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Identifying patients with axial spondyloarthritis

On a mission to achieve timely recognition

Marloes van Onna

Identifying patients with axial spondyloarthritis:

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PROEFSCHRIFT

door

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UPM

UNIVERSITAIRE
PERS MAASTRICHT

"In the beginning there was nothing.
God said, 'Let there be light!'
And there was light.
There was still nothing, but you could see it a whole lot better."

Ellen DeGeneres

Contents

CHAPTER 1

General introduction

1. INTRODUCTION

Spondyloarthritis comprises a group of clinically and genetically closely related inflammatory rheumatic disorders, including ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis and arthritis and/or spondylitis associated with inflammatory bowel disease (IBD).[1]

Depending on the location of the predominant clinical features, SpA is nowadays also divided into axial and peripheral disease.[2] Axial SpA (axSpA) can be further subdivided into AS and non-radiographic (nr)-axSpA, depending on presence of abnormalities on pelvic radiographs.[2] In nr-axSpA inflammation may already be detected on an MRI of the sacroiliac joints (SIJs). Patients with nr-axSpA may eventually progress to a radiographic stage, with an average progression rate of 10% after 2 years, and up to 60% after 10 years.[3-5]

The field of spondyloarthritis (SpA) has experienced major progress in the last decade, especially with regard to development of new therapeutic options and the use of magnetic resonance imaging (MRI) to establish an early diagnosis of SpA.[6] The recent developments in the field of SpA increased the need to timely recognize patients having the disease. However, several priorities on the research agenda to improve earlier diagnosis remain, such as further refining the role of MRI in the diagnosis, follow-up and prognosis of patients with SpA. Also, improving recognition and referral of patients with early SpA in primary care is an important challenge. The aim of this thesis is to provide more insight into the role of MRI in SpA and recognition of this disease in primary care. This chapter first provides an overview of the current knowledge about SpA and then elaborates on the specific objectives of this thesis.

1.1 Clinical features of spondyloarthritis

In patients with axSpA, the most important clinical feature is inflammatory back pain (IBP) caused by sacroiliitis and spondylitis.[7] IBP is typically characterized by awakening night pain, improvement of pain with exercise, no improvement with rest and a favourable response to non-steroidal anti-inflammatory drugs (NSAIDs).[8] Peripheral SpA is characterized by peripheral arthritis (predominantly of the lower limbs), enthesitis and dactylitis, as presenting symptom.[1] Extra-articular manifestations related to axial and peripheral SpA include psoriasis, anterior uveitis and IBD.[1] The main features of both axial and peripheral SpA are listed in Box 1.[9]

1.2 Pathophysiology

Although the clinical symptoms of the SpA are typically heterogeneous, there is evidence of shared genetic markers and linkage.[10] The strongest known contributing genetic factor for SpA is the major histocompatibility complex (MHC) class I molecule human leukocyte antigen (HLA)-B27. HLA-B27 is most strongly associated with axSpA. The risk of developing axSpA in HLA-B27-positive individuals is as high as 5–7%.[11,12] Approximately 80-90% of Northern European patients with axSpA are HLA-B27 positive.[11] Other subtypes of SpA have lower degrees of association with HLA-B27. For instance, the frequency of HLA-B27 in patients with psoriatic arthritis and peripheral arthritis is around 20%, but this increases to 60% in patients with associated sacroiliitis.[13] More recently, additional genetic links that contribute to the pathogenesis of SpA have been identified, e.g. polymorphisms of the interleukin-23 receptor (IL-23R) gene and endoplasmic reticulum aminopeptidase 1 (ERAP-1) gene. Genetic variants of IL-23R are also linked to concomitant psoriasis and IBD.[11,12]

In patients with SpA, the genetic susceptibility is, at least in part, responsible for an 'auto-inflammatory status'. This auto-inflammatory reaction may eventually initiate tissue remodelling which may eventually lead to ankylosis (immobilisation and consolidation of a joint).[12]

1.3 Epidemiology

The prevalence of SpA in Western European countries is estimated to be approximately 0.5-1%, similarly to that of rheumatoid arthritis.[14] The estimated prevalence of AS, the most frequent subtype of SpA, ranges from 0.1-0.9%.[14] The incidence and prevalence rates of SpA are strongly dependent and directly correlated to the prevalence of HLA-B27 in a given population.[14] Other important contributors to variation in prevalence of SpA include differences in selection of the target population, variation in the criteria used for case definition and study design.[9]

Unlike most other forms of arthritis, the first symptoms of SpA usually appear before the fourth decade of life.[15] Males are about three times more often affected with AS than females.[1] However, in the whole group of axSpA, the male : female ratio approaches 1:1.[1,16]

Box 1. SpA features

- Inflammatory back pain
- Good response to NSAIDs
- HLA-B27 positive
- A positive family history for SpA
- Increased CRP concentration
- Enthesitis
- Peripheral arthritis
- Dactylitis
- Prior urogenital or gastrointestinal infection
- Inflammatory bowel disease
- Psoriasis
- Acute anterior uveitis
- Sacroiliitis detected by imaging (conventional radiography or MRI)

SpA=spondyloarthritis; NSAID=non-steroidal anti-inflammatory drug; CRP=C-reactive protein; HLA-B27=human leukocyte antigen B27; MRI=magnetic resonance imaging.

2. CLASSIFICATION CRITERIA FOR SPONDYLOARTHRITIS

The idea that the disorders belonging to SpA were different from other rheumatological disorders e.g. rheumatoid arthritis was first described by the American Rheumatism Association in the "Nomenclature and Classification of Rheumatic diseases" in 1963.[17,18] The unifying concept of "seronegative spondyloarthritides", now known as "spondyloarthritis or SpA", was first introduced by Moll and Wright in 1974.[19]

Over the last decades, several sets of classification criteria for SpA have been developed in an attempt to define subgroups of patients to facilitate research studies. Figure 1 shows a historical timeline in which several classification criteria for SpA in general, for AS, and for axial and peripheral SpA are presented.[7,20-23]

The modified New York (mNY) criteria for the classification of AS rely on clinical and radiological findings (Figure 1.1).[20] Patients fulfil the mNY criteria when sacroiliitis on a conventional radiograph is present and at least one clinical criterion is present.[20] A major disadvantage of the mNY criteria is that advanced sacroiliitis on conventional radiography is required for fulfilment. Development of radiographic sacroiliitis may take up to several years. Some patients, especially females, may never develop radiographic sacroiliitis.[15] This means that the mNY criteria lack sensitivity especially at the early disease stage, which may result in a diagnostic delay up to 9 years.[15]
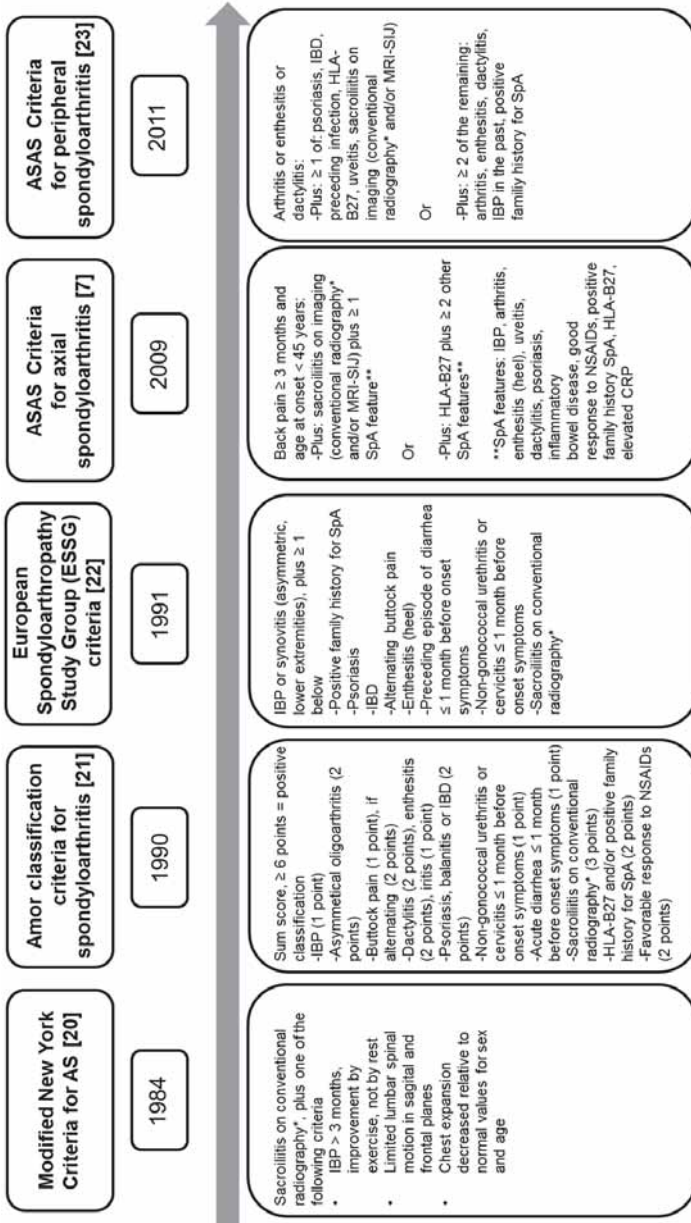
Figure 1.1   Classification criteria for axial spondyloarthritis (SpA), historical timeline.

AS, ankylosing spondylitis; IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; HLA-B27, Human Leukocyte Antigen B27; IBD, inflammatory bowel disease; MRI-SIJ, magnetic resonance imaging of the sacroiliac joints.

* Sacroiliitis on conventional radiography: bilateral sacroiliitis grade 2-4 or unilateral sacroiliitis grade 3 or 4.

The Amor and European Spondyloarthropathy Study Group (ESSG) criteria were both developed in the 1990s, in order to encompass the entire spectrum of SpA, including the axial and peripheral manifestations, and early as well as mild disease stages.[21,22] Notwithstanding, the Amor and ESSG criteria lacked sensitivity and specificity, especially in patients with early disease.[24,25] In addition, these criteria do not allow for a clear differentiation between axial and peripheral disease, while this distinction is important for etiologic studies and testing treatment strategies.[9,26]

To overcome the limitations of the mNY, ESSG and Amor criteria, it was necessary to develop new criteria sets. The most recently developed criteria sets are the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial and peripheral SpA.[7,23] The entry criterion for the ASAS axSpA criteria is back pain ≥ 3 months and age at onset <45 years (Figure 1.1). There are two arms in the ASAS axSpA criteria, an "imaging" and "clinical" arm. The imaging arm includes both sacroiliitis detected either by MRI or on a conventional radiograph; for classification one other additional SpA feature also needs to be present. HLA-B27 is the main criterion of the clinical arm; for classification two other additional SpA features also need to be present (Figure 1.1).[4] The entry criteria for the ASAS peripheral SpA criteria are arthritis, enthesitis, and/or dactylitis. For classification purposes, presence of additional features is needed (Figure 1). These additional features may include either one or more from the following list: psoriasis, IBD, preceding infection, HLA-B27, uveitis and sacroiliitis on imaging or two or more of the following list: arthritis (past or present), enthesitis (past or present), dactylitis (past or present), history of previous IBP and a positive family history of SpA.[23]

3. CRITERIA FOR INFLAMMATORY BACK PAIN

IBP is a key feature for the ESSG and ASAS axSpA classification criteria. To define this feature several criteria sets have been developed over the last years.[8,27,28] Single parameters lack sufficient discriminative ability to define IBP, because all parameters may also be present in patients with other causes of back pain.[27] The most recent criteria set for IBP is the ASAS classification criteria set for IBP, established in 2009 (Figure 1.2).[27] The ASAS IBP criteria were tested in a validation cohort and have a sensitivity of 77.6% and specificity of 72.4%, when at least four out of five parameters were fulfilled.[27] Other criteria sets for IBP are the Calin criteria and Berlin criteria (Figure 1.2).[8,28]
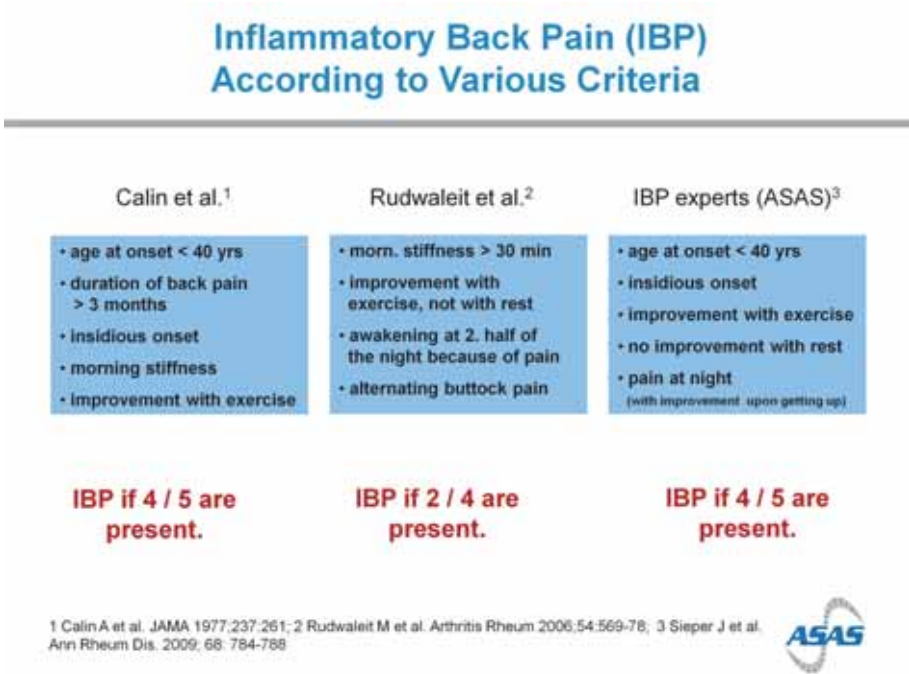
Figure 1.2.   Classification criteria for inflammatory back pain (IBP).
        morn., morning; ASAS, Assessment of SpondyloArthritis international Society.

4. IMAGING IN AXIAL SPONDYLOARTHRITIS

4.1 Conventional radiography

Conventional radiography is the most widely used imaging technique for assessing structural changes of the SIJs.[29,30] Radiographs of the SIJs can demonstrate sclerosis, erosions and ankylosis.[31] The presence of sacroiliitis is graded from 0 (normal) to 4 (ankylosis) (Table 1.1).[20]

The main disadvantage of conventional radiography in the clinical assessment of patients suspected for having axSpA is its low sensitivity, especially in early disease.[7,29] In addition, only structural damage of the SIJs, which is the consequence of inflammation, can be detected. Other major challenges when using conventional radiographs of the SIJs for detection of sacroiliitis are the low intra- and inter-observer agreement, projection artefacts and poor visibility.[29-33]

Table 1.1   Comparison of MRI and conventional radiography in the classification of sacroiliitis.

	Conventional radiograpgy	Magnetic resonance imaging (MRI)
Standard protocol and orientation	Anteroposterior (AP) pelvic radiograph	Semicoronal section orientation along axis of the sacral bone, using at least a T1-weighted turbo SE sequence, FS T2-weighted turbo SE sequence or STIR sequence* * Additional information to assess sacroiliitis: FS T1-weighted sequence after administration of Gd
Characteristic active lesions	Not applicable	Bone marrow edema (BME) (T2 / STIR / T1 post-gadolinium), capsulitis, synovitis, enthesitis
Characteristic structural changes	Widening/narrowing joint space, erosions, sclerosis, ankylosis	Subchondral sclerosis, erosions, fat deposition, bony bridges / ankylosis
Grading of changes and definition of sacroiliitis	Modified New York (mNY) criteria: Grade 0: normal Grade 1: suspicious changes Grade 2: minimal abnormalities with small areas of erosions or sclerosis without alteration in joint space width Grade 3: moderate or advanced erosions, sclerosis, widening, narrowing, and/or partial ankylosis of the joint Grade 4: total ankylosis Bilateral sacroiliitis grade 2-4 or unilateral sacroiliitis grade 3 or 4	ASAS/OMERACT definition of a positive MRI: At least 1 active lesion (BME), highly suggestive of axial SpA, is present in at least 2 successive slices or in case of ≥2 lesions (BME) are detected in 1 slice** ** The presence of synovitis, capsulitis, or enthesitis only without concomitant subchondral BME is compatible with sacroiliitis but not sufficient for making a diagnosis of active sacroiliitis ** Structural lesions only without concomitant subchondral BME is not sufficient for making a diagnosis of active sacroiliitis

MRI, magnetic resonance imaging; BME, bone marrow edema; mNY criteria, modified New York criteria; ASAS, Assessment of SpondyloArthritis international Society; OMERACT, Outcome Measures in Rheumatoid Arthritis Clinical Trials; SE, spin echo; STIR, short tau inversion recovery; FS, fat saturated; Gd, gadolinium; SpA, spondyloarthritis.[20,34]

4.2 Magnetic resonance imaging

Nowadays, MRI of the SIJs is considered an important imaging technique for making a diagnosis of axial SpA.[34] By using MRI, both active (inflammatory) lesions and structural changes can be visualized (Table 1.1).[34] Typical active lesions in the SIJs are subchondral bone marrow edema (BME) / osteitis, and to a lesser extent synovitis, enthesitis and capsulitis.[34] Active lesions are best visualised on T2 fat saturated (FS)-weighted spin-echo (SE) sequence, T1 FS gadolinium contrast-enhanced sequence or the short tau inversion recovery (STIR) sequence. Structural changes that can be detected by MRI are erosions, fat deposition (fatty lesions), sclerosis and ankylosis. These structural lesions are best detected on the T1-weighted SE sequence.[34]

A positive MRI of the SIJs in the context of identifying sacroiliitis, is defined as the presence of subchondral BME that is highly suggestive of axial SpA, and appears as two or more distinguishable lesions on one slice, or as one lesion on at least two successive slices (ASAS/ Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) definition).[34] The presence of synovitis, enthesitis or capsulitis without BME does not suffice. Only active lesions (BME) are currently considered for fulfilment of the ASAS/OMERACT definition.[34] Structural changes may also occur in conjunction with BME, or without BME as a sequel of previous inflammation.[34]

Several scoring methods for assessment and quantification of active lesions on MRI have been proposed throughout the years.[36-38] However, there is no preferred scoring system.[34] All of these scoring systems are primarily confined to the research setting.

5. EARLY REFERRAL AND RECOGNITION OF SPONDYLO-ARTHRITIS IN PRIMARY CARE

SpA is among the inflammatory rheumatic disorders with the longest delay between the onset of symptoms and the making of a diagnosis. Specifically in the case of AS, the delay up is up to 9 years.[15] An early diagnosis of axSpA is important not only to avoid unnecessary diagnostic procedures and inappropriate treatments, but a short disease duration is also associated with a favourable response to NSAIDs and anti-TNF-alpha therapy.[39] Furthermore, several studies have shown that effective treatment of active axSpA is associated with improved work capacity and quality of life [40-43]. Providing an early diagnosis can provide reassurance to patients and may optimise the

benefit of education and lifestyle modifications. Recognizing patients with axSpA early in the disease course is therefore important.

The general practitioner (GP) is a key role player in the identification and referral of patients suspected of having SpA.[44] However, knowledge and awareness about SpA and the associated extra-articular manifestations is low among GPs, resulting in poor recognition and delayed referral of patients.[45] A recent study has shown that 1 in 4 patients with chronic back pain of ≥3 months that had started before the age of 45 years and who were recruited from primary care, can be classified as having axSpA after careful evaluation.[46] These patients had not been recognized as such by the GP. Several referral tools for patients with chronic back pain have been proposed a few years ago, in order to improve recognition and hence referral of patients suspected for axSpA in primary care.[47-51] These tools included parameters such as IBP, sacroiliitis on imaging and / or HLA-B27. When patients fulfilled the referral criteria and were actually referred to the rheumatologist, up to 45% patients were found to have axSpA after a diagnostic work-up.[48-52]

6. THE CONTEXT OF RESEARCH IN THE FIELD OF SPONDYLOARTHRITIS AT THE START OF THIS THESIS

This thesis describes our research with regard to assessing the global prevalence of SpA and the early identification of patients with SpA, both in primary and secondary care.

Until about the turn of the millennium, SpA took the back seat in rheumatology, because of limited therapeutic options. Early diagnosis was simply not an area of major concern. This dramatically changed with the introduction of the highly effective TNF-alpha blockers that significantly improved quality of life of patients dealing with SpA.[53] The expansion of therapeutic armamentarium makes it necessary to provide reliable data on the prevalence of SpA, in order to gain insight in the societal impact and costs associated with SpA.

In addition, new and effective therapeutic options make it even more important to diagnose SpA at an early stage. In the light of these developments, the Early SpondyloArthritis Clinic (ESpAC) was established in 2000.[54] Sixty-eight patients with IBP of less than two years duration were included in this prospective cohort study and followed for two years with repeated clinical and radiological examinations. In 2009, when starting this PhD program, MRI had already evolved as an important imaging modality for diagnosis and classification of early axSpA but several research questions

remained, for example about the evolution of active lesions and structural changes on MRI over time. Such questions could only be answered using cohorts with a substantial follow-up period, like the ESpAC study, that was the basis for several studies in this thesis.

Next, recent research projects focussing on diagnosing and treating patients with early SpA, presume a timely referral of patients by their GPs. Several referral tools have been developed in order to shorten the diagnostic delay that is so characteristic for these patients, but these tools can only be successful if knowledge and awareness about SpA increases among GPs. Educational programmes with special focus on SpA might improve the recognition of SpA features, and consequently lead to an earlier referral of those suspected of having SpA.

7. AIMS OF THIS THESIS

The main research questions underlying this thesis are as follows:

Epidemiology of spondyloarthritis

What is the global prevalence of spondyloarthritis (SpA) and its phenotypes and which study characteristics might explain heterogeneity in prevalence estimates?

The use of MRI in detection of early axial spondyloarthritis

How can the use and interpretation of MRI of the SIJ in patients with early axial SpA be improved? Which determinants predict the presence of active and structural lesions on MRI over time?

Timely identification of spondyloarthritis in primary care

What is the current level of knowledge of GPs about axSpA?

How can the recognition and referral of SpA by GPs in clinical practice be improved?

8. OUTLINE OF THIS THESIS

This thesis is divided into three related parts. *Part I* describes the global prevalence of SpA **(Chapter 2)**. *Part II* of this thesis focuses on the use of MRI of the SIJs for detection of sacroiliitis in 68 patients with recent-onset IBP, included in the ESpAC. **Chapter 3** describes how active lesions on MRI of the SIJs in patients included in ESpAC evolve over time, and discusses which determinants are responsible for persisting active lesions on MRI of the SIJs. **Chapter 4** describes the association between BME on MRI of the SIJs and development of structural changes on both MRI and conventional

radiographs in patients included in the ESpAC. To assess active lesions on MRI of the SIJs, several MRI sequences can be used. In **Chapter 5**, the potential incremental value of the T1 post-Gd-DTPA MRI sequence of SIJs compared to the combination of the STIR MRI sequence and conventional radiographs is discussed. **Chapter 6** describes the natural course of BME on MRI of the SIJs over a 2-year follow-up period.

The optimization of identification and referral of patients suspected of having SpA in primary care is described in *part III* of this thesis. **Chapter 7** describes the level of knowledge and experiences of GPs with regard to axSpA. **Chapter 8** describes a study in which the current practice performance with regard to referral and recognition of patients with early SpA was investigated by using standardized patients. In addition, the influence of education on this performance was also studied. The research presented in this thesis is summarized and discussed in **Chapter 9 and 10**. **Chapter 10** also discusses how the research presented in this thesis can be translated to clinical and societal benefit.

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PART I

Epidemiology of spondyloarthritis

CHAPTER 2

The global prevalence of spondyloarthritis:
a systematic review and meta-regression analysis

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ABSTRACT

Objective
To summarize the prevalence of spondyloarthritis (SpA) and its subtypes in the general population, and to identify demographical and methodological characteristics that might explain heterogeneity in prevalence estimates.

Methods
A systematic literature search was performed to identify relevant articles. Risk of bias was assessed and data were extracted. Pooled prevalences were calculated. Potential sources of heterogeneity were explored by subgroup analysis and meta-regression analysis.

Results
In total, 84 articles were included. The pooled prevalence of SpA, based on a random effects model, was 0.55% (95% CI 0.37-0.77); for ankylosing spondylitis (AS) 0.18% (95% CI 0.15-0.23); and for psoriatic arthritis (PsA) 0.15% (95% CI 0.12-0.18), but substantial heterogeneity was revealed (I^2 >99%). The following characteristics were significantly associated with variation in prevalence of SpA, AS and/or PsA: proportion of females, mean age of the sample, geographic area and setting (demographical characteristics); year of data collection, case finding, and case ascertainment (methodological characteristics). For the other SpA subgroups too few studies were available to conduct a meta-analysis, but prevalence estimates of reactive arthritis (range 0.0%-0.2%), SpA related to inflammatory bowel disease (range 0.0%-0.1%), and undifferentiated SpA (range 0.0%-0.7%) were generally low.

Conclusion
SpA is a common disease, but with large variation in reported prevalence estimates, which can partly be explained by differences in demographical and methodological characteristics. Particularly, geographic area as well as case finding account for a substantial part of the heterogeneity.

INTRODUCTION

Since its establishment in the 1970s, the disease concept spondyloarthritis (SpA) has seen major developments with respect to identification and classification of the disease, measurement and prediction of outcome, and treatment options.[1] While SpA can be considered a condition itself, several subtypes can be distinguished, including ankylosing spondylitis (AS), psoriatic arthritis (PsA), SpA related to inflammatory bowel disease (IBD-SpA), reactive arthritis (ReA) and undifferentiated SpA (uSpA).[2] More recently, the Assessment of SpondyloArthritis international Society (ASAS) proposed to distinguish axial from peripheral SpA, depending on the predominant articular manifestations of the disease, and developed new classification criteria.[3,4] The treatment possibilities in patients with SpA have improved substantially in the last decade with the introduction of biologicals. On this line, it is relevant to gain insight into patterns of the prevalence of SpA and its subtypes, as this may contribute to our understanding of both the needs of healthcare systems - in terms of availability of healthcare resources and budgets - and the etiopathogenesis of the disease.

Considerable variation in the reported prevalence of SpA has already been recognized.[5] In particular, a wide range of estimates across geographic regions is found, which has classically been related to the presence of HLA-B27.[6] However, other yet unknown demographical and methodological characteristics of the studies may also play a role in this variation. *Demographical* characteristics refer to for example the mean age of the sample, the male:female ratio, or the geographic region. *Methodological* characteristics include for example year of data collection, sampling frame, and case finding.

Systematic approaches to gain insight into the epidemiology of SpA in the general population are limited.[7] No studies have been performed assessing and quantifying the effect of demographical and methodological characteristics on the prevalence of SpA. Therefore, the aims of the present study were 1) to perform a systematic review and meta-analysis of the literature on the prevalence of SpA and its subtypes, and 2) to identify demographical and methodological characteristics that might explain heterogeneity in prevalence.

METHODS

This systematic review was performed in accordance with the quality of reporting meta-analyses of observational studies (MOOSE) guidelines.[8]

Search strategy

MEDLINE (via PubMed) and EMBASE (OVID) were searched between 1975-2014 July 1st for primary studies investigating the prevalence of SpA or one of its subtypes. The search strategy consisted of a combination of text words and controlled vocabulary terms (e.g. MeSH terms) relating to SpA and its subtypes, and to prevalence or epidemiology. The detailed search strategy is outlined in Supplementary File 1. Two reviewers independently reviewed titles and abstracts on eligibility criteria for inclusion, after which full-text was read. In addition, hand search of references was performed. If the full-text of the articles could not be retrieved, authors were contacted via email. In case of any discrepancies between the two reviewers, a third reviewer was consulted for final decision.

Selection criteria

Only original research studies reporting primary data on the prevalence of SpA or its subtypes in the general population were included. Studies were excluded if: 1) the study was not observational; 2) the study was published in a language other than English, French, German, Dutch, Spanish or Italian; 3) the study was only describing the prevalence of young-onset (<16 years) SpA; 4) the article was not published in full-text; or 5) the study had a sample size <1000 subjects.

Data extraction

Data extraction was performed by two reviewers using a standardized form and included: study identification (first author, year of publication), and demographical as well as methodological characteristics. The *demographical* characteristics were mean age of the sample, proportion of females, geographic area and setting. Geographic area was subdivided into the following categories: Europe, North America, South America, Middle East and North Africa, Sub-Saharan Africa, Central Asia and Russia, South Asia, South-East Asia, East Asia, Oceania, and "Northern Artic indigenous communities". The last category was separated since it is known that the prevalence of HLA-B27 is higher in these populations.[9,10] The setting was subdivided into urban, rural, or a

combination of both. The *methodological* characteristics were starting year of data collection (or alternatively publication year if not reported), sampling frame, case finding and case ascertainment. Sampling frame was subdivided into census, household register, convenience sample, general practitioner database, hospital database, register, or a list of specific group of subjects (e.g. employees of a company). Case finding was based on the procedure to identify cases and included self-reported symptoms, self-reported diagnosis, self-reported diagnosis followed by external confirmation (2-step approach diagnosis), self-reported symptoms followed by external confirmation (2-step approach symptoms), diagnosis by an expert, and hospital medical records or International Classification of Disease (ICD) codes. Case ascertainment was based on an external criterion used for case definition and was subdivided into clinical diagnosis (i.e. diagnosis by a physician) and classification criteria used for each SpA subtype, such as the modified New York criteria for AS, the European Spondyloarthropathy Study Group (ESSG) criteria, the CIASsification for Psoriatic Arthritis (CASPAR) criteria, or ASAS SpA criteria.[3,11-13]

Finally, data related to prevalence were extracted (raw data were extracted or the numerator and denominator were calculated). If a study presented age- and/or sex-specific estimates, these data were extracted, instead of the total count.

