Pain and physical function in patients with spondyloarthritis

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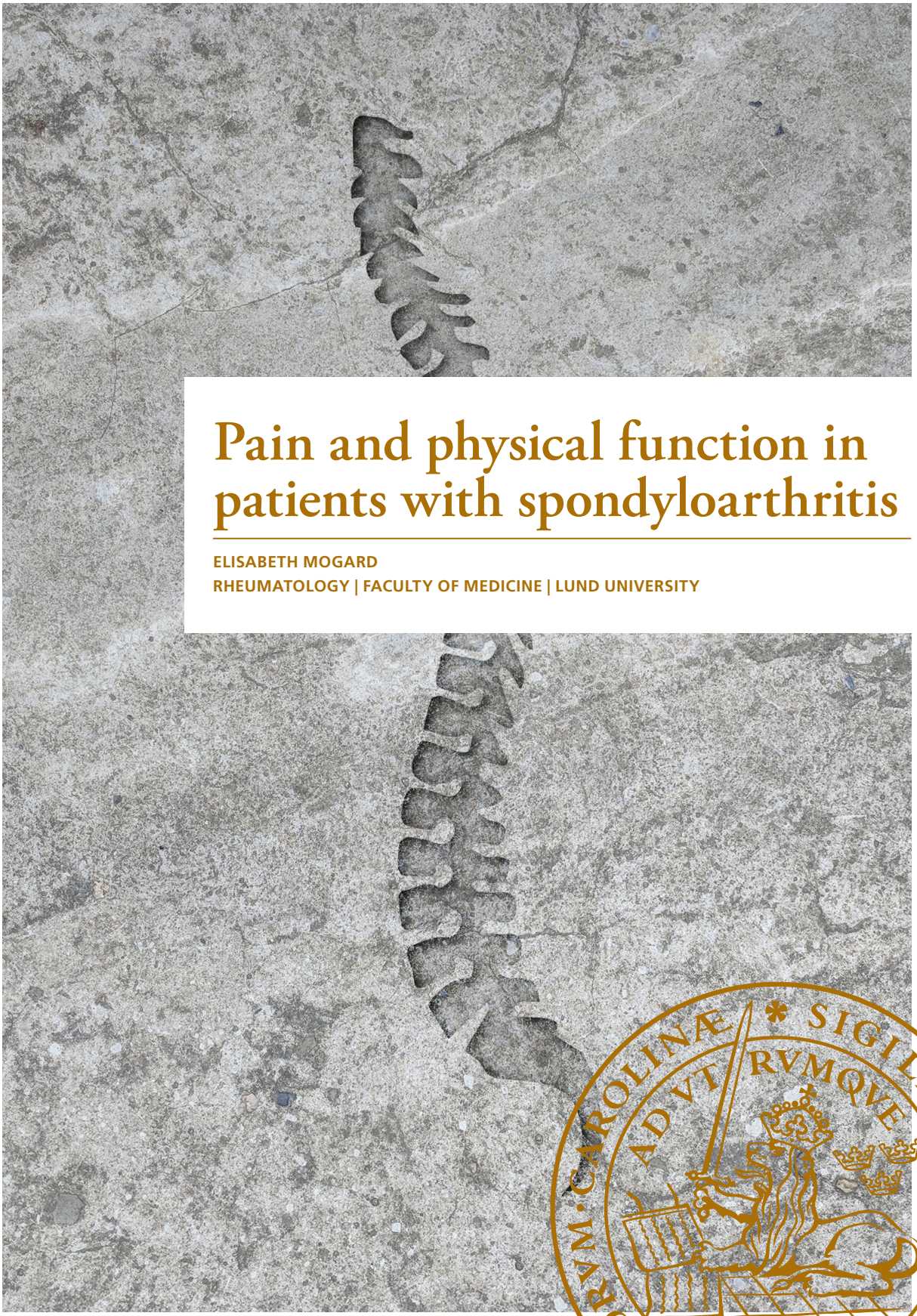

Pain and physical function in patients with spondyloarthritis

ELISABETH MOGARD
RHEUMATOLOGY | FACULTY OF MEDICINE | LUND UNIVERSITY

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Elisabeth Mogard is a physiotherapist specialised in rheumatology and works at the Department of Rheumatology at Skåne University Hospital in Lund. As a physiotherapist, she has a special interest in inflammatory rheumatic diseases and a focus on patients with spondyloarthritis, a patient group that often has experienced pain and stiffness many years before an adequate diagnosis and accordingly sufficient treatment.

This PhD thesis presents research from studies in both the clinical setting and from a large population-based survey and concerns chronic pain and physical function in patients with inflammatory back pain, spondyloarthritis.

The findings conclude that chronic widespread pain is a common consequence of spondyloarthritis, and even if more pronounced in women it affect four out of ten men. Another finding is that spinal mobility decreases with longer disease duration also in patients with milder disease and with few differences between women and men. The work enlighten risk factors for development and persistence of chronic widespread pain and associations with higher pain sensitivity, that may provide valuable information to identify patients at risk for chronic widespread pain. Together, the results highlight the need for early interventions with both pharmacological and non-pharmacological treatment in all patients with spondyloarthritis, and a multiprofessional approach included in the clinical routines.

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Elisabeth Mogard

LUND
UNIVERSITY

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Abstract
Ankylosing spondylitis (AS) and undifferentiated spondyloarthritis (USpA) are two subgroups of the rheumatic disease spondyloarthritis (SpA). The diseases typically debut in early adulthood with periods of fluctuating and persistent pain and stiffness, and can result in consequences such as impaired functioning and reduced quality of life. SpA is a heterogenous group but AS and USpA share many common fatures. Most evidence is based on studies of men with AS. The aim was to study chronic pain and physical function, including differences between AS and USpA, and between men and women, regarding (I) spinal mobility in relation to disease duration, (II) prevalence of chronic widespread pain (CWP), (III) possible risk factors for development of CWP and having persistent CWP, and (IV) different aspects of pain, including pain sensitivity (pain threshold, pain tolerance, and temporal summation of pain).

Adult patients with ICD-10 diagnoses corresponding to AS or USpA identified through registers in the Region Skåne, were included in the studies. In Papers I (n=183) and IV (n=226) two clinical cohorts with an axial disease at Skåne University Hospital were studied. In Papers II (n=940) and III (n=712), cross-sectional and longitudinal data from a population-based survey, including patients with AS or USpA were analysed.

Patients with SpA showed decreased spinal mobility over time, most evident in AS, and spinal mobility was more severely impaired in the lumbar and thoracic spine in AS compared to USpA. Few differences, between men and women were found, besides anthropometric measures (Paper I). The one-year period prevalence of CWP was 49% in USpA vs. 45% in AS, and more common in females. CWP was associated with female sex, higher BMI and smoking. Men and women with chronic pain reported similar pain intensity, a novel finding (Paper II). The prevalence of CWP remained high over time, and risk factors for development of, and having persistent CWP included more pain regions, and worse outcomes in health status, disease activity, mental and physical function, and self-efficacy at baseline. Higher age and being female also predicted persistent CWP (Paper III). Patients within the SpA-subgroups reported similar pain sensitivity and pain intensity, but women reported lower pain tolerance, and higher pain intensity compared to men. Lower pain tolerance was associated with worse outcomes in disease activity, fatigue and spinal mobility. In conclusion, concomitant CWP is common in AS and USpA and often persists over time. Together with the finding of impaired spinal mobility in all SpA, these consequences emphasise regular follow-ups, with attention to risk factors for CWP and an early and combined management with pharmacological and non-pharmacological treatment.

Key words;
Ankylosing spondylitis, undifferentiated spondyloarthritis, chronic pain, physical function, spinal mobility, sex

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I. **Mogard E,** Lindqvist E, Bergman S, Bremander A. Spinal Mobility in Axial Spondyloarthritis: A Cross-sectional Clinical Study. Musculoskeletal Care. 2017 Mar; 15:36-48.

II. **Mogard E**, Bremander A, Lindqvist E, Bergman S. Prevalence of Chronic Widespread Pain in a Population-based Cohort of Patients with Spondyloarthritis – a cross-sectional study. BMC Rheumatology. 2018 2:11.

III. **Mogard E**, Lindqvist E, Bremander A, Bergman S. Risk Factors for Development and Persistence of Chronic Widespread Pain in Spondyloarthritis – a Population-based Two Year Follow-up Study. Submitted.

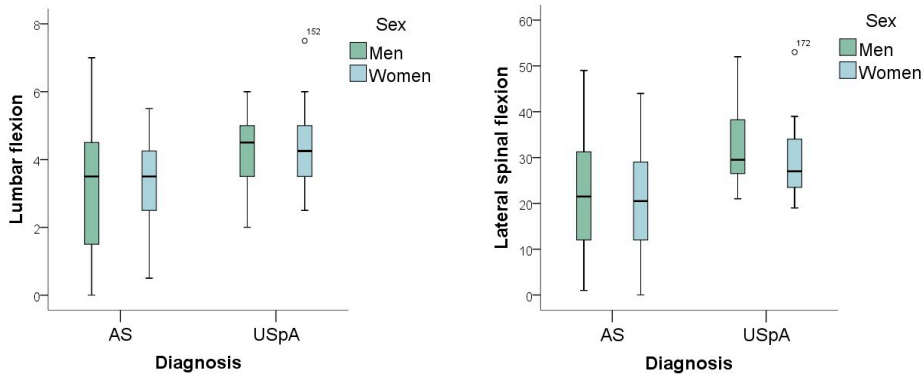
IV. **Mogard E**, Bergman S, Bremander A, Kristensen LE, Kvistgaard Olsen J, Olofsson T, Wallman JK, Lindqvist E. Chronic pain and assessment of pain sensitivity in patients with established axial spondyloarthritis – results from the SPARTAKUS study. Manuscript.

Thesis at a glance

Study I. Spinal mobility in axial spondyloarthritis

Patients and methods: This was a cross-sectional clinical study including 183 patients with axial involvement and a diagnosis of ankylosing spondylitis (AS) (n = 126) or undifferentiated spondyloarthritis (USpA) (n = 57), using the first measures of spinal mobility recorded between 1999 and 2012.

Conclusion: Patients with AS had more restricted thoracolumbar and lumbar spinal mobility than patients with USpA, but no difference was found in cervical and chest mobility measures. We found few differences in spinal mobility between women and men, apart from anthropometric measures.

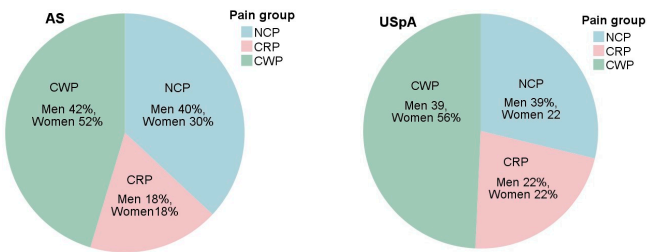


Illustrating worse thoracic and lumbar mobility in AS vs. USpA.

Study II. Prevalence of chronic widespread pain in patients with spondyloarthritis

Patients and methods: This was a cross-sectional population-based cohort study of chronic pain and associated factors. Responders (AS or USpA) to a postal survey (n = 887, 44% women) were categorised as having chronic widespread pain (CWP), chronic regional pain (CRP), or no chronic pain (NCP). Prevalence estimates of chronic pain for each SpA subgroup were obtained.

Conclusion: The prevalence of concomitant CWP in SpA is high (47%), and slightly more common in USpA than in AS, and in women compared to men (54% vs. 41%). There was no difference in pain intensity in women and men with chronic pain. Having CWP, as opposed to NCP/CRP, was associated with female sex, a higher BMI, and being an ever-smoker.

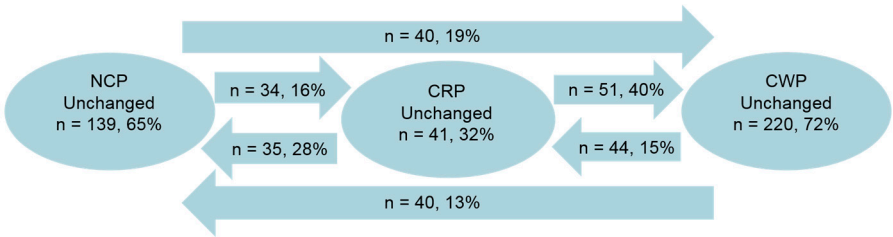


Prevalence estimates for CWP, CRP, and NCP in AS and USpA, and between men and women.

Study III. Risk factors for development and persistence of chronic widespread pain in spondyloarthritis

Patients and methods: This was a longitudinal population-based cohort study to identify risk factors for developing CWP and for having persistent CWP in patients with AS and USpA. Six hundred and forty-four patients (47% women) responded to a questionnaire, at baseline in 2009 and at follow-up in 2011.

Conclusion: The prevalence of concomitant CWP in SpA remained high over time. Risk factors for developing CWP and having persistent CWP included more pain regions, higher pain intensity, worse fatigue, worse global health, worse health status, higher disease activity, lower physical function, higher depression, and lower self-efficacy for handling pain and disease symptoms. In addition, female sex and older age were predictive of persistent CWP.



Illustrating patients who transitioned to and from the pain groups between 2009 and 2011.

Study IV. Chronic pain and assessment of pain sensitivity in patients with established axial spondyloarthritis – results from the SPARTAKUS study

Patients and methods: This was a cross-sectional clinical study to assess different aspects of pain (intensity, duration, distribution, and pain sensitivity) in subgroups of axial SpA (AS or USpA). Patients were enrolled consecutively over 2 years (n = 226, 51% women).

Conclusion: Forty-eight per cent of the patients with axial SpA reported having CWP, with similar pain intensity, pain threshold, pain tolerance, and temporal summation of pain in the AS and USpA subgroups. A higher proportion of women reported having CWP and had higher pain intensity levels, and lower pain tolerance than men. Lower pain tolerance was associated with worse outcomes in disease activity, fatigue, and spinal mobility.

Authors' contributions

Paper I
Study design: Elisabeth Mogard, Elisabet Lindqvist, Stefan Bergman, Ann Bremander.
Data collection: Elisabeth Mogard, Elisabet Lindqvist.
Data analysis: Elisabeth Mogard, Elisabet Lindqvist, Stefan Bergman, Ann Bremander.
Manuscript writing: Elisabeth Mogard.
Manuscript revision: Elisabet Lindqvist, Stefan Bergman, Ann Bremander.

Paper II
Study design: Elisabeth Mogard, Ann Bremander, Elisabet Lindqvist, Stefan Bergman.
Data collection: Ann Bremander, Stefan Bergman.
Data analysis: Elisabeth Mogard, Ann Bremander, Elisabet Lindqvist, Stefan Bergman.
Manuscript writing: Elisabeth Mogard.
Manuscript revision: Ann Bremander, Elisabet Lindqvist, Stefan Bergman.

Paper III
Study design: Elisabeth Mogard, Elisabet Lindqvist, Ann Bremander, Stefan Bergman.
Data collection: Ann Bremander, Stefan Bergman.
Data analysis: Elisabeth Mogard, Elisabet Lindqvist, Ann Bremander, Stefan Bergman.
Manuscript writing: Elisabeth Mogard.
Manuscript revision: Elisabet Lindqvist, Ann Bremander, Stefan Bergman.

Paper IV
Study design: Elisabeth Mogard, Stefan Bergman, Ann Bremander, Lars-Erik Kristensen, Tor Olofsson, Johan K Wallman, Elisabet Lindqvist.
Data collection: Elisabeth Mogard, Jack Kvistgaard Olsen, Tor Olofsson, Johan K Wallman, Elisabet Lindqvist.
Data analysis: Elisabeth Mogard, Stefan Bergman, Ann Bremander, Jack Kvistgaard Olsen, Tor Olofsson, Johan K Wallman, Elisabet Lindqvist.
Manuscript writing: Elisabeth Mogard.
Manuscript revision: Stefan Bergman, Ann Bremander, Lars-Erik Kristensen, Jack Kvistgaard Olsen, Tor Olofsson, Johan K Wallman, Elisabet Lindqvist.

Abbreviations

Aa-IBD	Arthritis associated with Inflammatory Bowel Disease
ACR	American College of Rheumatology
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASES	Arthritis Self-Efficacy Scale
AxSpA	Axial SpondyloArthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
bDMARD	biological Disease Modifying Anti-Rheumatic Drugs
BMI	Body Mass Index
CRP	Chronic Regional Pain
CWP	Chronic Widespread Pain
csDMARD	conventional synthetic Disease Modifying Anti-Rheumatic Drugs
DMARD	Disease Modifying Anti-Rheumatic Drugs
ESSG	European Spondyloarthropathy Study Group
EULAR	European League Against Rheumatism
EQ-5D	EuroQol-5 Dimensions
HADs	Hospital Anxiety and Depression scale
HLA-B27	Human Leukocyte Antigen B27
HRQoL	Health-Related Quality of Life
IASP	International Association for the Study of Pain
IBP	Inflammatory Bowel Disease
ICF	International Classification of Functioning, Disability and Health
ICD-10	International Classification of Diseases 10th revision
JIA	Juvenile Idiopathic Arthritis
MASES	Maastricht Ankylosing Spondylitis Enthesis Score
Mod NY	Modified New York
MRI	Magnetic Resonance Imaging
NCP	No Chronic Pain
nr-axSpA	non-radiographic axial SpondyloArthritis
NRS	Numeric Rating Scale
NSAID	Nonsteroidal Anti-Inflammatory Drugs
OMERACT	Outcome Measures in Rheumatology
PROM	Patient-Reported Outcome Measures
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis

r-axSpA	radiographic SpondyloArthritis
ReA	Reactive Arthritis
SHR	Skåne Healthcare Register
SpA	Spondyloarthritis
TNFi	Tumor Necrosis Factor inhibitor
TS	Temporal Summation
TSI	Temporal Summation Index
USpA	Undifferentiated SpondyloArthritis
VAS	Visual Analogue Scale
WHO	World Health Organization

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Introduction

Many patients with spondyloarthritis (SpA) suffer from chronic back pain and stiffness long before they get an accurate diagnosis and treatment. This can cause great suffering for the individual patient, and can lead to a variety of consequences that may impair quality of life throughout the lifelong disease course. For optimal management there are now international recommendations, which include a multidisciplinary approach with both non-pharmacological and pharmacological treatment alternatives for patients with SpA. The non-pharmacological treatment recommendations include education, but also individually tailored regular physical activity and exercise throughout the disease course. During the last two decades, the addition of biologic anti-rheumatic drugs has markedly widened the options for treatment of the underlying condition but, even so, many patients continue to report having chronic pain, impaired physical function, and consequences regarding their overall health.

