive MRI of the sacroiliac joints.[12] Patients diagnosed with axSpA were classified according to the ASAS axSpA criteria[13] to the clinical arm (HLA-B27 plus 2 SpA features) if patients fulfilled the clinical arm exclusively, and to the imaging arm (sacroiliitis plus 1 SpA feature) if patients fulfilled either the imaging arm alone or both arms.

Disease activity had been assessed by ASDAS (CRP-based).[14, 15] The ASDAS level was categorized as inactive disease (< 1.3), moderate disease activity (< 2.1), high disease activity (≤ 3.5), and very high disease activity (> 3.5).[16]

HRQoL was assessed by the Medical Outcomes Study Short Form-36 (SF-36).[17] Eight subscales were calculated and transformed into scale scores, with numeric scales ranging from 0 (worst health) to 100 (best health) after recoding and recalibration. These scale scores were weighted according to sex, age, and country.[18, 19] Because no Italian age- and sex-matched scores were available, Dutch age- and sex-matched scores were used for all Italian patients (n=26). The adjusted scores were used to calculate 2 summary measures, the physical (PCS) and mental component summary (MCS). In rare cases (n=6) of a negative PCS, scores were set to 0. The PCS and MCS were transformed to compare the scores to

the general population mean of 50. Higher scores indicated better HRQoL.[20]

The patient's job type was determined using a multiple-choice question with the following options: (1) management position (e.g., director, manager, member of the board of directors); (2) professional specialist (e.g., engineer, teacher, nurse practitioner, systems analyst); (3) commercial profession (e.g., representative, agent, clerk, salesperson); (4) technical support (e.g., laboratory technician, legal officer, information technology); (5) administrative support (e.g., secretary, invoice administration); (6) service profession (e.g., security officer, janitor); and (7) operator or laborer (e.g., assembler, mechanic, carpenter, builder). Answer options 1, 2, 3, 4, and 5 were considered to reflect "*white-collar workers*" and answer options 6 and 7 were considered to reflect "*blue-collar workers*".

The use of nonsteroidal anti-inflammatory drugs, conventional synthetic disease-modifying antirheumatic drugs (csDMARD), and biological (b-) DMARD were separately categorized as "*no medication*", "*stopped using medication*", "*started using medication*", and "*continued use of medication*" between baseline and 1 year. Twelve patients were already treated with csDMARD and 1 patient with bDMARD at baseline because of inflammatory bowel disease, uveitis, dactylitis, peripheral arthritis, psoriasis, or a combination thereof.

Analysis

Patients diagnosed with axSpA and fulfilling the ASAS classification were included in the analysis. Categorical variables were described as frequencies (proportions) and continuous variables as means ± SD. Linear regression models were built with change in ASDAS (ΔASDAS) as the independent variable and ΔPCS or ΔMCS as dependent variables between baseline and 1 year. Age at baseline, sex, ASAS axSpA subclassification (imaging versus clinical arm), and job type (white versus blue collar) at baseline were tested for effect modification 1 by 1 in each model, and stratification of the models was conducted if effect modification was found (P-value for the interaction term <0.10). To prevent spurious effects because of small sample sizes, stratification was only performed if each subgroup consisted of ≥ 15 patients. Subsequently, these factors and treatments were tested for confounding (crude regression coefficient changed by > 10% after adding each factor) and models were adjusted for each confounder. Data were analysed using STATA SE V.14 (Statacorp). P-values <0.05 were considered statistically significant.

RESULTS

In total, 361 patients had baseline and 1-year data. Of the 361 patients, 107 either did not have an axSpA diagnosis, the diagnosis was missing (n=7), or they did not fulfil the

classification criteria after diagnosis (n=73). ASDAS could not be calculated in 12 patients, and 1 patient did not fill out the SF-36.

Of the 161 patients with axSpA, 53% were male, mean ± SD age was of 29.7 ± 7.5 years, and mean symptom duration was 13.6 ± 7.2 months (**Table 1**). Patients had on average 5 SpA features, including imaging and HLA-B27 carriership. Mean level of confidence in diagnosis was 8 ± 2. Patients had a mean ASDAS of 2.5 ± 1.0 at baseline and 2.0 ± 0.8 at 1 year. At baseline, 11% of the patients had inactive disease, 27% moderate disease activity, 48% high disease activity, and 14% very high disease activity (**Table 2**).

The mean ± SD PCS was 28.4 ± 14.3 at baseline and increased to 36.9 ± 13.1 at 1 year (**Table 2**). The MCS remained constant between baseline and 1 year (48.2 ± 13.8 and 49.3 ± 12.0, respectively) and was comparable to the general population (MCS=50). No correlation was found between the change in ASDAS and the change in MCS (r=-0.05, P=0.54). Therefore, the regression analyses focused on PCS only.

Between baseline and 1 year, 1 unit ΔASDAS led on average to a 9.5-point change in PCS (**Figure 1**). The SF-36 subscales role physical, bodily pain, and physical functioning changed the most compared to other subscales between baseline and 1 year per unit change of the ASDAS (**Table 3**; β=-24.5, 95% CI -30.1 to -18.8; β=-17.2, 95% CI -19.9 to -14.5; and β=-12.6, 95% CI -15.2 to -10.1, respectively).

The association between ΔASDAS and ΔPCS was modified by sex (P=0.056 for the interaction term) and job type (P=0.077; **Table 4**). Information about profession was provided by 79 patients out of 129 who worked at baseline (61.2%). The association between ΔASDAS and ΔPCS was less strong in women (β=-7.7, 95% CI -9.9 to -5.5) than in men (β=-11.0, 95% CI -13.7 to -8.4), and in white-collar workers (β=-9.6, 95% CI -12.3 to -7.0) than in blue-collar workers (β=-15.6, 95% CI -23.0 to -8.3). No effect modification or confounding was found by age or ASAS classification arm (clinical or imaging arm). Also, no confounding by treatment was found.

In 102 out of 161 patients, 2-year data were also available. Similar results were found for ASDAS, PCS, and MCS at both baseline and 1 year for these patients as compared to patients with 1-year data only. Over 2 years, ASDAS (1.9 ± 0.9) and PCS (39.1 ± 12.2) improved slightly, and MCS remained stable (50.1 ± 11.2). Most importantly, the association between ΔASDAS and ΔPCS was similar between baseline and 1 year (β=-9.8, 95% CI -12.2 to -7.5), and 1-year and 2-year follow-up (β=-8.9, 95% CI -11.1 to -6.7).

Table 1. Baseline characteristics of patients with axSpA in the SPACE cohort included in the analysis

Characteristics	n=161
Age (years) at inclusion, mean ± SD	29.7 ± 7.5
Male	86 (53%)
Symptom duration (months), mean ± SD	13.6 ± 7.2
Inflammatory back pain	135 (84%)
Positive family history	84 (52%)
Enthesitis[a]	44 (27%)
Dactylitis[a]	14 (9%)
Peripheral arthritis[a]	36 (22%)
Good response to NSAIDs[b]	99 (62%)
Uveitis[a]	28 (17%)
Psoriasis[a]	25 (16%)
Inflammatory bowel disease[a]	8 (5%)
HLA-B27 positive	146 (91%)
Elevated ESR/CRP level	73 (45%)
X-SI positive	36 (22%)
MRI-SI positive	69 (43%)
Number of SpA features[c]**, mean ± SD**	5.0 ± 1.7
Confidence in axSpA diagnosis by rheumatologist, mean ± SD	8.1 ± 2.0
ASAS axSpA classification	
Clinical arm only	76 (47%)
Imaging arm only	22 (14%)
Both arms	63 (39%)
Use of NSAID	127 (79%)
Use of csDMARD	12 (8%)
Use of bDMARD	1 (1%)

Values are presented as n (%) unless otherwise specified. [a] Past or present condition, either diagnosed or confirmed by a physician. [b] Back pain not present or was much better 24–48 hours after a full dose of NSAID. [c] Included HLA-B27 testing and imaging. ASAS, Assessment of Spondyloarthritis international Society; axSpA, axial spondyloarthritis; bDMARD, biological disease-modifying antirheumatic drugs (DMARD); CRP, C-reactive protein; csDMARD, conventional synthetic DMARD; ESR, erythrocyte sedimentation rate; MRI-SI,magnetic resonance imaging of sacroiliac (SI) joints; NSAID, nonsteroidal anti-inflammatory drugs; X-SI, radiography of SI-joints.

Table 2. Characteristics of patients with axSpA at baseline and 1 year (n=161)

Characteristics	Baseline	1 year
BASDAI, mean ± SD	4.0 ± 2.1	3.1 ± 2.0
CRP, mean ± SD	7.5 ± 10.5	4.7 ± 6.6
ASDAS, mean ± SD	2.5 ± 1.0	2.0 ± 0.8
ASDAS		
Inactive disease, < 1.3	17 (11%)	37 (23%)
Moderate disease activity, < 1.2	44 (27%)	64 (40%)
High disease activity, ≤ 3.5	78 (49%)	50 (31%)
Very high disease activity, > 3.5	22 (14%)	10 (6%)
SF-36, mean ± SD		
PCS	28.4 ± 14.3	36.9 ± 13.1
MCS	48.2 ± 13.8	49.3 ± 12.0
BASFI, mean ± SD	2.3 ± 2.2	1.6 ± 2.0

Values are presented as n (%) unless otherwise specified. ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; MCS, mental component summary; PCS, physical component summary; SF-36, Medical Outcomes Study Short Form-36.

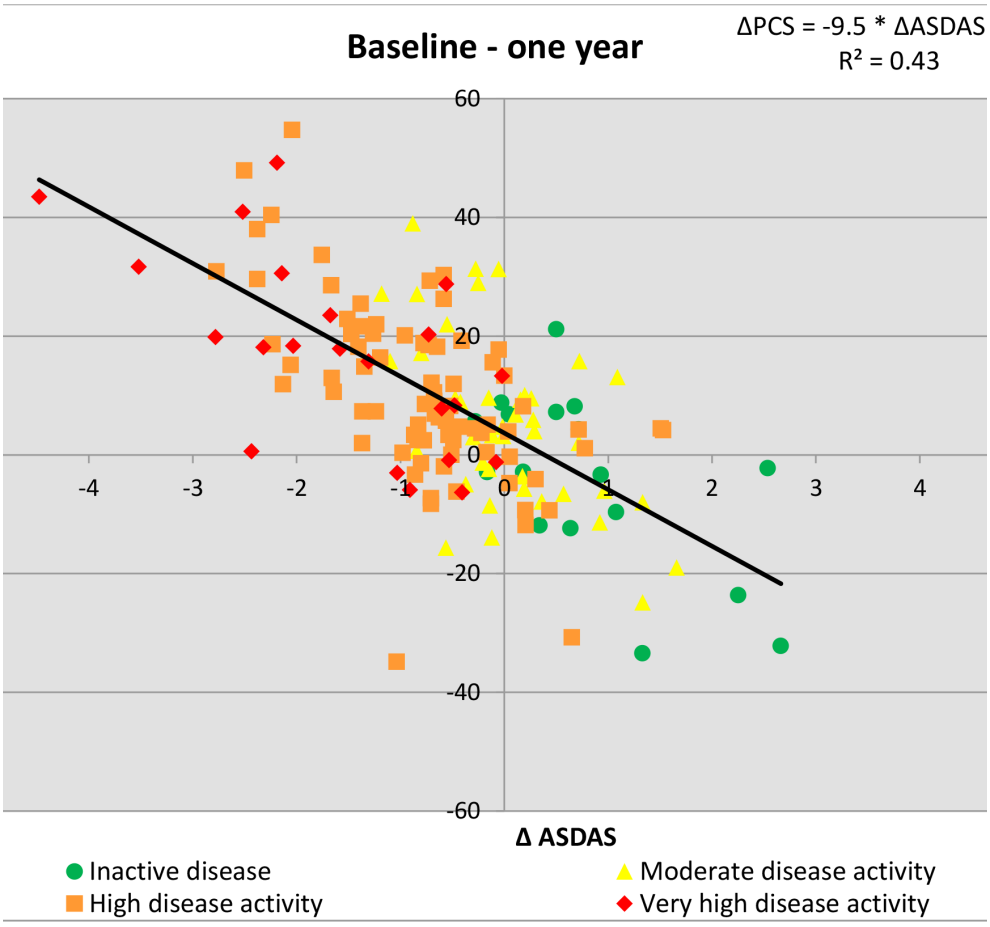

Figure 1. Scatterplot of the correlation between change in ASDAS (ΔASDAS) and change in PCS (ΔPCS) between baseline and 1 year, with the disease state at baseline indicated. ASDAS, Ankylosing Spondylitis Disease Activity Score; PCS, physical component summary.

Table 3. Association between change in disease activity and change in the subscales of the SF-36 between baseline and 1 year (n=161)

	ΔASDAS		
ΔSubscales	**B**	**95% CI**	**Adjusted R^2**
Physical functioning	-12.6	-15.2; -10.1	0.375
Role physical	-24.5	-30.1; -18.8	0.313
Bodily pain	-17.2	-19.9; -14.5	0.498
General health	-5.7	-8.2; -3.3	0.113
Vitality	-7.8	-10.6; -4.9	0.148
Social functioning	-7.3	-10.4; -4.2	0.112
Role emotional	-9.4	-15.7; -3.0	0.044
Mental health	-4.9	-7.0; -2.8	0.113

ASDAS, Ankylosing Spondylitis Disease Activity Score; SF-36, Medical Outcomes Study Short Form-36.

Table 4. Association between change in disease activity and change in PCS between baseline and 1 year (n=161)

		ΔPCS		
ΔASDAS	**n**	**B**	**95% CI**	**P-value**
Model stratified for gender (P=0.056 for the interaction)				
Male	86	-11.0	-13.7; -8.4	<0.001
Female	75	-7.7	-9.9; -5.5	<0.001
Model stratified for job-type (P=0.077 for the interaction)[a]				
White collar	61	-9.6	-12.3; -7.0	<0.001
Blue collar	18	-15.6	-23.0; -8.3	<0.001

Results are corrected for age and stratified in case of effect modification (P<0.10).[a] 79 of 129 working patients provided information about profession. ASDAS, Ankylosing Spondylitis Disease Activity Score; PCS, physical component summary.

DISCUSSION

Compared to the general population, patients with early axSpA are limited in physical HRQoL, but not in mental HRQoL. Further, our data indeed confirm that in a broad group of patients with early axSpA in clinical care, an increase in disease activity is associated with a decline in physical HRQoL over time. Moreover, to our knowledge, we have quantified for the first time the association between ASDAS and HRQoL. Our results confirm the hypothesis used for T2T, in that it is important to aim for lower disease activity in patients with early axSpA to improve HRQoL.

The most important finding of our study is that the strength of the association between disease activity and HRQoL is sex-specific and job type-specific. Knowledge is limited regarding the association in these subgroups of patients. A similar level of disease activity seems to affect HRQoL more adversely in men than in women. A possible explanation for this difference is that men and women appear to cope differently with the disease.[21, 22] In addition, the differences for job type could also be explained by sex. A similar proportion of males and females had white-collar jobs (49% vs 51%, respectively). But 61% of blue-collar workers were male. Unfortunately, no separate effects for subgroups stratified on both sex and job type could be evaluated because of the small patient population in these subgroups. It is possible that physical HRQoL is more important for blue-collar workers than for white-collar workers, because good physical HRQoL enables them to do their work. Our results show that a similar improvement in disease activity is associated with more improvement in HRQoL in blue-collar workers than in white-collar workers. Thus, blue-collar workers may benefit more from decreasing disease activity. However, the observed difference between blue- and white-collar workers should be interpreted with caution because only 61.2% of all working patients provided information about their job type. Consequently, these associations require further study.

The association found between disease activity and HRQoL may not be surprising because both ASDAS and SF-36 do contain several questions that appear similar. For instance, ASDAS includes spinal and peripheral pain questions and the SF-36 contains questions about bodily pain. However, the ASDAS is a disease-specific composite score developed and validated for axSpA and also contains CRP. The SF-36 is a generic questionnaire aimed at measuring HRQoL and includes measurements of role emotional and social functioning.

A strength of our study is the high diagnostic certainty of axSpA after a thorough diagnostic investigation in all patients. In addition, the mean values of ASDAS (baseline 2.5, 1 year 2.0) and PCS (baseline 28.4, 1 year 36.9) in our cohort are comparable to other axSpA cohorts. For example, in the Devenir des Spondyloarthrites Indifférenciées Récentes (DESIR) cohort, patients with early axSpA (symptom duration < 3 years) had a mean ASDAS of 2.6 and PCS of 41[23], and in the Herne[24] and Swiss Clinical Quality Management cohorts[25] (non-radiographic axSpA with a symptom duration > 5 years), the mean ASDAS ranged from 2.8 to 3.0 and PCS from 20 to 42, respectively. The ESPERANZA cohort has also found an association between the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire.[26] Because 2 different outcome measurements were used, no direct comparisons between this cohort and the SPACE cohort were possible.

Mental functioning of patients with early axSpA is comparable to that of the general population. However, even in the earliest phase of disease, patients with axSpA are already impaired in their physical HRQoL. Moreover, we showed that in a broad group of patients with early axSpA, increasing disease activity is associated with worsening in physical HRQoL over time. This finding supports the recommendation that in patients with early axSpA, inactive disease or low disease activity should be the treatment target.

REFERENCES

1. Smolen JS, Schöls M, Braun J, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis* 2018;77:3-17.
2. van der Heijde D, Deodhar A, Braun J, et al. The effect of golimumab therapy on disease activity and health-related quality of life in patients with ankylosing spondylitis: 2-year results of the GO-RAISE trial. *J Rheumatol* 2014;41:1095-103.
3. Boonen A, van der Linden SM. The burden of ankylosing spondylitis. *J Rheumatol Suppl.* 2006;78:4-11.
4. Deodhar AA, Dougados M, Baeten DL, et al. Effect of secukinumab on patient-reported outcomes in patients with active ankylosing spondylitis: a phase III randomized trial (MEASURE 1). *Arthritis Rheumatol* 2016;68:2901-10.
5. 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.
6. Boonen A, Sieper J, van der Heijde D, et al. The burden of non-radiographic axial spondyloarthritis. *Semin Arthritis Rheum* 2015;44:556-62.
7. 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.
8. Platts LG, Head J, Stenholm S, et al. Physical occupational exposures and health expectancies in a French occupational cohort. *Occup Environ Med* 2017;74:176-83.
9. Ward MM, Reveille JD, Learch TJ, et al. Occupational physical activities and long-term functional and radiographic outcomes in patients with ankylosing spondylitis. *Arthritis Rheum* 2008;59:822-32.
10. Tournadre A, Pereira B, Lhoste A, et al. Differences between women and men with recent-onset axial spondyloarthritis: results from a prospective multicenter French cohort. *Arthritis Care Res* 2013;65:1482-9.
11. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.
12. Rudwaleit M, Jurik AG, Hermann KG, et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis* 2009;68:1520-7.
13. 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.
14. Lukas C, Landewé R, Sieper J, et al. Assessment of SpondyloArthritis international Society. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009;68:18-24.
15. van der Heijde D, Lie E, Kvien TK, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009;68:1811-8.
16. Machado P, Landewé R, Lie E, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis* 2011;70:47-53.
17. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
18. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055-68.
19. Loge JH, Kaasa S. Short form 36 (SF-36) health survey: normative data from the general Norwegian population. *Scand J Soc Med* 1998; 26:250-8.
20. Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. *Qual Life Res* 2001;10:405-13.
21. Tamres LK, Janicki D, Helgeson VS. Sex

differences in coping behavior: a meta-analytic review and an examination of relative coping. *Pers Soc Psychol Rev* 2002;6:2-30.
22. 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.
23. Moltó 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.
24. Kiltz U, Baraliakos X, Karakostas P, et al. Do patients with non-radiographic axial spondylarthritis differ from patients with ankylosing spondylitis? *Arthritis Care Res* 2012;64:1415-22.
25. Ciurea A, Scherer A, Exer P, et al. Tumor necrosis factor alpha inhibition in radiographic and nonradiographic axial spondyloarthritis: results from a large observational cohort. *Arthritis Rheum* 2013;65:3096-106.
26. Fernández-Carballido C, Navarro-Compán V, Castillo-Gallego C, et al. Disease activity as a major determinant of quality of life and physical function in patients with early axial spondyloarthritis. *Arthritis Care Res* 2017;69:150-5.

Chapter 5

Disease activity decrease is associated with improvement in work productivity over 1 year in early axial spondyloarthritis (SPondyloArthritis Caught Early cohort)

Miranda van Lunteren, Zineb Ez-Zaitouni, Camilla Fongen, Robert Landewé, Roberta Ramonda Désirée van der Heijde, Floris van Gaalen

Rheumatology 2017;56:2222-8

ABSTRACT

Objective

To assess if a change in disease activity is associated with a change in work productivity loss (WPL) over 1 year in early axial SpA (axSpA) patients.

Methods

Baseline and 1 year data of axSpA patients in the SPondyloArthritis Caught Early cohort were analysed. Linear regression models were built explaining the change in the Ankylosing Spondylitis Disease Activity Score (ASDAS) over time by the change in absenteeism, presenteeism, WPL, and activity impairment over time. Effect modification and confounding were tested for age, gender, arm of Assessment of SpondyloArthritis international Society classification criteria, HLA-B27, duration of chronic back pain, profession, and medication.

Results

At baseline, in 105 axSpA patients (48% female, mean age 30.8 years, mean symptom duration 13.6 months, 92% HLA-B27 positive, 24% radiographic sacroiliitis), the mean ± SD ASDAS was 2.4 ± 1.0, absenteeism 9% ± 23, presenteeism 33% ± 28, WPL 36% ± 30, and activity impairment 37% ± 25. After 1 year, the mean ASDAS decreased to 2.0 ± 0.8 and absenteeism, presenteeism, WPL, and activity impairment improved to 6% ± 22, 26% ± 26, 27% ± 29, and 27% ± 26, respectively. Models showed that if ASDAS decreased 1 unit, absenteeism, presenteeism, WPL, and activity impairment improved by 5%, 17%, 16%, and 18%, respectively. The impact of disease activity on work productivity was higher in patients with shorter symptom duration and the impact on absenteeism was higher in patients starting pharmacological treatment.

Conclusion

In early axSpA patients, work productivity and daily activities are seriously impacted at baseline and 1 year. However, decreasing disease activity is associated with marked improvements in work productivity and daily activities.

INTRODUCTION

Axial spondyloarthritis (axSpA) has an early disease onset, usually in the second or third decade of life.[1, 2] As a consequence, patients are affected by axSpA at an early stage in their professional career. Patients with longstanding AS are three times more likely to withdraw from work due to disability than individuals in the general population.[3] A persistently high disease activity is associated with more sick leave and disability in patients with axSpA.[4] AxSpA patients lose productivity because of sick leave absenteeism), but also because of inefficiency at work (presenteeism). In addition, presenteeism is an important indicator for future sick leave in patients with AS.[5] Taken together, work productivity loss (WPL) in AS leads to substantial costs to patients and society.[3, 6]

There is little data suggesting that gender, age, and disease duration co-determine the impact of a diagnosis of axSpA on work productivity. One study showed that AS had more impact on days being absent from work in women than in men.[5] In line with this finding, Haglund et al.[7] reported that women with SpA experience more loss of work productivity than men. A Dutch study reported that younger AS patients more often withdrew from work than older patients when compared with age and gender-matched population controls. This study also showed that the likelihood of work withdrawal increased with longer disease duration.[3] Finally, a recent cohort study showed that gender, age, and disease duration are important determinants of absenteeism.[8]

Most studies on work productivity have focused on patients with AS with long disease duration. It is less well known if and how axSpA impacts work productivity in patients with short symptom duration and if prognostically relevant subgroups are similarly affected.

Thus the aims of this study are to describe WPL in patients with an early onset of axSpA at baseline and 1 year after diagnosis, to assess if a change in disease activity is associated with a change in work productivity and to assess if the impact of the Ankylosing Spondylitis Disease Activity Score (ASDAS) on work productivity is similar according to prognostically relevant subgroups.

METHODS

Design and subjects

The present study was conducted in the SPondyloArthritis Caught Early (SPACE) cohort. The design of this cohort has been described in detail previously.[9] The SPACE cohort is an ongoing inception cohort established in 2009 that includes patients ≥ 16 years of age with chronic back pain (CBP) persisting ≥ 3 months but ≤ 2 years with the onset of back

pain at < 45 years of age. Patients were excluded if they had another painful condition not related to axSpA that could interfere with evaluation of the disease. For this analysis we used baseline and 1 year data of patients who were diagnosed with axSpA, fulfilled the Assessment of SpondyloArthritis international Society (ASAS) criteria for axSpA at baseline, had paid work and had their baseline and 1 year visit between January 2009 and January 2017.

Data from four medical centres in Europe participating in the SPACE study were included in the current analysis: Leiden University Medical Center, Leiden, The Netherlands; Diakonhjemmet Hospital, Oslo, Norway; Academic Medical Center, Amsterdam, The Netherlands, and the University of Padua, Padua, Italy. The SPACE study protocol was approved by the Ethical Committee ''Azienda Ospedaliera di Padova'' (reference number 2438P), Regional Committee for Medical and Health Research Ethics in South East Norway (reference number 2010/426), the Medical Ethical Committee of the Leiden University Medical Center (reference number P08.105), and all participants provided informed consent, in accordance with the Declaration of Helsinki, before the start of the first visit. Data from 14 Italian patients included in this analysis have been published previously elsewhere.[10]

Methods of measurement

At baseline and 12 months, a medical history was taken followed by a physical examination, questionnaires, and laboratory assessments, including CRP, ESR, and HLA-B27. Radiographic images and MRIs (1.5 T, 4mm slice thickness) of the sacroiliac joints and spine were obtained at baseline. The diagnosis was made by the treating rheumatologist using local reading of the imaging. Treating rheumatologists were asked to provide a level of confidence regarding the diagnosis on a numerical scale ranging from 0 (not confident at all) to 10 (very confident). Patients diagnosed with axSpA were classified according to the ASAS axSpA criteria to the imaging arm or clinical arm[11] based on central reading, in which images were evaluated by three central readers per modality and were considered to be positive for sacroiliitis when two or more readers agreed. Patients were classified in the imaging arm if patients either fulfilled the imaging arm alone or fulfilled both the imaging and clinical arms. Patients were classified in the clinical arm if they fulfilled the clinical arm exclusively.

The Work Productivity and Activity Impairment questionnaire (WPAI, general health, version 1.0) was used to assess the impact of the disease on work productivity in the past 7 days. It consists of six questions, in which patients are asked to report about current employment status (Question (Q)1), amount of missed working hours due to axSpA (Q2), amount of missed working hours due to other reasons such as holidays (Q3), amount

of actually worked hours according to the patient (Q4), the impact of axSpA on work productivity on a visual analogue scale (VAS) scale (Q5), and the impact of axSpA on regular daily activities outside work on a VAS scale (Q6). Four summary measures could be calculated ranging from 0 to 100%; presenteeism is decreased functionality at work due to disease (calculated as Q5/10), absenteeism is absence at work due to disease (Q2/(Q2 + Q4)), WPL is the total work impairment due to disease (presenteeism + ((1 – presenteeism) * absenteeism)), and activity impairment is the impairment in daily activities (Q6/10). Percentages were calculated by multiplying all scores by 100. Higher scores indicate greater impairment.[12]

The CRP-based ASDAS was used to assess disease activity.[13, 14] For reference, a change of ASDAS ≥ 1.1 is considered to reflect a clinically important improvement and a change of ≥ 2.0 reflects a major improvement.[15]

Patients were asked to report the use of NSAIDs, conventional synthetic DMARDs (csDMARDs) and biologic DMARDs (bDMARDs) at baseline and 1 year. Medication was categorized as no change in treatment (i.e. either no medication or the same treatment group) between baseline and 1 year, start of any treatment (NSAID, csDMARD, or bDMARD) between baseline and 1 year, and stopping all treatment between baseline and 1 year. Eight patients were already treated with csDMARDs at baseline because of psoriasis, peripheral arthritis, IBD, uveitis, dactylitis or a combination thereof.