Risk of bias assessment

Two reviewers assessed independently the risk of bias for each included study, using a slightly modified version of a standardized tool by Hoy et al..[14] Supplementary File 2 shows the risk of bias tool including instructions on how each item was scored. We excluded the item "was the length of the shortest prevalence period for the parameter of interest appropriate" from the checklist, since this question is not applicable for a chronic disease, such as SpA.

Data synthesis and analysis

Because prevalence estimates were expected to be below 1%, the values were transformed with the double arcsine transformation for meta-analysis and meta-regression.[15] The pooled prevalence was estimated by combining the transformed prevalence estimates using a random-effects model. Studies from Northern Artic indigenous communities were excluded from the meta-analysis, because the risk for SpA in this group is clearly different from the rest of the world, which would bias (i.e. overestimate) the results. The pooled prevalence and 95% confidence intervals (CI)

were back transformed to prevalence estimates for ease of interpretation. The heterogeneity among studies was tested by the Cochran's Q test and the I^2 statistic, the latter describing the percentage of variation across studies.[16]

Potential sources of heterogeneity were investigated by an exploratory subgroup analysis, using random effects analogous to one-way analysis of variance, in which groups of estimates were arranged according to potentially relevant demographical (mean age of the sample, proportion of females, geographic area, and setting) and methodological characteristics (year of data collection, study size, sampling frame, case finding, and case ascertainment). Studies from Northern Artic indigenous communities were excluded in the subgroup-analysis.

Univariable and multivariable meta-regression analyses were performed to explore associations between demographical and methodological characteristics and the prevalence. Variables with a p-value of <0.20 in the univariable analysis were entered into the multivariable model. A backward procedure was used, removing variables with a p-value of >0.05 in the multivariable model in order of significance. The following variables were tested: mean age of the sample, proportion of females, geographic area, setting, year of data collection, case finding, case ascertainment, and the dichotomized risk of bias criteria not yet covered by the previous variables. Due to collinearity, sampling frame was not included in the model. If data on age or sex were missing, respectively the mean or 50% were imputed. For the meta-regression analysis, SPSS macros were used (Metareg.sps and MetaF.sps).[17]

RESULTS

Search results

The database search yielded 9,240 studies (Supplementary File 3). After removing duplicates and title/abstract screening, 179 articles remained for full paper review. Two papers could not be retrieved, despite contacting the authors.[18,19] After full-text reading, 80 articles were included. With hand search of references, 4 papers were added, leading to a total of 84 articles.

Characteristics of included studies

The prevalence of SpA was reported in 30 studies (100 age- and/or sex-specific estimates), of AS in 53 studies (179 estimates), of PsA in 35 studies (89 estimates), of ReA in 17 studies (67 estimates), of IBD-SpA in 4 studies (15 estimates), and of uSpA in

15 studies (88 estimates). A detailed overview of all included studies is provided in Supplementary File 4. A combined meta-analysis and meta-regression analysis could be performed for SpA, AS and PsA. Only a limited number of studies were available for ReA, IBD-SpA and uSpA, therefore these results are described and summarized narratively.

Table 2.1 shows a summary of the main characteristics of studies included in the largest groups; SpA, AS and PsA.

Risk of bias

An overview of the risk of bias assessment is provided in Supplementary File 5. High risk of bias was most common for item 1 (representativeness of sample for the national general population) and item 2 (representativeness of sampling frame).

Prevalence of spondyloarthritis

The pooled population prevalence of SpA was 0.55% (95%CI 0.37-0.77), with high heterogeneity (I^2=99.9%). Figure 2.1 shows the prevalence estimates of SpA according to different demographical and methodological characteristics. Mean age of the study population and geographic area contributed significantly to the observed heterogeneity. The prevalence of SpA was higher in studies from North America (1.35%, 95%CI 0.44-2.79, n=1 study) and Europe (0.54%, 95%CI 0.36-0.78) compared with South Asia (0.22%, 95%CI 0.01-0.66) and South-East Asia (0.20%, 95%CI 0.00-0.66). No studies from Sub-Saharan Africa, Central Asia and Oceania were available (Figure 2.2a). With respect to the sampling frame, true population studies reported higher prevalence estimates compared with hospital-based studies. The prevalence of SpA was also higher in more recent studies (year of data collection from 2000 onwards) and in smaller studies (<5000 subjects). Further, prevalence estimates were higher if based on the ESSG criteria compared with clinical diagnosis. Table 2.2 shows the results of the meta-regression analysis. The final model explained 51.8% of the heterogeneity. In this model, case finding (p<0.01), a lower proportion of females (p=0.01), geographic area (p<0.01), and more recent year of data collection (p=0.02) were positively associated with the prevalence of SpA.

Table 2.1. Characteristics of the included studies for spondyloarthritis, ankylosing spondylitis, and psoriatic arthritis.

	Spondyloarthritis			Ankylosing spondylitis			Psoriatic arthritis		
	N studies (estimates)*	Number of subjects	Mean (range)	N studies (estimates)*	Number of subjects	Mean (range)	N studies (estimates)*	Number of subjects	Mean (range)
Total	30 (100)	104,466,975	-	53 (179)	119,995,702	-	35 (89)	14,105,141	-
Age in years	21 (87)	-	49.4 (20.5-85)	35 (157)	-	48.2 (19.5-85)	17 (67)	-	50.6 (20.5-84.5)
% female	25 (84)	-	49.5 (0-100)	39 (154)	-	49.2 (0-100)	20 (33)	-	51.1 (0-100)
Starting year data collection (range)	-	-	2000 (1972-2011)	-	-	1990 (1960-2012)	-	-	1998 (1978-2012)
Geographic area sampled									
Europe	10 (24)	3,281,474	-	21 (43)	10,312,889	-	19 (46)	10,532,446	-
North America	1 (2)	5,103	-	2 (15)	109,414,800	-	4 (4)	3,416,497	-
South America	2 (3)	8,022	-	4 (6)	28,841	-	4 (5)	100,958	-
Sub-Saharan Africa	-	-	-	3 (3)	102,467	-	-	-	-
Middle East	5 (8)	23,316	-	5 (7)	34,821	-	1 (1)	7,670	-
East Asia	2 (15)	101,110,921	-	6 (44)	43,379	-	2 (15)	21,477	-
South-East Asia	2 (4)	4,574	-	2 (3)	5,600	-	1 (1)	2,594	-
South Asia	4 (4)	16,155	-	2 (2)	13,305	-	1 (1)	8,145	-
Indigenous	4 (40)	17,410	-	8 (56)	39,600	-	3 (18)	15,354	-

* Number of studies (number of estimates). One study can provide for example two estimates: one for female and one for male subjects. - : no data available.

Variable	N estimates	Prevalence (95% CI)	P-value	Prevalence (95% CI)
Gender			0.15	
Female	24	0.47 (0.32-0.64)		
Male	24	0.64 (0.47-0.84)		
Mean age			<0.01	
20-30	4	0.16 (0.04-0.37)		
30-40	13	0.34 (0.21-0.50)		
40-50	12	0.61 (0.43-0.82)		
50-60	7	0.74 (0.48-1.07)		
60-70	7	0.65 (0.43-0.93)		
70+	6	0.53 (0.26-0.88)		
Geographic area			<0.01	
Europe	24	0.54 (0.36-0.78)		
North America	2	1.35 (0.44-2.73)		
South America	3	0.52 (0.10-1.25)		
Middle East	8	0.32 (0.10-0.66)		
East Asia	15	0.79 (0.48-1.18)		
South-East Asia	4	0.20 (0.00-0.66)		
South Asia	4	0.22 (0.01-0.66)		
Setting			0.16	
Urban	29	0.64 (0.47-0.85)		
Rural	4	0.41 (0.11-0.89)		
Combination	27	0.42 (0.29-0.58)		
Year			0.04	
Before 2000	6	0.24 (0.06-0.53)		
After 2000	54	0.55 (0.44-0.68)		
Study size			0.04	
<5000	42	0.60 (0.46-0.76)		
>5000	18	0.37 (0.23-0.55)		
Sampling frame			<0.01	
Census	14	0.91 (0.62-1.26)		
Household register	30	0.42 (0.31-0.56)		
General practitioner	3	0.61 (0.22-1.20)		
Hospital	1	0.09 (0.00-0.34)		
Register/database	10	0.42 (0.24-0.64)		
Specific group of subjects	2	1.02 (0.45-1.86)		
Case finding			0.07	
Self-reported symptoms	2	1.35 (0.58-2.42)		
2-step approach diagnosis	5	0.47 (0.18-0.89)		
2-step approach symptoms	41	0.55 (0.42-0.71)		
Expert diagnosis	1	0.19 (0.00-0.94)		
Medical records/ register	11	0.36 (0.16-0.57)		
Case ascertainment			0.02	
ESSG	32	0.71 (0.54-0.89)		
ASAS	1	0.49 (0.29-1.52)		
Clinical diagnosis	19	0.38 (0.21-0.54)		
All estimates	60	0.55 (0.37-0.77)		

Figure 2.1 Prevalence of spondyloarthritis grouped by demographical and methodological characteristics. Estimates of Northern Artic communities were not included in the subgroup-analysis. ESSG=European Spondyloarthropathy Study Group; ASAS= Assessment of Spondyloarthritis International Society.

Axial and peripheral SpA

Two studies reported the prevalence of axial and/or peripheral SpA according to the ASAS classification criteria.[20,21] In a large population-based cohort consisting of 20,625 employees of the French national electricity and gas company, a crude prevalence of SpA of 0.48% was found (0.36% for axial SpA and 0.12% for peripheral SpA) (20). In a study from the US, in which a sample of medical records of patients with chronic back pain were reviewed against the ASAS criteria and extrapolated to other US rheumatology practices, the prevalence of axial SpA was estimated at 0.70%.[21]
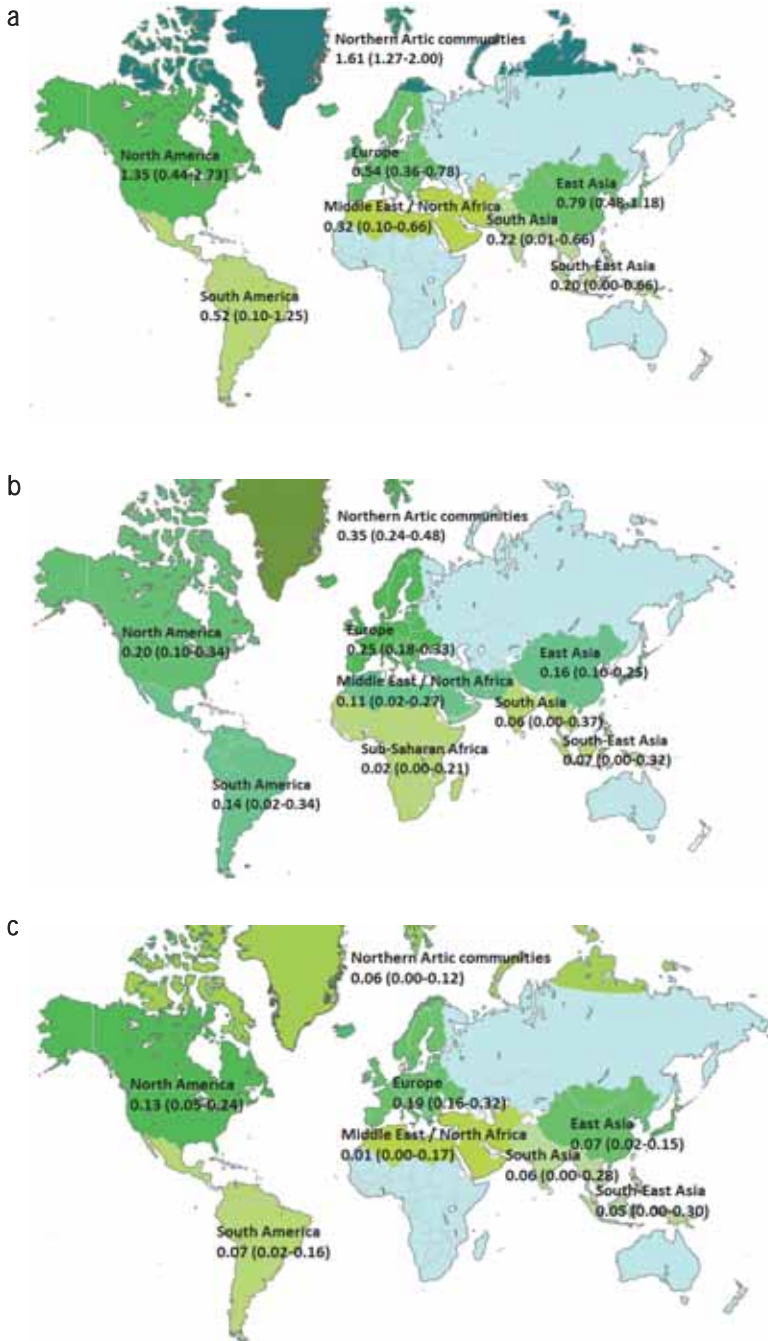
Figure 2.2   Maps showing the global prevalence of spondyloarthritis (a), ankylosing spondylitis (b), and psoriatic arthritis (c)

Table 2.2 Univariable and multivariable meta-regression analysis on the prevalence of spondyloarthritis.

Characteristic		Univariable analysis			Multivariable analysis	
		B (95% CI)	P-value	R2	B (95% CI)	P-value
Mean age		$0.4*10\text{-}3$ ($-0.9*10\text{-}3$; $0.2*10\text{-}2$)	0.52	0.4	NE	
% female		$-0.4*10\text{-}3$ ($-0.8*10\text{-}3$; 0.00)	0.04	4.2	$-0.4*10\text{-}3$ ($-0.6*10\text{-}3$; $-0.1*10\text{-}3$)	0.01
Region	North America	0.08 (-0.02; 0.12)	0.11	30.3	0.10 (0.01; 0.18)	0.02
Reference = Europe	South America	$-0.4*10\text{-}2$ (-0.09; 0.08)	0.93		-0.07 (-0.15; 0.00)	0.06
	Middle-East	-0.04 (-0.09; 0.02)	0.23		-0.09 (-0.15; -0.04)	<0.01
	East Asia	0.03 (-0.02; 0.08)	0.23		-0.01 (-0.06; 0.04)	0.66
	South-East Asia	-0.06 (-0.14; 0.02)	0.15		-0.08 (-0.16; -0.01)	0.02
	South Asia	-0.05 (-0.13; 0.02)	0.16		-0.10 (-0.16; -0.03)	<0.01
	Northern Artic Indigenous	0.10 (0.06; 0.14)	<0.01		0.18 (0.11; 0.24)	<0.01
Setting	Rural	0.10 (0.05; 0.16)	<0.01	15.8	NS	
Reference =urban	Combination	-0.01 (-0.05; 0.03)	0.68		NS	
Start data collection		$-0.3*10\text{-}2$ ($-0.7*10\text{-}3$; $-0.5*10\text{-}2$)	0.01	6.2	$0.4*10\text{-}2$ ($0.7*10\text{-}3$; $0.7*10\text{-}2$)	0.02
Risk of bias item 1, representativeness target population		0.03 (-0.05; 0.10)	0.51	0.3	NE	
Risk of bias item 2, representativeness sampling frame		$0.2*10\text{-}2$ (-0.04; 0.05)	0.92	0.0	NE	
Risk of bias item 3, random selection		-0.01 (-0.08; 0.07)	0.88	0.0	NE	
Risk of bias item 4, nonresponse bias		-0.07 (-0.11; -0.02)	<0.01	7.9	NS	
Risk of bias item 5, was a proxy used?		$0.8*10\text{-}3$ (-0.05; 0.05)	0.97	0.0	NE	
Risk of bias item 6, validity of case definition*		-0.06 (-0.12; 0.00)	0.05	3.3	NA	
Risk of bias item 7, valid and reliable study instrument		0.02 (-0.03; 0.07)	0.53	0.3	NE	
Risk of bias item 8, data collection mode		0.16 (0.10; 0.22)	<0.01	19.6	NS	
Risk of bias item 9, numerator/denominator appropriate		-0.06 (-0.14; 0.02)	0.12	2.2	NS	
Case finding	Two-step diagnosis	0.13 (0.08; 0.18)	<0.01	25.7	0.07 (0.02; 0.11)	<0.01
Reference = medical records	Two-step symptoms	0.01 (-0.03; 0.05)	0.61		0.08 (0.04; 0.13)	<0.01
	Expert diagnosis	0.11 (0.02; 0.20)	0.01		0.08 (0.01; 0.15)	0.03
	Self-report	0.09 (-0.02; 0.19)	0.11		0.10 (0.01; 0.18)	0.02
Case ascertainment	ESSG	0.08 (0.03; 0.14)	<0.01	17.3	NS	
Reference = clinical diagnosis	ASAS	0.02 (-0.14; 0.18)	0.80		NS	

* Risk of bias item 6 was not included in the multivariable analysis due to collinearity with case ascertainment. ESSG=European Spondyloarthropathy Study Group criteria; ASAS=Assessment of SpondyloArthritis International Society criteria; ICD=international classification of disease; NE=not entered in multivariable model (because p>0.20 in univariable analysis); NS=not significant; NA=not applicable (because of collinearity).

Ankylosing spondylitis

The pooled population prevalence of AS was 0.18% (95%CI 0.15-0.23). Heterogeneity was high (I^2=99.0%). Figure 2.3 shows the pooled prevalence of AS stratified by subgroups. The prevalence of AS was higher in males compared with females. The prevalence was higher in rural populations and different across geographic areas, with the highest prevalence rates in studies from Europe and North America (Figure 2.2b). With regard to the methodological characteristics, the prevalence was higher in studies with <5000 subjects, different among sampling frames, and higher when patients were classified according to the (modified) New York or ASAS criteria compared with clinical diagnosis.

The meta-regression analysis of the prevalence of AS is provided in Supplementary File 6. The final model explained 47.0% of heterogeneity. The prevalence of AS was higher in samples with a lower percentage of females (p<0.01), different across geographic areas (higher prevalence rates in studies from North America, Europe and Northern Artic indigenous communities compared with all other geographic regions), and higher in samples from rural areas compared with urban areas (p<0.01). The prevalence was lower in samples in which cases were found by medical records compared with two-step symptoms approaches (p<0.01), but higher in studies with high risk of bias for validity/reliability of the study instrument (p<0.01).

Psoriatic arthritis

The pooled population prevalence of PsA was 0.15% (95%CI 0.12-0.17). Heterogeneity was high (I^2=99.2%). The results of the subgroup analysis are shown in Figure 2.4. The prevalence of PsA was significantly different across age groups and related to geographic area (Figure 2.2c). The highest prevalence was found in Europe (0.19%, 95%CI 0.16-0.32) and the lowest in the Middle East (0.01%, 95%CI 0.00-0.17). The prevalence of PsA was further significantly related to sampling frame and case finding. The highest prevalence of PsA was found when diagnosis was based on self-report (0.26%, 95%CI 0.06-0.58).

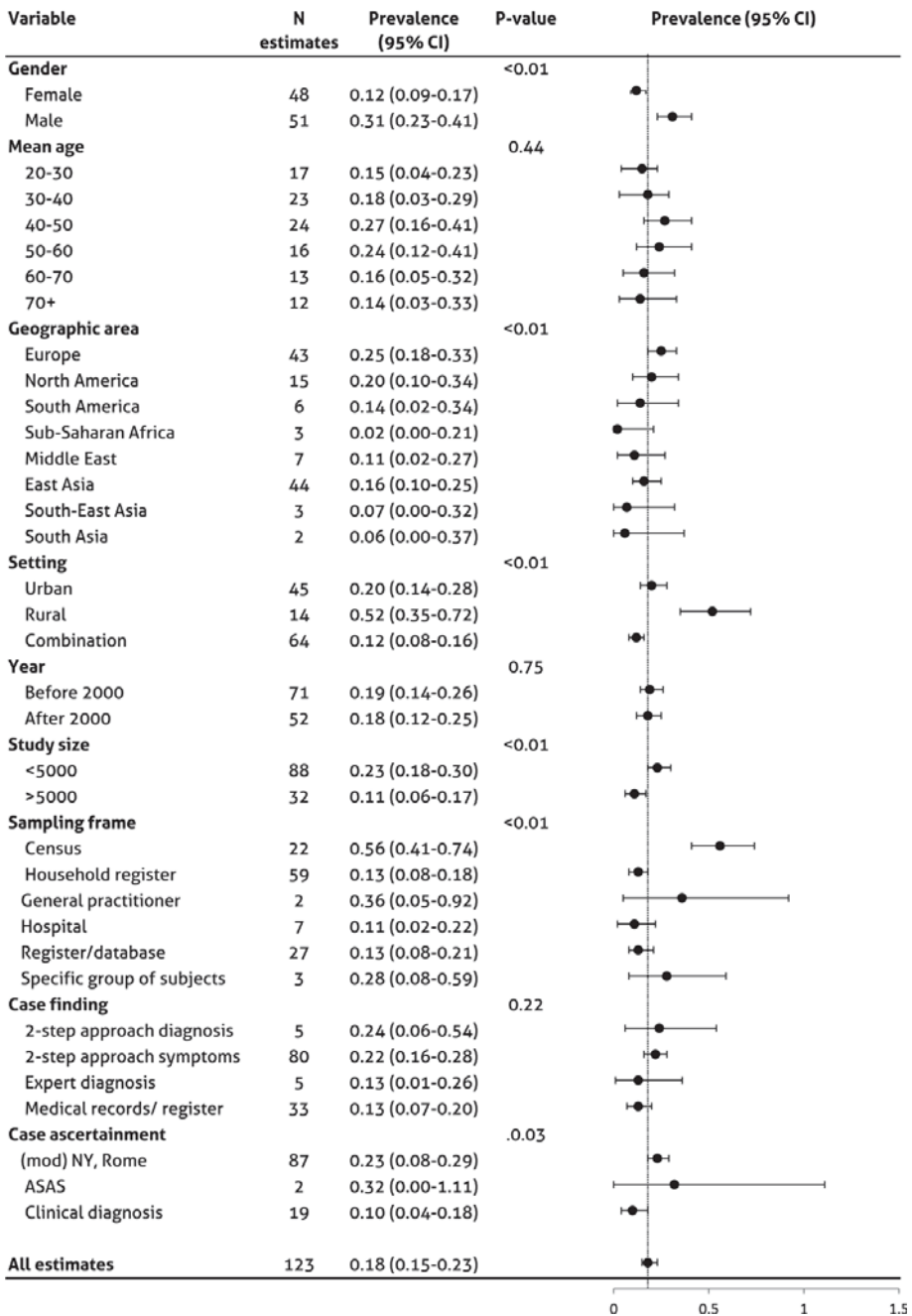| Variable	N estimates	Prevalence (95% CI)	P-value	Prevalence (95% CI)
Gender			<0.01	
Female	48	0.12 (0.09-0.17)		
Male	51	0.31 (0.23-0.41)		
Mean age			0.44	
20-30	17	0.15 (0.04-0.23)		
30-40	23	0.18 (0.03-0.29)		
40-50	24	0.27 (0.16-0.41)		
50-60	16	0.24 (0.12-0.41)		
60-70	13	0.16 (0.05-0.32)		
70+	12	0.14 (0.03-0.33)		
Geographic area			<0.01	
Europe	43	0.25 (0.18-0.33)		
North America	15	0.20 (0.10-0.34)		
South America	6	0.14 (0.02-0.34)		
Sub-Saharan Africa	3	0.02 (0.00-0.21)		
Middle East	7	0.11 (0.02-0.27)		
East Asia	44	0.16 (0.10-0.25)		
South-East Asia	3	0.07 (0.00-0.32)		
South Asia	2	0.06 (0.00-0.37)		
Setting			<0.01	
Urban	45	0.20 (0.14-0.28)		
Rural	14	0.52 (0.35-0.72)		
Combination	64	0.12 (0.08-0.16)		
Year			0.75	
Before 2000	71	0.19 (0.14-0.26)		
After 2000	52	0.18 (0.12-0.25)		
Study size			<0.01	
<5000	88	0.23 (0.18-0.30)		
>5000	32	0.11 (0.06-0.17)		
Sampling frame			<0.01	
Census	22	0.56 (0.41-0.74)		
Household register	59	0.13 (0.08-0.18)		
General practitioner	2	0.36 (0.05-0.92)		
Hospital	7	0.11 (0.02-0.22)		
Register/database	27	0.13 (0.08-0.21)		
Specific group of subjects	3	0.28 (0.08-0.59)		
Case finding			0.22	
2-step approach diagnosis	5	0.24 (0.06-0.54)		
2-step approach symptoms	80	0.22 (0.16-0.28)		
Expert diagnosis	5	0.13 (0.01-0.26)		
Medical records/ register	33	0.13 (0.07-0.20)		
Case ascertainment			.0.03	
(mod) NY, Rome	87	0.23 (0.08-0.29)		
ASAS	2	0.32 (0.00-1.11)		
Clinical diagnosis	19	0.10 (0.04-0.18)		
All estimates	123	0.18 (0.15-0.23)		

Figure 2.3   Prevalence of ankylosing spondylitis grouped by demographical and methodological characteristics.

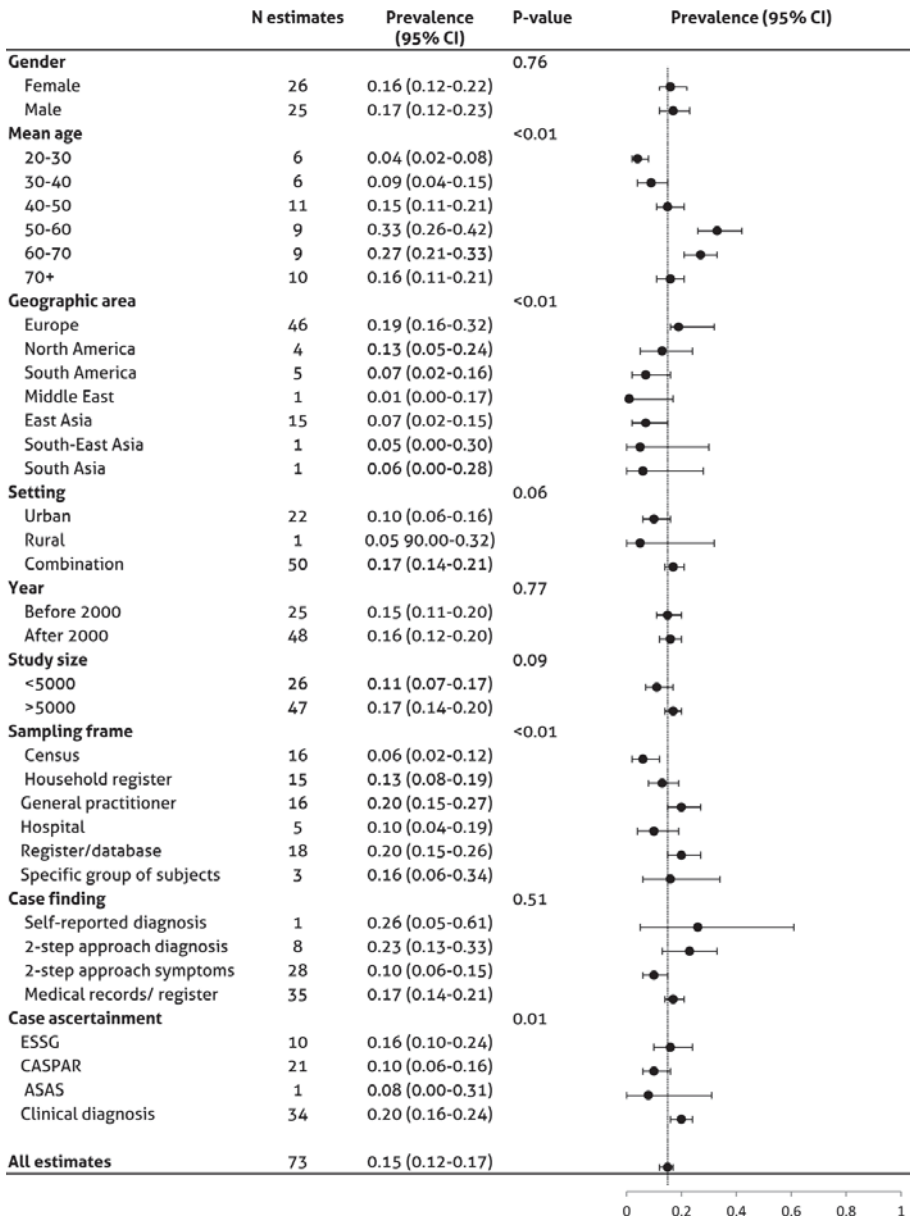|	N estimates	Prevalence (95% CI)	P-value	Prevalence (95% CI)
Gender			0.76	
Female	26	0.16 (0.12-0.22)		
Male	25	0.17 (0.12-0.23)		
Mean age			<0.01	
20-30	6	0.04 (0.02-0.08)		
30-40	6	0.09 (0.04-0.15)		
40-50	11	0.15 (0.11-0.21)		
50-60	9	0.33 (0.26-0.42)		
60-70	9	0.27 (0.21-0.33)		
70+	10	0.16 (0.11-0.21)		
Geographic area			<0.01	
Europe	46	0.19 (0.16-0.32)		
North America	4	0.13 (0.05-0.24)		
South America	5	0.07 (0.02-0.16)		
Middle East	1	0.01 (0.00-0.17)		
East Asia	15	0.07 (0.02-0.15)		
South-East Asia	1	0.05 (0.00-0.30)		
South Asia	1	0.06 (0.00-0.28)		
Setting			0.06	
Urban	22	0.10 (0.06-0.16)		
Rural	1	0.05 90.00-0.32)		
Combination	50	0.17 (0.14-0.21)		
Year			0.77	
Before 2000	25	0.15 (0.11-0.20)		
After 2000	48	0.16 (0.12-0.20)		
Study size			0.09	
<5000	26	0.11 (0.07-0.17)		
>5000	47	0.17 (0.14-0.20)		
Sampling frame			<0.01	
Census	16	0.06 (0.02-0.12)		
Household register	15	0.13 (0.08-0.19)		
General practitioner	16	0.20 (0.15-0.27)		
Hospital	5	0.10 (0.04-0.19)		
Register/database	18	0.20 (0.15-0.26)		
Specific group of subjects	3	0.16 (0.06-0.34)		
Case finding			0.51	
Self-reported diagnosis	1	0.26 (0.05-0.61)		
2-step approach diagnosis	8	0.23 (0.13-0.33)		
2-step approach symptoms	28	0.10 (0.06-0.15)		
Medical records/ register	35	0.17 (0.14-0.21)		
Case ascertainment			0.01	
ESSG	10	0.16 (0.10-0.24)		
CASPAR	21	0.10 (0.06-0.16)		
ASAS	1	0.08 (0.00-0.31)		
Clinical diagnosis	34	0.20 (0.16-0.24)		
All estimates	73	0.15 (0.12-0.17)		

Figure 2.4   Prevalence of psoriatic arthritis grouped by demographical and methodological characteristics.