During my career as a physiotherapist, I have met many patients in the diverse group with SpA, those with poorly differentiated disease and patients in the early or more established stages of the disease. The patients have presented with a variety of symptoms, including fluctuating pain or more chronic pain and stiffness, and many have had individual ways of handling their symptoms and other consequences of the disease. The work has been both challenging and rewarding, and has increased my interest in learning more about this heterogeneous patient group. An effort to coach each patient individually, and take into account his or her facilitators, barriers and goals, both in the early stages of the disease and later on, is essential in physiotherapy. Together with the team, the aim is to maintain or increase physical functioning, to limit pain and other consequences of the disease, and to increase each patient's independence and ability to engage in different treatment decisions. Our knowledge regarding patients with SpA is increasing rapidly, but is still mostly based on men with ankylosing spondylitis (AS), which is why studies that also include women and less typical SpA are needed. Different sets of classification criteria for SpA have been developed over time, and sometimes these have been used to aid in the diagnostic steps. However, the diagnosis as set in Sweden today using diagnostic codes does not completely correspond to the newest classification criteria in axial SpA and peripheral SpA. The clinical diagnoses AS and undifferentiated spondyloarthritis (USpA) have been used throughout the thesis, and in Paper I and IV the patients also had an axial disease. The overall objective in this thesis concern differences between patients with AS and those with USpA, and differences between women and men regarding pain and physical function. This work will hopefully add new knowledge to the diverse picture of SpA and its consequences, and also help in the clinical management of women and men in the wider perspective of SpA.

Background
Spondyloarthritis

The terms spondyloarthritides and seronegative spondarthritides were introduced for the first time in the mid-1970s by Moll et al. (1), who proposed a unifying concept for a heterogeneous group of rheumatic disorders with inter-related clinical and genetic features (2, 3). The history of SpA started long before with historic findings indicative of ankylosing spondylitis (AS), the prototype of the SpA family, in both animals and humans (4). The first description of AS can be dated back to 1559 when in the book De Re Anatomica, Realdo Colombo described anatomical anomalies suggestive of AS in two Egyptian mummies (2). The Irish physician Bernard Connor is acknowledged as the first to describe the clinical features of AS in his medical thesis in 1691, and a few years later he also wrote about the remains of a person with a fused spine and thorax with typical AS-related changes (3). In the late nineteenth century, AS became more recognized and regarded as a disease in itself (4), when three physicians, Vladimir von Bechterew in Russia, Adolph Strümpell in Germany, and Pierre Marie in France all described individual cases with AS (2, 3). For a long time, AS was then regarded as Bechterew`s disease, and still is in some places. In the mid-1900s advances in medicine (radiographic, epidemiological, clinical, and genetic) caused several rheumatologists to question whether AS was related to Reiter`s syndrome (today, reactive arthritis; ReA) and later to psoriatic arthritis (PsA), leading up to the modern concept of spondyloarthritis (1, 3).

As proposed by Moll et al. in 1974, the SpA family originally included AS, ReA, PsA, juvenile onset SpA, and arthritis associated with inflammatory bowel disease (Aa-IBD), but in 1991 this was modified by the European Spondylarthropathy Study Group (ESSG) to also include the undifferentiated forms of spondyloarthritis (USpA) (5). To facilitate communication among health professionals, the generic term “spondyloarthritis” is now recommended by the European League Against Rheumatism (EULAR), and the Assessment of SpondyloArthritis international Society (ASAS) (6-10). The term was chosen to capture the inflammatory nature, and also to cover the whole spectrum of the SpA diseases (6). The term spondyloarthritis is derived from the Greek words for vertebra, “spondylos”, and joint, “arthron”, and ends with the suffix “itis” which means inflammation.

Diagnosis and classification of SpA

This thesis focuses on patients with SpA and a diagnosis corresponding to AS (M45) or USpA (M46.0, M46.1, M46.8, M46.9) according to the International Classification of Diseases, Tenth Revision (ICD-10), (Table 1). The ICD-10 is a common and widely accepted classification system, developed and endorsed in 1990 by the World Health Organization (WHO) (11). The Swedish version of the ICD-10 (ICD-10-SE) was introduced by the Swedish National Board of Health and Welfare, and is used to describe and group diseases in clinical healthcare settings and in different registers. In Sweden, an overall tax-based system is used to finance both public and private healthcare. The system requires that all healthcare providers should submit information, including an ICD-10 diagnosis, for reimbursement purposes, which in turn ensures a high quality of information reported.

Table 1. The ICD-10 diagnostic codes for AS and USpA

SpA subgroup	ICD-10 code	Diagnosis, full description
AS	M45	Ankylosing spondylitis
USpA	M46.0	Spinal enthesopathy
	M46.1	Sacroilitis, not elsewhere classified
	M46.8	Other specified inflammatory spondylopathies
	M46.9	Inflammatory spondylopathy, unspecified

ICD-10, the International Classification of Diseases, 10th revision; AS, ankylosing spondylitis; USpA, undifferentiated spondyloarthritis; SpA, spondyloarthritis.

An early and correct diagnosis of SpA is important to initiate treatment and reduce functional impairment and other consequences of these lifelong diseases (12). In recent years, this has become even more important with the availability of new and more effective pharmacological treatments (13-15). There are no universal diagnostic criteria for SpA and most other rheumatic diseases, since diagnostic criteria must reflect the broad nature of the disease and also include patients at an undifferentiated stage of the disease, and patients with more unusual features. In rheumatology, physicians commonly base the individual diagnosis on a combination of signs and symptoms, different clinical tests, and information regarding the specific epidemiology in each area (16).

In contrast to diagnostic criteria, the purpose of classification criteria is to create well-defined and more homogenous cohorts for clinical research, and to provide a uniform language (17). The classification criteria for patients with SpA was for a long time focused on AS, with the first classification criteria presented in 1961 (the Rome criteria) (18), followed by the New York criteria in 1966 (19) and the well-established and widely used modified New York (mod NY) criteria in 1984 (20). Since the mod NY criteria require definite radiographic sacroiliitis for

fulfilment of the AS criteria, at the beginning of the 1990s it was acknowledged that patients with either early or more atypical forms of SpA were being inadequately recognized. Thus, the Amor criteria and the ESSG criteria (5, 21), were designed to cover the whole spectrum of the SpA diseases, including patients with USpA, and higher priority was given to clinical variables (Figure 1).

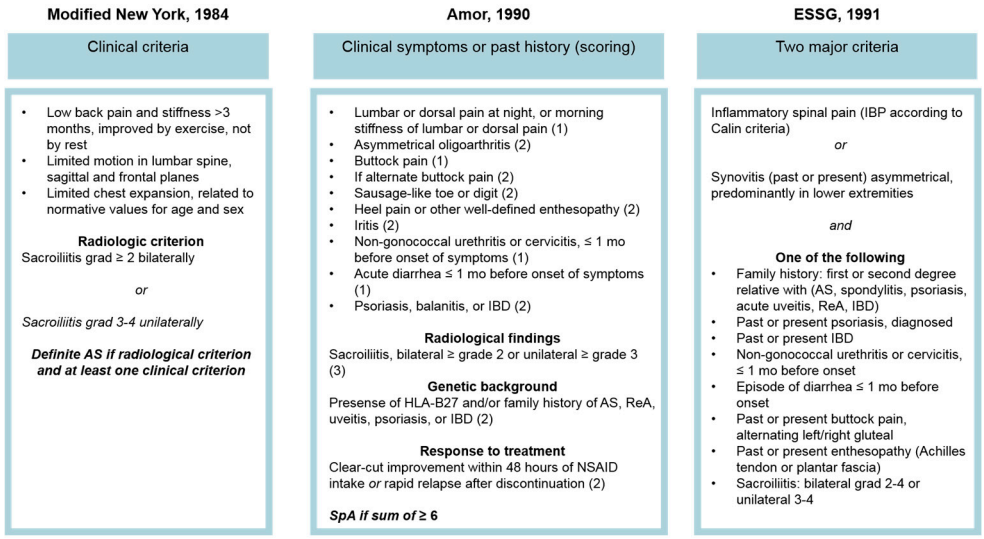

Figure 1. Classification criteria sets for ankylosing spondylitis and spondyloarthritis in general. Modified New York criteria: van det Linden et al,1984. Amor criteria: Amor et al, 1990. ESSG criteria: Dougados et al, 1991.

However, with the introduction of more effective treatments and the possibility of detecting inflammation in the sacroiliac joints by magnetic resonance imaging, the problem of a long delay to a definite diagnosis, or even a missed diagnosis in the absence of definite radiographic sacroiliitis, was brought to light (22). All of this contributed to the development of the new internationally agreed classification criteria by the ASAS, whereby patients are differentiated according to their clinical presentation as having predominantly peripheral SpA (pSpA) or predominantly axial SpA (axSpA) (8-10).

In addition, axSpA is differentiated as either non-radiographic axSpA (nr-axSpA) or radiographic axSpA (r-axSpA). A definition of axSpA has been presented as follows: *"the presence of sacroiliitis by radiography or by magnetic resonance imaging (MRI) plus at least one SpA feature ("imaging arm") or the presence of HLA-B27 plus at least two features ("clinical arm")*" (9) (Figure 2).

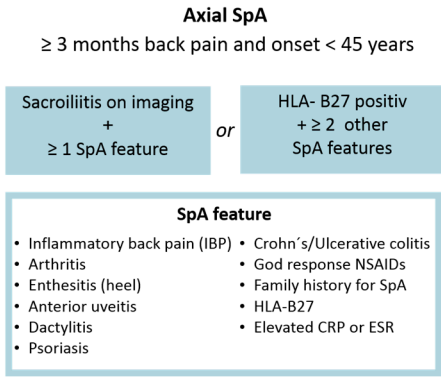

Figure 2.The Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial spondyloarthritis, Rudwaleit et al, 2009.

The new axSpA criteria were primarily intended to classify patients with nr-axSpA in clinical trials and observational studies, and were not for diagnostic purposes. However, the wider term axSpA has been proposed more recently to be used also in diagnosis of patients, unless there are medical reasons to differentiate AS from nr-axSpA (23) (Figure 3).

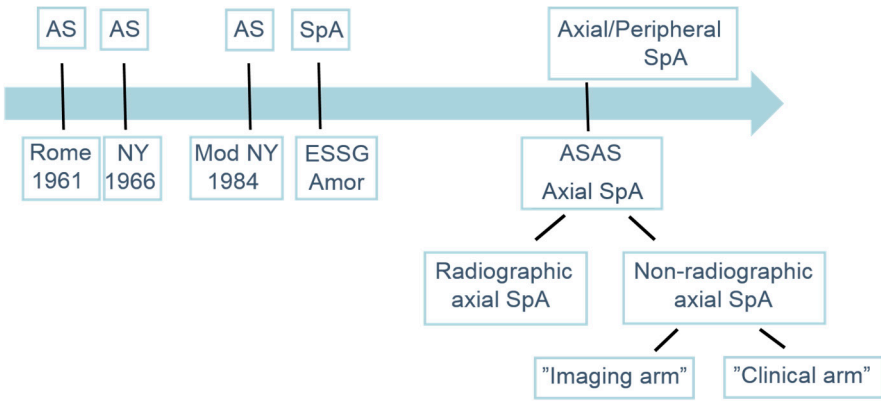

Figure 3. Timeline of different classification criteria developed for SpA.

Patients with SpA have several characteristics in common, including inflammatory back pain, arthritis in peripheral joints, enthesitis, and extra-articular features of the gut, eyes, and skin. They are also genetically associated with expression of the human leukocyte antigen (HLA)-B27 (5, 24-26). AxSpA typically starts with inflammatory back pain in a majority (80%) of the patients, causing pain and stiffness in the lower back and in the sacroiliac joints. Inflammatory back pain is

defined as onset < 40 years of age, back pain for more than 3 months, insidious onset, morning stiffness, and waking up during the night and in the early morning. Inflammatory back pain will improve with exercise but not with rest (27, 28).

AS, is the prototype in the SpA family of disease and is the most well-characterized and well-described subgroup. Most patients develop the first symptoms before the age of 30 years (29), and it is also the group with the strongest association with the HLA-B27 epitope, although there are differences in specific populations (30). Another typical feature is inflammation in the axial skeleton, particularly in the sacroiliac joints (2), with subsequent development of new bone formation, syndesmophytes, and ankylosis (31, 32). To fulfil the mod NY criteria for AS one of the requirements is impaired mobility in the lumbar spine. This differs from the ASAS criteria for r-axSpA, where impaired spinal mobility is not a requirement.

USpA is another common but less well specified and described SpA subgroup with a variable disease course (5, 33). There are no formal classification criteria for USpA, but the group can include patients who fulfil the Amor or ESSG criteria (34) and patients with nr-axSpA, peripheral SpA, or a combination of these (9, 10, 33). A proportion of the USpA population has been found to progress to AS after some years, while some of the patients remain at the undifferentiated stage (35-37). The progression to AS has been associated with a low-grade sacroiliitis, the HLA-B27 epitope, and buttock pain (38, 39). In this thesis, a predominantly axial disease could not be ensured in all included patients with USpA in Papers II and III. However, all patients who were diagnosed as PsA, ReA, or Aa-IBD were excluded; thus, a large proportion of the patients can be assumed to have axial disease or combined axial and peripheral disease.

Epidemiology

SpA is one of the most common rheumatic diseases, and prevalence estimates around the world has been reported to range from 0.01% in Japan to 2.5% in Alaskan Eskimos (34). The high variation in prevalence estimates of SpA among different ethnic groups and populations may to some extent depend on differences in the distribution of HLA-B27, but it can also be attributed to differences in methodology and the various classification criteria that have been used. In a recent study from the USA, the overall age-adjusted prevalence of SpA ranged between 0.9% (Amor criteria) and 1.4% (ESSG criteria) (40), and in Europe the prevalence estimates have been reported to range between 0.3% in France to 1.74% in Germany (41-45). In a population-based study carried out in the southern part of

Sweden, an overall crude prevalence of SpA was reported to be 0.45%, with the highest prevalence for PsA (0.25%), followed by AS (0.12%) and USpA (0.10%) (46), while a recent Swedish nationwide registry-based study, found a slightly higher prevalence of 0.18% for clinically diagnosed AS (47). Most studies that have estimated prevalence have been population-based or based on a selected population, which is why more accurate figures on axSpA according to the ASAS definition are difficult to obtain due to the requirement for either imaging (radiographic or MRI) or HLA-B27 testing. In a study from the United States that included patients aged 18–44 years seen by a rheumatologist, the age- and sex-adjusted axSpA prevalence was estimated to be 0.70%, where nr-axSpA represented half of the axSpA population with an estimated prevalence of 0.31–0.35%, and the prevalence of AS was 0.35% (48). There have been few studies on the incidence of SpA, and these reports have differed substantially, with incidence rates from 0.48 per 100,000 person-years in Japan to 62.5 per 100,000 person-years in Spain (49, 50).

In the overall population of patients with SpA the male-to-female ratio is most often reported to be about 1:1 (15, 40-42, 46, 51). Historically, AS has been reported to affect a higher proportion of men than women, with a current estimated male-to-female ratio of about 2:1 to 3:1 (29, 52). However, both in a recent study from Canada (53) where the authors reported an overall increase in the prevalence estimates of AS from 1995 to 2010 (diagnosed as ICD-9 720 or ICD-10 M45), and in a previous German survey (54), an increase in the percentage of female patients being diagnosed with AS has been found during the last few decades.

Consequences of the disease

The chronic, inflammatory nature and the fact that SpA often starts early in life, can have consequences for many aspects of patients' well-being and health. The disease course is also highly variable and can include a variety of features in addition to axial and peripheral arthritis, such as enthesitis, and other extra-articular manifestations, which all contribute to the burden of disease. Pain, fatigue, functional impairment, anxiety and depression, reduced quality of life, and reduced ability to work are all well-known consequences of SpA in general (55-60). In addition, similar prevalence of concomitant fibromyalgia, as in other rheumatic diseases (61) has been reported in patients with axSpA (62, 63). In comparison to AS patients, those with USpA are often younger, have a low-grade sacroiliitis, have less frequently inflammatory back pain, and less syndesmophytes (36). Even though patients with USpA appear to have a milder disease they often

report having a similarly high disease activity (33) and have similar consequences such as anxiety, depression (64), reduced physical activity, and reduced productivity at work as patients with AS (59). In addition, patients with nr-axSpA have been found to report similar burden of illness in regard to disease activity, physical function, pain, and health-related quality of life (HRQoL) as their counterparts, even though those with r-axSpA have more structural damage, a higher degree of inflammation (C-reactive protein and inflammation registered on MRI), and worse spinal mobility restrictions (65). In patients with AS, the main factors contributing to diminished HRQoL were found to be pain, stiffness, fatigue, poor sleep, and functional impairment (66). Moreover, there is evidence for an increased risk of cardiovascular disease in both patients with AS and USpA compared to the general population (67-72), and patients with AS have been found to have lower cardiorespiratory fitness than controls (73, 74). More recently, it has also been suggested that patients with axSpA and longer disease duration are less likely to attain remission (14, 75).

In addition to the described sex difference in the prevalence of AS, there are some other differences between men and women with SpA that should be considered. In previous studies it has been found that men with AS have more severe thoracic and lumbar radiographic findings than women, while women have more neck- and peripheral joint pain, and are more often treated with drugs used for peripheral arthritis, such as methotrexate, sulfasalazine, and prednisolone (76, 77). Women with SpA often report having higher disease activity, worse physical and mental functioning, worse fatigue, and lower HRQoL, compared to men with SpA (78-81). The above sex differences have been suggested to influence both the treatment of axSpA and how and when the diagnosis is set (76, 82), and the fact that AS was considered to be a male disease may also have contributed to under-recognition in women and a longer delay to diagnosis (77, 83). Moreover, it has been reported that a higher proportion of women are diagnosed with AS later in life (between 45 and 65 years) than men, who are more often diagnosed in early adulthood (53).

SpA management

The main goal in the treatment strategies for SpA is to maximise HRQoL and social participation throughout the lifelong disease course, by controlling signs and symptoms such as pain, structural changes, function, and comorbidities (84, 85). Through a collaboration between the ASAS and the EULAR, uniform recommendations for management of SpA were published in 2006 and have been

updated twice since then (2010 and 2016). The recommendations were initially developed for patients with AS (84, 86, 87), but with the version updated in 2016 they are also aimed for patients from the wider standpoint of axSpA, including patients at the non-radiographic stages (88). The overall principle in the recommendations is that an optimal management requires a multidisciplinary approach and a combination of pharmacological and non-pharmacological treatments. As in other rheumatic conditions, an individualised treatment strategy is important to control symptoms and inflammation, and to prevent structural damage, improve function, and improve the patient's ability to participate in society.

Pharmacological treatment

The primary treatment choice in patients with SpA and axial involvement is anti-inflammatory treatment such as NSAIDs, together with physiotherapy to effectively relieve pain and stiffness throughout the disease course (88-92). There are some findings that non-steroidal anti-inflammatory drugs (NSAIDs) may retard the progression of structural damage in the spine, but also some conflicting findings, and therefore needs to be investigated further (93-95). In patients with axSpA, long-term treatment with systemic glucocorticoids are not recommended in the management, but glucocorticoid injections for local musculoskeletal inflammation may be an optional treatment for both arthritis and enthesitis. Synthetic disease-modifying anti-rheumatic drugs (sDMARDs) have no clear effect in axial disease, but for those with combined axial and peripheral disease (and purely peripheral disease) sulfasalazine and methotrexate may be considered. The recommendations regarding biologics (bDMARDS) have recently been updated, and today the options also include bDMARDs other than the previously approved tumour necrosis factor inhibitors (TNFi) for patients with axSpA. Biologics should be considered in those patients that despite conventional treatment, continues to have high disease activity and the current practice is to start with TNFi (88). Also, the Swedish recommendations are updated by the Swedish Society for Rheumatology, on an annual basis. (96). As with all pharmacological treatments, a careful monitoring of the benefits and risks of the treatment initiated is advised (88).

