Axial spondyloarthritis

with special emphasis on prevalence, perceived health and predictors

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Gothenburg 2016

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ISBN 978-91-628-9939-4 (print), 978-91-628-9940-0 (electronic)
http://hdl.handle.net/2077/47405

Printed in Gothenburg, Sweden 2016
Ineko AB

To my family

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ABSTRACT

The objectives of this thesis were to assess the validity of the diagnostic codes for ankylosing spondylitis and undifferentiated spondyloarthritis in the national patient register (study I), and to estimate the prevalence of ankylosing spondylitis in Sweden, as well as to compare the prevalence according to geographic and demographic factors (study II). Further, to compare inflammatory back pain, and perceived health, in different subtypes of spondyloarthritis (study III), and to investigate predictive associations between perinatal characteristics, and childhood infections, with later development of ankylosing spondylitis (study IV and V).

The diagnoses in the register, were found to have a high validity. The point-prevalence of ankylosing spondylitis in Sweden, in 2009, was estimated to be 0.18%, with a higher prevalence associated with a shorter formal education, and a higher prevalence in northern Sweden compared to the southern parts. Current inflammatory back pain was common across the three subtypes of spondyloarthritis analyzed (43% of ankylosing spondylitis, 31% of psoriatic arthritis and 39% of other spondyloarthritis) and the groups reported similar levels of perceived health. Having older siblings (odds ratio[OR]: 1.23; 95% confidence interval[CI]: 1.09-1.39), and hospitalization with respiratory tract infections during childhood (OR: 1.24; 95% CI: 1.07-1.44), were associated with an increased risk for development of ankylosing spondylitis, and appendicitis with a decreased risk (OR: 0.59; 95% CI: 0.41-0.83).

In conclusion, axial spondyloarthritis is a significant health issue, and early life exposures appear to be associated with the disease development.

Keywords: axial spondyloarthritis, ankylosing spondylitis, epidemiology

ISBN: 978-91-628-9939-4 (print), 978-91-628-9940-0 (electronic)

SAMMANFATTNING PÅ SVENSKA

Spondylartriter är en grupp besläktade reumatiska sjukdomar, som ger inflammation i rygg, leder och muskelfästen. När spondylartrit engagerar ryggen brukar den benämnas som axial. Den bäst studerade formen av axial spondylartrit kallas ankyloserande spondylit och ger ofta karaktäristiska skelettförändringar i ryggraden och korsbenslederna. Axial spondylartrit är kopplat till en genetisk uppsättning, som kallas HLA-B27, och förekomsten av axial spondylartrit i världen följer ganska väl förekomsten av just HLA-B27, även om andra genetiska riskfaktorer också är kända. Det är troligt att även omgivningsfaktorer påverkar risken att insjukna, men detta är relativt outforskat.

Syftet med denna avhandling har varit att utvärdera hur tillförlitliga diagnoserna ankyloserande spondylit och odifferentierad spondylartrit är i det nationella patientregistret (delarbete I). Därefter beskrivs förekomst av ankyloserande spondylit i Sverige, geografisk/demografisk fördelning och skillnader mellan kön och åldersgrupper (delarbete II). Vidare jämförs förekomst av inflammatorisk ryggsmärta mellan olika typer av spondylartrit, samt hur detta återspeglas i självupplevd hälsa (delarbete III). Slutligen jämförs fall, som senare i livet utvecklar ankyloserande spondylit, med befolkningskontroller, avseende olika särdrag vid födseln och infektioner under uppväxten (delarbete IV och V). Studierna grundar sig i huvudsak på uppgifter insamlade från nationella och regionala register i Sverige. I delarbete III kompletteras detta med en enkät, som skickades till patienter med spondylartrit.

Förekomsten av ankyloserande spondylit i Sverige 2009 beräknades till 0,18%. Förekomsten var högre i norra Sverige, jämfört med södra, och även högre bland de med en kortare utbildningslängd jämfört med de med en längre utbildning. Inflammatorisk ryggsmärta var vanligt bland samtliga av de studerade typerna av spondylartrit och de rapporterade liknande självupplevd hälsa. De som utvecklade ankyloserande spondylit hade i en högre utsträckning äldre syskon och hade oftare vårdats för luftvägsinfektioner under barndomen, jämfört med matchade befolkningskontroller. Blindtarmsinflammation i barndomen tycktes istället vara kopplat till en lägre risk för att utveckla ankyloserande spondylit senare i livet.

Sammanfattningsvis medför axial spondylartrit en påtaglig hälsopåverkan, och infektioner i barndomen tycks vara förknippade med sjukdomsutvecklingen.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Lindström U, Exarchou S, Sigurdardottir V, Sundström B, Askling J, Eriksson J K, Forsblad-d'Elia H, Turesson C, Kristensen L E, Jacobsson L T H. Validity of ankylosing spondylitis and undifferentiated spondyloarthritis diagnoses in the Swedish National Patient Register. Scandinavian Journal of Rheumatology, 2015;44:369.

II. Exarchou S, Lindström U, Askling J, Eriksson J K, Forsblad-d'Elia H, Neovius M, Turesson C, Kristensen L E, Jacobsson L T H. The prevalence of clinically diagnosed ankylosing spondylitis and its clinical manifestations: a nationwide register study. Arthritis Research and Therapy, 2015;17:118.

III. Lindström U, Bremander A, Haglund E, Bergman S, Petersson I F, Jacobsson L T H. Back pain and health status in patients with clinically diagnosed ankylosing spondylitis, psoriatic arthritis and other spondyloarthritis: a cross-sectional population-based study. BMC Musculoskeletal Disorders, 2016;17:106.

IV. Lindström U, Forsblad-d'Elia H, Askling J, Kristensen L E, Lie E, Exarchou S, Jacobsson L T H. Perinatal characteristics, older siblings, and risk of ankylosing spondylitis: a case-control study based on national registers. Arthritis Research and Therapy, 2016;18:16.

V. Lindström U, Exarchou S, Lie E, Dehlin M, Forsblad-d'Elia H, Askling J, Jacobsson L T H. Childhood hospitalisation with infections and later development of ankylosing spondylitis: a national case-control study. Arthritis Research and Therapy, 2016;18:240.

CONTENT

ABBREVIATIONS

AD	anno Domini
AS	ankylosing spondylitis
ASAS	assessment of spondyloarthritis international society
ASDAS	ankylosing spondylitis disease activity score
ATC	anatomical therapeutic chemical
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
CASPAR	classification criteria for psoriatic arthritis
CD8	cluster of differentiation 8
CI	confidence interval
CRF	case report form
DESIRE	devenir des spondyloarthropathies indifférenciées récentes
DiPiS	diabetesprediktion i Skåne
DNA	deoxyribonucleic acid
EQ-5D	European quality of life-5 dimensions index
ERAP	endoplasmic reticulum aminopeptidase
ESSG	European spondyloarthropathy study group
IBD	inflammatory bowel disease
HAQ	health assessment questionnaire
HLA-B27	human leukocyte antigen B27

ICD	international classification of diseases
IL-17	interleukin 17
IL-23R	interleukin 23 receptor
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
NHANES	national health and nutrition examination survey
NRS	numerical rating scale
NSAID	non-steroidal anti-inflammatory drugs
OR	odds ratio
PCR	polymerase chain reaction
PPV	positive predictive value
PROMS	patient reported outcome measures
PsA	psoriatic arthritis
RNA	ribonucleic acid
SpA	spondyloarthritis
SPACE	spondyloarthritis caught early
STAGE	study of twin adults: genes and environment
TEDDY	the environmental determinants of diabetes in the young
TNF	tumor necrosis factor
uSpA	undifferentiated spondyloarthritis
WHO	world health organization

1 INTRODUCTION

1.1 Axial Spondyloarthritis

Spondyloarthritis is the collective term used for a group of related inflammatory diseases sharing several features, but also expressing distinct differences. Common to the spondyloarthritis diseases is that they tend to cause inflammation in the spine and sacroiliac joints, as well as in entheses, tendons and peripheral joints(1). The diseases normally classified as spondyloarthritis are presented in table 1.

Table 1. *The spondyloarthritis diseases and related inflammatory disorders*

Spondyloarthritis subtypes	Related inflammatory disorders
Ankylosing spondylitis	Inflammatory bowel disease
Juvenile spondyloarthritis	Psoriasis
Psoriatic arthritis	Anterior uveitis
Arthritis associated with inflammatory bowel disease	Cardiac involvement
Reactive arthritis	
Undifferentiated spondyloarthritis	

The group of spondyloarthritis diseases also belong to a wider spectrum of inflammatory disorders, which to different degrees appear to share similarities in risk factors, inflammatory pathways, and response to treatment(2-6). These inflammatory disorders often coexist and spondyloarthritis is thus often accompanied by other diseases in the family, most frequently psoriasis, inflammatory bowel disease and anterior uveitis (6), but other manifestations, such as involvement of the conduction system and valves of the heart(7, 8) are also well-known (included in table 1).

Axial spondyloarthritis is the term used when spondyloarthritis manifests with inflammation in the back, and it can include all of the different subtypes of spondyloarthritis mentioned above(9). Ankylosing spondylitis is a specific subtype of spondyloarthritis, which always includes inflammation in the axial skeleton, and it can therefore be considered the prototype of axial spondyloarthritis(10). This thesis focuses on axial spondylitis in general, and in

particular on ankylosing spondylitis, but it also touches on the other forms of spondyloarthritis and the related disorders when appropriate.

1.2 Classification

In clinical practice, the diagnoses comprising the spondyloarthritis group are often defined through their co-presentation with the other inflammatory disorders, such as psoriatic arthritis associated with psoriasis or spondylo-arthritis associated with inflammatory bowel disease(11). At present this approach of classification is complemented, or perhaps rivaled by, the strategy of instead categorizing the spondyloarthritis diseases into axial spondyloarthritis, predominantly affecting the spine and sacroiliac joints, or peripheral spondyloarthritis predominantly affecting joints, entheses or tendons in the extremities(12).

Table 2. *Frequently used classification criteria for spondyloarthritis.*

Classification criteria	Spondyloarthritis subtypes
New York (modified)(13)	ankylosing spondylitis
ESSG(14)	spondyloarthritis
Amor(15)	spondyloarthritis
ASAS(12, 16)	axial/peripheral spondyloarthritis
CASPAR(17)	psoriatic arthritis

Both strategies of classification are limited by the diversity within the subgroups, the variability of the disease expression, the wide range in disease severity and the overlap between the phenotypes. Several different sets of classification criteria have been developed, for research purposes, both for the whole group of spondyloarthritis, but also for the different subtypes, as well as for axial and peripheral spondyloarthritis(12-17), presented in table 2. As a result, in contemporary studies, it is not uncommon that several sets of classification criteria are included to describe the study population(18, 19). An alternative approach, of classifying rheumatic diseases according to inflammatory pathways has been suggested(20), but has yet to be developed.

1.3 Clinical presentation

In ankylosing spondylitis, the main symptom is chronic back pain, originating from inflammation in the sacroiliac joints and the spine(21). The pain presents with the characteristic features of so called “inflammatory back

pain", which includes insidious onset, pain at night, morning stiffness, and improvement with exercise(22). In ankylosing spondylitis, over time, the inflammation also leads to inflammatory damage and bone formation in the sacroiliac joints and spine, which may result in a fusion of the joints and vertebrae, giving it a typical appearance some-times referred to as bamboo spine(21, 23). The disease onset is usually in the early adult-hood, in about 80% the first symptoms start before the age of 30 years, and may over time lead to marked functional impairment(21).

In other forms of axial spondyloarthritis the effect on bone destruction and bone formation in the spine may be less pronounced, but the symptoms and progression can otherwise be similar(10). For the other subtypes of spondyloarthritis, such as psoriatic arthritis and arthritis associated with inflammatory bowel disease, the degree of axial involvement varies and less is known about what determines this and the extent to which it contributes to the overall morbidity.

1.4 Advances in diagnostics

Since ankylosing spondylitis causes disease specific bone pathology in the sacroiliac joints and vertebrae, the introduction of radiographs into clinical practice allowed physicians to diagnose the disease more accurately. This eventually led to the proposal of classification criteria for the disease in 1963, which with only minor changes, the latest from 1984, are still used: The modified New York criteria (table 3)(13).

Table 3. *The modified New York criteria for ankylosing spondylitis(13).*

Definitive ankylosing spondylitis if radiological criterion is associated with at least 1 clinical criteria
Clinical criteria:
a) Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest.
b) Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
c) Limitation of chest expansion relative to normal values corrected for age and sex.
Radiologic criterion:
Sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3-4 unilaterally.