The question about a patient's profession was a multiple-choice question with the following options: (i) management position (e.g. director, manager, member of the board of directors); (ii) professional specialist (engineer, teacher, nurse practitioner, systems analyst); (iii) commercial profession (representative, agent, clerk, sales person); (iv) technical support (lab technician, legal officer, information technology); (v) administrative support (secretary, invoice administration); (vi) service profession (security officer, janitor), and (vii) operator or labourer (assembler, mechanic, carpenter, builder). Answer options 1, 2, 4, and 5 were labelled as *white collar work*. Answer options 3, 6 and 7, were labelled as *blue collar work*.

Analysis

Continuous variables were described as mean ± SD; categorical variables were described as number (percentage). Linear regression models were built to explain the change in each WPAI measure (i.e. ΔWPL, Δpresenteeism, Δabsenteeism and Δactivity impairment) between baseline and 1 year (dependent variable) by the change in ASDAS (ΔASDAS; continuous) between baseline and 1 year (independent variable). Age at baseline, gender, ASAS axSpA subclassification (imaging versus clinical arm), HLA-B27 carrier status

(positive versus negative), duration of CBP, medication as well as profession were tested for their potential to modify the association between ASDAS and a WPAI measure one by one in these linear regression models. Effect modification was considered relevant if the P-value of the interaction term was <0.10. Models were stratified in subgroups if an effect modification was found. To prevent spurious effects due to small sample sizes, stratification for dichotomous variables was only performed if each subgroup consisted of at least 15 patients and stratification for continuous variables was only performed for the subgroups of at least 15 patients. These factors were also tested for relevant confounding (defined as a change >10% of the crude regression coefficient of the univariable model). Models were adjusted for each confounder. Data were analysed using STATA SE version 14 (StataCorp, College Station, TX, USA). P-values <0.05 were considered to be statically significant.

RESULTS

In total, 361 patients in the SPACE cohort provided data at baseline as well as 1 year. Rheumatologists diagnosed 247 patients with axSpA. Of the 247 axSpA patients, 174 patients fulfilled the ASAS classification criteria. Patients who did not have a job (n=46) could not complete the WPAI questionnaire. Of the remaining 128 patients, 16 patients missed the WPAI either at baseline or at 1 year and information to calculate the ASDAS at one or both time points was insufficient in 7 patients. The WPAI and ASDAS were available at both time points in 105/128 (82%) patients diagnosed with axSpA meeting the ASAS criteria. Excluded patients (n=23) did not differ from included patients, except for a good response to NSAIDs (P=0.034; included patients 69%, excluded patients 46%).

Of the 105 patients included in the analysis, 48% were female, the mean ± SD age was 30.8 years ± 7.2, and the mean symptom duration was 13.6 months ± 7.1 (**Table 1**). On average, patients had 3.3 ± 1.6 SpA features in addition to imaging and HLA-B27 status and the level of confidence regarding the diagnosis of SpA by the rheumatologist was 8 ± 2. In these patients, 46% fulfilled the clinical arm, 12% the imaging arm, and 42% both arms.

At baseline, the mean ± SD ASDAS was 2.4 ± 1.0. Twelve per cent of patients had inactive disease and 29% had moderate disease activity. The mean WPL was 36% ± 30, presenteeism 33% ± 28, absenteeism 9% ± 23, and activity impairment 37% ± 25 (**Table 2**). Thirty-four per cent of the patients had a '*blue collar*' job at baseline. Over 1 year, the mean ASDAS decreased to 2.0 ± 0.8, which was statistically significant; 22% had inactive disease and 37% had moderate disease activity. The mean WPL, presenteeism, absenteeism, and activity impairment improved statistically significantly (27% ± 29, 26% ± 26, 6% ± 22, and 27% ± 26, respectively). The mean number of missed working hours per

week due to CBP decreased from 4.3 at baseline to 1.9 at 1 year.

Figures 1 and 2 show the relationship between the 1 year change in ASDAS and the 1 year change in WPAI. Linear trend lines show that a 1 unit decrease in ASDAS is associated with a 16% decrease in WPL (**Figure 1A**), a 17% decrease in presenteeism (**Figure 1B**), a 5% decrease in absenteeism (**Figure 2A**), and 18% less activity impairment (**Figure 2B**). All associations between the ΔASDAS and ΔWPAI measures were statistically significant (P<0.001 for ΔWPL, ΔPresenteeism, and ΔActivity Impairment and P=0.016 for ΔAbsenteeism).

The duration of CBP was an effect modifier for ΔWPL (P=0.06) and Δpresenteeism (P=0.03) and the start of treatment between baseline and 1 year was an effect modifier for Δabsenteeism (P=0.08; **Supplementary Table S1**). Based on these results, patients were stratified for the duration of CBP and the start of medication in each model (**Table 3**).

Regardless of the duration of CBP or the start of medication use, an improvement in ASDAS remained positively associated with an improvement in WPL, presenteeism, and activity impairment. However, an improvement in ASDAS was only associated with an improvement in absenteeism in patients with a short duration of CBP and in patients who started any treatment between baseline and 1 year. The impact on work productivity and activity impairment was higher per unit ASDAS in patients with a shorter symptom duration. HLA-B27 positivity was a statistically significant effect modifier, however, the HLA-B27-negative group had < 15 patients, so patients were not stratified for this factor (**Supplementary Table S1**). No confounding for age, gender, arm of the ASAS classification criteria for axSpA, HLAB27 positivity and profession was found (**Supplementary Table S2**).

Table 1. Baseline characteristics of patients with axSpA in the SPACE cohort included in the analysis

Characteristics	n=105
Age (years) at inclusion, mean ± SD	30.8 ± 7.2
Female	50 (48%)
Symptom duration (months), mean ± SD	13.6 ± 7.1
Inflammatory back pain	87 (83%)
Good response to NSAIDs[a]	72 (69%)
Uveitis[b]	19 (18%)
Psoriasis[b]	17 (16%)
Inflammatory bowel disease[b]	4 (4%)
Positive family history	54 (51%)
Enthesitis[b]	26 (25%)
Dactylitis[b]	7 (7%)
Peripheral arthritis[b]	19 (18%)
HLA-B27 positive	97 (92%)
Elevated ESR/CRP level	45 (43%)
X-SI positive	25 (24%)
MRI-SI positive	46 (44%)
Number of SpA features[c], mean ± SD	3.3 ± 1.6
Confidence of diagnosis by rheumatologist, mean ± SD	8 ± 2
ASAS classification	
Clinical arm only	48 (46%)
Imaging arm only	13 (12%)
Both arms	44 (42%)
Use of NSAIDs	83 (79%)
Use of csDMARDs	8 (8%)
Use of bDMARDs	0 (0%)

Results are presented as n (%) unless otherwise indicated. [a] Back pain not present anymore or is much better 24-48 h after a full dose of an NSAID. [b] Past or present condition, either diagnosed or confirmed by a physician. [c] Excluding HLA-B27 testing and imaging. ASAS, Assessment of SpondyloArthritis international Society; bDMARD, biological disease-modifying antirheumatic drugs (DMARD); CRP, C-reactive protein; csDMARD, conventional synthetic DMARD; ESR, erythrocyte sedimentation rate; MRI-SI, MRI of the sacroiliac (SI) joint; NSAID, nonsteroidal anti-inflammatory drugs; X-SI, radiography of the SI-joint.

Table 2. Disease activity, work impairment, and activity impairment at baseline and 1 year of axSpA patients

Characteristics	Baseline	1 year
ASDAS, mean ± SD	2.4 ± 1.0	2.0 ± 0.8
Inactive disease (< 1.3)	13 ± 12	23 ± 22
Moderate disease activity (< 2.1)	30 ± 29	39 ± 37
High disease activity (< 2.1)	48 ± 46	38 ± 36
Very high disease activity (> 3.5)	14 ± 13	5 ± 5
BASDAI, mean ± SD	3.8 ± 2.1	3.1 ± 2.0
Blue collar job[a,b]	25 (34%)	26 (36%)
Working hours, mean ± SD	29.5 ± 15.6	30.2 ± 15.5
Missed working hours due to chronic back pain, mean ± SD	4.3 ± 12.4	1.9 ± 6.6
Work productivity loss (%), mean ± SD	36 ± 30	27 ± 29
Presenteeism (%), mean ± SD	33 ± 28	26 ± 26
Absenteeism (%), mean ± SD	9 ± 23	6 ± 22
Activity Impairment (%), mean ± SD	37 ± 25	27 ± 26

Results are presented as n (%) unless otherwise indicated. [a] Blue collar job is defined as a physically demanding job. [b] Available for 73 patients. ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.

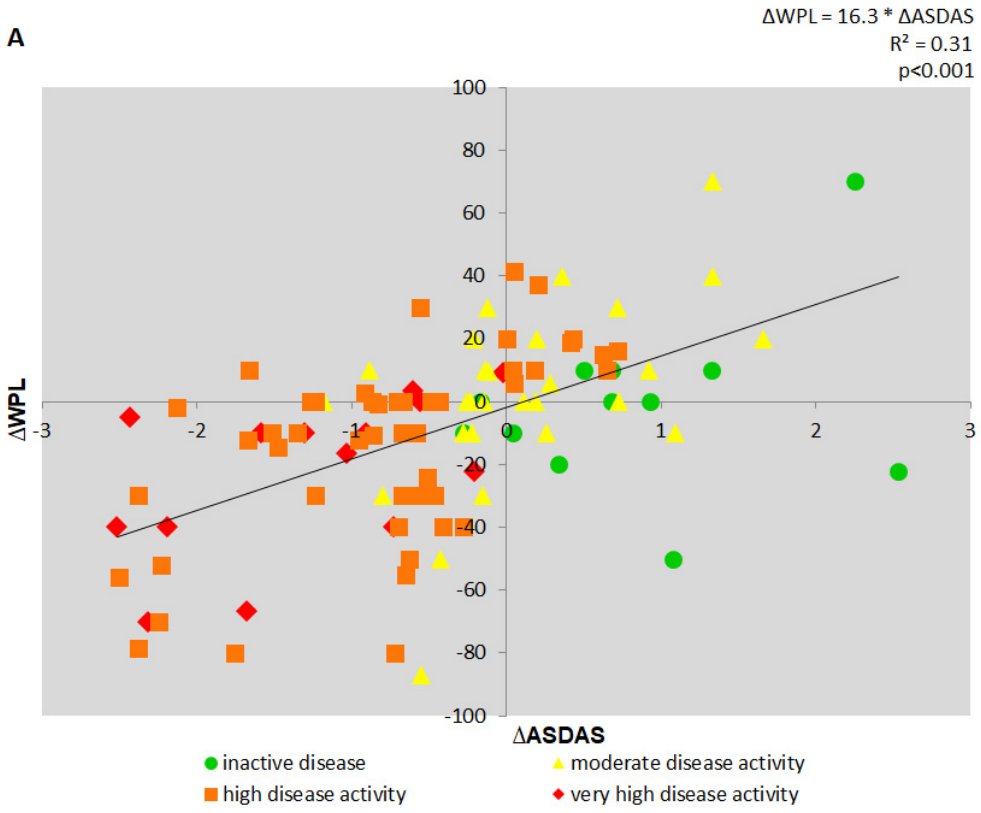

Figure 1. Scatter plot of the results between 0 and 1 year with baseline disease status indicated by symbols. (A) Results between change in ASDAS and change in WPL.

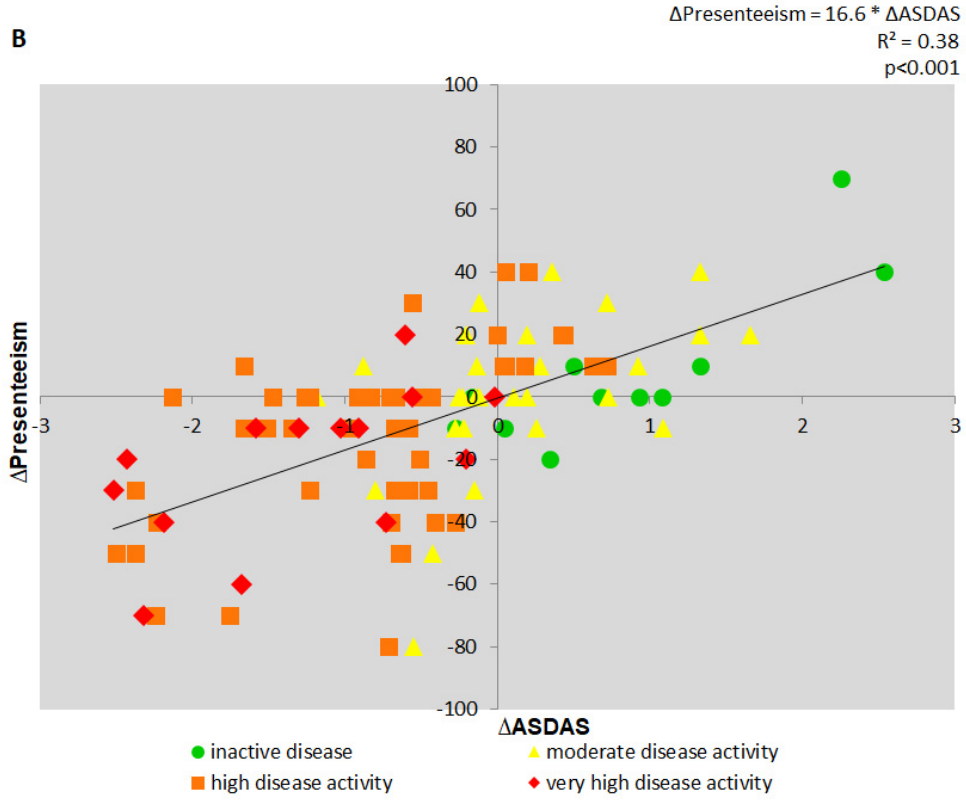

Figure 1. Scatter plot of the results between 0 and 1 year with baseline disease status indicated by symbols. (B) Results between change in ASDAS and change in presenteeism.

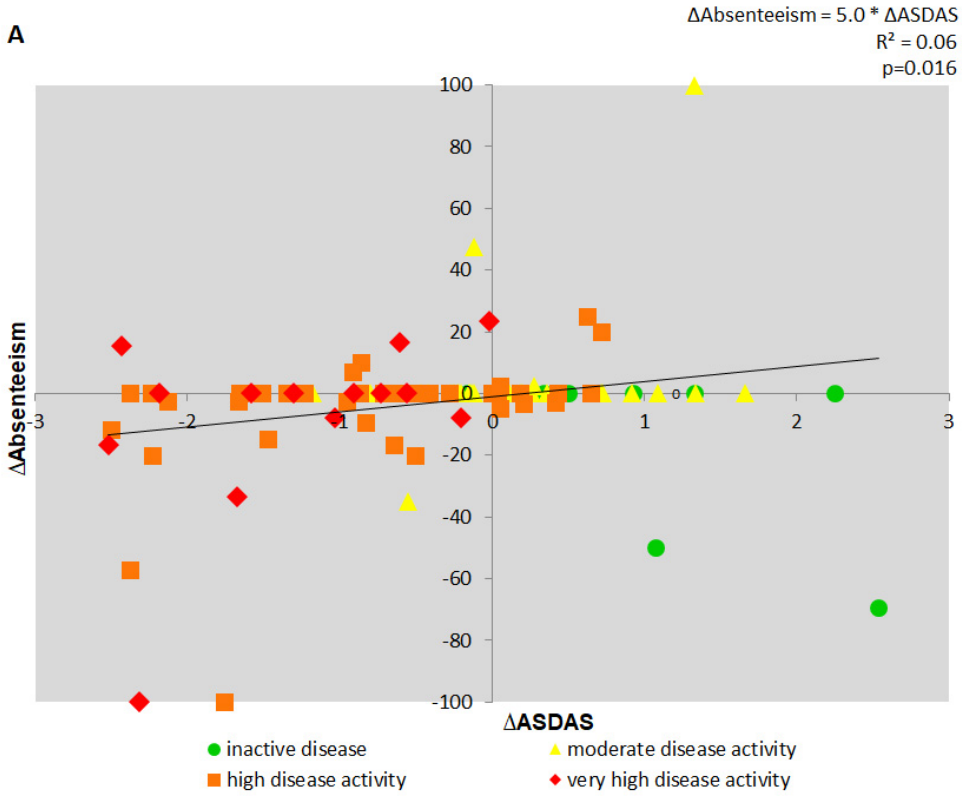

Figure 2. Scatter plot of the results between 0 and 1 year with baseline disease status indicated by symbols. (A) Results between change in ASDAS and change in absenteeism.

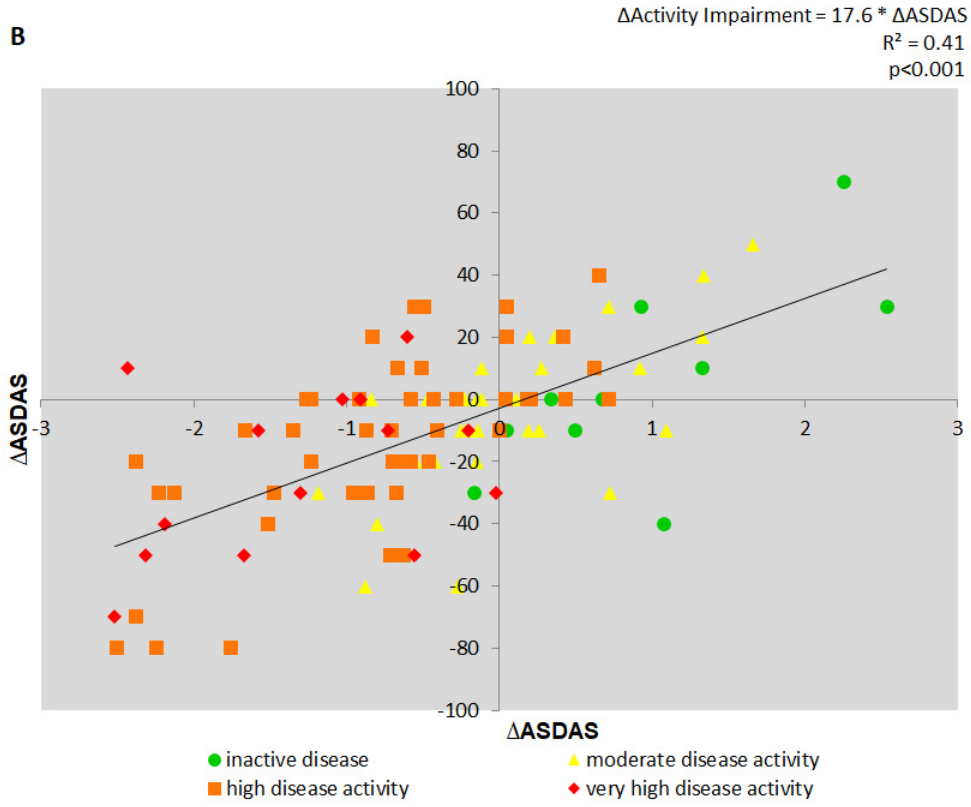

Figure 2. Scatter plot of the results between 0 and 1 year with baseline disease status indicated by symbols. (B) Results between change in ASDAS and change in activity impairment.

Table 3. Association between change in disease activity and change in work productivity and daily activities

		ΔWPL		ΔPresenteeism		ΔAbsenteeism		ΔActivity Impairment	
	n	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value
Model stratified for mean duration of chronic back pain[a]									
<13.6 months ΔASDAS	56	19.5 (3.0)	<0.001	19.8 (2.5)	<0.001	6.6 (3.2)	0.046	20.0 (2.5)	<0.001
≥13.6 months ΔASDAS	47	9.0 (3.9)	0.027	8.9 (3.9)	0.026	0.6 (1.2)	0.640	12.4 (3.7)	0.002
Model stratified for medication use[b]									
No change[c] ΔASDAS	55	17.4 (3.6)	<0.001	18.0 (3.2)	<0.001	1.7 (1.7)	0.310	16.8 (3.6)	<0.001
Started[d] ΔASDAS	42	16.7 (3.8)	<0.001	16.0 (3.3)	<0.001	9.4 (4.2)	0.031	18.2 (2.5)	<0.001

Results are corrected for age and gender and stratified in case of effect modification P<0.10. [a] No exact duration of chronic back pain was available for 2 patients. [b] Patients who stopped all treatment were excluded from the table as stated in the methods (this subgroup consisted of 8 patients). [c] No medication or same treatment group (NSAID, csDMARD, bDMARD). [d] Started with any treatment (NSAID, csDMARD, bDMARD). ASDAS, Ankylosing Spondylitis Disease Activity Score; WPL, Work productivity Loss.

DISCUSSION

In early axSpA patients, in which the majority has non-radiographic axSpA, work productivity and daily activities were already seriously impacted at baseline and 1 year. Over a 1 year period, a reduction in disease activity was associated with improvement in both work productivity and daily activities, while an increase in disease activity leads to more work and activity impairment.

In our cohort, presenteeism, absenteeism, WPL, and activity impairment were comparable to recent results from a European cross-sectional study of non-radiographic axSpA patients with disease duration ranging from 3 to 7 years. In this study, presenteeism ranged from 16% to 28%, absenteeism 9% to 10%, WPL 19% to 37%, and activity impairment 23% to 31% among patients treated with bDMARDs and patients not treated with bDMARDs, respectively.[16] Due to differences in methodology, it is challenging to compare our results with the general population. In the European Working Conditions Survey of 44 000 workers in 35 European countries, 41% of men and 44% of women reported any form of presenteeism in the past year.[17] In our cohort, presenteeism (defined as presenteeism > 0) was present in 76% of men and 82% of women. In addition, in The Netherlands, sick leave percentages in the general population are available for various age categories for 2015. The majority of the patients who were included in our analyses were Dutch (51%). Compared with the Dutch population, absenteeism was slightly lower in our Dutch patients in the 15–25 years age category but considerably higher in the last two age categories (0% vs 2% for 15–25 years, 10% vs 3% for 25–35 years, and 26% vs 4% for 35–45 years in the SPACE cohort vs the general population).[18] Taken together, presenteeism and absenteeism are higher in early axSpA compared with the general population.

Previously it has been shown that in patients with AS, increased disease activity is associated with increased WPL and presenteeism in particular.[19-21] Several randomized controlled trials (RCTs) have shown that an improvement in disease activity invoked by active drug treatment led to an improvement in work productivity in AS patients.[22, 23] This was also confirmed for patients with non-radiographic axSpA in a recent RCT.[24] Our data show that even in the earliest phase of the disease, work productivity is greatly reduced and daily activities are impaired and fluctuations in disease activity are associated with fluctuations in WPL and activity impairment.

In our cohort, the impact of disease activity on work productivity and daily activities was higher in patients with a shorter duration of CBP as compared with patients with a longer duration of CBP. A possible explanation for this difference is that patients cope differently with limitations, depending on the symptom duration. This is currently being evaluated

in our cohort. Change of work or work adaptations may also play a role. Of note, the proportion of patients with blue collar jobs remained rather stable over 1 year. Medication may also play a role, but in our study, patient groups became too small to detect meaningful differences if stratified for both disease duration and medication. The impact of disease activity on absenteeism was higher in patients who started any treatment than in patients who did not change their treatment. This might be explained by a response to the new treatment.

An important finding in our cohort was that, on average, disease activity remained high 1 year after diagnosis. Recently an international task force recommended remission or low disease activity as the preferred treatment target in SpA, although it was acknowledged that the evidence was not strong and needed to be expanded by future research.[25] Consequently, clinical trials are under way aimed at improving disease outcomes in axSpA using more intensive treatment (treat to target) approaches in order to obtain remission or low disease activity (e.g. NCT02897115 and NCT03043846 at ClinicalTrials.gov). Our results suggest that in early axSpA, lowering disease activity is associated with less WPL and activity loss, which may imply that remission or low disease activity in early axSpA is a valuable target.

The strength of this study is the thorough diagnostic workup according to protocol, including imaging (MRI and radiographs) in all patients, leading to a high diagnostic certainty. Self-reported questionnaires were used to determine work productivity and activity loss. The response rate was 82%, which is in line with previous cohort studies.[26] Due to the limited sample size, no additional effect modification could be studied except for the duration of CBP and medication. Unfortunately, no separate effect per treatment group (NSAIDs, csDMARDs, and bDMARDs) could be evaluated because of small numbers in several subgroups. In particular, the subgroup of patients who are starting a bDMARD is small. However, this is a result of the short duration of CBP as an inclusion criteria (42 years). Multiple NSAIDs are prescribed before patients are treated with bDMARDs. Another limitation is that the exact starting and/or stopping date of csDMARDs and bDMARDs are unknown. We therefore recommend addressing these issues in future studies. Finally, absenteeism has many zeroes, which causes skewness of the data, and this might explain the different effect of disease activity on absenteeism per subgroup.

In conclusion, in patients with early axSpA, absenteeism, presenteeism, WPL, and activity impairment were considerably increased at baseline, showing that WPL and impairment of daily activities already affects patients with axSpA in the earliest phase of the disease. More importantly, although WPL and activity impairment improved somewhat over a 1 year period, they remained rather substantial. Finally, our data show that in early axSpA,

decreasing disease activity is associated with improvement in work productivity and daily activities.

REFERENCES

1. Braun J, Sieper J. Ankylosing spondylitis. *Lancet* 2007;369:1379-90.
2. Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet* 2017;390:73-84.
3. 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.
4. Moltó A, Tezenas du Montcel S, Wendling D, et al. Disease activity trajectories in early axial spondyloarthritis: results from the DESIR cohort. *Ann Rheum Dis* 2016;76:1036-41.
5. Tran-Duy A, Nguyen TT, Thijs H, et al. Longitudinal analyses of presenteeism and its role as a predictor of sick leave in patients with ankylosing spondylitis. *Arthritis Care Res* 2015;67:1578-85.
6. 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.
7. Haglund E, Bremander A, Bergman S, et al. Work productivity in a population-based cohort of patients with spondyloarthritis. *Rheumatology* 2013;52:1708-14.
8. Wallman JK, Joud A, Olofsson T, et al. Work disability in non-radiographic axial spondyloarthritis patients before and after start of anti-TNF therapy: a population-based regional cohort study from southern Sweden. *Rheumatology* 2017;56:716-24.
9. 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.
10. de Hooge M, Ramonda R, Lorenzin M, et al. Work productivity is associated with disease activity and functional ability in Italian patients with early axial spondyloarthritis: an observational study from the SPACE cohort. *Arthritis Res Ther* 2016;18:265-70.
11. 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. *Arthritis Care Res* 2009;68:777-83.
12. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics* 1993;4:353-65.
13. van der Heijde D, Lie E, Kvien TK, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009;68:1811-8.
14. Lukas C, Landewé R, Sieper J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009;68:18-24.
15. Machado P, Landewé R, Lie E, et al. Ankylosing spondylitis disease activity score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis* 2011;70:47-53.
16. Sieper J, Holbrook T, Black CM, et al. Burden of illness associated with non-radiographic axial spondyloarthritis: a multiperspective European cross-sectional observational study. *Clin Exp Rheumatol* 2016;34:975-83.
17. Eurofound. Perspectives on working life in Europe. In: Sixth European Working Conditions Survey – Overview report. Luxembourg: *Publications Office of the European Union*, 2016:102-25.
18. Statistics Netherlands. CBS – StatLine – Ziekteverzuim volgens werknemers; geslacht en leeftijd. 2016 [accessed 19 December 2016]. *http://statline.cbs.nl/Statweb/publication/DM=SLNL&PA=83056NED&D1=0-3&D2=a&D3=1-3&D4=a&VW=T.*
19. Healey EL, Haywood KL, Jordan KP, et al. Impact of ankylosing spondylitis on work in patients across the UK. *Scand J Rheumatol* 2011;40:34-40.
20. Boonen A, Brinkhuizen T, Landewé R, et al. Impact of ankylosing spondylitis on sick leave, presenteeism and unpaid productivity, and estimation of the societal cost. *Ann Rheum Dis* 2010;69:1123-8.
21. Boonen A, Boone C, Albert A, Mielants H. Understanding limitations in at-work productivity in patients with active ankylosing spondylitis: the role of work-related contextual factors. *J Rheumatol* 2015;42:93-100.
22. Maksymowych WP, Gooch KL, Wong RL, et al. Impact of age, sex, physical function, health-related quality of life, and treatment

with adalimumab on work status and work productivity of patients with ankylosing spondylitis. *J Rheumatol* 2010;37:385-92.
23. van der Heijde D, Deodhar A, Braun J, et al. The effect of golimumab therapy on disease activity and health-related quality of life in patients with ankylosing spondylitis: 2-year results of the GO-RAISE trial. *J Rheumatol* 2014;41:1095-103.
24. 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.
25. Smolen JS, Braun J, Dougados M, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. *Ann Rheum Dis* 2014;73:6-16.
26. Galea S, Tracy M. Participation rates in epidemiologic studies. *Ann Epidemiol* 2007;17:643-53.