Non-pharmacological treatment

Non-pharmacological treatments have an important role in the management of all patients with SpA, and the inclusion of different team members is required. Guidelines and EULAR/ASAS recommendations include patient education to increase the involvement of the patient in disease management and health

promotion (88, 97). Lifestyle changes such as regular exercise, cessation of smoking, and self-management to handle pain and other disease manifestations are also part of the recommendations (98, 99). In general, these treatment recommendations are the same in patients with different chronic inflammatory diseases. Recently, EULAR also published recommendations for the management of pain in patients with inflammatory arthritis (100). Important principles in those recommendations state that assessment and treatment should be patient-centred and include a biopsychosocial approach. Treatment modalities representing both pharmacological treatment for optimal control of the underlying disease and non-pharmacological treatment are emphasised. Moreover, health professionals should have sufficient knowledge regarding different types of pain, including CWP and when needed more comprehensive and multidisciplinary pain management is advocated.

Physiotherapy interventions in rheumatology have changed considerably over the past decades and the focus today is on more active exercises to improve muscle function, aerobic capacity, and overall health—as opposed to mostly passive treatments to improve joint mobility. That regular, home-based exercises are encouraged in patients with SpA is well known, but group exercises on land or in water that are supervised by physiotherapists have been found to be even more effective for improving spinal mobility and patients global assessment (92). Different forms of rehabilitation have also been found to reduce disease activity and pain, and improve general functioning, spinal mobility, HRQoL (101-105), and aerobic capacity (106).

In physiotherapy in general, one aim is to maintain or regain optimal mobility and movement behavior, as this is a base for a person's functional ability and a way to reach individual goals (107). To promote physical activity and exercise is therefore essential in SpA, and was just recently recommended by EULAR as an integral part in the individual care for all patients with inflammatory arthritis. The recommendations emphasise, that physical activity and exercise interventions should be performed by competent healthcare providers, such as physiotherapists, and with regular assessments of each person's individual aims (108). Physical exercise is a subcategory of the broader term physical activity, and is defined as a planned, structured, and repetitive intervention, and the aim is to improve or maintain physical fitness to be able to perform activities in daily life (109). In patients with AS, improved spinal mobility has been reported to correlate with both short- and long-term physical function (110), and flexibility training in combination with cardiovascular exercise has been found to reduce pain and increase fitness in patients with AS (111). In a pilot study, high-intensity cardiorespiratory and strength exercises were also found to improve disease activity and reduce cardiovascular risk factors in patients with axSpA (112). Most mobility and exercise studies have been performed in patients with AS or with

established axSpA, including a high percentage of men, and little is known regarding patients with USpA and women with SpA.

Health

The World Health Organization (WHO) has stated that "health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (113). This definition does not distinguish between physical bodily well-being, and mental and social well-being. Thus, health outcomes in general and in inflammatory arthritis aim to include different aspects of health and illness to capture all the different consequences for a person's life (114, 115), adhering to a biopsychosocial perspective. The biopsychosocial model proposed by Engel in 1977, was intended as a development and a challenge of the biomedical model of disease. Engel wanted to include both emotional, subjective aspects of illness and disease, and the social context for the patient, including the treating physician and the health system (116). The WHO's International Classification of Functioning, Disability and Health (ICF) is also a biopsychosocial model designed to provide a coherent view of various dimensions of health and disability at the biological, individual, and social levels (114). The ICF provides domains to describe human functioning in terms of body structure, body function, activity, and participation—all viewed in relation to the health condition, and personal, environmental, and contextual factors. A large number of categories within the domains serve as descriptions of what could be relevant for a person with a specific condition, and the actual state of functioning. (114). The universal principle of ICF is that functioning and disability are applicable to every human and vary over a person's lifetime (117). The ICF can also facilitate communication among health professionals regarding functioning and health, and be of use to assess patient's needs to plan and evaluate rehabilitation interventions (118-120).

Physical function

Movement is the basis of a person's functional ability, and a way of reaching individual goals—and accordingly, health and HRQoL (107). For patients with chronic inflammatory arthritis, impaired physical function contributing to activity limitations and participation restrictions is a major consequence. This has also been found in patients with AS who report substantial limitations in functioning and limitations in daily activities (78, 121, 122). Patients with nr-axSpA report

similar disease burden and impaired physical function as their counterparts with radiographic disease (65, 123), and already in early axSpA, physical function has been reported to be mildly affected and related to worse disease activity (124). Moreover, in AS functional limitations have been found to be greater for those with longer disease duration, with more physically demanding jobs, with more comorbid conditions, and in smokers (125). In patients with USpA, however little is known about physical functioning in any stages of disease duration.

Contributing to impaired physical function, reduced spinal mobility is an important clinical feature frequently affecting patients with AS. Reduced spinal mobility is associated with a number of factors such as radiographic changes, age, disease duration, function, and general health (31, 126-128), and both spinal inflammation and irreversible structural damage may independently account for impaired spinal mobility. The finding that inflammation more often causes the limitations in early disease and structural damage more often causes the limitations in later disease highlights the importance of early treatment to maintain spinal mobility (31, 128). Few clinical studies have assessed spinal mobility in patients with USpA (33).

Assessments of physical functioning in SpA

To assess physical functioning, methods such as self-reported questionnaires and performance tests are frequently used. They have all different strengths and limitations, and should be used complementary (129). Self-reported measures captures the patient's perception of their own overall physical functioning (130), and are easy to administer. Assessment of physical function is valuable for several reasons, such as to help in planning of interventions (131), in assessments regarding the impact of a health condition for a patient, and in evaluating the effects of health interventions (132). Moreover, information on functioning is important when it comes to healthcare planning, resource allocation, and health policy (133).

To reflect function in a standardised way, with a minimal number of categories that accurately describe typical and relevant impairments, limitations, and restrictions, the network Outcome Measures in Rheumatology (OMERACT) and the ASAS Core sets of outcome measures were developed (134). A majority of the components in the core sets for AS relate to pain and mobility, to reflect the inflammatory process in the spine, joints, and entheses (135, 136). The core sets are intended to be used in clinical trials and clinical practice with AS and axial SpA subgroups. There are core sets for three different settings with a minimum of variables recommended for each domain. All the instruments included are validated and feasible (137). The core set for symptom-modifying Anti-rheumatic Drugs (SM-ARDs) and/or physiotherapy is the "inner circle", and includes,

physical function, spinal stiffness, patient's global assessment, spinal mobility, pain, and fatigue. In addition to the above variables, peripheral joint count, entheses, and acute-phase reactants are also included for clinical record keeping. In the core set for DMARDs, a radiographic assessment of the spine is also included in addition to all the above-mentioned variables. The core domains physical functioning and spinal mobility are also important outcomes in the wider concept axSpA, and are included to follow disease severity (138, 139).

In subjects with axSpA, a common method to follow physical functioning is the BASFI (140), it was designed by a multiprofessional team to assess the patients' perception of daily activities. It is included in the ASAS core sets and the preferred measure to assess physical function in axSpA (137, 141). Measures of spinal mobility are valuable in the clinic, as loss of mobility can be an early feature of axSpA, and can be used to guide and follow treatments during the disease course. The recommended spinal mobility measures in the ASAS core sets include: chest expansion, *and* modified Schober (lumbar flexion), *and* occiput to wall, *and* cervical rotation, *and* lateral spinal flexion, *or* the Bath Ankylosing Spondylitis Metrology Index (BASMI) (138, 142). Spinal mobility measures are used in the classification criteria of AS (20) and has been reported to be a prognostic factor for the long-term outcome in AS (143).

Pain

Back pain, a prominent feature in patients with SpA, is common in the general population with a global age-standardised point prevalence of 9.4%. The prevalence is highest in ages 40-80 years and has a great impact on disability (144). Only a very small percentage of this large group has axial inflammation typical of SpA. Patients with axial inflammation commonly report their back pain to be a dull, localized pain deep in the pelvic and/or the spinal region (2), but pain in other locations such as peripheral joints and entheses is also often described by patients with SpA (25, 26). Measures of pain does not always correlate well with inflammation or radiographic measures (145), and some patients report continued pain despite being well treated (146, 147). It has been suggested that pain in SpA, as in other diseases, has a multifactorial background with both peripheral and central mechanisms being involved. This may in part be due to ongoing chronic inflammation and joint damage (148), but it may also involve other biopsychosocial factors (149, 150). There is still limited information on chronic pain in patients with SpA, and on possible differences between SpA subgroups and between men and women.

The International Association for the Study of Pain (IASP) has described pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (151). The

definition is widely accepted and it highlights an important principle in the concept of pain, that it is a subjective emotional and personal phenomenon and a unique experience for every individual. To interpret pain, it is important to view it as a complex physiological experience, with differences in meaning and importance for different peoples and in different contexts (152).

Clinical classification of pain

There are different clinical types of pain based on the underlying mechanisms, which are important to recognize (153). One is nociceptive pain, an acute warning and protective signal that detects and protects us from damaging or noxious stimuli. This includes inflammatory pain caused by an activation of the immune system after tissue damage (e.g. injury, infection). It assists in the healing process through heightened sensory sensitivity that promotes healing and reduces further risk of damage. Even though this pain is protective and adaptive, it still needs to be reduced in patients with ongoing inflammation or severe injury. A second type of pain is neuropathic pain, where there is damage or disease in the somatosensory system, leading to pain. In rheumatology, this can be due to direct mechanical pressure on the nerves from inflammatory swelling, and deformed joints or vertebrae. A third type of pain, nociplastic pain, results from a dysfunction of the nervous system, with central sensitisation and loss of central inhibition in the spinal cord. This type of pain often has a complex background and can be seen concomitant with other causes of pain (nociceptive or neuropathic), but in itself it can also be the main cause of a disorder such as in fibromyalgia (154).

Chronic widespread pain

Musculoskeletal pain is a common complaint in different rheumatic diseases, and also in individuals without any specific pathological process. When pain becomes chronic it can lead to more widespread pain conditions (155), as the risk of developing pain at other sites increases with having pain at one site (156). The term chronic pain is used in the meaning of “longstanding pain”, a term more often used in the clinical practice in Sweden. The classic definition (by IASP) of chronic pain used to be “pain which persists past the normal time of healing” (157); however, this term has been updated since the previous definition suggested that chronic pain was a prolonged acute pain. The updated IASP definition of chronic pain is “persistent or recurrent pain lasting longer than three months” (158). The three-month limit for chronic pain has also been used for a long time in the ACR definition of fibromyalgia from 1990 (159).

In this thesis, the focus will be on chronic pain classified as chronic regional pain (CRP) and chronic widespread pain (CWP). There are different definitions of

CWP, and one has been developed by the ACR as part of the definition of fibromyalgia. It describes CWP as "pain that is present in both the left and right side of the body, above and below the waist, and in the axial skeleton (the cervical spine, the anterior chest, the thoracic spine, and the lower back)". Another is the Manchester definition, a more strict definition that was developed from the ACR definition, but it requires that there should be pain in the axial skeleton and pain in two sections in two contralateral limbs (160). Chronic pain that not fulfil criteria for a widespread condition could be defined as CRP (161).

CWP is a prerequisite for fibromyalgia (159), a condition that has been proposed to represent the more severe end of the CWP continuum (162). Fibromyalgia is a diagnosis that involves patients with generalized pain together with physical and psychological symptoms with no clear pathology (159). The prevalence of fibromyalgia in the general population has been estimated to range between 1% and 8%, depending on the criteria used (163-166), as compared to 11–15% for CWP (161, 167, 168). Fibromyalgia and CWP are both more common in women and in older individuals (161, 167, 168), and CWP has been reported to have a large effect on a person's health status (169). It is also associated with factors such as fatigue, depression, anxiety, poor sleep, and the ability to work (170-173). More severe symptoms, including higher pain intensity and greater consequences for daily life, have been reported in individuals classified as having fibromyalgia (compared to those with CWP, who did not fulfil the criteria for having fibromyalgia) (174).

Chronic widespread pain in SpA

Pain is a frequent and multidimensional symptom in inflammatory arthritis (175, 176), and today it is seen in a wider biopsychosocial context in which both the perception of and the reaction to pain are involved (149, 150). A number of factors can influence the experience of pain, including the underlying disease, personal susceptibility, and different psychosocial and environmental factors, so all these factors are important to acknowledge in the management of each individual (177). In chronic pain conditions such as SpA, peripheral ongoing inflammatory input can generate increased sensitivity in peripheral nociceptors and cause peripheral sensitisation. This may appear as allodynia (low-energy stimuli that are not normally painful), hyperalgesia (increasing pain with usually painful events), or a combination of the two, but it can also include resting pain (175, 178). The continuous nociceptive input (e.g. inflammation) and a heightened pain perception have also been suggested to eventually lead to central sensitisation, and subsequent chronic and persistent pain in some patients (179, 180).

Assessment of pain

Pain is multifaceted, and therefore pain assessments often include different dimensions, such as the duration, frequency, intensity, distribution, and quality of pain, but also how the pain may affect the patient's life, or the pain management. Pain is a subjective and personal experience, which is why objective assessments are not possible. This thesis will concentrate on different aspects of pain, including the duration and distribution of pain, the intensity of pain, and sensitivity to pain.

The duration of pain can be divided in acute or chronic, and the common definition of chronic pain is recurrent or persistent pain for more than three months (158). Pain drawings are commonly used and are reliable measures for assessment of the distribution of pain; these can include full-body drawings, more joint-specific drawings, or drawings with predefined body regions (181). To quantify pain intensity, the visual analogue scale (VAS) (182) or the numeric rating scale (NRS) (183) are simple and frequently used. Pressure algometry is a technique used to quantify sensitivity to pain, by inducing deep-tissue pain. Manually applied pressure to nociceptors in deep tissue is a widely used and validated technique (184, 185). To minimise the variability associated with a manual tool, computer-controlled pressure stimulation can be used to assess pain sensitivity by relating the pressure intensity to the pain response from the patient (186). One such device, the Dolocuff, was used for pressure algometry in this thesis (Paper IV).

Rationale for this thesis

An early onset of pain and stiffness is common in patients with SpA, and can result in a variety of physical and mental limitations affecting the patient's overall health throughout the lifelong disease course. Patients with SpA can during the disease course, experience periods with both fluctuating and more persistent pain, and development of chronic pain despite effective treatment. Recently, our general awareness of chronic pain and the difficulties in the management of chronic widespread pain in patients with rheumatic diseases, such as SpA have increased. Even so, up to now the few studies on chronic pain in patients with SpA have mainly focused on patients with AS and pain corresponding to fibromyalgia, a diagnosis that represents the severe end of the chronic widespread pain continuum. Improved knowledge regarding the whole spectrum of chronic pain, also in other SpA subgroups, is therefore essential for early and adequate treatment options.

A well-known consequence of the typical inflammatory back pain in patients with SpA is a progressive limitation in spinal mobility, which can be caused by both inflammation, particularly in early disease, and structural damage, in later disease. Assessments of spinal mobility can therefore be used as a tool to follow disease severity. In clinical practice, it is important to tailor the treatment to the individual and to help patients adhere to the recommendations of regular exercise throughout the long and variable disease course. As in most research in patients with SpA, knowledge regarding impaired spinal mobility has been based on patients with AS, which is why studies to gain information on patients with USpA, and on differences between men and women, may add to the overall picture of spinal mobility limitations in patients with SpA.

The USpA diagnosis refers to a less well-studied and variable group of patients, and has been suggested to include both patients with nr-axSpA and those with peripheral SpA, or a combination of the two. It has also been argued that USpA can in some cases be an early form of AS. However, the overall disease burden is equally high, and patients with USpA appear to respond to anti-TNF as well as patients with AS. Thus, a better understanding of similarities and differences between patients with USpA and AS, and between men and women, is essential—as an early diagnosis and adequate treatment, including both pharmacological and non-pharmacological treatment options, are of utmost importance for prognosis.

Aims

The overall aim was to study chronic pain and physical function in patients with SpA, diagnosed as AS or USpA, and to explore differences between the subgroups and between women and men.

Specific aims of the thesis

Paper I

To investigate differences in cervical, thoracic, and lumbar spinal mobility between patients with axial SpA, diagnosed as AS or USpA, and to study differences in spinal mobility with regard to disease duration and between women and men.

Paper II

To study differences in the prevalence of self-reported chronic widespread pain (CWP) in a population-based cohort of patients with SpA (AS or USpA), including differences between women and men.

Paper III

To study how CWP develops over time in patients with SpA, and to identify possible risk factors that would predict development of, and persistence of CWP.

Paper IV

To investigate different aspects of pain in subgroups of axial SpA, and associations between pain sensitivity and different health outcome measures.

Methods
Study design

This thesis involves patients with spondyloarthritis (SpA), diagnosed as ankylosing spondylitis (AS) or undifferentiated spondyloarthritis (USpA), from three different cohorts in the county of Skåne, the most southerly region of Sweden. Today, Skåne has a population of approximately 1.3 million inhabitants and is the second largest region in Sweden. Two of the studies were clinical observational studies (Papers I and IV) and two were population-based studies (Papers II and III). The studies in Papers I, II, and, IV had cross-sectional designs and that in Paper III was a longitudinal prospective study using two questionnaire-based postal surveys (Table 2). All patients who were eligible for inclusion were required to have a diagnosis corresponding to AS (M45.9) or USpA (M46.0, M46.1, M46.8, M46.9) according to ICD-10 codes (11).

Table 2. Characteristics of studies I–IV

Paper	I	II	III	IV
Subject of study	Spinal mobility	Prevalence CWP	Development of CWP	Chronic pain, pain sensitivity
Study design	Clinical Cross-sectional	Population-based Cross-sectional	Population-based Longitudinal	Clinical Cross-sectional
Data sources	Clinical cohort	SpAScania	SpAScania	SPARTAKUS
No of participants	183	940	712	226
Women, %	30	44	46	51
Age, years	46 (13)	52 (14)	53 (13)	51 (13)
Disease duration, years	21 (13)	23 (14)	24 (14)	25 (14)
Diagnosis, ICD-10 Selection criteria	AS or USpA, axial disease	AS or USpA	AS or USpA	AS or USpA axial disease

Presented as mean and SD unless otherwise indicated. CWP, chronic widespread pain; SPARTAKUS, SPondylARtrit TvÄrsnittsKohort Universitetssjukhuset i Skåne; AS, ankylosing spondylitis; USpA, undifferentiated spondyloarthritis

The Skåne Healthcare Register

Data from the Skåne Healthcare Register (SHR) were used to identify patients for the SpAScania cohort, and in Paper IV to validate the allocation of patients by the clinical booking system. Healthcare visits are predominantly tax-funded in Sweden and each region is responsible for providing equal health and medical care of good quality. The SHR includes information on all healthcare visits in primary

and specialised inpatient and outpatient care (public and private), including the healthcare provider, date of visit, and diagnostic codes according to ICD-10. The SHR is also linked to the Swedish Population Register through the use of a unique personal 10-digit identification number that is given to every resident in Sweden, which also provides information on age and sex.