Supplementary File 7 shows the meta-regression analysis of the prevalence of PsA. The final model explained 44.7% of the total heterogeneity. A higher mean age of the sample was positively related to the prevalence of PsA (p<0.01) and prevalence was significantly different across geographic areas. With respect to the methodological characteristics, prevalence was significantly higher when case finding was based on self-report compared with medical records.

Reactive arthritis

The prevalence of ReA was reported in 17 studies: 6 from Europe, 1 from South-East Asia, 1 from Sub-Saharan Africa, and 9 from Northern Arctic indigenous populations. In Europe, the prevalence of ReA ranged from 0.03% in Greece to 0.21% in Lithuania.[22,23] In a study from India, in which 8,145 individuals were interviewed, no cases of ReA were identified (prevalence 0%).[24] In a hospital-based study from Zimbabwe a prevalence of 0.001% was found.[25] In Northern Artic indigenous people, the prevalence ranged from 0.25% to 1.0%.[26,27]

Spondyloarthritis associated with inflammatory bowel disease

The prevalence of IBD-SpA was reported in only 4 studies, all from Europe. Prevalence ranged from 0.0% in Greece to 0.09% in Italy.[22,28] No formal criteria exist to classify IBD-SpA. In these 4 studies, classification was based on the ASAS-criteria, the ESSG criteria in combination with IBD, or ICD codes.[20,22,28,29]

Undifferentiated spondyloarthritis

The prevalence of uSpA was reported in 15 studies. Different criteria were used to classify patients with uSpA. In most European studies, the prevalence ranged from 0.03% to 0.10%.[20,22,23,28-30] In an urban population from Turkey, a prevalence of 0.56% was found.[31] In a study in blood donors from Germany a prevalence of 0.67% was reported.[32] In two Asian studies, the reported prevalence was 0.15% in a study from India [24] and 0.55% in a study from China.[33] In Northern Artic indigenous people, prevalences ranged from 0.20% to 1.3%.[26,27,34-36]

DISCUSSION

In this systematic review, pooled population prevalence estimates were calculated for SpA (0.55%, 95%CI 0.37-0.77), AS (0.18%, 95%CI 0.15-0.23) and PsA (0.15%, 95%CI 0.12-0.18). Heterogeneity across studies was high, therefore estimates should be interpreted with caution. For ReA, IBD-SpA and uSpA too few studies were available to conduct a meta-analysis and, therefore, results were only summarized. Prevalence estimates of ReA (range 0.0%-0.2%), IBD-SpA (range 0.0%-0.1%), and uSpA (range 0.0%-0.7%) were generally low.

This study is the first that pooled prevalences of SpA and its subtypes in the general population, and additionally investigated demographical and methodological characteristics influencing the estimates. Geographic area was in the multivariable meta-regression analysis one of the most important characteristics explaining heterogeneity in prevalence estimates of SpA. This variation might particularly be explained by genetic characteristics, such as HLA-B27. Independent of other characteristics, the highest prevalence estimates of SpA were found in Northern Artic indigenous communities, in which up to 50% of people have been reported to be HLA-B27 positive.[9] Further, higher prevalence estimates were found in studies from North America and Europe compared with Asia, Africa and the Middle East, corresponding with reported HLA-B27 prevalences in these areas.[37] A relatively high pooled prevalence of SpA was found in North America, however, the estimates came from a single study with a high risk of bias.[38] In this study, the prevalence of SpA was estimated according to the ESSG and the Amor criteria, resulting in estimates of 1.4% and 0.9% respectively.[38] This finding also illustrates that the choice of different classification criteria in epidemiological studies have a large impact on the reported prevalence. For reasons of comparability, we used estimates from this study based on the ESSG criteria when reporting the pooled prevalence in the present review, because these were also applied in most other studies.[38] Also the prevalence of SpA in East Asia was unexpectedly high (0.79%), and seems to be explained by a high prevalence of uSpA in China (0.55%).[33]

Among the methodological characteristics explored, prevalence estimates of SpA were positively and independently related to the year of data collection with more recent studies reporting higher prevalences. This may either be a true increase in the prevalence of SpA, or, more likely, an increased awareness and recognition of SpA. Further, prevalence estimates were higher in studies where populations were screened for SpA compared with studies in which cases were identified from medical records.

This finding suggests that there is under-recognition of SpA. In the subgroup analyses this is supported by the fact that sampling form census lists yielded the highest prevalence. With respect to case ascertainment, no significant difference was found between classification based on the ESSG criteria compared with clinical diagnoses. In the present review, too few studies using the new ASAS criteria were available to draw a conclusion. Future studies are needed to gain more insight into the impact of the ASAS criteria on the prevalence of SpA in population studies, although application of these criteria might be less feasible in large epidemiological studies, because of inclusion of HLA-B27 and MRI.[39]

Similarly to SpA, also the prevalence of AS was significantly different among geographic areas in multivariable meta-regression and generally higher in regions of the northern hemisphere. Further, the prevalence of AS was higher in the male population. Traditionally, AS is considered as a disease predominantly occurring in males, although it has been shown that this may in part be an artefact induced by deficits in the diagnosis of AS in females.[40-42] Non-radiographic axial SpA, on the other hand, is as common in female as in male subjects, indicating that females develop structural changes later or less frequently than males.[39,43] In contrast, no difference in the prevalence of PsA in gender distribution was found with the multivariable meta-regression. The prevalence of PsA, however, was significantly related to age, and peaked in the age category between 50 and 60 years.

Some limitations of the present study should be addressed. First, we applied a language restriction; therefore language bias cannot be excluded. Second, because the majority of the studies came from Europe, geographical bias could have occurred. This undoubtedly influenced the pooled population prevalence, which should, therefore, be interpreted with caution. Further, even within the defined geographic areas, variation in prevalence might exist, for example between North and South Europe. However, further subdivision would have hampered the meta-regression analysis. Third, direct comparisons between the results of the meta-analyses and meta-regression analyses of SpA, AS, and PsA are hampered, because often populations from different studies were used. Last, meta-regression analysis itself has some limitations.[44] Results from meta-regressions are observational, and therefore, can suffer from bias by confounding. Patients' characteristics are based on group-averages, and the relationship on study level may not be the same as the relationship on patient level. Consistent with these concerns, high risk of bias was found for the items on representativeness of the sample and the sampling frame. Only a few studies were

truly representative for the general population, which may hamper the generalization of the results.

In conclusion, this systematic review with meta-analysis summarized the prevalence of SpA and its subtypes. A large part of the heterogeneity could be explained by geographic characteristics. However, also other demographical and methodological characteristics, such as the proportion of females, year of data collection and case finding accounted for the observed variation. The results also suggested that there might still be an under-diagnosis of SpA. It is to be expected that better recognition of SpA will likely further increase the prevalence. High quality studies are needed to estimate the prevalence of axial and peripheral SpA in the general population, and to estimate the prevalence of SpA in developing countries.

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SUPPLEMENTARY FILE 1

Search strategy

1. Spondylarthropathies /
2. Spondylarthr*
3. Spondyloarthr*
4. Spondyloarthritis.tw
5. (1 OR 2 OR 3 OR 4)
6. Bechtere* .tw.
7. (ankylos* AND spondyl*).tw.
8. (Marie AND struempell*).tw.
9. (6 OR 7 OR 8)
10. Arthritis, Psoriatic/
11. (psoria* AND (arthriti* or arthropath*)).tw.
12. (10 OR 11)
13. Arthritis, Infectious/
14. reactive arthritis.tw.
15. (reiter* AND (disease or syndrome)).tw.
16. ((sexual* or chlamydia or yersinia or postyersinia or postdysenteric or salmonella or Shigella or b27 or postinfectious or post infectious) AND arthrit*).tw.
17. (13 OR 14 OR 15 OR 16)
18. Inflammatory Bowel Diseases/
19. exp Arthritis/
20. (18 AND 19)
21. COPCORD
22. (5 OR 9 OR 12 OR 17 OR 20 OR 21)
23. Prevalence.tw.
24. Prevalence/
25. Incidence.tw.
26. Incidence/
27. Epidemiology/
28. Epidemiolog*.tw.
29. (23 OR 24 OR 25 OR 26 OR 27 OR 28)
30. 12 AND 29

SUPPLEMENTARY FILE 2

Risk of bias tool

This risk of bias tool is based on the risk of bias tool by Hoy et al. [1], adapted to assess the risk of bias in prevalence studies of spondyloarthritis (SpA).

Risk of bias item	Criteria for answers	Additional notes and examples
1. Was the target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	- Yes (LOW RISK): The study's target population was a close representation of the national population. - No (HIGH RISK): The study's target population was clearly NOT representative of the national population	The target population refers to the group of people or entities to which the results of the study will be generalised. Examples: -The study was a national health survey of people 15 years and over and the sample was drawn from a list that included all individuals in the population aged 15 years and over. The answer is: Yes (LOW RISK). -The study was conducted in one province only, and it is not clear if this was representative of the national population. The answer is: No (HIGH RISK). -The study was undertaken in one village only and it is clear that this was not representative of the national population. The answer is: No (HIGH RISK).
2. Was the sampling frame a true or close representation of the target population?	-Yes (LOW RISK): The sampling frame was a true or close representation of the target population. - No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	The sampling frame is a list of the sampling units in the target population and the study sample is drawn from this list. Examples: - The sampling frame was a list of almost every individual within the target population. The answer is: Yes (LOW RISK). -The cluster sampling method was used and the sample of clusters/villages was drawn from a list of all villages in the target population. The answer is: Yes (LOW RISK). -The sampling frame was a list of just one particular ethnic group within the overall target population, which comprised many groups. The answer is: No (HIGH RISK).
3. Was some form of random selection used to select the sample?	-Yes (LOW RISK): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling). -No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was	A census collects information from every unit in the sampling frame. In a survey, only part of the sampling frame is sampled. In these instances, random selection of the sample helps minimise study bias. Examples: -The sample was selected using simple random sampling. The answer is: Yes (LOW RISK). - The target population was the village and every person in the village was sampled. The answer is:

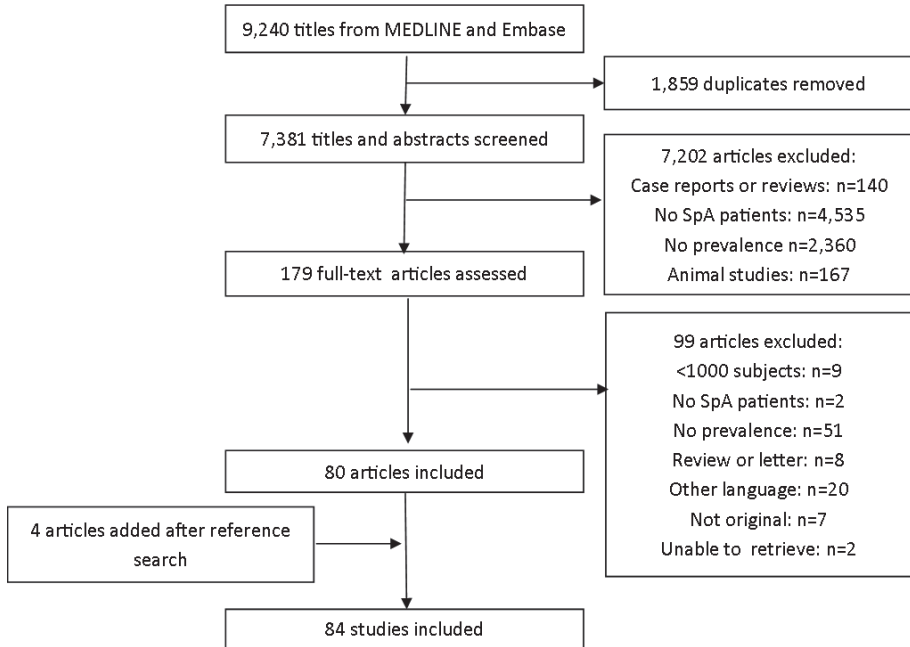|	NOT used to select the sample.	Yes (LOW RISK). - The nearest villages to the capital city were selected in order to save on the cost of fuel. The answer is: No (HIGH RISK).
4. Was the likelihood of nonresponse bias minimal?	A census collects information from every unit in the sampling frame. In a survey, only part of the sampling frame is sampled. In these instances, random selection of the sample helps minimising study bias. Examples: - The sample was selected using simple random sampling. The answer is: Yes (LOW RISK). - The target population was the village and every person in the village was sampled. The answer is: Yes (LOW RISK). - The nearest villages to the capital city were selected in order to save on the cost of fuel. The answer is: No (HIGH RISK).	A census collects information from every unit in the sampling frame. In a survey, only part of the sampling frame is sampled. In these instances, random selection of the sample helps minimising study bias. Examples: - The sample was selected using simple random sampling. The answer is: Yes (LOW RISK). - The target population was the village and every person in the village was sampled. The answer is: Yes (LOW RISK). - The nearest villages to the capital city were selected in order to save on the cost of fuel. The answer is: No (HIGH RISK).
5. Were data collected directly from the subjects?	-Yes (LOW RISK): All data were collected directly from the subjects. - No (HIGH RISK): In some instances, data were collected from a proxy.	Examples: - All eligible subjects in the household were interviewed separately. The answer is: Yes (LOW RISK). - A representative of the household was interviewed and questioned about the presence of low back pain in each household member. The answer is: No (HIGH RISK). -Data were collected from medical records or a dataset: No (HIGH RISK)
6. Was an acceptable case definition used	- Yes (LOW RISK): An acceptable case definition was used. - No (HIGH RISK): An acceptable case definition was NOT used.	Examples: -SpA: case definition was based on the ASAS criteria, ESSG criteria, expert opinion, medical records, or ICD-codes: Yes (LOW RISK). -AS: case definition was based on the (modified) New-York criteria, the Rome criteria, medical records, or ICD-codes: Yes (LOW RISK). -PsA: case definition was based on: the CASPAR criteria, ESSG criteria + psoriasis, ASAS criteria + psoriasis, medical records, or ICD-codes: Yes (LOW RISK) -There was no description of classification criteria used: No (HIGH RISK)
7. Was the study instrument reliable and valid?	-Yes (LOW RISK): The study instrument is shown to be reliable and valid (if this was	- The authors used the COPCORD questionnaire, which had previously been validated. They also tested the inter-rater reliability of the

	necessary), e.g. test-retest, piloting, validation in a previous study, etc. -No (HIGH RISK): the study instrument is not shown to be reliable and valid (if this was necessary)	questionnaire. The answer is: Yes (LOW RISK). -The authors developed their own questionnaire and did not test this for validity or reliability. The answer is: No (HIGH RISK).
8. Was the same mode of data collection used for all subjects?,	-Yes (LOW RISK): The same mode of data collection was used for all subjects. - No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	The mode of data collection is the method used for collecting information from the subjects. The most common modes are face-to-face interviews, telephone interviews and self-administered questionnaires. Examples: -All eligible subjects had a face-to-face interview. The answer is: Yes (LOW RISK). -Some subjects were interviewed over the telephone and some filled in postal questionnaires. The answer is: No (HIGH RISK).
9. Were the numerator and denominator for the parameter of interest appropriate?	- Yes (LOW RISK): The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of SpA). - No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of	There may be errors in the calculation and/or reporting of the numerator and/or denominator. Examples: -There were no errors in the reporting of the numerator(s) AND denominator(s) for the prevalence of SpA. The answer is: Yes (LOW RISK). - In reporting the overall prevalence of low back pain (in both men and women), the authors accidentally used the population of women as the denominator rather than the combined population. The answer is: No (HIGH RISK).

Reference

1. Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol 2012;65:934-9.

SUPPLEMENTARY FILE 3

Selection of studies for the systematic review on the prevalence of spondyloarthritis

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┌──────────────────────────────────────┐
│  9,240 titles from MEDLINE and Embase │
└──────────────────────────────────────┘
                │          ┌──────────────────────────────┐
                │─────────▶│   1,859 duplicates removed    │
                ▼          └──────────────────────────────┘
┌──────────────────────────────────────┐
│   7,381 titles and abstracts screened │
└──────────────────────────────────────┘
                │          ┌──────────────────────────────┐
                │          │   7,202 articles excluded:    │
                │─────────▶│  Case reports or reviews: n=140│
                │          │   No SpA patients: n=4,535    │
                │          │   No prevalence n=2,360       │
                ▼          │   Animal studies: n=167       │
┌──────────────────────────────────────┐ └──────────────────────────┘
│     179 full-text articles assessed   │
└──────────────────────────────────────┘
                │          ┌──────────────────────────────┐
                │          │   99 articles excluded:       │
                │          │   <1000 subjects: n=9         │
                │          │   No SpA patients: n=2        │
                │─────────▶│   No prevalence: n=51         │
                │          │   Review or letter: n=8       │
                │          │   Other language: n=20        │
                │          │   Not original: n=7           │
                ▼          │   Unable to retrieve: n=2     │
┌──────────────────────────────────────┐ └──────────────────────────┘
│          80 articles included         │
└──────────────────────────────────────┘
  ┌─────────────────────────────┐  │
  │ 4 articles added after      │──│
  │ reference search            │  │
  └─────────────────────────────┘  ▼
┌──────────────────────────────────────┐
│          84 studies included          │
└──────────────────────────────────────┘
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SUPPLEMENTARY FILE 4

Characteristics of included studies

Characteristics of included studies

Author, publication year	Country	Target population	Sampling frame / sampling method	Diagnostic method	Total population	Prevalence (%)					
						SpA	AS	PsA	ReA	IBD-SpA	USpA
Adomavicute, 2008 [1]	Lithuania	Vilnius & Kaunus, 18+	Random sample of phone numbers	Two step: interview → medical examination	4,244	0.64	0.09	0.24	0.21		0.09
Alamanos, 2004 [2]	Greece	North-west Greece, 16+	Identification from general hospital and private rheumatologist medical records	Diagnosis from medical record	488,435		0.02				
Alamanos, 2003 [3]	Greece	North-west Greece, 16+	Identification from general hospital and private rheumatologist medical records	Diagnosis from medical record	488,435			0.04			
Al-awadhi, 2004 [4]	Kuwait	Kuwait, 15+	Random sample of households	Two step: interview → medical examination	7,216		0.01	0.01			
Al-rawi, 1978 [5]	Iraq	10/16 counties of Iraq, 16+	Random sample of households	Interview + medical examination	6,999		0.07				
Alvarez-Negemgyei, 2011 [6]	Mexico	Yucatán region, 18+	Random sample of households	Two step: interview → medical examination	3,915		0.03	0.03			
Anagnostopoulos, 2010 [7]	Greece	Central Greece, 18+	Random sample of poll catalogues	Two step: questionnaire → medical examination	1,705	0.65	0.29	0.35			
Asgari, 2013 [8]	USA	Northern California, 18+	Identification from health-care delivery system	ICD-codes	3,200,000			0.07			
Atkins, 1988 [9]	Canada	Nuu-Chah-Nulth Native Indians, age ns	Identification of patients referred to rheumatologist from medical records and interviews	Data from medical records	2,300		0.00		0.04		
Bakland, 2005 [10]	Norway	Northern Norway, 16+	Identification from hospital diagnostic database	Data from medical records	217,000		0.04				
Barisic-Drusko, 1994 [11]	Croatia	Osijek region, age ns	Random sample of inhabitants, not further specified	Not specified	10,500			0.10			
Bardin, 1985 [12]	Greenland	Egedesminde and Jakobshavn, 15+	Identification from hospital medical records	Two step: medical records → examination	5,001				0.92		
Bardin, 1987 [13]	Greenland	Inuits from four Greenland cities	Identification from hospital medical records	Two step: medical records → examination	12,249				0.60		

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						SpA	AS	PsA	ReA	IBD-SpA	USpA
Benevolenskaya, 1996 [14]	Russia & Alaska	Siberian Eskimo, chucki residents, inupias Eskimo, yupik Eskimo, 20+	Community survey (Siberia), identification from patient registries and patient care database (Alaska)	Interview + examination (Siberia); two step: medical records → interview + examination (Alaska)	731 (Siberia); 3,786 (Alaska)	2.5	0.53	0.08	0.97		1.04
Boyer, 1988 [15]	Alaska	Inupiat Eskimos, 20+	Identification from patient care information system	Review of medical records	2,419		0.12		0.70		0.33
Boyer, 1990 [16]	Alaska	Yupik Eskimos, 20+	Identification from computerized patient record system	Review of medical records	7,052	0.75	0.21	0.01	0.25		0.20
Boyer, 1994 [17]	Alaska	Inupiat and Yupik Eskimos, 20+	Identification from rheumatic disease registries and patient care information database	Two step: identification from medical records → interview + examination	3,785	2.5	0.4	<0.1	1.0		1.3
Boyer, 1991 [18]	Alaska	Tlingit, Haida, Tsimshian Indians, 20+	Identification from patient care information system	Medical records	5,223		0.36		0.36		0.36
Braun, 1998 [19]	Germany	Berlin	HLA-B27 positive blood donors from 5 blood banks, matched with HLA-B27 negative blood donors	Two step: Questionnaire → examination	348	1.9	0.86	0.29	0.1		0.67
Brown, 1997 [20]	Gambia	Fula ethnic group, 25+	Family members of B27 positive twins from database (215) and 900 randomly selected males, not further specified	Interview + examination	1,115		0.0				
Cakir, 2012 [21]	Turkey	Havsa region (western Turkey), 20+	Every household in Havsa	Three step: interview → examination health care centre → university hospital	12,500		0.12				
Cardiel, 2002 [22]	Mexico	Mexico City, 18+	Stratified sample of subjects from census	Two step: questionnaire + medical evaluation	2,500		0.08				
Carter, 1979 [23]	USA	Rochester, Minnesota, 15+	Medical records linkage system	Identification of patients with diagnosis	33,000 (1950); 52,000 (1973)		0.13				

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						SpA	AS	PsA	ReA	IBD-SpA	USpA
Chaaya, 2012 [24]	Lebanon	Lebanon, 15+	National representative stratified sample of households	Two step: interview → examination	3,530	0.3					
Chaiamnuay, 1998 [25]	Thailand	Rural Thailand, 15+	Random selection of 3 villages, all inhabitants, not further specified	Two step: interview → examination	2,455	0.12					
Chou, 1994 [26]	Taiwan	Hen-San (rural), Sien-Dien (suburban), Cu-Tien (urban), 20+	Random selection of subjects from 3 district units	Two step: questionnaire → medical evaluation	8,998	0.17					
Constantino, 2013 [27]	France	Cohort among employees of the French national electricity and gas company	Subjects of cohort with DNA sample available	Two step: questionnaire → phone interview + evaluation	6,556	0.49		0.11		0.02	
Dai, 2003 [28]	China	4 communities in Shanghai, 15+	All persons in the selected communities	Two step: questionnaire and physical examination → evaluation by rheumatologist	6,584		0.12				
Dans, 1997 [29]	Philippines	Urban community in Manilla, 15+	Random selection of 8 barangays → every 5th house in each of the 8 barangays	Two step: interview + examination → evaluation by rheumatologist	3,006		0.03				
Davatchi, 2008 [30]	Iran	Tehran, 15+	Random selection of 50 addresses (cluster head) from 22 districts → adjacent houses to cluster head	Two step: interview → examination	10,291	0.17	0.12				
Davatchi, 2009 [31]	Iran	5 villages in Tuyserkan County (Northwest Iran), 15+	Random selection of households in each village	Two step: interview → examination	1,565	1.09					
De Angelis, 2007 [32]	Italy	Marche region (central Italy), 18+	Random sample of individuals, selected from list of 16 general practices	Two step: questionnaire → rheumatologic evaluation	2,155	1.07	0.37	0.42	0.09	0.09	0.09
Eaton, 2010 [33]	Denmark	Denmark (nationwide)	Identification from Danish Civil Registration system and National hospital register	ICD-codes	5,506,574		0.07				

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						SpA	AS	PsA	ReA	IBD-SpA	USpA
Farooqi, 1998 [34]	Pakistan	Sagri (rural), Mohallah Hukum Dad (inner-city poor), Islamabad (affluent urban)	Cluster sampling of households	Two step: questionnaire → examination	1,997	0.10					
Geirsson, 2010 [35]	Iceland	Iceland (nationwide), 18+	Identification by screening of hospital records and private rheumatology services	Diagnosis from medical records	220,441		0.13				
Gelfand, 2005 [36]	USA	Continental USA, 18+	Random sample of phone numbers	Self-reported physician made diagnosis	27,220			0.26			
Gömör, 1977 [37]	Hungary	Hungary, not specified, 15+	Seven samples of general population, not specified	Questionnaire + examination	6,469		0.23				
Gran, 1985 [38]	Norway	Tromso, northern Norway, 20-54	Two step: questionnaire to all inhabitants → random sample of subjects who reported back pain	Two step: questionnaire → examination	14,539		1.4				
Granados, 2014 [39]	Venezuela	Urban community in Monagas State, 18+	Homes in the community of Las Cocuizas, not further specified	Two step: COPCORD questionnaire → examination	3,973	0.15					
Haglund, 2011 [40]	Sweden	Southernmost county, 15+	Skane health care register	ICD-code	849,253	0.45	0.12	0.25		0.015	0.10
Hanova, 2010 [41]	Czech	City of Ceske Budejovice & district of Cheb, 16+	Referred patients to rheumatologists	Diagnosis by rheumatologist	154,374		0.09	0.05	0.09		
Haq, 2005 [42]	Bangladesh	Bhargaon (rural), Mohammadpur (Urban Slum and Urban Affluent), 15+	All inhabitants of the three clusters	Two step: questionnaire → examination	5,160		0.06				
Hoff, 2013 [43]	Norway	Nord-Trondelag county (central Norway), 20+	Participants of the Nord-Trondelag Health Study 3	Two step: questionnaire → medical records review	50,804			0.67			

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						SpA	AS	PsA	ReA	IBD-SpA	USpA
Hukuda, 2001 [44]	Japan	Japan (nationwide), 15+	Medical records from all hospitals and clinics in Japan	Medical records review	101,100,000	0.011 0.48*					
Joshi, 2009 [45]	India	Narayan Peth area in Pune metropolis, 15+	All households in area	Two step: interview → examination	8,145	0.27	0.06	0.06	0.0		0.15
Kaipiainen-Seppänen, 1997 [46]	Finland	Finland, 30+	representative population sample	interview + examination	1,000,000		0.15				
Karkucak, 2010 [47]	Turkey	Eastern Black Sea Region, 5 cities, 20+	At random from primary health center households registration records	Two step: interview → evaluation	4,031	0.27	0.25				
Kassimos, 2014 [48]	Greece	Military service of young Greek males, 18-30	Medical records of General Military Hospital of Athens	Medical records	347,184		0.08				
Koko, 2014 [49]	Albania	Region of Gjirokaster, 14+	Identification from hospital, health care clinics and family practitioners	Medical records	82,567		0.06				
Li, 2011 [50]	China	Random selection of 10/42 villages within the Longquan and Yongding areas, 16+	Random selection of subjects	Two step: questionnaire → clinical examination	10,556			0.27			
Liao, 2009 [51]	China	Dalang Town, 16+	All officially registered residents of Dalang	Two step: interview → evaluation	10,921	0.84	0.27	0.03			0.55
Löfvendahl, 2014 [52]	Sweden	Skane region, 0+	Identification from Skane Healthcare Register	ICD-codes	1,055,766			0.28			
Love, 2007 [53]	Iceland	Reykjavik, 18+	Identification of possible PsA patients from database of patients with verified psoriasis, and from hospital electronic registry	Interview and examination	134,253			0.16			

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						SpA	AS	PsA	ReA	IBD-SpA	USpA
Lutalo, 1985 [54]	Zimbabwe	Gwery city and surrounding area	Identification from medical records	Medical records	100,000		0.001		0.001		
Madland, 2005 [55]	Norway	County of Hordaland (Western Norway), 20+	Identification from diagnostic codes at the 4 rheumatology centers	ICD-codes	321,454			0.20			
Mahajan, 2003 [56]	India	Jammu, 15+	Random selection of households within certain rural and urban localities of Jammu	Two step: interview → examination	1,014	0.0					
Minh Hoa, 2003 [57]	Vietnam	Trung Liet Commune (urban), 15+	All residents of Trung Liet Commune	Two step: questionnaire → examination	2,119	0.28	0.10				
Moghimi, 2013 [58]	Iran	Sanandaj (Kurdish), 15+	Random selection of 100 clusters	Two step: COPCORD questionnaire → examination	5,830	0.22					
Nossent, 2009 [59]	Norway	Two northernmost counties of Norway	Identification from hospital patient registries	ICD-codes	224,565			0.13			
Oen, 1986 [60]	Canada	Inuit people in the Keewatin District of the Northwest Territories, 15-65	Identification of possible patients from medical records	Interview + examination	2,055	0.84	0.19		0.12		
Ogdie, 2013 [61]	United Kingdom	UK, 18-90	Identification from The Health Improvement Network (THIN) GP database	Read code for PsA in database	4,785,619			0.19			
Onen, 2008 [62]	Turkey	Urban population in Izmir, 20+	Random selection of 26/845 clusters	Two step: interview → examination	2,835	1.09	0.47		0.04		
Paul, 2013 [63]	India	Rural unit of Calicut District in North Kerala, 15+	Random selection of 2/6 subcenters in the unit, entire population	Two step: questionnaire → examination	4,999	0.62					0.56