SUPPLEMENTARY MATERIAL

Supplementary Table S1. Effect modifiers in model ΔASDAS and Δwork productivity and Δactivity measures between baseline–one year

	ΔWPL	ΔPresenteeism	ΔAbsenteeism	ΔActivity Impairment
Variable	**p-value**	**p-value**	**p-value**	**p-value**
Gender	0.52	0.76	0.68	0.68
Age (mean)	0.76	0.63	0.24	0.87
Arm of ASAS classification	0.71	0.92	0.74	0.86
HLA-B27 positivity	0.11	0.97	*0.01*	**0.35**
Duration of chronic back pain (mean)	*0.06*	*0.03*	0.22	0.14
Profession[a]	0.94	0.97	0.79	0.52
Medication between 0-1 year				
No change (n=55)[b]	(ref.)	(ref.)	(ref.)	(ref.)
Started (n=42)[c]	0.903	0.706	*0.080*	0.758
Stopped (n=8)[d]	0.758	0.591	0.661	0.458

Statistically significantly p-values (p<0.10) are printed in italics. ASAS, Assessment of Spondyloarthritis International Society; HLA-B27, Human Leucocyte Antigen B27; ref., reference; WPL, Work productivity Loss. [a] Data available of only 73 patients. [b] No medication or same treatment group (NSAID, csDMARD, bDMARD). [c] Started with any treatment (NSAID, csDMARD, bDMARD). [d] Stopped with all treatment (NSAID, csDMARD, bDMARD).

Supplementary Table S2. Confounders in the model of ΔASDAS–Δwork productivity and activity measures between baseline–one year

	ΔWPL		ΔPresenteeism		ΔAbsenteeism		ΔActivity Impairment	
	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Univariable model (n=105)								
ΔASDAS	16.3 (2.4)	<0.001	16.6 (2.1)	<0.001	5.0 (2.0)	0.016	17.6 (2.1)	<0.001
Model corrected for age (n=105)								
ΔASDAS	16.3 (2.4)	<0.001	16.6 (2.1)	<0.001	5.0 (2.0)	0.017	17.6 (2.1)	<0.001
Model corrected for gender (n=105)								
ΔASDAS	16.4 (2.4)	<0.001	16.7 (2.1)	<0.001	5.0 (2.0)	0.017	17.6 (2.1)	<0.001
Model corrected for the arm of ASAS classification for axSpA (n=105)								
ΔASDAS	16.3 (2.4)	<0.001	16.6 (2.1)	<0.001	4.9 (2.0)	0.019	17.4 (2.0)	<0.001
Model corrected for HLA-B27 positivity (n=105)								
ΔASDAS	16.4 (2.4)	<0.001	16.7 (2.1)	<0.001	5.0 (2.0)	0.014	17.6 (2.1)	<0.001
Univariable model with the axSpA patients with data about profession (n=73)								
ΔASDAS	18.9 (2.5)	<0.001	16.4 (2.4)	<0.001	9.5 (2.4)	<0.001	18.8 (2.5)	<0.001
Model corrected for profession (n=73)								
ΔASDAS	18.9 (2.6)	<0.001	16.4 (2.4)	<0.001	9.6 (2.4)	<0.001	18.8 (2.6)	<0.001

Variables were considered to be confounder is the regression coefficient (β) changed with >10%. ASAS, Assessment of Spondyloarthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; HLA-B27, Human Leucocyte Antigen B27; WPL, Work productivity Loss.

Chapter 6

The impact of illness perceptions and coping on the association between back pain and health outcomes in patients suspected of having axial spondyloarthritis: data from the SPondyloArthritis Caught Early cohort

Miranda van Lunteren, Margreet Scharloo, Zineb Ez-Zaitouni, Anoek de Koning, Robert Landewé, Camilla Fongen, Roberta Ramonda, Ad Kaptein, Floris van Gaalen, Désirée van der Heijde

Arthritis Care & Research 2018;70:1829-39

ABSTRACT

Objective

To investigate whether illness perceptions and coping influence the relationship between back pain and health outcomes in patients suspected of having axial spondyloarthritis (axSpA).

Methods

In the SPondyloArthritis Caught Early cohort, regression models were computed at baseline, with back pain intensity (range 0-10) as the determinant and health-related quality of life, the physical component summary score (PCS) and mental component summary (MCS) of the Short Form 36 (SF-36) health survey, or work productivity loss as outcomes. Subsequently, using Leventhal's Common Sense Model of Self-Regulation, illness perceptions and, thereafter coping were added to the models. Analyses were repeated for patients diagnosed and classified as having axSpA according to the Assessment of SpondyloArthritis international Society axSpA criteria (ASAS axSpA), patients only diagnosed with axSpA (axSpA-diagnosed only), and those with chronic back pain.

Results

A total of 424 patients (145 with ASAS axSpA, 81 with only a diagnosis of axSpA, and 198 with chronic back pain); 64% of the total group were female, the mean ± SD age was 30.9 ± 8.1 years, and the mean ± SD symptom duration was 13.3 ± 7.1 months) were studied. In all patients, the strength of the associations between back pain and the PCS, back pain and the MCS score, and back pain and loss of work productivity were decreased by adding illness perceptions to the model, but explained variance improved. Adding coping to these models did not change the results. Comparable results were observed in all subgroups.

Conclusion

Illness perception, but not coping, is important in the relationship between back pain and HRQoL and work productivity loss in patients suspected of having axSpA, irrespective of subgroup. This finding suggests that targeting illness perceptions could improve health outcomes in patients suspected of having axSpA.

INTRODUCTION

The disease burden in patients with axial spondyloarthritis (axSpA) is significant. Treatment aimed at reducing the burden of disease consists of a combination of pharmacologic treatment, education, and exercise.[1] Leventhal's Common-Sense Model of Self-Regulation ('*Common-Sense Model*' (CSM))[2] has been shown to be helpful for understanding patients' responses to various rheumatic diseases and diseases related to axSpA such as psoriasis or inflammatory bowel disease.[3-5] However, the CSM has not yet been studied in patients with axSpA or in patients with chronic back pain who are suspected of having axSpA.[6] The CSM is a theoretical framework used to describe and understand a patient's responses to an illness and its characteristics (e.g. swollen joints, see **Figure 1**).[2] According to the CSM, patients perceive an illness and its characteristics as a health threat and respond to this threat by generating illness perceptions. According to this model, illness perceptions directly influence coping strategies, which in turn influence health outcomes such as health-related quality of life (HRQoL) and loss of work productivity, in order to re-establish a patient's normal health state. Illness perceptions are ideas formulated by patients that help them make sense of their illness, such as perceived personal control over the disease or the experienced negative emotions that they attribute to the disease. In contrast, coping strategies are cognitive and behavioural strategies used to manage stress associated with having to live with the illness (e.g., actively diverting attention from the illness or adapting the level of physical activity).

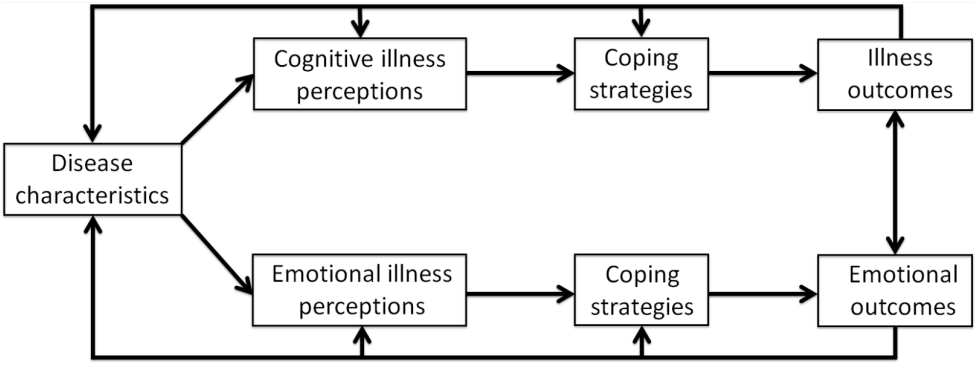

Figure 1. Flow diagram representing Leventhal's Common-Sense Model of Self-Regulation.
Adapted by Daleboudt GM (2014)[38]

Relatively little is known about illness perceptions in patients with axSpA, especially those with early axSpA. In a study by Hyphantis and colleagues in patients with longstanding ankylosing spondylitis (AS), '*illness concern*' (i.e., more concerns about the disease) was found to be associated with worse physical HRQoL.[7] Different results concerning illness

perceptions in patients with chronic back pain have been reported. Most studies showed that patients with chronic back pain strongly believe in '*severe consequences*' (e.g. held strong beliefs in severe consequences), strong beliefs that the disease is '*chronic*', and have '*negative emotions*' toward their disease.[8-10]

Two studies in patients with AS showed that avoidant coping styles '*decreasing activities*' and '*pacing*' were associated with more pain and worse physical and mental functioning.[11, 12] These two coping strategies were also strongly related to withdrawal from the workforce.[13] In patients with chronic back pain, maladaptive coping strategies such as '*avoiding physical activity*' were associated with negative health outcomes such as increased pain and disability.[14] However, knowledge about illness perceptions and coping in patients with early axSpA is lacking. Furthermore, little is known about how both illness perceptions and coping impact health outcomes in (early) axSpA.

Exploring use of the CSM in patients with early axSpA and chronic back pain is important, because it may enable health care professionals to identify illness perceptions and coping strategies that are susceptible to additional treatment strategies aimed at decreasing the burden of disease in these patients. In the current study, we first investigated the association between back pain and HRQoL or loss of work productivity, and subsequently, we investigated the influence of illness perceptions and coping on these associations in patients suspected of having axSpA and in subgroups. We used the CSM as the theoretical model. We hypothesized that having severe back pain is associated with lower HRQoL and greater loss of work productivity, and that the strengths of these associations are amplified by negative illness perceptions and maladaptive coping strategies inpatients suspected of having axSpA. We further hypothesized that the relationship between illness perceptions and coping strategies differs across subgroups.

Back pain is a self-reported and subjective symptom that is prevalent among patients with axSpA. Therefore, we thought it would be interesting to additionally investigate the previously mentioned associations, using an objective sign that is typical for axSpA. We considered inflammation on magnetic resonance imaging of the sacroiliac joints (MRI-SI) as measured by the Spondyloarthritis Research Consortium of Canada score for the SI joints (SPARCC-SI) to be a good candidate for being the objective sign. We hypothesized that illness perceptions and coping strategies have little influence on these associations, because a patient is unaware of his or her SPARCC-SI score. Consequently, all analyses were also performed using the SPARCC-SI score instead of backpain as the independent variable in a group of patients who were diagnosed and classified as having axSpA.

METHODS

Baseline data from the SPondyloArthritis Caught Early (SPACE) cohort of patients who were included between January 2009 and February 2017 were used. Briefly, the SPACE cohort is a prospective inception cohort of patients with chronic back pain (≥ 3 months but ≤ 2 years, and onset before age 45 years).[15] Dutch, Norwegian, and Italian rheumatology outpatient clinics participated in the SPACE study. Approval by local medical ethics committees (Medical Ethics Committee, Leiden University Medical Center [approval no. P08.105]; regional committee for medical and health research ethics in South-East Norway [approval no./ID 2014/426]; and Azienda Ospedaliera di Padova [approval no. 2438P]) was obtained. Informed consent was obtained from all study participants prior to inclusion.

All patients underwent the same diagnostic evaluation at baseline, consisting of medical history, physical examination, questionnaires, laboratory assessments (i.e., HLA–B27), and imaging including plain radiographs of the pelvis and coronal oblique MRI-SI (1.5T, 4-mm slice thickness). Patients were unaware of their diagnosis until the full assessment was performed. Treating rheumatologists provided the diagnosis, using clinical findings and local readings of the images. Patients in whom axSpA was diagnosed were classified according to the Assessment of SpondyloArthritis international Society (ASAS) axSpA criteria[16], based on central reading of images.

Analyses were performed in all patients as well as the following subgroups: patients diagnosed with axSpA and classified according to the ASAS axSpA criteria (ASAS axSpA), patients diagnosed with axSpA only (axSpA-diagnosed only), and patients diagnosed with chronic back pain.

Back pain intensity was assessed by asking patients to report the extent of back pain in the past 7 days on a numeric rating scale (NRS) ranging from 0 (no pain) to 10 (unbearable pain). Inflammation suspected of being axSpA on MRI-SI was quantified by 3 central readers according to the SPARCC-SI scoring method, and the average continuous SPARCC-SI score from 3 readers was calculated. Four quadrants were scored for each SI joint, and additional scores were given to lesions characterized by depth or intensity, resulting in a total score ranging from 0 to 72.[17]

Illness perceptions were assessed with the Revised Illness Perception Questionnaire (IPQ-R), which consists of 3 sections.[18, 19] The first section is the illness identity dimension, in which patients are asked about their experience with particular symptoms (15 items) and the perceived relationship with back pain. The numbers of symptoms with a perceived relationship is summed. The second section of the IPQ-R consists of 7 dimensions:

'*consequences*' (perceived impact of the disease on the patient's life), '*acute/ chronic timeline*' (perceived likeliness of chronicity of the disease), '*personal control*' (perceived personal control over the disease), '*treatment control*' (perceived efficacy of treatment), '*illness coherence*' (extent to which patients feel they understand their disease), '*cyclical timeline*' (the patient's perceptions of variability of her or her disease), and '*emotional representation*' (the patient experienced negative emotions due to the disease). The third section (causal attributions) consists of 18 possible causes that patients may attribute to their disease. Five dimensions were calculated: '*psychological attributions*', '*risk factors*', '*immunity*', '*accident*', and '*chance*'. The subscales of the second and third sections used Likert scales to score all items (1=strongly disagree and 5=strongly agree). Higher scores indicate stronger beliefs in that dimension (second section) or stronger beliefs in a dimension being a cause of the disease (third section).[19]

Coping strategies were assessed with the Coping with Rheumatic Stressors (CORS) questionnaire. The questionnaire is aimed at dealing with the most important stressors in rheumatic diseases: pain, limitations, and dependence.[20, 21] '*Comforting cognitions*' (putting pain in perspective), '*decreasing activities*', and '*diverting attention*' (thinking about/focusing on something else) refer to coping with pain. Coping with limitations is measured by '*optimism*', '*pacing*' (adapting/lowering the level of activity), and '*creative solution seeking*' (searching for creative solutions to cope with the limitations in daily life). The 2 styles of coping with dependence are '*accepting*' (making efforts to accept the level of dependence) and '*showing consideration*' (considering the feelings of others). Higher scores indicate preferential use of a particular coping strategy. The mean scores for each subscale of both the IPQ-R and CORS questionnaires were calculated.

Work productivity was assessed by the Work Productivity and Activity Impairment questionnaire (WPAI: general health, version 1.0). Patients were asked to report, e.g., the number of work hours missed due to their disease, the number of hours that they actually worked, and the impact of their disease on work productivity, scored on an NRS from 0 (health problems had no effect on work) to 10 (health problems completely prevented working) in the past week. The summary measure work productivity loss (i.e., total work impairment due to chronic back pain) on a scale from 0% (no work productivity loss) to 100% (total work productivity loss) was calculated. Greater impairment is indicated by higher percentages.[22]

HRQoL was assessed with the Short Form 36 (SF-36) health survey[23], which consists of 8 subscales. After recoding and recalibration were performed, raw scale scores were transformed into scale scores ranging from 0 (worst health) to 100 (best health). These scores were weighted according to sex- and age-matched scores for patients in each

country.[24, 25] Dutch-weighted scores were used for all Italian patients (n=57; [13%]), because no Italian sex- and age-matched scores were available. Two summary scores, the physical component summary score (PCS) and the mental component summary score (MCS), were calculated and transformed to compare the scores with the general population mean of 50. Higher scores indicate better HRQoL.[26]

Statistical analysis

Categorical variables are presented as the number (frequency) and continuous variables as the mean ± SD. Back pain was used in models as an independent variable in analyses of all patients and subgroup analyses, while the SPARCC-SI score was used only in models that included patients with ASAS axSpA. Pearson's correlation coefficients were calculated to determine differences between back pain or SPARCC-SI score, illness perceptions, coping, and outcome measures (PCS, MCS, or work productivity loss) were calculated. All variables that had a significant correlation (P<0.05) with the dependent variables (PCS, MCS, or work productivity loss) were included in a multistep linear regression model for that outcome. Models were adjusted for age and sex, by default. Illness perceptions were added to the basic model with back pain intensity or SPARCC-SI score as an outcome in the first step, and coping strategies were added in the second step. Likelihood ratio tests were used to determine whether the addition of each step independently improved the model. Data analyses were performed using Stata SE version 14.

RESULTS

Baseline data were available for 550 patients included in the SPACE cohort. Patients were excluded from further analyses when a complete questionnaire (n=39) or scales of the questionnaires (n=87) were missing. For the current analysis, 424 patients were used. Compared with all patients included in the analyses, patients who were excluded from the analyses less often had a diagnosis of axSpA (axSpA diagnosis in 53% of included patients and 39% of excluded patients; P=0.012) and fewer clinical SpA features (2.6 features in included patients and 2.0 features in excluded patients; P=0.002).

In total, 145 of 424 patients were categorized as having ASAS axSpA (diagnosed by the rheumatologist and classified as axSpA), 81 of 424 were categorized as having a diagnosis of axSpA only (diagnosed by a rheumatologist as axSpA only), and 198 of 424 were categorized as having chronic back pain. The mean ± SD age of all patients was 30.9 ± 8.1 years, and the mean ± SD symptom duration was 13.3 ± 7.1 months; these values were comparable with those in the different subgroups (**Table 1**). The majority of patients were female (50% of patients with ASAS axSpA, 65% of patients with axSpA-diagnosed only, and 74% of patients with chronic back pain).

Table 1. Baseline characteristics and assessment results for 424 patients with chronic back pain in the SPACE cohort, according to subgroups

	All patients (n=424)	ASAS axSpA (n=145)	axSpA diagnosis only (n=81)	Chronic back pain (n=198)
Baseline characteristics				
Age at inclusion (years), mean ± SD	30.9 ± 8.1	30.1 ± 7.8	32.5 ± 7.8	30.8 ± 8.5
Female sex	272 (64%)	73 (50%)	53 (65%)	146 (74%)
Symptom duration (months), mean ± SD	13.3 ± 7.1	13.7 ± 7.2	12.2 ± 6.3	13.4 ± 7.4
Inflammatory back pain	295 (70%)	120 (83%)	64 (79%)	111 (56%)
Good response to NSAIDs[a]	190 (45%)	87 (60%)	46 (57%)	57 (29%)
Uveitis	36 (9%)	26 (18%)	4 (5%)	6 (3%)
Psoriasis	51 (12%)	22 (15%)	18 (22%)	11 (6%)
Inflammatory bowel disease	32 (8%)	7 (5%)	13 (16%)	12 (6%)
Positive family history	188 (44%)	76 (52%)	33 (41%)	79 (40%)
Enthesitis	91 (22%)	34 (24%)	43 (53%)	14 (7%)
Dactylitis	28 (7%)	13 (9%)	11 (14%)	4 (2%)
Peripheral arthritis	69 (16%)	28 (19%)	24 (30%)	17 (9%)
HLA-B27 positive	178 (42%)	130 (90%)	5 (6%)	43 (22%)
Elevated ESR /CRP level	177 (42%)	61 (42%)	25 (32%)	31 (16%)
X-SI positive	32 (8%)	28 (19%)	0 (0%)	4 (2%)
MRI-SI positive	64 (15%)	60 (41%)	2 (3%)	2 (1%)
Use of NSAIDs	281 (66%)	112 (77%)	54 (67%)	115 (58%)
Number of SpA features[b], mean ± SD	2.6 ± 1.7	3.3 ± 1.6	3.5 ± 2.0	1.7 ± 1.2
Assessment results				
Back pain (0-10 scale), mean ± SD	4.8 ± 2.4	4.4 ± 2.3	4.4 ± 2.6	5.4 ± 2.3
SPARCC-SI (range 0-72), mean ± SD	1.8 ± 4.9	4.8 ± 7.4	0.4 ± 1.3	0.1 ± 0.6
PCS (range 0-100), mean ± SD	26.9 ± 14.8	28.2 ± 15.0	29.1 ± 13.8	25.1 ± 14.9
MCS (range 0-100), mean ± SD	47.2 ± 12.7	48.2 ± 13.9	44.8 ± 12.2	47.5 ± 12.0
WPL (range 0-100), mean ± SD	42.5 ± 32.1[c]	37.8 ± 31.5[d]	35.1 ± 30.4[e]	49.5 ± 32.0[f]

Values are presented as number (%) unless specified otherwise. [a] Back pain no longer present or is much better 24-48 hours after administration of a full dose of NSAID. [b] Excluding HLA-B27 testing and imaging.[c] Only 326 patients were evaluated. [d] Only 110 patients were evaluated. [e] Only 65 patients were evaluated. [f] Only 144 patients were evaluated. ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial Spondyloarthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MCS, mental component summary; MRI-SI, magnetic resonance imaging of sacroiliac (SI) joints, NSAIDs, non-steroidal anti-inflammatory drugs; PCS, Physical Component Summary; SPARCC-SI, Spondyloarthritis Research Consortium of Canada score of the SI-joints; WPL, work productivity loss; X-SI, radiography of SI-joints.

Patients with ASAS axSpA and those with only axSpA diagnosed had more SpA features (excluding HLA-B27 and imaging) (mean 3.3 and mean 3.5 features, respectively) compared with patients with chronic back pain (mean 1.7 features). In patients with chronic back pain, back pain was more severe than that in the ASAS axSpA and the axSpA diagnosed-only group (**Table 1**). A greater percentage of patients in the ASAS axSpA group had inflammation on MRI-SI compared with the percentage in the axSpA-diagnosed only group and the chronic back pain group. The mean PCS was decreased in all groups compared with the general population (mean of 50), but the mean MSC was comparable with that in the general population (**Table 1**). Seventy-seven percent (n=326) of all patients were in the work force at baseline. In 7 patients, loss of work productivity could not be calculated. Work productivity loss was comparable in the ASAS axSpA group and the axSpA-diagnosed only group but was higher in patients with chronic back pain (see **Table 1**). Statistically significant differences in mean scores were observed for the illness perceptions '*personal control*' (mean scores 3.3 in the axSpA group, 3.2 in the axSpA-diagnosed only group, and 3.0 in the group with chronic back pain), '*treatment control*' (mean scores 3.5 in the ASAS axSpA group, 3.3 in the axSpA-diagnosed only group, and 3.3 in the group diagnosed as having chronic back pain), '*illness coherence*' (mean scores 3.3 in the ASAS axSpA group, 3.1 in the axSpA-diagnosed only group, and 2.8 in the group with chronic back pain), '*emotional representation*' (mean scores 2.7 in the ASAS axSpA group, 2.9 in the axSpA-diagnosed only group, and 2.9 in the group with chronic back pain), and '*psychological attributions*' (mean scores 1.9 in the ASAS axSpA group, 2.2 in the axSpA-diagnosed only group, and 2.1 in the group with chronic back pain). No differences in other illness perceptions or coping strategies between the 3 subgroups were observed (data not shown).

Analysis in all patients

In the basic model including all patients, the PCS decreased by 3.5 points (R^2=0.37, P<0.001), the MCS decreased by 0.9 points (R^2=0.03, P<0.001), and work productivity loss increased by 7.7% (R^2=0.36, P<0.001) per point increase in the severity of back pain (**Tables 2** and **3**). After adding illness perceptions to the model, the impact of a 1-point increase in back pain on the PCS and work productivity loss became smaller and resulted in a decrease of 2.7 points (P<0.001) and an increase of 6.3% (P<0.001), respectively, and the association between back pain and the MCS was no longer statistically significant (B=-0.1, P=0.838) (**Tables 2** and **3**). The model performance improved by adding illness perceptions: more variance was explained in the PCS (R^2=0.47), the MCS (R^2=0.32), and work productivity loss (R^2=0.40) compared with the basic model, and these differences were statistically significant. After further adding coping strategies to the model, the associations between back pain and the PCS or work productivity loss changed only slightly (-2.3 points (P<0.001) and 5.9% (P<0.001), respectively, per point increase in back pain)

while the association with the MCS score remained the same (-0.01 points per point back pain; P=0.762) compared with the model with illness perceptions only (**Tables 2** and **3**). Explained variance did not further improve statistically significantly (PCS, R^2=0.53; MCS, R^2=0.32; work productivity loss, R^2=0.42) by adding coping strategies.

In the third model, having stronger beliefs in severe consequences (illness perception '*consequences*'; B=-4.7) or chance as a cause for the disease (illness perception '*chance*'; B=-1.0), and more use of the coping strategies '*decreasing activities*' (B=-4.0) and '*pacing*' (B=-3.3) were statistically significantly associated with a lower PCS. The illness perception '*emotional representation*' (having more negative emotions toward the disease) was associated with a better PCS (B=2.2). Attributing more symptoms to the disease (illness perception '*identity*'; B=-0.6), having more negative emotions toward the disease (B=-5.1), and having stronger beliefs in psychological attributions as a cause (illness perception '*psychological attributions*'; B=-4.4) were statistically significant associated with a lower MCS. Having stronger beliefs in severe consequences was statistically significantly associated with more work productivity loss (B=6.4).