The modified New York criteria depend on the detection of radiographic pathology in the sacroiliac joints. However, the bone pathology that can be seen on plain radiographs takes time to develop, which is one of the reasons

for the considerable diagnostic delay (e.g. in one study of disease duration the average time from the first symptoms to the final diagnosis was 8.8-10.4 years(24)). This poses problems both in the clinical setting and in research. From the patient perspective, relying on traditional radiographs to reveal sacroiliitis, before diagnosing ankylosing spondylitis, may not only cause a diagnostic delay, but a number of patient may not develop radiographic sacroiliitis at all, even after a prolonged time of symptomatic disease(25). In a research setting, using the modified New York criteria, also prevents the inclusion of early disease phases of ankylosing spondylitis, before development of radiographic pathology.

During the last decade advances in detection, of sacroiliitis and spine inflammation, based on magnetic resonance imaging (MRI) has challenged the use of traditional radiographs(26). The advantage of MRI is that it can visualize both the typical bone destruction seen on radiographs, but also earlier stages of the inflammation, before the bone damage has occurred(26). In clinical practice this has offered a means to diagnose axial spondyloarthritis at an earlier stage, although not ankylosing spondylitis for which radiographic damage is still required. For research purposes, MRI has also greatly improved the prospects of detecting and studying early phases of axial spondyloarthritis(27).

Table 4. *The ASAS-criteria for axial spondyloarthritis(12). To be applied in patients with ≥3 months of back pain and age of onset < 45 years.*

Axial spondyloarthritis is present if:	
1. Sacroiliitis on imagining (either definitive radiographic sacroiliitis according to the modified New York criteria or active inflammation on MRI highly suggestive of sacroiliitis) plus ≥1 other of the following spondyloarthritis features OR 2. HLA-B27 plus ≥ 2 other of the following spondyloarthritis features	
inflammatory back pain	good response to NSAIDs
arthritis	family history for spondyloarthritis
enthesitis (heel)	HLA-B27
uveitis	elevated C-reactive protein
dactylitis	inflammatory bowel disease
psoriasis	

Table 4 presents the current ASAS-criteria (Assessment of SpondyloArthritis international Society) for axial spondyloarthritis(12), which incorporates MRI findings. Axial spondyloarthritis, fulfilling the ASAS-criteria for axial

spondyloarthritis, but lacking definitive structural changes in the sacroiliac joints, according to the modified New York criteria, is now often called non-radiographic axial spondyloarthritis(6).

The exact nature of non-radiographic axial spondyloarthritis, and how it relates to the traditional diagnoses of ankylosing spondylitis, and the other subtypes of spondyloarthritis, is not entirely determined or globally excepted(28). In some studies a progression rate of around 12% over 2 years, from non-radiographic axial spondyloarthritis to ankylosing spondylitis has been shown(10, 29), although other results have suggested that a substantial proportion of patients with non-radiographic axial spondyloarthritis do not develop radiographic sacroiliitis even after 15 years of follow-up(25).

1.5 Treatment

The basis for treating axial spondyloarthritis consists of physiotherapy and exercise, often in combination with non-steroidal anti-inflammatory drugs(NSAID)(21). This treatment approach can give a remarkably good effect(30), but many patients still fail to achieve an acceptable level of disease activity(21). During the last decades, major advances have been made in the treatment, mainly due to the introduction of tumor necrosis factor (TNF) inhibitors and more recently other targeted biological treatments(31, 32). But, as we still lack an understanding of the causes of the diseases and what mechanisms initiate and uphold the inflammation, there is no curative treatment to offer.

1.6 History and causes

The characteristic disease expression of ankylosing spondylitis led to an early recognition of the disease, and accurate descriptions can be traced back through history in different geographical areas(33), and also arguably in archeological remains(34, 35). The oldest studied remains in Sweden, with probable ankylosing spondylitis, of a man buried in the church ruins of St Clemens in the town of Visby (900-1300 AD), exhibits the both the characteristic skeletal pathology and the HLA-B27 (human leucocyte antigen B27) genotype typically associated with the disease(36). The geographical and historical distribution suggests that the pathogenic factors leading to ankylosing spondylitis are neither new nor geographically confined.

The risk of acquiring ankylosing spondylitis is now thought to be predominantly genetic. The most studied genotype is HLA-B27, which is

also known to correspond closely to the prevalence of ankylosing spondylitis in different populations(37), but a growing number of other genetic associations are also being described, such as IL23R (interleukin 23 receptor) and ERAP (endoplasmic reticulum aminopeptidase)(2).

In contrast, the role of environmental risk factors is still obscure and though such factors are suspected to be involved in the pathogenesis(38), the interplay between genes and environment is poorly understood. Lately, the understanding that ambient exposures, such as smoking(39) and occupation(40), may be associated with the rate of radiographic progression in axial spondyloarthritis has increased. From an epidemiological point of view this is of interest, since such observations could also lead to a better understanding of risk factors contributing to the disease onset.

1.7 This thesis

This thesis describes the prevalence of ankylosing spondylitis in Sweden, and compares the prevalence of inflammatory back pain between different subtypes of spondyloarthritis, and how this reflects on self-perceived health. Further, it also investigates possible non-genetic predictors for development of ankylosing spondylitis.

2 PREVALENCE

Chronic low back pain is the key feature in axial spondyloarthritis(12). However, low back pain is also very common in the general population, with studies indicating a 1-month prevalence in the adult population of about one third(41, 42), and the 1-year consultation prevalence in southern Sweden has been estimated to be close to 4%(43). The prevalence of chronic low back pain (lasting more than 3 month) has been estimated to be 10%(44). In a primary care setting the prevalence of inflammatory back pain, among patients with back pain has been reported to be 15%(45), and axial spondyloarthritis (according to the ASAS-criteria) has in one study been described in as many as 24% of patients with chronic low back pain(46).

Having a reliable method for case-identification is a prerequisite in prevalence studies, and in the case of axial spondyloarthritis the subjects must be distinguished from sufferers of other forms of chronic back pain, in the general population. In prevalence studies of ankylosing spondylitis, the general approach has been, and still is, to classify the disease according to the modified New York criteria(47, 48).

For axial spondyloarthritis overall, the recently developed ASAS-criteria for axial spondyloarthritis have been estimated to have a sensitivity of 82.9% and a specificity of 84.4%(49), while the definition used to identify "inflammatory back pain", within this criteria set, has been estimated to have a sensitivity of 79.6% and a specificity of 72.4%(50). The respective sensitivity and specificity were determined in the specific setting of patients with chronic back pain, and onset before the age of 45 years, referred to rheumatology clinics, but the criteria have also been applied in studies with a population-based setting(51) and in a primary care setting(52).

However, since the ASAS-criteria, and the current concept of axial spondyloarthritis are rather new, they are not congruent with other classification systems frequently used in health care, such as the International Classification of Diseases (ICD) issued by the World Health Association (WHO)(53). This may pose a problem when identifying subjects with axial spondyloarthritis from pre-existing data sources, such as health care registers, insurance register and medical records.

In epidemiological studies of ankylosing spondylitis, a number of different methods have been used for data collection, which can roughly be sorted into two categories. First, identifying cases through existing data sources, such as medical records or health care registers. Second, identifying the cases through different types of surveys, screening for symptoms or other findings compatible with ankylosing spondylitis.

An example of the first approach is a study from Rochester (USA) in 1979, where the cases were identified through the medical records of the Mayo clinic(54). An example of the survey-based approach is a French study from 2005(55), where a random sample was selected from the national telephone directory, and subsequently phoned and asked whether they had pain in their joints or back, and if affirming this, if they had been given any of a number of specified rheumatic/inflammatory disorders. The subjects thus identified were then screened more thoroughly through telephone interviews, and if needed through further examination. Another example, of the survey approach, is a study from Norway in 1985(48), where all men (age 20-54 years) and women (age 20-49 years) in the municipality of Tromsø, were invited to participate in a survey. Those who accepted were sent a questionnaire, and from the subjects reporting back pain or back stiffness, a random sample was clinically examined. The prevalence estimates determined through the examples above are presented in table 5 (page 10).

2.1 Geographical distribution of ankylosing spondylitis

Much of the variation in the prevalence of ankylosing spondylitis, between different ethnical populations and geographical regions, can be explained by variations in the HLA-B27 prevalence(37). Globally, a north-south gradient for HLA-B27 appears to exist, but also distinct differences between different ethnical groups, with a high prevalence among indigenous people in the arctic regions of the northern hemisphere, and a low prevalence in the southern hemisphere(56).

Using Scandinavia as an example, the HLA-B27 prevalence of the indigenous Sami people in northern Norway has been estimated to be 24%(57), compared to 16% among non-Sami Norwegians in the same area(58) and 17% in the population of northern Sweden(59). In contrast to this, in the southern part of Sweden only 10% have HLA-B27(60). Corresponding to this, estimates of ankylosing spondylitis in northern Norway have indicated a prevalence of 1.1-1.4%(48), and in southern

Sweden of 0.12%(61), although it should be noted that there are considerable differences in the methods used to obtain these estimates, in that the first is based on a population-based survey (described in the previous section) and the second on a regional health care register.

Geographical differences in HLA-B27 prevalence

The cause of the north-south gradient of HLA-B27 is not known. HLA type A, B and C codes for the major histocompatibility complex (MHC) class I in humans, and are instrumental in cell-surface antigen presentation(62). As HLA plays a central role in the adaptive immune-system, it has been suggested that the geographical differences may be a result of an evolutionary pressure from endemic micro-organisms, where certain HLA types could give an evolutionary advantage or disadvantage depending on the local spectrum of infectious diseases(63, 64).

One such theory suggests that HLA-B27 prevalence may be associated with an evolutionary pressure from the malaria parasite *Plasmodium falciparum*. This theory is based on comparisons of HLA-B27 prevalence and *P. falciparum* prevalence, both on a global level but also within indigenous populations in neighboring areas(65). Such a relationship is hard to prove, and hitherto data describing the outcome for *P. falciparum* infection in HLA-B27 positive individuals appear to be lacking, although one study has indicated that HLA-B27 may be overrepresented in patients treated for severe *P. falciparum* malaria(66).

HLA-B27 has also been associated with differences in the outcome for other severe infections. In HIV, it has been demonstrated that HLA-B27 is associated with a slower disease progression(67) and in hepatitis C with a more favorable outcome(68). A lower anti-body response to rubella vaccination(69) has also been found in HLA-B27 carriers. The relationship between HLA-B27, and ankylosing spondylitis on one side, and infections on the other side, needs to be further studied.

2.2 Prevalence of ankylosing spondylitis

A sample of studies on the prevalence of ankylosing spondylitis in Europe and North America are presented in table 5. It can be seen that the prevalence estimates vary considerably between the studies, even for studies performed in the same population, which is unlikely to be explained only by true variations in prevalence. Instead, it is probable some of this variation is due to methodology, and in particular the different methods used to identify the cases. For example in the 2004 study in north-western Greece, by

Alamanos(70), the cases were identified from patients referred to local rheumatology clinics, while in the 2010 study by Anagnostopoulos(71), indicating a 10-fold higher prevalence in central Greece, a postal questionnaire was used for the initial screening of a population sample.

Table 5. *A sample of prevalence (%) studies on ankylosing spondylitis.*

Year	First author	Region	Case identification	Prevalence
North America				
1972	Gofton(72)	Canada*	males +25 on reserve list	6.7
1979	Carter(54)	USA	Mayo clinic records	0.13
2013	Strand(73)	USA	rheumatology clinics	0.35
Europe				
1985	Gran(48)	Norway	survey	1.1 - 1.4
2005	Bakland(74)	Norway	rheumatology clinic	0.21
2011	Haglund(61)	Sweden	health care register	0.12
1998	Braun(47)	Germany	survey among blood-donors	0.86
2005	Saraux(55)	France	survey	0.08
2013	Costantino(75)	France	population cohort	0.31
2004	Alamanos (70)	Greece	rheumatology clinics	0.03
2010	Anagnostopoulos(71)	Greece	postal survey	0.29
Systematic reviews				
2014	Dean(76)	Europe	systematic review	0.24
2015	Stolwijk(77)	Europe	systematic review	0.25

*) Haida - Native American tribe

However, considering the differences in methodology and taking into account two recent systematic reviews, arriving at very similar estimates(76, 77), the prevalence of ankylosing spondylitis is probably somewhere around 0.2% in Europe, but can vary significantly between different populations in this area.

2.3 Demographic distribution of ankylosing spondylitis

Ankylosing spondylitis has previously been considered a predominantly male disease, with accounts of the sex ratio usually in the order of 6:1or more(78). In later studies, and in particular in population-based studies, the ratio is often less pronounced(54), and in one of the recent systematic reviews the male-

female ratio in Europe was 3.8:1(76). In contemporary "early disease" cohorts of axial spondyloarthritis a 1:1 ratio is more common(18, 79), which is consistent with the belief view that non-radiographic axial spondyloarthritis is more common in women(10).

In studies of ankylosing spondylitis, and spondyloarthritis in general, the prevalence normally increases gradually up to an age around 60 years(54, 55) and then levels out. The explanation for the increase and plateau is that the debut of ankylosing spondylitis occurs early in life, in about 80% before the age of 30 years and rarely after the age of 45 years(21), and since it is a chronic disease the prevalence at a specific age equals the cumulative incidence. Little is known about other possible demographic factors influencing the prevalence of ankylosing spondylitis, such as socioeconomic status or occupation.