Study populations

The patients in the spinal mobility cohort and the SPARTAKUS (SPondylARtrit TvÄrsnittsKohort Universitetssjukhuset i Skåne) cohort were identified from Skåne University Hospital registers at two different inclusion periods, and the patients in the SpAScania cohort were identified through the SHR. In Papers I and IV, patients with USpA had an axial disease; in Paper I, this was verified from medical records; and in Paper IV, it was verified using an initial screening procedure and thereafter by the physician. In Papers II and III, the patients were derived from the SpAScania cohort, and patients with USpA (ICD-10 code) could not all be distinguished regarding peripheral or axial SpA. The overlap between the four studies and the numbers of patients included are described in Figures 4 and 5.

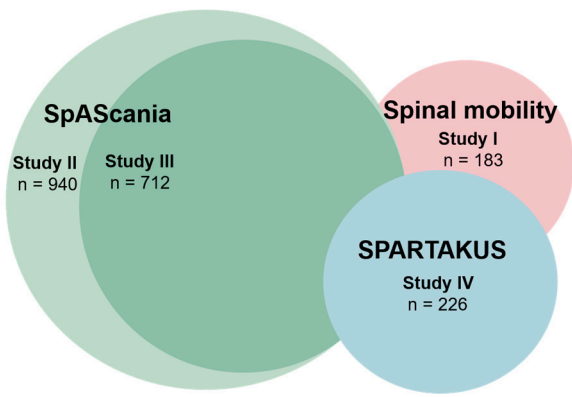

Figure 4. The study populations, no of participants and illustration of the overlap in Papers I–IV.

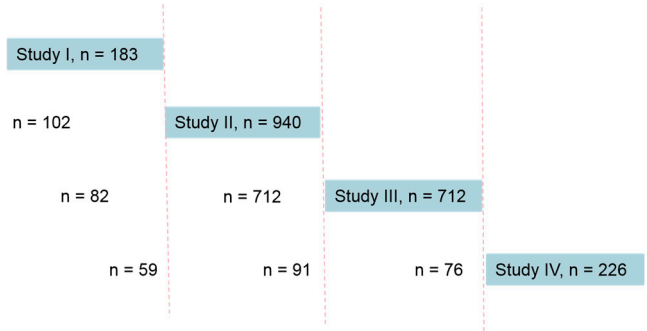

Figure 5. The study populations with numbers of participants included in more than one study.

The spinal mobility cohort

The patients in Paper I were identified from a clinical cohort at the Department of Rheumatology in Lund, Skåne University Hospital. The cohort included adult patients with a diagnosis of SpA who resided in the middle-Skåne healthcare district and attended the Department of Rheumatology in Lund during the period 2003–2007 (n = 723). All diagnoses were set by specialists in rheumatology according to ICD-10 codes, and a survey of the medical records was performed to verify the diagnoses during the period 2008–2009. The patients included were a subgroup of the clinical cohort, (Figure 6).

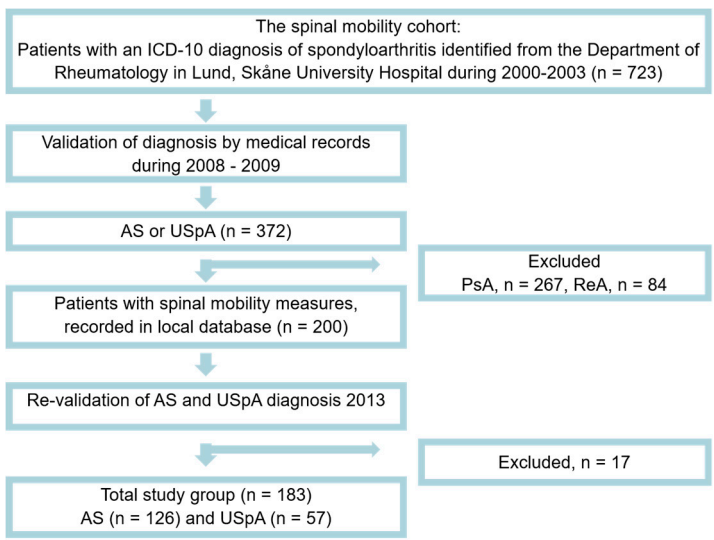

Figure 6. Flow chart of Study I.

Paper I involved patients with a diagnosis of AS, according to the mod NY criteria or USpA with axial involvement, according to medical records, i.e. they can be regarded as axial SpA. To be eligible for inclusion, the patients were also required to have measures of spinal mobility recorded in the journal system at the Department of Rheumatology in Lund, at least once between 1999 and 2012 (n = 200). All diagnoses were also verified in 2013 from medical records. Seventeen patients did not fulfil the diagnostic requirements for AS or USpA and were excluded. The final study population included 183 patients (AS, n = 126; USpA, n = 57). Experienced physiotherapists at the Department of Rheumatology in Lund had performed the spinal mobility assessments, and the first available measures recorded in the electronic medical records were collected in 2013. Variables included in Paper I are described in Table 3.

Table 3. Outcome variables included in papers I-IV.

Variables		Paper I	Paper II	Paper III	Paper IV
BASMI		x			x
Cervical lateral flexion		x			
Cervical flexion/extension		x			
Chest expansion		x			x
Thoracic flexion		x			
Thoracolumbar flexion		x			
Vital capacity		x			x
BASDAI			x	x	x
BMI			x	x	x
Fatigue			x	x	x
Pain intensity			x	x	x
Pain regions			x	x	x
Smoking, never/ever			x	x	x
ASES Pain/Symptom				x	
BASFI				x	x
EQ-5D				x	x
Global health				x	x
HADs Anxiety/Depression				x	x
ASDAS-CRP*					x
MASES					x
Pain sensitivity	Pain threshold				x
	Pain tolerance				x
	Temporal summation index (TSI)				x

*ASDAS-CRP is a combined measure with patient's assessment of back pain, peripheral pain/swelling, duration of morning stiffness and patient's global assessment and C-reactive protein. BASMI, Bath Ankylosing Spondylitis Metrology Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, Body Mass Index; ASES, Arthritis Self-Efficacy Scale; BASFI, Bath Ankylosing Spondylitis Functional Index; EQ-5D, EuroQol-5 Dimensions; HADs, Hospital Anxiety and Depression scale; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score-C reactive protein; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; TSI, Temporal summation Index.

The SpAScania cohort

Papers II and III involved patients with a diagnosis corresponding to AS or USpA, identified from the population-based SpAScania cohort. This cohort was identified at the end of 2007 by searching in the SHR for all healthcare-seeking patients (aged ≥15 years) who had received a SpA diagnosis, according to chosen ICD-10 codes, during the period 2003–2007 (46). To ensure a higher specificity of the SpA diagnoses included, a "strict criterion" was used. This required that the diagnosis was given on at least one occasion by a rheumatologist or a physician specialised in internal medicine, or twice (on two separate occasions) by any other specialist. In Paper II and III only patient's ≥ 18 years were included.

The SpAScania questionnaires

Self-reported information from two questionnaire-based postal surveys sent to patients in the SpAScania cohort was used to answer the research questions posed in Papers II and III. The baseline questionnaire was sent out in 2009 (from May to August) to all patients who were still alive, 18 years old or more, and resided in the county of Skåne in 2009. The stricter SpAScania cohort included 3,716 patients, 2,162 (58%) of whom returned the 2009 questionnaire. The second questionnaire was sent out 2.5 years later (November 2011 to January 2012).

In both postal surveys, reminders were sent on two separate occasions, within ten weeks of the first mailing of each questionnaire (Figure 7).

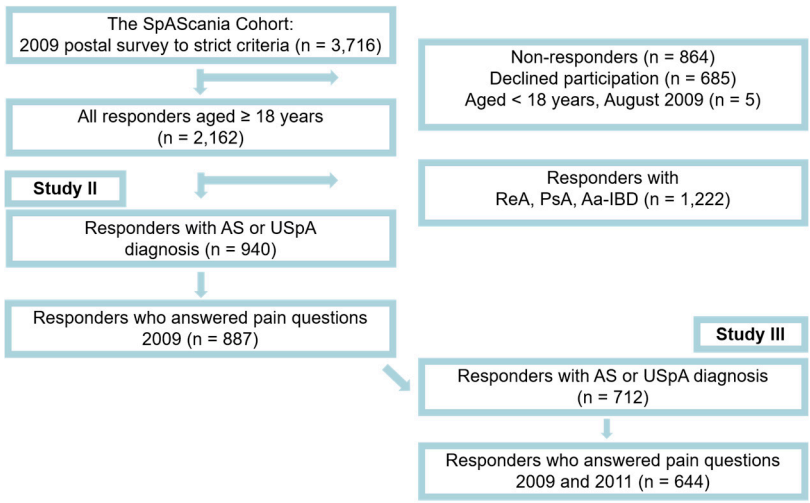

Figure 7. Flow chart describing Studies II and III.

Paper II included all patients with AS or USpA who answered the 2009 SpAScania questionnaire (n = 940). Information from the Swedish census population in 2009 was also retrieved to make age and sex adjustments in Paper II. In Paper III, all patients with AS or USpA who answered both the baseline and the follow-up SpAScania questionnaires in 2011 were included (n = 712).

The SpAScania questionnaire included a number of commonly used and well-validated patient-reported outcome measures (PROMs), and questions on patient characteristics, demographics, and pain. The questionnaire was tested in three focus groups consisting of a total of 20 patients with different SpA diagnoses and a patient research partner from the Swedish Rheumatism Association, to improve face validity and content validity. This resulted in minor corrections to improve patient's understanding before the first survey. Data from the SpAScania questionnaire have already been published (46, 59, 60, 64, 187-190). Variables included in Papers II and III are described in detail in Table 3.

The SPARTAKUS cohort

The patients in Paper IV were identified from an ongoing clinical cross-sectional study, SPARTAKUS, at the Department of Rheumatology (Lund and Malmö), Skåne University Hospital. The cohort included all patients with a diagnosis corresponding to AS or USpA who resided in the middle-Skåne healthcare district, and who—during the period 2011–2014—had at least one outpatient visit at the Department of Rheumatology (n = 645). SPARTAKUS is focused on axial spondyloarthritis (axSpA), according to the ASAS definition, which is why all patients with the ICD-10 codes M46.8 and M46.9 had to have reported back pain ≥ 3 months before the age of 45 years to be eligible for inclusion. The SPARTAKUS enrolment started in November 2015 and is still going on (August 2018). A validation of the eligible patients for inclusion in the SPARTAKUS was performed by using the same inclusion parameters as the initial search in the clinical booking system in the SHR. This search resulted in 651 eligible patients.

Paper IV included patients enrolled in the SPARTAKUS study during the first two years (n = 230). Of these, four patients were excluded, one due to not residing in the specified region, one due to an accident, and two because they did not fulfil the diagnostic requirements (n = 226). Patients treated with anticoagulant drugs were excluded from the pain sensitivity assessment.

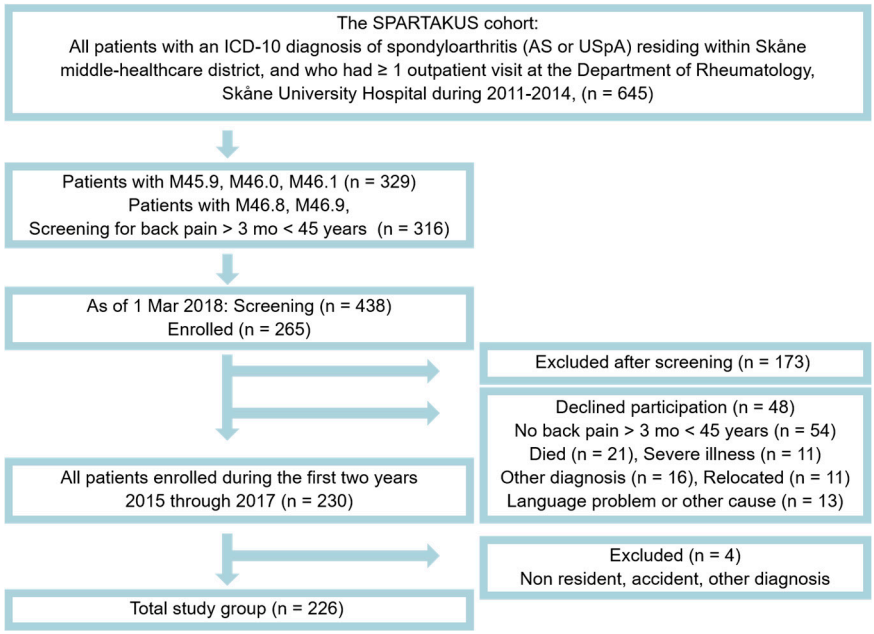

Figure 8 Flow chart for study IV.

The SPARTAKUS protocol

All enrolled patients attended a visit according to a specified study protocol. This included a thorough medical history, clinical examinations performed on the same day, questionnaires regarding demographics, patient characteristics, treatment, comorbidities, and several PROMs. The examination by the rheumatologist included a physical examination, assessment of disease activity, and a decision regarding complementary radiology. The physiotherapist assessed spinal mobility (BASMI), chest expansion, vital capacity, enthesitis, and performed a submaximal cycle ergometer test to estimate cardiorespiratory fitness. The research nurse performed all pain sensitivity tests with the Dolocuff, and measured the patient's weight and length, and the occupational therapist assessed grip strength. A number of validated PROMs were included in Paper IV (Table 3). After the completion of all required information, the patients were also classified according to ASAS axSpA criteria and the mod NY criteria for AS, rad-axSpA, and nr-axSpA.

Outcome measures

Descriptive data regarding disease duration, BMI, smoking habits, and pharmacological treatment were self-reported, or—in Paper I, collected from the medical records and in Paper IV collected at the visit. The different outcome measures in Papers I-IV are outlined in Table 3.

Physical function and spinal mobility

BASFI

The patient-reported Bath Ankylosing Spondyloarthritis Functional Index (BASFI) measures physical function and comprises ten questions; eight refer to specific physical activities and two refer to the ability to perform physical work in daily life. The questions are scored on an NRS (0-10) (Papers II and III) or a VAS (0-19) (Paper IV), and the total score is estimated by calculating the mean of the ten scales (0 = easy and 10 = impossible). BASFI has been validated not only in AS (140, 191) but also in the broad population of axSpA patients (192).

Individual spinal mobility measures and the BASMI

Spinal mobility was assessed with 11 commonly used observed measures representing mobility in all areas of the spine and the hip, and with the Bath Ankylosing Spondylitis Metrology Index (BASMI). The BASMI is a measure combining four examinations of spinal mobility (cervical rotation, tragus-to-wall distance, lateral spinal flexion, lumbar flexion) and one hip measure (maximal intermalleolar distance) (142, 193). The total score ranges from 0 to10 (where higher scores indicate more severe limitations) and is calculated as the mean of the five scores. All spinal mobility measures have been assessed according to international and national recommendations, and have acceptable validity and reliability (135, 142, 193-196) or have been used frequently in the management of AS (197).

The BASMI and the chest expansion measure were performed as recommended by the ASAS (139). The cervical lateral flexion and cervical flexion/extension measures were performed with the patient in an optimal sitting posture, and with the "Myrin" goniometer at the top of the head. The total ranges of maximal cervical lateral flexion (left to right) and maximal flexion-extension were recorded in degrees. Thoracic flexion and thoracolumbar flexion were assessed from standing in upright position (optimal posture) to maximal forward flexion, the difference being measured in cm. Thoracic flexion is the distance from the seventh cervical vertebra (C7) and 30 cm caudal. Thoracolumbar flexion is the distance

from C7 to the level of the posterior superior iliac spine. Vital capacity was measured using a vitalograph with the patient standing upright. The best of three attempts was recorded in litres.

Pain

Questions regarding pain in this thesis included measures such as the duration, distribution, and pain intensity of pain (Papers II–IV), and measures of pain sensitivity: pain threshold (PT), pain tolerance (PTol), and temporal summation of pain (TS) (Paper IV), and an examination of entheses (assessment of tenderness).

Chronic pain

To distinguish chronic pain, the patients were asked "have you experienced pain or aches persistently or recurring over more than three months during the last 12 months?" Information regarding the distribution of pain (number of pain regions) was obtained from a pain mannequin adopted from Bergman et al. (161) with 18 predefined body regions and an explanatory text for each site (Figure 9).

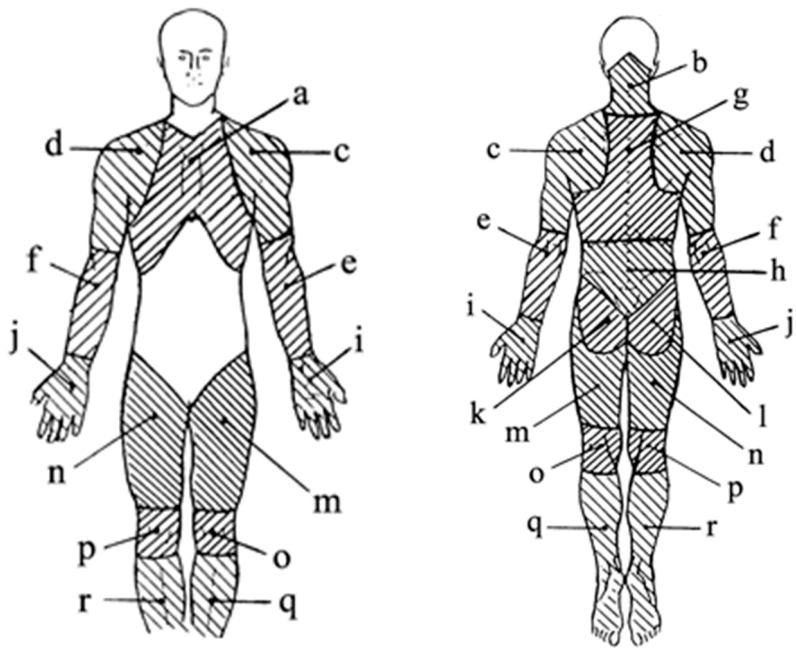

Figure 9. The pain mannequin with predefined body regions used in the questionnaire. The letters refer to explanation of the areas in the questionnaire

The definition of chronic pain (159) and the categorisation according to the distribution of pain regions in chronic widespread pain (CWP), chronic regional pain (CRP), and no chronic pain (NCP) were used in Papers II–IV. The definition of CWP was adopted from the 1990 American College of Rheumatology (ACR) definition of widespread pain as described in the criteria for fibromyalgia (159). This states that pain was widespread if pain was present in the left and right side of the body, above and below the waist, and when axial skeletal pain was present (the cervical spine, the anterior chest, the thoracic spine, or the lower back). According to this definition, pain in three sites qualifies as widespread pain. Patients who reported having chronic pain but did not fulfil the criteria for the widespread condition were considered as having CRP, and patients who answered "no" to the chronic pain question were considered to have NCP. The definitions of CRP and NCP have been used previously (161).