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						SpA	AS	PsA	ReA	IBD-SpA	USpA
Pedersen, 2008 [64]	Denmark and Norway	Twins from Denmark and Norway, 20+	Two nationwide Danish twin cohorts and one nationwide Norwegian twin cohort	Two step: questionnaire → interview + examination, Danish national patient registry	74,618		?	6			
Peláez-Ballestas, 2013 [65]	Mexico	Urban population (Cuajimalpa, Mexico City), 18+	All households	Two step: questionnaire → examination	4,059	0.6	0.1				
Pelaez-Ballestas, 2011 [66]	Mexico	5 regions, 18+	Stratified random sample of households	Two step: interview → examination	19,213		0.14				
Reveille, 2012 [67]	USA	USA, 20-69	Complex multistage probability design to obtain nationally representative sample	Interview & examination	5,103	1.4					
Reyes-Llerena, 2009 [68]	Cuba	Lawton (Havana), 15+	Random sample	Two step: interview + examination → confirmation by rheumatologist	3,155		0.19				
Rodriguez-Amado, 2011 [69]	Mexico	State of Nuevo Leon, 18+	Stratified random sample of entire state	Two step: questionnaire → examination	4,713		0.04	0.08			
Sandoughi, 2013 [70]	Iran	City of Zahadan, southeast Iran, 15+	Random selection of one house in each cluster (20), 100 right neighboring consecutive houses in each cluster	Two step: COPCORD interview → examination	2,100	0.25					
Saraux, 1999 [71]	France	Region of Brittany (west France), 18+	Random sample of phone numbers	Two step: interview + confirmation by rheumatologist (interview or examination)	2,873	0.47					
Saraux, 2005 [72]	France	20 counties across France	Random sample of phone numbers	Two step: interview → confirmation by rheumatologist (interview or examination)	9,395	0.31	0.15	0.13			0.04

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						SpA	AS	PsA	ReA	IBD-SpA	USpA
Sheeb, 2000 [73]	USA	Olmsted county, Minnesota	Identification from medical records from Rochester Epidemiology Project	Medical records	65,000			0.10			
Solomon, 1975 [74]	South-Africa	North-western Transvaal (rural), Johannesburg (urban), 15+	Random selection of blocks of houses, complete census of people living there	Examination	1,352		0.07				
Soriano, 2011 [75]	Argentina	Buenos Aires, members of hospital, 18+	Identification from medical records in University Hospital	Medical record	138,288			0.07			
Steven, 1992 [76]	Scotland	Highland region, all	Patients registered with 29 general practitioners	Diagnosis made by GP	35,251	0.21					
Strand, 2013 [77]	USA	Nationwide	Random selection of rheumatology practices, random selection of medical records	Medical records	109,377,973	0.7	0.35				
Trontzas, 2005 [78]	Greece	Nationwide, 19+	All residents in seven areas in mainland Greece and random selection of subjects in one rural and one suburban area	Two step: interview → examination	8,740	0.45	0.20	0.16	0.03	0.0	0.03
Tsujimoto, 1978 [79]	Japan	Suburbs of Osaka and Kamitonada area	Inhabitants of districts, not further specified	Interview + examination	7,552		0.013				
Van der Linden, 1984 [80]	Netherlands	Zoetermeer, 44+	2 districts of the town, not further specified	Two step: x-ray → clinical examination	2,957		0.10				
Veerapen, 2007 [81]	Malaysia	Semirural suburb on the outskirts of Banting town, 15+	House to house registry of individuals	Two step: questionnaire → examination	2,594		0.08	0.04			
Wigley, 1994 [82]	China	Beijing (north) and Shantou (south) areas, 20+	Subjects were selected from the village registers	Two step: questionnaire → examination	9,249		0.26				

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						SpA	AS	PsA	ReA	IBD-SpA	USpA
Wilson, 2009 [83]	USA	Olmsted county, Minnesota, 18+	Data from Rochester epidemiology project	Identification from database and confirmation in medical records	124,277			0.16			
Zeng, 2004 [84]	China	Chenghai City, 16+	All residents in areas of the neighborhood committees 1,2,3 and 19 of the East administration	Two step: COPCORD questionnaire → examination	2,040		0.2				

SpA = spondyloarthritis, AS = ankylosing spondylitis, PsA = psoriatic arthritis, ReA = reactive arthritis, USpA =undifferentiated spondyloarthritis, ICD = international classification of disease, HLA-B27 = human leucocyte antigen B27, GP = general practitioner

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SUPPLEMENTARY FILE 5

Results of risk of bias assessment

Author, year	ROB-1*	ROB-2*	ROB-3*	ROB-4*	ROB-5*	ROB-6*	ROB-7*	ROB-8*	ROB-9*
Adomaviciute, 2008	High	High	Low	High	Low	Low	Low	Low	Low
Alamanos, 2004	High	High	Low	Low	High	Low	Low	Low	Low
Alamanos, 2003	High	High	Low	Low	High	Low	Low	Low	Low
Al-awadhi, 2004	High	Low	Low	Low	Low	High	Low	Low	Low
Al-rawi, 1978	Low	Low	Low	Low	Low	High	High	Low	Low
Alvarez-Nemegyei,2011	High	High	Low	Low	Low	High	Low	Low	Low
Anagnostopoulos, 2010	High	Low	Low	High	Low	Low	Low	Low	Low
Asgari, 2013	High	High	Low	Low	High	Low	Low	Low	Low
Atkins, 1988	High	High	Low	Low	Low	Low	Low	High	Low
Bakland, 2005	High	High	Low	Low	High	Low	Low	Low	Low
Barisic-Drusko, 1994	High	High	Low	High	Low	High	High	Low	Low
Bardin, 1985	High	High	Low	Low	Low	Low	Low	Low	Low
Bardin, 1987	High	High	Low	Low	Low	Low	Low	Low	Low
Benevolenskaya (Russia), 1996	High	Low	Low	Low	Low	Low	Low	Low	Low
Benevolenskaya (Alaska), 1996	High	High	Low	Low	High	Low	Low	Low	Low
Boyer, 1988	High	High	Low	Low	High	Low	Low	Low	Low
Boyer , 1990	High	High	Low	Low	Low	Low	Low	Low	Low
Boyer, 1994	High	High	Low	Low	Low	Low	Low	High	Low
Boyer, 1991	High	High	Low	Low	High	Low	Low	Low	Low
Braun, 1998	High	High	High	Low	Low	Low	Low	Low	High
Brown, 1997	High	High	High	High	Low	High	Low	High	Low
Cakir, 2012	High	Low	Low	Low	Low	Low	Low	Low	Low
Carter, 1979	High	High	Low	Low	High	Low	Low	Low	High
Cardiel, 2002	High	High	Low	High	Low	High	Low	Low	Low
Chaaya, 2012	Low	Low	Low	Low	Low	High	Low	Low	Low
Chaiamnuay, 1998	High	High	Low	Low	Low	Low	Low	Low	Low
Chou, 1994	High	Low	Low	Low	Low	Low	Low	Low	Low
Constantino, 2013	High	High	High	High	Low	Low	Low	Low	Low
Dai, 2003	High	High	Low	Low	Low	Low	Low	Low	Low
Dans, 1997	High	High	Low	Low	Low	High	Low	Low	Low
Davatchi, 2008	High	Low	Low	High	Low	Low	Low	Low	Low
Davatchi, 2009	High	High	Low	Low	Low	Low	Low	Low	Low
De Angelis, 2007	High	High	Low	High	Low	Low	High	Low	Low
Eaton, 2010	Low	High	Low	Low	High	Low	Low	Low	High
Farooqi, 1998	High	High	Low	Low	Low	Low	Low	Low	Low
Geirsson, 2010	Low	High	Low	Low	High	Low	Low	High	Low
Gelfand, 2005	High	High	Low	High	Low	High	High	Low	Low
Gomor, 1977	High	High	High	High	Low	Low	Low	Low	Low
Gran, 1985	High	Low	Low	Low	Low	Low	High	Low	Low
Granados, 2014	High	High	High	Low	Low	Low	Low	Low	Low
Haglund, 2011	High	High	Low	Low	High	Low	Low	Low	Low
Hanova, 2010	High	High	High	High	High	Low	Low	Low	Low
Haq, 2005	High	Low	Low	Low	Low	High	Low	Low	Low
Hoff, 2013	Low	Low	Low	High	Low	Low	Low	Low	Low

Author, year	ROB-1*	ROB-2*	ROB-3*	ROB-4*	ROB-5*	ROB-6*	ROB-7*	ROB-8*	ROB-9*
Hukuda, 2001	High	High	Low	High	High	Low	Low	Low	High
Joshi, 2009	High	High	High	High	Low	High	Low	Low	Low
Kaipiainen-Seppanen, 1997	High	High	Low	Low	Low	Low	Low	Low	Low
Karkucak, 2010	High	High	Low	Low	Low	Low	High	Low	Low
Kassimos, 2014	High	High	Low	Low	High	Low	Low	Low	Low
Koko, 2014	High	High	Low	Low	High	Low	Low	Low	Low
Li, 2011	High	High	High	High	Low	Low	Low	Low	Low
Liao, 2009	High	Low	Low	Low	Low	Low	High	Low	Low
Löfvendahl , 2014	High	High	Low	Low	High	Low	Low	Low	Low
Love, 2007	High	High	Low	High	High	Low	Low	Low	Low
Lutalo, 1985	High	High	Low	Low	High	High	Low	Low	High
Madland, 2005	High	High	Low	Low	High	Low	Low	Low	Low
Mahajan, 2003	High	High	Low	High	Low	Low	Low	Low	Low
Minh Hoa, 2003	High	High	Low	High	Low	High	Low	Low	Low
Moghimi, 2013	High	High	Low	High	Low	High	Low	Low	Low
Nossent, 2009	High	High	Low	Low	High	Low	Low	Low	Low
Oen, 1986	High	High	Low	Low	High	Low	Low	Low	Low
Ogdie, 2012	Low	High	Low	Low	High	Low	Low	Low	Low
Onen, 2008	High	High	Low	Low	Low	Low	Low	Low	Low
Paul, 2013	High	High	Low	High	Low	High	Low	Low	High
Pedersen, 2008	High	Low	Low	Low	Low	Low	Low	Low	Low
Pelaez-Ballestas, 2013	High	High	Low	High	Low	Low	Low	Low	Low
Pelaez-Ballestas, 2011	High	High	Low	High	Low	Low	Low	Low	High
Reveille, 2012	Low	High	High	Low	Low	High	High	Low	Low
Reyes-Llerena, 2009	High	High	Low	High	Low	High	Low	Low	Low
Rodriguez-Amado, 2011	High	Low	Low	Low	Low	High	Low	Low	Low
Sandoughi, 2013	High	Low	Low	Low	Low	Low	Low	Low	High
Saraux, 1999	High	High	Low	Low	Low	Low	High	Low	Low
Saraux, 2005	High	High	Low	High	Low	Low	Low	Low	Low
Sheeb, 2000	High	High	Low	Low	High	Low	Low	Low	High
Solomon, 1975	High	High	Low	High	Low	High	High	Low	Low
Soriano, 2011	High	High	Low	Low	High	Low	Low	Low	Low
Steven, 1992	High	High	Low	High	Low	High	High	Low	High
Strand, 2013	High	High	High	High	High	Low	Low	Low	High
Trontzas, 2005	Low	Low	Low	Low	Low	Low	Low	Low	Low
Tsujimoto, 1978	High	Low	Low	Low	Low	High	High	Low	Low
Van der Linden, 1984	High	High	Low	High	Low	Low	Low	Low	Low
Veerapen, 2007	High	Low	Low	High	Low	High	Low	Low	Low
Wigley , 1994	High	High	Low	Low	Low	High	Low	Low	Low
Wilson, 2009	High	High	Low	Low	High	Low	Low	Low	Low
Zeng, 2004	High	High	Low	Low	Low	Low	Low	Low	Low

* ROB=Risk of bias.

ROB-1 = Was the target population representative for the general population? ROB-2 = Was the sampling frame a close representation of the target population? ROB-3 = Was some form of random selection used to select the sample? ROB-4 = Was the likelihood of nonresponse bias minimal (participation >75% or non-responder analysis) ROB-5 = Were data collected directly from the subjects? ROB-6 = Was an acceptable case definition used (i.e. validated classification criteria or a diagnosis by a health professional)? ROB-7 = Was the study instrument reliable and valid? ROB-8 = Was the same mode of data collection used for all subjects? ROB-9 = Were the numerator and denominator for the parameter of interest appropriate?

SUPPLEMENTARY FILE 6

Univariable and multivariable meta-regression analysis on the prevalence of ankylosing spondylitis

Variable		Univariable analysis			Multivariable analysis	
		B (95% CI)	P-value	R²	B (95% CI)	P-value
Mean age		0.4×10^{-3} (-0.2×10^{-3}, 0.1×10^{-2})	0.23	0.9	NE	
% female		-0.5×10^{-3} (-0.7×10^{-3}, -0.3×10^{-3})	<0.01	14.6	-0.5×10^{-3} (-0.6×10^{-3}, -0.3×10^{-3})	<0.01
Region Reference = Europe	North America	-0.01 (-0.04; 0.02)	0.54	9.3	0.02 (-0.01; 0.05)	0.18
	South America	-0.03 (-0.07; 0.02)	0.26		-0.04 (-0.07; -0.00)	0.04
	Sub-Saharan Africa	-0.07 (-0.13; -0.01)	0.03		-0.07 (-0.12; -0.03)	<0.01
	Middle East	-0.03 (-0.07; 0.01)	0.11		-0.07 (-0.10; 0.04)	<0.01
	East Asia	-0.02 (-0.04; 0.01)	0.13		-0.05 (-0.08; -0.03)	<0.01
	South-East Asia	-0.05 (-0.11; 0.02)	0.14		-0.08 (-0.13; -0.03)	<0.01
	South Asia	-0.05 (-0.12; 0.02)	0.17		-0.06 (-0.11; -0.01)	0.02
	Indigenous	0.02 (-0.01; 0.04)	0.19		0.03 (0.00; 0.05)	0.02
Setting Reference = urban	Rural	0.04 (0.02; 0.07)	<0.01		0.03 (0.07; 0.05)	0.01
	Combination	-0.01 (-0.03; 0.00)	0.14		-0.01 (-0.03; 0.01)	0.18
Start data collection		-0.00 (-0.00; 0.00)	0.81		NE	
Risk of bias item 1, target population		0.02 (-0.02; 0.07)	0.31		NE	
Risk of bias item 2, sampling frame		-0.02 (-0.03; 0.00)	0.10		NE	
Risk of bias item 3, random selection		-0.01 (-0.04; 0.03)	0.74		NS	
Risk of bias item 4, nonresponse bias		-0.01 (-0.04; 0.01)	0.30		NE	
Risk of bias item 5, was a proxy used?		-0.01 (-0.03; 0.01)	0.27		NE	
Risk of bias item 6, case definition*		-0.04 (-0.06; -0.01)	<0.01		NA	
Risk of bias item 7, study instrument		0.03 (0.01; 0.05)	<0.01		0.04 (0.02; 0.06)	<0.01
Risk of bias item 8, data collection mode		-0.02 (-0.07; 0.03)	0.49		NE	
Risk of bias item 9, numerator/denominator		-0.01 (-0.03; 0.02)	0.51		NE	
Case finding** Reference = medical records	Two-step diagnosis	0.02 (-0.01; 0.06)	0.20	1.3	0.02 (-0.00; 0.05)	0.09
	Two-step symptoms	0.01 (-0.01; 0.03)	0.43		0.05 (0.02; 0.07)	<0.01
	Diagnosis health professional	0.02 (-0.02; 0.07)	0.34		0.03 (-0.01; 0.07)	0.10
Case ascertainment Reference = clinical diagnosis	(Mod) New York, Rome	0.04 (0.01; 0.02)	<0.01	7.7	NS	-
	ASAS	0.05 (-0.04; 0.15)	0.28		NS	-

Total number of studies=53, number of age and/or sex specific estimates=179. *Risk of bias item 6 was not included in the multivariable analysis due to collinearity with case ascertainment. (Mod) New York=modified New York criteria; ASAS=Assessment of SpondyloArthritis International Society criteria; ICD=international classification of disease; NE=not entered in multivariable model (because p>0.20); NS=not significant; NA=not applicable (because of collinearity).

SUPPLEMENTARY FILE 7

Univariable and multivariable meta-regression analysis on the prevalence of psoriatic arthritis

Variable		Univariable analysis B (95% CI)	P	R²	Multivariable analysis B (95% CI)	P-value
Mean age		0.9×10^{-3} (0.5×10^{-3}; 0.1×10^{-2})	<0.01	18.4	0.7×10^{-3} (0.3×10^{-3}; 0.1×10^{-2})	<0.01
% female		0.00 (-0.2×10^{-3}; 0.2×10^{-3})	0.91	0.02	NE	
Region				25.4		
	Reference = Europe					
	North America	-0.01 (-0.04; 0.01)	0.28		-0.02 (-0.04; -0.1×10^{-2})	0.03
	South America	-0.03 (-0.06; -0.01)	0.01		-0.03 (-0.05; -0.6×10^{-2})	0.01
	Middle East	-0.06 (-0.12; -0.01)	0.03		-0.05 (-0.10; -0.2×10^{-3})	0.05
	East Asia	-0.03 (-0.06; -0.01)	0.01		-0.02 (-0.09; -0.1×10^{-2})	0.01
	South-East Asia	-0.04 (-0.10; 0.02)	0.20		-0.03 (-0.09; 0.02)	0.28
	South Asia	-0.04 (-0.09; 0.02)	0.19		-0.03 (-0.08; -0.01)	0.17
	Indigenous	-0.04 (-0.07; -0.02)	<0.01		-0.03 (-0.06; -0.8×10^{-2})	0.01
Setting				5.1	NS	
	Reference = urban					
	Rural	-0.01 (-0.05; 0.03)	0.79		NS	
	Combination	0.02 (-0.00; 0.03)	0.07		NS	
Start data collection		0.6×10^{-3} (-0.3×10^{-3}; 0.1×10^{-2})	0.18		NS	
Risk of bias item 1, target population		-0.02 (-0.04; -0.04×10^{-1})	0.01	6.8	NS	
Risk of bias item 2, sampling frame		0.01 (-0.01; 0.03)	0.19	2.1	NS	
Risk of bias item 3, random selection		-0.4×10^{-2} (-0.03; 0.02)	0.75	0.1	NE	
Risk of bias item 4, nonresponse bias		0.01 (-0.3×10^{-2}; 0.03)	0.12	2.9	NS	
Risk of bias item 5, was a proxy used?		0.01 (-0.2×10^{-3}; 0.03)	0.11	2.9	NS	
Risk of bias item 6, case definition*		-0.02 (-0.04; 0.2×10^{-2})	0.07	3.7	NE	
Risk of bias item 7, study instrument		-0.01 (-0.04; 0.01)	0.23	1.7	NE	
Risk of bias item 8, data collection mode		-0.03 (-0.08; 0.02)	0.25	1.6	NE	
Risk of bias item 9, numerator/denominator		0.01 (-0.03; 0.05)	0.68	0.2	NE	
Case finding				14.6		
	Self-report	0.05 (0.01; 0.09)	0.01		0.06 (0.02; 0.09)	<0.01
	Reference = medical records					
	Two-step diagnosis	-0.01 (-0.03; 0.01)	0.23		-0.3×10^{-2} (-0.02; 0.01)	0.75
	Two-step symptoms	0.02 (-0.06; 0.10)	0.04		0.6×10^{-2} (-0.01; 0.02)	0.52
	Diagnosis expert	-0.02 (-0.07; 0.04)	0.58		0.06 (-0.01; 0.14)	0.13
Case ascertainment				7.4		
	ESSG + psoriasis	0.01 (0.01; 0.01)	<0.01		NS	
	Reference = clinical diagnosis					
	CASPAR	-0.6×10^{-2} (-0.01; -0.2×10^{-2})	<0.01		NS	
	ASAS + psoriasis	-0.01 (-0.04; 0.01)	0.13		NS	

Number of studies n=35, number of age and/or sex specific estimates n=89. * Risk of bias item 6 was not included in the multivariable analysis due to collinearity with diagnostic approach and case definition. CASPAR=ClASsification Psoriatic Arthritis criteria; ASAS=Assessment of Spondyloarthritis International Society criteria; ICD=international classification of disease; NE=not entered in multivariable model (because p>0.20); NS=not significant; NA=not applicable (because of collinearity).

PART II

The use of MRI in detection of
early axial spondyloarthritis

CHAPTER 3

HLA-B27 and gender independently determine the likelihood of a positive MRI of the sacroiliac joints in patients with early inflammatory back pain: A two-year MRI follow-up study

Marloes van Onna, Anne Grethe Jurik, Désirée van der Heijde, Astrid van Tubergen, Liesbeth Heuft-Dorenbosch, Robert Landewé

ABSTRACT

Objectives
To describe how inflammation on MRI of the sacroiliac joints in patients with recent-onset inflammatory back pain (IBP) evolves over time, and to study determinants of activity on MRI of the sacroiliac joint.

Methods
A 2-year follow-up study with annual MRI of the sacroiliac joints was conducted in patients with IBP of less than 2 years' duration. Images were scored for bone marrow edema on short τ inversion recovery and enhancement after administration of gadolinium on T1.

Results
Of the 68 patients (38% male; mean age 34.9 ± 10.3 years) enrolled, 44 had a negative baseline MRI. Of these 44 patients, 39 patients had at least 1 follow-up MRI of whom 6 patients (15%) developed activity on MRI during follow-up. Twenty-four patients (35%) had an abnormal MRI at baseline. In 23 of these 24 patients follow-up MRI was available. The MRI became negative in 7 of these 23 patients (30%) during follow-up. HLA-B27 positivity and male gender determined independently the likelihood of a positive MRI at any time point. In an HLA-B27 positive patient the likelihood of a positive MRI during follow-up is 88% if the baseline MRI is positive and 27% if the baseline MRI is negative. In an HLA-B27 negative patient with a negative MRI at baseline the likelihood of a positive MRI during follow up is less than 5%.

Conclusions
A positive MRI at baseline predicts a positive MRI during follow-up in HLA-B27 positive patients. A negative MRI at baseline in HLA-B27 negative patients strongly predicts a negative MRI during follow-up.

INTRODUCTION

The concept of spondyloarthritis (SpA) covers a family of seronegative rheumatic disorders that share distinct clinical and genetic characteristics. General symptoms include inflammatory back pain (IBP), peripheral arthritis, enthesitis, dactylitis and anterior uveitis. Ankylosing spondylitis (AS) is the prototype of SpA with predominant axial involvement.[1,2] Other subtypes of SpA are characterised by predominant peripheral involvement, such as psoriatic arthritis. To classify patients with SpA, several criteria sets are available. These are the European Spondyloarthropathy Study Group criteria (ESSG) and Amor criteria for SpA and the modified New York criteria specifically for AS.[3-5] Recently, a new criteria set for classifying axial SpA has been developed, mainly because available classification criteria were considered too insensitive, especially in early and mild disease.[6] Although not intended for this purpose, classification criteria are frequently used in daily practice. As a consequence, the diagnosis of AS is often delayed for 10 years, since according to modified New York criteria sacroiliitis should be demonstrated on a conventional radiograph, which is a relatively late feature of the disease.[7]

Magnetic resonance imaging (MRI) can play an important role in the non-radiographic stage of axial SpA. It has been shown that MRI can detect the early inflammatory stages of sacroiliitis, months to years before structural damage can be detected on a conventional radiograph.[8]

Although activity (inflammation) detected on MRI is considered an important manifestation in early SpA, there is still uncertainty about how activity on MRI evolves over time. MRI follow-up studies in patients with a short duration of symptoms are limited. Oostveen et al. suggested that chronic changes on radiographs are preceded by inflammatory lesions on MRI.[8] More recently, Bennett et al. showed that both severe sacroiliitis on MRI at baseline as well as HLA-B27 positivity predict the development of abnormalities on radiographs 8 years later.[9] It is, however, unclear whether activity in the sacroiliac (SI) joints as seen on MRI is stable over time, becomes quiescent after an initial period of activity, or fluctuates over time. More knowledge about this is important with regard to the reliability of the new ASAS classification criteria in which activity on MRI is considered one of the entry criteria. Furthermore, it is extremely important for clinical practice to know if one single MRI is sufficient or that it is necessary to repeat the MRI in certain patients during the diagnostic process.

The aim of the present paper is to describe the evolution of active changes on MRI of the SI joints in a group of patients presenting with inflammatory back pain (IBP) of short duration that were followed for 2 years with repeated MRIs.

PATIENTS AND METHODS

Design and study population

Patients with IBP of less than 2 years' duration were included in the Early SpondyloArthritis Cohort (ESpAC) study. The details of this study have been described previously.[10] In brief, IBP was defined according to the Calin criteria, and was considered present if 4 out of 5 of the following criteria were present: onset of back pain before the age of 40 years with a persistence of at least 3 months, insidious onset, association with morning stiffness and improvement with exercise.[11] Patients that fulfilled only 3 out of 5 of the Calin criteria but reported night pain, were also included in ESpAC. Presence of other common SpA features as defined in the ESSG criteria, such as a positive family history, anterior uveitis or a history of psoriasis or inflammatory bowel disease (IBD), was preferred but not mandatory.

The study was designed as a prospective cohort study that consisted of three identical clinical and radiological examination rounds performed at baseline and after 1 and 2 years. Data obtained at baseline have been published previously.[10,12-13]

The study was approved by the institutional review board and all patients have provided written informed consent.

MRI

MRI of the SI joints was obtained with a 1.5 Tesla Philips Gyro Scan ACS-NT (Philips, The Netherlands). Patients were examined in a supine position with their knees bent. The following sequences were used in an oblique coronal orientation: T1-weighted spin echo (SE), short τ inversion recovery (STIR), T2 weighted fast SE with fat saturation and T1-weighted SE with fat suppression (FS) after administration of the intravenous contrast agent gadolinium diethylenetriaminepentate (Gd-DTPA, 0.1 mmol/kg body weight). The slice thickness was 4 mm with intervals of 0.4 mm. The matrix was 512 for the T1 FS post Gd-DTPA sequence and 256 for the remaining sequences. The MRIs of each patient were scored as one set with random time sequence, by one experienced radiologist (AGJ), who was blinded to clinical, laboratory and radiographic results.

The MR images were scored using a combination of the Spondyloarthritis research Consortium of Canada (SPARCC) method and a modified version of the Aarhus MRI scoring method.[14,15] The SI joints were divided into four quadrants: upper iliac, lower iliac, upper sacral and lower sacral. In contrast to the original SPARCC system, there was no maximum to the number of evaluated slices, in order to maximise the detection of abnormal MR findings. The total number of evaluated slices in individual patients remained stable. Inflammation in the cartilagenous part of the joint was scored per slice in a dichotomous manner (present vs. absent). Both subchondral bone marrow edema and enhancement after administration of Gd-DTPA were scored. Bone marrow edema was defined as areas of increased signal intensity on STIR images compared with normal bone marrow. Its presence was estimated in each of the four quadrants. Lesions extending at least 1 cm from the joint space or demonstrating high signal intensity comparable to that of spinal fluid, were given an additional score on a per joint and per slice basis.

Subchondral enhancement was defined as areas of increased signal intensity compared with normal bone marrow on post Gd-DTPA images. Scoring was comparable to scoring edema, including additional scores for depth and high signal intensity comparable to enhanced vessels, respectively.

An MRI was considered positive for active sacroiliitis according to the ASAS/Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) MRI working group definition: the presence of at least one active lesion in at least two successive slices or the presence of more than one lesion in only one slice which is highly suggestive of sacroiliitis.[16]

Statistical analysis

The MRI scores were analyzed and described in three different manners. First, we described the MRI status over time (positive or negative). Second, we have investigated the likelihood of having a positive MRI at any time during follow-up, as well as factors determining MRI-positivity, making use of generalized estimating equation (GEE) analysis for binomial outcome variables, with MRI status as dependent variable, and HLA-B27 status and gender as independent explanatory variables. The contribution of C-reactive protein (CRP) in explaining a positive MRI was tested by adding CRP in the model as a covariate. GEE is an appropriate technique to study time trends in data sets with missing values while adjusting for within-patient correlation. Thirdly, we have investigated the likelihood of finding a positive MRI if the baseline MRI is either negative or positive.

SPSS software version 15.0 was used for all descriptive statistics and the GEE analysis. All P values were two-tailed and statistical significance was set at the 0.05 level.

RESULTS

Patient characteristics

In total, 68 patients with IBP were included in this study. Baseline characteristics are shown in Table 3.1. Details of these patients have been described previously.[10] Ninety-seven percent of all patients fulfilled at least four out of five Calin criteria. Almost half of the patients was HLA-B27 positive. Anterior uveitis and IBD were reported in 10 (15%) patients each, and 16 (24%) patients had a history of psoriasis. Twenty-five patients had a positive family history for AS. Table 3.1 also provides information about the 44 patients that completed the 2-year follow-up. These patients did not differ from the complete group at baseline.

Table 3.1   Baseline characteristics of 68 patients included in the ESpAC study.