Table 2. Multiple-step linear regression model with back pain, illness perceptions, and coping, explaining HRQoL and work productivity loss among all patients (n=424)

		PCS		MCS		WPL[a]	
	Range	**B**	**95% CI**	**B**	**95% CI**	**B**	**95% CI**
Model 1: Basic model							
Back pain	0-10	**-3.5**	**-3.9; -3.0**[b]	**-0.9**	**-1.4; -0.4**[b]	**7.7**	**6.5; 8.9**[b]
Age, years		**0.4**	**0.3; 0.6**[b]	-0.1	-0.3; 0.04	-0.1	-0.5; 0.3
Female		**2.7**	**0.3; 5.1**[d]	0.7	-1.9; 3.3	5.7	-0.3; 11.6
Model 2: Basic model plus illness perceptions							
Back pain	0-10	**-2.7**	**-3.2; -2.2**[b]	-0.1	-0.5; 0.4	**6.3**	**5.0; 7.7**[b]
Age, years		**0.5**	**0.4; 0.6**[b]	-0.1	-0.2; 0.1	-0.2	-0.5; 0.2
Female		**3.5**	**1.2; 5.8**[c]	1.7	-0.5; 4.0	4.7	-1.3; 10.7
Identity	0-15	-0.3	-0.8; 0.1	**-0.6**	**-1.1; -0.2**[c]	0.3	-0.9; 1.5
Consequences	1-5	**-6.9**	**-8.6; -5.1**[b]	-0.2	-1.8; 1.5	**8.6**	**3.9; 13.2**[b]
Timeline (acute/chronic)	1-5	0.5	-1.1; 2.2	-	-	-	-
Personal control	1-5	0.9	-1.1; 2.8	0.8	-1.0; 2.6	-2.3	-7.2; 2.6
Treatment control	1-5	0.7	-1.7; 3.1	-	-	-	-
Illness coherence	1-5	0.03	-1.4; 1.5	0.1	-1.3; 1.4	-2.4	-6.2; 1.4
Emotional representation	1-5	**2.4**	**0.8; 4.1**[c]	**-5.0**	**-6.6; -3.4**[b]	-0.2	-4.6; 4.2

Table 2. Continued

		PCS		MCS		WPL	
	Range	**B**	**95% CI**	**B**	**95% CI**	**B**	**95% CI**
Model 2: Basic model plus illness perceptions (continued)							
Psychological attributions	1-5	1.4	-0.3; 3.1	**-5.4**	**-7.2; -3.7**[b]	-0.4	-4.3; 3.4
Risk factors	1-5	-	-	2.0	-0.5; 4.5	-	-
Immunity	1-5	-1.3	-3.3; 0.4	-1.0	-2.8; 0.7	-	-
Accident	1-5	-0.9	-2.0; 0.3	0.5	-0.7; 1.7	-	-
Chance	1-5	**-1.2**	**-2.1; -0.2**[d]	-	-	-	-
Model 3: Basic model plus illness perceptions and coping							
Back pain	0-10	**-2.3**	**-2.8; -1.9**[b]	-0.1	-0.5; 0.4	**5.9**	**4.7; 7.2**[b]
Age, years		**0.5**	**0.4; 0.6**[b]	-0.1	-0.2; 0.1	-0.2	-0.6; 0.2
Female		**3.7**	**1.6; 5.8**[c]	1.1	-1.1; 3.3	4.3	-1.4; 10.0
Identity	0-15	-	-	**-0.6**	**-1.0; -0.2**[c]	-	-
Consequences	1-5	**-4.7**	**-6.4; -3.1**[b]	-	-	**6.4**	**2.2; 10.6**[c]
Emotional representation	1-5	**2.2**	**0.8; 3.6**[c]	**-5.1**	**-6.5; -3.7**[b]	-	-
Psychological attributions	1-5	-	-	-4.4	-5.8; -3.1[b]	-	-
Chance	1-5	**-1.0**	**-1.9; -0.1**[d]	-	-	-	-
Comforting cognitions	1-4	-	-	2.1	-1.0; 5.2	-	-
Decreasing activities	1-4	**-4.0**	**-6.7; -1.3**[c]	-0.6	-2.7; 1.4	7.3	-0.2; 14.8
Diverting attention	1-4	-	-	-0.7	-3.2; 1.9	-	-
Optimism	1-4	1.7	-0.2; 3.6	0.3	-2.1; 2.8	-	-
Pacing	1-4	**-3.3**	**-6.3; -0.3**[d]	-	-	5.1	-3.2; 13.5
Creative solution seeking	1-4	-1.0	-3.4; 1.3	-	-	-0.6	-7.1; 5.9
Accepting	1-4	-0.8	-2.6; 1.1	-	-	0.1	-5.2; 5.3
Consideration	1-4	-1.6	-3.8; 0.7	-	-	1.9	-3.9; 7.7

Statistically significant associations with the outcome are indicated in bold. [a] WPL was assessed in only 319 patients. [b] P<0.001. [c] P<0.01. [d] P<0.05. 95% CI, 95% Confidence Interval; HRQoL, health-related quality of life; MCS, Mental Component Summary; PCS, Physical Component Summary; WPL, work productivity loss.

Table 3. Adjusted R^2 and -2 log likelihood ratios of the multiple-step linear regression model for each group of patients

	PCS		MCS		WPL	
	adjusted R^2	-2 log likelihood	adjusted R^2	-2 log likelihood	adjusted R^2	-2 log likelihood
All patients						
Basic model	0.37	-1645.4	0.03	-1672.7	0.36	-1486.3
Basic model + illness perceptions	0.47	-1601.3[a]	0.32	-1593.1[a]	0.40	-1473.4[a]
Basic model + illness perceptions + coping	0.53	-1578.8	0.32	-1593.3	0.42	-1467.0
ASAS axSpA patients						
Basic model	0.28	-573.5	0.04	-581.7	0.33	-511.8
Basic model + illness perceptions	0.42	-553.9[a]	0.36	-548.3[a]	0.40	-503.3[a]
Basic model + illness perceptions + coping	0.45	-552.7	0.38	-547.0	0.43	-499.9
AxSpA-diagnosed only						
Basic model	0.37	-306.6	0.02	-314.5	0.29	-300.8
Basic model + illness perceptions	0.48	-296.6[a]	0.26	-299.9[a]	0.35	-297.0[a]
Basic model + illness perceptions + coping	0.49	-295.7	0.25	-303.3[b]	0.36	-297.1[b]
Chronic back pain						
Basic model	0.42	-760.8	0.03	-768.6	0.37	-668.6
Basic model + illness perceptions	0.48	-747.0[a]	0.29	-731.5[a]	0.39	-664.3[a]
Basic model + illness perceptions + coping	0.59	-722.1[a]	0.29	-734.1	0.47	-654.3[a]

[a] Statistically significant (P<0.05) for the model compared with previous model. [b] If no coping dimension could be added to model 2 (basic model + illness perceptions), all nonsignificant illness perceptions were removed from model 3 (basic model + illness perceptions and coping). ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial Spondyloarthritis; HRQoL, health-related quality of life; MCS, Mental Component Summary; PCS, Physical Component Summary; WPL, work productivity loss.

Subgroup analyses

Similar results were observed in the ASAS axSpA group (**Tables 3** and **4**), the axSpA-diagnosed only group (**Tables 3** and **5**), and the chronic back pain group (**Tables 3** and **6**) separately. The negative association between back pain and the MCS was observed only in the basic model. The strength of the associations between back pain and the PCS or work productivity loss decreased after adding illness perceptions to all basic models, although the model performance improved. Results did not change when coping strategies were added to illness perceptions. The same illness perceptions and coping strategies that were associated with PCS, MCS, and work productivity loss in all patients were also associated with these outcomes in each subgroup of patients. Only small differences were found (see **Tables 3-6**).

SPARCC-SI score in patients with ASAS axSpA

All analyses were repeated using the SPARCC-SI score instead of back pain in patients with ASAS axSpA to investigate whether an objective disease measure would yield results similar to those obtained using back pain intensity. In the basic model, the PCS decreased by 0.8 point (P<0.001), the MCS increased by 0.6 point (P<0.001), and work productivity loss increased by 0.9% (P=0.035) per point increase in the SPARCC-SI score (**Supplementary Table S1**). After illness perceptions and coping strategies were added, the PCS decreased by 0.8 point and 0.7 point, respectively, the MCS increased by 0.5 point and 0.5 point, respectively, and work productivity loss 1.1% and 0.9%, respectively. These results are different from those using models with back pain, because the strength of the associations was not influenced by adding illness perceptions and coping strategies.

Table 4. Multiple-step linear regression model with back pain, illness perceptions, and coping explaining variance in HRQoL and work productivity loss among ASAS axSpA patients (n=145)

		PCS		MCS		WPL[a]	
	Range	B	95% CI	B	95% CI	B	95% CI
Model 1: Basic model							
Back pain	0-10	**-3.4**	**-4.3; -2.4**[b]	**-1.0**	**-2.0; -0.02**[d]	**7.7**	**5.5; 9.9**[b]
Age, years		**0.4**	**0.1; 0.7**[c]	-0.2	-0.5; 0.1	0.3	-0.4; 0.9
Female		3.3	-1.0; 7.6	4.2	-0.3; 8.7	5.6	-4.3; 15.5
Model 2: Basic model plus illness perceptions							
Back pain	0-10	**-2.3**	**-3.2; -1.4**[b]	-0.3	-1.2; 0.6	**5.7**	**3.3; 8.0**[b]
Age, years		**0.6**	**0.3; 0.8**[b]	-0.1	-0.4; 0.1	0.03	-0.6; 0.7
Female		3.5	-0.5; 7.6	2.9	-1.0; 6.8	2.5	-7.6; 12.6
Identity	0-15	-0.7	-1.5; 0.1	-0.4	-1.2; 0.4	1.7	-0.2; 3.6
Consequences	1-5	**-8.4**	**-11.9; -4.9**[b]	1.6	-1.8; 4.9	**9.3**	**0.8; 17.8**[d]
Timeline (acute/chronic)	1-5	-0.1	-2.8; 2.7	-	-	0.8	-5.8; 7.5
Personal control	1-5	-	-	-	-	-2.9	-10.4; 4.6
Illness coherence	1-5	-	-	-0.5	-3.0; 2.0	-	-
Emotional representation	1-5	1.6	-1.3; 4.5	**-6.8**	**-10.0; -3.7**[b]	3.5	-4.0; 11.0
Psychological attributions	1-5	-	-	**-7.6**	**-11.1; -4.1**[b]	-	-
Risk factors	1-5	-	-	2.9	-1.7; 7.5	-	-
Immunity	1-5	0.7	-2.1; 3.5	-1.0	-4.2; 2.3	-	-
Accident	1-5	-2.0	-4.0; 0.1	-	-	-	-
Model 3: Basic model plus illness perceptions and coping							
Back pain	0-10	**-2.1**	**-3.0; -1.2**[b]	-0.2	-1.1; 0.7	**5.5**	**3.2; 7.8**[b]
Age, years		**0.6**	**0.3; 0.8**[b]	-0.1	-0.3; 0.2	0.1	-0.5; 0.8
Female		2.9	-1.1; 6.8	2.6	-1.2; 6.4	7.6	-2.3; 17.1
Consequences	1-5	**-7.1**	**-10.2; -3.9**[b]	-	-	**8.9**	**1.3; 16.6**[d]
Emotional representation	1-5	-	-	**-5.6**	**-8.3; -2.8**[b]	-	-
Psychological attributions	1-5	-	-	**-5.6**	**-8.2; -3.1**[b]	-	-
Comforting cognitions	1-4	-	-	3.8	-1.4; 9.0	-	-
Decreasing activities	1-4	-2.7	-8.4; 3.0	-2.7	-6.4; 1.1	2.6	-11.2; 16.4
Optimism	1-4	-	-	-1.3	-5.6; 3.0	-	-
Pacing	1-4	-2.8	-9.0; 3.4	-	-	13.4	-2.2; 28.9
Creative solution seeking	1-4	-0.3	-4.3; 3.8	-	-	-4.4	-14.3; 5.5
Accepting	1-4	-1.8	-5.2; 1.6	2.6	-0.6; 5.8	5.5	-2.8; 13.7

Statistically significant associations with the outcome are indicated in bold. [a] WPL was assessed in only 110 patients. [b] P<0.001. [c] P<0.01. [d] P<0.05. ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial Spondyloarthritis; HRQoL, health-related quality of life; MCS, Mental Component Summary; PCS, Physical Component Summary; WPL, work productivity loss.

Table 5. Multiple-step linear regression model with back pain, illness perceptions, and coping, explaining variance in HRQoL and work productivity loss among axSpA-diagnosed only patients (n=81)

		PCS		MCS		WPL[a]	
	Range	B	95% CI	B	95% CI	B	95%CI
Model 1: Basic model							
Back pain	0-10	**-3.2**	**-4.2; -2.3[b]**	-0.6	-1.7; 0.4	**6.9**	**4.3; 9.6[b]**
Age, years		0.2	-0.1; 0.5	0.1	-0.3; 0.4	0.2	-0.7; 1.1
Female		**5.5**	**0.3; 10.7[d]**	-4.6	-10.4; 1.2	-0.3	-14.0; 13.4
Model 2: Basic model plus illness perceptions							
Back pain	0-10	**-2.6**	**-3.5; -1.7[b]**	0.1	-0.9; 1.1	**6.2**	**3.5; 8.8[b]**
Age, years		**0.3**	**0.03; 0.6[d]**	0.1	-0.2; 0.4	0.1	-0.8; 1.0
Female		**5.9**	**1.1; 10.6[d]**	-4.0	-9.3; 1.3	3.4	-10.3; 17.1
Identity	0-15	-0.6	-1.6; 0.5	-0.8	-2.0; 0.3	-	-
Consequences	1-5	**-5.1**	**-8.2; -2.0[c]**	1.3	-2.1; 4.8	1.4	-6.8; 9.7
Illness coherence	1-5	-	-	2.0	-1.3; 5.2	**-8.7**	**-17.1; -0.3[d]**
Emotional representation	1-5	2.3	-1.0; 5.6	**-4.5**	**-8.3; -0.7[d]**	-	-
Psychological attributions	1-5	-	-	-2.0	-5.7; 1.8	-	-
Immunity	1-5	-2.3	-5.5; 0.9	-1.2	-5.0; 2.6	-	-
Model 3: Basic model plus illness perceptions and coping							
Back pain	0-10	**-2.4**	**-3.4; -1.5[b]**	-0.1	-1.1; 0.8	**6.2**	**3.7; 8.9[b]**
Age, years		**0.3**	**0.1; 0.6[d]**	0.1	-0.2; 0.4	0.1	-0.7; 1.0
Female		**6.4**	**1.4; 11.3[d]**	-4.3	-9.4; 0.8	3.8	-9.6; 17.2
Consequences	1-5	**-3.7**	**-7.2; -0.2[d]**	-	-	-	-
Illness coherence	1-5	-	-	-	-	**-9.5**	**-16.6; -2.4[d]**
Emotional representation	1-5	-	-	**-6.8**	**-9.6; -4.1[b]**	-	-
Decreasing activities	1-4	-2.5	-8.2; 3.2	-	-	-	-
Pacing	1-4	-0.9	-8.3; 6.5	-	-	-	-
Creative solution seeking	1-4	-2.0	-7.2; 3.2	-	-	-	-

Statistically significant associations with the outcome are indicated in bold. [a] WPL was assessed in only 65 patients. [b] P<0.001. [c] P<0.01. [d] P<0.05. axSpA, axial Spondyloarthritis; CI, 95% Confidence Interval; HRQoL, health-related quality of life; MCS, Mental Component Summary; PCS, Physical Component Summary; WPL, work productivity loss.

Table 6. Multiple-step linear regression model with back pain, illness perceptions, and coping, explaining variance in HRQoL and work productivity loss in patients with chronic back pain (n=198)

		PCS		MCS		WPL[a]	
	Range	**B**	**95% CI**	**B**	**95%CI**	**B**	**95% CI**
Model 1: Basic model							
Back pain	0-10	**-3.7**	**-4.4; -3.0[b]**	**-1.0**	**-1.8; -0.3[c]**	**7.8**	**5.9; 9.6[b]**
Age, years		**0.5**	**0.3; 0.7[b]**	-0.03	-0.2; 0.2	-0.4	-0.9; 0.1
Female		1.0	-2.7; 4.7	-0.2	-4.0; 3.7	8.4	-1.1; 17.9
Model 2: Basic model plus illness perceptions							
Back pain	0-10	**-3.0**	**-3.8; -2.2[b]**	-0.1	-0.8; 0.7	**6.5**	**4.5; 8.6[b]**
Age, years		**0.5**	**0.3; 0.7[b]**	-0.01	-0.2; 0.2	-0.4	-0.9; 0.1
Female		2.5	-1.1; 6.1	1.0	-2.4; 4.4	7.2	-2.3; 16.7
Identity	0-15	-	-	**-0.6**	**-1.2; -0.01[d]**	-	-
Consequences	1-5	**-6.4**	**-8.9; -3.9[b]**	-0.8	-3.2; 1.7	**10.1**	**2.8; 17.4[c]**
Timeline (acute/chronic)	1-5	-	-	-1.6	-4.0; 0.9	-	-
Personal control	1-5	0.5	-2.6; 3.5	1.4	-1.6; 4.3	0.3	-7.8; 8.4
Treatment control	1-5	1.6	-1.7; 4.9	1.8	-1.7; 5.2	-	-
Illness coherence	1-5	-0.2	-2.3; 2.0	1.0	-1.1; 3.1	-	-
Emotional representation	1-5	**3.0**	**0.7; 5.4[d]**	**-4.1**	**-6.4; -1.8[b]**	-1.1	-7.2; 5.0
Psychological attributions	1-5	-	-	**-4.2**	**-6.7; -1.8[c]**	-	-
Immunity	1-5	-	-	0.2	-2.2; 2.6	-	-
Accident	1-5	-	-	0.2	-1.6; 1.9	-	-
Model 3: Basic model plus illness perceptions and coping							
Back pain	0-10	**-2.2**	**-2.9; -1.5[b]**	-0.2	-0.9; 0.5	**5.1**	**3.2; 7.1[b]**
Age, years		**0.5**	**0.3; 0.7[b]**	-0.04	-0.2; 0.2	**-0.5**	**-1.0; -0.03[d]**
Female		**3.6**	**0.4; 6.8[d]**	0.8	-2.6; 4.2	5.2	-3.7; 14.2
Identity	0-15	-	-	**-0.7**	**-1.3; -0.1[d]**	-	-
Consequences	1-5	**-3.4**	**-5.7; -1.0[c]**	-	-	4.8	-1.6; 11.2
Emotional representation	1-5	**2.6**	**0.7; 4.6[c]**	**-5.0**	**-6.9; -3.1[b]**	-	-
Psychological attributions	1-5	-	-	**-3.4**	**-5.6; -1.3[c]**	-	-
Comforting cognitions	1-4	-	-	-0.2	-4.4; 4.0	-	-
Decreasing activities	1-4	**-5.9**	**-9.7; -2.2[c]**	-0.5	-3.6; 2.5	10.2	-1.1; 21.5
Optimism	1-4	**2.8**	**0.2; 5.4[d]**	2.5	-1.3; 6.4	-	-
Pacing	1-4	**-4.5**	**-8.5; -0.5[d]**	-	-	7.4	-4.0; 18.8
Creative solution seeking	1-4	-2.5	-5.6; 0.6	-	-	7.3	-1.6; 16.3
Accepting	1-4	-1.3	-4.0; 1.5	-	-	-	-

Statistically significant associations with the outcome are indicated in bold. [a] WPL was assessed in only 144 patients. [b] P<0.001. [c] P<0.01. [d] P<0.05. HRQoL, health-related quality of life; MCS, Mental Component Summary; PCS, Physical Component Summary; WPL, work productivity loss.

DISCUSSION

To our knowledge, this is the first study that used the CSM as a theoretical framework to investigate patients' responses to 1) back pain in patients with chronic back pain referred to a rheumatology outpatient clinic due to a suspicion of axSpA and 2) inflammation on the MRI-SI in patients with ASAS axSpA. As expected, our study demonstrated that an increasing level of self-reported back pain is associated with worsening of the physical HRQoL and loss of work productivity. In addition, we show for the first time that illness perceptions are important in the relationship between back pain and HRQoL and work productivity loss in patients suspected of having axSpA, irrespective of subgroup. However, we observed no effect of coping on HRQoL or work productivity loss in our cohort. As hypothesized, in patients with ASAS axSpA, illness perceptions and coping strategies did not change the association between levels of bone marrow edema in the sacroiliac joints (which was chosen to represent objective levels of inflammation), although the model performance improved. Our study suggests that in order to improve physical HRQoL and work productivity, the focus should also be on targeting negative illness perceptions.

These findings are important for managing patients with axSpA and chronic back pain. Rheumatologists and health care professionals should be aware that illness perceptions play an important role in determining medical outcomes in these patients. Illness perceptions should, therefore, be actively explored and taken into consideration in the management plan. To maximally improve health outcomes in patients with axSpA, psychological support could be given in addition to targeting back pain using drug treatment and physiotherapy. Several studies in other diseases have shown that psychological interventions could potentially change illness perceptions.[27-30]

The main aim of our study was to investigate the clinical question of how rheumatologists and health care professionals can maximally improve health outcomes and whether and which illness perceptions and coping strategies are important for disease management in patients with early onset of axSpA. Therefore, we performed a stepwise regression analysis rather than a mediation analysis. In the regression analysis, the effect of illness perceptions and coping strategies on the relationship between back pain and outcomes can be clearly seen. In a mediation analysis, back pain would be included as a control variable, and therefore this effect would no longer be apparent. The advantage of a mediation analysis would be that all direct and indirect effects of illness perceptions and coping could be evaluated, but the clinical interpretation of the various coefficients in the model is unclear.

In patients with chronic back pain, no associations between illness perceptions and HRQoL or work productivity loss have been investigated, as far as we know. Only one previous

study investigated the association between illness perceptions and HRQoL in patients with longstanding AS. In that study, the Brief Illness Perception Questionnaire[31] was used and showed that higher scores on the illness perception '*concern*', part of the '*emotional representation*' of the disease, were associated with worse physical HRQoL.[7] Those findings contrast with the findings in our cohort, in which it was shown that '*consequences*' and '*chance*' were associated with decreased physical HRQoL, and that '*identity*', '*emotional representation*', and '*psychological attributions*' were associated with decreased mental HRQoL. '*Consequences*' was also associated with increased loss of work productivity. Differences between our study and the study including AS patients might be explained by the use of different questionnaires (Brief IPQ versus IPQ-R in our cohort) and different patient populations (longstanding AS versus early axSpA or suspected axSpA in our cohort). It is possible that other illness perceptions become more important when the disease is longstanding.

Further, several studies showed that the maladaptive coping strategies '*decreasing activities*' and '*pacing*' were associated with worse HRQoL and withdrawal from the workforce in patients with AS[11-13], and that '*avoiding physical activity*' was associated with increased pain and disability in patients with chronic back pain.[14] In our study, increased use of the '*decreasing activities*' and '*pacing*' strategies were associated with lower physical HRQoL. These coping strategies were not related to work productivity loss, which could be explained by the fact that work productivity loss and withdrawal from the work force are different concepts. Moreover, this difference could also reflect the difference between early versus longstanding disease.

In contrast to our expectations, a positive association between illness perception '*emotional representation*' (having more negative emotions toward the disease) and physical HRQoL was observed in our study. When examining correlations between '*emotional representation*' and the PCS, we observed negative associations in all patients and in each subgroup, as expected. Therefore, this effect appears only in the multivariable model, in the context of the other illness perceptions that play a significant role. The context of other illness perceptions might explain why the association between '*emotional representation*' and HRQoL reversed. Additionally, in our study coping strategies did not have an additional influence over illness perceptions for the association between back pain and HRQoL or work productivity loss, in contrast to our hypothesis. These unexpected findings could be explained by the CSM itself, because the CSM is a self-regulatory model. The CSM implies that individuals use coping strategies based on his or her illness perceptions, and illness perceptions are adapted based on coping strategies by a feedback loop from HRQoL to these factors. Using maladaptive coping strategies decreases HRQoL, and according to the CSM, illness perceptions will be adapted in a manner such that

worsening in HRQoL is reduced. Furthermore, the effect of illness perceptions may be balanced by coping strategies. Having more negative emotions associated with a disease could lead to a change in coping strategies from maladaptive toward adaptive in order to decrease worsening of HRQoL. Future studies are needed to investigate this notion further. The effect of coping strategies could have been disadvantaged or changed or different due to the fact that coping strategies cannot be added to the model before illness perceptions are added. However, testing the coping strategies first would violate the CSM.

Our main analysis was performed in all patients suspected of having axSpA. Remarkably, comparable results were observed in all analyses in all subgroups. This finding may be explained by the fact that patients were unaware of the results of laboratory and imaging tests and diagnosis when they filled out the questionnaires. Therefore, it would be interesting to study the impact of receiving a diagnosis on illness perceptions and coping. Unfortunately, in our cohort we currently have no data on this subject.

Our results suggest that HRQoL and work productivity can be further improved by interventions targeting patients' cognitions and behaviour along with treatment that suppresses pain and inflammation. Targeting patients' cognitions and behaviour along with treatment that suppresses pain is more established not only in studies but also in treatment strategies for patients with back pain compared to SpA.[1, 32, 33] These interventions could be used for the patients with chronic back pain who were not diagnosed with axSpA in the SPACE cohort, because nonspecific back pain is the most common diagnosis.[34] Illness perceptions and coping strategies are potentially modifiable factors, and several studies have already shown that in various diseases cognitive behavioural interventions based on the CSM were able to change illness perceptions and coping strategies, leading to a decreased disease burden.[35, 36] The results of our study suggest that the illness perceptions '*consequences*' and '*chance*' should be targeted in order to improve physical HRQoL, '*emotional representation*' should be targeted for improving mental HRQoL, and '*consequences*' should be targeted to decrease work productivity loss. For example, health care specialists could discuss with patients how consequences can be minimized, explain the causal attributions to patients, and pay attention to the emotions of patients. Additionally, aiming for positive illness perceptions, having social support, and belief in self-efficacy may also help to improve health outcomes.[37] Furthermore, the use of '*decreasing activities*' and '*pacing*' as coping strategies should be discouraged in order to improve physical HRQoL.

One of the limitations of this study is that no causal relationship could be investigated, because of the cross-sectional character of the study. Only longitudinal studies enable the investigation of causality. Another limitation is that the CORS questionnaire, which was

used in our study, is designed to measure coping strategies directed at the stressors of inflammatory rheumatic diseases.[20, 21] In our cohort, patients with chronic back pain also filled out this questionnaire. However, all patients were unaware of their diagnosis at the time they filled out the questionnaires. A statistical limitation that should be mentioned is that we used R^2 values to justify certain variable choices in the models. These values may be spuriously inflated because of covariance of components of the HRQoL and illness perceptions. Therefore, absolute R^2 values should be interpreted with caution. This limitation will, however, not jeopardize the main finding of this study, namely, that illness perceptions influence the relationship between backpain and HRQoL.

In conclusion, in patients suspected of having axSpA, high intensity of back pain is associated with worsening of physical HRQoL and increasing loss of work productivity. Our results suggest that, in addition to treating back pain, targeting negative illness perceptions could improve HRQoL and work productivity. Our study supports the development of interventions targeting patients' cognitions in addition to use of existing treatment options to decrease the burden of disease in patients suspected of having axSpA. Future research is needed to investigate whether the impact of illness perceptions and coping strategies vary over time, the differences between these factors in early and longstanding disease, as well as the impact of targeting illness perceptions on back pain and physical HRQoL.