Pain intensity

In Papers II and III, intensity of pain was assessed using an NRS ranging from 0 (representing no pain) to 10 (representing worse possible pain), whereas in Paper IV, a VAS was used, ranging from 0 mm (representing no pain) to 100 mm (representing worse possible pain)—regarding the pain experienced during the previous week. The NRS and VAS pain scales are valid and reliable methods for measurement of pain intensity (182, 183, 198, 199) .

Pain sensitivity

The pain sensitivity examinations were performed using the Dolocuff, a computerised pneumatic cuff pressure algometry (CPA) device. Software version 2.0.5.1 was used (Unique Electronic ApS, Hvidovre, Denmark) (200) (Figure 10). The Dolocuff is a development of a hand-held algometer and is designed to assess pain sensitivity (pain threshold (PT), pain tolerance (PTol) and facilitated temporal summation (TS)) primarily in muscles and deep tissue. The Dolocuff device consists of a textile tourniquet cuff with two chambers (reference number: 20-50-727; VBM Medizin-technik GmbH, Sulz, Germany) and a computer-controlled air compressor (Unique Electronic ApS). To enable continuous feedback from the patients, an electronic 10-cm VAS is attached to the system (where 0 = "no pain", 10 = "worse possible pain"). The same research nurse conducted all pain measurements, according to a specific protocol to standardise the procedure and the instructions. All examinations were performed in a quiet room, with the patient in supine position. The pain measurements were performed on the dominant leg (as judged by the response to the question "which foot would you kick a ball with?").

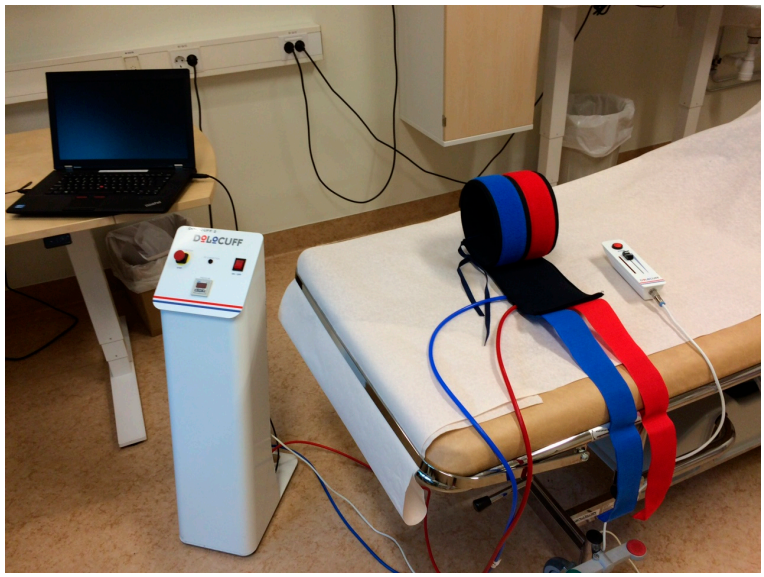

Figure 10. The Dolocuff device

The pain sensitivity examinations consisted of three sequences, performed in a certain order; short, auto, and long. The initial short sequence was primarily performed to accustom the patient to the assessments. Then the auto sequence was started (three short sequences), and this continued automatically with three minutes' pause between each assessment. The inflation rate during the short/auto sequences was 1.0 kPa/s. The pain threshold and pain tolerance levels were assessed from the short assessments. Pain threshold (PT) was defined as the pressure, measured in kiloPascals (kPa), at the moment when the sensation of pressure from the cuff changes from strong pressure to the first sensation of pain. This was also the first time the VAS pain exceeded 0. Pain tolerance (PTol) (in kPa) was defined as the pressure from the cuff at the moment when the pressure was stopped due to intolerable pain. During the long sequence, maintained for ten minutes, each patient's individual degree of temporal summation (TS) was assessed. Data from the auto sequences determined the individual continuous pressure (constant pressure = $PT_{mean} + [0.50 \times (PTol_{mean} - PT_{mean})]$). The rate to inflate the tourniquet cuff was set at 20 kPa/s. All patients were instructed not to indicate on their VAS until the cuff was fully inflated, to ensure correct starting conditions. The patients were then instructed to continuously report their level of pain on the electronic VAS, and all of them were kept unaware of the fact that the pressure remained the same over the whole session. Again, if the sensation of pain became intolerable, the patients were instructed to press the stop button. A Temporal Summation Index (TSI) was calculated by determining the VAS

endpoints during the long sequence. The TSI was calculated as follows: $TSI=\log([VAS_{end}/VAS_{max}]*[10/T_{stimulation}]*VAS_{end})$.

The Dolocuff has been found to be a reliable tool for assessment of pain sensitivity (201), and it has been used in patients with other rheumatic diseases such as RA, fibromyalgia, and osteoarthritis (202-205).

MASES

Pain or tenderness on entheses was examined according to the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) (206), an instrument that has been found to reliably reflect enthesitis in axSpA (195). It was developed from the Mander Enthesial Index (MEI) (207) and includes 13 sites originally. The MASES is here modified to include also the plantar fascia in accordance with the Spondyloarthritis Caught Early (SPACE) study (208) as used at the Department of Rheumatology, Skåne University Hospital. The intensity of pain is assessed through a local firm pressure at each site (where 0 = "not tender" and 1 = "tender"). The entheses sites included in the MASES (0–15) are the fifth lumbar processus spinous, and bilateral sites of: the first and seventh costochondral joints, the spina iliac posterior superior (SIPS), the spina iliac anterior superior (SIAS), the iliac crest, the insertion of the Achilles tendons to the calcaneus, and the insertion of the plantar fascia to the calcaneus.

Additional measures

BASDAI

Two composite scores were used to assess disease activity. One was the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), a patient-reported index with six questions on fatigue, spinal pain, peripheral joints, localized tenderness, and morning stiffness (intensity and duration). Each question in the BASDAI is scored on an NRS (0-10) (Papers II and III) or a VAS (0-10) (Paper IV) and the total score is estimated by calculating the mean. It ranges from 0 (representing no disease activity) to 10 (representing very active disease). The BASDAI was originally developed and validated for patients with AS (209, 210), but it has since been found to be valid also in the broad spectrum of axSpA diseases (15, 192).

ASDAS

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is another composite score for assessment of disease activity in axSpA (211), and has been

validated in patients with AS (212). It was developed to reflect both the patient's and the physician's standpoint, and to account for different domains of disease activity, by combining the patient-reported outcomes with an acute-phase reactant (erythrocyte sedimentation rate, ESR; or C-reactive protein, CRP). The patient-reported variables include three questions from the BASDAI (on back pain, peripheral joints, and duration of morning stiffness) and a fourth question regarding the patient's global assessment of disease activity. Validated cut-off levels have been developed, representing inactive disease (< 1.3), moderate disease activity (between 1.3 and 2.1), high disease activity (between 2.1 and 3.5), and very high disease activity (> 3.5) (213).

EQ-5D

Health status was assessed using the EuroQol–5 domain instrument (EQ-5D) (214), a valid and reliable generic questionnaire with five dimensions: mobility, self-care, pain/discomfort, usual activities, and psychological status (anxiety/depression). The EQ-5D total score ranges from 0 (representing no health) to 1 (representing full heath), and is based on a health profile for each domain (three levels). The tariff from the UK was used for calculation.

Fatigue and Patient's global assessment

Fatigue and the patient's global assessment during the previous week was assessed on an NRS (0–10) (Paper II and III) or a VAS (0–100 mm) (Paper IV) ranging from best to worst. The NRS and VAS are valid, reliable, and easy to use and are suitable as global assessments of fatigue in patients with arthritis (215). The NRS and the VAS have previously been used to assess patient's global assessment in other rheumatic diseases (216, 217).

ASES

Perceived self-efficacy was assessed with the Arthritis Self-Efficacy Score (ASES) (218). This is an instrument developed for patients with arthritis, and it asks how sure a patient is about his/her ability to cope with, or handle, consequences of the disease regarding function, pain, and other symptoms. The ASES has been validated in patients with AS (219). The score ranges between 10 and 100 (worst to best). The subscale for handling pain has five items and the subscale for other symptoms have six items.

HAD scale

For assessment of psychological status, the Hospital Anxiety and Depression (HAD) scale was used (220). This instrument detects symptoms regarding anxiety and depression and comprises 14 questions, seven for anxiety and seven for depression. Each score for each question ranges from 0 to 3 (on a four-point Likert scale) and the final score for each subscale (anxiety or depression) ranges from 0 to 21 (representing no symptoms to severe symptoms). The HAD scale is a frequently used instrument, and has been used in patients with SpA (60, 64, 189).

Statistics

In Paper I, the data on spinal mobility measures were not normally distributed and were therefore presented as median and interquartile range. Differences in spinal mobility between or within the AS and USpA groups were calculated using analysis of covariance (ANCOVA), beta-estimates (β-est), and 95% confidence intervals (CIs), and controlled for sex and disease duration. To study differences in spinal mobility in relation to disease duration, the larger AS group was stratified in tertiles regarding disease duration. Differences between the tertiles were calculated with the Kruskal-Wallis method, and followed with the Mann-Whitney U-test if differences were found. Owing to the smaller sample size (n = 57), the USpA group was not stratified in tertiles according to disease duration.

In Paper II, both crude and age- and sex-adjusted prevalence estimates for self-reported pain in patients with AS and USpA were calculated. Differences in mean values were analysed with Student's t-test and differences in proportions were analysed with the Chi-squared test. To adjust for differences regarding age and sex in the AS and USpA groups, age- and sex-adjusted prevalence rates were calculated by the direct method, using the Swedish census population of 2009 as a standard population. Multivariate logistic regression analyses with odds ratios (ORs) and 95% CI were used to study associations between (i) chronic pain (CRP and CWP) and NCP, and (ii) between CWP and NCP/CRP, as dependent variables. Age, sex, SpA subgroup, smoking (ever-/never-smoker), and BMI were all included in the analyses as independent variables.

In Paper III, comparisons of prevalence estimates of CWP in 2009 and 2011 were performed with two-sided Chi-square test. Multivariate logistic regression analyses with OR and 95% CI were then calculated to study predictors for development of CWP and having persistent CWP. Some potential risk factors were highly correlated, so a basic model with age, sex, and SpA subgroup was

used initially. Each of the other independent variables (disease duration, BMI, smoking, pain regions, pain intensity, fatigue, general health, EQ-5D, BASDAI, BASFI, ASES pain/symptom, HADs anxiety, and HADs depression) were added in separate logistic regressions with simple contrast to a reference group.

In Paper IV, comparisons between the AS and USpA subgroups regarding the different aspects of pain, including pain sensitivity measures were done with Student's t-test and Chi-squared test as appropriate. Multivariate linear regression analyses with β-estimates and 95% CI were used to study factors associated with the dependent variables pain threshold, pain tolerance, and temporal summation index. The analyses were done separately for the AS and USpA subgroups, due to differences regarding clinical characteristics and possible associated variables. All analyses were adjusted for age and sex, except spinal mobility (BASMI), which was found to be highly correlated to age ($r = 0.64$) and was therefore adjusted only for sex. The independent variables (enthesitis, anxiety, depression, fatigue, pain regions, unacceptable pain (pain intensity levels were dichotomized in VAS pain > 40 vs. VAS pain ≤ 40), disease activity, physical function, health status, and spinal mobility were added separately in each model. One-way analysis of variance (ANOVA) was used to study differences in pain tolerance, in different disease activity categories (ASDAS-CRP). All tests in Papers I–IV were two-tailed and any p-value < 0.05 was considered to be statistically significant. The analyses were performed with SPSS software versions 20 and 23 for Windows (IBM Corp., Armonk, NY, USA).

Ethics

The four studies were carried out in compliance with the declaration of Helsinki, and were approved by the Regional Ethical Review Board, Lund University, Sweden (Paper I: Dnr 2013-208; Papers II and III: Dnr 301/2007, 406/2008, 2011/547, and 2013/128; and Paper IV: Dnr 2015/436). Informed written consent was obtained from all the participants in the SpAScania 2009 and 2011 surveys. All the patients in Paper IV received oral and written information about the study and gave their informed written consent.

Results
Spinal mobility in axial spondyloarthritis
Paper I

Patients with USpA and an axial disease (n = 57, 54% men) showed less limited spinal mobility, most evident in the thoracic and lumbar spine, than patients with AS (n = 126, 77% men) ($p \leq 0.011$) when adjusted for sex and disease duration (Figure 11). Few differences between men and women in the total study group were found, and these were mainly for anthropometric measures (vital capacity ($p < 0.001$) and maximal intermalleolar distance ($p = 0.006$)), with lower values in women. The men in the entire study group also showed less thoracic flexion than women ($p = 0.019$) and men with AS showed less cervical flexion/extension than women with AS ($p = 0.033$).

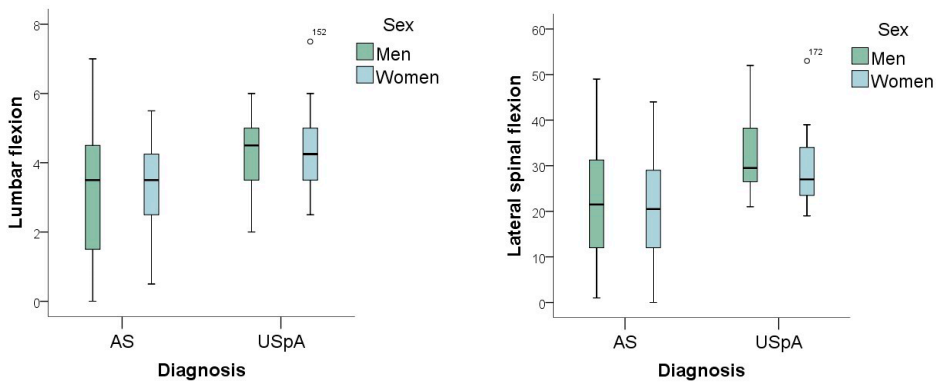

Figure 11. Two spinal mobility measures illustrating worse thoracic and lumbar spinal mobility in patients with AS than in patients with USpA.

Patients with USpA and AS showed decreased spinal mobility over time, representing all areas of the spine, although this was more evident in AS (6/11 ($p \leq 0.046$) for patients with USpA, and 11/11 ($p \leq 0.007$) for patients with AS). When we stratified for disease duration, patients with AS and a disease duration of 18–30 years had more severely decreased mobility in thoracic and lumbar areas than those with shorter disease duration. In patients with an even longer disease duration, cervical measures—in addition to thoracic and lumbar measures—were also more restricted than in those with a shorter disease duration.

Prevalence of chronic widespread pain in spondyloarthritis

Paper II

Chronic widespread pain (CWP) was common in patients with SpA (n = 887), with a one-year period prevalence of 49% in USpA as opposed to 45% in AS (p = 0.033), and it was more common in women than in men (54% vs. 41%, p ≤ 0.001). About one-fifth of the patients with SpA reported having chronic regional pain (CRP), with no significant difference between women and men. One-third reported having no chronic pain (NCP), with a higher proportion in men than in women (AS: 40% vs. 30% (p = 0.059); USpA, 39% vs. 22% (p = 0.002) (Figure 12).

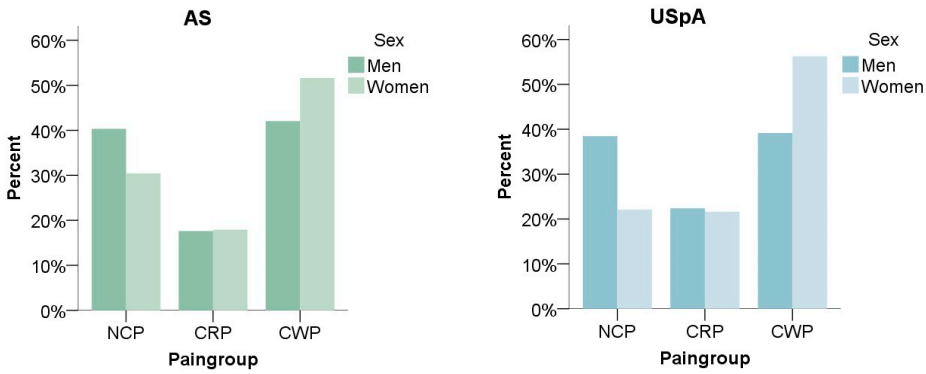

Figure 12. Prevalence of pain (%) in men and women, for both AS and USpA, based on the pain groups NCP, CRP and CWP. For definitions, see footnote to Table 4.

Women with SpA generally reported higher pain intensity than men (mean 4.2 (SD 2.5) vs. 3.5 (2.4); p ≤ 0.001), but there was no statistically significant difference in pain intensity levels between women and men who reported having chronic pain: CRP (mean 4.0 (SD 2.3) vs. 3.5 (2.0); p = 0.095), and CWP (5.1 (2.3) vs. 5.0 (2.2); p = 0.622) (Table 4).

Table 4. Pain intensity in women and men in different pain groups (NCP, CRP, and CWP).

	NCP			CRP			CWP		
Pain intensity	Women	Men	p-value	Women	Men	p-value	Women	Men	p-value
All SpA	2.4±2.1	2.0±1.8	0.09	4.0±2.3	3.5±2.0	0.95	5.1±2.3	5.0±2.2	0.6
AS	2.4±2.2	1.7±1.5	0.01	3.8±2.5	3.4±2.0	0.4	5.2±2.3	5.1±2.2	0.6
USpA	2.3±2.1	2.6±2.4	0.5	4.1±2.2	3.5±2.1	0.2	5.0±2.3	4.9±2.2	0.69

Presented as mean and ± SD. AS, ankylosing spondylitis; USpA, undifferentiated spondyloarthritis; NCP, no chronic pain; CRP, chronic regional pain; CWP, chronic widespread pain.

Assuming that patients who did not answer the pain duration and pain distribution questions (53/940, 5%) would have no chronic pain (NCP) gave a minimum age- and sex-adjusted one-year prevalence of CWP for the total SpA population of 45%. The higher prevalence of CWP in women than in men was mainly explained by the higher prevalence of CWP in women with USpA (57%, 95% Cl: 42–72) than in women with AS (50%, 95% Cl: 35–65).

The multivariate logistic regression analyses showed that female sex and having a higher BMI, was associated with having chronic pain as opposed to having NCP and with having CWP rather than NCP or CRP, when all other variables were controlled for. Having CWP as compared to NCP or CRP was also associated with being an ever-smoker, while SpA subgroup (AS as opposed to USpA) and longer disease duration were not associated with either chronic pain or CWP (Table 5).

Table 5. Results from the logistic regression analyses with odds ratios (ORs) and 95% confidence intervals (CI) for having (i) chronic pain rather than NCP, and (ii) CWP rather than NCP or CRP. The independent variables were all included in the same regression model.