Characteristic	All patients	Patients with complete follow-up examinations
	(n=68)	(n=44)
Male gender	26 (38)	15 (34)
Mean age (years) (SD)	34.9 (10.3)	36.0 (11.7)
Median symptom duration (months) [IQR]	18 [12-24]	18 [12-24]
HLA-B27 positive	31 (46)	17 (39)
History of inflammatory bowel disease	10 (15)	7 (16)
History of anterior uveitis	10 (15)	8 (18)
History of psoriasis	16 (24)	12 (27)
History of peripheral arthritis	19 (28)	12 (27)
Positive family history of AS	25 (37)	17 (39)
CRP (in mg/l) (mean (median))	9 (7)	9 (7)
ESR (in mm) (mean (median))	13 (6)	13 (6)
Patients with elevated acute phase reactants (in %)	41	37

The values are expressed as number (percentage) of patients or as stated otherwise. ESpAC=Early Spondyloarthritis Clinic; AS=ankylosing spondylitis; IQR=interquartile range; SD=standard deviation; CRP= C-reactive protein; ESR=erythrocyte sedimentation rate.

MRI findings

MRI of the SI joints was performed in all patients at baseline. Sixty-two patients had at least one follow-up MRI after 1 or 2 years follow-up and 44 patients completed all

3 examinations. Table 3.2 shows the MRI status (positive or negative) at baseline according to the ASAS/OMERACT MRI working group definition as well as how these findings develop over time.

In total, 44 patients (65%) had a negative MRI at baseline, of which 15 patients (34%) were HLA-B27 positive. Of these 44 patients, 39 (89%) completed either one or two follow-up MRIs. In six of these 39 patients (15%), the MRI became positive at 1 or 2 years follow-up. In one HLA-B27 positive patient of these six patients the MRI remained positive at 2 years follow-up, in one HLA-B27 negative patient the MRI became negative again at 2 years follow up, in two HLA-B27 negative patients the MRI became positive at 2 years follow-up, and in 2 HLA-B27 positive patients no MRIs were available at 2 years follow up.

Table 3.2   MRI status over time according to the ASAS/OMERACT MRI working group definition in 68 patients with early inflammatory low back pain who were included in the Early SpondyloArthritis Cohort (ESpAC).

Number of patients	MRI availability			HLA-B27 +
	Baseline	1-year	2-years	
9	+	+	+	8
5	+	+	NA	4
2	+	-	+	2
1	+	+	-	0
2	+	-	-	0
2	+	NA	+	1
2	+	NA	-	0
1	+	NA	NA	1
26	-	-	-	6
2	-	-	+	0
7	-	-	NA	3
1	-	+	+	1
1	-	+	-	0
2	-	+	NA	2
5	-	NA	NA	3

+=positive MRI; -=negative MRI, ASAS=Assessment of SpondyloArthritis international Society; ESpAC=Early Spondyloarthritis Cohort; HLA-B27=human leukocyte antigen B27; NA=not available; OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials.

Twenty-four patients (35%) had a positive MRI at baseline, of which 16 (66%) patients were HLA-B27 positive. In total 23 of these 24 patients completed either one or two follow-up MRIs. The MRI became negative in seven of these 23 patients (30%) during follow-up at one or at both assessments. Five of these seven patients were HLA-B27 negative and in three of them the MRI was only weakly positive at baseline. In the

remaining two patients a strongly positive MRI was detected at baseline, but the MRI became negative during follow-up. In two HLA-B27 positive patients with a negative MRI at 1 year follow up, the MRI was positive again at 2 years follow-up.

Factors determining a positive MRI

In the GEE analysis, both male gender (odds ratio (OR) 3.0 (95% confidence interval (CI); 1.1–8.2), p=0.035) and HLA-B27 positivity (OR 5.1 (95% CI 1.9-13.6), p<0.001) independently determined the likelihood of a positive MRI at any time point. CRP did not contribute to explaining variation in the model. The effects of these determinants are visualised in an absolute manner in Figure 3.1, showing that the likelihood of a positive MRI in HLA-B27-negative females with IBP is only about 10% as compared to HLA-B27 positive males with IBP in whom this likelihood is close to 70%.
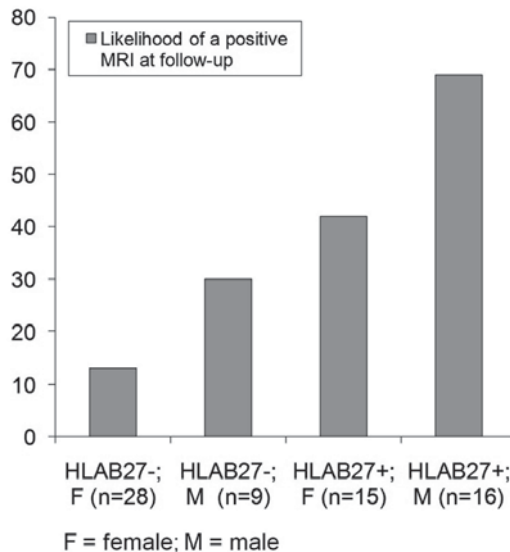
Figure 3.1   Likelihood of a positive MRI at any time point in patients with short-standing inflammatory back pain assessed at baseline, 1-year and 2-years of follow-up in function of HLA-B27 status and gender. HLA-B27, human leukocyte antigen B27.

Likelihood of a positive MRI during follow-up

The likelihood of finding a positive MRI if the baseline MRI is either negative or positive was also investigated. Both HLA-B27 status (OR 8.1 (95% CI 2.3–28.3), p<0.001) and MRI status at baseline (OR 22.0 (95% CI 6.1–79.6), p<0.001) appeared to be strongly and independently contributory to a positive MRI of the SI joints over time. Figure 3.2

shows the likelihood of a positive MRI in relation to HLA-B27 status. The likelihood of a positive MRI is negligible (<5%) in case of an HLA-B27 negative patient with a negative MRI at baseline. The likelihood is close to 90% in case of an HLA-B27 positive patient with a positive MRI at baseline. The likelihood is intermediate in patients with either HLA-B27 positivity but a negative MRI at baseline (27%) or a positive MRI but negative HLA-B27 status at baseline (49%).
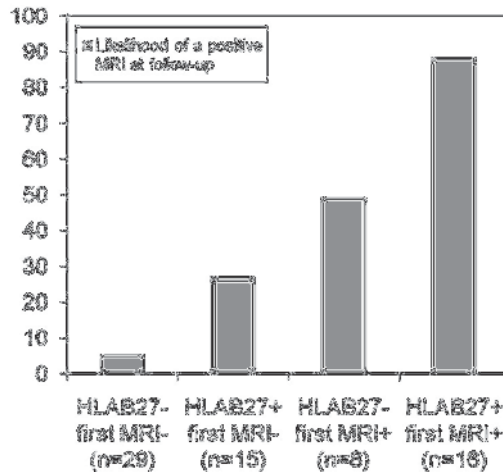
Figure 3.2   Likelihood of a positive MRI at 1- or 2-years of follow-up in patients with short-standing inflammatory back pain assessed at baseline, 1-year and 2-years of follow-up, in function of the result of the baseline MRI (negative or positive) and HLA-B27 status. HLA-B27, human leukocyte antigen B27.

DISCUSSION

In this cohort of patients with early IBP, almost two-thirds of the patients had a negative MRI at baseline. Interestingly, in only a minority of these patients (15%), the MRI status changed during follow-up. A negative MRI at baseline in combination with a negative HLA-B27 status had a likelihood of 95% of finding a negative MRI in the next 2 years. This finding may be of clinical relevance, since it suggests that in HLA-B27 negative patients with a negative MRI sacroiliitis can be excluded with a high level of certainty.

A similar conclusion can be drawn from the group of patients with a positive MRI. One can conclude that if sacroiliitis is detected by MRI, there is a high likelihood that sacroiliitis remains present in HLA-B27 positive patients (88%). This finding therefore

adds to the credibility of MRI as a pivotal measure in the axial SpA criteria. It is of note that there was no use of biologicals in this cohort of patients with early IBP during this 2 year period.

In general, both male gender and HLA-B27 positivity independently determined the likelihood of a positive MRI at any time point. This is not surprising, since SpA and in particular AS is strongly associated with HLA-B27 and has an overall male predominance. In this study it was found that HLA-B27 positive male patients with IBP have the highest chance of a positive MRI at any time.

It is now well recognised that MRI is superior to conventional radiography in diagnosing early SpA. However, insight in the evolution in MRI findings in patients with early SpA and sacroiliitis is limited, since follow-up studies are scarce. To our knowledge, this is the first study in patients with early IBP with three successive MRI examinations spanning 2 years of follow-up. Puhakka et al. performed a 1-year follow-up study to describe changes in MRI findings of the SI joints in 34 patients with SpA of recent onset.[17] In this study, 30 out of 34 patients already had signs of inflammation on their MRI at baseline, which is a higher proportion than in our cohort. Results from this study showed that the general MRI activity score did not change at 1 year; however, bone marrow edema decreased significantly during follow-up.

The MRI scoring method used in the present study is a combination of the published SPARCC and the Aarhus grading methods.[14, 15] Both systems have proven to be reliable and reproducible. With the SPARCC scoring method, a maximum of six consecutive slices are evaluated. Instead, we chose to score the entire SI joint on all qualitatively optimal slices. This was done to maximise the detection of active lesions. In practice, it implied that in the majority of patients between 5 and 8 slices were evaluated, while taking care that the same (number of) slices were scored per patient over time. The scoring of active lesions was done dichotomously as by the SPARCC method. Due to the unlimited number of slices evaluated, the present scoring method demands MR scans of the same anatomical area of each patient examined at follow-up to secure that scoring starts and ends at the same anatomic level. This may cause some limitation of the method if the technique for obtaining oblique coronal slices is not standardized. With a scoring based on both oblique coronal and axial slices this problem does not exist as the SI joints then can be evaluated three-dimensionally.[18]

The present study has several limitations that need to be acknowledged. Although we had MRIs of all patients at baseline, a substantial number of MRIs was missing at one or at both follow-up visits. Missing data may have influenced the results, since it is possible that patients with missing MRIs represent a proportion of patients in whom

the symptoms that made them eligible for inclusion in the ESpAC study have disappeared. Although such a bias cannot be excluded, GEE adjusts to some extent for such spurious effects, by adjusting for within-patient correlation and not excluding patients with missing time points. Another limitation of this study is that the MRI sets were scored by one reader. However, the scoring system used in the present study uses a combination of scoring systems that already have proven to be reliable with respect to inter-reader agreement.[19] A general issue regarding assessment of MRIs of the SI joints, is that in a previous study in up to 30% of the SI joints of individuals with chronic low back pain or healthy controls abnormalities were detected [20] Such lesions may have contributed to some extent to the results we have found, but it is likely that these abnormalities will disappear in non-inflammatory conditions over time in contrast to male patients with IBP that are HLA-B27 positive. At last, the ESpAC cohort in which the analyses were performed is a rather small cohort with characteristics that do not necessarily resemble the average patient presenting with complaints suggestive of SpA. Extrapolation of findings should therefore be done cautiously.

In conclusion, MRI is a very useful imaging technique in establishing inflammation in the SI joints and may contribute to making a diagnosis of axial SpA in patients with IBP. In this cohort of patients with IBP of recent-onset, it seems that during a 2-year follow-up period, the proportion of patients with and without signs of MRI activity remains stable to a great extent. This is an important finding, since it suggests that in case of both a negative MRI and a negative HLA-B27 status, a classifying diagnosis of axial SpA can be excluded with great certainty. In this cohort we found that the combination of a positive MRI scan and HLA-B27 positivity is associated with a high likelihood of a persistent positive MRI during follow-up. In HLA-B27 positive patients with a negative MRI at baseline, in whom a classifying diagnosis of axial SpA cannot be made by the route of HLA-B27 presence plus two additional SpA features, a follow-up MRI can be considered since a reasonable proportion of these patients will develop MRI activity over time, especially in male patients.

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CHAPTER 4

Bone marrow edema on MRI of the sacroiliac joints is associated with development of fatty lesions on MRI over a 1-year interval in patients with early inflammatory low back pain: a 2-year follow-up study

Marloes van Onna, Astrid van Tubergen, Désirée van der Heijde, Anne Grethe Jurik, Robert Landewé

ABSTRACT

Objective

To assess whether bone marrow edema (BME) detected on MRI of the sacroiliac joints (MRI-SIJ) is associated with development of structural changes on both MRI and pelvic radiographs in patients with early inflammatory back pain (IBP).

Methods

Patients with IBP ≤2 years were followed for 2 years with annual MRI-SIJ. MRIs were scored for BME and structural changes (erosions and fatty lesions). Pelvic radiographs were graded according to the modified New York (mNY) criteria. With generalized estimated equation analysis, a time trend in the structural change scores was investigated.

Results

Sixty-eight patients (38% male; mean (SD) age 34.9 (10.3) years) were included. During the 2-year follow-up, pelvic radiograph grading remained constant. On MRI, the number of erosions per patient increased significantly (mean score 2.5 at baseline and 3.5 at 2-years follow-up; p=0.05). A trend was found for an increase in the number of fatty lesions per patient (mean score 5.4 at baseline and 8.5 at 2-years follow-up; p=0.06). Overall, BME was associated with the development of fatty lesions (right SIJ: odds-ratio (OR) 3.13, 95% confidence interval (CI) 1.06-9.20; left SIJ: OR 22.13, 95%-CI 1.27-384.50), preferentially in quadrants showing resolution of BME. In contrast, BME (or the resolution thereof) was not associated with the development of erosions.

Conclusion

BME at baseline, especially when it disappears over time, results in the development of fatty lesions, but an association with erosions could not be demonstrated.

INTRODUCTION

MRI of the sacroiliac joints (MRI-SIJ) and pelvic radiographs play an important role in the diagnosis and classification of axial spondyloarthritis (axSpA). Both imaging techniques are included in the "imaging arm" of the Assessment in SpondyloArthritis international Society (ASAS) criteria for axSpA.[1] MRI-SIJ has especially proven to be useful in the early stage of axSpA, because MRI may detect sacroiliitis years before it is seen on a pelvic radiograph. Moreover, MRI can detect both active lesions and structural changes, in contrast to pelvic radiographs which only detect structural changes.[2] Patients without radiographic sacroiliitis, but with active lesions on MRI suggestive for sacroiliitis, are labelled non-radiographic axSpA (nr-axSpA).[1]

Active (inflammatory) lesions that can be detected on MRI are bone marrow edema (BME), capsulitis, synovitis and enthesitis. Structural changes on MRI are erosions, fat deposition (fatty lesions), sclerosis and ankylosis.[1,3] To date, only BME is considered mandatory for fulfilment of the ASAS/Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) working group definition of a positive MRI.[2] However, Weber et al. suggested that also the detection of erosions on MRI-SIJ may be helpful in making a diagnosis in early axSpA.[3] There is, however, limited knowledge about the development of structural changes as detected on MRI-SIJ in patients with early IBP who may possibly have or develop axSpA. Furthermore, data on the association between BME and development of structural changes are scarce. Only one study suggested that fatty lesions on MRI-SIJ may be the first sign of structural damage after previous active inflammation.[4]

The aims of this study were to assess the presence 1) of structural changes on both MRI-SIJ and pelvic radiographs and 2) whether BME detected on MRI-SIJ is associated with the development of structural changes on both MRI-SIJ and pelvic radiographs in patients with recent onset IBP over a 2 year follow-up period.

PATIENTS AND METHODS

Study population

Patients with IBP of less than 2 years duration were enrolled in the Early SpondyloArthritis Clinic (ESpAC) study. In this prospective inception cohort study, three identical clinical and radiological examinations were performed at baseline and after 1 and 2 years. A more detailed description of the study population and inclusion can be

found in previous reports.[5-7] The Calin criteria were used to define the presence of IBP. Patients had to fulfil at least 4 of the criteria: onset before the age of 40 years, duration of back pain more than 3 months, insidious onset, morning stiffness, and improvement with exercise.[8] Patients who fulfilled only 3 out of 5 of Calin criteria, but reported night pain were also included. Presence of other SpA features was preferred but not obligatory. Patients were not treated with biological therapy during the entire study period, the use of non-steroidal anti-inflammatory drugs (NSAIDs) was allowed. The study was approved by the ethics committee from the Maastricht University Medical Center. All patients gave written informed consent.

MRI protocol

MRI-SIJ was performed using a 1.5 Tesla Philips Gyro scan ACS-NT (Philips, The Netherlands). Patients were placed in supine position in a spine surface coil. The following sequences were used in an oblique coronal plane: T1-weighted spin echo (SE), short tau inversion recovery (STIR) and T2-weighted fast SE with fat saturation. The MRI set of each individual was scored independently and in a random time order by 1 experienced radiologist (AGJ), without knowledge of clinical or laboratory findings. The SIJs were scored using a combination of the Spondyloarthritis Research Consortium of Canada (SPARCC) method and a modified version of the Aarhus MRI scoring system.[9,10] In contrast to the original SPARCC system, there was no maximum to the number of evaluated slices, but the number of slices within a patient was kept the same for all time points. First, each SIJ was divided into 4 quadrants (upper/lower sacral and upper/lower iliac quadrant) and both BME and structural changes were scored separately per slice in a dichotomous manner (absent vs. present). Second, a total count of both BME and structural changes per SIJ was performed. The method for scoring BME has been published.[11] The structural changes scores included scoring of both erosions and fatty deposition of the bone marrow (fatty lesions). Erosions, defined as cortical defects of the SIJ lining, are detected as hypointense signal on the T1 sequence. Subcortical fatty lesions, defined as replacement of normal bone marrow by fatty tissue, are detected as an increased signal on the T1 sequence. According to the ASAS/OMERACT working group definition for active lesions on MRI-SIJ, an MRI-SIJ is considered positive for active sacroiliitis when at least 1 active lesion is present in at least 2 successive slices or when ≥2 lesions are detected in 1 slice.[2] Analogous to the ASAS/OMERACT working group definition for active lesions on MRI-SIJ, we defined an MRI-SIJ as positive for structural changes

when at least 1 erosion or fatty lesion is present in at least 2 successive slices or when ≥2 erosions or fatty lesions are detected in 1 slice.

Pelvic radiographs

Antero-posterior pelvic radiographs of the SIJ were obtained and independently scored in a random time order by 2 readers (AT and RL) who were blinded to clinical and laboratory findings and were not involved in the MRI reading. In case of disagreement, the judgment of a third reader (DH) was decisive. The pelvic radiographs were scored according to the modified New York (mNY) criteria for sacroiliitis, in which sacroiliitis of at least grade 2 bilaterally or grade 3-4 unilaterally must be present for fulfillment of the mNY criteria.[12]

Statistical analysis

Descriptive statistics were used to describe the presence or absence of structural changes on MRI-SIJ and pelvic radiographs during the 2-year follow-up period.

The presence of BME at baseline and during follow-up in relation to the development of fatty lesions and/or erosions at the site of BME was investigated per quadrant of SIJ (8 quadrants per patient) using descriptive analysis. Generalized estimated equation (GEE) analysis was performed to investigate a time trend in the MRI and pelvic radiograph structural changes scores. GEE is a model that allows studying time trends while taking the within-subject correlation into account in a dataset with missing values. Furthermore, this technique was used to test whether BME on MRI is associated with erosions and fatty lesions on MRI and structural changes on a pelvic radiograph 1 year later. This was done using a GEE autoregressive time-lag model that correlates the presence of BME on MRI to each structural change score on either MRI or pelvic radiograph 1 year later. On a per SIJ level, BME was used as independent variable and the continuous (sum of) MRI or the pelvic radiograph mNY grading in the same location were used as dependent variables. SPSS software version 18.0 was used for all statistical analyses. All p-values were two-tailed and statistical significance was set at 0.05.

RESULTS

Patient characteristics

Baseline characteristics of the 68 patients included in ESpAC are shown in Table 4.1. MRI-SIJ and pelvic radiographs were obtained in all patients at baseline. Sixty-two (91%) patients had at least 1 follow-up MRI and 44 (65%) patients completed both follow-up MRIs. Sixty-five (96%) patients had at least 1 follow-up pelvic radiograph and 48 (71%) patients completed both follow-up pelvic radiographs. In 10 (15%) of 68 patients adjudication of pelvic radiographs was considered necessary because of disagreement between the first 2 readers.

Table 1. Baseline characteristics of 68 patients included in the ESpAC.

Characteristic	All patients (n=68)	Patients with complete MRI follow-up data (n= 44)
Male sex	26 (38)	15 (34)
Mean age (SD) [years]	34.9 (10.3)	36.0 (11.7)
Median symptom duration (IQR) [months]	18 (12-24)	18 (12-24)
HLA-B27 positive	31 (46)	17 (39)
History of inflammatory bowel disease	10 (15)	7 (16)
History of anterior uveitis	10 (15)	8 (18)
History of psoriasis	16 (24)	12 (27)
History of peripheral arthritis	19 (28)	12 (27)
Family history of SpA	37 (54)	26 (59)
Mean CRP (SD) [mg/l]	9 (11)	9 (12)
Elevated CRP[a]	16 (24)	10 (22)
Mean ESR (SD) [mm]	13 (15)	13 (16)
Elevated ESR[a]	24 (36)	13 (30)
Presence of BME on MRI-SIJ	24 (35)	14 (32)
Fulfillment ESSG criteria	58 (85)	39 (89)
Fulfillment Amor criteria	48 (71)	31 (70)
Fulfillment ASAS axSpA criteria	40 (59)	22 (50)
Fulfillment mNY criteria	15 (22)	9 (20)

The values are expressed as number (percentage) of patients unless stated otherwise. ESpAC=Early Spondyloarthritis Clinic; SpA=spondyloarthritis; IQR=interquartile range; SD=standard deviation; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; BME=bone marrow edema; MRI-SIJ=magnetic resonance imaging of the sacroiliac joints; ESSG=European Spondyloarthropathy Study Group; ASAS= Assessment in SpondyloArthritis international Society; axSpA=axial spondyloarthritis; mNY criteria=modified New York criteria. [a] In 66 of 68 patients baseline CRP and ESR measurements were available. ESR normal range: ≤7 mm for males; ≤12 mm for females. CRP cut-off value, normal range: <10 mg/l.

At baseline, 64 (94%) out of 68 patients fulfilled the European Spondyloarthropathy Study Group (ESSG) and/or Amor and/or ASAS axSpA classification criteria. Sixty-six (97%) patients fulfilled 4 of the 5 Calin criteria. The remaining 2 (3%) patients fulfilled 3

of the 5 Calin criteria and reported 'night pain' as well. Forty (59%) patients fulfilled the ASAS axSpA criteria at baseline, of which 22 fulfilled the imaging and clinical arm of the ASAS axSpA criteria, 9 patients fulfilled only the imaging arm, and 9 other patients fulfilled only the clinical arm. Fifteen (22%) patients fulfilled the mNY criteria at baseline.

Structural changes on MRI-SIJ

Scores for BME on MRI-SIJ have been presented in a previous report.[11] Table 4.2 and 4.3 show the baseline and follow-up MRI findings for erosions and fatty lesions, respectively and the relation with fulfillment of the mNY criteria and ASAS axSpA criteria at baseline, and HLA-B27 status.

Table 4.2   Erosions on MRI-SIJ at baseline and during follow-up.

Number of patients	MRI-SIJ			mNY criteria +[a]	ASAS axSpA criteria+[b]	HLA-B27+[c]
	Baseline	1-Year	2-Years			
5	+	+	+	3	4	4
2	+	+	NA	1	2	2
3	+	NA	+	2	3	1
1	+	+	-	1	1	1
1	+	NA	NA	1	1	1
35	-	-	-	3	14	11
11	-	-	NA	1	7	6
1	-	-	+	1	1	1
2	-	+	+	1	2	0
1	-	+	NA	1	1	1
1	-	NA	-	0	1	0
5	-	NA	NA	0	3	3

The number of patients with present or absent signs of erosions on MRI-SIJ at baseline and during follow-up is shown. [a] Number of patients that fulfil the mNY criteria at baseline. [b] Number of patients that fulfil the ASAS axSpA criteria at baseline. [c] Number of patients that are HLA-B27 positive. +=structural changes present; -=structural changes absent, NA=MRI not available, MRI-SIJ=magnetic resonance imaging of the sacroiliac joints; HLA-B27=human leukocyte antigen B27, mNY criteria=modified New York criteria, ASAS axSpA criteria=Assessment in SpondyloArthritis international Society axial spondyloarthritis criteria.

At baseline, erosions and/or fatty lesions on MRI were detected in 17 (25%) patients, of which 71% were HLA-B27 positive and 9 (53%) fulfilled the mNY criteria. Erosions were detected in 12 (18%) out of 68 patients of which 8 (66%) patients also fulfilled the mNY criteria (Table 4.2). Fatty lesions were detected in 13 (19%) out of 68 patients of which 7 (54%) patients also fulfilled the mNY criteria (Table 4.3). Coexistence of both erosions and fatty lesions on MRI occurred in 8 (9%) out of 68 patients of which 6 (75%) patients also fulfilled the mNY criteria.

Table 4.3   Fatty lesions on MRI-SIJ at baseline and during follow-up.

Number of patients	MRI-SIJ			mNY criteria +[a]	ASAS axSpA criteria+[b]	HLA-B27+[c]
	Baseline	1-Year	2-Years			
6	+	+	+	3	5	5
2	+	+	NA	1	2	2
1	+	NA	+	1	1	0
1	+	NA	-	0	1	0
2	+	-	+	1	2	1
1	+	NA	NA	1	1	1
35	-	-	-	4	14	11
9	-	-	NA	1	5	4
1	-	NA	-	0	1	0
1	-	+	+	1	1	0
3	-	+	NA	1	3	3
1	-	NA	+	1	1	1
5	-	NA	NA	0	3	3

The number of patients with present or absent signs of fatty lesions on MRI-SIJ at baseline and during follow-up is shown. [a] Number of patients that fulfil the mNY criteria at baseline. [b] Number of patients that fulfil the ASAS axSpA criteria at baseline. [c] Number of patients that are HLA-B27 positive. +=structural changes present; -=structural changes absent, NA=MRI not available, MRI-SIJ=magnetic resonance imaging of the sacroiliac joints; HLA-B27=human leukocyte antigen B27, mNY criteria=modified New York criteria, ASAS axSpA criteria=Assessment in SpondyloArthritis international Society axial spondyloarthritis criteria.

During follow-up, 4 (8%) out of 51 patients with no signs of erosions at baseline, and at least 1 follow-up MRI present, have developed erosions, of which 2 patients were HLA-B27 positive and 3 patients already fulfilled the mNY criteria at baseline (Table 4.2). In 2 of these 4 patients, the erosions were accompanied by simultaneous appearance of fatty lesions on MRI. Five (10%) out of 50 patients without fatty lesions at baseline and at least 1 follow-up MRI developed fatty lesions during follow-up, four of them were HLA-B27 positive and 3 patients fulfilled the mNY criteria at baseline (Table 4.3).

In 1 (8%) out of 12 patients with erosions on MRI at baseline, the erosions were not detected anymore at the 2-year time point (Table 4.2). In 3 (23%) out of 13 patients with fatty lesions on MRI at baseline, the fatty lesions were not detected during follow-up (Table 4.3).

Structural changes on pelvic radiographs

At baseline, 15 (22%) patients fulfilled the mNY criteria for radiographic sacroiliitis of which 80% were HLA-B27 positive. Eight (53%) of these 15 patients also had BME at baseline and in 9 (60%) patients erosions and/or fatty lesions were detected on MRI. During follow-up no changes in mNY grading were found in these 15 patients. Four patients who fulfilled the mNY criteria at baseline developed new erosions and/or fatty

lesions on MRI (Table 4.2 and 4.3). No patients were newly classified with radiographic sacroiliitis according to the mNY criteria at follow-up.

Association between BME and structural changes on MRI-SIJ

The first analysis was a GEE analysis (scores of 58 patients with at least 2 successive time points available included) showing that the number of erosions per patient increased significantly during follow-up (estimated marginal (EM) mean score of 2.5 at baseline, 3.3 at 1-year follow-up and 3.5 at 2-year follow-up; p=0.05). There was also a trend for an increase in the number of fatty lesions (EM mean score of 5.4 at baseline, 7.7 at 1-year follow-up and 8.5 at 2-year follow-up; p=0.06).

The second analysis was a GEE analysis per SIJ (2 per patient) showing an association between BME and the development of fatty lesions on MRI (Table 4.4). An association between BME and subsequent development of erosions on MRI could not be proven (Table 4.4).

Table 4.4   GEE analysis (continuous MRI-SIJ score) showing association between bone marrow edema on MRI-SIJ and the development of structural changes on MRI-SIJ during follow-up.

Per joint analysis, structural changes MRI-SIJ			Odds ratio (95% CI)	p-value
MRI development of structural changes (per unit change)	Fatty degeneration (per unit)	Right SIJ	3.13 (1.06 - 9.20)	0.04
		Left SIJ	22.13 (1.27 – 384.50)	0.03
	Erosions (per unit)	Right SIJ	0.24 (0.07 – 8.24)	0.43
		Left SIJ	1.24 (0.09 – 18.03)	0.88

N=58. GEE=generalized estimated equation, MRI-SIJ = magnetic resonance imaging of the sacroiliac joints. 95% CI = 95% confidence interval

The third analysis was a detailed descriptive analysis at the level of quadrants of SIJ, in order to investigate the association between the presence of BME and the development of erosions and/or fatty lesions at the same site. This analysis was done to investigate how an inflammatory lesion at a particular site associates with the development of a structural lesion at the same site. Every patient had 8 quadrants (4 left and 4 right) available for comparison.

The starting point of this analysis was the presence of BME. Continuous presence of BME over time vs. resolution of BME was taken into consideration. The results of this analysis which are presented in Table 4.5 show that an increase of fatty lesions preferentially occurs in quadrants in which BME has resolved over time (55%) in comparison with quadrants in which BME has persisted over time (26%). With regard to the development of erosions such a disparity could not be confirmed (26% vs. 30%).

Table 4.5 Presence of bone marrow edema on MRI at baseline and follow-up in relation to the subsequent development of fatty lesions and erosions at the same sacroiliac joint quadrant.