REFERENCES

1. 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;6:978-91.
2. 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.
3. Hagger MS, Orbell S. A meta-analytical review of the common-sense model of illness representations. *Psychol Health* 2003;18:141-84.
4. Van der Have M, Brakenhoff LK, van Erp SJ, et al. Back/joint pain, illness perceptions and coping are important predictors of quality of life and work productivity in patients with inflammatory bowel disease: a 12-month longitudinal study. *J Crohns Colitis* 2015;9:76-83.
5. Scharloo M, Kaptein AA, Weinman J, et al. Illness perceptions, coping and functioning in patients with rheumatoid arthritis, chronic obstructive pulmonary disease and psoriasis. *J Psychosom Res* 1998;44:573-85.
6. Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet* 2017;390:73-84.
7. 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.
8. Foster NE, Bishop A, Thomas E, et al. Illness perceptions of low back pain patients in primary care: what are they, do they change and are they associated with outcome? *Pain* 2008;136:177-87.
9. Siemonsma PC, Stuive I, Roorda LD, et al. Cognitive treatment of illness perceptions in patients with chronic low back pain: a randomized controlled trial. *Phys Ther* 2013;93:435-48.
10. Glattacker M, Heyduck K, Meffert C. Illness beliefs, treatment beliefs and information needs as starting points for patient information: evaluation of an intervention for patients with chronic back pain. *Patient Educ Couns* 2012;86:378-89.
11. 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.
12. Pelaez-Ballestas I, Boonen A, Vazquez-Mellado J, et al. Coping strategies for health and daily-life stressors in patients with rheumatoid arthritis, ankylosing spondylitis, and gout: STROBE-compliant article. *Medicine* 2015;94:e600.
13. 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.
14. DiNapoli EA, Craine M, Dougherty P, et al. Deconstructing chronic low back pain in the older adults: step by step evidence and expert-based recommendations for evaluation and treatment. Part V: maladaptive coping. *Pain Med* 2016;17:64-73.
15. 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.
16. 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.
17. Maksymowych WP, Inman RD, Salonen D, et al. Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. *Arthritis Rheum* 2005;53:703-9.
18. 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.
19. Moss-Morris R, Weinman J, Petrie KJ, et al. The Revised Illness Perception Questionnaire (IPQ-R). *Psychol Health* 2002;17:1-16.
20. Van Lankveld W, Näring G, van der Staak C, et al. Development of the CORS: coping with rheumatic stressors. *Gedrag Gezondheid* 1993;21:40-8.
21. 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;33:106773

22. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353-65.
23. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
24. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epi-demiol* 1998;51:1055-68.
25. Loge JH, Kaasa S. Short form 36 (SF-36) health survey: normative data from the general Norwegian population. *Scan J Soc Med* 1998;26:250-8.
26. Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. *Qual of Life Res* 2001;10:405-13.
27. Petrie KJ, Cameron LD, Ellis CJ, et al. Changing illness perceptions after myocardial infarction: an early intervention randomized controlled trial. *Psychosom Med* 2002;64:580-6.
28. Goodman D, Morrissey S, Graham D, Bossingham D. The application of cognitive-behaviour therapy in altering illness representations of systemic lupus erythematosus. *Behaviour Change* 2005;22:156-71.
29. Chilcot J, Moss-Morris R. Changes in illness-related cognitions rather than distress mediate improvements in irritable bowel syndrome (IBS) symptoms and disability following a brief cognitive behavioural therapy intervention. *Behav Res Ther* 2013;51:690-5.
30. Christensen SS, Frostholm L, Ornbol E, Schroder A. Changes in illness perceptions mediated the effect of cognitive behavioural therapy in severe functional somatic syndromes. *J Psychosom Res* 2015;78:363-70.
31. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *J Psychosom Res* 2006;60:631-7.
32. Henschke N, Ostelo RW, van Tulder MW, et al. Behavioural treatment for chronic low-back pain. Cochrane Database Syst Rev 2010:Cd002014
33. Engers A, Jellema P, Wensing M, et al. Individual patient education for low backpain. *Cochrane Database Syst Rev* 2008:Cd004057
34. Ez-Zaitouni Z, Landewé RB, van der Heijde D, van Gaalen FA. Alternative diagnoses in patients with chronic backpain not diagnosed with axial spondyloarthritis: data from the SPACE cohort. *Ann Rheum Dis* 2018;77:e34.
35. Wearden A, Peters S. Therapeutic techniques for interventions based on Leventhal's common sense model. *Br J Health Psychol* 2008;13:189-93.
36. Jones CJ, Smith HE, Llewellyn CD. A systematic review of the effectiveness of interventions using the Common Sense Self-Regulatory Model to improve adherence behaviours. *J Health Psychol* 2016;21:2709-24.
37. Jansen DL, Heijmans M, Rijken M, Kaptein AA. The development of and first experiences with a behavioural self-regulation intervention for end-stage renal disease patients and their partners. *J Health Psychol* 2011;16:274-83.
38. Daleboudt GM. Systemic lupus erythematosus: a behavioural medicine perspective. Ridderkerk, the Netherlands. *Ridderprint*; 2014.

6

SUPPLEMENTARY MATERIALS

Supplementary Table S1. Multiple step linear regression model with inflammation on the MRI-SI, illness perceptions, and coping, explaining variance in health-related quality of life and work productivity loss among ASAS axSpA patients (n=145)

		PCS		MCS		WPL (n=110)	
	Range	B	95%CI	B	95%CI	B	95%CI
Model 1: Basic model							
SPARCC-SI	0-72	**-0.8**	**-1.1;-0.5**[a]	**0.6**	**0.3; 0.9**[a]	**0.9**	**0.1; 1.7**[c]
Age, years		0.3	-0.002; 0.6	-0.2	-0.5; 0.1	0.7	-0.1; 1.5
Female		-2.7	-7.5; 2.0	**5.6**	**1.1; 10.1**[c]	**14.1**	**2.0; 26.2**[a]
Model 2: Basic model plus illness perceptions							
SPARCC-SI	0-72	**-0.8**	**-1.0; -0.5**[a]	**0.5**	**0.2; 0.7**[a]	**1.1**	**0.3; 1.8**[b]
Age, years		**0.5**	**0.3; 0.8**[a]	-0.1	-0.3; 0.1	0.2	-0.5; 1.0
Female		0.1	-4.0; 4.1	**4.8**	**0.9; 8.6**[c]	6.9	-4.2; 18.0
Identity	0-15	**-1.3**	**-2.1; -0.6**[b]	-0.4	-1.1; 0.3	**2.9**	**0.9; 4.9**[b]
Consequences	1-5	**-9.4**	**-12.8; -6.0**[a]	0.1	-3.0; 3.3	**14.9**	**6.2; 23.6**[b]
Timeline (acute/chronic)	1-5	-0.3	-3.0; 2.4	-	-	2.1	-4.9; 9.2
Personal control	1-5	-	-	-	-	-6.0	-13.9; 1.8
Treatment control	1-5	-	-	-	-	-	-
Illness coherence	1-5	-	-	-0.03	-2.4; 2.3	-	-
Emotional representation	1-5	1.2	-1.7; 4.1	**-6.4**	**-9.4; -3.4**[a]	3.2	-4.8; 11.2
Psychological attributions	1-5	-	-	**-7.3**	**-10.6; -4.0**[a]	-	-
Risk factors	1-5			3.6	-0.8; 8.0	-	-
Immunity	1-5	-0.9	-3.8; 1.9	-0.5	-3.5; 2.7	-	-
Accident	1-5	-0.7	-2.8; 1.3	-	-	-	-
Model 3: Basic model plus illness perceptions and coping							
SPARCC-SI	0-72	**-0.7**	**-1.0; -0.5**[a]	**0.5**	**0.3; 0.8**[a]	**0.9**	**0.2; 1.6**[c]
Age, years		**0.5**	**0.3; 0.7**[a]	-0.1	-0.3; 0.2	0.2	-0.4; 0.9
Female		-0.5	-4.3; 3.4	**4.6**	**0.9; 8.3**[c]	**12.1**	**1.8; 22.5**[c]
Identity	0-15	**-1.3**	**-2.0; -0.6**[b]	-	-	**2.8**	**0.9; 4.6**[b]
Consequences	1-5	**-7.2**	**-10.2; -4.3**[a]	-	-	**11.7**	**3.8; 19.5**[b]
Emotional representation	1-5	-	-	**-5.7**	**-8.2; -3.1**[a]	-	-
Psychological attributions	1-5	-	-	**-4.9**	**-7.3; -2.5**[a]	-	-

Supplementary Table S1. Continued

		PCS		MCS		WPL (n=110)	
	Range	**B**	**95%CI**	**B**	**95%CI**	**B**	**95%CI**
Model 3: Basic model plus illness perceptions and coping (continued)							
Comforting cognitions	1-4	-	-	4.2	-0.8; 9.1	-	-
Decreasing activities	1-4	**-5.6**	**-10.8; 0.4**[c]	**-3.8**	**-7.1; -0.4**[c]	10.5	-3.3; 24.4
Optimism	1-4	-	-	-1.6	-5.6; 2.4	-	-
Pacing	1-4	-0.5	-6.4; 5.4	-	-	8.6	-7.7; 24.8
Creative solution seeking	1-4	0.5	-3.4; 4.4	-	-	-5.7	-16.1; 4.8
Accepting	1-4	-3.2	-6.4; 0.03	2.7	-0.3; 5.7	8.0	-0.6; 16.5
		adj. R^2	**-2 log likelihood**	**adj. R^2**	**-2 log likelihood**	**adj. R^2**	**-2 log likelihood**
Basic model		0.15	-585.0	0.10	-577.4	0.06	-530.5
Basic model + illness perceptions		0.44	-551.1[d]	0.42	-541.8[d]	0.31	-510.2[d]
Basic model + illness perceptions + coping		0.50	-543.9	0.46	-538.9	0.39	-503.4[d]

Statistically significant associations are indicated in bold. [a] P<0.001. [b] P<0.01. [c] P<0.05.[d] Likelihood ratio test is statistically significant (p<0.05) for the model compared to the previous model. ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial Spondyloarthritis; CI, Confidence Interval; MCS, Mental Component Summary; MRI-SI; Magnetic Resonance Imaging of the sacroiliac joints; PCS, Physical Component Summary; SPARCC-SI, Spondyloarthritis Research Consortium of Canada Score of the sacroiliac joints; WPL, work productivity loss.

Chapter 7

Do illness perceptions and coping strategies change over time in patients recently diagnosed with axial spondyloarthritis? A two-year follow-up study in the SPACE cohort

Miranda van Lunteren, Robert Landewé, Camilla Fongen, Roberta Ramonda, Désirée van der Heijde, Floris van Gaalen

Submitted

ABSTRACT

Objective

It is unknown if in axial spondyloarthritis (axSpA) patients illness perceptions and coping strategies change when disease activity changes.

Methods

Patients diagnosed with axSpA and ≥1 follow-up visit (1 and/or 2 year(s)) in the SPACE-cohort were included. Mixed linear models were used for illness perceptions (range: 1-5), coping (range: 1-4), back pain (NRS: 0-10), health-related quality of life (HRQoL range: 0-100; (physical (PCS) and mental component summary (MCS)), work productivity loss (WPL), and activity impairment (AI, range:0-100%), separately, to test if they changed over time.

Results

At baseline, 150 axSpA patients (mean age 30.4 years, 51% female, 65% HLA-B27+) had a mean (SD) VAS back pain of 4.0 (2.5), PCS of 28.8 (14.0), MCS of 47.8 (12.4), WPL of 34.1% (29.8) and AI of 38.7% (27.9). Over two years, clinically and statistically significant improvements were seen in the proportion of patients with ASDAS low disease activity (from 39% to 68%), back pain (-1.5 (2.2)), AI (14.4% (27.2)), PCS (11.1 (13.3)) and WPL (-15.3% (28.7)), but MCS did not change (0.7 (13.9), p=0.201).

In contrast, illness perceptions and coping strategies did not change over a period of two years. For example, at two years patients believed that their illness had severe '*consequences*' (2.8 (0.9)) and they had negative emotions (e.g. feeling upset or fear) towards their illness ('*emotional representation*', 2.5 (0.8)). Patients most often coped with their pain by putting pain into perspective ('*comforting cognitions*', 2.8 (0.6)) and tended to cope with limitations by being optimistic ('*optimism*', 2.9 (0.7)).

Conclusion

Whilst back pain, disease activity, and health outcomes clearly improved over 2 years, illness perceptions and coping strategies remained remarkably stable.

INTRODUCTION

We have previously shown that in patients with chronic back pain, including chronic back pain caused by axial spondyloarthritis (axSpA), negative illness perceptions had a substantial impact on the relationship between reported back pain intensity and more generic health outcomes.[1] Illness perceptions are patient-formulated beliefs about their illness, which may help them to better understand their illness but they also reflect the emotional state of the patient.[2] In this study a similar intensity of back pain was associated with more impairment in health-related quality of life (HRQoL) and more work productivity loss when patients had negative illness perceptions such as a belief in severe '*consequences*' of their illness, beliefs in (bad) '*chance*' as the cause of their back pain, and negative emotions around their back pain ('*emotional representation*').[1] We further found that certain coping strategies (i.e. decreasing physical activities and adapting the level of activities following back pain) had a negative influence on the impact of back pain on HRQoL.[1] Coping strategies are cognitive and behavioral strategies helping patients to better manage stress associated with having to live with an illness. Choices for coping strategies are determined by illness perceptions. Coping strategies could for example help in reducing, mastering, minimizing, or tolerating pain.[2]

So, the results of the previous study demonstrated that health outcomes are also determined by illness perceptions and not only by biomedical factors such as inflammation. It leaves open the option that health outcomes in axSpA patients can be improved by influencing illness perceptions in a positive manner and possibly by interfering with coping strategy choices. In this regard, it is unknown if illness perceptions and coping strategies remain stable over time, especially if disease activity improves, as literature reports conflicting results among patients with other rheumatic diseases.[3-5] Moreover, it is also not well investigated if a decrease in disease activity is associated with an adjustment of illness perceptions and a change in the use of certain coping strategies.

One longitudinal study has investigated coping strategies over time in patients with radiographic axSpA (r-axSpA) and only slight changes in coping strategies were found over a 4-year time period, while these changes were not related to changes in pain or physical functioning.[6] While this particular study investigated patients with longstanding disease and r-axSpA only, it is possible that illness perceptions and coping strategies are more susceptible to change in patients in an early phase of a disease, as over time patients receive more information about their disease, gain more experience and understand their disease better.[7]

A first step in investigating this hypothesis is to assess if illness perceptions and usage of

particular coping strategies in patients with axSpA are susceptible to changes in disease activity. We have explored this question in patients with axSpA in the SPondyloArthritis Caught Early (SPACE)-cohort, the first two years after receiving the diagnosis.

METHODS

Patients included in the SPACE-cohort with data at baseline, one, and/or two year(s) between January 2009 and August 2018 were included. An extensive description of the SPACE-cohort is available elsewhere.[8] In brief, the SPACE-cohort is a multicentre ongoing inception cohort of patients with chronic back pain ≥3 months and ≤2 years and an onset before <45 years from the Netherlands, Norway, and Italy. Local medical ethics committees provided approval for the study (Medical Ethical Committee Leiden University Medical Center: P08.105, regional committee for medical and health research ethics in South-East Norway: 2014/426, Azienda Ospedaliera di Padova: 2438P) and informed consent was obtained from all study participants before inclusion.

A fixed diagnostic work-up according to protocol was performed for all patients at baseline, one year, and two years. This work-up consisted of medical history, physical examination, laboratory assessments, imaging, and questionnaires. The clinical diagnosis was provided by treating rheumatologists based on clinical findings and local reading of imaging.
Only patients who received an axSpA diagnosis with a level of confidence regarding the diagnosis of ≥7 from the treating rheumatologist at baseline were included in the analysis.
We did not involve patients to comment on study design or interpretation of the results. Patients were not invited to contribute to the writing or editing of this manuscript for readability or accuracy.

Patients were asked to report their back pain intensity in the past seven days on a Numeric Rating Scale (NRS) ranging from 0 (no pain) to 10 (unbearable pain).

Illness perceptions were assessed with the Revised Illness Perception Questionnaire (IPQ-R) which covers eight dimensions, see **Table 1**.[9, 10] Likert scales were used to score all items of each dimension ranging from 1 (strongly disagree) to 5 (strongly agree), except '*identity*' which ranges from 0-15. Higher scores on '*consequences*' dimension indicate stronger beliefs in the negative impact of the illness by the patient on his life. Higher scores on '*acute/chronic timeline*' or '*cyclical timeline*' dimension indicate stronger beliefs that the illness is chronic or cyclical, respectively. When patients have high scores on '*personal control*' or '*treatment control*' dimension, they feel that they have (a lot) personal control over the illness or they think that the prescribed treatment of their illness is effective. Patients with high scores on '*illness coherence*' feel that they understand their

illness, while patients with high scores on '*emotional representation*' dimension have more negative emotions such as fear, angriness or depressive feelings towards their illness. Higher scores on the dimensions representing possible causes ('*psychological attributions*', '*risk factors*', '*immunity*', '*accident*', and '*chance*') indicate that a patient has strong beliefs that a certain factor such as genes or an accident is the cause of their illness.[10]

A particular illness perception may have a negative, positive, or mixed impact on health outcomes depending on the coping strategies that were used.[7] Combination of illness perceptions and coping strategies are numerous, which makes the interpretation of a single illness perception or coping strategy difficult. However, in general it is assumed that strong beliefs in severe '*consequences*', attributing many symptoms to an illness ('*illness identity*'), strong beliefs that the disease is chronic ('*timeline acute/chronic*'), and having negative emotions towards an illness ('*emotional representation*'), are associated with a worse health outcome; feeling a lot of control over the illness ('*personal control*' and '*treatment control*') and better understanding of the illness ('*illness coherence*') are associated with better health outcomes.[11] The mean scores of each subscale of the IPQ-R were analyzed.

The Coping with Rheumatic Stressors (CORS) questionnaire measures coping strategies used by patients and addresses the most important stressors of rheumatic diseases, namely pain, limitations, and dependence (see **Table 1**).[12, 13] Coping with pain is addressed by '*comforting cognitions'*, '*decreasing activities*', and '*diverting attention*'. '*Optimism*', '*pacing*', and '*creative solution seeking*' are covered by coping with limitations. Coping strategies that reflect coping with dependence are '*accepting*' and '*showing consideration*'. All items of each coping strategy were scored on Likert scales ranging from 1 (never/ seldom used) to 4 (very often used). Frequent use of a particular coping strategy is indicated by higher scores. Interpretation of a single coping strategy is difficult and hardly investigated but frequent use of '*decreasing activities*' for coping with pain or adapting the level of activity ('*pacing*') for coping with limitations seem to be associated with worse health outcomes in rheumatic diseases.[1, 14-16] Other coping strategies described by the CORS were thus far not found to be associated with health outcomes in literature. For each subscale of the CORS mean scores were analyzed.

It was assumed that measuring the impact of axSpA on generic quality of life, on work productivity, and on the participation in daily activities provides insight in the total burden of axSpA. The 36-item Short-Form Health Survey (SF-36) was used to assess HRQoL.[17] The eight subscale scores were recoded, recalibrated and transformed into scale scores ranging from 0 (worst health) to 100 (best health). Age- and gender-matched scores of each country were used to weight the scores. No Italian age- and gender-matched

scores were available, therefore Dutch weighted scores were used for these patients.[18, 19] Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were calculated, converted, and compared to the general population mean score of 50. Better HRQoL is indicated by higher PCS and MCS.[20]

The Work Productivity and Activity Impairment questionnaire (WPAI), general health version 1.0, was used to assess work productivity. Patients were asked to fill out questions about the amount of actually worked hours, amount of missed working hours due to axSpA, amount of missed working hours due to other reasons (e.g. holidays), and the impact of axSpA on work productivity and daily activities on an NRS from 0 (health problems had no effect on work) to 10 (health problems completely prevented working) in the past seven days. Work productivity loss (WPL, i.e. total work impairment due to axSpA) and activity impairment (i.e. total impact of axSpA on daily activities) summary scores were calculated on a scale from 0% (no work productivity loss/activity impairment) to 100% (total work productivity loss/activity impairment). Higher percentages indicate greater impairment.[21]

Table 1. Overview of illness perceptions and coping strategies measured by the IPQ-R and CORS questionnaires[9, 10, 12, 13]

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"*

Table 1. Continued

Label/Dimension	Explanation	Example
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"*
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 dependency		
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"*

CORS, Coping with Rheumatic Stressors; IPQ-R, Revised Illness Perception Questionnaire.

Statistical analysis

Continuous variables were presented as mean (standard deviation (SD)) and categorical variables as number (frequencies). Mixed linear models were run to investigate if each illness perception and coping strategy changed over 2 years taking into account the correlation between visits within patients. Median age and gender were tested for effect modification. Results were stratified for gender and age (median) when the interaction

term was statistically significant (p<0.10). P-values of <0.002 (p<0.05/21, corrected for multiple testing) of illness perceptions and coping strategies were considered to be statistically significant. Back pain, HRQoL, WPL, and activity impairment were also assessed for change over time by mixed linear models. STATA SE V.14 (Statacorp, Texas, USA) was used for data analysis.

RESULTS

A baseline and at least one follow-up visit at one year or two years was available for 193 axSpA patients. Forty-three patients were excluded from the analyses as they did not complete all questionnaires (IPQ-R n=16, CORS n=27). Of the 150 remaining patients, 94 had data on all visits, 36 had data at baseline and one year, and 20 had data at baseline and two years.

At baseline, patients had a mean (SD) age of 30.4 years (7.9), a mean symptom duration of 13.2 (6.9) months, about half of patients was female (51%), 65% of the patients was HLA-B27 positive, 27% had radiographic sacroiliitis, and 64% had sacroiliitis on MRI (**Table 2**). Baseline characteristics were similar for patients with one or two follow-up visits.

Baseline mean back pain (SD) was 4.0 (2.5), PCS was 28.8 (14.0), MCS was 46.6 (13.6), WPL was 34.1% (29.8), and activity impairment was 38.7% (27.9) (**Table 3**). Over two years, back pain (mean change (SD) -1.5 (2.2)) and activity impairment (-14.4% (27.2)) decreased clinically and statistically significantly, PCS (11.1 (13.3)) and WPL (-15.3% (28.7)) improved clinically and statistically significantly, while MCS did not change (0.7 (13.9)). At baseline, 39% of the patients had an ASDAS of <2.1 and at 2 years 68% of the patients had an ASDAS of <2.1, reflecting a situation of low disease activity.

Gender was found to be an effect modifier for the illness perception '*accident*' (interaction term p=0.015), for coping strategies '*pacing*' (p=0.004) and '*creative solution seeking*' (p=0.004), and median age was an effect modifier for illness perceptions '*identity*' (p=0.090) and '*acute/chronic timeline*' (p=0.077), which indicates that these illness perceptions and coping strategies differ between gender and age subgroups. Therefore, results were stratified for these factors (**Table 4**) and only small changes were found between these subgroups.

In contrast to disease activity parameters, illness perceptions and coping strategies showed minimal changes over time (**Table 4**). For example, after 2 years patients still had strong beliefs in severe consequences ('*consequences*', mean (SD) 2.8 (0.9)), had still strongly negative emotions towards their illness ('*emotional representation*', 2.5 (0.8)) and had still

strong beliefs in (bad) chance ('*chance*', 3.3 (1.2)) being the cause for axSpA.

Table 2. Baseline characteristics of axSpA patients in the SPACE cohort

	All patients	Patients with 2 follow-up visits	Patients with 1 follow-up visit
Baseline characteristics	**n=150**	**n=94**	**n=56**
Age in years, mean ± SD	30.4 ± 7.9	30.0 ± 7.9	31.2 ± 7.7
Female	77 (51)	48 (51)	29 (52)
Symptom duration in months, mean ± SD	13.2 ± 6.9	13.7 ± 6.7	12.4 ± 7.0
IBP	107 (71)	65 (69)	42 (75)
Good response to NSAIDs [a]	73 (49)	47 (51)	26 (46)
Uveitis	23 (15)	14 (15)	1 (16)
Psoriasis	35 (23)	22 (23)	13 (23)
IBD	14 (9)	8 (9)	6 (11)
Positive family history	71 (47)	41 (44)	30 (54)
Enthesitis (heel)	62 (41)	49 (52)	13 (23)
Dactylitis	23 (15)	18 (15)	5 (9)
Peripheral arthritis	43 (29)	30 (32)	13 (23)
HLA-B27 positivity	97 (65)	56 (60)	41 (75)
Elevated ESR (mm)/CRP (mg/L)	65 (43)	45 (48)	20 (36)
Sacroiliitis on X-rays (local)	40/148 (27)	25/93 (27)	15/55 (27)
Sacroiliitis on MRI (local)	94/147 (64)	62/92 (67)	32/55 (58)
Use of NSAIDs	119 (79)	76 (81)	43 (78)
Use of bDMARDs	5 (3)	5 (3)	0 (0)
Number of SpA features [b]**, mean ± SD**	3.4 ± 1.7	3.6 ± 1.8	3.2 ± 1.6

Results are presented as number (%) unless stated otherwise. [a] Back pain not present anymore or is much better 24–48 hours after a full dose of NSAID. [b] Excluding imaging and HLA-B27 positivity. CRP, C-reactive protein; DMARDs, disease modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; HLA-B27, Human Leucocyte Antigen B27; IBD, inflammatory bowel disease; IBP, inflammatory back pain; MRI, magnetic resonance imaging; NSAIDs, Non-Steroidal Anti-inflammatory Drugs; SpA, Spondyloarthritis; X-rays, radiography.

Patients most often coped with pain by putting pain into perspective ('*comforting cognitions*', mean 2.8, SD 0.6), most often coped with limitations by trying to be optimistic ('*optimism*', mean 2.9, SD 0.7), and most often coped with dependence of other people by considering the feelings of these people ('*consideration*', mean 2.7, SD 0.6) after 2 years. Similar results were found for patients with one or two follow-up visits (data not shown).

Table 3. Health outcomes over time in axSpA patients in the SPACE cohort

	Range	Baseline n=150	Year 1 n=130	Year 2 n=114	Change per year B (95%CI)
Back pain	0-10	4.0 (2.5)	3.1 (2.4)	2.5 (2.2)	**-0.8 (-1.0; -0.5)**
PCS	0-100	28.8 (14.0)	36.4 (14.3)	39.4 (12.4)	**5.4 (4.2; 6.6)**
MCS	0-100	46.6 (13.6)	47.9 (12.0)	47.8 (12.3)	0.7 (-0.4; 1.7)
WPL[a]	0-100	34.1 (29.8)	23.5 (27.1)	19.7 (24.1)	**-7.5 (-10.5; -4.5)**
Activity impairment	0-100	38.7 (27.9)	27.6 (25.9)	24.0 (23.1)	**-7.4 (-9.7; -5.2)**

Results are presented as mean (SD). Statistically significant results are printed in bold (p<0.05).
[a] Only patients who were employed at a time point are described; baseline n=111, 1 year n=103, 2 years n=94. PCS, Physical Component Summary; MCS, Mental Component Summary; WPL, Work Productivity Loss.

Table 4. Illness perceptions and coping over time in axSpA patients with baseline and/or 1- or 2 years data in the SPACE cohort (n=150)

Illness perceptions	Range	Baseline n=150	Year 1 n=130	Year 2 n=114	Change per year B (95%CI)
Identity	0-15				
Age <29 years		4.6 (2.3)	4.6 (2.5)	4.1 (2.0)	-0.3 (-0.5; 0.02)
Age ≥29 years		4.9 (2.6)	5.3 (2.8)	5.1 (2.7)	0.09 (-0.2; 0.4)
Consequences	1-5	2.9 (0.7)	2.8 (0.8)	2.8 (0.9)	-0.09 (-0.2; -0.03)
Timeline (acute/chronic)	1-5				
Age <29 years		3.7 (0.8)	3.7 (0.8)	3.7 (0.8)	0.05 (-0.06; 0.2)
*Age ≥29 years**		3.6 (0.8)	3.8 (0.8)	4.0 (0.7)	0.2 (0.08; 0.3)
Personal control	1-5	3.3 (0.6)	3.3 (0.6)	3.4 (0.6)	0.06 (0.008; 0.1)
Treatment control	1-5	3.5 (0.5)	3.4 (0.6)	3.5 (0.6)	0.01 (-0.04; 0.07)
Illness coherence*	1-5	3.3 (0.8)	3.5 (0.8)	3.6 (0.7)	0.2 (0.1; 0.2)
Timeline (cyclical)	1-5	3.6 (0.8)	3.6 (0.8)	3.6 (0.8)	-0.04 (-0.1; 0.04)
Emotional representation*	1-5	2.7 (0.8)	2.6 (0.8)	2.5 (0.8)	-0.1 (-0.2; -0.08)
Possible causes for illness					
Psychological attributions	1-5	2.1 (0.9)	2.1 (0.9)	2.1 (0.9)	-0.005 (-0.06; 0.05)
Risk factors	1-5	2.2 (0.6)	2.2 (0.6)	2.1 (0.6)	-0.01 (-0.06; 0.03)
Immunity	1-5	2.3 (0.8)	2.4 (0.9)	2.3 (0.9)	-0.03 (-0.1; 0.04)
Accident	1-5				
Male		2.3 (1.2)	2.1 (1.1)	2.0 (1.1)	-0.2 (-0.3; -0.04)
Female		1.8 (1.0)	2.1 (1.2)	1.9 (1.1)	0.07 (-0.07; 0.2)
Chance	1-5	3.3 (1.2)	3.2 (1.2)	3.3 (1.2)	-0.02 (-0.1; 0.08)

Table 4. Continued

Coping strategies	Range	Baseline n=150	Year 1 n=130	Year 2 n=114	Change per year B (95%CI)
Coping with pain					
Comforting cognitions	1-4	2.8 (0.6)	2.9 (0.6)	2.8 (0.6)	0.01 (-0.04; 0.06)
Decreasing activities	1-4	2.1 (0.6)	2.1 (0.6)	2.0 (0.6)	-0.05 (-0.1; -0.008)
Diverting attention	1-4	2.3 (0.6)	2.4 (0.6)	2.4 (0.6)	0.03 (-0.02; 0.07)
Coping with limitations					
Optimism	1-4	2.8 (0.7)	2.9 (0.7)	2.9 (0.7)	0.08 (0.02; 0.1)
Pacing	1-4				
Male		2.1 (0.6)	2.1 (0.6)	2.0 (0.6)	-0.05 (-0.1; 0.006)
Female		2.2 (0.6)	2.3 (0.6)	2.4 (0.6)	0.08 (0.007; 0.2)
Creative solution seeking	1-4				
Male		2.3 (0.6)	2.4 (0.6)	2.3 (0.07)	0.01 (-0.05; 0.07)
*Female**		2.3 (0.6)	2.4 (0.6)	2.6 (0.06)	0.1 (0.07; 0.2)
Coping with dependency					
Accepting	1-4	1.8 (0.6)	1.8 (0.6)	1.7 (0.6)	-0.03 (-0.09; 0.02)
Consideration	1-4	2.7 (0.6)	2.7 (0.6)	2.7 (0.6)	0.004 (-0.05; 0.06)

Results are presented as mean (SD) unless stated otherwise. *Changes in illness perceptions and coping strategies were considered to be statistically significant when p<0.002 (p<0.05/21, correction for multiple testing).