	Chronic pain (n = 773)		CWP (n = 767)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex				
Men	1		1	
Women	1.91 (1.37–2.67)	≤0.001	1.70 (1.25–2.32)	0.001
Age, year	1.01 (1.00–1.03)	0.080	1.01 (1.0–1.03)	0.088
Diagnosis				
AS	1		1	
USpA	1.41 (0.99–2.00)	0.055	1.11 (0.80–1.53)	0.546
Smoking				
Never	1		1	
Ever	1.33 (0.97–1.83)	0.081	1.44 (1.07–1.95)	0.016
BMI	1.05 (1.01–1.10)	0.022	1.05 (1.01–1.09)	0.010
Disease duration, year	0.99 (0.97–1.01)	0.184	1.00 (0.98–1.01)	0.656

AS, ankylosing spondylitis; USpA, undifferentiated spondyloarthritis; NCP, no chronic pain; CRP, chronic regional pain; CWP, chronic widespread pain; BMI, body mass index.

Risk factors for development and persistence of chronic widespread pain in spondyloarthritis

Paper III

Of the 712 patients with AS and USpA who responded to the SpAScania questionnaires in 2009 and 2011, 644 (90.4%) also answered the questions regarding pain on both occasions and could be categorised in three groups according to pain duration and pain distribution (NCP, CRP, and CWP). The overall prevalence of CWP in 2011 was 48%, as compared to 47% in 2009, and that of CRP was 19% as compared to 20% in 2009.

Due to missing answers to the pain questions in 2009 and 2011, 68 patients (10%) could not be categorised into any of the pain groups. The non-responders had a mean age of 54 (SD 14) years, a higher proportion were men (68%), and a higher proportion had a diagnosis corresponding to AS (69%). Those patients who responded to either the 2009 or the 2011 questionnaire (n = 63) reported having mean (SD) 4.3 (5.1) and 4.7 (5.6) pain regions.

Seven out of ten patients (72%) who reported having CWP in 2009 reported having persistent CWP at follow-up (2.5 years later), and only a smaller group had transitioned to CRP and NCP (15% and 13%). Of those patients who initially reported having CRP in 2009, four out of ten developed CWP in 2011. Moreover, about one-third of the patients who initially reported having NCP in 2009 developed chronic pain at follow-up 2.5 years later (16% to CRP and 19% to CWP) (Figure 13).

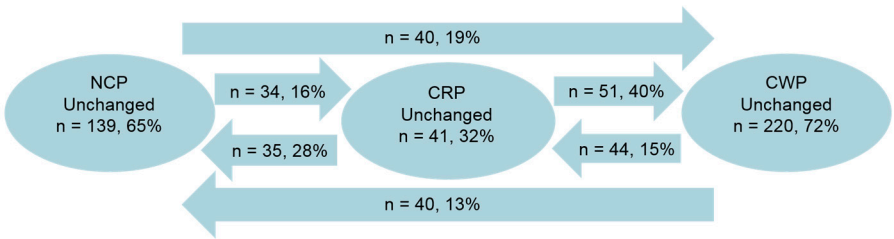

Figure 13. Transition of patients to and from the pain groups NCP, CRP, and CWP between 2009 and 2011.

A higher proportion of the patients with USpA (25%) than those with AS (15%) transitioned to chronic pain from NCP. The same scenario was found in women (24%) compared to men (16%), and this was mainly explained by a higher frequency of transition in women with USpA than in women with AS.

In the multivariate regression analyses, development into CWP in 2011 from initially having NCP or CRP, was predicted by a higher number of pain regions (OR 1.36; CI 1.20–1.53), higher pain intensity (OR 1.35; CI 1.20–1.52), worse fatigue (OR 1.25; CI 1.13–1.38), worse global health (OR 1.35; CI 1.19–1.54), and worse health status (OR 0.05; CI 0.01–0.19) after adjustment for age, sex, and SpA subgroup. In addition, worse self-reported disease activity (OR 1.25; CI 1.07–1.45), worse physical function (OR 1.32; 1.16–1.50), worse self-efficacy for handling pain (OR 0.97; 0.96–0.99) and other symptoms (OR 0.98; 0.97–0.99), and higher depression score (OR 1.10; 1.02–1.19) also predicted the development of CWP.

Persistent CWP was predicted by the same variables as those for development of CWP, but in addition, female sex (OR 1.82; CI 1.06–3.10), age (OR 1.02; CI 1.00–1.04) and anxiety (OR 1.07; CI 1.00–1.14) were found to be predictive of having persistent CWP after 2.5 years.

Chronic pain and pain sensitivity in established axial spondyloarthritis

Paper IV

The majority of patients with established axial spondyloarthritis (AS: n = 110; USpA with axial disease: n = 116) in this study from the SPARTAKUS cohort had chronic pain, and almost every other patient reported having CWP (AS: 42%; USpA: 53%). Patients diagnosed as USpA reported having more pain regions than patients with AS ($p = 0.039$), but no significant differences regarding pain intensity or in the proportion of unacceptable pain levels (VAS > 40 mm) were found between the subgroups. Pain sensitivity assessments were performed in 173 (77%) patients. Pain thresholds, pain tolerance, and temporal summation of pain (measured with Temporal Summation Index; TSI) were not significantly different between patients with AS or USpA (Table 6).

Table 6. Comparisons of the pain variables by SpA sub-group

Variables	AS	USpA	Mean difference (95% CI)	p - value
Pain regions, no	4.4 (4.0)	5.6 (4.3)	-1.2 (-2.3 : -0.1)	0.039
Pain, 0-100	33 (27)	39 (27)	-5.4 (-12.6 : 1.7)	0.138
Pain > 40 mm, n (%)	40 (37)	55 (48)	11 (-2 : 24)	0.104
Pain threshold, kPa	32.0 (16.6)	29.5 (12.2)	2.5 (-1.76 : 6.83)	0.247
Pain tolerance, kPa	64.6 (28.2)	60.4 (24.3)	4.2 (-3.61 : 11.92)	0.293
TSI	0.72 (0.52)	0.60 (0.52)	0.11 (-0.04 : 0.27)	0.148

Presented with mean and standard deviation (SD) unless otherwise indicated. AS, ankylosing spondylitis; USpA, undifferentiated spondyloarthritis; TSI, Temporal Summation Index.

A larger proportion of the women in the entire study group than men reported having CWP (AS: 69% vs. 28%; USpA: 56% vs. 46%). Women also reported having more pain regions, and higher pain intensity levels than men. Pain tolerance was lower in both women with AS and USpA, than in their male counterparts, and pain thresholds were also lower in women with USpA than in men with USpA. No statistically significant difference between women and men was found in TSI, even though women with AS had numerically higher TSI than men with AS and men and women with USpA.

In the multivariate linear regression analyses, possible associations with pain thresholds, pain tolerance, and TSI were studied, and in patients with AS, lower pain thresholds were associated with more enthesitis (β –1.0, 95% CI –2; –0.1), worse depression (β –1.5, 95% CI –2.6; –0.5), and higher disease activity (ASDAS-CRP) (β –4.9, 95% CI –8.7; –1.0), adjusted for age and sex. In USpA, lower pain thresholds were associated with female sex (β –7.4, 95% CI –12.8; –2.0), adjusted for age, and with worse spinal mobility (β –2.4, 95% CI –4.6; –0.1) after adjustment for sex.

Lower pain tolerance was found to be associated with older age and female sex, adjusted for each other in both patients with AS and in patients with USpA. In both subgroups, lower pain tolerance was also associated with worse fatigue, VAS > 40 mm, and worse disease activity (ASDAS-CRP) after adjustment for age and sex, and with worse spinal mobility adjusted for sex. In addition to the above variables, higher enthesitis scores, more pain regions, and lower health status were associated with lower pain tolerance in patients with AS, and worse anxiety in patients with USpA, after adjustment for age and sex (please see table 7).

Table 7. General linear regression, potential associations with pain tolerance for patients with AS or USpA, adjusted for age and sex.

		AS			USpA		
Potential associations		no	β-est (95% CI)	p-value	no	β-est (95% CI)	p-value
Age,* years		86	-0.7 (-1.2 : -0.2)	0.004	92	-0.4 (-0.8 : -0.04)	0.031
Sex,*	Men		0			0	
	Women	86	-13.9 (-25.8 : -1.9)	0.023	92	-13.4 (-23.9 : -2.9)	0.013
MASES, no		86	-1.7 (-3.3 : -0.2)	0.032	92	-1.2 (-2.7 : 0.3)	0.108
HADs,	Anxiety	79	-1.5 (-3.1 : 0.2)	0.075	88	-1.4 (-2.7 : -0.2)	0.024
	Depression	79	-1.5 (-3.4 : 0.3)	0.102	88	-0.9 (-2.5 : 0.7)	0.258
Fatigue, 0-100		84	-0.3 (-0.6 :-0.1)	0.005	92	-0.2 (-0.3 : -0.02)	0.033
Pain regions, no		82	-1.6 (-3.2 : -0.1)	0.035	91	-0.7 (-1.8 : 0.5)	0.255
Pain	≤ 40 mm	32	0		39	0	
	> 40 mm	52	-16.6 (-28.6 : -4.5)	0.008	53	-12.1 (-21.5 : -2.6)	0.013
ASDAS-CRP		79	-10.2 (-16.0 : -4.4)	0.001	78	-6.9 (-12.9 : -0.9)	0.024
BASFI, 0-10		82	-2.7 (-5.7 : 0.3)	0.073	89	-2.3 (-4.8 : 0.2)	0.070
EQ-5D, 0-1		82	36.3 (7.1 : 65.4)	0.015	89	19.2 (-0.3 : 38.8)	0.053
BASMI,** 0-10		86	-4.6 (-8.0 : -1.2)	0.009	91	-6.9 (-11.3 : -2.6)	0.002

*Sex is age adjusted and age is sex adjusted, ** adjusted for sex only. AS, ankylosing spondylitis; USpA, undifferentiated spondyloarthritis; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; HADs, Hospital Anxiety and Depression scale; VAS, Visual Analogue Scale; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score-C reactive protein; BASFI, Bath Ankylosing Spondylitis Functional Index; EQ-5D, EuroQol 5 Dimensions; BASMI Bath Ankylosing Spondylitis Metrology Index.

A sub-analysis of the total study group to analyse pain tolerance levels stratified into different disease activity levels (ASDAS-CRP) showed that pain tolerance was significantly higher in patients with inactive disease than in those with low or high/very high disease activity ($p = 0.009$ and $p \leq 0.001$, respectively) (Figure 14).

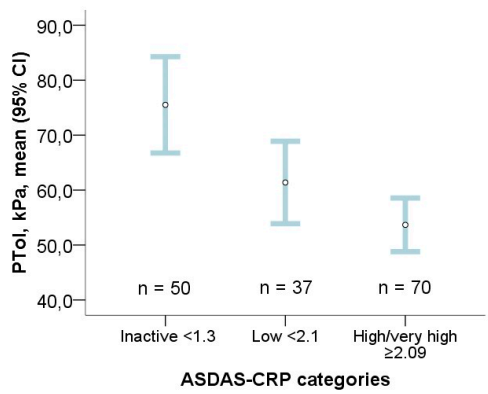

Figure 14. Error bars for 95% CI showing the distribution of pain tolerance in different disease activity categories according to the ASDAS-CRP score for the total study population. (The "high" and "very high" categories are presented together; "very high" n = 7).

Higher pain sensitivity as measured by Temporal Summation Index (TSI) was only associated with worse spinal mobility (BASMI) (β 0.1, 95% CI: 0.04; 0.2) and older age (β 0.01, 95% CI: 0.00; 0.02) with adjustment for sex in patients with AS. No associations between TSI and any of the possible variables were found in patients with USpA.

Of the 226 patients in the study, 197 (87%) had complete information and were eligible for classification in axSpA subgroups according to ASAS. Of these, 124 (63%) were classified as having radiographic SpA (Mod NY: 59%) and 49 (25%) were classified as having nr-axSpA, whereas 24 patients (12%) did not fulfil the axSpA criteria (Table 8).

Table 8. Patients with a clinical diagnosis of AS or USpA (axial disease) fulfilling ASAS axSpA classification critera (r-axSpA/nr-axSpA)

	AS (n = 102)	**USpA** (n = 95)	**Total** (n = 197)
r-axSpA, n (%)	77 (75)	47 (50)	124 (63)
nr-axSpA, n (%)	20 (20)	29 (30)	49 (25)
no axSpA	5 (5)	19 (20)	24 (12)

*For whole table. AS, ankylosing spondylitis; USpA, undifferentiated spondyloarthritis; ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; r-axSpA, radiographic-axial spondyloarthritis; nr-axSpA, non-radiographic axial spondyloarthritis;

Discussion

Chronic back pain and stiffness are important and frequent symptoms that may affect the overall disease burden and general health of patients with AS and USpA. The aim of the work for this thesis was to study consequences, such as chronic pain and impaired spinal mobility in SpA, and differences between patients in the well-characterized subgroup AS and patients diagnosed as having USpA, which is a diverse and less studied subgroup. Chronic pain is an important contributor to disability in the general population (221), and subjects with CWP have been found to have a generally poor health status and functional impairment (222). In SpA, chronic pain has not been well-studied, so improved knowledge regarding the occurrence of concomitant chronic pain and possible associations and predictive factors for CWP in this heterogeneous patient group would be valuable, and would contribute to our understanding of CWP in the clinical setting—and enhance early and optimal treatment options. Another aim was to study physical function, and more specifically spinal mobility, to add information to the previous body of knowledge regarding impaired physical function in patients with axSpA, which still largely applies to men with AS. The four studies also aimed to investigate differences between men and women more closely.

SpA subgroups

Patients with AS and USpA share several characteristic factors and have been found to report similar disease activity and response to treatment (33). Also in this work, patients with AS and USpA were found to report similar disease consequences with no differences regarding pain intensity levels, fatigue, health status, anxiety, and depression. However, patients with USpA are often younger, they have shorter disease duration, and a higher proportion are women compared to patients with AS (33, 38, 39). This is also in line with the findings of this thesis, with similar figures in all the papers included.

In recent years, efforts to improve the time from first onset of symptoms to a clear diagnosis have increased, as there are improved diagnostic tools, there are more effective treatments available, and the response to treatment has been found to be greater in patients with shorter disease duration (75). Despite this, a delayed diagnosis is still common for many patients (223, 224) and is more pronounced in women (80, 225). This is in accordance with the three cohorts included in this thesis where both patients with AS and patients with USpA had long diagnostic

delays ranging from a mean of six to ten years in the different cohorts, and in Paper III women had significantly longer time to diagnosis than men (8 years vs. 6 years). Differences in mean age at disease onset, in age at diagnosis, or in disease duration have not been found to explain the difference in diagnostic delay between men and women (83). Therefore possible sex differences are important to take into account in the research on SpA, to further explain differences between men and women and shorten the diagnostic delay in all patients. Moreover, patients with early disease have been found to experience similar levels of pain and disease activity as those in later stages (226, 227), so an early diagnosis is important to avoid prolonged suffering for the individual. The lower prevalence of AS in women has been questioned, and attributed to a possible under-diagnosis in women, due (among other things) to the fact that some decades ago AS was mainly perceived as a predominantly male disease (48). In Paper I, only 23% of the AS population was female, as compared to Papers II–IV, where the proportion of women was 33–38%. This could be a consequence of a longer diagnostic delay, or an under-diagnosis in women, possibly as a result of differences in disease presentation (80). Factors such as anatomical or biological changes, but also psychological and social factors, have been put forward to explain the differences in disease presentation between men and women (78).

In daily practice, it is important not to miss any patients, so a diagnosis must be more sensitive than the classification criteria and also include patients who have a probable or possible diagnosis of SpA (16). However, there are no diagnostic criteria for nr-axSpA or AS, even though the Mod NY criteria are widely used in the clinical setting. More recently, the ASAS criteria for peripheral and axial SpA have been discussed, and a need for modification proposed (228). One reason for this was that patients with SpA can have both axial and peripheral symptoms, and that the predominant symptom may fluctuate with time.

In this work, we have used the clinical diagnosis AS or USpA (according to ICD-10) due to several reasons. In the first clinical study (Paper I), all patients were identified for the cohort before the ASAS axSpA criteria were presented in 2009. However, a verification using the medical records showed that all patients had axial symptoms, and this was also one reason for the referral to the physiotherapists and assessments of spinal mobility. In Paper IV, 197 of the 226 (87%) included patients were classified according to the ASAS axSpA criteria, and of those 88% fulfiled the criteria (Table 8). There were too few patients yet classified as nr-axSpA to perform statistical analysis, so comparisons between axSpA groups, and between women and men, were not possible. In previous clinical trials, the sensitivity and specificity of the axSpA criteria have been reported to be about 80%. This means that some cases may be either falsely positive or falsely negative. It has also been pointed out that the absence of radiographic changes does not preclude classification of (or a diagnosis of) axSpA

(229). In Paper IV, a large proportion (50%) of the patients with longstanding USpA were classified as having r-axSpA. This indicates that it may be valuable to re-evaluate the diagnosis in patients with increasing pain or impaired physical function, to guide both pharmacological and non-pharmacological treatment options. Moreover, in a sub-analysis of those classified as having r-axSpA or nr-axSpA, we found the same prevalence of CWP, and similar pain sensitivity, as in USpA and AS but the small and skewed patient sample did not allow comparisons between men and women.

In Papers II and III, we used the population-based SpAScania cohort, in which patients in different subgroups of SpA were included, based on the ICD-10 codes used in clinical practice. A large proportion (65%) of the patients with USpA in Paper II reported having ongoing axial pain. In the two clinical studies, all diagnoses were set by rheumatologists, and in the SpAScania cohort a strict criterion was used, meaning that the diagnosis was set at least once by a rheumatologist or specialist in internal medicine, or twice (on at least two separate occasions) by any physician in secondary or primary care. In addition, all patients with an ICD-10 code of PsA, ReA, or Aa-IBD together with an USpA diagnosis were excluded from this thesis, so most patients in the included USpA group most likely did have axial SpA.

The findings from this thesis, as assessed in the four studies on patients with AS and USpA, are easily applicable to the clinical setting in Sweden and other countries where ICD-10 codes are frequently used, both in secondary and primary care. Findings from studies in patients with nr-axSpA may impose a greater pedagogic challenge regarding use in the clinic, as the ASAS axSpA criteria are not (yet) primarily intended for use in the clinic or for diagnostic purposes.

Physical function in SpA

In patients with axial SpA, loss of spinal mobility is a well-known and important finding (2, 230). Assessments of spinal mobility are therefore not only valuable in the clinical setting where they can contribute to the detection of loss of mobility and guide individual treatment options in all phases of the disease. Spinal mobility measures are also used in the Mod NY criteria for AS, and may add information regarding disease progression (20, 143). However, spinal mobility measures are not included in ASAS axSpA criteria, as they were unable to discriminate axSpA from no SpA in early disease, according to the validation article by Rudwaleit et al. (9). That inflammation more often causes limitations in early disease and structural damage in later disease (128)—and that reduced spinal mobility is

associated with impaired activity and participation (231), radiographic damage (31), age (232), disease duration, and HRQoL (127)—also highlights the need for early treatment to maintain spinal mobility.