	Baseline	Last follow-up MRI*			
	BME (present)	BME (present)	BME (present) AND increase of FL at the same quadrant	BME (absent)	BME absent AND increase of FL at the same quadrant
All quadrants	89	47	12 (26)	42	23 (55)
	BME (present)	BME (present)	BME (present) AND increase of erosions at the same quadrant	BME (absent)	BME absent AND increase of erosions at the same quadrant
All quadrants	89	47	14 (30)	42	11(26)

n=62 patients.* Follow-up at 1 or 2 years, depending on last MRI. SIJ=sacroiliac joint; BME=bone marrow edema, FL=fatty lesion, MRI=magnetic resonance imaging.

DISCUSSION

The present study has demonstrated that BME on MRI-SIJ is associated with the development of fatty lesions in a cohort of patients with early IBP. Such an association could not be demonstrated for erosions, despite a significant overall numerical increase of erosions over time. Furthermore, approximately 10% of the patients without erosions and fatty lesions at baseline developed new structural changes on MRI during the 2-year follow-up period.

An increase in the number of structural changes on MRI over time has been demonstrated in a previous study evaluating MRI-SIJ abnormalities in patients with early axSpA.[13] In this study by Madsen et al. 80 out of 94 (85%) patients with axSpA had erosions and fatty lesions present on MRI at baseline. After a mean follow-up period of 51 months, both the number of erosions and fatty lesions had significantly increased.[13] We have also found a significant increase in the number of erosions, as well as a strong trend for an increase in the number of fatty lesions. In the study by Madsen et al., the proportion of patients with structural changes was higher at baseline compared with our cohort (85% versus 25%), and also their follow-up duration was longer, which might explain the difference in time trends found for fatty lesions. The presence of fatty lesions might also be underestimated in our study due to the fact that the presence of intense BME may prevent the detection of fatty lesions due to counteracting MR signals on the T1 MRI sequence (BME low signal intensity; fatty lesions high signal intensity).[4]

In the present study, we have statistically demonstrated an association between the presence of BME and the subsequent development of fatty lesions on MRI. Even more important is the indication that these fatty lesions seem to have preferentially occurred at the sites (quadrants) in which existing BME has resolved over time. This is entirely in line with existing theories about the role of fatty lesions as a repair reaction in response to inflammatory triggers. A study by Song et al. has described an association between disappearance of BME on MRI in both the SIJ and spine and the subsequent appearance of fatty lesions on MRI in patients with early axial SpA treated with either etanercept or sulfasalazine over a 1 year follow-up period. In patients in whom BME resolved, fatty lesions occurred in 10.5% of the SIJ quadrants 1 year later, but in those in whom BME persisted, fatty lesions occurred in only 2.4% of the SIJ quadrants 1 year later.[4] In a study by Maksymowych et al., 76 patients with axSpA were followed for 1 year with repeated MRIs of the spine.[14] The chance of developing new fatty lesions was significantly higher at vertebral corners with BME at baseline as compared to vertebral corners without BME at baseline (18% vs. 3%).[14] A correlation between BME and the subsequent development of fatty lesions on MRI-SIJ could not be demonstrated in the SPondyloArthritis Caught Early (SPACE)-cohort over a 3-month follow-up period.[15] This last finding suggests that a longer follow-up period is necessary before fatty lesions can be detected in response to subsiding BME.

Whilst we have found an increase in the number of erosions in this study, we have failed to demonstrate a significant association between the presence of BME and the development of erosions. A possible explanation is that the erosions occur independently of inflammation. Larger cohorts are necessary to provide sufficient statistical power to clarify the relation between BME and development of both fatty lesions and erosions.

The rate of development from non-radiographic to radiographic axSpA in patients with a clinical diagnosis of axSpA without signs of radiographic sacroiliitis is estimated to be approximately 10% per 2 years.[16] In patients with BME on MRI-SIJ, this percentage increases to around 20% per 2 years.[17] Our study has failed to demonstrate an association between BME and development of structural changes detected on pelvic radiographs, nor could we demonstrate a change in the level of sacroiliitis according to the mNY criteria during the 2-year follow-up. The short follow-up period and the relatively small sample size may have hampered to detect these changes.

There are several concerns when assessing structural changes of the SIJ on either an MRI or pelvic radiograph and it is debatable which imaging modality is approaching the truth or whether they are complementary. Both imaging modalities are subject to

observer errors and especially the evaluation of pelvic radiographs may be hampered by projection artifacts and poor visibility.[18,19] Erosions on MRI may not be reliably detected if the slice thickness is not small enough or movement artifacts may limit an accurate image interpretation. The natural irregular shape of the cortical lining of the SIJ may also limit detection of erosions. In the present study, of the 15 patients with sacroiliitis on pelvic radiographs according to independent readers, erosions and/or fatty lesions on MRI were detected in only 9 (60%) patients at baseline. The majority of the patients, who developed new erosions and/or fatty lesions on MRI during follow-up, already fulfilled the mNY criteria at baseline.

Some limitations of the present study need to be addressed. First, the MRIs were scored by one reader only, which may in theory influence the reliability of the data. However, the reader was very experienced and the MRI scores showed a high consistency over time despite scoring each MRI set independently and blinding of the reader for time order. Furthermore, and in contrast to scoring pelvic radiographs, a number of studies have shown a rather high inter-observer agreement when scoring MRI-SIJs.[9,20] Second, in the present study, the T1 and STIR sequence were simultaneously scored for active lesions and structural changes. This scoring method could have resulted in reader bias, since the presence of BME on the STIR sequence may possibly have triggered the reader to screen more carefully for structural changes on the T1 sequence or vice versa. This may influence the sensitivity for scoring structural changes on MRI-SIJ. In 16 of the 17 patients with erosions and/or fatty lesions at baseline, concomitant BME was also found. However, one could also postulate that concomitant BME decreases the specificity of scoring structural changes on MRI, since a reader is more likely to score an indeterminate lesion as a structural change. Scoring the T1 and STIR sequence independently could possibly lower the risk of reader bias when evaluating the presence of active lesions and structural changes on MRI-SIJ. Third, in the MRI scoring system used in the present study, we applied an unlimited number of evaluated slices. Serial image acquisition of the same anatomical region offers advantages to monitor changes over time. However, this scoring method may be limited by the possibility of misalignment between 2 successive MRI examinations, which may cause measurement error. Last, ESpAC is a relatively small cohort with selected patients. Patients were referred by (related) medical specialties (i.e. dermatology, gastroenterology) and through family members of the local ankylosing spondylitis society. This referral strategy may explain the relative high proportion of patients with extra-axial manifestations and/or positive family history for SpA. As a consequence, a high proportion of patients fulfilled at least one of the

classification criteria for SpA. Furthermore, the proportion of female patients in ESpAC is relatively high (62%) and the proportion of patients with a positive HLA-B27 status is relatively low (46%). However, these percentages are in accordance with other cohorts that included patients with early IBP.[21,22] Nevertheless, extrapolation of the study findings should be done with caution.

In conclusion, in this cohort of patients presenting with IBP of recent onset and suspected for axSpA, the number of patients with erosions and fatty lesions detected on MRI-SIJ remained relatively stable during the 2 years of follow-up, but the overall number of MRI erosions in patients who already had erosions at baseline has increased. Signs of BME on MRI, and especially the resolution of it, were significantly correlated with the development of fatty lesions on MRI, but not with the development of structural changes visible on pelvic radiographs.

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CHAPTER 5

Gadolinium contrast-enhanced MRI sequence does not have an incremental value in the assessment of sacroiliitis in patients with early inflammatory back pain by using MRI in combination with pelvic radiographs: A 2 year follow up study

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ABSTRACT

Objective
To evaluate the potential incremental value in detecting sacroiliitis of the T1 post-gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) MRI sequence of the sacroiliac joints (SIJ) compared with the combination of short tau inversion recovery (STIR) MRI sequence and pelvic radiographs in patients with inflammatory back pain (IBP) suspected for axial spondyloarthritis.

Methods
A 2-year follow-up study was conducted in patients with IBP of less than 2 years duration. Annual MRI of the SIJ (MRI-SIJ) was performed and scored for bone marrow edema (BME). Pelvic radiographs were scored according to the modified New York (mNY) criteria. Agreement on the presence of BME detected by the STIR and post-Gd-DTPA sequence and the incremental value of post-Gd-DTPA sequence over STIR plus radiographs was analysed by descriptive methods and kappa statistics.

Results
At baseline, 20 (29%) out of 68 patients (38% male; mean (SD) age 34.9 (10.3) years) enrolled had BME both on the STIR and post-Gd-DTPA sequences; 4 patients (6%) on the STIR sequence only; none on the post-Gd-DTPA sequence only (kappa value: 0.87). Fifteen (22%) patients fulfilled the mNY criteria at baseline.
Sixty-two (91%) patients had at least 1 follow-up MRI-SIJ. At 2-year follow-up, 2 patients had BME on the post-Gd-DTPA sequence without BME on the STIR sequence. These 2 patients already fulfilled the mNY criteria at baseline.

Conclusion
In this cohort of patients with early IBP, the post-Gd-DTPA sequence of the MRI-SIJ did not have an incremental value in the detection of sacroiliitis compared with the STIR sequence plus pelvic radiographs.

INTRODUCTION

Pelvic radiographs and magnetic resonance imaging (MRI) are important imaging techniques to detect sacroiliitis in patients with a suspicion of axial spondyloarthritis (axSpA). In the Assessment in SpondyloArthritis international Society (ASAS) axSpA classification criteria, sacroiliitis on either MRI or pelvic radiograph is used as the entry criterion for fulfillment of the 'imaging arm'.[1]. With MRI, both active lesions and structural changes can be detected, in contrast to pelvic radiographs that only visualize structural changes. Typical 'active lesions' in the sacroiliac joints (SIJ) detected by MRI are subchondral bone marrow edema (BME), as well as synovitis, enthesitis and capsulitis.[2] Different MRI techniques can be used to detect active lesions; these are short tau inversion recovery (STIR) that suppresses the signal intensity of fat, and T1 with or without fat suppression after administration of the contrast agent gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA). Only BME on the STIR or post-Gd-DTPA sequence is considered for the definition of active sacroiliitis according to the ASAS/Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) consensus.[2] The ASAS/OMERACT MRI working group further states that the STIR sequence alone is usually sufficient to detect sacroiliitis. This statement is supported by several studies that found no additional value of the post-Gd-DTPA sequence compared with the STIR sequence in detecting sacroiliitis in patients with early or established axSpA.[3,4] However, these studies were cross-sectional[3] or had a 3-month follow-up period only.[4] Furthermore, these studies did not include pelvic radiographs. Besides that in the ASAS classification criteria both pelvic radiographs and MRI-SIJ are considered for fulfilment of the imaging arm, also in daily practice, usually the first step for making a diagnosis is to perform a pelvic radiograph. When negative of equivocal, the next step is to make an MRI-SIJ. Although on the short term, the post-Gd-DTPA MRI sequence does not seem to be of additional value, it is unknown what its value is over a longer follow-up period, especially in patients with early disease, and taking the pelvic radiograph into account. Fluctuating or subsiding BME on either the STIR or post-Gd-DTPA sequence may affect the sensitivity and specificity of MRI in detecting sacroiliitis and hamper the diagnostic process.[5] Combining the information on pelvic radiographs with the information on MRI-SIJ may yield an higher probability of detecting sacroiliitis.[6]

The aim of this study was to evaluate the potential incremental value of the post-Gd-DTPA sequence for detecting sacroiliitis compared with the combination of STIR MRI sequence and pelvic radiographs in patients presenting with IBP of short duration

suspected for axSpA. These patients were followed for 2 years with repeated radiological examinations.

MATERIALS AND METHODS

Study population

Patients with IBP of less than 2 years duration were enrolled in the Early SpondyloArthritis Clinic (ESpAC) study. In this prospective cohort study, systematic clinical and radiological examinations were performed at baseline and after 1 and 2 years. A more detailed description of the study population has been reported previously.[7] For IBP to be present, patients had to fulfil 4 of the following 5 Calin criteria: onset of symptoms before the age of 40 years, duration of back pain more than 3 months, insidious onset, morning stiffness and improvement with exercise.[8] Patients who fulfilled only 3 out of 5 of the Calin criteria but reported night pain, were also eligible. Presence of extra-axial manifestations of SpA was preferred but not obligatory. Patients were not treated with biological therapy during the entire study period. The use of non-steroidal anti-inflammatory drugs (NSAIDs) was allowed. The study has been approved by the ethics committee of the Maastricht University Medical Center. All patients have given written informed consent.

MRI protocol

MRI of the SI joints was obtained with a 1.5 Tesla Philips Gyro Scan ACS-NT (Philips, The Netherlands). Patients were examined while lying in a supine position. By using an oblique coronal slice orientation, the following sequences were obtained:
- T1-weighted spin echo (SE), 256 x 256 matrix
- STIR, 256 x 256 matrix
- T1-weighted SE with fat suppression after administration of the intravenous contrast agent Gd-DTPA (0.1 mmol/kg body weight), 512 x 256 matrix

The slice thickness was 4 mm with 0.4 mm intervals. Each MRI set was scored with unknown time sequence by one experienced radiologist (AGJ), without knowledge of clinical or laboratory findings.

MRI and pelvic radiograph scoring

The MR images were scored using a combination of the Spondyloarthritis Research Consortium of Canada (SPARCC) method and a modified version of the Aarhus MRI scoring method.[9,10] In contrast to the original SPARCC system, there was no maximum to the number of evaluated slices, in order to maximise the detection of abnormal MRI findings. The number of evaluated slices within a individual patient was kept the same for all time points. Each SIJ was divided into 4 quadrants: upper iliac, lower iliac, upper sacral and lower sacral. All images (STIR and post-Gd-DTPA) were scored for the presence of subchondral BME with the corresponding T1 sequence without contrast simultaneously. BME present in the cartilaginous part of the joint was scored per slice in a dichotomous manner (present vs. absent). BME was defined as areas of increased signal intensity on both the STIR and post-Gd-DTPA images compared with normal bone marrow, and its presence was estimated in each of the 4 quadrants. Since synovitis, capsulitis and enthesitis are not considered sufficient for the definition of a positive MRI according to the ASAS/OMERACT definition, only the MRI scores of BME were taken into account.[2]

An MRI was considered positive when at least one BME lesion was present in at least two consecutive slices, or when two or more BME lesions were detected in one slice, following the ASAS/OMERACT working group definition for BME lesions on MRI-SIJ.[2]

Anteroposterior pelvic radiographs of the SIJ were obtained from all patients at baseline and during one- and 2-year follow up. Two readers (AT and RL), who were blinded to the clinical and laboratory findings and were not involved in the MRI reading, independently scored all radiographs with unknown time sequence according to the modified New York (mNY) criteria.[11] In case of disagreement, judgment of a third reader (DH) was conclusive.

Statistical analysis

Descriptive statistics were used to analyse the presence of BME on MRI-SIJ and structural changes on pelvic radiographs at baseline and during the 2-year follow-up period. Agreement on the presence of BME suggestive for sacroiliitis detected by STIR and post-Gd-DTPA sequences was analyzed on a per patient basis by kappa statistics. A kappa value of 0-0.20 indicated poor agreement, 0.21-0.40 indicated fair agreement, 0.40-0.60 indicated moderate agreement, 0.60-0.80 indicated substantial agreement and 0.80-1.0 indicated (almost) perfect agreement.[12] Descriptive statistics were used

to compare the presence of sacroiliitis detected on either pelvic radiographs or STIR MRI with findings on the post-Gd-DTPA MRI sequences. SPSS software version 18.0 was used for all statistical analyses.

RESULTS

Patient characteristics

Baseline MRI-SIJ and pelvic radiographs were available in all 68 patients included in the ESpAC. Baseline characteristics are shown in Table 5.1.

Sixty-two (91%) patients had at least 1 follow-up MRI and 44 (65%) patients completed both follow-up MRIs. Sixty-five (96%) patients had at least 1 follow-up pelvic radiograph and 48 (71%) patients completed both follow-up pelvic radiographs.

At baseline, 64 (94%) out of 68 patients fulfilled the European Spondyloarthropathy Study Group (ESSG) and/or Amor and/or ASAS axSpA classification criteria. Fifteen (22%) patients fulfilled the mNY criteria at baseline and in 24 (35%) patients BME was detected on MRI-SIJ. Eight (53%) of 15 patients who fulfilled the mNY criteria at baseline had signs of BME on both the STIR and post-Gd-DTPA sequence at baseline.

Agreement between the STIR- and post-Gd-DTPA MRI sequences

At baseline, a good agreement between the STIR and post-Gd-DTPA sequence on a per patient basis was found (kappa=0.87). Twenty (29%) patients showed BME on MRI-SIJ suggestive for sacroiliitis on both STIR and post-Gd-DTPA sequences. In 4 (6%) patients, BME was detected on the STIR sequence only, but this was minimal in 3 of these 4 patients. None of the patients had signs of BME on the post-Gd-DTPA sequence only. Twenty-three (96%) of 24 patients with BME on MRI at baseline had at least one follow-up MRI. A moderate to good agreement between the STIR and post-Gd-DTPA sequence on a per patient basis was also found at 1-year (kappa=0.83) and 2-year (kappa=0.75) follow-up.

Table 5.1   Baseline characteristics of 68 patients included in the ESpAC.

Characteristic	All patients	Patients with complete MRI follow-up data
	(n=68)	(n=44)
Male sex	26 (38)	15 (34)
Mean age (SD) [years]	34.9 (10.3)	36.0 (11.7)
Median symptom duration (IQR) [months]	18 (12-24)	18 (12-24)
HLA-B27 positive	31 (46)	17 (39)
History of inflammatory bowel disease	10 (15)	7 (16)
History of anterior uveitis	10 (15)	8 (18)
History of psoriasis	16 (24)	12 (27)
History of peripheral arthritis	19 (28)	12 (27)
Family history of SpA	37 (54)	26 (59)
Mean CRP (SD) [mg/l]	9 (11)	9 (12)
Elevated CRP[a]	16 (24)	10 (22)
Mean ESR (SD) [mm]	13 (15)	13 (16)
Elevated ESR[a]	24 (36)	13 (30)
Presence of BME on MRI	24 (35)	14 (32)
Fulfillment ESSG criteria	58 (85)	39 (89)
Fulfillment Amor criteria	48 (71)	31 (70)
Fulfillment ASAS axSpA criteria	40 (59)	22 (50)
Fulfillment mNY criteria	15 (22)	9 (20)

The values are expressed as number (percentage) of patients unless stated otherwise. ESpAC=Early Spondyloarthritis Clinic; SpA=spondyloarthritis; IQR=interquartile range; SD=standard deviation; CRP= C-reactive protein; ESR=erythrocyte sedimentation rate; BME = bone marrow edema; MRI=magnetic resonance imaging; ESSG=European Spondyloarthropathy Study Group; ASAS=Assessment in Spondylo-Arthritis international Society; axSpA=axial spondyloarthritis; mNY criteria = modified New York criteria. [a] In 66 of 68 patients baseline CRP and ESR measurements were available. ESR normal range: ≤7 mm for males; ≤12 mm for females. CRP cut-off value, normal range: <10 mg/l

Detection of BME on the STIR and post-Gd-DTPA sequence at follow-up

Table 5.2 shows that in 5 (26%) of 19 patients with BME on both STIR and post-Gd-DTPA sequences at baseline, BME could no longer be detected on STIR sequence at 2-years follow-up. In 2 of these 5 patients, however, BME was still visible on the post-Gd-DTPA sequence. In the remaining 3 patients BME has disappeared on both the STIR and post-Gd-DTPA sequence at 2-years follow-up. These 3 patients were all HLA-B27-negative. In 2 of 4 patients with BME on the STIR sequence only at baseline, BME was no longer present at 2-years follow-up. Both patients were HLA-B27-negative.

Five (13%) of 39 patients without signs of BME on both the STIR and post-Gd-DTPA sequences at baseline, developed BME at follow-up. None of these 5 patients developed BME on the post-Gd-DTPA sequence only.

Table 5.2   Detection of BME on the STIR and post-Gd-DTPA sequences per patient at baseline and follow-up.

| | | Follow-up[*] | | | |
		BME on both STIR and post- Gd-DTPA	BME on STIR only	BME on post-Gd-GTPA only	No BME
Baseline	BME on both STIR and post- Gd-DTPA (n=19)	13	1	2	3
	BME on STIR only (n=4)	1	1	0	2
	No BME (n=39)	3	2	0	34

Bone marrow edema (BME) on the Short τ Inversion Recovery (STIR) and post-gadolinium diethylenetriaminepentaacetic acid (post-Gd-DTPA) sequence in 62 patients with at least 1 follow-up MRI. * Follow-up MRI at 1 or 2 years, depending on last available MRI

Incremental value of the post-Gd-DTPA sequence compared with the combination of STIR sequence and pelvic radiograph

At baseline, 31 (46%) patients had BME on MRI-SIJ and/or fulfilled the mNY criteria for radiographic sacroiliitis. None of these 31 patients had signs of BME on the post-Gd-DTPA sequence only at baseline. Thirty (97%) of 31 patients had both at least one follow-up MRI-SIJ and at least one follow up pelvic radiograph. At follow-up, no new patients fulfilled the mNY criteria for radiographic sacroiliitis. BME on the post-Gd-DTPA sequence only was found in 2 (7%) of these 30 patients at follow up. However, both patients already fulfilled the mNY criteria.

DISCUSSION

The present study showed that the post-Gd-DTPA MRI sequence does not have an incremental value in the detection of sacroiliitis in a cohort of patients with early IBP who were followed for 2 years compared to the combination of STIR MRI sequence and pelvic radiographs.

Both MRI sequences can be used to detect sacroiliitis with similar efficiency, as is reflected in the high kappa values found in our study. Earlier studies also compared the concordance between STIR and post-Gd-DTPA sequences in detecting BME on MRI-SIJ.[3,4] De Hooge et al. found a 100% agreement between the STIR and post-Gd-DTPA MRI sequence in detecting BME on MRI-SIJ in a prospective cohort study of 127 patients with chronic back pain of less than 2 years duration with onset below

45 years.[4]. In 8 (6%) of the 127 patients, synovitis and/or capsulitis and/or enthesitis was detected on the post-Gd-DTPA sequence, but without corresponding BME. However, these findings are not solely considered in the ASAS/OMERACT definition of active sacroiliitis. Also in this study, it was concluded that the post-Gd-DTPA sequence does not have an additional value in the assessment of active sacroiliitis over the STIR sequence.[4] Madsen et al. found in 40 patients with established axSpA, who were assessed by an oblique transaxial MRI of the SIJ, that the STIR sequence can replace the post-Gd-DTPA sequence.[3] There was agreement between both imaging sequences in 60 (75%) of the 80 SIJs. With the STIR sequence more BME, mainly in the periphery of structural changes, was detected. However, the authors suggested that the post-Gd-DTPA sequence might be superior to the STIR sequence with respect to detecting small subcortical lesions.[3] In contrast to these two studies, our longitudinal study also compared the MRI findings to the findings of pelvic radiographs over a 2-year follow-up period. In a small subset of patients, BME could be detected on the post-Gd-DTPA sequence only during follow-up. However, these patients already fulfilled the mNY criteria. This suggests that post-Gd-DTPA sequence does not provide additional diagnostic information in the detection of sacroiliitis in this cohort of patients with early IBP when information from the STIR sequence and pelvic radiographs are combined.

The present study shows that in case of discordance between the STIR and post-Gd-DTPA sequences, BME was mainly detected on the STIR sequence. In a previous study in the same cohort we have demonstrated that the combination of a positive MRI scan for BME and a positive HLA-B27 status is associated with a high likelihood of persistent signs of BME on MRI during follow-up.[13] Five patients in our cohort showed subsiding BME on the STIR sequence without BME on the post-Gd-DTPA sequence during follow-up, and all of them were HLA-B27 negative. Three of these 5 patients did not fulfil the mNY criteria. Whether the MRI in these 5 patients gave false-positive results or whether these patients showed fluctuating disease activity remains unclear because in ESpAC patients were not given a clinical diagnosis of axSpA that could serve as an external standard.

The MRI scoring method used in the present study is a combination of the SPARCC and Aarhus grading method.[9,10] Both scoring systems have proved to be reliable with respect to inter-reader agreement.[14] In contrast to the SPARCC method, we applied an unlimited number of slices to be evaluated, and the same (number of) slices were scored per MRI examination per patient over time. The advantage of this method is that all qualitatively optimal slices are scored, thereby maximising the chance of

detecting active lesions. A general concern when scoring MRIs of the SIJs is the possibility of misalignment between two successive MRI examinations, which may cause measurement error. We ensured that scoring started and ended at the same anatomical level to minimize the chance of misalignment between two successive MRI examinations.

Some limitations of the present study need to be addressed. First, the MRI sets were scored by one reader. However, the reader was experienced and the MRI scores showed high consistency over time despite independent scoring of each MRI set and blinding of the reader for time order. Second, the STIR sequence was not scored independently of the post-Gd-DTPA sequence. This might have contributed to the high per patient kappa values at baseline and follow-up. Third, a number of MRIs and pelvic radiographs was missing at follow-up. Baseline MRIs and pelvic radiographs were nevertheless complete and the baseline results already led to the conclusion that the post-Gd-DTPA sequence can be omitted, a conclusion that did not change when assessing the follow-up MRIs combined with the information from pelvic radiographs. Fourth, discordances between the STIR sequence and the post-Gd-DTPA sequence can be due to MRI coil artefacts, which may have contributed to an overestimation of the presence of BME on the STIR sequence.[15] Fifth, in ESpAC, the use of NSAIDs was allowed. The actual use of NSAIDs per patient was not recorded. It is possible that continuous or on-demand treatment with NSAIDs may have led to subsiding BME.[16] However, a number of BME lesions may also have subsided due to the natural fluctuating course of the disease.[17] Last, patients included in ESpAC were recruited via local rheumatologists, (related) medical specialties (i.e. dermatology, gastroenterology) and through family members of the local ankylosing spondylitis society. This selective recruitment may explain the relative high proportion of patients that fulfilled a least one of the classification criteria for axSpA. Furthermore, the proportion of female patients in ESpAC is relatively high (62%) whereas the proportion of patients with a positive HLA-B27 status is relatively low (46%). However, these percentages are in accordance with other cohorts that included patients with early IBP.[18,19] Nevertheless, extrapolation of the study findings should be done cautiously.

In conclusion, combined use of pelvic radiographs and the STIR MRI sequence is sufficient for detecting sacroiliitis in this early IBP cohort suspected for axSpA. The post-Gd-DTPA MRI sequence does not have an incremental value in detecting sacroiliitis, neither at baseline nor during 2 years of follow-up.

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CHAPTER 6

Natural course of bone marrow edema on
magnetic resonance imaging of the sacroiliac joints
in patients with early inflammatory back pain:
a 2-year follow-up study

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ABSTRACT

Objective

To describe the distribution and evolution over time of bone marrow edema (BME) on MRI of the sacroiliac joints (MRI-SIJ) in patients with recent-onset inflammatory back pain (IBP) suspected for axial spondyloarthritis (axSpA).

Methods

A 2-year follow-up study with annual MRI-SIJ was conducted in patients with IBP of duration ≤ 2 years. Each SIJ was divided into 4 quadrants and MRI scores were analyzed on a per patient and per SIJ-quadrant basis. The presence of BME in each SIJ-quadrant was recorded. Fulfilment of the Assessment of SpondyloArthritis International Society (ASAS) axSpA criteria was assessed at baseline and follow-up.

Results

At baseline, 68 patients (38% male; mean age 34.9±10.3 years) were included. BME was visible at baseline in 24 (35%) patients, all fulfilling the ASAS axSpA criteria. Twenty-three of these 24 patients had a follow-up MRI. Not taking into account the baseline MRI, 3 (13%) of these 23 patients would no longer fulfill the ASAS criteria during follow-up because of subsiding BME. Forty-four (65%) patients had a negative baseline MRI, of whom 39 have a follow-up MRI available. New BME at follow-up meant that 3 (8%) of these 39 patients now fulfilled the ASAS criteria. At follow-up, baseline BME lesions subsided completely in mean 47% of SIJ-quadrants (range 33%-71%), new BME lesions were detected in mean 8% of SIJ-quadrants (range 2%-11%).

Conclusion

BME shows a fluctuating course in patients with early IBP suspected for axSpA. This may have an impact on diagnosis making and the overall performance of the ASAS axSpA criteria.

INTRODUCTION

Inflammation of the sacroiliac joints (SIJ) detected on magnetic resonance imaging (MRI) is a common finding in axial spondyloarthritis (axSpA).[1] In daily practice, MRI is frequently used as a diagnostic tool in those patients suspected for axSpA but with normal pelvic radiographs. In addition to pelvic radiographs, MRI is incorporated in the imaging arm of the Assessment in SpondyloArthritis international Society (ASAS) classification criteria for axSpA.[2] Active inflammatory lesions that can be detected on MRI are bone marrow edema (BME), synovitis, capsulitis and enthesitis. Of these, only BME is considered mandatory for fulfilment of the ASAS/Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) working group definition of a positive MRI.[1]

To date, there is limited knowledge about the exact distribution, frequency of occurrence, and evolution over time of BME detected on MRI of the SIJ (MRI-SIJ), especially in patients with short duration of disease. Knowledge about the natural course of BME is important both for research and daily practice. MRI is frequently used as an "objective" measure of outcome to examine the efficacy of (biological) therapy in clinical trials. However, as an example, subsiding lesions may give the impression of efficacy of treatment, whereas this may in fact be the natural course. Also, fluctuating or subsiding BME may affect the sensitivity and specificity of MRI in detecting sacroiliitis, which may hamper the diagnostic process.

The aims of this study were first to describe the distribution and frequency of occurrence of BME, and second to assess the evolution over time of BME on MRI-SIJ in patients with early inflammatory back pain (IBP) followed for 2 years with annual MRI.