2.4 Axial disease in other spondyloarthritis subtypes

In ankylosing spondylitis, and the more recent concept of non-radiographic axial spondyloarthritis, an axial component is obligatory for the diagnosis. However, the disease activity and clinical expression in axial spondyloarthritis can vary over time and with treatment, so that not all individuals will have axial symptoms at any given time, and a minority may even go into spontaneous remission(80).

It has been suggested that the prevalence of non-radiographic axial spondyloarthritis is likely to be similar to the prevalence of ankylosing spondylitis(10, 73), and that ankylosing spondylitis and non-radiographic axial spondyloarthritis may be different expressions of the same disease. This could be supported by studies showing similar frequencies of extra-articular manifestations(9), as well as similar response to treatment(81).

The other clinical subtypes of spondyloarthritis, such as psoriatic arthritis, arthritis associated with inflammatory bowel disease, and reactive arthritis, may also have an axial expression, but can manifest without symptoms from the back(1). To what degree the other spondyloarthritis subtypes have axial disease is less studies, and the results may be influenced by the fact that e.g. psoriatic arthritis with sacroiliitis may also correctly be classified as ankylosing spondylitis or axial spondyloarthritis, and vice versa, according to preference of which set of classification criteria are used. Prevalence of axial disease in the other subtypes are discussed in the following sections.

2.4.1 Psoriatic arthritis

The prevalence of psoriatic arthritis is largely determined by the prevalence of cutaneous psoriasis, which in Europe is about 2%(4). The prevalence of psoriatic arthritis is less studied than that of cutaneous psoriasis, and reported estimates vary significantly. One reason for this is that a number of different methods have been used to classify psoriatic arthritis in the studies, sometimes based on classification criteria for spondyloarthritis in general (such as the ESSG), which may not be optimal for this purpose(82). Another reason is that the estimates have been determined either through identifying the cases in a normal population or within a population with cutaneous psoriasis(82). Both using generic criteria for spondyloarthritis and identifying cases within a population with psoriasis may cause errors, since not all arthritis coexisting with psoriasis is psoriatic arthritis, and since psoriatic arthritis can occur without previous cutaneous psoriasis(83). Hence, the described prevalence estimates for psoriatic arthritis, within patients with psoriasis, rage from 1-48%(83-86), a variation which is however also affected by regional differences and genetic factors.

Having said that, one population-based, survey in England(87), performed on patients with psoriasis identified through a primary care register, estimated a prevalence of 13.8% of psoriatic arthritis (according to the CAPAR-criteria(17)) within the population with psoriasis. Another, large population-based telephone survey in the US(88) estimated a similar prevalence of 11%, and a recent population-based study in southern Sweden (register-based) also found a similar prevalence of 17.3% of psoriatic arthritis within a population with psoriasis(89).

The prevalence of axial disease in psoriatic arthritis has been described as 20-40%, and it has been suggested that it may have a more favorable out-come than in ankylosing spondylitis(90). The current CASPAR-classification criteria for psoriatic arthritis(17) only include a rather vague definition of axial disease, and population based studies are rare. As an example, in a comparison of patients with psoriatic arthritis, ankylosing spondylitis and undifferentiated spondyloarthritis, at a rheumatology clinic in 2013(91), 49% of the patients with psoriatic arthritis reported a history of inflammatory back pain, and 22% presented a “high grade” sacroiliitis on radiographs (fulfilling the modified New York radiographic criteria). However, the frequencies obtained in such a population of patients, at a dedicated spondyloarthritis clinic, can not necessarily be generalized to the general population. In another example, a population-based study in Greece found a prevalence of psoriatic arthritis of 0.17%, in the general population, of which 39.8% had

sacroiliitis(92). In another large population-based survey(93) (NHANES), 17% of the responders, reporting a history of cutaneous psoriasis, also fulfilled the Berlin criteria for inflammatory back pain. These latter results suggest that axial disease may be more common in psoriasis than previously thought, but further studies are needed.

2.4.2 Spondyloarthritis associated with inflammatory bowel disease

Inflammatory bowel disease (Crohn's disease and ulcerative colitis) is often associated with extra-intestinal manifestations, such as anterior uveitis or arthritis(5). The prevalence of axial disease in inflammatory bowel disease has been estimated at 5-12%(94). A higher prevalence has been noted in Crohn's disease than in ulcerative colitis(95), and asymptomatic sacroiliitis has also been described(96). Conversely, axial spondyloarthritis is also accompanied by inflammatory bowel disease. In a recent meta-analysis, the pooled prevalence of inflammatory bowel disease in ankylosing spondylitis was 6.4% and in non-radiographic axial spondyloarthritis 4.1%(9). Nearly 50% of patients with axial spondyloarthritis have also been shown to have a subclinical gut inflammation(97).

2.4.3 Reactive arthritis

Traditionally, reactive arthritis has been defined as "a sterile synovitis precipitated by an extra-articular infection"(98). No generally accepted classification criteria exist for the whole group of reactive arthritis(99, 100). At the fourth international workshop for reactive arthritis in 1999 it was, somewhat indistinctly, suggested that the term reactive arthritis should be used only for cases with symptoms typical for reactive arthritis, following an infection with microbes commonly associated with reactive arthritis(101).

Since reactive arthritis often follows a self-limiting course, estimates of incidence in conjunction with different infections, are more common than estimates of prevalence. Peaks in incidence have been repeatedly described in the aftermath of outbreaks of infectious enteritis, e.g. after an out-break of *Salmonella* in southern Sweden in 1974, 13 out of 330 enteritis-cases (4%) developed reactive arthritis(60), and similarly after an out-break of *Campylobacter* in Finland in 2000, 9 out of 350 enteritis-cases (2.6%) also developed reactive arthritis(102). After the water supply being contaminated with sewage in the town of Nokia in Finland 2007, only 21 cases (0.2%) of reactive arthritis were diagnosed, in the 8453 persons estimated to have caught gastroenteritis(103). More steady levels around 4-15% are reported in conjunction with symptomatic genital *Chlamydia* infections(99).

Axial disease in reactive arthritis is well described, but the estimates differ. HLA-B27 has been shown to predict a poorer prognosis, and the proportion of patients who develop a chronic axial phenotype, or progress to ankylosing spondylitis, likely depends on both HLA-B27 status and the infectious agent(101, 104).

3 ETIOLOGY

Studies of familiar disease aggregation of ankylosing spondylitis in the 1950s showed that hereditary factors must play a major role in the disease etiology(78). The same, and subsequent, studies also indicated that not all individuals who inherit a genetic vulnerability for ankylosing spondylitis will develop the disease, and that heredity alone cannot predict disease phenotype(105). From this was hypothesized that the risk for an individual to acquire ankylosing spondylitis was likely conveyed through a combination of hereditary and exogenous factors, which will be discussed in the following sections.

3.1 Genetic risk factors

In 1973 the strong association between HLA-B27 and ankylosing spondylitis was described(106, 107). Since then, different models for the possible pathogenic effect of HLA-B27 have been suggested, but the evidence is still inconclusive. One proposed mechanism is the presentation of arthritogenic peptides. This is based on the theory that HLA-B27, during antigen presentation, can present microbial peptides similar to the individual's own peptides (so called "molecular mimicry"), eliciting an auto-immune response(108). Other prosed mechanisms focus on the tendency of HLA-B27 to fold incorrectly during synthesis and for the heavy chains to form dimers, which in turn may trigger inflammatory response through intra- and extra-cellular pathways(108). Different types of HLA-B27, with only minor differences, are known to be more prevalent in different populations, and also have different degrees of association with ankylosing spondylitis, e.g. HLA-B*27:05 is commonly associated with ankylosing spondylitis, but HLA-B*27:06 is not(108, 109).

Following the development of new genetic methods, in particular genome wide association studies, the understanding of the genetic base for ankylosing spondylitis has expanded rapidly. Now a number of different HLA-B alleles have been associated with ankylosing spondylitis, and a growing number of other genes as well, such as ERAP and IL23R(110, 111).

Studies of the genetic overlap between ankylosing spondylitis and the related inflammatory disorders psoriasis and inflammatory bowel disease have also revealed a number of shared genes, among them IL23R and ERAP 1 and

2(2). IL23 is now considered to be central in the inflammatory pathway of ankylosing spondylitis and drugs targeting this have been developed both for ankylosing spondylitis and psoriatic arthritis, the IL-17 inhibitors(32, 112). Up to date, more than 40 genes have been associated with ankylosing spondylitis and the number is growing(2).

3.2 Environmental risk factors

A prevailing theory has been that either infections or traumatic exposures may trigger the development of ankylosing spondylitis(113, 114). The suspicion of traumatic risk factors was initially based on observations of trauma or prolonged mechanical stress, in the medical history of cases with ankylosing spondylitis, such as reports of long transports on trucks during the second world war and a high disease frequency among athletes(113). One suggested theoretical explanation, was that the axial predilection of the inflammation may be a result of a greater mechanical stress on the back and pelvis, compared to other locations(115).

In the search for an infectious trigger for ankylosing spondylitis, urogenital infections were early seen as possible culprits(115). In one example from Sweden Romanus, in his thesis 1953, strongly favored a urogenital infectious etiology(116). This historical reasoning may partly be contributed to a lack of methods to differentiate between ankylosing spondylitis and reactive arthritis at that time, a problem which still exists.

The support for a role for environmental triggers was further strengthened by studies of disease-concordance in mono- and dizygotic twins(105). While the twin-studies primarily supported the strong hereditary component of ankylosing spondylitis, the occurrence of discordant twins, in particular discordant monozygotic and HLA-B27 positive dizygotic twins, also implicated environmental exposures in the pathogenesis(117, 118). Later twin studies have confirmed this and have suggested that while genetic effects probably contribute to more than 90% of the risk, the remaining risk could be explained by environmental exposures(38, 119).

3.2.1 Mechanical stress and non-infectious exposures

In patients with an established diagnosis of ankylosing spondylitis, there are indications that non-infectious exogenous factors may affect the rate of radiographic progression. Two studies have shown that workers with “blue-collar” occupations have a higher progression rate, compared to workers with “white-collar” occupations(40, 120). This would fit nicely with a hypothesis

suggesting that micro damage at entheses insertion, and the resulting inflammation, drives the new bone formation in spondyloarthritis(121). This has been supported by studies in a mouse model, based on mice with a chronic overproduction of TNF, that develop arthritis and gut inflammation, similar to spondyloarthritis(122). In this model, mice with unloaded hind legs (suspended by the tail) fail to develop arthritis in the ankle and hind paws(123). Furthermore, in a collagen-antibody-induced arthritis model, mice with unloaded hind legs developed significantly smaller osteophytes compared to controls(123). However, it is not known if the possible effect of mechanical stress on disease progression have any effect on onset of ankylosing spondylitis and other spondyloarthritis, or if it is only of importance in the established disease.

A similar association between smoking, and a higher rate of radiographic progression, has also been shown(124), and one study has found that smoking may be a risk factor for incident ankylosing spondylitis (125), but this remains to be replicated. One case-control study has also suggested a protective effect associated with breastfeeding. This was theoretically attributed to the effect of breastfeeding on the development of the gut microbiota(126).

Two studies have focused on birth order and the risk for developing ankylosing spondylitis. In the first, an increased risk was found for firstborns(127), but the second, much larger but otherwise similar, study did not confirm this(128). Birth order has been shown to be associated with the risk for a number of different immune-related disease, e.g. asthma and allergy(129). This is often attributed to the "hygiene hypothesis", which suggests that having siblings may act as a proxy for an increased risk of exposure to infections at an early age, and that this may alter the immune-phenotype. However, other explanations are also possible, such as different intrauterine conditions for firstborns compared to younger siblings.

3.2.2 Infections

Simultaneous to the description of the association between HLA-B27 and ankylosing spondylitis, a similar association was also shown for reactive arthritis(130), further strengthening the suspicions of an infectious origin for ankylosing spondylitis. A possible mechanism for such an association was provided when the possibility of antigen cross-reactivity between microbes and host was demonstrated (molecular mimicry discussed previously)(131). However, no such cross-reactivity mechanism has been conclusively proved in ankylosing spondylitis or the other spondyloarthritis diseases, and this

theory has been contradicted by studies indicating that HLA-B27 transgenic rats develop spontaneous spondyloarthritis, even when lacking CD8+ T-cells(132).

Intestinal flora and Klebsiella

One attempt to link a specific infectious trigger to ankylosing spondylitis involved a study, published in 1977, analyzing the presence of Klebsiella and Yersinia in the feces and urine of patients with ankylosing spondylitis(133). The initial study, and subsequent studies, did demonstrate that Klebsiella was more common in feces of patients with active ankylosing spondylitis and that its presence predicted later development of active disease in patients with a low disease activity(134). Further studies also demonstrated elevated levels of antibodies, in particular IgA (suggesting a link to gut-mucosa), against Klebsiella in patients with ankylosing spondylitis(135, 136), a finding that has also been replicated in several independent cohorts(137-139).