The findings in Paper I showed that patients with USpA had less limited spinal mobility in the lumbar and thoracic regions and a lower BASMI than patients with AS, which is in agreement with clinical experience. However, a novel finding is that there were no significant differences in the cervical measures or in chest measures between the two subgroups, even though patients with AS were older and had longer disease duration than patients with USpA. These findings strengthen our scientific knowledge regarding spinal mobility in patients with USpA. As expected, we also found that spinal mobility decreased with longer disease duration in all axSpA patients, but we found few differences between men and women. This is both in accordance with and in contrast to earlier reports (78, 79, 233-235), and the finding that differences between men and women were primarily related to anthropometric measures, have not always been acknowledged in earlier studies (234). Assessments of spinal mobility may be confounded by different factors that are unrelated to the disease, such as age, sex, and height. When comparing the figures in our USpA group to age-stratified normative spinal mobility measures (236-238), range of motion was impaired in the neck, and in the thoracic and lumbar parts of the spine, resulting in a worse BASMI score. This indicates that impaired spinal mobility also in USpA is a consequence to acknowledge and treat. The above, together with the finding that higher physical activity is associated with better spinal mobility (239), highlights the importance of referring all patients with SpA, irrespective of diagnosis or sex, to physiotherapists early during the disease course, in order to educate, coach, and follow patients individually through difficult phases of the disease. In AS, the findings from the data stratified by disease duration showed low correlations between different measures and regions in the group with the shorter disease duration, but in the group with a disease duration of more than 30 years, high correlations were found. This indicates that more specific assessments in all parts of the spine—than just the endorced BASMI score—may be valuable in early disease, to guide flexibility treatment.

In Paper IV, spinal mobility (according to the BASMI) was associated with lower pain tolerance in both patients with AS and patients with USpA; and in Paper III, worse self-reported physical function (BASFI) was found to be a predictor of both developing CWP and having persistent CWP in SpA. These findings are difficult to compare, as there to our knowledge are no previous studies that have investigated pain sensitivity or development of CWP in SpA. In the general population, however, development and persistence of CWP has been found to be predicted by both physical and psychological factors (169). Physical and

psychosocial function and other aspects of QoL are important to determine, as these may be modifiable factors in patients with rheumatic diseases (177).

Chronic pain in SpA

Musculoskeletal chronic pain is a predominant symptom in patients with rheumatic diseases, and may substantially affect a person's overall health. It is a challenging problem in the clinical setting and in research, not least in the varied spectrum of SpA, where chronic pain may be poorly recognized. The ACR Task Force has also proclaimed that pain is probably the most important PROM in rheumatology (177). In the two epidemiological studies in this thesis, the idea was to investigate the occurrence of concomitant chronic pain and possible risk factors for the development and persistence of CWP in patients with AS and USpA, and in the fourth study, aspects of pain sensitivity were also included.

Prevalence of chronic pain

To our knowledge, Paper II is the first study to investigate the prevalence of CWP in patients with SpA without limiting it to the more complex fibromyalgia syndrome, which represents the most severe end of the CWP continuum, and also includes several non-pain symptoms such as cognitive problems and severe fatigue (240). The main finding was that concomitant CWP is a common consequence in patients with SpA, affecting almost 50% of those with USpA and slightly less of those with AS. The minimal age- and sex-adjusted prevalence was 43% in AS and 48% in USpA, which was explained by a higher prevalence in women with USpA than in women with AS. Similar figures were also found in the established SpA cohort in Paper IV, where a major proportion of the patients reported having chronic pain, and 42% of the patients with AS and 53% with USpA reported having CWP. These figures are clearly higher than in the general population (11–15%) (161, 167, 168), and also compared to a study on RA, where concomitant CWP was reported by 34% of the patients. A larger proportion of RA patients reported having CRP (46%) than SpA patients (19%), using the same methodology (241). The results are important to acknowledge, as chronic pain may cause great suffering for the individual patient—and also complicate both the clinical evaluation and the treatment of SpA.

We found no significant difference in the prevalence of CRP in women and men, but a higher proportion of women reported having CWP, and being female was associated with a higher risk for CWP. The female predominance in the

distribution of chronic pain is consistent with previous studies of fibromyalgia in SpA (61, 62, 242, 243), and is in accordance with previous reviews of sex differences in pain (244, 245). Even so, men with SpA, irrespective of diagnosis, also had a high prevalence of CWP in Paper II (41%). According to a review of clinical and experimental pain, there is limited evidence regarding sex differences in pain intensity (245), but there are some indications that women experience more severe pain than men (244). In a review of inflammatory arthritis, women had somewhat higher pain scores than men, as assessed with VAS (246). This is consistent with our results where women in both SpA subgroups had significantly higher mean pain intensity, and a higher number of pain regions than men. However, there was no significant difference in pain intensity between men and women who reported having chronic pain (CRP and CWP). These findings are novel, and indicate the importance of an awareness of concomitant CWP and increased pain intensity also in men within the overall SpA population, and relevant for optimized treatment interventions in the clinic.

Neither SpA subgroup nor disease duration was found to be associated with a higher risk of CWP in Paper II, while smoking and a higher BMI were. The associations between chronic pain and obesity have previously yielded conflicting results, and the relationship appears to be mediated by other factors such as biomechanical changes, mood, poor sleep, lifestyle and personal factors (247), and that persons with obesity may have a low-grade systemic inflammation (248) (249). In our cross-sectional study, being an ever-smoker was associated with having CWP. To our knowledge, this has not been shown in SpA before, but a variety of other factors such as worse disease activity, poor function, QoL, inflammation on MRI, structural damage, and pain intensity have also been associated with smoking in axSpA (250, 251).

The association between CWP and SpA has been argued to lead to diagnostic and treatment dilemmas because symptoms, such as pain at entheses, fatigue, stiffness, and tenderness are also present in patients with fibromyalgia (148, 252), and to some extent also in those with CWP that does not fulfil the criteria for fibromyalgia. Even though we could not examine for tender points or enthesitis in this study, it is important to acknowledge that CWP can include pain of different origins. Thus, a thorough evaluation, including a pain assessment, is important in all patients with increasing or prolonged pain or other symptoms before starting or changing treatment.

Risk factors for development and persistence of CWP

Increasing pain intensity and the spread of pain in multiple body parts—together with psychological, and social factors—has been found to result in CWP, both in the general population (253, 254) and in subjects with chronic low back pain and neck pain (255). To our knowledge, Paper III was the first study to investigate possible risk factors for the development of CWP, and persistent CWP, in patients with SpA, which is why comparisons are difficult. The prevalence of CWP remained stable over the 2.5 years, even though more than 30% of the patients transitioned between the pain groups during the study period. This transition is in agreement with findings in the general population (254, 256), and may reflect both the variability in the CWP group (with varied pain severity) and the varying disease course, as described in AS (257). In addition, four out of ten patients who developed CWP at follow-up reported having CRP at baseline, and most of them (80%) also reported having pain in one or more of the axial regions. Interestingly, patients with spinal regional pain have been suggested to be more likely to develop CWP than patients with peripheral pain syndromes (255), and that this may reflect a greater risk for sensitization to painful stimulation when pain is axial (258). Moreover, CWP has been reported to persist in about 50% or more in the general population (254, 256, 259, 260), and also this is in line with our study results—with 72% reporting having persistent CWP. Even though all patients with persistent CWP were not the same in the 2009 and 2011 surveys; the findings suggest that a large group of patients with SpA experience persistent pain in the long term, either continuous or recurrent.

Risk factors for development of CWP and having persistent CWP included a higher number of pain regions, higher pain intensity, worse fatigue, worse general health and health status, worse disease activity, lower physical function, higher depression, and lower self-efficacy in handling pain and symptoms. In two previous studies, the number of painful regions has been found to predict development of CWP in patients with RA (241), and persistent CWP in the general population (254), whereas both development and persistence of CWP have been found to be predicted by different physical and mental aspects of health status in the general population (169). Chronic pain, regardless of the type of pain, may have consequences for both cognitive factors and emotional factors (261). Our results also showed that female sex and being older were risk factors for persistent CWP, but not for development to CWP in patients with SpA. In the general population, age and female sex have both been identified and rejected as risk factors for development of CWP (254, 255), and found to be protective of persistent CWP (259). Moreover, smoking and obesity have been found to predict persistent CWP in the general population (259), but these results are in conflict with the results of Paper III where neither BMI nor smoking were identified as risk factors for development of CWP or persistent CWP in patients with SpA. The

differences in study populations, designs, and classification criteria for CWP may account for the conflicting results. In addition, SpA subgroup was included in the basic model of each logistic regression analysis, but was not found to be a risk factor for developing, or having, persistent CWP. This may reflect the similarities in disease expression, as reported by patients with AS and USpA (33).

We found that CWP both develops and persists in a large group of patients with SpA, and the finding that CWP persists may indicate that chronic pain is inadequately recognized and treated in patients with SpA. Thus special attention to risk factors and increasing pain is important in the clinic, and also better knowledge regarding treatment strategies, where a combination of treatment alternatives for both the inflammatory- and non-inflammatory-driven pain are essential.

Chronic pain and pain sensitivity

In patients with inflammatory arthritis such as RA, development of hyperalgesia, allodynia, and pain sensitivity, has been attributed to an ongoing painful stimulation due to inflammation (179), and with only low nociceptive input, this stimulation may lead to a sensitisation of the nociceptive system (175, 180). In patients with SpA, periods of both fluctuating and more persistent pain have been reported (262, 263), and in some patients this may develop into chronic pain, which is a more complex biopsychosocial phenomenon (264). Little is known about pain sensitivity in patients with SpA, but in AS pain perception has been proposed to also involve factors other than inflammation, such as emotional well-being (265). In Paper IV, a study of established axial SpA, we aimed to assess different quantitative aspects of pain, including measures of pain sensitivity, and found few differences between patients with AS and USpA, even though a higher proportion of patients with USpA were women. As in Papers II and III, and in the general population, a higher proportion of women than men reported having CWP (161, 245) in paper IV, and even more pronounced in women with AS. Women also had higher pain sensitivity than men, with lower pressure pain tolerance in both subgroups and lower pressure pain thresholds in USpA. In addition, a higher proportion of women with AS reported having unacceptable pain levels (VAS > 40 mm) than men (61% vs. 24%). There is strong evidence that women have a greater risk of different clinical pain conditions, and that they are more sensitive to pain than men (245), which was also found in this study. Thus, different analyses to reveal sex differences in all clinical studies are important for a better understanding of sex-specific mechanisms of pain in patients with SpA.

In the evaluation of temporal summation, we found no significant differences for TSI, but women with AS had numerically higher TSI than women with USpA (0.78 vs. 0.58). If these findings also apply to a larger sample, one possible

explanation for this might be the longer disease duration with longer exposure to inflammation with pain and stiffness in female AS patients. In a study of women with active RA (disease activity score-28 ≥ 2.6), increased TSI was found and interpreted as an indicator of central sensitisation, as compared to healthy controls (TSI: 0.98 vs. 0.71) (202). The findings from our study were lower, but the figures are difficult to compare, considering the different diagnoses and that our patients had an established longstanding disease. Quantitative sensory testin,g has been suggested to be an appropriate method to assess changes in evoked pain, such as hyperalgesia or allodynia. However, it should be interpreted with care and in the context of the pain condition, and with cognitive and affective factors taken into account (266). To further explore pain sensitivity in patients with SpA, larger and possibly controlled studies may be needed.

The analyses to assess possible associations with pain sensitivity were stratified by diagnostic subgroup (ICD-10), as the patients were clinically different in several respects, such as age, sex, symptom duration, spinal mobility, number of enthesitis sites, and disease activity (BASDAI). Lower pain tolerance was associated with a higher number of pain regions, with a higher number of painful entheses in AS, and with unacceptable pain levels in both AS and USpA. However, neither TSI (a suggested measure of sensitisation) nor pain thresholds were related to any of the other pain measures. Lower pain tolerance was associated with worse fatigue in both subgroups, with worse health status in AS, and worse anxiety in USpA. Moreover, we found that lower pain tolerance was associated with higher disease activity (ASDAS-CRP) in both subgroups, and higher pain tolerance was found in patients with inactive disease than in those with low or high/very high disease activity (Figure 12). ASDAS-CRP is an index, that also includes self-reported measures of pain, and the findings may indicate that different aspects of disease activity in longstanding disease play a role in pain tolerance. An elevated acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein) is only present in about 30% of patients with SpA, so the diagnosis cannot be ruled out with a normal value (137). Moreover, in patients with RA, longer disease duration were found to increase pressure pain sensitivity (allodynia) over pain-free areas, and the authors therefore suggested that a widespread altered central processing of somatosensory functions was involved in patients with longer disease duration (267). Pain perception is challenging to assess, due to the multidimensionality of the phenomenon. In this first study to assess pain sensitivity with computerised cuff pressure algometry (CPA) in patients with SpA, we attempted to address quantitative aspects, while qualitative aspects and other considerations such as sleep would certainly have added important and more detailed knowledge.

Strengths and limitations

A combination of data from two well-defined clinical cohorts and one large population-based cohort in the Skåne Region, where patients from both tertiary and secondary settings were included, enabled a wider view of the disease consequences chronic pain and physical function. In addition, the use of both self-reported data and clinical assessments might bring a broader approach to the research issues. Papers II and III had relatively large sample sizes, which permitted more detailed sub-analyses regarding sex differences in the subgroups. Another strength was that Paper III included longitudinal data to reveal changes in pain distribution and possible risk factors related to those. The questionnaires included were all valid and reliable PROMs—both disease-specific instruments, most often validated for AS, and generic instruments. The spinal mobility measures had acceptable validity and reliability and were performed according to international and national guidelines by physiotherapists experienced in rheumatic diseases. The pain sensitivity measures with computerised cuff pressure algometry (CPA) were conducted in a standardised way following a predefined protocol, and performed by the same examiner. CPA is a reliable tool (201), and has been used in patients with RA, fibromyalgia, and osteoarthritis previously (202-205, 268), and it might therefore add information regarding pain mechanisms to the overall picture of pain in SpA.

Limitations of the studies that should be acknowledged are that we cannot exclude the possibility of misclassification of the SpA diagnosis by ICD-10 codes, and that the results might have been different if ASAS criteria for axial and peripheral SpA had been used. However, ICD-10 codes for AS and USpA have previously been validated, indicating that ICD-10 codes can be used to identify patients with AS and USpA who fulfil the SpA classification criteria. In addition, all patients with psoriatic arthritis, IBD-related arthritis, or reactive arthritis were excluded from the four papers. An axial disease for patients with USpA was verified by medical records in Papers I and with a screening procedure in Paper IV. In Papers II and III, a large proportion (63–65%) of the patients with USpA reported having current chronic axial involvement. The cross-sectional design in Papers I, II, and IV also makes us unable to draw any conclusions about causality for the associations detected.

There were some limitations in each of the four studies, which also should be acknowledged. In Paper I, the smaller number of patients with USpA and the differences in disease duration between the subgroups may have introduced recruitment bias, as the physicians may have referred mainly patients with the most severe symptoms for spinal mobility assessments. The spinal mobility measures were collected in clinical practice and by a number of physiotherapist,

which may have affected the reliability. In addition, some spinal mobility measures were not available for every patient, which is why careful interpretation and generalization of the extent of change for the groups is emphasised. Moreover, the data were collected in a tertiary rheumatology setting and therefore the inclusion of patients with more severe disease, and differences in treatment, might affect the generalisability to other settings. The study lacked information on self-reported physical function, such as the BASFI, which would have been desirable.

Limitations to consider in Papers II and III include the limited response rate to the SpAScania questionnaire, which could have introduced response bias and affected the generalisability, although the response rate was comparable to other population-based surveys (161, 259). Moreover, the questionnaire lacked information on qualitative pain measures, other comorbid diseases, and sleep habits that could have had an impact on chronic pain or might have added important information to the analyses. Another limitation was that the questionnaires lacked information on pharmacological treatment for pain, anxiety, and depression, and that data on anti-inflammatory treatment with sDMARDs, bDMARDs, and corticosteroids were self-reported. An analysis of non-responders to the large SpAScania has previously been published (187). The non-responders to the pain questions in paper III (5%) did not differ significantly regarding age or subgroup, but a higher proportion were men (62%) and had AS (64%).

In Paper IV, one limitation was the difference in disease duration between the subgroups. This may reflect the study design, with consecutively included patients in a tertiary referral setting, where more severe axSpA may be over-represented. Another limitation was that the data could not be analysed in subgroups based on ASAS axSpA criteria, since some patients lacked information on MRI, resulting in a small sample size for nr-axSpA that did not allow comparisons between men and women. The experimental setting may also have induced bias, as this was a short-lasting and controlled pain assessment and therefore may have affected pain perception.

Clinical implications

Our current knowledge regarding patients with SpA requires a number of important issues to be considered in clinical practice.

Individualised and early non-pharmacological treatment, including education in combination with adequate pharmacological treatment is essential early during the disease course to encourage self-management and adherence to different treatment modalities. When needed, an multidisciplinary approach is recommended in all patients with SpA, to achieve better outcomes.

Attention to patients who report increasing pain, spread of pain, and worse fatigue in all phases of the disease course is important, as a large proportion of patients may develop chronic pain and concomitant CWP over time. In patients with chronic pain, a biopsychosocial approach is emphasised, with evaluation of pain, physical function, disease activity, mental functioning, mood, sleep, lifestyle, and social factors. This often requires an multidisciplinary team approach, to more effectively deal with challenges in the overall pain management.

Better and up to date knowledge regarding pain physiology and pain management for health personnel regarding both the inflammatory and non-inflammatory driven pain is also essential.

Considering the consequences of stiffness and chronic pain, clinical strategies to refer all patients, irrespective of diagnosis or sex to physiotherapists early during the disease course is emphasised. Interventions, such as education, guidance, and individually tailored treatment can help to maintain or improve spinal mobility, and physical function. Moreover, regular follow-up in different phases of the disease is important, especially with increasing symptoms to enhance compliance and help patients to stay physically active.

Conclusions

Study-specific conclusions in Papers I–IV

- Spinal mobility restrictions are present and increase over time in patients with axial SpA. Differences between patients with AS and USpA were most obvious in the thoracic and lumbar spine, and were less severe in patients with USpA.
- There were few sex differences in spinal mobility, and they mainly involved anthropometric measures in patients with axSpA.
- The prevalence of concomitant self-reported chronic widespread pain (CWP) was high in patients with AS (45%) and patients with USpA (49%), and higher than in the general population (11–15%).
- In men with SpA, the prevalence of concomitant CWP was also high (41%), even though women had a significantly higher prevalence (54%). No sex-related differences were found in prevalence rates of chronic regional pain (CRP).
- Men with chronic pain (CRP or CWP), had pain intensity levels similar to those reported by women with chronic pain.
- Female sex, a higher body mass index (BMI), and being a smoker were found to be associated with having CWP as opposed to having no chronic pain (NCP) or CRP.
- The prevalence rates of CWP (almost 50%), CRP, and NCP remained fairly consistent over the 2.5-year study period, but with individual transitions between the pain groups being evident in more than one-third of the patients with SpA.
- A higher proportion of patients with USpA transitioned from NCP in 2009 to CWP at follow-up than patients with AS (25% vs. 15%), and a higher proportion of patients with USpA than patients with AS reported having persistent CWP (77% vs. 69%).
- The development and persistence of CWP in patients with SpA are predicted by similar risk factors, including more pain regions, higher pain intensity, worse fatigue, worse general health, worse health status, worse disease activity, lower physical function, lower self-efficacy in handling pain and symptoms, and higher depression scores. In addition to the above, female sex, higher age, and anxiety also predicted persistent CWP.