METHODS

Patients with IBP of less than 2 years duration were enrolled in the Early SpondyloArthritis Clinic (ESpAC) study. In this prospective cohort study, systematic clinical and radiological examinations were performed at baseline and after 1 and 2 years. A more detailed description of the study population has been reported previously.[3] For IBP to be present, patients had to fulfil at least 4 of the following 5 Calin criteria: onset of symptoms before the age of 40 years, duration of back pain more than 3 months, insidious onset, morning stiffness and improvement with exercise.[4] Patients who fulfilled only 3 out of 5 of the Calin criteria but reported night pain, were also included. Presence of extra-axial manifestations of SpA was preferred but not obligatory. Patients were not treated with biological therapy during the entire

study period. The use of non-steroidal anti-inflammatory drugs (NSAIDs) was allowed. Fulfilment of the ASAS axSpA criteria [2], modified New York (mNY) criteria [5], European Spondyloarthropathy Study Group (ESSG) criteria [6], and Amor criteria [7] was assessed. The study was approved by the ethics committee from the Maastricht University Medical Center. The study was conducted according to the principles of the Declaration of Helsinki. All patients gave written informed consent.

The MR images were scored using a combination of the Spondyloarthritis Research Consortium of Canada (SPARCC) method and a modified version of the Aarhus MRI scoring method.[8,9] In contrast to the original SPARCC scoring method, there was no maximum to the number of evaluated slices, but the number of slices within a patient was kept the same for all time points. MRIs were scored as series per patient with unknown time sequence by an experienced reader for the presence of bone marrow edema (BME) on the Short Tau Inversion Recovery (STIR) sequence. Each SIJ was divided into 4 quadrants and the presence of BME was recorded for each SIJ-quadrant. The ASAS/OMERACT definition was followed for fulfilment of a positive MRI for sacroiliitis.[1] An MRI-SIJ is considered positive for active sacroiliitis when at least 1 active lesion that is characteristic of sacroiliitis is present in at least 2 successive slices or when ≥ 2 of such lesions are detected in 1 slice.[1]

Anteroposterior pelvic radiographs of the SIJ were obtained and independently scored according to the mNY criteria in a random time order by 2 readers who were not involved in the MRI reading.[5] In case of disagreement, judgment of a third reader was conclusive.

Descriptive statistics were used to analyse the presence of BME detected on MRI on a per patient and per SIJ-quadrant basis, and the consequences of fluctuations in BME on MRI-SIJ for fulfilment of the ASAS axSpA criteria at baseline and at follow-up.[2] Generalized estimated equation (GEE) analysis was used to investigate if there was a time trend for the MRI BME lesion scores in individual patients. SPSS software version 18.0 was used for all statistical analyses.

RESULTS

Patient characteristics

Baseline MRI-SIJ and pelvic radiographs were available in all 68 patients included in the ESpAC study. Table 6.1 shows the baseline demographics and clinical characteristics of

all included patients. Sixty-two (91%) patients had at least 1 follow-up MRI and 44 (65%) patients completed both follow-up MRIs. Sixty-five (96%) patients had at least 1 follow-up pelvic radiograph and 48 (71%) patients completed both follow-up pelvic radiographs. Adjudication of pelvic radiographs was considered necessary in 10 (15%) of 68 patients because of disagreement between the first 2 readers.

Table 6.1   Baseline characteristics.

Characteristic	All patients (n=68)	Patients with complete MRI follow-up data (n=44)
Male sex	26 (38)	15 (34)
Mean age (SD) [years]	34.9 (10.3)	36.0 (11.7)
Median symptom duration (IQR) [months]	18 (12-24)	18 (12-24)
HLA-B27 positive	31 (46)	17 (39)
History of inflammatory bowel disease	10 (15)	7 (16)
History of anterior uveitis	10 (15)	8 (18)
History of psoriasis	16 (24)	12 (27)
History of peripheral arthritis	19 (28)	12 (27)
Family history of SpA	37 (54)	26 (59)
Mean CRP (SD) [mg/l]	9 (11)	9 (12)
Elevated CRP[a]	16 (24)	10 (22)
Mean ESR (SD) [mm]	13 (15)	13 (16)
Elevated ESR[a]	24 (36)	13 (30)
Presence of BME on MRI	24 (35)	14 (32)
Fulfillment ASAS axSpA criteria	40 (59)	22 (50)
Fulfillment mNY criteria	15 (22)	9 (20)
Fulfillment ESSG criteria	58 (85)	39 (89)
Fulfillment Amor criteria	48 (71)	31 (70)

The values are expressed as number (percentage) of patients unless stated otherwise. ESpAC=Early Spondyloarthritis Clinic; SpA=spondyloarthritis; IQR=interquartile range; SD=standard deviation; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; BME = bone marrow edema; MRI=magnetic resonance imaging; ESSG=European Spondyloarthropathy Study Group; ASAS=Assessment in SpondyloArthritis international Society; axSpA=axial spondyloarthritis; mNY criteria=modified New York criteria. [a] In 66 of 68 patients baseline CRP and ESR measurements were available. ESR normal range: ≤7 mm for males; ≤12 mm for females. CRP cut-off value, normal range: <10 mg/l.

Sixty-six (97%) patients fulfilled the Calin criteria at baseline. The remaining 2 (3%) patients fulfilled 3 of the 5 Calin criteria and reported 'night pain'. At baseline, 40 (59%) out of 68 patients fulfilled the ASAS axSpA criteria. Twenty-two patients fulfilled both the imaging and clinical arm of the ASAS axSpA criteria; 9 patients only fulfilled the imaging arm and 9 patients only fulfilled the clinical arm. At baseline, 58 (85%) patients fulfilled the ESSG criteria, 48 (71%) patients the Amor criteria, and 15 (22%) patients the mNY criteria. None of the patients met the mNY criteria for the first time at follow-up visits.

The estimated marginal (EM) mean score for BME lesions on MRI was 6.8 at baseline; 4.6 at 1-year follow-up; 5.0 at 2-years follow-up (p=0.21).

Baseline distribution and frequency of occurrence of BME

Per patient. In total, 24 (35%) patients had signs of BME on MRI-SIJ at baseline.
Per SIJ-quadrant. Table 2 shows that in all four quadrants of the SIJ, BME could be detected on MRI. The right caudal iliac quadrant of the SIJ was slightly more affected than other SIJ-quadrants. BME was detected in the right caudal iliac quadrant in 16 (24%) out of 68 patients at baseline. In the remaining SIJ-quadrants, BME was detected in 8 to 13 (12%-19%) out of 68 patients at baseline.

Evolution of BME in the SIJs at follow-up

Per patient. Figure 6.1 shows the fulfilment of the ASAS axSpA criteria at baseline and at the last follow-up in 62 patients with at least one follow-up MRI and pelvic radiograph available. In 23 of 24 patients with BME at baseline, follow-up MRI was available. BME subsided completely in 7 (30%) of these 23 patients at the last available follow-up MRI. Four of these 7 patients fulfilled the mNY criteria at baseline and follow-up, and would therefore remain in the imaging arm of the ASAS axSpA criteria at the last available follow-up examination. The other 3 patients did not fulfil the mNY criteria, were HLA-B27 negative, and because BME on MRI also completely subsided, these patients would - without prior knowledge of the baseline MRI - not longer fulfil the ASAS axSpA criteria at the last available follow-up examination. All these 3 patients, however, still fulfilled the ESSG and Amor classification criteria because of various combinations of other SpA features such as psoriasis, anterior uveitis, peripheral arthritis and/or a positive family history for SpA, besides the presence of IBP.
At least one follow-up MRI was available in 39 of the 44 patients without BME on MRI at baseline. In 6 (15%) of these patients, BME was detected on at least 1 follow-up MRI. Three of these patients already fulfilled the imaging and clinical arm of the ASAS axSpA criteria, because of radiographic sacroiliitis at baseline and a positive HLA-B27 status. The other 3 patients newly fulfilled the ASAS axSpA criteria at follow-up (Figure 6.1). However, 2 of these 3 patients already fulfilled the ESSG and Amor criteria at baseline.
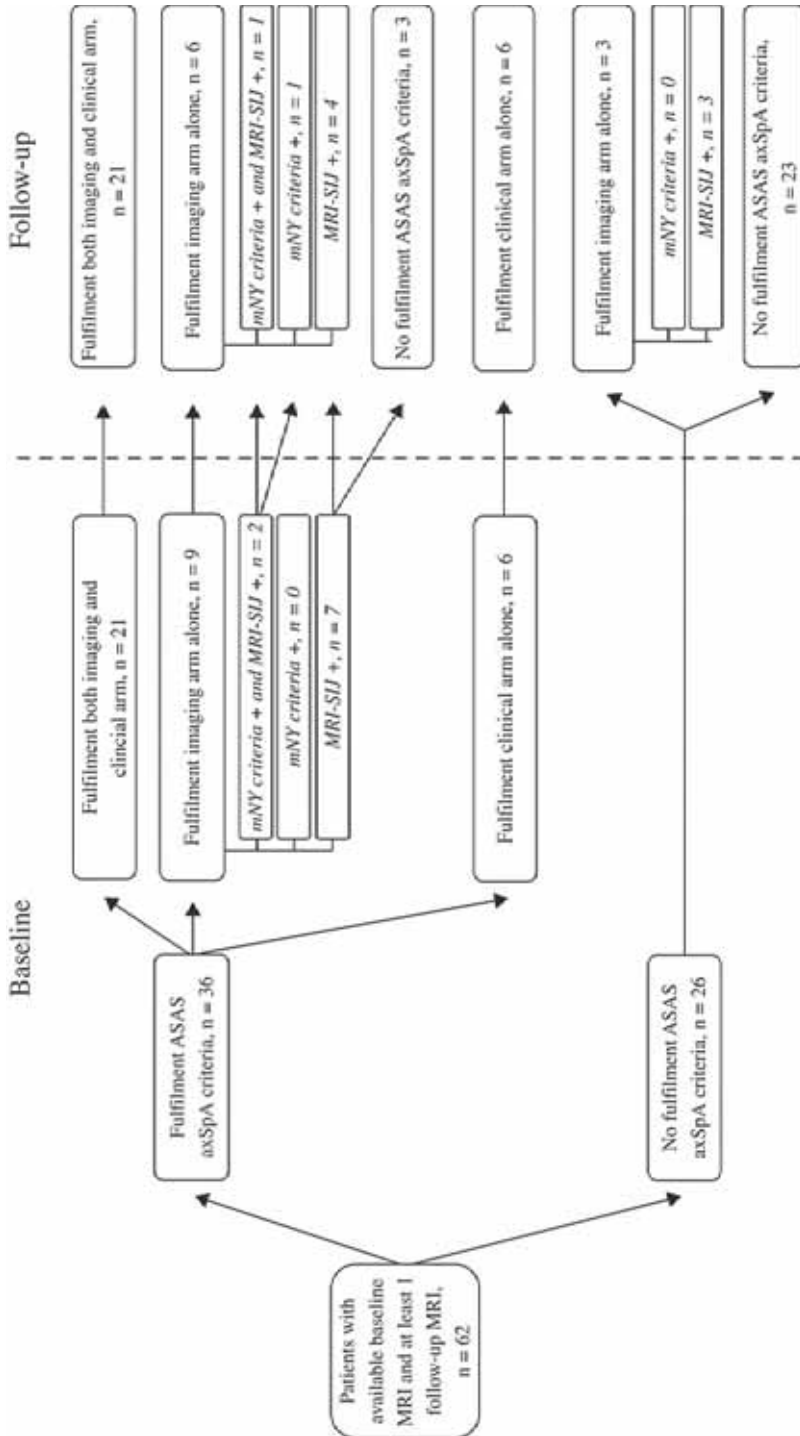
Figure 6.1   Fulfilment of ASAS axSpA criteria at baseline and follow-up.

Per SIJ-quadrant. Table 6.2 shows that BME remained present in 53% of the SIJ-quadrants (range 29% to 69%) at follow-up and was persistent most frequently in the right and left caudal iliac quadrants (table 2). BME subsided in 47% of the SI-quadrants (range 33% to 71%) and was newly detected at the last follow-up moment in approximately 8% of the SI-quadrants (range 2% to 11%). Most of these lesions were detected in the right and left caudal sacral quadrants (Table 6.2).

Table 6.2   Presence of BME on MRI per SIJ quadrant at baseline and follow-up.

SIJ quadrant	Baseline	Last follow-up MRI*	
	Presence of BME (yes vs no)	Presence of BME	Absence BME
Right proximal iliac quadrant	Yes (n = 10)	3 (30)	7 (70)
	No (n = 52)	1 (2)	51 (98)
Right proximal sacral quadrant	Yes (n = 8)	5 (62)	3 (38)
	No (n = 54)	3 (6)	51 (94)
Right caudal iliac quadrant	Yes (n = 16)	9 (56)	7 (44)
	No (n = 46)	5 (11)	41 (89)
Right caudal sacral quadrant	Yes (n = 8)	5 (62)	3 (38)
	No (n = 54)	6 (11)	48 (89)
Left proximal iliac quadrant	Yes (n = 11)	6 (55)	5 (45)
	No (n = 51)	3 (6)	48 (94)
Left proximal sacral quadrant	Yes (n = 14)	4 (29)	10 (71)
	No (n = 48)	3 (6)	45 (94)
Left caudal iliac quadrant	Yes (n = 13)	9 (69)	4 (31)
	No (n = 49)	4 (8)	45 (92)
Left caudal sacral quadrant	Yes (n = 9)	6 (67)	3 (33)
	No (n = 53)	6 (11)	47 (89)

n=62 patients.* Follow-up at 1 or 2 years, depending on last MRI. The values are expressed as number (percentage) of patients unless stated otherwise. SIJ=sacroiliac joint; BME=bone marrow edema, MRI=magnetic resonance imaging.

DISCUSSION

The present study, in a cohort of patients with early IBP suspected for axSpA, demonstrated that BME subsided completely in approximately half of the SI-quadrants during follow-up and in 30% of the patients with a positive MRI-SIJ at baseline. On average, in less than 10% of the SI-quadrants, BME was newly detected at some point in time during follow-up. Not taking into account the baseline MRI, 13% of the patients would not fulfil the ASAS axSpA criteria at a follow-up moment, as a consequence of fluctuations of BME on MRI. Another 8% of patients newly fulfilled the ASAS axSpA criteria at follow-up.

In daily practice, MRI-SIJ is ordered when a diagnosis of non-radiographic (nr)-axSpA is suspected on clinical grounds and conventional pelvic radiographs are normal or inconclusive. In this context, subsiding or fluctuating BME may affect the sensitivity of MRI in detecting sacroiliitis and subsequently could cause a delay in the diagnosis of axSpA. In addition, for clinical trials it is important to be aware of the fluctuating course of BME on MRI, which may in fact be the natural course instead of any treatment effect. This is illustrated by a study of Barkham et al. that evaluated the efficacy of infliximab on inflammation detected on MRI in HLA-B27 positive patients with recent-onset IBP.[10] In the treatment group, 62.7% of the BME lesions detected on MRI-SIJ at baseline had completely subsided at week 16. Remarkably, in the placebo group, 29.4% of BME lesions detected at baseline had also completely subsided at week 16.[10] In a study by Marzo-Ortega et al., the frequency of BME lesions on MRI-SIJ was evaluated over a 1-year follow-up period in patients with early IBP.[11] Of the 34 patients with a baseline and follow-up MRI, the majority (73.5%) of the patients still had BME on MRI-SIJ at 1-year follow-up, but the overall disease activity score, defined by the extent of BME, had decreased.[11] These findings are consistent with the results of our present study. However, in contrast to the study of Barkham and Marzo-Ortega et al., our study not only evaluated the presence of BME per SIJ-quadrant over a 2-year follow-up period, but also incorporated its exact localisation. In a previous study with data from the ESpAC study, we have demonstrated that both HLA-B27 status (odds ratio (OR) 8.1, 95% confidence interval (CI) 2.3 - 28.3, p<0.001) and MRI status at baseline (OR 22.0, 95% CI 6.1 - 79.6, p<0.001) were strongly and independently associated with a positive MRI-SIJ over time.[12]

Some MRI studies reported that the caudal parts of the SIJ are more frequently affected than the proximal parts in patients with nr-axSpA and ankylosing spondylitis.[13,14] These findings contribute to the notion that inflammation is merely present in the lower synovial dorsocaudal part of the SIJ. This assumption is supported by histologic studies.[15,16] In our study we found that the percentage of affected SI-quadrants is rather equally distributed, although there is a slight preference for the caudal iliac SI-quadrants, observed both at baseline and at follow-up. This corresponds with a study by Althoff et al., in which no difference in the amount of BME between SI-quadrants was detected in patients with axSpA with a symptom duration of ≤ 5 years.[17]

It is known that approximately one third of the patients with axSpA according to experts do not fulfil the imaging arm of the ASAS axSpA criteria.[2,18] Several factors might contribute to this restricted sensitivity of the imaging arm. First, MRI of the spine

is not included in the imaging arm of the ASAS axSpA criteria. However, up to 70% of the patients with axSpA may have spinal inflammation, even in the absence of active lesions on MRI of the SIJs.[18] Second, structural changes (i.e. erosions) on MRI are not considered for the definition of a positive MRI-SIJ.[2] Recent data, however, suggest that assessment of erosions on MRI-SIJ may enhance the diagnostic utility of MRI in early axSpA.[19] Finally, although MRI might be the most sensitive imaging modality for detection of SIJ inflammation, not all inflammation is captured by MRI. A study has shown that in biopsies taken from the SIJ clear inflammation on histology was found, whereas this was not visible on the concurrently performed MRI.[20]

There are several limitations of this study that need to be addressed. First, the MR images were scored by one reader only for reasons of experienced reader availability, which may in theory influence the reliability of the data. However, this reader (a musculoskeletal radiologist, and member of the ASAS/OMERACT MRI working group) was highly experienced, the MRIs were scored with unknown time sequence, and blinding was preserved for clinical and laboratory findings.[1] The intra-observer agreement of our reader was very good in another study that evaluated BME on MRI-SIJs in patients with early axial spondyloarthritis, using the Danish (Aarhus) scoring method (weighted kappa value 0.96 (95%-confidence interval: 0.92-0.98)).[21] Further, a high inter-observer agreement among experienced readers for scoring of MRI-SIJs has been reported in previous studies.[8,22] These arguments reasonably justify an unbiased acquisition of MRI-scores.

Second, the interval between 2 MRI examinations was 1 year. Serial MRI examinations at for instance 3- or 6 months follow-up could provide more information about short term fluctuations of BME on MRI-SIJ. Third, the MRI scoring method used in the present study is a combination of the SPARCC and Aarhus grading method which is not as such formally validated.[8,9] The disadvantage of the SPARCC grading method is that a maximum of 6 slices are scored. With our modification an unlimited number of slices could be evaluated, while ensuring that the same (number of) slices were scored per patient over time. The advantage of this method is that all qualitatively optimal slices are scored, thereby maximising the chance of detecting active lesions. Furthermore, a general concern when scoring MRI-SIJ is the possibility of misalignment between two successive MRI examinations, which may eventually result in measurement error. We have ensured that the scoring starts and ends at the same anatomical level, so that the risk of misalignment is minimized.

Fourth, in ESpAC, the use of NSAIDs was allowed. Detailed information about the use of NSAIDs per patient is not available, so that the effects of NSAIDs on MRI-scores could

not be studied. It is therefore unclear whether continuous or on-demand treatment with NSAIDs may ultimately have led to subsiding inflammation detected on MRI. Results from the second part of the Infliximab as First Line Therapy in Patients with Early Active Spondyloarthritis Trial (INFAST) suggest that it may not be different. In this study, patients who continued naproxen were compared with patients who discontinued therapy. At the end of the follow-up period, complete absence of lesions on MRI-SIJ was found in similar numbers of patients in the naproxen and no-treatment groups (7.5% vs. 10.0%).[23] Fifth, ESpAC patients were not given a clinical diagnosis of axSpA. However, 40 (59%) patients fulfilled the ASAS axSpA criteria at baseline. The overall sensitivity and specificity of the ASAS axSpA criteria is 82.9% and 84.4%, respectively. The diagnostic performance of the ASAS axSpA criteria is good, with an overall post-test probability of 89%.[2] Considering the characteristics of the ASAS axSpA criteria and the caveats related to the diagnostic utility of MRI in axSpA, most patients included in the ESpAC that fulfil the ASAS axSpA criteria, will probably also have or develop a clinical diagnosis of axSpA. Unfortunately, patients were not actively followed after the study was terminated. Finally, ESpAC is a relatively small cohort including patients referred by (related) medical specialties (i.e. dermatology, gastroenterology) and relatives of members of the local ankylosing spondylitis society. This recruitment strategy may therefore explain the high proportion of patients fulfilling at least one of the classification criteria for SpA. Furthermore, the proportion of male patients in ESpAC is relatively low (38%) and the proportion of patients with a negative HLA-B27 status is relatively high (54%). However, these percentages are in accordance with other cohorts that included patients with early IBP suspected for axSpA (24,25). In the SPondyloArthritis Caught Early (SPACE)-cohort, for example, the proportion of male patients among axSpA patients is 48%, and the proportion of patients with a negative HLA-B7 status is 20%.[24] In the Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR)-cohort these proportions are 46% and 43%, respectively.[25]

In conclusion, in this cohort of 68 patients presenting with recent-onset IBP, BME on MRI was equally distributed throughout the SIJs, with a slight preference for the caudal iliac quadrants. Nearly half of the BME lesions subsided during follow-up. These changes in MRI status are important and should be taken into account in clinical practice when evaluating patients with IBP suspected for axSpA and may have an impact on the overall performance of the ASAS axSpA criteria.

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PART III

Timely identification of spondyloarthritis in primary care

CHAPTER 7

General practitioners' perceptions of their
ability to identify and refer patients with suspected
axial spondyloarthritis: a qualitative study

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ABSTRACT

Objectives

To explore the knowledge, beliefs and experiences of general practitioners (GPs) about inflammatory back pain (IBP) and axial spondyloarthritis (axSpA) and potential barriers for referral of patients suspected for axSpA.

Methods

A qualitative study involving semi-structured interviews with GPs was conducted. Transcripts of the interviews were independently read and annotated by 2 readers. Illustrative themes were identified and a coding system to categorize the data was developed.

Results

Ten GPs (all men; mean age 49 years) were interviewed. All could adequately describe "classic" ankylosing spondylitis (AS) and mentioned chronic back pain and/or stiffness as key features. All GPs thought that AS is almost exclusively diagnosed in men. Six GPs knew that there is a difference between mechanical back pain (MBP) and IBP, but could recall only a limited number of parameters indicative of IBP, such as: awakening night pain (4 GPs), insidious onset of back pain (1 GP), improvement with movement (1 GP) and (morning) stiffness (2 GPs). Two GPs mentioned peripheral arthritis as other SpA features, none mentioned dactylitis or enthesitis. GPs' awareness of associated extra-articular manifestations was low. Most GPs expressed that (practical) referral parameters would be useful.

Conclusion

GPs are aware of "classic", but long-term features of axSpA. Knowledge about the disease spectrum and early detection is, however, limited. Addressing these issues in training programmes may improve better recognition of axSpA in primary care. This may ultimately contribute to earlier referral, diagnosis, and initiation of effective treatment in patients with axSpA.

INTRODUCTION

Spondyloarthritis (SpA) comprises a group of interrelated inflammatory disorders with overlapping clinical features and shared genetic markers. The estimated prevalence of SpA in Caucasian populations is approximately 1%, similarly to that of rheumatoid arthritis.[1] Symptom patterns and physical signs of SpA can be divided into predominantly axial involvement, with inflammatory back pain (IBP) as the most important clinical feature and predominantly peripheral involvement including peripheral arthritis, dactylitis and enthesitis.[2] Extra-articular manifestations related to axial and peripheral SpA include psoriasis, anterior uveitis and inflammatory bowel disease.

Axial SpA (axSpA) comprises a disease continuum, including both non-radiographic axSpA and ankylosing spondylitis (AS).[3] Patients with non-radiographic axSpA have similar clinical characteristics, disease activity and response to treatment as patients with established AS, emphasizing the need for early and correct diagnosis.[4] However, the diagnosis of axSpA is often delayed due to the insidious onset, the heterogeneous clinical picture, and a limited knowledge about the manifestations belonging to axSpA by general practitioners (GPs) or other referring physicians.[5] Offering tools for referral may be helpful in improving early diagnosis. Several initiatives have been performed to study the effect of referral strategies in primary care. The objectives of these referral programs were to identify patients with possible axSpA early, make a correct diagnosis, and to provide the best possible care as early as possible.[6] However, limited knowledge of manifestations belonging to axSpA might prevent successful implementation of these referral strategies in the primary care setting.

The aim of the present qualitative study is to explore by using semi-structured interviews the knowledge, beliefs and experiences of GPs about IBP and axSpA, and the potential barriers for referral of patients suspected for axSpA.

MATERIALS AND METHODS

Study design and participants

For this qualitative study, GPs, acquainted with the interviewers, without known specific interest or knowledge of musculoskeletal diseases and with various years of experience, were invited for a semi-structured interview. A semi-structured interview is a technique to collect qualitative data about the topic of interest by combining open

questions with the option to further explore particular answers.[7] The duration of one interview was about one hour. The interviews took place in 2012 and all invited GPs were working in the region of Limburg, The Netherlands. The study was approved by the ethics committee from the Maastricht University Medical Center. All participants provided written informed consent and thereby agreed to present the collected data and quotes in anonymized form.

Data collection

An interview guide that consisted of both open- and closed-ended questions was developed to secure uniform data quality and comparability. A pilot interview was conducted to ensure that the questions were clear and addressed all important topics. Each interview was audio-taped and afterwards fully transcribed. Each transcript was offered to the matching GP to review for validation.

The topics addressed in the interview included:

- General questions: age, working experience in years as a GP, specific medical interests.
- Approach to patients presenting with chronic back pain, knowledge about symptoms indicative of mechanical back pain (MBP) or IBP, management of back pain, motivating factors to refer a patient to a rheumatologist.
- Perceptions and knowledge about axSpA, including non-radiographic axSpA and AS. Awareness about diagnostic delay, knowledge of extra-articular manifestations of axSpA.
- Approach to patients already diagnosed with axSpA, disease management.
- Awareness about treatment options and opinion of GPs about the current standards of care for patients with axSpA.

Data analysis

The transcripts were independently analyzed by 2 readers. All transcripts were repeatedly read and annotated. A coding system based on the grounded theory approach was developed by defining categories and developing a taxonomy of the data.[7] The readers met regularly to discuss coding and interpretation of data. In case of disagreement, consensus was reached between the two readers after re-reading the specific passage of the transcript. While analyzing the data, illustrative quotes made by GPs were collected.

RESULTS

Participant characteristics

Ten of 16 invited GPs agreed to participate and were interviewed. All included GPs were men and the mean age was 49 years (range 37-58 years; standard deviation (SD) 6.4 years). The mean number of years of experience as a GP was 20 years (range 10-29 years; SD 6.0 years). Three GPs had a specific interest in musculoskeletal disorders. When GPs were asked to estimate the mean number of patients with AS registered in their practice, the range of answers was between 0 and "more than 10" patients (without further specification).

When analyzing the data, a number of themes and patterns were identified across the interviews. These themes and patterns are described below and exemplified in quotes (Table 7.1).

Ability to differentiate MBP from IBP

Four GPs were not familiar with the terms MBP and IBP (quote 1). Six GPs knew that there is a difference between MBP and IBP, but these GPs could recall only a limited number of typical parameters to differentiate MBP from IBP. Four of these 6 GPs mentioned awakening night pain as a typical feature of IBP and considered it a relevant symptom that needed attention (quote 2). Two GPs also mentioned insidious onset of back pain and improvement of back pain with movement as typical features of IBP. Morning stiffness was mentioned by 2 GPs. Seven GPs mentioned stiffness of the back as typical for AS but did not elaborate on the course of stiffness during the day.

Knowledge about the terms "classic" AS and axSpA and awareness about diagnostic delay

All GPs were familiar with the term AS and mentioned back pain and/or stiffness of the back as prominent features of AS. Three GPs also considered (severe) kyphosis as an important feature of AS. None of the GPs could give an adequate description of the term axSpA.

When asked about the age at onset of first symptoms, all GPs answered that symptoms first appear in early adulthood. All GPs thought that AS is almost exclusively diagnosed in men. Two GPs thought that the delay in diagnosis was less than one year. The remainder of GPs answered that the delay in diagnosis was up to several years, without

further specification. A few GPs commented that this is probably due to a patients' and doctors' delay (quote 3).

Table 7.1   Illustrative quotes made by general practitioners.

Quote*	
1	"I really do not know the difference between mechanical and inflammatory back pain. I do not see a lot of patients with a history of inflammatory back pain. (...)When a patient has back pain for a long period of time, I usually refer them to a rheumatologist. But it certainly would not surprise me if there are several undiagnosed patients with AS in my practice."
2	" If a patient presents with a history of back pain, I ask if he or she can still perform household chores and work-related duties. I ask if the pain is continuous or not and if there is night pain or pain when waking-up. (...) When there are signs of awakening night pain, I tend to look more seriously at the symptoms. During the physical examination I check the range of motion and the stiffness of the back."
3	"I think that the time between first complaints and diagnosis of AS varies. There is a patient delay, but also a doctor delay. When there are family members with AS, you tend to look more seriously and will probably refer this patient to a rheumatologist at an early stage. But if this is not the case... How long it will take before a GP will refer a patient with chronic back pain? I do not know, months to years maybe?"
4	"Whether I can mention other symptoms associated with AS? Eye complaints probably, but I do not think it is very typical. Conjunctivitis maybe? Psoriasis also, but that is not really inflammation, but it belongs to another group of auto-immune disorders. It is not really clear to me."
5	"If the HLA-B27 test is positive or negative, it will not solve the diagnostic problem. When the test is positive, you think, "OK, maybe...", but what to do when the test is negative? In case of a negative test result, that does not mean that the patient does not have AS. I still have to refer the patient to the rheumatologist."
6	"When a patient presents with a history of low back pain and there are no abnormalities on the X-ray, I will refer this patient to the neurologist. It is very unlikely that I refer this patient to the rheumatologist. Provided that low back pain is the only symptom."
7	"I want to know more about how to recognize AS. Are there specific tools or diagnostic tests you can use as a GP to make a diagnosis of AS more or less likely? If so, I will perform those tests and consult a rheumatologist or I will refer the patient. I also want to know more about how you treat patients with AS. What are the results?"
8	"I think that I miss the diagnosis frequently. Yes, too many times. The reason for this? Probably due to lack of knowledge."