DISCUSSION

Over two years, back pain intensity decreased over time, HRQoL improved, and WPL and activity impairment decreased. Thus, a general conclusion of improved disease activity is more than justified. However, patients' illness perceptions and coping strategies proved to be remarkably stable. Female and male patients and younger and older patients did not markedly differ in this regard. As illness perceptions did not change over time, patients remained having illness perceptions that had a negative impact on the association between back pain and health outcomes as shown in the previous study.[1]

It is often assumed that in the first period after a diagnosis changes in illness perceptions may take place and during a late phase of the disease it might be more difficult to change illness perceptions.[22, 23] Hagger et al (2017) also hypothesized that illness perceptions and coping strategies change between an early and late disease phase. It is thought that patients in an early disease phase perceive an illness as a health threat. Patients therefore form illness perceptions which are reflecting a negative emotional state (e.g. having strong

beliefs in '*consequences*', and having strong negative emotions towards their illness, '*emotional representation*', which may lead to more passive coping strategies. Over time, patients gain more experience with their disease and treatment and form other illness perceptions such as more '*illness coherence*' (understanding their illness better) which may lead to more active coping strategies.[7]

Others believe that illness perceptions are already formed before patients are seen by a physician. In fact, one of the consequences of forming these illness perceptions is seeking care. The medical information that patients receive from their physicians will be assessed in the context of previously gathered information and integrated in such a way that it fits into a patient's view of life.[24] This in turn suggests that once formed, illness perceptions and chosen coping strategies are less susceptible to change when patients are seeking care of their physician.

These theories are contradicting theories and unfortunately data on illness perceptions and coping strategies in axSpA is scarce. The only longitudinal study among patients with longstanding r-axSpA suggested that coping strategies did change over 4-years' time.[6] However, this study only showed numerically small changes in coping strategies. For example, the mean (SD) increase in score for coping with pain by using decreasing activities was only 0.77 (4.6) on a scale from 8 to 32. Moreover, the changes in coping strategies were not related to changes in pain nor in physical functioning, which is compatible with the vision that coping strategies are not susceptible for changes in disease status, and are in line with our findings in a much earlier phase of the disease. Other observational studies also reported that illness perceptions and coping strategies remained relatively stable over time among patients with various diseases including other rheumatic diseases and chronic low back pain.[4, 5, 25-30]

In contrast, randomized controlled trials seem to suggest that illness perceptions can actually be changed. These trials showed that illness perceptions changed after being specifically targeted by an intervention such as a group education program or cognitive behavioral therapy among patients with other diseases (e.g. asthma, diabetes).[31-39] One study in patients with myocardial infarction even claimed that by changing illness perceptions patients could return to work sooner than the patients who did not receive the intervention.[32] Another study in chronic back pain patients also reported that patients who received an intervention (i.e. providing information based on patients' illness perceptions) changed their illness perceptions to a greater extent than patients who received usual care.[40]

At this moment it remains unclear if illness perceptions and coping strategies change

spontaneously or can be targeted by an intentional intervention. Furthermore, no data are available on clinically important changes in illness perceptions or coping strategies which makes it difficult to assess whether changes are truly relevant changes.

In the current study no clinically relevant differences in illness perceptions and coping strategies were found by gender or age, while in literature differences were found in illness perceptions and coping strategies between males and females in other diseases.[41, 42] In patients with r-axSpA, higher age was associated with more frequent use of '*pacing*' in order to cope with limitations.[6] This could not be confirmed in the current study.

A limitation of this study is that we were not able to investigate why illness perceptions and coping strategies remained relatively stable while back pain and health outcomes showed substantial improvements. We do not expect that the impact of illness perceptions and coping strategies differ over time, as health outcomes are still substantially impacted and not comparable to the general population after two years even though they have improved. This suggests that health outcomes are still under the influence of illness perceptions and coping strategies and that health outcomes can be further improved by targeting unfavorable illness perceptions and coping strategies. A randomized controlled trial might be conducted comparing usual care with usual care plus an additional intervention targeting negative illness perceptions in order to investigate if illness perceptions change if they are targeted and if a change in illness perceptions is related to a change in health outcomes. It is important to not only target negative illness perceptions but to target also coping strategies as illness perceptions are known to influence the usage of coping strategies.[7]

In summary, our results suggest that illness perceptions and coping strategies are rather independent of variation (decrease) in disease status. It is unclear if illness perceptions and coping strategies could be improved by specific therapeutic interventions in patients with axSpA and if an improvement in illness perceptions is associated with an improvement in health outcomes.

REFERENCES

1. van Lunteren M, Scharloo M, Ez-Zaitouni Z, et al. The impact of illness perceptions and coping on the association between back pain and health outcomes in patients suspected of axial spondyloarthritis: data from the SPACE cohort. *Arthritis Care Res* 2018;70:1829-39.
2. 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.
3. Gåfvels C, Hägerström 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. Moss-Morris R, Weinman J, Petrie K, et al. The Revised Illness Perception Questionnaire (IPQ-R). *Psychol Health* 2002;17:1-16.
11. Hagger MS, Orbell S. A meta-analytical review of the common-sense model of illness representations. *Psychol Health* 2003;18:141-84.
12. van Lankveld W, Näring G, van der Staak C, et al. Development of the CORS: coping with rheumatic stressors. *Gedrag Gezond* 1993;21:40-8.
13. 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.
14. 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.
15. 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.
16. Liu R, Damman W, Kaptein AA, et al. Coping styles and disability in patients with hand osteoarthritis. *Rheumatology* 2016;55:411-8.
17. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
18. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055-68.
19. Loge JH, Kaasa S. Short form 36 (SF-36) health survey: normative data from the general Norwegian population. *Scand J Soc Med* 1998;26:250-8.
20. Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. *Qual Life Res* 2001;10:405-13.
21. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353-65.
22. Rutter CL, Rutter DR. Longitudinal analysis of the illness representation model in patients with irritable bowel syndrome (IBS). *J Health Psychol* 2007;12:141-8.
23. Lawson VL, Bundy C, Harvey JN. The development of personal models of diabetes in the first 2 years after diagnosis: a prospective longitudinal study. *Diabet Med* 2008;25:482-90.

24. Benyamini Y. Health and Illness Perceptions. In: Friedman HS, editor. The Oxford Handbook of Health Psychology. New York, United States. *Oxford University Press Inc* 2011:290-2.
25. Foster NE, Bishop A, Thomas E, et al. Illness perceptions of low back pain patients in primary care: what are they, do they change and are they associated with outcome? *Pain* 2008;136:177-87.
26. Fischer M, Scharloo M, Abbink J, et al. The dynamics of illness perceptions: testing assumptions of Leventhal's common-sense model in a pulmonary rehabilitation setting. *Br J Health Psychol* 2010;15:887-903.
27. De Gucht V, Garcia FK, den Engelsman M, Maes S. Do changes in illness perceptions, physical activity, and behavioural regulation influence fatigue severity and health-related outcomes in CFS patients? *J Psychosom Res* 2017;95:55-61.
28. Johansson AC, Brink E, Cliffordson C, Axelsson M. The function of fatigue and illness perceptions as mediators between self-efficacy and health-related quality of life during the first year after surgery in persons treated for colorectal cancer. *J Clin Nurs* 2018;27:e1537-48.
29. McCorry NK, Dempster M, Quinn J, et al. Illness perception clusters at diagnosis predict psychological distress among women with breast cancer at 6 months post diagnosis. *Psychooncology* 2013;22:692-8.
30. van Lankveld W, Näring G, van 't Pad Bosch P, van de Putte L. The negative effect of decreasing the level of activity in coping with pain in rheumatoid arthritis: an increase in psychological distress and disease impact. *J Behav Med* 2000;23:377-91.
31. Broadbent E, Ellis CJ, Thomas J, et al. Can an illness perception intervention reduce illness anxiety in spouses of myocardial infarction patients? A randomized controlled trial. *J Psychosom Res* 2009;67:11-5.
32. Broadbent E, Ellis CJ, Thomas J, et al. Further development of an illness perception intervention for myocardial infarction patients: a randomized controlled trial. *J Psychosom Res* 2009;67:17-23.
33. Broadbent E, Leggat A, McLachlan A, Kerr A. Providing cardiovascular risk management information to acute coronary syndrome patients: a randomized trial. *Br J Health Psychol* 2013;18:83-96.
34. Jonsbu E, Martinsen EW, Morken G, et al. Change and impact of illness perceptions among patients with non-cardiac chest pain or benign palpitations following three sessions of CBT. *Behav Cogn Psychother* 2013;41:398-407.
35. Keogh KM, Smith SM, White P, et al. Psychological family intervention for poorly controlled type 2 diabetes. *Am J Manag Care* 2011;17:105-13.
36. Petrie KJ, Perry K, Broadbent E, Weinman J. A text message programme designed to modify patients' illness and treatment beliefs improves self-reported adherence to asthma preventer medication. *Br J Health Psychol* 2012;17:74-84.
37. Rees G, Lamoureux EL, Nicolaou TE, et al. Feedback of personal retinal images appears to have a motivational impact in people with non-proliferative diabetic retinopathy and suboptimal HbA1c: findings of a pilot study. *Diabet Med* 2013;30:1122-5.
38. Davies MJ, Heller S, Skinner TC, et al. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. *BMJ* 2008;336:491-5.
39. Petrie KJ, Cameron LD, Ellis CJ, et al. Changing illness perceptions after myocardial infarction: an early intervention randomized controlled trial. *Psychosom Med* 2002;64:580-6.
40. Glattacker M, Heyduck K, Meffert C. Illness beliefs, treatment beliefs and information needs as starting points for patient information--evaluation of an intervention for patients with chronic back pain. *Patient Educ Couns* 2012;86:378-89.
41. Tamres LK, Janicki D, Helgeson VS. Sex Differences in Coping Behavior: A Meta-Analytic Review and an Examination of Relative Coping. *Pers Soc Psychol Rev* 2002;6:2-30.
42. Petrie KJ, Jago LA, Devcich DA. The role of illness perceptions in patients with medical conditions. *Curr Opin Psychiatry* 2007;20:163-7.

Chapter 8

Summary and General Discussion

In this final chapter, the most important findings of the studies presented in this thesis are summarized, placed in a broader perspective, and possibilities for future research are discussed grouped by three themes. The three themes are: the value of a positive family history of spondyloarthritis (SpA), the impact of axial SpA (axSpA) on health outcomes in the early phase of axSpA, and illness perceptions and coping strategies of patients with axSpA.

The studies presented in this thesis were performed using data from three cohorts of patients suspected of axSpA with (inflammatory) back pain ≥ 3 months: the worldwide Assessment in SpondyloArthritis international Society (ASAS) cohort[1-3] which included patients with a back pain onset < 45 years, the French DEvenir des Spondyloarthropathies Indifférenciées Récentes (DESIR) cohort[4] which included patients aged between 18-50 years with inflammatory back pain persisting < 3 years, and the European SPondyloArthritis Caught Early (SPACE) cohort[5] which included patients aged ≥ 16 years with back pain persisting ≤ 2 years and an onset of back pain < 45 years.

The ASAS defined a positive family history of SpA as a documented history of radiographic axSpA, but also of uveitis, psoriasis, inflammatory bowel disease (IBD), or reactive arthritis in first- or second-degree relatives.[3] In the early 1990s a positive family history was introduced as a feature in classification criteria for axSpA patients in the Amor and ESSG criteria and nowadays it is part of the widely used ASAS classification criteria. Although these classification criteria for axSpA were extensively tested and validated, it is quite striking that the definition of a positive family history was never tested nor validated before it was being used in any of the classification criteria. This definition is simply based on consensus of experts. However, it is apparently regarded as useful for identifying patients with axSpA as experts support this definition and the definition has remained essentially unchanged in the last 30 years.

In **Chapter 2** we studied the value of various aspects of this definition in identifying patients who are human leukocyte antigen-B27 (HLA-B27) positive and therefore have an increased risk of axSpA. In the ASAS cohort, a worldwide cohort of patients suspected of axSpA, only a positive family history of axSpA could be used to identify patients who are HLA-B27 positive, while a positive family history of uveitis, reactive arthritis, IBD, and psoriasis were not useful in this regard. Similar results were found irrespective of ethnicity or in the presence of a positive family history in first- or second-degree family members.

These findings were also confirmed in the DESIR and SPACE cohorts investigated by Ez-Zaitouni et al (2018)[6], but in addition to a positive family history of axSpA in this study they reported that a positive family history of uveitis was also associated with HLA-B27

positivity. However, if a choice can be made testing the HLA-B27 status is preferred as HLA-B27 positivity has a higher positive predictive value than a positive family history as referral tool to secondary care for patients suspected of axSpA.[7, 8]

The potentially added value of a positive family history in diagnosing axSpA when the HLA-B27 status is already known was assessed in **Chapter 3**. Three definitions of a positive family history were tested; the current ASAS definition of a positive family history for SpA (including all five diseases), a positive family history for radiographic axSpA, and a positive family history for uveitis. A positive family history is common among patients suspected of axSpA as one-third of the patients had a positive family history in all three cohorts in **Chapter 3**. We showed that when HLA-B27 status was known none of the three definitions of a positive family history was associated with a diagnosis of axSpA anymore in patients with different ethnical backgrounds. We found that HLA-B27 negative familial axSpA exists but is relatively rare and that even in absence of HLA-B27 positivity a positive family history did not contribute to an axSpA diagnosis. Thus, a positive family history of SpA has a limited value in diagnosing axSpA when HLA-B27 status is known.

The results of **Chapters 2** and **3** have implications for the use of the criterion 'positive family history'. When broad HLA-B27 testing is not useful (e.g. in general practice because of too low prevalence of SpA), the presence of a positive family history of axSpA and a positive family history of uveitis in first- and second-degree family members can to some extent be used to predict HLA-B27 positivity in patients suspected of axSpA as demonstrated in **Chapter 2** and the study by Ez-Zaitouni et al (2018). However, it is important to realize that a positive family history is usually reported by patients themselves and the validity of such a report is often at stake for obvious reasons. Moreover, a substantial number of patients with HLA-B27 positive axSpA do not have a positive family history. When diagnosing patients suspected of axSpA, **Chapter 3** suggests that rheumatologists should rather not give extra weight to a positive family history when a patient's HLA-B27 status is already known.

Our findings from **Chapter 3** could have also implications for classifying axSpA patients. Since the introduction of the ASAS classification criteria there have been concerns about the criteria for various reasons. For example, there have been concerns that the clinical arm might not have sufficient sensitivity and specificity. At this moment, a positive family history is one of the SpA features in the ASAS classification criteria for axSpA and in these criteria a positive family history has an independent contribution on top of HLA-B27 positivity. **Chapter 3** raises questions about the relative weight of a positive family history in the ASAS classification criteria for axSpA. The performance of the ASAS classification criteria for axSpA is currently re-evaluated in a worldwide prospective cohort, named the

CLassification of Axial Spondyloarthritis Inception Cohort (CLASSIC) study. Refinements of the criteria may be proposed and tested if the current ASAS classification criteria for axSpA do not meet a sufficiently high level of specificity (≥90%) while preserving sensitivity of ≥75%. This setting is appropriate to test if the criterion 'positive family history' is redundant and should be removed from these classification criteria, reweighted, or combined with the criterion HLA-B27 positivity. These options could be considered while preserving a similar level of specificity and sensitivity as set out in the analysis plan of the CLASSIC study and obtained with the original ASAS classification criteria for axSpA when using the rheumatologist's diagnosis as external standard.

The definition of a positive family history for SpA according to ASAS might be questioned as only a positive family history of axSpA and a positive family history of uveitis were associated with HLA-B27 carriership. This indicates that the associations between a positive family history (of all five diseases) and HLA-B27 carriership are mostly driven by a positive family history of axSpA and a positive family history of uveitis. Therefore, limiting the ASAS definition of a positive family history for SpA into a positive family history of axSpA and/or uveitis may be considered.

In our study, the majority of the analysed patients had a white or Asian ethnicity, the two largest axSpA populations worldwide.[9] However, there was an under-representation of patients with for example an African or Arabic ethnicity. Moreover, other ethnicities than a white or Asian ethnicity are also hardy addressed in existing literature. Therefore, it would be recommended to address also other ethnicities in future studies. It might be difficult to replicate our findings in populations in which the prevalence of HLA-B27 is low or virtually absent, such as in Arabic and African black populations.[10, 11]

The studies in **Chapters 2** and **3** investigated patients with predominantly axial symptoms and not patients with predominantly peripheral symptoms. Future research could further investigate the value of a positive family history among patients with or at risk of peripheral disease, as currently the same definition of a positive family history is used for both axial and peripheral SpA. Different definitions of a positive family history for axial and peripheral SpA might be necessary as for example psoriasis might be more relevant for patients with peripheral disease.[12]

The previous part discussed how the identification of patients at risk of axSpA could be improved. This is important as patients could be treated earlier if we are able to better identify patients. The earlier patients with axSpA are treated, the earlier the burden of disease could be reduced. Moreover, the course of the disease could possibly be influenced by a timelier treatment. However, the disease burden in an early phase of

axSpA is not well investigated. We studied the disease burden of early axSpA by measuring the impact of axSpA on quality of life, work productivity, and participation in daily activities. In **Chapters 4** and **5** we assessed and quantified the impact of disease activity on Health-Related Quality of Life (HRQoL) and work productivity over time in patients with early axSpA. We also assessed if the impact is similar in prognostically relevant subgroups. The impact of axSpA on work productivity was assessed by four variables; absenteeism, presenteeism, work productivity loss, and activity impairment. Absenteeism represents the working hours lost due to axSpA (i.e. sick leave), presenteeism represents the decreased performance at work due to the axSpA (i.e. inefficiency at work), work productivity loss is a summary measure representing the total work impairment due to axSpA, and activity impairment represents the impairment in daily activities outside work due to axSpA.

Chapters 4 and **5** demonstrate that physical HRQoL, work productivity, and daily activities are seriously impacted even in the earliest phase of the axSpA and are as substantially impacted as longstanding axSpA. Disease activity decreased over time, which was associated with improvements in physical HRQoL, work productivity, and daily activities. Nevertheless, the burden of early axSpA remained substantial over time despite these improvements. The mental HRQoL was comparable to the general population and remained stable over time. These chapters show that there is still a lot of room of improvement to decrease the burden of early disease further.

Gender and job-type defined important prognostically relevant subgroups when considering HRQoL as outcome in **Chapter 4**; the same level of disease activity had less impact on physical HRQoL in women and white-collar workers. When considering work productivity as outcome in **Chapter 5**, the duration of chronic back pain and start of medication use defined important prognostically relevant subgroups; an improvement in disease activity was associated with less absenteeism over one year only in patients with the shortest duration of chronic back pain and in patients who started treatment. The impact of disease activity on other work outcomes (work productivity loss, presenteeism, and activity impairment) remained similar between patients with the shortest vs. the longest duration of chronic back pain or with no change vs. started any treatment.-

Chapters 4 and **5** demonstrate that the burden of axSpA remains substantial over time even in an early disease phase. It is therefore important to further decrease this burden, as axSpA does not only affect patients with axSpA, but also their friends, family and society. About one-fifth of the patients with radiographic axSpA (r-axSpA) needed help from friends and family.[13] Partners of patients with r-axSpA also experienced impairments in their HRQoL compared to healthy controls and partners experienced difficulties with managing axSpA from limitations in leisure time activities to altered relational roles.[14, 15] Moreover,

the financial burden is also substantial in axSpA. Patients and society are affected by significant costs associated with medication, expenses by the health care provider for medical services, and non-health care costs (e.g. help in household) but also by indirect costs such as loss of work productivity and work disability.[16-18] In a large European study nearly half of the axSpA patients took their disease into account in their career choices, nearly three-fourth of the patients had difficulties with finding a job due to axSpA and more than 40% of the patients required adaptations of their work place.[19] It has even been suggested that the costs related to the impairment in work productivity are the largest financial burden.[17] As axSpA affects patients in their early adult and working life, patients but also society will experience the impact of axSpA for many years which could lead to an excessive burden of axSpA on long-term. For example, leaving the work force was predicted by prior absenteeism and absenteeism was predicted by prior presenteeism among patients with early axSpA.[20] This suggests that it is important to treat axSpA early, to strive for less impairment in work and daily life by axSpA, and possibly by providing support to partners of patients with axSpA. The European League Against Rheumatism (EULAR) indeed already recommends that in disease management individual, medical and societal costs including work productivity should be taken into account.[21]

A promising way for further decreasing the burden of (early) axSpA might be treat-to-target (T2T). Treatment of for example rheumatoid arthritis (RA) has been improved by both the development of biologics but also by aggressive T2T strategies. However, axSpA is a more heterogeneous disease and the natural disease course of axSpA may be more variable than RA. Recently, an international task force of experts published recommendations for T2T in axSpA but this task force also acknowledged that evidence is limited and more knowledge of the association between disease activity and health outcomes is necessary.[22] Our findings in **Chapter 4** and **5** support the hypothesis of T2T that T2T should aim for lower disease activity in patients with axSpA in order to maximize HRQoL and social participation over time and support the recommendation that the preferred treatment target of T2T should be clinical remission or low disease activity. Our findings demonstrate also that it is important to intervene already in an early disease phase. At this moment, one clinical trial among axSpA patients is conducted aiming at improving health outcomes by using T2T strategies in order to achieve clinical remission or low disease activity (e.g. TICOSPA NCT03043846). The trial results will provide more insight in the feasibility and cost-effectiveness in treating axSpA by a T2T strategy compared to usual care.

Moreover, the focus should not only be on T2T strategies. To date, pharmacological treatment does not completely resolve impairments in work and quality of life and a substantial unmet need for additional treatment options remains. Other factors such as

illness perceptions and coping strategies which might also impact these health outcomes are investigated in **Chapters 6** and **7**, discussed in the third part.

In clinical practice, it would be useful to be able to identify patients at a high risk of serious impairments in HRQoL or work productivity. However, it difficult to identify these patients as knowledge is limited regarding the association between disease activity and work productivity and HRQoL. In **Chapters 4** and **5** several factors have been found for defining clinically important subgroups based on gender, job type, duration of chronic back pain, start of medication use. However, it might be better to consider several factors together in defining these subgroups to better identify patients at a high risk of impairments in work and daily life. This is often not possible due to relatively small sample sizes of a subgroups considering only one of these factors, such as in **Chapters 4** and **5**. Disease trajectories describe patterns of disease activity over time and help to identify subgroups of patients which could be used for a more individualised treatment.[23] Future research could use disease trajectories in exploring which factors form clinically relevant subgroups in the association between disease activity and health outcomes and taking several of these factors into account at the same time.

Of note, work productivity loss is a patient reported outcome, consisting of absenteeism and presenteeism. It might be better to measure absenteeism by using records for employers as patients might underestimate the amount of sick leave. However, work productivity loss is mostly driven by presenteeism and the best way to measure this is by asking patients about their presenteeism as this is difficult to objectively measure. In **Chapter 4** a generic questionnaire was used to measure the HRQoL. One could argue that a disease-specific questionnaire would be more suited to measure HRQoL as generic questionnaires might underestimate the HRQoL by having no questions that are disease-specific or being adapted to the disease. However, with a generic questionnaire it is possible to make a comparison between the patients with the disease and the general population showing how large the burden of disease is.

As discussed as above, health outcomes are not only affected by biomedical factors but also by contextual factors such as illness perceptions and coping strategies.[24] 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 is described by a theoretical model, the Leventhal's Common Sense Model of self-regulation (CSM).[25] In the CSM 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. As a response to these illness perceptions, coping strategies

are developed. Coping strategies are cognitive and behavioural strategies and help patients to manage stress associated with having to live with their illness.[25, 26]

In **Chapter 6** we investigated if illness perceptions and coping strategies influenced the association between back pain and health outcomes in patients with axSpA (or a suspicion thereof). **Chapter 6** demonstrates that the association between increasing self-reported back pain intensity and worsening of HRQoL and work productivity loss is substantially impacted by negative illness perceptions. A similar level of back pain intensity was associated with more impairment in physical HRQoL when patients had negative illness perceptions such as belief in severe consequences due to the illness ('*consequences*') and beliefs in chance as a cause for their illness ('*chance*'). When patients attributed more symptoms to their illness ('*identity*'), had strong negative emotions towards their illness ('*emotional representation*'), and had strong beliefs in psychological attributions as a cause such as thinking about life negatively ('*psychological attributions'*) a similar level of back pain was associated with more impairment in mental HRQoL. A similar level of back pain was related to more work productivity loss when patients had strong beliefs in severe '*consequences*'. We did not find such an impact by coping strategies.

Health outcomes might be improved by influencing illness perceptions in a positive manner and possibly by interfering with coping strategy choices. As a first step in investigating this hypothesis we investigated in **Chapter 7** if illness perceptions and usage of particular coping strategies are susceptible to changes in disease status or remain stable over time. **Chapter 7** showed that whilst back pain, disease activity, and health outcomes clearly improved over 2 years in patients recently diagnosed with axSpA, illness perceptions and coping strategies remained remarkably stable.

Chapter 6 suggests that illness perceptions might be considered in the treatment of patients with axSpA in addition to existing treatment options when aiming to (further) improve health outcomes. Although we did not find that coping strategies impacted the association between back pain and health outcomes in **Chapter 6**, coping strategies should not be excluded. According to the CSM illness perceptions influence the usage of coping strategies and illness perceptions could be adapted based on if health outcomes improve or diminish by the impact of coping strategies due to feedback loops.[25, 26] Therefore, it is important to consider illness perceptions and related coping strategies jointly and not separately in both research and treatment.[26] Unfortunately, studies have often investigated illness perceptions and coping strategies separately and at one point in time. More steps need to be taken before the hypothesis could be confirmed that influencing illness perceptions and interfering with related coping strategies in a positive manner could be used to improve health outcomes in axSpA.