- A large proportion of the patients with established axial SpA reported having chronic pain (AS: 74%; USpA: 83%), with no difference in self-reported chronic pain, pain intensity levels, or observed pressure pain sensitivity within the subgroups.
- In established axial SpA, women reported having more pain regions and higher pressure pain sensitivity than men, with lower pain tolerance in AS and USpA and lower pain thresholds in USpA. A larger proportion of women with AS reported unacceptable pain levels than men with AS.
- Factors such as high disease activity, impaired spinal mobility, worse fatigue, and pain were found to be associated with lower pain tolerance in patients with established axial SpA.

General conclusions

The main findings of this thesis highlight the importance of a thorough analysis of both pain and physical function, and an individualised management, in the clinical assessment—to adequately recognize risk factors for development of chronic pain and symptoms related to impaired function and health, in the wide context of SpA. The high prevalence of chronic widespread pain and the fact that it persists in a large group of patients also highlights a need for increased knowledge among health professionals regarding chronic pain and adequate treatment, for both the underlying disease and the non-inflammatory pain, which require a combination of both pharmacological and non-pharmacological treatment strategies. Throughout the lifelong disease course patients may also require multimodal treatment options and should be referred to a multidisciplinary team when needed, as the disease and its consequences may have an impact on both function and overall health. As part of the team, the physiotherapist has an important role to educate, encourage, and guide the patient regarding physical activity and exercise, and together with the patient, plan interventions according to individual needs and periods of disease activity—as pain, stiffness, and other consequences may complicate the management and overall health of each patient throughout the lifelong disease.

Future work

Larger longitudinal studies to determine the impact of limited spinal mobility and physical function in the wide context of axSpA could be of interest. Further studies to improve our knowledge of physical function and pain in relation to physical activity and cardiovascular fitness may also add important knowledge and guide treatment options. In addition, qualitative studies to capture the experiences and/or the views of the patients regarding spinal mobility and chronic pain could add important knowledge.

Better understanding of concomitant chronic pain and CWP is important to explain the complex interactions driving both the spread and persistence of CWP in patients with SpA. Longitudinal studies to investigate other aspects of pain, such as pain quality together with mental and social aspects may add valuable information to what we know about chronic pain, while larger studies to explore pain sensitivity may improve our knowledge of mechanisms related to peripheral and central sensitisation in patients with SpA.

Another important consideration is to address sex differences in all studies of patients with SpA as most evidence regarding SpA has been based on men with AS. Stratification according to age and disease duration might also add valuable information regarding long-term outcomes.

Further studies of patients who do not fulfil the ASAS classification criteria, may also add information to better understand the complex and diverse spectrum of patients with SpA.

Summary in English

This thesis concerns chronic pain and physical function in patients with spondyloarthritis (SpA). The term SpA includes different inflammatory rheumatic diseases with similar clinical symptoms, and the work focused on patients in two of the subgroups, ankylosing spondylitis (AS) and undifferentiated spondyloarthritis (USpA). AS is the most well-characterized subgroup and the most typical of the diseases in the SpA family, while USpA is a variable and less well-studied subgroup. The diagnosis can be difficult, and despite recent improvements, a delay until there is a clear diagnosis is common. Chronic back pain and stiffness are prominent and often early symptoms of these lifelong diseases. Inflammatory back pain typically starts in early adulthood and has an insidious onset, with morning stiffness and pain that awakens the patient during the night or in the early morning. It often improves with exercise but not with rest. Patients with AS and USpA frequently report having a reduced quality of life, and that symptoms such as stiffness, pain, and fatigue are important contributors. Pain is an important and multidimensional symptom in SpA, and can include inflammatory pain from axial and peripheral joints, and entheses, but also a heightened perception of pain that may lead to more complex chronic widespread pain. Inflammatory back pain can also lead to limited spinal mobility and physical function. Most research has been based on men with AS, while little is known regarding women and the more variable USpA group. The overall aim of this thesis was to study chronic pain and physical function in patients diagnosed as having AS or USpA, and differences between the subgroups and between men and women.

The first study was a clinical one on spinal mobility, and included 183 patients with axial involvement (AS: n = 126; USpA: n = 57). Spinal mobility measures recorded between 1999 and 2012 were analysed and showed that patients with USpA and AS had similar cervical and chest mobility, while thoracic and lumbar spinal mobility was more severely restricted in patients with AS. There were few differences between women and men besides anthropometric measures.

Studies II and III were epidemiological studies, based on a population-based cohort, SpAScania, that included patients with SpA identified from the Skåne Healthcare Register. Patients corresponding to AS or USpA, according to diagnostic codes, and who responded to questionnaires in 2009 and/or 2011 were included.

Study II assessed the prevalence of chronic widespread pain and associated factors (CWP) in SpA (n = 940). Patients who responded to the pain questions (n = 887) were categorised as having chronic widespread pain (CWP), chronic regional pain

(CRP), or no chronic pain (NCP). Analyses showed that concomitant CWP was common in SpA (47%) and even though more frequent in women, four out of ten men reported having CWP. In addition, no difference in pain intensity between men and women with chronic pain was found. Having CWP was associated with female sex, higher BMI, and being an ever-smoker.

Study III was longitudinal and assessed development of and persistent CWP in SpA (n = 712). In patients who responded to pain questions in 2009 and 2011 (n = 644), the prevalence of concomitant CWP remained high over time. Risk factors for development and persistence of CWP included more pain regions, higher pain intensity, worse fatigue, worse global health, and worse health status, but also higher disease activity, lower physical function, lower self-efficacy, and depression. In addition, female sex and age also predicted persistent CWP.

Study IV was a clinical one and assessed different aspects of pain in patients with established axial SpA (AS or USpA), who were consecutively enrolled in the SPARTAKUS cohort over 2 years (n = 226). Pain intensity, duration, distribution, and sensitivity (pain tolerance, pain threshold, and temporal summation of pain) were analysed. CWP was common and reported by almost 50% of the patients, and more pronounced in women. Similar pain thresholds, pain tolerance, temporal summation index (TSI), and pain intensity were found in the subgroups (AS and USpA), while women reported having lower pain tolerance and higher pain intensity than men. Lower pain tolerance was associated with worse outcomes in disease activity, fatigue, and spinal mobility.

In conclusion, concomitant CWP, a complex and multidimensional phenomenon, is common in patients with SpA, with few differences between patients with AS and those with USpA. Even though CWP and pain sensitivity is more pronounced in women, four out of ten men reported having CWP. A novel finding was that men with chronic pain reported having similar pain intensity as women with chronic pain. Once developed, CWP persists over time in most of the patients, and risk factors for development and persistence of CWP are similar and included worse outcomes for pain, fatigue, health, disease activity, physical function, self-efficacy, and depression. Additional risk factors for persistent CWP are female sex and being older. We found similar pain sensitivity between the subgroups and lower pain tolerance was associated with worse outcomes in disease activity, fatigue, and spinal mobility. These findings highlight the need for increased knowledge regarding CWP and attention to possible risk factors in the clinical setting, as early identification of patients at risk of developing CWP is of utmost importance. Better knowledge regarding individualised pain management strategies, including pharmacological and non-pharmacological treatment alternatives for also the non-inflammatory pain among health professionals is also essential. The finding, that patients with USpA also showed impaired spinal

mobility that deceases with longer disease duration, and the few differences found between women and men, besides anthropometric measures, emphasise the need for early intervention and structured and regular follow-up to maintain physical function, regardless of diagnosis or sex during the lifelong disease course. Moreover, efforts to coordinate treatment options among team members and together with the patient are important to enhance pain management, and promote self-efficacy, maintenance of a healthy lifestyle and overall health.

Populärvetenskaplig sammanfattning

Spondylartrit (SpA) är en grupp inflammatoriska reumatiska ryggsjukdomar som bland annat inkluderar den typiska gruppen ankyloserande spondylit (AS) och en mer blandad form som kallas odifferentierad spondylartrit (USpA). SpA kan delas upp i två varianter beroende på om inflammationen huvudsakligen drabbar leder, sen- och ligamentfästen i ryggen och bäckenet ”axial SpA” eller främst övriga leder ”perifer SpA”. Att identifiera och diagnosticera patienter med SpA kan vara svårt, vilket gör att många patienter kan ha haft återkommande eller ständig värk och stelhet under många år innan de får adekvat behandling. Typiskt för inflammatorisk ryggsmärta är att den startar tidigt i vuxenlivet och har en smygande debut i den nedre delen av ryggen. Morgonstelhet och smärta som stör sömnen under natten eller tidig på morgonen är vanliga symtom och ryggsmärtan förbättras vanligtvis av rörelser och träning men inte av vila. Sjukdomen är livslång och faktorer som värk/smärta, stelhet och trötthet kan ge konsekvenser som begränsad fysisk funktion och nedsatt livskvalitet.

Hos patienter med en reumatisk sjukdom är smärta ett vanligt symtom och vid SpA kan den vara orsakad av både inflammation från rygg, perifera leder och omkringliggande sen- och ligamentfästen men den kan även bero på en s.k. störd smärtmodulering, vilket innebär en förstärkt smärtupplevelse och att beröring som normalt inte orsakar smärta gör ont. Allt detta kan leda till långvarig ”kronisk” generaliserad smärta som kan påverkas av både fysiska, psykologiska och sociala faktorer. En annan välkänd konsekvens av SpA är nedsatt rörlighet i ryggen, vilken kan bero på inflammation, särskilt i den tidiga delen av sjukdomen men även hos vissa patienter på förbeningar av leder och ligament i rygg och bäcken senare i sjukdomsförloppet. Smärta och ryggrörlighet är viktiga att följa för att utvärdera sjukdomen och dess svårighetsgrad.

Under senare år har kunskapen kring SpA ökat men forskningen som gjorts har främst baserats på män med AS, vilket gör att det finns begränsad kunskap om konsekvenser för kvinnor och patienter med USpA. Det övergripande syftet med avhandlingen var att undersöka kronisk smärta och fysisk funktion hos patienter med SpA, diagnosticerade som AS och USpA och skillnader mellan de två undergrupperna och mellan kvinnor och män.

Patienterna i avhandlingen ingår i tre kohorter i Region Skåne. Delstudie I och IV består av patienter från sektionen för reumatologi på Skånes universitetssjukhus som har varit sjuka under relativt lång tid och antingen har AS eller USpA och en axiell sjukdom. Patienterna i delstudie I identifierades under 2003 och består av 183 patienter. Delstudie IV ingår i en större pågående studie och består av 226 patienter som inkluderats under två år (2015-2017). Patienterna i delstudie II och

III identifierades via Region Skånes vårdhälsodatabas och ingår i en större populationsbaserad SpA kohort.

Delstudie I, är en klinisk studie vars syfte var att undersöka skillnader i rörlighet i nacke, bröst- och ländrygg mellan 126 patienter med AS och 57 patienter med USpA och mellan kvinnor och män samt i förhållande till hur länge patienterna varit sjuka. De första ryggrörlighetsmåtten som registrerats mellan 1999 och 2012 analyserades. Resultaten visade att patienter med USpA hade bättre rörlighet i bröst- och ländrygg jämfört med patienter med AS men det var ingen skillnad i nack- och bröstkorgsrörlighet mellan grupperna. Det fanns få skillnader mellan män och kvinnor och dessa var främst i mått som påverkas av kroppsstorlek.

Delstudie II och III är baserade på två enkäter som skickades ut med 2,5 års mellanrum, i maj 2009 och i november 2011. Enkäterna innehöll flera olika patientrapporterade utvärderingsinstrument som ofta används på reumatologiska kliniker. Frågor om smärta handlade om hur länge smärtan pågått, hur utbredd smärtan var, det senare markerades på en smärtmannekäng med 18 specificerade regioner och hur ont de hade. Kronisk smärta innebär smärta som varat i minst tre månader under de senaste 12 månaderna.

Delstudie II hade som syfte att studera skillnader i förekomst av kronisk generaliserad smärta hos patienter med AS eller USpA och mellan kvinnor och män. Totalt besvarade 940 patienter 2009 år enkät och av dessa besvarade 887 frågorna om smärta. De kunde kategoriseras i tre smärtgrupper; kronisk generaliserad smärta vilket innebär smärta i höger och vänster kroppshalva, över och under midjan och i ryggen eller kring bröstbenet. Patienter med kronisk smärta som inte uppfyllde kraven för generaliserad smärta, kategoriserades som kronisk regional smärta. En tredje grupp utgjorde de patienter som inte rapporterade kronisk smärta. Resultaten visade att nästan hälften av patienterna med SpA (USpA 49% och AS 45%) hade kronisk generaliserad smärta och trots att det är vanligare hos kvinnor så rapporterar även en av fyra män med SpA kronisk generaliserad smärta. Män och kvinnor med kronisk smärta rapporterade lika hög smärtintensitet och att ha kronisk generaliserad smärta visade samband med att vara kvinna, ha högre BMI och att någon gång ha varit rökare.

Delstudie III är en longitudinell studie med data från båda enkäterna (2009 och 2011). Den hade som syfte att studera utveckling av kronisk generaliserad smärta över tid (2,5 år) hos patienter med AS eller USpA och att försöka identifiera riskfaktorer för att utveckla och ha kvarstående kronisk generaliserad smärta. Totalt besvarade 712 patienter enkäterna, varav 644 besvarade frågorna om smärta vid båda tillfällena. Analyserna visade att det var lika vanligt att ha kronisk generaliserad smärta vid de två tidpunkterna, även om en tredjedel av patienterna hade förflyttat sig mellan smärtgrupperna. Faktorer som utbredd smärta, högre smärtintensitet, svårare trötthet, sämre upplevd hälsa, högre sjukdomsaktivitet,

lägre fysisk funktion, sämre förmåga att hantera symtom och högre grad av depression kunde förutsäga både utveckling av och kvarstående kronisk generaliserad smärta. Ytterligare faktorer som kunde förutsäga kvarstående kronisk generaliserad smärta var att vara kvinna och att vara äldre.

Delstudie IV hade som syfte att undersöka olika aspekter av smärta hos patienter med axial SpA och samband mellan smärtkänslighet och olika patientrapporterade hälsoutfall. Vid ett studiebesök på reumatologiska kliniken fick patienterna genomgå ett flertal undersökningar, bland annat en smärtevaluering för att undersöka smärtkänslighet och undersökning av ryggrörlighet. De fick även fylla i olika frågeformulär och lämnade blodprover. Frågorna om smärta handlade åter om hur länge smärtan pågått, hur utbredd smärtan var samt hur ont de hade. Resultaten visade att nästan hälften av patienterna rapporterade kronisk generaliserad smärta och det var vanligare hos kvinnor. Patienter med AS och USpA hade lika hög smärtkänslighet (smärttröskel- och smärttolerans) och smärtintensitet men kvinnor hade lägre smärttolerans och rapporterade högre smärtintensitet än män. Lägre smärttolerans visade samband med högre sjukdomsaktivitet, ökad trötthet och sämre ryggrörlighet.

Sammanfattningsvis visade resultaten att nästan hälften av alla patienter med SpA har kronisk generaliserad smärta, vilket är klart högre än i befolkningen och även om kronisk smärta och högre smärtkänslighet var vanligare bland kvinnor så rapporterade även fyra av tio män kronisk generaliserade smärta. Män med kronisk smärta rapporterade lika hög smärtintensitet som kvinnor, vilket är ny kunskap. Faktorer som ökade risken för att utveckla och bibehålla kronisk generaliserad smärta var högre smärtintensitet, ökad trötthet, ökad sjukdomsaktivitet, sämre fysisk och psykisk funktion, sämre hälsa och nedsatt förmåga att hantera smärta och symtom. Resultaten visade också att även om patienter med USpA hade bättre rörlighet i ryggen än patienter med AS så försämrades rörligheten även hos dem i alla delar av ryggen under sjukdomens gång och att det var få skillnader i ryggrörlighet mellan kvinnor och män, förutom i mått som har med kroppsstorlek att göra.

En ökad spridning och kännedom om dessa resultat skulle förhoppningsvis kunna bidra till att personal inom både primärvård och specialistvård kan uppmärksamma de patienter som har en ökad risk att utveckla kronisk smärta och nedsatt fysisk funktion tidigare, oavsett diagnos och kön. Därmed skulle även behandling kunna sättas in tidigare under sjukdomen, vilket ofta kräver en kombination av farmakologisk behandling, för både den smärta som orsakas av inflammationen och smärta som har annat ursprung samt behandling för att förbättra fysisk och psykisk funktion och allmän hälsa.

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Appendix I

Värk och smärta

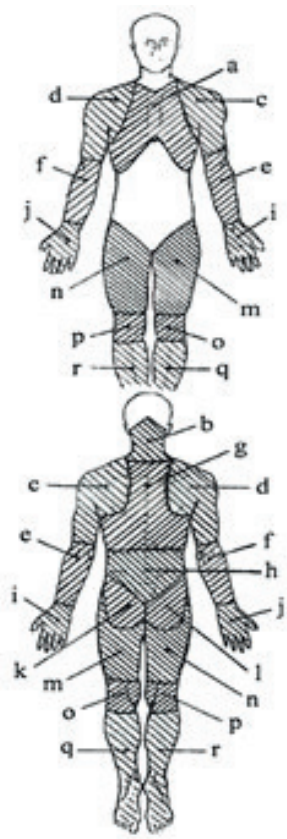
Frågorna avser värk och smärta i leder och mjukdelar som är ihållande eller regelbundet återkommande.

1. Har du under de senaste 12 månaderna haft värk eller smärta som varat mer än 3 månader?

- ☐ Ja
- ☐ Nej
- ☐ Vet ej

Om ja

Markera med **ett eller flera kryss** i rutorna nedan alla de ställen på kroppen där du upplevt värk eller smärta **mer än 3 månader under de senaste 12 månaderna.** Notera att de små bokstäverna syftar till bestämda områden av kroppen som är avgränsade i nedanstående figur.



- ☐ a. Bröstkorgens framsida
- ☐ b. Nacke
- ☐ c. VÄ skuldra/överarm
- ☐ d. HÖ skuldra/överarm
- ☐ e. VÄ armbåge/underarm
- ☐ f. HÖ armbåge/underarm
- ☐ g. Bröstrygg
- ☐ h. Ländrygg/korsrygg
- ☐ i. VÄ hand/handled
- ☐ j. HÖ hand/handled
- ☐ k. VÄ skinka
- ☐ l. HÖ skinka
- ☐ m. VÄ höft/lår
- ☐ n. HÖ höft/lår
- ☐ o. VÄ knä
- ☐ p. HÖ knä
- ☐ q. VÄ underben/fot
- ☐ r. HÖ underben/fot