However, a more recent study comparing antibody pattern in axial spondyloarthritis, ankylosing spondylitis, blood donors and subjects with non-specific low back pain found no differences between the groups(140). Yet another study, comparing cellular and humoral immune response to Klebsiella, between members with and without ankylosing spondylitis, in families with ankylosing spondylitis, also found no differences(141).

More contemporary studies of gut flora, have not been able to replicate the previous findings of Klebsiella in the feces of subjects with ankylosing spondylitis, or that it would correlate to disease activity(142, 143). What has been found, using 16s-RNA sequencing, is that patients with ankylosing spondylitis have a different microbial composition in the gut, compared to healthy controls, and that this composition at least partly corresponds to species known to be associated with inflammatory bowel disease(144-146). It has also been shown that patients with ankylosing spondylitis, and their first-degree relatives, may have an increased gut-permeability in the small intestine(3), providing a potential locus for exposure to microbial antigens.

In a transgenic rat-model of ankylosing spondylitis, expressing HLA-B27, the animals spontaneously develop a disease similar too human spondyloarthritis, including gut inflammation. If reared under germ-free conditions, the rats fail to develop both arthritis and gut-inflammation, strongly suggesting a pathogenic role of microbes in this particular animal model(147). Similar results have also been presented for a mouse model(148). However, is has also been shown that HLA-B27 transgenic rats have a different gut microbiota, compared to co-reared wild type rats,

indicating that the host genotype may also influence the microbial composition in the gut(149).

The hypothetical role of Klebsiella in the development of ankylosing spondylitis is still debated, and there are strong opinions offered both in favor of it(150) and against it (151). It could be that Klebsiella is rather a marker of gut lesions, than involved in the pathogenesis, but considering the sheer amount of data published on the topic a systematic review, by an independent researcher, may be appropriate to sort out the results. Further, the link between the microbial flora of the gut, intestinal inflammation, and spondyloarthritis is a current focus for research.

3.3 Comparisons with related diseases

Considering the genetic overlap (described previously), between the inflammatory disorders related to spondyloarthritis, it is possible that they also share environmental risk factors, which may justify a comparison as follows.

3.3.1 Inflammatory bowel disease

In inflammatory bowel disease, there are more epidemiological data supporting a role for environmental factors in the pathogenesis, compared to ankylosing spondylitis. For both ulcerative colitis and Crohn's disease it is accepted that bacterial enteritis may trigger disease onset, and both animal and human data indicates that gut flora is important both in the pathogenesis and for the severity of the conditions (5, 152). In ulcerative colitis a protective association has also repeatedly been described for smoking and breastfeeding(152), while in Crohn's disease smoking appears to increase the risk(5).

Elevated serological markers for Klebsiella have also been previously described in inflammatory bowel disease(153), but at least one study has failed to detect Klebsiella in tissue cultures from inflammatory bowel disease(154).

Appendectomy and appendicitis have been linked to a decreased risk of subsequent development of ulcerative colitis(155, 156). For Crohn's disease, the results have been more divergent, and a recent meta-analysis found the over-all effect to be an increase in risk(157). Much of this increase in risk was, however, related to an increase in incidence of Crohn's disease in the

year following the appendectomy, wherefore it can be suspected that it was instead incipient Crohn's disease.

At least ten epidemiological studies have investigated the association between inflammatory bowel disease and season, or month, of birth. The results are not consistent, in that some point to increases in risk depending on season or month(158), or a cyclic pattern(159), but others find no association(160). Different mechanisms have been suggested for the associations seen between season of birth and risk for later disease development in some diseases, such as seasonal variations in infectious exposure, or seasonal variations in Vitamin-D levels.

3.3.2 Psoriasis

Infections with streptococci, usually throat infections, can trigger the acute guttate form of psoriasis(161), and some data indicate that it can also be associated with exacerbations in the chronic plaque disease(162). Cutaneous psoriasis can also manifest as a Koebner phenomenon, affecting previously scarred or traumatized skin(163). There some are data suggesting that both infections and trauma, including mechanical stress, may be associated with the development of psoriatic arthritis in subjects with cutaneous psoriasis(164-166), but the exact role, or mechanism, of this has not been determined.

3.3.3 Reactive arthritis

The typical infections associated with reactive arthritis (and originally with Reiters syndrome) are bacteria causing enteritis (*Salmonella, Shigella, Campylobacter* and *Yersinia*) or urogenital infections (*Chlamydia*), but many other bacteria have also been reported to trigger it(101). The mechanisms, by which the infections trigger reactive arthritis, are not conclusively determined.

There are reasons to suspect that the mechanisms involved in the pathogenesis may differ between different pathogens. Specifically, research on *Chlamydia*-induced reactive arthritis has challenged the concept of an aseptic arthritis, as both DNA and RNA of *Chlamydia* can be detected in the synovial tissues, including examples of detection in the sacroiliac joints(167). In addition, DNA from *Yersinia enterocolitica* has also been detected in synovial fluid in reactive arthritis(168) and there is also some support for an effect of antibiotics in chlamydia induced arthritis(169). However, detection of *Chlamydia* in joints, with PCR, have also been reported for other types of arthritis, as well as from osteoarthritis, so its role is unclear(170).

4 SUMMARY OF METHODS

4.1 Objectives

To validate the diagnoses of ankylosing spondylitis and undifferentiated spondyloarthritis in the Swedish national patient register, and to investigate the possible identification of incident cases in the register (study I).

To estimate the prevalence of ankylosing spondylitis in Sweden, and to stratify the prevalence according to age, sex, geographical and socioeconomic factors, and in relation to clinical manifestation and pharmacological treatment. And to compare pharmacological treatment and disease manifestations between men and women (study II).

To assess, and compare the frequency of current inflammatory back pain in ankylosing spondylitis, psoriatic arthritis and "other spondyloarthritis", and to compare self-reported disease activity between the subsets with current inflammatory back pain (study III).

To investigate predictive associations between perinatal characteristics, (in particular birth order, birth weight and season of birth), as well as childhood infections (in particular enteric and urogenital infection), with later development of ankylosing spondylitis (study IV and V).

4.2 Data sources

The studies in this thesis are based on subjects identified through two different register. In study I, II, IV and V the subjects were identified through the Swedish national patient register, and study III through the Skåne Health Care Register. Apart from these sources, data were also cross-linked from five other national registers, and in study III from a postal survey. The registers and the survey are described in the following section.

National patient register

The national patient register started in 1964 as a hospitalization register, recording medical, demographic and administrative data on patients discharged from inpatient care. The coverage of the register increased gradually and is considered to be almost 100% (covering both private and public hospitals) since 1987. In 2001 a register for specialized outpatient care was added to the patient register, this has a lower coverage, around 80%,

primarily due to missing data from private care. There is no register on a national level including primary care. Diagnoses are registered according to International Classification of Diseases (ICD) codes.

Prescribed drugs register

The register was started in July 2005 and collects data on all prescribed drugs, at the time they are dispensed from a pharmacy, in Sweden. It does not cover over-the-counter drugs or drugs that are prescribed but not collected by the patient.

Swedish Rheumatology Quality Register

A treatment and follow-up register for rheumatic diseases that was initiated in the 1990s. It includes patients with rheumatoid arthritis, spondyloarthritis and a growing number of systemic rheumatic diseases. The coverage for patients treated with biologics was recently estimated to be around 95% for rheumatoid arthritis and 86% for spondyloarthritis.

Population register

This register is managed by the Swedish administrative authority, Statistics Sweden, and collects demographic data on people living in Sweden, such as migration, level of education and income.

Medical Birth Register

Initiated in 1973, the medical birth register collects medical, administrative, and some demographic data concerning prenatal care, delivery and postnatal care.

Skåne Health Care register

The Skåne Health Care register is a regional register in the region of Skåne (southern part of Sweden). It contains much of the same medical and administrative data as the national patient register, of which it is also a part, but it also covers public and private primary care in the region.

Cause-of-Death register

A national register that collects data on date of death and cause of death in Sweden.

SpAScania Questionnaire

The questionnaire, sent to patients with spondyloarthritis diagnoses, in study III was composed by a group of two specialists in rheumatology, one general practitioner, one health economist and two physiotherapists. It included questions related to health and disease, lifestyle, exercise, demographics,

treatment, health economics and a number of disease outcome measures. Examples of outcome measures included in the questionnaire were the Bath ankylosing spondylitis disease activity and functional indices (BASDAI and BASIF), the health assessment questionnaire (HAQ), and the European quality of life-5 dimensions index (EQ-5D). The questionnaire was tested in, and adjusted according to, three small focus groups with patients with spondyloarthritis and one patient research partner, before being sent to the study group in 2009. Two reminders were sent to the subject who did not respond.

4.3 Study design and statistical analysis

4.3.1 Study I

The primary objective was to identify patients with ankylosing spondylitis and undifferentiated spondyloarthritis, in the national patient register, and to determine the validity of these diagnoses. The secondary objective was to determine if incident cases of ankylosing spondylitis or undifferentiated spondyloarthritis could be identified through the register.

All patients receiving a registered diagnosis of ankylosing spondylitis and undifferentiated spondyloarthritis in the patient register 1966-2009, still living and residing in Sweden in 2009, were identified. 1966 was set as the start of the period, since the first version of the New York criteria was proposed then(171).

In order to determine the validity of the diagnoses, the medical records of a sample of patients identified through the register were examined. The sample was selected randomly, but on the premises that the patients had been given the diagnosis at least once in 2007-2009, in one of five rheumatology clinics (100 at each, a total of 500 patients) in Sweden. Half of the cases were selected as possible prevalent cases, also having a registered diagnosis prior to 2007, and half as possible incident cases, with no registered diagnosis prior to 2007. The five clinics were selected to represent the different geographical regions in Sweden, as well as to include larger and smaller clinics.

The medical records were examined according to a pre-specified Case Report Form (CRF), extracting the data needed to determine if the patients fulfilled the following classification criteria for spondyloarthritis: the modified New York criteria(13), the ESSG criteria(14), the Amor criteria(15) and the ASAS

criteria for both axial(12) and peripheral(16) spondyloarthritis. Information was also sought for weather the treating physician was certain that they had the diagnosis or not – the "expert opinion".

The secondary objective was to determine if incident cases could be identified in the register. In order to determine if the patients in the sample population, without a registered diagnosis prior to 2007, were incident cases, data was collected from the medical records concerning the time-point of symptom onset.

For the purpose of assessing the generalizability of the results from the validation exercise, comparisons were made to all cases registered in the patient register, with the respective diagnoses, in terms of the frequencies of the related inflammatory disorders; anterior uveitis, inflammatory bowel disease and psoriasis. A comparison was also made to a subset of the register population, who had been given the respective diagnosis at least once at a clinic of rheumatology or internal medicine.

Statistical methods

Positive predictive values (PPV) for fulfilling the different criteria sets, being given a diagnosis of ankylosing spondylitis or undifferentiated spondyloarthritis in the register, were calculated. Subset analyses were performed for the portion of cases where information on imaging results and HLA-B27 status were available.

Chi2 test were used to compare the frequencies of fulfilling the different criteria sets between the five different hospitals and stratified on sex and age (above/below median).

4.3.2 Study II – cross sectional study

The primary objective was to determine the point prevalence of ankylosing spondylitis in Sweden on the 31 of December 2009, and to stratify this on age, sex, pharmacological treatment, disease manifestations, and geographical and socioeconomic factors. The secondary objective was to compare disease manifestations and treatment between men and women

All individuals, aged 16-64 years in 2009, given a diagnosis of ankylosing spondylitis in the patient register 1967-2009 were identified. Two case definitions of ankylosing spondylitis were analyzed, a (i) "base case" and a (ii) "strict case", corresponding to (i) the whole population in the register, and (ii) the subset with at least one diagnosis from a clinic of rheumatology or internal medicine (the same categories described in study I). Data were cross-

linked from the prescribed drugs register, the Rheumatology Quality Register, the population register and the cause-of-death register.

Comparisons of prevalence stratified on socioeconomic status were based on the individual patients' highest recorded level of formal education. In this comparison, only patients 30 years or older were included, since by then the majority were assumed to have finished their formal education.

Statistical methods

The point-prevalence was calculated based on the cumulative incidence of registered codes for ankylosing spondylitis up until 31 December 2009. Subgroup prevalence was determined for men/women, age-groups, disease manifestations and pharmacological treatment. Age- and sex-standardized prevalence was calculated for the different health care regions in Sweden and for the different levels of formal education, standardizing to the Swedish population in 2009.

For statistical comparisons, non-overlap of 95% confidence intervals were used in the comparison of geographic distribution and level of education. Chi2-tests and t-tests were used to compare the demographics, treatment and disease manifestations between men and women. In order to further analyze the difference in treatment, between men and women, a logistic regression model was used to adjust for potential confounders (age and disease manifestations).