The results of **Chapter 7** suggest that illness perceptions and coping strategies do not change spontaneously and are rather independent of a decrease in disease status in patients with early axSpA. Our findings are in line with other observational studies among patients with other diseases including rheumatic disease and the only other study among patients with (longstanding r-)axSpA.[27-35] Nevertheless, randomized controlled trials showed that illness perceptions changed after being specifically targeted by an intervention such as a cognitive behavioral therapy or a group education program among patients with other diseases including diabetes.[36-45] This suggest that illness perceptions and related coping strategies might be improved in patients with axSpA when they are targeted by specific therapeutic interventions.

The next step would be performing a randomized controlled trial which compares usual care with usual care plus an additional intervention targeting negative illness perceptions and related coping strategies. Based on **Chapter 6** the following illness perceptions form possible targets for this intervention; '*consequences*', '*chance*', '*emotional representation*', '*identity*', and '*psychological attributions*'. Possibly the use of the coping strategies '*decreasing activities*' and '*pacing*' could be discouraged as these coping strategies were negatively associated to physical HRQoL in **Chapter 6**. The choice for the type of intervention could be based on a comparison of the results of interventions performed in other randomized controlled trials, the feasibility of these interventions, and consulting experts in the field of psychological interventions.

Another step would be to determine when changes in illness perceptions and coping strategies are truly relevant changes. This is difficult to assess because no data are available on clinically important changes in illness perceptions and coping strategies. Future research could focus on defining minimally clinically important differences. However, a particular illness perception may have a negative, positive, or mixed impact on health outcomes depending on which coping strategies are used. This makes the interpretation of a single illness perception or coping strategy difficult as the combination of illness perceptions and coping strategies are numerous. Mediation analyses might be used to reveal the most commonly used pathways and show all direct and indirect effects of illness perceptions and coping strategies.

Furthermore, it would be interesting to investigate if patients in an early disease phase differ in illness perceptions and coping strategies from patients with longstanding disease. It is important to explore illness perceptions and coping strategies in these disease phases as different treatment strategies might be necessary or illness perceptions and coping strategies might be more susceptible to change in a certain disease phase. It has been hypothesized that over time patients gain more experience with their illness and

treatment which could lead to different illness perceptions and coping strategies.[26] It has also been hypothesized that illness perceptions mainly change in the initial period after a diagnosis and in a late phase of the disease it might be more difficult to change these illness perceptions.[46, 47] However, other theories assume that illness perceptions and coping strategies are not susceptible to change anymore once illness perceptions have been formed and coping strategies have been chosen, which may have taken place already before patients are seeking medical care for their complaints.[48]

The only study which investigated the association between illness perceptions and HRQoL among patients with longstanding axSpA, using the brief version of the questionnaire in **Chapter 6**, suggests that illness perceptions might differ between early and longstanding axSpA. This study found that having more concerns, part of the '*emotional representation*' of the illness[49], was associated with worsening of the physical HRQoL[50] while in **Chapter 6** the illness perceptions '*consequences*' and '*chance*' were associated with decreased physical HRQoL. This suggest that other illness perceptions might become more important in a later disease stage. However, coping strategies do not seem to differ between early and late phases of the disease. We found that '*decreasing activities*' and '*pacing*' were often used by patients with early axSpA and another study also showed that '*pacing*' was often used as a coping strategy among patients with longstanding axSpA.[27] Future research may address if illness perceptions and coping strategies differ between early and late phases of the disease by comparing patients with a short symptom duration to patients with longstanding disease. This is important to investigate, because different treatment strategies might be used for patients in an early vs. longstanding disease phase.

Concluding remarks

In summary, the studies reported in this thesis have brought us more knowledge for better identifying patients with axSpA, more insight in the impact of early axSpA on health outcomes, and more knowledge of illness perceptions and the use of coping strategies in patients with axSpA. Better knowledge and insights could help us in making a timely diagnosis, providing treatment sooner, and exploring additional treatment options, which in turn could hopefully reduce the burden of axSpA.

Based on this thesis, future axSpA research should focus on investigating the relative weight of a positive family history in classifying patients, investigating patients with other ethnicities than white or Asian ethnicity, and investigating how the burden of axSpA could be decreased. Possibly, T2T strategies could be used to improve health outcomes among patients with axSpA. Another promising way, which needs extensive research, could be influencing illness perceptions and coping strategies by targeted therapeutic interventions to decrease the impact of axSpA on health outcomes. These are both challenging and exiting times as for early axSpA only the tip of the iceberg has been revealed and underwater more is waiting to be revealed.

REFERENCES

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. Sieper J, Srinivasan S, Zamani O, et al. Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study. *Ann Rheum Dis* 2013;72:1621-7.
8. Poddubnyy D, Vahldiek J, Spiller I, et al. Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care. *J Rheumatol* 2011;38:2452-60.
9. Dean LE, Jones GT, MacDonald AG, et al. Global prevalence of ankylosing spondylitis. *Rheumatology* 2014;53:650-7.
10. Mustafa KN, Hammoudeh M, Khan MA. HLA-B27 Prevalence in Arab Populations and Among Patients with Ankylosing Spondylitis. *J Rheumatol* 2012;39:1675-7.
11. Khan MA. HLA-B27 and its subtypes in world populations. *Curr Opin Rheumatol* 1995;7:263-9.
12. Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011;70:25-31.
13. Boonen A. A review of work-participation, cost-of-illness and cost-effectiveness studies in ankylosing spondylitis. *Nat Clin Pract Rheumatol* 2006;2:546-53.
14. Uludag M, Unalan H, Tuzun S, et al. Assessment of quality of life and depression in spouses of patients with ankylosing spondylitis. *Rheumatol Int* 2012;32:3511-6.
15. Raybone K, Family H, Sengupta R, Jordan A. (Un)Spoken realities of living with axial spondyloarthritis: a qualitative study focused on couple experiences. *BMJ Open* 2019;9:e025261.
16. Boonen A, Brinkhuizen T, Landewé R, et al. Impact of ankylosing spondylitis on sick leave, presenteeism and unpaid productivity, and estimation of the societal cost. *Ann Rheum Dis* 2010;69:1123-8.
17. Franke LC, Ament AJ, van de Laar MA, et al. Cost-of-illness of rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol* 2009;27:S118-23.
18. Boonen A, van der Linden SM. The burden of ankylosing spondylitis. *J Rheumatol Suppl* 2006;78:4-11.
19. Garrido-Cumbrera M, Poddubnyy D, Gossec L, et al. The European Map of Axial Spondyloarthritis: Capturing the Patient Perspective-an Analysis of 2846 Patients Across 13 Countries. *Curr Rheumatol Rep* 2019;21:19.
20. Macfarlane GJ, Shim J, Jones GT, et al. Identifying Persons with Axial Spondyloarthritis At Risk of Poor Work Outcome: Results from the British Society for Rheumatology Biologics Register. *J Rheumatol* 2019;46:145-52.
21. 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.
22. 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.
23. 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;76:1036-1041.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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;57:2190-2199.
30. Foster NE, Bishop A, Thomas E, et al. Illness perceptions of low back pain patients in primary care: what are they, do they change and are they associated with outcome? *Pain* 2008;136:177-87.
31. Fischer M, Scharloo M, Abbink J, et al. The dynamics of illness perceptions: testing assumptions of Leventhal's common-sense model in a pulmonary rehabilitation setting. *Br J Health Psychol* 2010;15:887-903.
32. De Gucht V, Garcia FK, den Engelsman M, Maes S. Do changes in illness perceptions, physical activity, and behavioural regulation influence fatigue severity and health-related outcomes in CFS patients? *J Psychosom Research.* 2017;95:55-61.
33. Johansson AC, Brink E, Cliffordson C, Axelsson M. The function of fatigue and illness perceptions as mediators between self-efficacy and health-related quality of life during the first year after surgery in persons treated for colorectal cancer. *J Clin Nurs* 2018;27:e1537-e48.
34. McCorry NK, Dempster M, Quinn J, et al. Illness perception clusters at diagnosis predict psychological distress among women with breast cancer at 6 months post diagnosis. *Psychooncology* 2013;22:692-8.
35. van Lankveld W, Naring G, van't Pad Bosch P, van de Putte L. The negative effect of decreasing the level of activity in coping with pain in rheumatoid arthritis: an increase in psychological distress and disease impact. *J Behav Med* 2000;23:377-91.
36. Glattacker M, Heyduck K, Meffert C. Illness beliefs, treatment beliefs and information needs as starting points for patient information--evaluation of an intervention for patients with chronic back pain. *Patient Educ Couns* 2012;86:378-89.
37. Broadbent E, Ellis CJ, Thomas J, et al. Can an illness perception intervention reduce illness anxiety in spouses of myocardial infarction patients? A randomized controlled trial. *J Psychosom Res* 2009;67:11-5.
38. Broadbent E, Ellis CJ, Thomas J, et al. Further development of an illness perception intervention for myocardial infarction patients: a randomized controlled trial. *J Psychosom Res* 2009;67(1):17-23.
39. Broadbent E, Leggat A, McLachlan A, Kerr A. Providing cardiovascular risk management information to acute coronary syndrome patients: a randomized trial. *Br J Health Psychol* 2013;18:83-96.
40. Jonsbu E, Martinsen EW, Morken G, et al. Change and impact of illness perceptions among patients with non-cardiac chest pain or benign palpitations following three sessions of CBT. *Behav Cogn Psychother* 2013;41:398-407.
41. Keogh KM, Smith SM, White P, et al. Psychological family intervention for poorly controlled type 2 diabetes. *Am J Manag Care* 2011;17:105-13.
42. Petrie KJ, Perry K, Broadbent E, Weinman J. A text message programme designed to modify patients' illness and treatment beliefs improves self-reported adherence to asthma preventer medication. *Br J Health Psychol* 2012;17:74-84.
43. Rees G, Lamoureux EL, Nicolaou TE, et al.

Feedback of personal retinal images appears to have a motivational impact in people with non-proliferative diabetic retinopathy and suboptimal HbA1c: findings of a pilot study. *Diabet Med* 2013;30:1122-5.
44. Davies MJ, Heller S, Skinner TC, et al. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. *BMJ* 2008;336:491-5.
45. Petrie KJ, Cameron LD, Ellis CJ, et al. Changing illness perceptions after myocardial infarction: an early intervention randomized controlled trial. *Psychosom Med* 2002;64:580-6.
46. Rutter CL, Rutter DR. Longitudinal analysis of the illness representation model in patients with irritable bowel syndrome (IBS). *J Health Psychol* 2007;12:141-8.
47. Lawson VL, Bundy C, Harvey JN. The development of personal models of diabetes in the first 2 years after diagnosis: a prospective longitudinal study. *Diabet Med* 2008;25:482-90.
48. Benyamini Y. Health and Illness Perceptions. In: Friedman HS, editor. The Oxford Handbook of Health Psychology. New York, United States. *Oxford University Press Inc* 2011:290-2.
49. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *J Psychosom Res* 2006:631-7.
50. 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 Rheum* 2013;32:635-44.

8

Chapter 9

Nederlandse samenvatting

Axiale spondyloarthritis (axSpA) is een chronische reumatische aandoening gekenmerkt door niet-infectieuze ontstekingen (inflammatie) in het bekken (sacro-iliacale gewrichten) en de wervelkolom. De klachten ontwikkelen zich meestal tussen het 20e en 30e levensjaar en ontstaan zelden na het 45e levensjaar. De meest kenmerkende symptomen van axSpA zijn chronische rugpijn en stijfheid van de rug. Daarnaast kan men ook last hebben van verschillende andere symptomen die erg kunnen variëren van patiënt tot patiënt. Andere kenmerken van deze aandoening zijn onder te verdelen in musculoskeletale aandoeningen (aandoeningen van spieren, pezen, ligamenten, zenuwen en gewrichten) en extra-articulaire aandoeningen (aandoeningen buiten de gewrichten). Onder de musculoskeletale aandoeningen vallen ontstekingen van de gewrichten zoals de knieën (perifere artritis), ontstekingen van de peesaanhechtingen (enthesitis) en ontstekingen die worstvormige zwellingen van de tenen of vingers veroorzaakt (dactylitis). Extra-articulaire aandoeningen passend bij axSpA komen voor in de ogen (uveïtis), de huid (psoriasis) en de darmen (de ziekte van Crohn en colitis ulcerosa; inflammatoire darmziektes, IBD).

AxSpA is een vorm van spondyloartritis (SpA). SpA is een verzamelnaam voor een groep reumatische aandoeningen en kan worden onderverdeeld in axSpA en perifere SpA (pSpA). Waar bij axSpA met name het bekken en de wervels zijn aangedaan, zijn bij pSpA de perifere gewrichten (zoals de knieën) en pezen aangedaan. Wel hebben axSpA en pSpA enkele klinische en genetische overeenkomsten, zoals een hoge prevalentie van het gen human leukocyte antigen B27 (HLA-B27). De prevalentie van SpA varieert wereldwijd en wordt geschat op 0.2% van de bevolking in Zuid-Azië tot 1.3% van de bevolking in Noord-Amerika. In Europa wordt de prevalentie geschat op 0.5%.

Verder kan er binnen axSpA nog onderscheid gemaakt worden tussen radiografische axiale spondyloartritis (r-axSpA), welke ook wel bekend staat als ankyloserende spondylitis (AS) of de ziekte van Bechterew, en non-radiografische axSpA (nr-axSpA). Bij patiënten met r-axSpA is er structurele schade in het bekken (sacro-iliacale gewrichten) zichtbaar op röntgenfoto's terwijl dat bij patiënten met nr-axSpA niet zichtbaar is. Het natuurlijke ziektebeloop van axSpA is nog niet geheel bekend en varieert aanzienlijk van patiënt tot patiënt. Sommige patiënten ontwikkelen nooit radiografische schade, terwijl bij anderen nr-axSpA zich ontwikkelt tot r-axSpA in een kort tijdsbestek. Momenteel zijn we nog niet in staat om te voorspellen welke patiënten uiteindelijk wel en welke patiënten geen r-axSpA zullen ontwikkelen.

Een reumatoloog stelt via de anamnese, lichamelijk onderzoek, laboratoriumonderzoek en beeldvorming vast welke kenmerken en symptomen de patiënt heeft. Patroonherkenning van bepaalde kenmerken en symptomen (het 'Gestalt') door een (ervaren) reumatoloog

zijn leidend voor de diagnose axSpA. In 2009 heeft ASAS, een internationale groep van experts op gebied van SpA, classificatie criteria voor axSpA ontwikkeld. Deze criteria worden gebruikt om patiënten voor wetenschappelijke studies te includeren zodat er groepen van patiënten met vergelijkbare karakteristieken ontstaan. De classificatie criteria kunnen worden toegepast bij patiënten met een axSpA diagnose die bijna dagelijks rugpijn ervaren voor ten minste 3 maanden en welke ontstaan zijn voor het 45e levensjaar. De ASAS classificatie criteria voor axSpA zijn ontwikkeld om zowel patiënten met r-axSpA als patiënten met nr-axSpA te classificeren en bestaan uit verschillende kenmerken die typerend zijn voor SpA. Er zijn dus wel classificatie criteria beschikbaar die worden toegepast bij patiënten die de diagnose al hebben, maar er zijn geen diagnostische criteria om de diagnose te stellen.

De behandeling van axSpA is toegespitst op de individuele klachten van de patiënt en bestaat uit zowel farmacologische als niet-farmacologische behandeling. De eerste keus geneesmiddelen voor patiënten met axSpA die pijn en stijfheid ervaren zijn non-steroïdale anti-inflammatoire geneesmiddelen (NSAIDs). NSAIDs zoals naproxen of ibuprofen zijn ontstekingsremmende pijnstillers. Voor patiënten waarbij NSAIDs niet afdoende werken, zijn er de afgelopen jaren zogenoemde biologicals op de markt gekomen. Deze biologicals zorgen ervoor dat een specifiek eiwit (zoals TNF), dat ontsteking veroorzaakt, geblokkeerd wordt. Onder de niet-farmacologische behandeling vallen educatie, fysiotherapie, het stimuleren van fysieke activiteit en het stoppen met roken. Alhoewel de beschikbare behandelopties effectief zijn, zijn er nog veel patiënten die klachten blijven houden en een behoorlijke ziektelast ervaren.

Ondanks dat er enorme stappen zijn gezet in het diagnosticeren, classificeren en behandelen van axSpA, is er nog ruimte voor verbetering en zijn er nog vele vragen onbeantwoord gebleven. In dit proefschrift hebben we enkele vraagstukken onderzocht. In dit laatste hoofdstuk worden de meest belangrijke bevindingen van dit proefschrift samengevat, in een breder perspectief geplaatst en worden aanbevelingen voor toekomstig onderzoek gedaan. Dit proefschrift heeft zich geconcentreerd rondom drie thema's: 1) de betekenis van het hebben van een familielid met SpA (positieve familieanamnese) voor de kans op het krijgen van axSpA, 2) de impact van axSpA op gezondheidsuitkomsten in een vroege fase van de ziekte en 3) ziektepercepties en copingstrategieën van patiënten die recent gediagnosticeerd zijn met axSpA.

Voor dit proefschrift zijn de gegevens gebruikt van drie cohortstudies van patiënten met chronische (inflammatoire) rugpijn (≥ 3 maanden) die een verdenking hebben op axSpA. Cohortstudies zijn onderzoeken waar een groep patiënten een tijd lang gevolgd worden bijvoorbeeld om het ziektebeloop in kaart te brengen wanneer patiënten de gebruikelijke

zorg krijgen. Het wereldwijde Assessment in SpondyloArthritis international Society (ASAS) cohort heeft patiënten geïncludeerd waarbij chronische rugpijn vóór het 45e levensjaar zich heeft ontwikkeld, het Franse DEvenir des Spondyloarthropathies Indifférenciées Récentes (DESIR) cohort heeft patiënten tussen 18-50 jaar met inflammatoire rugpijn (duur < 3 jaar) geïncludeerd en het Europese SPondyloArthritis Caught Early (SPACE) cohort heeft patiënten ≥ 16 jaar met chronische rugpijn ≤ 2 jaar die ontstaan zijn vóór het 45e levensjaar geïncludeerd.

Eén van de SpA kenmerken in de ASAS classificatie criteria voor axSpA is de aanwezigheid van een positieve familieanamnese voor SpA. ASAS heeft een positieve familieanamnese voor SpA gedefinieerd als de aanwezigheid van r-axSpA, uveïtis, reactieve artritis, IBD of psoriasis in eerste- of tweedegraads familieleden (eerstegraads: moeder, vader, zus, broer, dochter en zoon; tweedegraads: tante, oom, nicht, neef, grootmoeder en grootvader). Deze definitie van een positieve familieanamnese is gebaseerd op overeenstemming tussen experts en is nooit eerder getest of gevalideerd, ondanks dat het een onderdeel is van verschillende classificatie criteria. Echter, de definitie wordt als belangrijk beschouwd in het identificeren van patiënten met axSpA en is de afgelopen 30 jaar onveranderd gebleven.

De sterkste genetische factor die voor axSpA bekend is, is HLA-B27. HLA-B27 lijkt een belangrijke rol te spelen bij een positieve familieanamnese. Daarnaast is het hebben van het gen HLA-B27 ook één van de SpA kenmerken in de ASAS classificatiecriteria voor axSpA. In **hoofdstuk 2** hebben we daarom in het ASAS cohort de waarde van de verschillende aspecten van een positieve familieanamnese bepaald in het identificeren van patiënten die HLA-B27 positief zijn en daarmee een verhoogd risico lopen op axSpA. We hebben geconcludeerd dat alleen een positieve familieanamnese voor axSpA gebruikt kan worden om patiënten te identificeren die een grotere kans hebben om HLA-B27 positief zijn en bij wie dit dus onderzocht moet worden. Een positieve familieanamnese voor uveïtis, reactieve artritis, IBD of psoriasis waren niet bruikbaar in dit opzicht. Vergelijkbare resultaten werden gevonden bij patiënten met diverse etnische achtergronden en ook bij een positieve familieanamnese bij een eerste- of tweedegraads familielid.

Onze bevindingen werden bevestigd door Ez-Zaitouni en collega's (2018) in het DESIR en het SPACE cohort. Echter, zij vonden naast de associatie tussen een positieve familieanamnese voor axSpA en HLA-B27 tevens een associatie tussen een positieve familieanamnese voor uveïtis en HLA-B27. Bij het selecteren van de juiste patiënt voor doorverwijzing naar de reumatoloog is het beter om te varen op de aanwezigheid van HLA-B27 dan op een positieve familieanamnese omdat dit een hogere kans geeft dat een patiënt daadwerkelijk axSpA heeft.

In **hoofdstuk 3** hebben de vraag omgedraaid: heeft een positieve familieanamnese een toegevoegde waarde in het diagnosticeren van axSpA wanneer de HLA-B27 status van een patiënt al bekend is? Hiervoor werden drie definities voor een positieve familieanamnese onderzocht, namelijk 1) de huidige ASAS-definitie voor een positieve familieanamnese (dit omvat alle vijf aandoeningen), 2) een positieve familieanamnese voor alleen r-axSpA en 3) een positieve familieanamnese voor alleen uveïtis. Een positieve familieanamnese is veel voorkomend onder patiënten met een verdenking van axSpA: namelijk één-derde van alle patiënten in de drie cohortstudies (ASAS, DESIR en SPACE) heeft een positieve familieanamnese . Het bleek dat géén van deze drie definities van een positieve familieanamnese geassocieerd was met een axSpA diagnose. Hieruit kunnen we concluderen dat een positieve familieanamnese voor SpA van geringe waarde is in het diagnosticeren van axSpA wanneer de HLA-B27 status al bekend is.

De resultaten van **hoofdstukken 2** en **3** hebben implicaties voor het gebruik van een positieve familieanamnese voor de diagnostiek. **Hoofdstuk 2** en de studie door Ez-Zaitouni en collega's (2018) laten zien dat, wanneer het testen van HLA-B27 niet mogelijk is, de aanwezigheid van een positieve familieanamnese voor axSpA en/of uveïtis in een eerste- en tweedegraads familielid gebruikt kan worden om de aanwezigheid van HLA-B27 te voorspellen in patiënten met een verdenking op axSpA. Het is echter belangrijk om te realiseren dat een positieve familieanamnese meestal door patiënten zelf gerapporteerd wordt en daardoor onderhevig is aan de interpretatie van de patiënt. Dit kan leiden tot een overschatting, bijvoorbeeld wanneer symptomen van familieleden onterecht gezien worden als een SpA-gerelateerde aandoening, maar ook tot een onderschatting, bijvoorbeeld wanneer men geen contact heeft met een familielid. Daarnaast heeft een substantieel aantal HLA-B27 positieve patiënten met de diagnose axSpA geen positieve familieanamnese.

Onze bevindingen in **hoofdstuk 3** hebben ook implicaties voor het classificeren van patiënten met axSpA. Een positieve familieanamnese is één van de SpA kenmerken in de ASAS classificatie criteria voor axSpA en levert daarnaast een onafhankelijke bijdrage (aan deze criteria) bovenop HLA-B27 positiviteit. **Hoofdstuk 3** zet vraagtekens bij het relatieve gewicht van een positieve familieanamnese in de huidige ASAS classificatie criteria voor axSpA. Op dit moment worden de ASAS classificatie criteria opnieuw gevalideerd in een wereldwijd prospectief cohort, de CLassification of Axial Spondyloarthritis Inception Cohort (CLASSIC) studie. Deze studie zou gebruikt kunnen worden om te testen of het criterium 'een positieve familieanamnese' overbodig is en verwijderd kan worden uit de classificatie criteria, een ander gewicht moet worden toegekend of dat het gecombineerd moet worden met het criterium HLA-B27 positiviteit.

In onze studie had het merendeel van de geanalyseerde patiënten een Kaukasische of Aziatische etniciteit (tevens ook de grootste axSpA populaties wereldwijd) en waren patiënten met een andere etniciteit ondervertegenwoordigd. Patiënten met een andere etniciteit worden vaak nauwelijks onderzocht en het is dan ook aan te raden in de toekomst juist deze patiënten ook te onderzoeken.

De studies in **hoofdstukken 2** en **3** hebben zich gericht op patiënten met voornamelijk axiale symptomen en niet op patiënten met voornamelijk perifere symptomen. In de toekomst zou er verder onderzocht kunnen worden wat de waarde is van een positieve familieanamnese voor patiënten met perifere SpA of een verdenking hierop, aangezien dezelfde definitie gebruikt wordt voor patiënten met zowel axiale als perifere SpA.

In de vorige paragrafen is er bediscussieerd hoe de identificatie van patiënten met een verhoogd risico op axSpA verbeterd kan worden. Dit is belangrijk omdat patiënten hierdoor eerder behandeld kunnen worden en daardoor kan ook eerder de ziektelast verminderd worden. Mogelijk zou zelfs het beloop van de ziekte beïnvloed kunnen worden door een (vroeg)tijdige behandeling. Echter, de ziektelast van axSpA in een vroege fase is niet goed bekend. Tot nu toe hebben de meeste studies zich gericht op patiënten met een lange ziekteduur en alleen op patiënten met r-axSpA of alleen op patiënten met nr-axSpA, terwijl de vroege fase gekenmerkt wordt door zowel patiënten met r-axSpA als met nr-axSpA.

De ziektelast is in dit proefschrift onderzocht door de impact van axSpA op de kwaliteit van leven, de werkproductiviteit en de participatie in dagelijkse activiteiten te meten. In **hoofdstukken 4** en **5** hebben we de impact van de ziekteactiviteit op de gezondheid gerelateerde kwaliteit van leven (Health-Related Quality of Life, HRQoL) en werkproductiviteit over tijd bij patiënten met vroege axSpA onderzocht en gekwantificeerd. Daarnaast hebben we ook onderzocht of de impact vergelijkbaar is in verschillende subgroepen zoals tussen mannen en vrouwen of tussen patiënten met een weinig tot geen zwaar fysiek beroep en patiënten met een zwaar fysiek beroep. HRQoL kan worden onderverdeeld in de fysieke en mentale kwaliteit van leven. De werkproductiviteit is onderzocht aan de hand van vier variabelen; absenteïsme, presenteïsme, werkproductiviteitsverlies en beperking in activiteiten. Absenteïsme is het aantal werkuren dat men verliest door axSpA (ziekteverzuim), terwijl presenteïsme de prestatievermindering op werk door axSpA omschrijft (op werk aanwezig zijn maar niet efficiënt kunnen werken). Werkproductiviteitsverlies is een samenvattende maat die totale beperking op werk door axSpA weergeeft en de beperking in activiteiten wordt bepaald door de beperkingen in dagelijkse activiteiten door axSpA buiten het werk om.

Hoofdstukken 4 en **5** rapporteren al in de vroegste fase van axSpA aanzienlijke beperkingen in de fysieke kwaliteit van leven, werkproductiviteit en dagelijkse activiteiten. De beperkingen in deze vroege fase zijn zelfs vergelijkbaar met patiënten met langdurige axSpA. Het goede nieuws is dat de ziekteactiviteit afneemt over tijd en dat dit gepaard gaat met minder beperkingen in de fysieke kwaliteit van leven, werkproductiviteit en dagelijkse activiteiten. Maar ondanks deze verbeteringen blijft de ziektelast van vroege axSpA substantieel over de eerste jaren na het ontstaan van de klachten. De mentale kwaliteit van leven van patiënten met axSpA was vergelijkbaar met de algemene populatie. Deze hoofdstukken demonstreren dat er nog steeds veel ruimte voor verbetering is om de ziektelast van vroege axSpA verder te verlagen.