4.3.3 Study III – cross sectional study.

The objectives were to describe and compare the frequency of current inflammatory back pain, between patients with a diagnosis of ankylosing spondylitis, psoriatic arthritis and other spondyloarthritis, and to compare the self-perceived health status in the subsets with current inflammatory back pain. The rationale behind this comparison was the assumption that symptoms of inflammatory back pain may be used as a marker for an axial disease in cases diagnosed with spondyloarthritis.

The patients were identified through the Skåne Health Care Register, based on having been given a diagnosis of any type of spondyloarthritis, in 2003-2007, and aged 15 years or older. In 2009 all subjects, then aged 18 years or older and still residing in the county, were sent a postal survey (the SpAScania questionnaire described previously). Data were also collected from the prescribed drugs register and the Rheumatology Quality Register, for anti-rheumatic treatment.

Among the responders to the survey, all subjects reporting symptoms compatible with current inflammatory back pain were identified, based on reporting more than three months of low back pain during the last 12 months, and fulfilling the Berlin criteria(22) for inflammatory back pain. The proportion of subjects with current inflammatory back pain were compared between the three groups. Comparisons of patient reported outcome measures, treatment, demographics and related inflammatory disorders, were then performed between the groups reporting current inflammatory back pain.

Statistical methods

Comparisons between the different subgroups of spondyloarthritis, and between responders and non-responders, were done using Fisher's exact test and independent sample t-tests, also applying a Bonferroni correction due to multiple testing. Concordance between register data and survey data was determined through Cohen's kappa.

4.3.4 Study IV – case-control study

The objective was to investigate possible associations between perinatal characteristic, in particular birth weight, birth order and season of birth, and later development of ankylosing spondylitis.

Cases with ankylosing spondylitis were identified through the national patient register, but limited to those borne in Sweden in 1973 or later (when the medical birth register started). A control population was retrieved from the population register, matched on sex, birth year and county of birth at the time-point of the index cases´ first registered spondyloarthritis diagnosis (the closest approximation to the time-point of disease onset available in the register). Data were then retrieved from the medical birth register, for perinatal characteristics, and linked to data from the prescribed drugs register, the Rheumatology Quality Register and the national patient register.

The cases and controls were compared in terms of the frequencies of the specific perinatal features and both simple and adjusted odds ratios were computed for each characteristic.

Statistical methods

Comparisons between the cases and controls, with regard to level of formal education (2008), maternal diabetes and disposable income (2008) were performed using Chi2-test, Fisher's exact test and t-tests. Odds ratios were determined though simple conditional logistic regression and a multiple conditional logistic regression model also adjusting for possible confounders

(gestational length, maternal age, type of birth). Two measures of socioeconomic status (the mother's civil status and country of birth) and the size of the delivery unit were also included in the model.

The multiple logistic regression model was also applied in four sensitivity analyses. First, excluding cases and controls with a registered diagnosis of psoriasis, inflammatory bowel disease or anterior uveitis up until two years after the first registered diagnosis of ankylosing spondylitis. Second, only including cases with anti-rheumatic treatment during 2011. Third, including only cases who had received a diagnosis of ankylosing spondylitis at least once at a clinic of rheumatology or internal medicine (in analogy with the definitions used on study I and II). Fourth, only including cases receiving the diagnosis at least once in outpatient specialized care in 2001-2009.

4.3.5 Study V – case-control study

The objective was to investigate associations between childhood infections and later development of ankylosing spondylitis. It was specifically hypothesized that there may be an association with enteric and urogenital infections, considering the similarities with reactive arthritis and the possible role of gut inflammation in ankylosing spondylitis.

Cases were identified based on a diagnosis of ankylosing spondylitis in the specialized care outpatient register 2001-2010. Controls were retrieved from the population register, matched on sex, birth year and county of birth, at the time-point of the index cases' first registered diagnosis of spondyloarthritis. Both cases and controls had to be born in Sweden in 1964 or later (start of the patient register) and to have lived in Sweden at least up to their 17th birthday (exposure period 0-16 years).

Data on pharmacological treatment were obtained from the prescribed drugs register and the Rheumatology Quality Register, and data on other rheumatic diseases and related inflammatory disorders from the patient register. All cases and controls matched before the age of 17, or receiving any other rheumatic diagnosis or related inflammatory diagnosis before match were excluded, as well as all receiving a diagnosis of reactive arthritis or juvenile arthritis at any time-point.

Occasions of hospitalization with an infection before the age of 17 were extracted from the patient register, and compared between the cases and controls based on frequencies and through determining odds ratios. The infectious diagnoses were analyzed as a whole as well as categorized according to their primary focus.

Statistical methods

Odds ratios were determined though simple conditional logistic regression. Two sensitivity analyses were performed as a result of the risk for reverse causality. First, only including cases and controls matched at an age of 27 years or older, giving a minimum of 10 years between exposures and match. Second, only including those matched in 2007-2010, making it possible to also exclude anyone treated with immunosuppressive or cytostatic drug in the year prior to match. In the latter analysis, the use of antibiotics during the year prior to match, was also compared between the cases and controls using Fisher's exact test.

A third sensitivity analysis included only cases with anti-rheumatic treatment, likely to represent a more severe/active phenotype. One post hoc sensitivity analysis was also performed, excluding all cases and controls with a diagnosis of inflammatory bowel disease. Three additional, stratified, analyses were also included, stratifying on median age at match, and median age at appendectomy and tonsillectomy.

5 SUMMARY OF RESULTS

5.1 Study I

15120 patients with ankylosing spondylitis and 14553 with undifferentiated spondyloarthritis (and never a diagnosis of ankylosing spondylitis), living in Sweden in 2009, were identified through the national patient register. Of the patients with ankylosing spondylitis, 76% had at least one registered diagnosis at a clinic of rheumatology or internal medicine, for undifferentiated spondyloarthritis this was 59%.

For the sample population of 500 patients, selected for the validation exercise, the medical records were located for 499. For 220, of the 250 patients identified as ankylosing spondylitis, the radiographic data needed to apply the modified New York criteria were found. Based on these 220 patients, the PPV for fulfilling the modified New York criteria was 80% (table 6).

For 166 of the 186 patients, identified as undifferentiated spondyloarthritis, and never having been given a registered diagnosis of ankylosing spondylitis, either imaging or HLA-B27 status was found, making it possible to assess the different spondyloarthritis criteria. Of these 166, 89% fulfilled at least one of the criteria for spondyloarthritis and 82% either of the ASAS-criteria. Only 26% of the patients identified as undifferentiated spondyloarthritis, with available radiographic data on the sacroiliac joints, fulfilled the modified New York criteria, as seen in table 6. Patients with registered diagnoses of both ankylosing spondylitis and undifferentiated spondyloarthritis were overall more similar to the ankylosing spondylitis group.

Part of the validation was also intended to depend on the “expert opinion” of the physician, concerning the diagnosis, since this is often considered the golden standard. This was not possible to determine, due to the difficulty to extract this information from the medical records in a structured manner.

For the secondary objective of identifying incident cases the hypothesis was that if a patient had not received a diagnosis in either the inpatient register 1966-2006, or in the outpatient specialized care register 2001-2006, they could be an incident case. This however, proved to be false as the mean time from symptom debut (according to the medical records) and the first

diagnosis (in the register), for this subgroup was 16.6 years for ankylosing spondylitis and 9.2 years for undifferentiated spondyloarthritis.

Table 6. *The frequency of criteria fulfillment in the validated sample.*

Criteria fulfillment	AS	uSpA without AS	Overlap AS and uSpA
All validated cases	(n=250)	(n=186)	(n=137)
New York (modified)	176 (70)	37 (20)	96 (70)
ASAS-axial	197 (79)	82 (44)	111 (81)
ASAS-peripheral	122 (49)	106 (57)	85 (62)
ASAS-axial/peripheral	215 (86)	136 (73)	125 (91)
ESSG	200 (80)	111 (60)	119 (87)
Amor	207 (83)	120 (65)	127 (93)
Any of the SpA-criteria	222 (89)	147 (79)	131 (96)
Available data on radiographic sacroiliitis	(n=220)	(n=143)	(n=124)
New York (modified)	176 (80)	37 (26)	96 (77)
Available data on imaging and/or HLA-B27	(n=230)	(n=166)	(n=131)
ASAS-axial	197 (86)	82 (49)	111 (85)
ASAS-axial/peripheral	215 (93)	136 (82)	125 (95)
Amor	207 (90)	120 (72)	127 (97)
Any of the SpA-criteria	222 (97)	147 (89)	131 (100)

Data are based on review of 500 medical records. Results are given separately for patients with a diagnosis of ankylosing spondylitis (AS), undifferentiated spondyloarthritis (uSpA, without AS) and the overlapping cases (73 of which are also included in the AS group).

The generalizability of the PPVs were assessed through a comparison of the frequencies of psoriasis, inflammatory bowel disease and anterior uveitis in the validated sample, with different register subsets, as presented in table 7. The conclusion was that the frequencies were similar in the validated sample, compared to both the whole population in the register (AS-1/uSpA-1), and the subset with a diagnosis from a clinic of rheumatology or internal medicine (AS-2/uSpA-2), supporting the generalizability.

Table 7. *The frequency of anterior uveitis, psoriasis and inflammatory bowel disease (IBD) in the cohorts of ankylosing spondylitis (AS) and undifferentiated spondyloarthritis (uSpA) (without AS) in the national patient register, 1966-2009, and in the validated sample.*

	Ankylosing spondylitis			Undifferentiated spondyloarthritis		
	AS-1	AS-2	Validated	uSpA-1	uSpA-2	Validated
Total number	15120	11472	250	14553	8617	186
Women	5325	3899	86	8865	5062	103
(%)	(35)	(34)	(34)	(61)	(59)	(55)
Uveitis	3229	2601	86	1166	1146	44
(%)	(21)	(23)	(34)	(8)	(13)	(24)
Psoriasis	1094	899	15	1095	901	15
(%)	(7)	(8)	(6)	(8)	(11)	(8)
IBD	1202	995	10	643	517	9
(%)	(8)	(9)	(4)	(4)	(6)	(5)

AS-1: ≥1diagnosis of AS in the whole patient register.

AS-2: ≥ 1 diagnosis of AS at department of rheumatology or internal medicine

uSpA-1: ≥1diagnosis of uSpA, and never an AS-diagnosis, in the whole patient register

uSpA-2: ≥1 diagnosis of uSpA at department of rheumatology or internal medicine, and never an AS-diagnosis

5.2 Study II

The point prevalence of ankylosing spondylitis in Sweden 31 December 2009, in the age-group 16-64 years, was calculated to be 0.14% with the strict case definition and 0.18% with the base case definition, and 64% were men. There were differences between men and women both regarding disease manifestations and treatment, with a higher proportion of men having a registered diagnosis of anterior uveitis and more women having psoriasis and peripheral arthritis. Men also received treatment with TNF-inhibitors more frequently, and women treatment with glucocorticoid steroids. When the treatment differences were analyzed in the logistic regression model, adjusting for disease manifestations and age, the same pattern was observed.

The crude and standardized prevalence, stratified on health care regions, are presented in figure 1. The prevalence was higher in northern Sweden compared to the southern parts. Prevalence in relation to socioeconomic status, based on the highest recorded level of formal education, is presented in figure 2. There was a lower prevalence of ankylosing spondylitis in the group with more than 12 years of formal education, compared to the other groups. This difference remained after stratifying on age, but was more pronounced in the older age-groups.

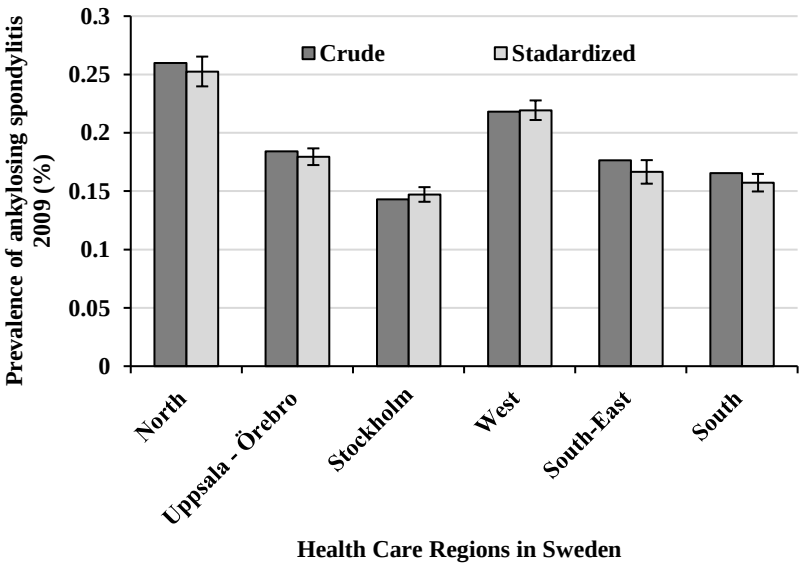

Figure 1. The point-prevalence of ankylosing spondylitis in Sweden, 31 December 2009, in the different health care regions in Sweden, presented as crude prevalence and standardized according to age and sex, to the Swedish population. In the figure corresponding to figure 1 in the published study there was a computational error concerning the standardized rates, which is corrected in this version.

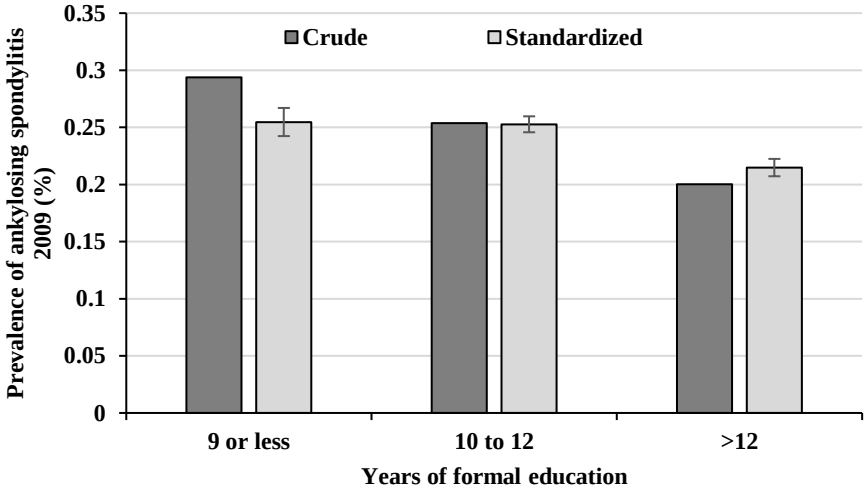

Figure 2. The point-prevalence of ankylosing spondylitis in Sweden, 31 December 2009, stratified on length of formal education, presented as crude prevalence and standardized according to age and sex, to the Swedish population. In the figure corresponding to figure 2 in the published study there was a computational error concerning the standardized rates, which is corrected in this version.

5.3 Study III

5771 patients were identified in the Skåne Health Care Register, given a spondyloarthritis diagnosis in 2003-2007, and being 18 years or older and still living in the county in 2009, of which 2785 (48%) responded to the survey. 1010 (36% of responders) reported more than three months of low back pain during the last 12 months and fulfilled the Berlin criteria for inflammatory back pain at the time of the survey, based on self-reported symptoms. Within the responder group the proportion of subjects reporting current inflammatory back pain, was higher, but similar, for ankylosing spondylitis (43%), compared to the other two groups (31% for psoriatic arthritis and 39% for "other spondyloarthritis").

The three groups, reporting current inflammatory back pain, had similar levels of self-perceived health status, but with a consistent trend for worse reporting from the groups other than ankylosing spondylitis, and a higher proportion of pharmacological treatment in the group with psoriatic arthritis, as presented in table 8. The kappa-values and proportion of agreement, between the survey and register data, were very good indicating a high concordance between the different sources.

Table 8. *Comparisons of demographics, frequency of related inflammatory disorders, patient reported outcome measures and pharmacological treatment, between clinically diagnosed ankylosing spondylitis, psoriatic arthritis and" other spondyloarthritis", all reporting current inflammatory back pain.*

	AS with current IBP n=319	PsA with current IBP n=409	Other-SpA with current IBP n=282
Demographics			
Age 2009, mean (sd)	54 (13)	57 (13)	53 (15)
Sex, n men (%)	182 (57)	129 (32)[2]	87 (31)[2]
SpA-related disease, n (%)			
Uveitis	63 (20)	9 (2)[2]	37 (13) [2, 4]
Psoriasis	19 (6)	407 (100)[2]	0
Inflammatory bowel disease	25 (8)	21 (5)	36 (13)[4]
PROMS, mean (95% Cl)			
NRS-spinal pain	5.9 (5.6-6.1)	6.1 (5.9-6.4)	6.2 (6.0-6.5)[1]
NRS-fatigue	5.8 (5.6-6.1)	6.2 (5.9-6.4)[1]	6.1 (5.8-6.4)
NRS-patients global	5.2 (4.9-5.4)	5.4 (5.2-5.6)	5.5 (5.2-5.7)
BASDAI	5.1 (4.8-5.3)	5.7 (5.5-5.8)[2]	5.5 (5.3-5.8)[1]
BASFI	4.4 (4.2-4.7)	4.8 (4.5-5.0)	4.4 (4.1-4.7)
EQ-5D	0.68 (0.66-0.70)	0.65 (0.63-0.67)	0.67 (0.64-0.69)
Treatment, n (%)			
Etanercept	27 (9)	54 (13)[1]	15 (5)[4]
Adalimumab	12 (4)	32 (8)[1]	9 (3)[3]
Methotrexate	37 (12)	151 (37)[2]	33 (12)[4]
Sulphasalazine	28 (9)	14 (3)[1]	24 (9)[3]

AS=ankylosing spondylitis, IBD= inflammatory bowel disease; NRS= Numerical Rating Scale 1–10; BASDAI= Bath Ankylosing Spondylitis Activity Index; BASFI= Bath Ankylosing Spondylitis Functional Index, PROMs = Patient-reported outcome measures, IBP= inflammatory back pain.
1) $p<0.05$ compared with AS; 2) $p<0.00125$ (Bonferroni correction) compared with AS; 3) $p<0.05$ compared with PsA; 4) $p<0.00125$ compared with PsA (Bonferroni correction)

5.4 Study IV

Based on 1960 cases with ankylosing spondylitis and 8377 matched controls, the proportion of cases with older siblings was slightly higher than that of the controls (62% vs. 58%), with an odds ratio of 1.18 (1.06 to 1.30) based on the simple conditional logistic regression analysis. For the other two perinatal characteristics primarily assessed (birth weight and season of birth), as well as the other features included in the comparison (see study IV for details), there were no differences between the cases and the controls. However, birth weight was found to be sensitive to how the cut-offs for categorization were chosen, so that while using the WHO definitions for birth weight (<2500g, 2500g-4200g, >4200g) no differences were detected. But when using more evenly balanced categorizations, either based on tertiles or on categories used in previous studies, there appeared to be a signal for an increased risk of ankylosing spondylitis associated with low birth weight.

Birth order and birth weight were included in the multiple logistic regression model, as well as the confounding factors, socioeconomic measures and size of delivery unit, as described in the methods section. Season of birth was not entered in the model, since it did not differ between cases and controls, with regard to proportions or simple odds ratios. The odds ratios for birth order and birth weight, computed through the model, are presented in figure 3. Overall the sensitivity analyses resulted in endpoints with similar magnitude and direction.

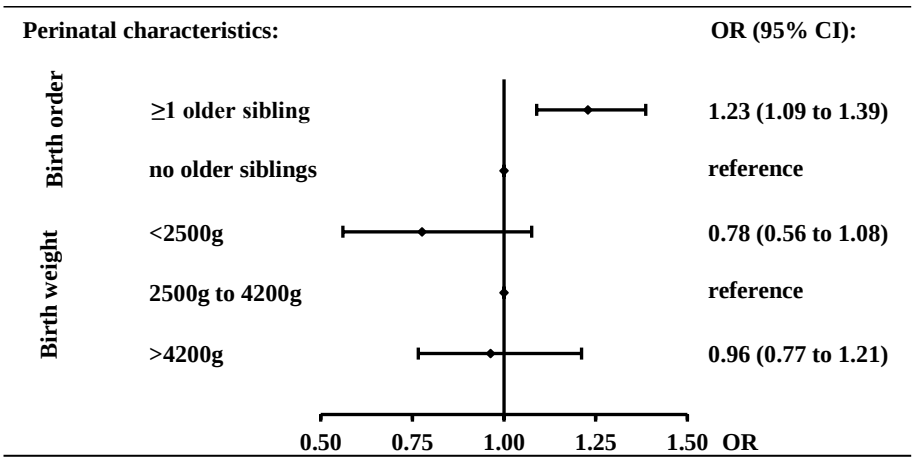

Figure 3. Forest plot presenting the odds ratios (OR) and 95% confidence intervals (CI) for being diagnosed with ankylosing spondylitis, with regard to birth order and birth weight, in the multiple conditional logistic regression model.

5.5 Study V

2453 cases, with ankylosing spondylitis, and 10257 matched controls, fulfilled the study criteria. For the two types of infections, enteric and urogenital, where there were hypothesized to be an association with later development of ankylosing spondylitis, no such relationship was detected. Instead, there was an increased risk associated with respiratory tract infections, and in particular with tonsillitis. There was also a negative association with appendicitis and appendectomy, see figure 4.

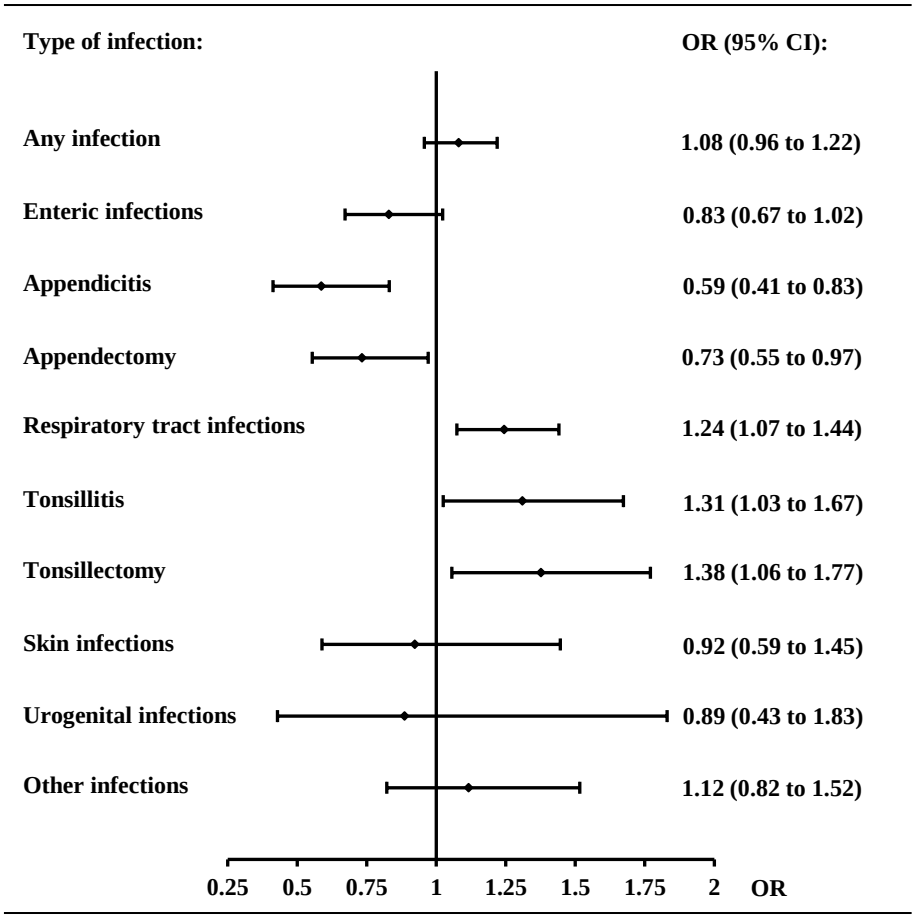

Figure 4. Forest plot presenting the odds ratios (OR) and 95% confidence intervals (CI) for being diagnosed with ankylosing spondylitis, with regard to hospitalization with different types of infections during childhood.

The direction and magnitude of the point estimates were similar in the sensitivity analyses, and in the second sensitivity analysis there was no statistical difference between the cases and controls with regard to prescriptions of antibiotics in the year prior to match. The stratified analyses suggested a stronger association with appendectomy if performed at a young age, and a stronger association with tonsillitis/tonsillectomy for the group receiving their first spondyloarthritis diagnosis at a younger age.

6 DISCUSSION

6.1 Methodology – study design

The quality of a study relies on the choice of an appropriate study design, how it is conducted, and the internal and external validity. Internal validity refers to how accurate the results of the study are, within the studied sample population. The internal validity can be reduced by faults in study design, systematic errors (bias) and confounding. External validity refers to how well the results of the study can be generalized to other populations. The external validity can be reduced by limitations in the internal validity, but is also dependent of the specific situation of the generalization. In this section the strengths and limitations of the different study designs, used in this thesis, will be discussed.

Study I

The main objective of study I was to determine the validity of the diagnoses in the register population. For this purpose, a sample of the population was chosen, on premises that were partly set up in order to maximize the probability of retrieving the relevant medical records. This was in fact a trade-off, between finding the relevant data and validating a representative sample. This limitation in the study design introduced a selection bias, which needed to be addressed.