In **hoofdstuk 4** onderzochten we verschillende subgroepen op basis van leeftijd, geslacht, type beroep (niet tot matig vs. zwaar fysiek beroep) en classificatie van de ASAS criteria voor axSpA. De ASAS classificatie criteria voor axSpA maken namelijk verder onderscheid in twee groepen patiënten op basis van de kenmerken die de patiënten hebben, namelijk de beeldvormende subgroep en de klinische subgroep. Bij de patiënten in de beeldvormende subgroep is er botschade in het bekken en/of ontstekingen, typerend voor axSpA, op MRI of röntgenfoto zichtbaar en bij patiënten in de klinische subgroep is dit niet zichtbaar. Het bleek dat geslacht en het type beroep een belangrijke invloed hadden op de associatie tussen ziekteactiviteit en kwaliteit van leven. Een zelfde mate van ziekteactiviteit had minder impact op de fysieke kwaliteit van leven van vrouwen in vergelijking met mannen en van personen met een niet tot matig fysiek beroep in vergelijking met personen met een lichamelijk zwaar beroep. Voor de overige factoren werd er geen invloed gevonden op deze associatie In **hoofdstuk 5** onderzochten we dezelfde subgroepen als in **hoofdstuk 4** plus nog een aantal andere subgroepen op basis van het hebben van HLA-B27 gen, de duur van chronische rugpijn en medicatiegebruik. Alleen de duur van chronische rugklachten (heel kort vs. iets langere klachtenduur) en de start van medicatiegebruik hadden een belangrijke invloed op de associatie tussen ziekteactiviteit en werkproductiviteit. Alleen in patiënten met de kortste duur van chronische rugpijn en in patiënten die met medicatie gestart waren, ging een verbetering in ziekteactiviteit gepaard met minder ziekteverzuim over 1 jaar. De impact van ziekteactiviteit op productiviteitsverlies op werk, presenteïsme en beperking in activiteiten was echter vergelijkbaar voor alle patiënten ongeacht de duur van chronische rugpijn en het al dan niet starten met medicatie.

Hoofdstukken 4 en **5** laten zien dat de ziektelast van axSpA over tijd substantieel blijft, zelfs in een vroege fase van de ziekte. Het is daarom belangrijk om deze ziektelast verder te verlagen, omdat axSpA niet alleen de patiënten met axSpA treft maar ook hun vrienden, familie en de maatschappij. Ongeveer één-vijfde van de patiënten met r-axSpA heeft hulp nodig van hun vrienden en familie. De partners van patiënten met r-axSpA ervaren ook

beperkingen in hun eigen kwaliteit van leven. Tevens ervaren zij moeilijkheden met het omgaan met r-axSpA van hun partner zoals beperkingen in vrijetijdsbestedingen maar ook veranderde rollen binnen de relatie. Bovendien is de financiële ziektelast ook substantieel. Zowel de patiënt als de maatschappij worden geconfronteerd met aanzienlijke kosten voor medicatie, medische zorg, niet-medische kosten (zoals hulp bij het huishouden) maar ook door indirecte kosten zoals het verlies van werkproductiviteit en arbeidsongeschiktheid. In een grote Europese studie moest bijna de helft van de patiënten met axSpA rekening houden met hun ziekte in hun carrièrekeuzes, bijna drie-vierde van de patiënten ervoer problemen in het vinden van een baan door axSpA en meer dan 40% van de patiënten had aanpassingen van hun werkplek nodig. Er wordt zelfs gesuggereerd dat de kosten gerelateerd aan de beperkingen in werkproductiviteit de grootste financiële last vormen van de ziekte. Doordat axSpA vaak al op relatief jonge leeftijd ontstaat en patiënten al vroeg in hun beroepsleven treft, ervaren patiënten en de maatschappij de impact vele jaren wat kan leiden tot een grote ziektelast op lange termijn. Het is belangrijk om axSpA vroeg te behandelen, te streven naar minder beperkingen in zowel werk als in het dagelijks leven en waar mogelijk ondersteuning te bieden aan partners van patiënten met axSpA. De European League Against Rheumatism (EULAR), Europese organisatie van de reumatologie, beveelt daarom aan dat in het ziektemanagement van axSpA zowel de individuele als de medische en maatschappelijke kosten, inclusief werkproductiviteit, mee moeten worden genomen.

Een manier om de ziektelast van axSpA verder te verlagen is *treat-to-target* (T2T). T2T is een intensieve behandelstrategie gericht op het snel bereiken van een bepaald doel, zoals een lage ziekteactiviteit, om zo de kwaliteit van leven en deelname in de maatschappij op lange termijn te optimaliseren. Bij T2T wordt de ziekteactiviteit frequent gemeten en op basis daarvan wordt de medicatie aangepast. De behandeling van bijvoorbeeld reumatoïde artritis is verbeterd, niet alleen door de ontwikkeling van biologicals maar ook door T2T behandelstrategieën.

Recentelijk heeft een internationale werkgroep van experts een aantal aanbevelingen voor T2T bij axSpA gepubliceerd. Deze werkgroep erkent echter dat er geen onderzoek naar T2T bij patiënten met axSpA is gedaan en dat er meer kennis nodig is voordat deze strategie ook bij axSpA geïmplementeerd kan worden. De bevindingen in **hoofdstukken 4** en **5** ondersteunen de basisaanname van T2T, namelijk dat het streven naar een lagere ziekteactiviteit bij patiënten met axSpA kan helpen om de kwaliteit van leven en sociale participatie over tijd te verbeteren. Daarnaast ondersteunen onze bevindingen ook de aanbeveling dat een inactieve ziekte of een lage ziekteactiviteit als behandeldoel van T2T de voorkeur heeft. Onze resultaten laten zien dat het belangrijk is om al in een vroege ziektefase met een behandeling te starten. Momenteel wordt er één studie uitgevoerd die

T2T als behandelstrategie voor patiënten met axSpA onderzoekt (TICOSPA NCT03043846). De resultaten van deze studie zullen meer inzicht geven in uitvoerbaarheid en kosteneffectiviteit (inclusief de kans op bijwerkingen) van T2T als behandeling voor axSpA.

Echter, de focus moet niet alleen op medicatie liggen. Tot op heden werkt farmacologische behandeling niet afdoende om alle beperkingen in werk en kwaliteit van leven weg te nemen en is er een grote behoefte aan aanvullende behandelopties. Andere factoren zoals ziektepercepties en copingstrategieën hebben mogelijk ook een invloed op gezondheidsuitkomsten, dit is verder onderzocht in **hoofdstukken 6** en **7**.

Het is belangrijk om te realiseren dat werkproductiviteitsverlies bestaat uit absenteïsme en presenteïsme, welke door de patiënt zelf worden gerapporteerd. Het is misschien beter om absenteïsme te meten door gebruik te maken van de gegevens die werkgevers hebben omdat patiënten mogelijk de hoeveelheid ziekteverzuim onderschatten. Echter, het verlies in werkproductiviteit wordt vooral gedreven door presenteïsme en dit kan alleen gemeten worden met vragenlijsten bij patiënten. Verder is uit onderzoek gebleken dat dit ook een valide methode is.

Gezondheidsuitkomsten worden niet alleen beïnvloed door biomedische factoren zoals ontstekingen maar ook door contextuele factoren zoals ziektepercepties en copingstrategieën. Ziektepercepties en copingstrategieën staan centraal in Leventhal's Common Sense Model of self-regulation (CSM). Het CSM is een theoretisch model wat er als volgt uitziet: patiënten reageren op hun aandoening door het vormen van ziektepercepties. Ziektepercepties zijn ideeën of gedachtes die een patiënt vormt over zijn of haar aandoening. Ziektepercepties kunnen een patiënt helpen in het beter begrijpen van zijn of haar aandoening en een beeld vormen over die aandoening maar het weergeeft ook de emotionele status van een patiënt. Twee voorbeelden van ziektepercepties zijn "*Wanneer ik aan mijn ziekte denk, raak ik van streek*" en "*Mijn ziekte heeft grote gevolgen voor mijn leven*". Als een reactie op ziektepercepties worden copingstrategieën ontwikkeld. Copingstrategieën zijn cognitieve of gedragsmatige handelingen die patiënten helpen in het omgaan met de stress die veroorzaakt wordt door het hebben van een aandoening, denk aan bijvoorbeeld het omgaan met pijn, beperkingen of afhankelijkheid. Twee voorbeelden van copingstrategieën zijn "*Als ik pijn heb, dan denk ik aan plezierige gebeurtenissen*" en "*Ik zoek oplossingen voor mijn beperkingen*". Deze twee copingstrategiën zorgen er voor dat men op een positieve manier met de pijn en beperkingen omgaat zodat de stress, die de aandoening in het leven van een patiënt veroorzaakt, verminderd wordt. Hierdoor zal men bijvoorbeeld een betere kwaliteit van leven ervaren dan wanneer men minder gebruik maakt van deze positieve copingsstrategiën.

In **hoofdstuk 6** hebben we onderzocht of ziektepercepties en copingstrategieën de associatie tussen rugpijn en gezondheidsuitkomsten beïnvloeden bij patiënten met (een verdenking op) axSpA. **Hoofdstuk 6** laat zien dat negatieve ziektepercepties een substantiële impact hebben op de associatie tussen rugpijn en de kwaliteit van leven en werkproductiviteit. Een vergelijkbaar niveau van rugpijn was geassocieerd met méér beperkingen in de fysieke kwaliteit van leven wanneer patiënten negatieve ziektepercepties hadden, zoals een sterke overtuiging dat hun aandoening ernstige consequenties heeft ('consequences') en dat toeval de oorzaak is voor hun aandoening ('chance'). Wanneer patiënten meer symptomen toeschreven aan hun aandoening ('identity'), sterke negatieve emoties door hun aandoening ervoeren ('emotional representation') en de sterke overtuiging hadden dat psychologische factoren de oorzaak zijn van hun aandoening ('psychological attributions') zoals negatief in het leven staan, dan gaf een vergelijkbaar niveau van rugpijn méér beperkingen in de mentale kwaliteit van leven. Daarnaast was een vergelijkbaar niveau van rugpijn ook gerelateerd aan méér verlies van werkproductiviteit wanneer patiënten een sterke overtuiging hadden dat hun aandoening ernstige consequenties ('consequences') had. Als we de effecten van ziektepercepties in acht namen, konden we geen impact door copingstrategieën aantonen.

Hoofdstuk 6 laat zien dat het beïnvloeden van ziektepercepties misschien een onderdeel van de al bestaande behandelopties voor axSpA zou moeten worden om gezondheidsuitkomsten verder te verbeteren. Alhoewel er geen impact van copingstrategieën op de associatie van rugpijn en gezondheidsuitkomsten werd gevonden in **hoofdstuk 6**, moeten copingstrategieën nog niet uitgesloten worden in onderzoek of behandeling. De reden hiervoor is dat, volgens het CSM, ziektepercepties het gebruik van copingstrategieën beïnvloeden en daarnaast beïnvloeden copingstategieën ziektepercepties weer wanneer gezondheidsuitkomsten veranderen. Het is daarom belangrijk dat ziektepercepties en gerelateerde copingstrategieën gezamenlijk worden meegenomen in zowel onderzoek als behandeling. Echter, de meeste studies bestuderen ziektepercepties en copingstrategieën apart van elkaar en op slechts één tijdspunt. Er zijn meerdere stappen nodig voordat bevestigd kan worden of het beïnvloeden van ziektepercepties en sturen in de keuze in copingstrategieën gebruikt kan worden om gezondheidsuitkomsten in axSpA te verbeteren.

Mogelijk zouden gezondheidsuitkomsten verbeterd kunnen worden door ziektepercepties op een positieve manier te beïnvloeden en door het sturen in de keuze voor copingstrategieën. Als eerste stap wilden we weten of ziektepercepties en het gebruik van bepaalde copingstrategieën stabiel blijven over tijd. In **hoofdstuk 7** hebben we dit onderzocht, ook in relatie tot de klachten. Alhoewel rugpijn, ziekteactiviteit en gezondheidsuitkomsten duidelijk verbeterden over twee jaar tijd, bleven ziektepercepties

en copingstrategieën opmerkelijk stabiel in patiënten die recent gediagnosticeerd zijn met axSpA.

De resultaten in **hoofdstuk 7** laten zien dat ziektepercepties en copingstrategieën in de eerste twee jaren na diagnose niet spontaan veranderen en onafhankelijk zijn van de afname in ziekteactiviteit in patiënten met vroege axSpA. Deze bevindingen komen overeen met observationele studies bij patiënten met andere aandoeningen, zoals reumatoïde artritis, en de enige studie naar patiënten met lang bestaande r-axSpA. Desalniettemin, gerandomiseerde gecontroleerde studies (randomized controlled trial, RCT) bij patiënten met andere chronische aandoeningen zoals diabetes laten zien dat ziektepercepties wel degelijk veranderden als interventies zich specifiek op ziektepercepties richten zoals cognitieve gedragstherapie of een educatie programma. Dit suggereert dat ziektepercepties en bijbehorende copingstrategieën van patiënten met axSpA mogelijk verbeterd kunnen worden wanneer therapeutische interventies zich specifiek hierop zouden richten.

De volgende stap is het verrichten van een RCT waarbij de gebruikelijke zorg vergeleken wordt met de gebruikelijke zorg plus een aanvullende interventie die negatieve ziektepercepties en de daaraan gerelateerde copingstrategieën aanpakt. De interventie zou zich kunnen richten op de ziektepercepties en copingstrategieën die geassocieerd waren met verminderde kwaliteit van leven of werkproductiviteit in **hoofdstuk 6**. De keuze voor het type interventie moet gebaseerd worden op eerdere onderzoeken en de uitvoerbaarheid van interventies in samenspraak met experts op het gebied van psychologische interventies.

Een andere stap die genomen moet worden, is het bepalen of de veranderingen in ziektepercepties en copingstrategieën relevante veranderingen zijn. Dit is ingewikkeld om te bepalen omdat er geen gegevens beschikbaar zijn over klinische belangrijke veranderingen (veranderingen die waardevol zijn voor de patiënt) in ziektepercepties en copingstrategieën. Toekomstig onderzoek moet zich richten op het definiëren van deze klinische belangrijke verschillen. Echter, een bepaalde ziekteperceptie kan zowel een negatieve, positieve als wisselende impact op gezondheidsuitkomsten hebben afhankelijk van welke copingstrategie(ën) gebruikt worden. Door de grote hoeveelheid combinaties die mogelijk zijn tussen ziektepercepties en copingstrategieën is de interpretatie van één enkele ziekteperceptie of copingstrategie moeilijk.

Verder zou het interessant zijn om te onderzoeken of ziektepercepties en copingstrategieën van patiënten in de vroege ziektefase verschillen van patiënten met langdurige axSpA. Mogelijk zijn ziektepercepties en copingstrategieën meer ontvankelijk

voor verandering in een bepaalde ziektefase(s) en zouden er daarom verschillende behandelstrategieën gebruikt moeten worden voor de verschillende ziektefases. Echter, er zijn verschillende theorieën over wanneer ziektepercepties en copingstrategieën gevormd worden en veranderen, wat onderzoek uitdagend maakt.

De enige studie die de associatie tussen ziektepercepties en kwaliteit van leven bij patiënten met langdurige axSpA heeft onderzocht, vond andere ziektepercepties die geassocieerd waren met een verslechtering in de fysieke kwaliteit van leven dan de ziektepercepties die wij in **hoofdstuk 6** vonden. Dit suggereert dat andere ziektepercepties mogelijk belangrijker worden in een latere fase van de ziekte. Echter, copingstrategieën lijken niet te verschillen tussen de vroege en late fase van de ziekte wanneer we onze resultaten van patiënten met vroege axSpA vergelijken met een ander onderzoek bij patiënten met langdurige ziekte.

Tot slot

De studies in dit proefschrift hebben geleid tot meer kennis en inzicht over het identificeren van patiënten met axSpA, over de impact van vroege axSpA op gezondheidsuitkomsten en over ziektepercepties en het gebruik van copingstrategieën. Meer kennis en inzicht zal ons niet alleen helpen bij het maken en geven van een (vroeg)tijdige diagnose en behandeling maar ook bij het onderzoeken van aanvullende behandelingsmogelijkheden. Hiermee is pas echter het topje van de ijsberg voor axSpA onthuld en om de ziektelast verder te kunnen verminderen bij patiënten zullen er nog meer stappen gezet moeten worden.

9

Appendices

Curriculum Vitae
List of publications
Dankwoord

CURRICULUM VITAE

Miranda van Lunteren is geboren op 12 augustus 1990 te Naarden. Na het behalen van haar VWO diploma in 2008 aan het Vechtstede College in Weesp, is Miranda begonnen aan de opleiding fysiotherapie aan de Hogeschool van Amsterdam. In 2009 besloot ze om de overstap te maken naar de bachelor Biomedische Wetenschappen aan de Vrije Universiteit van Amsterdam. Gedurende haar bachelor trad ze op als minor vertegenwoordigster. In 2012 rondde zij deze bachelor af. In datzelfde jaar begon ze aan de master Health Sciences aan de Vrije Universiteit van Amsterdam met als specialisaties 'Prevention and Health' en 'Nutrition and Health'. Haar masterstage voltooide Miranda bij het Nederlands Kanker Instituut waar zij onderzoek deed naar epidemiologie en de leefstijlfactoren van nachtwerkers en waar haar liefde voor wetenschap verder groeide. In september 2013 studeerde ze cum laude af en bleef ze vervolgens werkzaam bij het NKI als wetenschappelijk medewerkster.

In april 2014 is zij gestart met haar promotietraject op de afdeling Reumatologie van het Leids Universitair Medisch Centrum (LUMC) onder begeleiding van prof. dr. D. van der Heijde, prof. dr. R. Landewé en dr. F.A. van Gaalen. Naast haar promotietraject begeleidde zij wetenschappelijke stages. Momenteel werkt Miranda als studiecoördinator voor de ASAS CLASSIC studie bij het LUMC.

LIST OF PUBLICATIONS

1. **van Lunteren M**, van der Heijde D, Sepriano A, Berg IJ, Dougados M, Gossec L, Jacobsson L, Ramonda R, Rudwaleit M, Sieper J, Landewé R, van Gaalen FA. Is a positive family history of spondyloarthritis relevant for diagnosing axial spondyloarthritis once HLA-B27 status is known? *Rheumatology* 2019;58:1649-54

2. Ramiro S, van der Heijde D, Sepriano A, **van Lunteren M**, Moltó A, Feydy A, d'Agostino MA, Loeuille D, Dougados M, Reijnierse M, Claudepierre P. Spinal radiographic progression in early axial Spondyloarthritis: Five-year results from the DESIR cohort. *Arthritis Care Res* 2019;71:1678-84

3. Bakker PAC, Ramiro S, Ez-Zaitouni Z, **van Lunteren M**, Berg IJ, Landewé R, Ramonda R, van Oosterhout M, Reijnierse M, van Gaalen FA, van der Heijde D. Is it useful to repeat MRI of the sacroiliac joints after three months or one year in the diagnostic process of patients with chronic back pain suspected of axial spondyloarthritis? *Arthritis Rheumatol* 2019;71:382-91

4. Ortolan A, **van Lunteren M**, Ramiro S, Ramonda R, Landewé RBM, Dagfinrud H, Jacobsson LTH, van der Heijde D, van Gaalen FA. Are gender-specific approaches needed in diagnosing early axial spondyloarthritis? Data from the SPondyloArthritis Caught Early cohort. *Arthritis Res Ther* 2018;20:218

5. **van Lunteren M**, Sepriano A, Landewé R, Sieper J, Rudwaleit M, van der Heijde D, van Gaalen FA. Do ethnicity, degree of family relationship, and the spondyloarthritis subtype in affected relatives influence the association between a positive family history for spondyloarthritis and HLA-B27 carriership? Results from the worldwide ASAS cohort. *Arthritis Res Ther* 2018;20:166

6. Ramiro S, Claudepierre P, Sepriano A, **van Lunteren M**, Moltó A, Feydy A, Antonietta d'Agostino M, Loeuille D, Dougados M, Reijnierse M, van der Heijde D. Which scoring method depicts spinal radiographic damage in early axial spondyloarthritis best? Five-year results from the DESIR cohort. *Rheumatology* 2018;57:1991-2000

7. **van Lunteren M**, Scharloo M, Ez-Zaitouni Z, de Koning A, Landewé R, Fongen C, Ramonda R, Kaptein AA, van Gaalen FA, van der Heijde D. The impact of illness perceptions and coping on the association between back pain and health outcomes in patients suspected of axial spondyloarthritis: data from the SPondyloArthritis Caught Early cohort. *Arthritis Care Res* 2018;70:1829-39

8. Bakker PA, van den Berg R, Hooge M, **van Lunteren M**, Ez-Zaitouni Z, Fagerli KM, Landewé R, van Oosterhout M, Ramonda R, Reijnierse M, van Gaalen FA, van der Heijde D. Impact of replacing radiographic sacroiliitis by magnetic resonance imaging structural lesions on the classification of patients with axial spondyloarthritis. *Rheumatology* 2018;57:1186-93

9. Ez-Zaitouni Z, Landewé R, **van Lunteren M**, Bakker PA, Fagerli KM, Ramonda R, Jacobsson LTH, van der Heijde D, van Gaalen FA. Imaging of the sacroiliac joints is important for diagnosing early axial spondyloarthritis but not all-decisive. *Rheumatology* 2018;57:1173-9

10. **van Lunteren M**, Ez-Zaitouni Z, de Koning A, Dagfinrud H, Ramonda R, Jacobsson L, Landewé R, van der Heijde D, van Gaalen FA. In early axial spondyloarthritis, increasing disease activity is associated with worsening of health-related quality of life over time. *J Rheumatol* 2018;45(6):779-84

11. Ez-Zaitouni Z, Bakker PAC, **van Lunteren M**, Berg IJ, Landewé R, van Oosterhout M, Lorenzin M, van der Heijde D, van Gaalen FA. Presence of multiple spondyloarthritis (SpA) features is important but not sufficient for a diagnosis of axial spondyloarthritis: data from the SPondyloArthritis Caught Early (SPACE) cohort. Ann Rheum Dis 2017;76:1086-92

12. Dougados M, Sepriano A, Moltó A, **van Lunteren M**, Ramiro S, de Hooge M, van den Berg R, Navarro-Compán V, Demattei C, Landewé R, van der Heijde D. Sacroiliac radiographic progression in recent onset axial spondyloarthritis: the 5-year data of the DESIR cohort. *Ann Rheum Dis* 2017;76:1823-8

13. Ez-Zaitouni Z, Bakker PA, **van Lunteren M**, de Hooge M, van den Berg R, Reijnierse M, Fagerli KM, Landewé RB, Ramonda R, Jacobsson LTH, Saraux A, Lenczner G, Feydy A, Pialat JB, Thévenin F, van Gaalen FA, van der Heijde D. The yield of a positive MRI of the spine as imaging criterion in the ASAS classification criteria for axial spondyloarthritis: results from the SPACE and DESIR cohorts. *Ann Rheum Dis* 2017;76:1731-6

14. Ez-Zaitouni Z, **van Lunteren M**, Bakker PAC, van den Berg R, Reijnierse M, Fagerli KM, Landewé RBM, Ramonda R, Jacobsson LTH, van Gaalen FA, van der Heijde D. The influence of discrepant imaging judgements on the classification of axial spondyloarthritis is limited: a replication in the SpondyloArthritis Caught Early (SPACE) cohort. *Ann Rheum Dis* 2018;77:e1

15. **van Lunteren M**, Ez-Zaitouni Z, Fongen C, Landewé R, Ramonda R, van der Heijde D, van Gaalen FA. Disease activity decrease is associated with improvement in work productivity over 1 year in early axial spondyloarthritis (SPondyloArthritis Caught Early cohort). *Rheumatology* 2017;56:2222-

16. Bakker PA, Ez-Zaitouni Z, **van Lunteren M**, van den Berg R, de Hooge M, Fagerli KM, Landewé R, van Oosterhout M, Ramonda R, Reijnierse M, van der Heijde D, van Gaalen FA. Are additional tests needed to rule out axial spondyloarthritis in patients ages 16-45 years with short-duration chronic back pain and maximally one spondyloarthritis feature? *Arthritis Care Res* 2016;68:1726-30

17. Rubio Vargas R, van den Berg R, **van Lunteren M**, Ez-Zaitouni Z, Bakker PA, Dagfinrud H, Ramonda R, Landewé R, Molenaar E, van Gaalen FA, van der Heijde D. Does body mass index (BMI) influence the Ankylosing Spondylitis Disease Activity Score in axial spondyloarthritis?: Data from the SPACE cohort. *RMD Open* 2016;2:e000283

DANKWOORD

Velen hebben bijgedragen aan de totstandkoming van dit proefschrift. In het bijzonder dank ik graag de volgende betrokkenen.

Ik ben alle patiënten die hebben deelgenomen aan de SPACE-, DESIR-, en ASAS-cohort ontzettend dankbaar. Bedankt aan alle reumatologen, onderzoekers, onderzoeksverpleegkundigen en andere betrokkenen, geen van deze studies had tot stand kunnen komen zonder jullie tijd en inspanning.

Ik dank mijn promotores prof. dr. van der Heijde en prof. dr. Landewé en co-promotor dr. van Gaalen voor hun kennis, begeleiding en steun om mij te laten groeien als onderzoeker. Bedankt voor de kans om de CLASSIC studie te coördineren.
Beste Désirée, bedankt voor je kritistische blik en doortastendheid. Jouw passie en enthousiasme voor de wetenschap zijn voor mij een inspiratiebron.
Beste Floris, ik ben dankbaar dat je me als onderzoeker als dokter hebt leren denken en voor je humor en onuitputtelijke optimisme.
Beste Robert, bedankt voor je altijd alles overziende blik, je uitleg en hulp bij ingewikkelde analysemethoden en het begrijpelijk opschrijven van de methoden en onderzoeksresultaten.

Prof. Huizinga, beste Tom, bedankt voor de kans om te leren als onderzoeker op een afdeling waar wetenschap op een hoog niveau bedreven wordt.

To all co-authors and our colleagues in participating centres; it has been a real privilege and it was inspiring to collaborate with you.

Prof. Rudwaleit and prof. Sieper, dear Martin and Jochen, thank you for giving me the opportunity to become the study coordinator of the CLASSIC study. I am looking forward to continue working with you.

De innerSPACE-'familie': Zineb, Rosaline, Pauline, Manouk, Anoek, Queeny, Anne en Roos. Het is erg waardevol om in dit leuke team te kunnen werken. Bedankt voor jullie advies en hulp, maar ook voor alle gezelligheid en humor.
The outerSPACE-'family': Sofia, Alexandre, Augusta, Victoria, Mary Lucy, I have enjoyed our collaboration together and thank you for all our conversations about science and Dutch culture. I hope to continue collaborating with you all.

Bedankt aan alle mede-promovendi en post-docs waarmee ik de afgelopen jaren met veel

plezier mee heb mogen samenwerken. Dit maakt(e) voor mij de afstand tussen Weesp en Leiden nooit te ver.

Lieve paranimfen, Anne en Sytske Anne, bedankt dat jullie mij willen helpen tijdens de voorbereidingen en de verdediging zelf.

Nancy, Joyce, Hughine, Sandra, Jozé en Cedric bedankt voor niet alleen alle praktische ondersteuning en betrokkenheid maar ook voor jullie gezelligheid en luisterend oor. Jullie zijn onmisbaar voor de afdeling.
Poli secretaresses, en in het bijzonder Marie-Josée, bedankt voor jullie hulp bij de logistieke zaken rondom visites van de patiënten.

Lieve vrienden en familie, ik ben jullie ontzettend dankbaar voor jullie interesse in het promoveren en onderzoek maar ook jullie luisterend oor als het even tegen zat.

Lieve Ricardo, lief broertje, en lieve schoonfamilie, bedankt voor al jullie liefde, positieve energie en dat jullie altijd voor me klaar staan.

Lieve paps en mams, bedankt voor jullie onvoorwaardelijke liefde en steun. Ik ben dankbaar voor de kansen en de mogelijkheden die jullie mij hebben gegeven om mijn hart te volgen en mijn dromen waar te maken.

Tot slot, lieve Remco, bedankt voor je oneindige liefde, steun en interesse in alles wat ik doe. Ik ben dankbaar voor al onze mooie momenten samen en ik kan niet wachten om te zien wat de toekomst ons zal brengen.

A