The problem of selection bias in study I was dealt with by comparing the frequencies of the related inflammatory disorders, within different subsets of the register population (table 7), and it was concluded that the validated sample was similar enough to the register populations to extrapolate the results. The frequencies of anterior uveitis, psoriasis and inflammatory bowel disease in the whole register cohort, were also very similar to the frequencies of extra-articular manifestations presented in a meta-analysis 2014 (25.8%, 9.3% and 6.8%, respectively)(172), further supporting the validity.

Retrieving data from medical records spanning several decades is cumbersome and information will be missed or lost, frequently in a biased way. For example, single episodes of dactylitis or enthesitis are more likely not to be recorded, or not found in the review, compared to radiographic findings. It is therefore probable that PPVs calculated in study I rather underestimates the validity of the diagnoses in the register, since a criterion not found was treated as a negative finding.

Study II and III

Study II and III were designed as cross-sectional analyses, which can be a suitable design when studying disease occurrence and comparing different groups. One drawback is that there is no temporal aspect in the study design and therefore also very little opportunity for any causal inference. In study II this limits the conclusions that can be reached, for possible reasons for a difference in prevalence, depending on length of education. It cannot be differentiated, in a cross-sectional study, whether having ankylosing spondylitis may lead to a lower level of education, for example due to an impact on daily function, or whether having a shorter education is a risk factor for developing ankylosing spondylitis.

In study I the validity of the diagnostic codes were determined based on PPVs. In a prevalence study, such as study II, the accuracy of the prevalence estimates would depend more on the sensitivity and specificity of the method for case-identification (in this case ICD-codes), than on PPVs. If the specificity of the diagnostic codes, for ankylosing spondylitis, is low in the register, the prevalence would be overestimated in study II. And if the sensitivity is low it would instead lead to an underestimation. The sensitivity and specificity cannot be determined for the diagnostic codes in the register, since there are no data on the "true negative" and "false negative" cases in the Swedish population.

Study IV and V

Study IV and V were conducted as case-control studies, which is often an efficient design for studying the effect of exposures when the outcome is relatively rare. Due to the study design, there was a risk for reverse causality in study V, since the time point of disease onset cannot be precisely determined through the registers. To increase the probability of the exposures occurring before the outcome, several sensitivity analyses were performed, excluding cases and controls with any suspicion of a pre-existing inflammatory disorder prior to matching, which resulted in no substantial changes in the point estimates. In study IV a number of possible confounders were also included in the regression model, but residual confounding may still affect the results.

6.1.1 Systematic errors - bias

When designing, and interpreting the results of an epidemiological study two main categories of bias must be considered: selection bias, referring to any bias resulting from the selection procedure, and information bias, referring to any bias introduced in the data for exposures or outcomes. Selection bias can,

for instance, result in a study sample that is not representative, hence decreasing the external validity, while information bias may affect both the internal and external validity. To determine how much the bias threatens the validity of the study, the magnitude and direction of it should be estimated.

In all register based studies there are also to some extent a problem with misclassification. Misclassification can result in a bias if, for example in a case-control study, classification of exposures is different between cases and controls. Misclassification resulting in a bias is often referred to as directional misclassification, in contrast to non-directional misclassification where the effect is the same in the different studied groups. Non-directional misclassification can still result in underestimations of the associations searched for.

Potential problems with the study design and validity in study I, where the possibility of selection bias is closely related to the objectives and design of the study, have been discussed in the previous section, the possible impact of bias in the other studies is discussed below.

Study II

In study II there is a risk of selection bias influencing the prevalence estimates. Selecting cases based on codes in the national patient register, only detects individuals who have sought help from the health care system, or who are not exclusively treated in primary care, which may result in an underestimation of the true prevalence in the population (the population in this context being the population of Sweden).

Few studies have described the frequency of undiagnosed ankylosing spondylitis or spondyloarthritis, in settings that are comparable to Sweden. In a population-based study from Greece 2005(92) the prevalence of ankylosing spondylitis was estimated to be 0.24%, and the total prevalence of spondyloarthritis 0.49%. In this cohort 95% of the spondyloarthritis cases had sought medical care for their symptoms previously and only the remaining 5% were diagnosed by the researchers during the study. Another study, comparing the consultation prevalence for musculoskeletal disorders in England and Sweden, found that only a small minority (3%) of patients with ankylosing spondylitis were exclusively treated in primary care (in the Skåne region in southern Sweden)(173). If the results from these two studies are possible to generalize to the general population of Sweden, this selection bias is unlikely to have a significant impact on the prevalence estimates.

Concerning the comparisons of length of formal education, there is also a risk of selection bias, if a shorter education increases the likelihood of being diagnosed with ankylosing spondylitis and receiving health care. For example, this could be true if a shorter formal education leads to a physical occupation where the symptoms of ankylosing spondylitis is more of a hindrance. But an alternative bias could also occur if subjects in higher socioeconomic groups chose private health care to a larger extent and thus are not detected through the national outpatient register. The proportion of patients with ankylosing spondylitis in Sweden, who are exclusively seen in private care is not known. However, based on unpublished data, from the Swedish Rheumatology Quality Register, only 4.6% of patients with ankylosing spondylitis receiving treatment with TNF-inhibitors are treated in private care, but it is difficult to assess the combined magnitude and direction of these possible biases more precisely in this cross-sectional study.

Study III

Since the comparisons between the study-groups only include the 48% of the subjects responding to the survey, there is an obvious risk of non-response bias, here acting as a selection bias. In order to asses this a comparison was made between responders and non-responders, where it was shown that the responders had a statistically significant higher proportion of chronic diseases (ankylosing spondylitis, psoriatic arthritis and undifferentiated spondylo-arthritis), and anti-rheumatic treatment, compared to the non-responders, who had significantly more reactive arthritis. From this it can be deduced that the study subgroup called “other-spondyloarthritis” are more likely to be non-responders, compared to the other two groups. The direction of the bias is likely to cause overestimations of the frequency of current inflammatory back pain, as well as of the self-reported disease burden and treatment in all three groups, but especially in the “other-spondyloarthritis” group. A comparison of the initial responders, with the responders after the first and second reminder may have given additional information on how the responders differed from the non-responders, but this was not performed.

There is also a possibility of recall bias (information bias), if for example, the cases with ankylosing spondylitis are more likely to have paid notice to, or remember, the symptoms defining inflammatory back pain, compared to the other sub-groups. The possible types of bias in study III, which are difficult to quantify, reduces the external validity with regard to the prevalence of axial symptoms, whereas the internal validity of the comparison of patient reported outcome measures should be less compromised.

Study IV and V

In study IV and V, being case-control studies, selection bias would imply any systematic difference between the cases and controls, other than having ankylosing spondylitis, which would have been introduced during the selection process. This is not likely to occur. Possibly, there could be a selection bias in terms of severity of the disease (prevalence bias). If there was a large proportion of cases with ankylosing spondylitis with a less severe disease, who did not seek health care, or were only treated in primary care, and thus were not identified as cases, but this seems unlikely (see discussion under "Study II").

A similar problem arises from only including patients with ankylosing spondylitis as cases, if this is indeed only a radiographically more severe phenotype of all axial spondyloarthritis. If the associations with the analyzed exposures are, in turn, related to the severity of the disease, the resulting bias would then cause an overestimation of the differences between cases and controls. In both study IV and V sensitivity analyses were included, selecting presumably more severe subsets, with little effect on the point estimates.

Misclassification should not introduce a bias in study IV and V, since there are no obvious reasons why the classification of exposures should differ between the cases and controls. The non-directional misclassification that remains will lower the efficiency of the studies, underestimating the differences between the groups, i.e. increasing the likelihood of making a type II error.

6.2 Implications and future perspectives

6.2.1 Prevalence and perceived health

The prevalence of ankylosing spondylitis, determined in study II, is close to the prevalence estimates reported in other similar populations in Europe and North America. In particular, our base case prevalence of 0.18% was very similar to the weighted mean for Europe (0.186%) in a systematic review from 2014(76). If standardizing our crude prevalence based on age-groups and sex, using the European Standard Population 2013 (not presented in study II), it was 0.19%.

The consistency with previous estimates strengthens the validity of our methods for determining the prevalence on a national level in Sweden, although considering the high HLA-B27 prevalence in Sweden, perhaps an even higher prevalence could have been expected, compared to other parts of Europe.

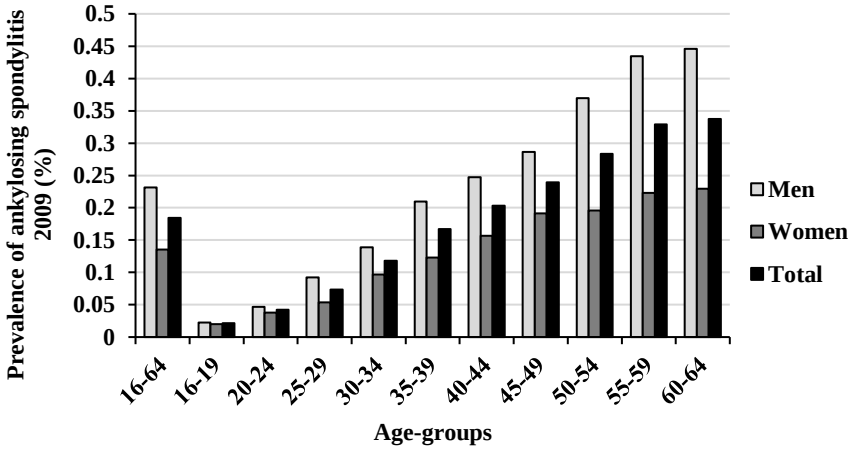

Figure 5. The point-prevalence of ankylosing spondylitis in Sweden, 31 December 2009, stratified on sex and age-groups.

When the prevalence was stratified on sex and age-groups (figure 5) it was apparent that the difference between men and women increased with age. It is possible that this is at least partly due to a previously inadequate recognition of the disease in women, which may have improved more recently. If ankylosing spondylitis is not seen as a separate disease entity, but rather a radiologically more severe expression of the whole group of axial spondyloarthritis, future studies of prevalence should also include the non-radiographic forms, both in order to detect cases with an earlier disease but also to avoid bias based on severity and sex.

Detection of axial disease and perceived health

Using patient registers, based on ICD-codes, to identify non-radiographic axial spondyloarthritis is problematic, since the current ICD-classification system is not congruent with the evolving concept of axial spondyloarthritis. Patients with other axial spondyloarthritis diseases, apart from ankylosing spondylitis, cannot easily be identified in the register, and therefore additional data would be needed to confirm an axial manifestation. Features that could be used to support the existence of an axial disease in this setting,

includes imaging (MRI/radiographs), symptoms of inflammatory back pain, and limitations in spine motion.

In study III, we combined spondyloarthritis diagnoses from the register, with self-reported symptoms of inflammatory back pain, with the purpose of identifying axial disease. However, only 43% of the patients with ankylosing spondylitis, who per definition have an axial disease, reported current inflammatory back pain, although previous studies have confirmed the validity of the diagnoses in the regional register. In fact, while 82% of the cases with ankylosing spondylitis reported having back pain during the last year, only 52% reported having it for more than three months, which is the entry criterion for both the Berlin and the ASAS definitions of inflammatory back pain and a clinical criterion in the modified New York criteria (although not specified as occurring in the last year). The relatively low frequency of chronic back pain among the responders may partly be a result of the patients receiving an adequate treatment, but this also illustrates the fact that axial symptoms are not constant in spondyloarthritis. Hence, using reported back pain of more than three months, in the preceding year, may not be sensitive for detecting axial disease in patients with spondyloarthritis.

In “early disease” cohorts, of axial spondyloarthritis, inflammatory back pain is the most frequent symptom/sign(27), but it is also common in patients who do not fulfill the classification criteria for axial spondyloarthritis(79). The approach of using self-reported inflammatory back pain to detect axial disease, in patients with a spondyloarthritis diagnosis, has been used in other studies. In one study 2012(19), the prevalence of axial spondyloarthritis in the US (based on the NHANES-survey) was estimated using self-reported data. Another study(93), also based on the NHANES-survey, used self-reported data to determine the prevalence of spondyloarthritis and inflammatory back pain in subject with psoriasis.

The tree groups compared in study III reported similar levels of axial symptoms, based on the PROMs for spinal pain, BASDAI and BASFI, which may support the existence of axial disease. However, the PROMs used are not necessarily specific for axial spondyloarthritis, but may reflect pain or impairment related to other disorder as well. Other forms of chronic pain, such as fibromyalgia, frequently co-exists with axial spondyloarthritis, and differentiating this from an inflammatory axial disease is not straight forward(174). The prevalence of fibromyalgia in ankylosing spondylitis has been described as 4-15%(175, 176), although higher numbers have also been reported. A preliminary report has indicated that patients with fibromyalgia

do not falsely fulfil the ASAS-criteria for axial spondyloarthritis(177), but this needs to be replicated.

Fibromyalgia will affect the scores of many of the frequently used outcome measures in axial spondyloarthritis. As an example, two studies of fibromyalgia in ankylosing spondylitis found that both the BASDAI and BASFI scores were strongly influenced (increased) by concurrent fibromyalgia(175, 176). In another recent (2016) study patients with both axial spondyloarthritis and fibromyalgia were compared with patients with only fibromyalgia, with regard to BASDAI and ASDAS, and were not statistically different, although the scores for BASDAI were if anything higher in the group with only fibromyalgia(178). Another study, comparing patients with psoriatic arthritis with patients with fibromyalgia, found no statistical difference in the frequency of inflammatory back pain (43.2% vs. 35.8%) and a higher enthesitis score (Maastrich Ankylosing Spondylitis Enthesitis Score) in the fibromyalgia patients(179).

Using more objective biomarkers of inflammation to distinguish inflammatory back pain from non-inflammatory back pain in spondyloarthritis is tempting, but clinically widely used markers of inflammation such as the C-reactive protein are often normal in axial spondyloarthritis(10). Furthermore, MRI of the sacroiliac joints and the spine frequently reveal bone marrow edema congruent with the ASAS-criteria, both in patients with non-specific back pain and in healthy controls(180). There are also few studies examining the frequency of radiographic sacroiliitis in the normal population, but in the first NHANES study(181) (1971-1975), moderate or severe sacroiliitis was detected in 0.73% of men ages 25-74 years(182). However, only 54% of those with moderate or severe sacroiliitis, reported having received treatment for joint problems, and only 7.6% reported current significant low back pain(182). Several studies have also indicated a low to moderate reliability and reproducibility for radiographic assessment of sacroiliitis(183-185). Better methods/protocols for detection of axial spondyloarthritis are therefore needed.

Future perspectives

The ASAS-criteria for axial spondyloarthritis have a high sensitivity and specificity, but were constructed based on consecutive patients with chronic back pain included by rheumatologists(49). Further evaluation is needed to determine how they perform in detecting axial spondyloarthritis in a broader population setting.

To facilitate the use of health-care registers in epidemiological research, and health-care planning, an update of the axial spondyloarthritis concept in the ICD-classification system would be appropriate.

Further population-based studies are also needed to verify the high frequencies of axial disease we found in other forms of spondyloarthritis than ankylosing spondylitis, and to find ways to better differentiate symptoms due to an axial disease from other types of chronic pain. The latter aspect could be addressed by including cohorts with other causes of chronic pain, such as fibromyalgia and degenerative back disease.

Comments on age distribution of ankylosing spondylitis

In study II we determined the prevalence in the age-groups 16-64 years, if we alternatively estimate the total (base case) prevalence in all age-groups it was 0.21% (cases 20044/Swedish population 9.3 million on the 31 December 2009). In a chronic disease, such as ankylosing spondylitis, the cumulative incidence up until a certain time-point, represents the point-prevalence at that time. Taking into account that ankylosing spondylitis is considered to start before the age of 30 years in 80% of the cases, and almost exclusively before the age of 45 years (21), the peak in prevalence in the age-groups 55-64 years (around 0.33%) can therefore be seen as an estimate of the proportion of the population, who over the whole lifetime is diagnosed with ankylosing spondylitis.

In the age-groups above 64 years (data not presented in study II) there was a gradual decline in prevalence. This is likely to, at least partly, be an artefact. The probability of ankylosing spondylitis being registered in the patient register can be expected to drop in the older age-groups, as other health-problems over-shadow the rheumatic complaints, and it has also been suggested that the symptoms of axial disease may decrease in the elderly(186).

Interestingly, several other studies have reported a similar decline in the prevalence of both HLA-B27 and ankylosing spondylitis, in specific older age-groups (75, 187). There are some data supporting an increased mortality for HLA-B27 carriers in some age-groups, even after adjusting for spondyloarthritis disease(188). One suggested explanation is that HLA-B27 is associated with an increased susceptibility to particular childhood infections, more prevalent in specific time-periods, and thereby to a higher mortality early in life. This mechanism was proposed in the French GAZELLE study, as a possible explanation for a lower HLA-B27 prevalence

in age-groups older than 70-years (75). This would need to be replicated and investigated further.

6.2.2 Predictors

The role of non-genetic risk factors in ankylosing spondylitis are still largely unknown. In reactive arthritis, guttate psoriasis, and inflammatory bowel disease, the triggering infections are sometimes very conspicuous, and it is unlikely that a similar trigger for ankylosing spondylitis would have been over-looked. The fact that ankylosing spondylitis occurs worldwide, and roughly follows the prevalence of HLA-B27, suggests that any contributing environmental risk factors are likely to be ubiquitous. In the studies included in this thesis four parameters have been presented, that may be predictive or etiologically linked with ankylosing spondylitis: having a shorter formal education, having older siblings, and appendicitis and respiratory tract infections during childhood.

In study II, not described previously, we found a higher prevalence of ankylosing spondylitis associated with fewer years of formal education. A higher prevalence related to a shorter formal education, used as a marker for lower socioeconomic status, has been described for many types of chronic diseases(189), such as rheumatoid arthritis(190), but it is not clear how this would apply to ankylosing spondylitis. As discussed in the previous section, several methodological explanations are possible, but it is also possible that a low level of education is a proxy for other exposures, such as smoking or occupation (mechanical stress) which affect the disease development. This needs to be investigated further.

In study IV the only detected difference in characteristics at birth, between cases and controls, was the increased risk associated with having older siblings. Having older siblings is different from the other perinatal characteristics evaluated, such as birth weight or season of birth, in that it may be a proxy for exposure to infections during an extended period of time in early childhood, while the other characteristics rather represent a phenotype at the time of birth, or reflect the intrauterine conditions.

In study V the negative association with appendicitis was stronger in the group having had the procedure before the age of 13 years, compared to 13-16 years, suggesting a more prominent impact early in life, compared to later in childhood. Acute appendicitis is currently regarded as triggered primarily by infections, although a genetic component is also present(191). One previously proposed mechanism for HLA-B27's association with ankylosing

spondylitis is that it affects the composition of the gut-flora(192). Very sparse data have indicated that HLA-B27-status is not linked to differences in microbial composition of the gut, in patients with established spondyloarthritis(145), but further studies are needed to explore this, and if HLA-B27 may be associated with appendicitis.

Since, ankylosing spondylitis is not a mono-genetic disease, it is possible that differences in genetic predisposition may also cause differences in susceptibility to exposure to non-genetic risk factors. Future studies should therefore aim to include data on known genetic risk factors, as a minimum HLA-B27-status, and preferably also data on familiar occurrence of ankylosing spondylitis. Future studies, on non-genetic risk factors for ankylosing spondylitis, may focus on smoking (including maternal smoking during pregnancy and passive smoking during childhood); mechanical stress, trauma, occupation and other socioeconomic aspects, as well as a wider spectrum of microbial exposures.

Future perspectives

In studies of environmental exposures, in axial spondyloarthritis, ideally it should be possible to pin-point the time of disease onset. Unfortunately, disease onset is poorly defined in spondyloarthritis, and it is unknown what time elapses between the initiation of the underlying disease mechanisms and the first symptoms. In cohort-studies of early axial spondyloarthritis, such as the SPACE(79) and the DISIRE(193) (back pain less than two and three years, respectively), a substantial proportion of the patients already have inflammatory co-morbidities and radiographic pathology at inclusion, suggesting that by the time such patients are identified and included in studies they already have a well-established disease. Using such “early disease” cohorts to identify predisposing exposures might therefore not be the best solution.

The many similarities between reactive arthritis and other spondyloarthritis subtypes (such as oligo arthritis, enthesitis, dactylitis, sacroiliitis(101), HLA-B27(130), and response to treatment(99)) may support the use of reactive arthritis as a model for early spondyloarthritis overall. Most cases with reactive arthritis start as a sub-acute peripheral oligo arthritis. Assuming that the disease onset occurs at the same time that the symptoms start, this could present an opportunity to study disease mechanisms in a very early (days-weeks?) phase of spondyloarthritis. This could be done by including incident cases prospectively at a referral center, providing that the delay between the patients´ first contact with health care (primary care or emergency unit) could be minimized. This type of study is obviously not suited for studying specific

triggering factor for ankylosing spondylitis, but it could be used to investigate the early immune phenotype (e.g. expansion of inflammatory cells, such as innate lymphoid cells (194)), and how the course of the arthritis relates to parameters such as intestinal inflammation and normalization of gut microbiota (after enteritis).

Case-control studies have an advantage if the outcome is rare and may be more cost-effective, compared to cohort studies. However, if the data on exposures are collected retrospectively, e.g. through surveys, there is a considerable risk for recall bias, especially in spondyloarthritis where both the time of disease onset and the time of the exposures are poorly characterized. Another example where the case-control setup is limited, is if the data on exposures are identified after the disease onset, e.g. serological markers for Klebsiella, where this may prevent causal inference. Using a nested case-control design, analyzing existing data already collected prospectively, such as the register data on exposures in study IV and V, may be more reliable in that aspect, since it eliminates the risk of recall bias, and establishes a temporal order. Limitations with using register data, not originally collected for research purposes, includes misclassification and restrictions in how precisely the exposures can be defined. Retrospective cohort studies, using register data, would have similar limitations. Some regional registers in Sweden (such as the Skåne Health Care Register) also includes primary care, which would allow for a more complete analysis of some exposures, such as infections, trauma and perhaps smoking. Case-control studies may also be suitable for assessing the effect of maternal smoking and passive smoking during childhood, if reliable data sources can be identified for such exposures.

Prospective cohort studies investigating multiple potential exposures, with the rare out-come of developing axial spondyloarthritis, would need to be very large, and thus very expensive. A potential solution may be to tap into an existing prospective cohort, such as the DiPiS/TEDDY birth cohort study(195), and collect complementary data on exposures and outcome from additional sources, such as registers. Using axial spondyloarthritis (or ankylosing spondylitis) as the outcome in such a study would necessitate an observation period of several decades, in order for the disease to develop. But other hypotheses could be tested earlier, such as the effect of HLA-B27 on the spectrum of childhood infections.

Previous studies on the composition of the early gut microbiome (Bäckhed 2015(196)) have described how the gut flora develops during the first year. Such cohorts, or similar, could be complemented by data on HLA-B27-status

and occurrence of spondyloarthritis in the family, to assess whether this affects the composition.

The Swedish twin-studies (197, 198), include twins born since 1954. Using existing twin-cohorts like these may also be a good alternative, when studying environmental risk factors, in particular if HLA-B27 status is known. The advantage of twin studies is that it gives a good opportunity to assess the effect of the familial risk contra non-genetic factors. Similar benefits could also be gained from using the Swedish multi-generation register(199). If combined with national or regional registers, the association with both childhood infections, smoking and perhaps occupation, could be explored further.

7 CONCLUSIONS

The diagnoses of ankylosing spondylitis and undifferentiated spondyloarthritis in the Swedish national patient register were determined to have a high validity, but the register could not be used to identify incident cases.

The point-prevalence of ankylosing spondylitis in Sweden, in 2009, was 0.14% or 0.18%, depending on the case-definition, with a higher prevalence in northern Sweden, compared to the southern parts, and a higher prevalence associated with fewer years of formal education. The prevalence increased linearly up to the age of 55 years, and then plateaued. 64% were men, and there were differences between men and women, both with regard to clinical manifestations and pharmacological treatment.

Current inflammatory back pain was common across the three subtypes of spondyloarthritis analyzed (43% of ankylosing spondylitis, 31% of psoriatic arthritis and 39% of other spondyloarthritis) and the groups, with current inflammatory back pain, reported similar levels of disease activity.

Having older siblings was associated with an increased risk for later development of ankylosing spondylitis (odds ratio 1.23; 95% confidence interval 1.09 to 1.39), while birth weight and season of birth were not. Hospitalization with infections overall, or with enteric infections or urogenital infections, during childhood were not associated with later development of ankylosing spondylitis. Instead, respiratory tract infections (odds ratio 1.24; 95% confidence interval 1.07 to 1.44) and in particular with tonsillitis (odds ratio 1.31; 95% confidence interval 1.03 to 1.67), were associated with an increased risk for development of ankylosing spondylitis, and appendicitis with a decreased risk (odds ratio 0.59; 95% confidence interval 0.41 to 0.83).

ACKNOWLEDGEMENT

Ett stort tack till alla som bidragit till denna avhandling!

Speciellt tack till:

De **patienter** som bidragit till forskningen.

Samtliga **medförfattare** i de olika studierna, och ett extra stort tack till **Sofia**.

Min bihandledare **Helena**, för stöd, uppmuntran och ovärderlig noggrannhet.

Tatiana för all hjälp med datahantering och alla diskussioner kring statistiska metoder.

Min **familj** som alltid stöttar mig.

Min huvudhandledare **Lennart**, för vägledning och uppmuntran, men framför allt för att ha gjort det så roligt att forska! En utmärkt förebild i både forskning och läkargärning.

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