* Quotes were translated from Dutch.

Knowledge about associated clinical manifestations of axSpA

Most GPs could describe only a limited number of clinical features belonging to axSpA. Two GPs considered peripheral arthritis as belonging to the spectrum of axSpA; dactylitis and enthesitis were not mentioned at all. When asked about extra-articular manifestations of patients with axSpA, 5 GPs mentioned anterior uveitis and 1 GP

mentioned "eye complaints" (quote 4). Inflammatory bowel disease was mentioned by 2 GPs and psoriasis by 3 GPs.

Use of diagnostic tests in the primary care setting

None of the GPs would order a Human Leukocyte Antigen (HLA)-B27 test when a patient presents with chronic back pain. A few GPs commented that this test should only be ordered by the rheumatologist (quote 5). Most GPs specifically commented that they would only order a conventional radiograph in case of chronic back pain. One GP mentioned that a normal pelvic radiograph in a patient presenting with back pain, would be a motivating factor to refer this patient to a neurologist and not a rheumatologist (quote 6).

Perceptions about management of axSpA

A decrease in pain and stiffness of the back and maintaining function were judged as the most important treatment goals by the majority of the GPs. The use of non-steroidal-anti-inflammatory drugs (NSAIDs) were considered an adequate treatment option by all GPs. Most GPs also mentioned physical therapy or that the patient should do home-based exercises. Five GPs indicated that anti-TNF-alpha therapy can be prescribed to patients with axSpA. Four GPs were aware of the fact that an increased risk of (serious) infections is an important side effect of anti-TNF-alpha therapy.

Preferences for educational programmes about axSpA

Most GPs expressed that (practical) referral parameters to decrease the delay in diagnosis would be useful in clinical practice (quote 7). Most GPs also wanted to know more about the treatment options, including anti-TNF-alpha therapy. One GP revealed that he recently visited an educational training that focused on axSpA. At the end of this training he realized that there were probably several undiagnosed patients in his practice (quote 8).

DISCUSSION

The present study demonstrated that there are several inconsistencies in the perceptions of GPs about diagnosis and management of axSpA, including AS. Most GPs could provide an adequate description about "classic" AS and were aware of the fact

that there is a substantial delay in diagnosis. GPs also knew that there is a difference between MBP and IBP, but were unable to explain how to differentiate MBP from IBP. Knowledge about the disease spectrum of axSpA and associated extra-articular manifestations was limited. All GPs were aware of the benefits of physiotherapy and NSAIDs, and half of the GPs knew that anti-TNF-alpha therapy can be prescribed in patients with axSpA.

Chronic back pain is a common symptom in the general population and it is estimated that in 5% of these cases axSpA is the underlying disease.[8] In approximately 75% of the patients with axSpA, the chronic back pain has an inflammatory character. Several criteria sets to define IBP have been proposed, consisting of several parameters in order to differentiate IBP from MBP. Single parameters were insufficiently predictive in defining IBP, because they are also frequently present in patients without an inflammatory cause of their back pain.[9] Overall, the IBP criteria sets have a comparable sensitivity and specificity of about 75-80%.[9-11] IBP has been tested as a single referral parameter and as part of a composite referral strategy in several studies.[5,12-14] When patients were referred by GPs because of IBP alone, axSpA was diagnosed in 16-33% of the referred patients.[5,12-13] However, when patients were referred because of IBP in combination with other parameters such as HLA-B27 or sacroiliitis on imaging, axSpA was diagnosed in 35-56% of the referred patients.[5,12,14]

Knowledge of important features associated with axSpA is essential before a referral strategy can successfully be implemented in the primary care setting. Six GPs in our study could recall only a few items indicative of IBP and 4 GPs were not familiar with the terms MBP and IBP. This was also observed in a study by Jois et al.[15] Only 5% of GPs in their study could identify all parameters indicative of IBP when a list of pre-specified response choices was presented to them. Furthermore, recent studies have shown that the degree of agreement between referring physicians (including GPs) and rheumatologists when evaluating IBP in patients with suspected axSpA is poor (kappa values between 0.04 – 0.20).[5,16] Educating GPs about the full range of parameters indicative of IBP therefore seems the first step before IBP can successfully be used in a referral tool. The term "axial spondyloarthritis" will also increasingly be used in correspondence from rheumatologists to GPs. It is therefore important to make GPs also familiar with this new terminology.

In the present study, GPs could recall only a limited number of extra-articular manifestations associated with axSpA. In a some cases, GPs mentioned "eye complaints" or "skin problems". Dactylitis and enthesitis were not at all mentioned by

the GPs in our study. Jois et al. also investigated the recognition of extra-articular manifestations of SpA by GPs.[15] Psoriasis, inflammatory bowel disease and uveitis were recognized as an extra-articular manifestation by respectively 96%, 68% and 60% of GPs, which is a higher proportion than in our small-sized study.[15] However, in our study open-ended questions were used, which probably resulted in lower response rates than the survey used in the study of Jois et al. All GPs in the present study also indicated that AS is almost exclusively diagnosed in men. Several recent studies that included patients with undifferentiated and non-radiographic axSpA, however, demonstrated that the gender ratio is more equally distributed.[17-19] Male gender has however been found to be a risk factor for developing radiographic sacroiliitis.[20,21] Furthermore, patients with radiographic sacroiliitis have in general higher inflammatory markers than patients with non-radiographic axSpA.[4,22] Increasing awareness among GPs that axSpA is equally present in females and males, and making them aware of the "SpA concept", which includes axial, but also peripheral and extra-articular manifestations, will likely facilitate referral and timely diagnosis.

Half of GPs in the present study were aware that the therapeutic armamentarium in patients with axSpA is broadened with the introduction of anti-TNF-alpha therapy. When GPs were asked about the side-effects of anti-TNF-alpha therapy, 6 GPs were not aware of the higher risk of (serious) infections. Collaboration and co-management together with the rheumatologist is essential in managing patients with axSpA. Education about (the side-effects of) anti-TNF therapy is therefore an important step to maintain and improve the general health status of a patient with axSpA.

In general, the level of knowledge about axSpA was low. None of the GPs could provide a specific reason for this lack of knowledge. Possible explanations are relatively low attention to this topic in medical school or at continuous medical education, and the large emphasis on a non-specific cause of chronic back pain.[23]

There are limitations in this present study that need to be addressed. The design of the study is qualitative and the number of GPs included is small. Furthermore, only male and experienced GPs were included in this study. Several female GPs were asked, but they unfortunately declined to participate. Logistically, it was extremely difficult to include recently qualified GPs, because in the Netherlands almost none of them have own practices. We cannot rule out that selection bias or knowledge bias has occurred. This may limit reproducibility of results and the ability to generalize them to a wider population. However, the main goal of this study was not to extrapolate the current findings to all GPs, but to explore the level of knowledge and awareness that probably

need attention in future educational programmes. Furthermore, theoretical saturation was reached with this number of GPs.

In conclusion, most GPs were familiar with "classic" but long-term features of axSpA. Knowledge about parameters indicative of IBP and awareness about the full range of SpA features, including the associated extra-articular manifestations, was limited. The disease spectrum and management of axSpA have substantially changed over the last few years. Educating GPs about the leading presenting symptoms of axSpA and providing information about extra-articular disease manifestations and management of axSpA, will play a pivotal role in the successful referral of patients with suspected axSpA by GPs. This may ultimately contribute to earlier initiation of effective treatment and the improvement of quality of life.

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CHAPTER 8

Education improves referral of patients suspected of having spondyloarthritis by general practitioners. A study with unannounced standardized patients in daily practice

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ABSTRACT

Objectives

To evaluate the practice performance of general practitioners (GPs) and GP residents in recognising and referring patients suspected for having axial or peripheral spondyloarthritis (SpA), and to investigate the influence of education on this performance.

Methods

GP (residents) were visited in 2 rounds by standardised patients (SPs) simulating axial SpA, peripheral SpA or carpal tunnel syndrome (CTS) with in between an educational intervention on SpA for part of the participants. Participants were unaware of the nature of the medical problem and study purpose. CTS was included as diversionary tactic. The primary outcome was ≥40% improvement in (considering) referral of the SPs with SpA to the rheumatologist after education. Secondary outcomes included ordering additional diagnostic tests, correct recognition of SpA and identification of variables contributing to this.

Results

Sixty-eight participants (30 GPs and 38 GP residents) were included, of which 19 received education. The primary outcome was met. A significantly higher proportion of GP (residents) from the intervention group referred patients to the rheumatologist compared with the control group after education (change scores, axial SpA +71% vs. +15% ($p<0.01$); peripheral SpA +48% vs. 0% ($p<0.001$)). Participants who received education, more frequently correctly recognised SpA compared with controls (change scores, axial SpA +50% vs. -5% ($p<0.001$); peripheral SpA +21% vs. 0% ($p=0.01$).

Conclusions

Recognition and referral of patients suspected for having SpA by GP (residents) is low, but targeted education markedly improved this. This supports the development of educational initiatives to improve recognition of SpA and hence referral to a rheumatologist.

INTRODUCTION

Musculoskeletal complaints account for 20% of all consultations in primary care.[1-3] The challenge for general practitioners (GPs) is to filter patients with a high suspicion of an inflammatory rheumatic disorder.[4] Insufficient knowledge might result in a diagnostic delay, which subsequently may have a negative impact on physical functioning, social participation and quality of life in an individual patient.[5,6] Among all rheumatic diseases, spondyloarthritis (SpA) has the longest diagnostic delay, which may be up to 10 years or even longer.[7,8]

Many SpA patients are not adequately recognised, as illustrated by a study in primary care where 24% of the patients with chronic low back pain that started before the age of 45 years, were classified as having axial SpA after careful evaluation.[9] It is important to obtain an early diagnosis in order to tailor treatment to the individual needs of a patient and to prevent a debilitating disease course.[10] A short disease duration before initiation of treatment is also a good predictor of achieving a major clinical response on treatment.[11-13]

In order to improve timely diagnosis, several referral tools, which include characteristic features of SpA, have been proposed for axial SpA.[14-18] Application of a referral tool increases the probability of a disease in referred patients from 5% to 33-45%.[18] However, for successful implementation of such a tool, knowledge about SpA in primary care is essential.[19,20] A qualitative study involving GPs showed that GPs were aware of "classic", but long-term features of axial SpA, i.e. hyperkyphosis and a bamboo spine. Knowledge about the entire disease spectrum, including early disease, extra-articular manifestations and other characteristic SpA features, was limited.[21]

We hypothesised that education with special focus on SpA might improve the recognition of SpA features and early referral of patients suspected for having SpA. The objectives of this study were to evaluate (1) the current practice performance of GPs and GP residents in recognizing and (considering) referral of patients suspected for having axial or peripheral SpA, and (2) to assess the influence of education on this performance, by using unannounced standardised patients (SPs) who visit GP (residents) in their own practices.

METHODS

Study design and participants

This study is a prospective controlled multicenter educational intervention study in primary care. GP residents and their supervising GPs were recruited through the department of General Practice from the Maastricht University Medical Centre (MUMC). Every trimester, 1-2 group(s) of 10-12 GP residents enter the final year of their residency. Once a week, they meet at the MUMC for training. We used this structure for providing an educational programme, 'the intervention', to half of the groups. Each group was alternately assigned to either the intervention group or the control group. This allocation strategy was only applied to the GP residents. The groups did not have direct contact hours with each other. A similar training structure was not available for GPs. It was logistically not possible to organize an extra training conference for GPs without revealing the topic of interest in advance. Therefore, despite GPs may be supervising a resident who received intervention, we decided to assign all GPs to the control group.

The ethics committee of the academic hospital Maastricht considered this study as "evaluation and improvement of daily clinical practice". No further approval was required. The GP (residents) were informed about SPs visiting their practice for "evaluation of using SPs in daily practice and education", and were asked to sign informed consent. No further specification was provided on the purpose of the study and the nature of the medical problems, nor were they informed that the education was related to the study with unannounced SPs.

The SP encounters took place 3 months before and 3 months after the intervention.

The study started in September 2012, and was ended prematurely in May 2014.

Standardised patients

SPs, recruited from a pool of SPs working at the Maastricht University medical school and among clerkships, had to meet the following criteria: stable health, ability to play the role and to fill out the case-specific checklists, no confounding physical symptoms and sufficient time available for the visits.[22]

All SPs were trained to simulate one case. Two 2-hour training sessions were organised and guided by several GPs and rheumatologists, during which the SPs were trained in playing their role, and how to behave during the physical examination, in a valid and reliable way. GPs and a rheumatologist not involved in the development of the cases

judged whether the SP simulated realistically. Close attention was paid on completion of the checklist to secure uniform data quality and comparability. Discrepancies in checklist rating scores were discussed.[22] Based on good reproducibility demonstrated in previous studies, and after this thorough training, we assumed good representation of the cases by the SPs.[23-25]

All participants faced two cases of axial SpA, two cases of peripheral SpA, and one case of carpal tunnel syndrome (CTS). Figure 8.1 shows an example of a predefined schedule for two participants. The CTS case was included as a diversionary tactic, preventing premature identification of the objectives of the study, but was also considered as 'common knowledge'. Recognition of CTS by the far majority of participants was expected and therefore only simulated during round 1. Each SpA case was simulated by a male and a female SP, in random order, according to a predefined schedule (Figure 8.1 shows an example). A short description of the included cases is provided in Box 8.1. The SPs were unaware which participants received education. The SPs received a small allowance for every visit.

	Round 1 (baseline)	Education (3 months)	Round 2 (6 months)
Participant 1	Axial SpA, male	Yes	Axial SpA, female
	Dactylitis (toe), female		Dactylitis (finger), male
	CTS, male		
Participant 2	Axial SpA, female	No	Axial SpA, male
	Dactylitis (finger), female		Dactylitis (toe), male
	CTS, female		
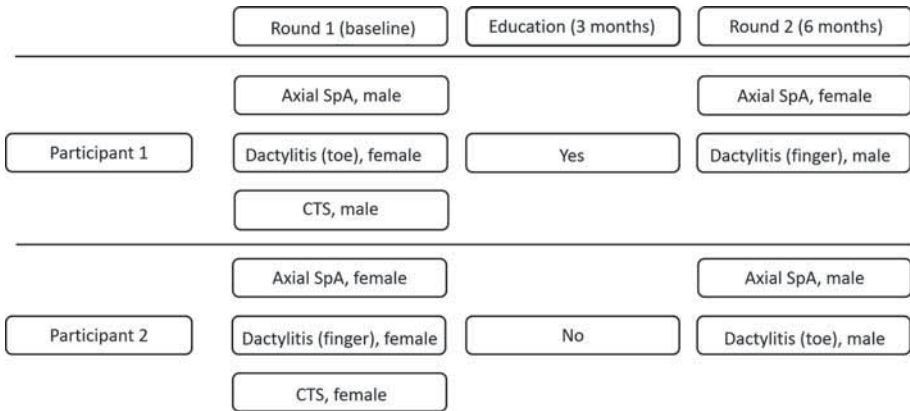
Figure 8.1   Example of a predefined schedule for 2 participants. SpA = spondyloarthritis.

Practice visits and checklist

At the practice visit, the SPs identified themselves as an SP, without providing further information. The duration of one consultation was 10-15 minutes, corresponding to the standard consultation time by a GP (resident).

After the visit, the SP immediately completed the case-specific checklist reporting the activities of participants during the visit, which consisted of:

- Disease related items (e.g. onset of symptoms, presence of low back pain, family medical history);
- Items on physical examination (e.g. of the joints and/or back).

The GP (residents) indicated for this specific case which additional diagnostic investigations they would have ordered, which medication they would have prescribed (if any), and whether referral to another health care professional (and which) would be advised. Participants also ranked their differential diagnosis, from 1 (most likely) to 3 (less likely). The SPs were responsible for collecting and returning all forms to the study coordinator.

Box 8.1   Summary of included cases, simulated by standardized patients.

Early axial SpA:
- Case 1a: a 27-year-old male / female, suffering from chronic back pain with an inflammatory character since one year. He/she has a history of Achilles tendinitis. Physical therapy has a limited effect in back pain relief. The patient visits the GP (resident) because the back pain is now also present in the thoracic spine. An aunt has Crohn's disease.
- Case 1b: a 26-year-old male / female with chronic back pain with an inflammatory character since 1.5 years. There are also symptoms of anterior chest wall pain. Physical therapy has a limited effect on back pain relief. The patient visits the GP (resident) because of progressive work disability. A brother has psoriasis.

Early peripheral SpA:
- Case 2a: a 27-year-old male / female, who presents with a painful and swollen middle finger of the right hand with morning stiffness since a few weeks. The SP hands over a photograph to the GP (resident), showing dactylitis of the affected finger. He/she has a history of knee arthritis three years ago that resolved with non-steroidal anti-inflammatory drugs (NSAIDs). The mother has psoriasis.
- Case 2b: a 26-year-old male / female, who presents with and a painful and swollen second toe of the right foot with morning stiffness since a few weeks. The SP hands over a photograph to the GP (resident), showing dactylitis of the affected toe. The patient experienced similar complaints of a finger about one year ago. The brother has psoriasis.

CTS:
- Case 3: a 50-year-old male / female, with a tingling and burning sensation of the index, middle and ring finger since three months. The symptoms are worst at night. Flicking the wrist gives symptom relief.

Educational intervention

The interactive 3-hour case-based educational programme took place at the department of General Practice of the MUMC. Three topics, were presented and discussed by two rheumatologists:

- Diagnosis and management of gout (duration 45 minutes);

- Axial and peripheral SpA (duration 90 minutes), i.e. concept and epidemiology of SpA, history taking and physical examination of patients suspected for having SpA, and criteria for referral of these patients to the rheumatologist.
- Safety considerations for biologic therapy (i.e. anti-Tumor Necrosis Factor (TNF)-alpha therapy; duration 45 minutes).

Printed materials, including SpA features, were supplied to the participants supporting self-directed learning after the training.

Study outcomes

Our primary outcome was referral or considering referral of the SP to a rheumatologist by the GP (resident). We decided to combine both referral and considering referral, because GPs may spread diagnostic interventions over several consultations or only refer to secondary care when complaints fail to resolve within a few weeks after the first consultation. Secondary outcomes included (1) correct recognition of axial SpA, peripheral SpA and CTS respectively by the GP (resident), (2) ordering of additional diagnostic tests, (3) identification of variables contributing to correct recognition of SpA or CTS (GP versus GP resident, and gender of the SPs).

Statistical analysis

The sample size calculation was based on the primary outcome, (considering) referral of the SP to the rheumatologist. We estimated that 20% of the SPs would be referred without education and aimed at increasing this by 40%. In order to detect a 40% difference in the change scores between the intervention group and control group in the proportion of SPs referred to the rheumatologist, 23 complete pre- and post-education SP encounters were needed per group (80% power, alpha of 0.05).

Descriptive analyses were used for the demographic data. Chi square tests and fisher's exact tests, as appropriate, were used to analyse the primary and secondary endpoints. The difference in change scores between the intervention group and control group with regard to (considering) referral of the SP and correct recognition of SpA was compared with the Mann-Whitney U test. Within-group changes in referral and recognition of SpA before and after education were analysed with McNemar tests. Only participants that completed both rounds of SP encounters were included in these analyses. Descriptive analysis was used for investigating which diagnoses were mentioned by GP (residents) and the frequency of ordering additional diagnostic tests by GP (residents). SPSS software 20.0 was used for all analyses.

RESULTS

Participant characteristics

In total, 117 GPs residents and their supervising GPs were invited, of which 68 (38 GP residents and 30 GPs) participated in the study. Reasons for non-participation were not collected. The study was ended prematurely, because many GP (residents) declined participation, and the chance that newly enrolled GP residents came into direct contact with GP (residents) that already participated was considered high. The a priori sample size was therefore not pursued.

Baseline characteristics of the participants are shown in Table 8.1. Three (4%) participants mentioned an interest in musculoskeletal disorders.

In total, 256 SP encounters took place, excluding the CTS cases. Both rounds were completed by 61 (90%) and 59 (87%) participants for the axial SpA and peripheral SpA case, respectively. Reasons for incomplete SP visits were: illness (n=6), unable to schedule an appointment within the given time frame (n=4), late arrival by SP due to traffic problems (n=3), GP left for a medical emergency (n=2), and maternity leave (n=1).

Table 8.1   Characteristics of the participating general practitioners and residents.

	GP residents (n = 38)	GPs (n = 30)	All participants (n = 68)
Age [years]	28 (1.6)	52 (5.9)	39 (12.9)
Male	12 (32%)	24 (80%)	36 (53%)
Working experience, including training [years]	2 (0.4)	22 (7.2)	11 (10.9)
Weekly consultations [number]	62 (15.6)	107 (26.5)	82 (30.6)
Specific interest in musculoskeletal disorders	2 (7%)	1 (3%)	3 (4%)

The values are expressed as mean (standard deviation) or as number (%). GP = general practitioner.

Axial spondyloarthritis

Primary endpoint

Referral of SPs simulating axial SpA. In the first round of SP encounters, 6% of the participants in the intervention group (n=18) and 10% of participants in the control group (n=43) referred or considered referral of the SP to the rheumatologist (Figure 8.2). Participants who received the educational programme clearly more often referred

or considered referral in the second round of SP encounters than controls (changes scores: +71% vs. +15% (p<0.001); Figure 8.2).
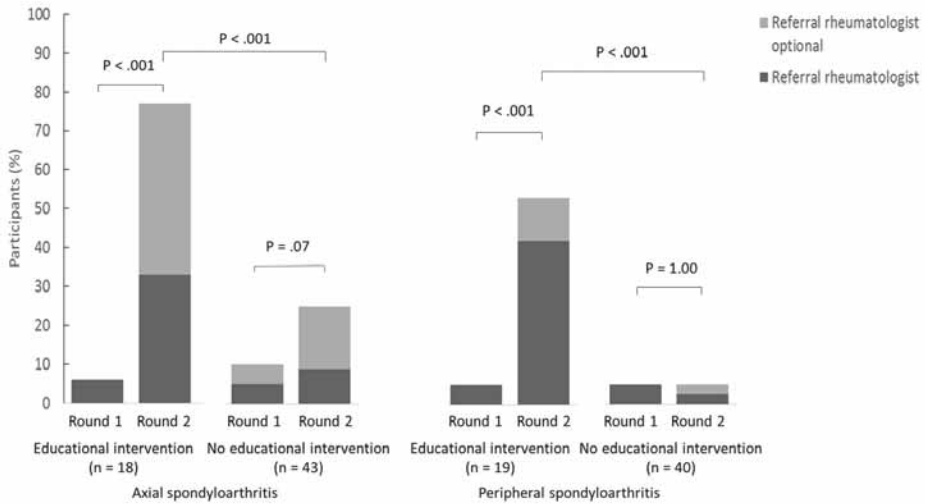
Figure 8.2   Referral of standardized patients simulating axial and peripheral spondyloarthritis to a rheumatologist.

Secondary endpoints

Recognition of axial SpA. In the first round of SP encounters, 4 (22%) out of 18 participants in the intervention group and 8 (19%) out of 43 participants in the control group ranked axial SpA as their no. 1 diagnosis. Non-specific back pain was most frequently ranked as no. 1 diagnosis by 10 (56%) out of 18 participants in the intervention group and 31 (72%) out of 43 participants in the control group (Table 82). In total, 34 (56%) out of 68 participants ranked axial SpA as no. 1, 2 or 3 in their differential diagnosis before education.

In the second round, the intervention group more frequently ranked axial SpA as their no. 1 diagnosis (round 1: 22% vs. round 2: 72% (p=0.01); Table 8.2), which was statistically significantly different from the control group (changes scores: +50% intervention group vs. -5% control group, (p<0.001); Table 8.2). In the second round, non-specific back pain remained the no. 1 diagnosis in 74% of the participants from the control group (Table 8.2).

Additional diagnostic tests. In the intervention group less HLA-B27 tests were ordered in the second round, whereas in the control group the opposite was seen (changes scores: -22% intervention group vs. +12% control group, (p=0.01); Table 8.2).

Table 8.2 Diagnosis and management in standardized patients simulating axial spondyloarthritis.

	Educational group (n=18)				Control group (n=43)				
	Round 1 (%)	Round 2 (%)	Change score (%)	P Value (within group)	Round 1 (%)	Round 2 (%)	Change score (%)	P Value (within group)	P Value (change scores, between groups)
Number 1 diagnosis									
Axial SpA	4 (22)	13 (72)	9 (50)	.01	8 (19)	6 (14)	-2 (-5)	.73	<.001
Non-specific back pain	10 (56)	5 (28)	-5 (-28)	.23	31 (72)	32 (74)	1 (2)	1.00	.05
Sacroiliac joint dysfunction	2 (11)	0 (0)	-2 (-11)	.50	2 (5)	4 (9)	2 (5)	.50	.03
Herniated nuclei pulposi	1 (6)	0 (0)	-1 (-6)	1.00	2 (5)	1 (2)	-1 (-2)	1.00	.66
Poor posture	1 (6)	0 (0)	-1 (-6)	1.00	0 (0)	0 (0)	0 (0)	NA	.12
Additional diagnostic tests									
Laboratory tests (general)	5 (28)	6 (33)	1 (5)	1.00	13 (30)	18 (42)	5 (12)	.18	.78
HLA-B27 test	6 (33)	2 (11)	-4 (-22)	.13	4 (9)	9 (21)	5 (12)	.13	.01
Pelvic radiograph	3 (17)	3 (17)	0 (0)	1.00	4 (9)	8 (19)	4 (10)	.22	.43
Management									
NSAIDs prescribed	4 (22)	5 (28)	1 (5)	1.00	8 (19)	8 (19)	0 (0)	1.00	.65
Follow-up consultation with GP (resident) arranged	14 (78)	13 (72)	-1 (-6)	1.00	29 (67)	30 (70)	1 (3)	1.00	.66

SpA=spondyloarthritis; SPs=standardized patients; GP=general practitioner; HLA-B27=Human Leukocyte Antigen B27; NSAIDs=non-steroidal anti-inflammatory drugs; NA=not assessed. Values are expressed as number (percentage) of participants. Numbers may not add up due to rounding. NcNemar tests were used within groups and Mann-Whitney U tests were used between groups.

Variables contributing to recognition of axial SpA. No difference between the GPs and GP resident characteristics with regard to correct recognition of axial SpA was found (data not shown). In addition, male and female SPs were equally considered to have axial SpA (data not shown).

Peripheral spondyloarthritis

Primary endpoint

Referral of SPs simulating peripheral SpA. In the first round, participants in both the intervention (n=19) and control group (n=40) referred the SPs to the rheumatologist in 5% of cases (Figure 8.2). The intervention group referred or considered referral more frequently compared to the control group in the second round (change scores: +48% vs. 0% (p<0.01); Figure 8.2).

Secondary endpoints

Recognition of peripheral SpA. In the first round of SP encounters, 2 (11%) out of 19 participants in the intervention group and 4 (10%) out of 40 participants in the control group ranked peripheral SpA as their no. 1 diagnosis (Table 8.3). All specified this as "reactive arthritis". Two participants ranked psoriatic arthritis in their differential diagnosis as no. 2 or 3. "Arthritis not otherwise specified" was ranked by most participants as no. 1 diagnosis (5 (26%) participants in the intervention group and 15 (38%) participants in the control group; Table 8.3).
Four (21%) of the 19 participants from the intervention group correctly recognized "spondyloarthritis" or "psoriatic arthritis" after education, compared with none of the participants in the control group (change scores: +21% vs. 0% (p=0.01); Table 8.3).
Additional diagnostic tests. No differences between the intervention and control group regarding ordering laboratory and diagnostic imaging tests were found in both rounds of SP encounters (Table 8.3).
Variables contributing to recognition of peripheral SpA. No difference between the GPs and GP residents with regard to correct recognition of peripheral SpA was found in the first round of SP encounters. However, in general, GPs ordered more additional diagnostic tests in both rounds of SP encounters (Table 8.4).
In the first round of SP encounters, gout was more often ranked as no. 1 diagnosis in male than in female SPs (male SPs: 8 (26%) out of 31 diagnoses; female SPs: 1 (4%) out of 28 diagnoses (p=0.03)).

Table 8.3 Diagnosis and management of standardized patients simulating peripheral spondyloarthritis.

	Educational group (n=19)				Control group (n=40)				P Value (change scores, between groups)
	Round 1 (%)	Round 2 (%)	Change score (%)	P Value (within group)	Round 1 (%)	Round 2 (%)	Change score (%)	P Value (within group)	
Number 1 diagnosis									
Peripheral SpA	2 (11)	5 (26)	3 (16)	.45	4 (10)	4 (10)	0 (0)	1.00	.21
Reactive arthritis	2 (11)	1 (5)	-1 (-6)	1.00	4 (10)	3 (8)	-1 (-2)	1.00	.79
Spondyloarthritis	0 (0)	3 (16)	3 (16)	.25	0 (0)	0 (0)	0 (0)	NA	.01
Psoriatic arthritis	0 (0)	1 (5)	1 (5)	1.00	0 (0)	0 (0)	0 (0)	NA	.15
Tenosynovitis	0 (0)	0 (0)	0 (0)	NA	0 (0)	1 (3)	1 (3)	1.00	.49
Arthritis, not otherwise specified	5 (26)	8 (42)	3 (16)	.45	15 (38)	16 (40)	1 (2)	1.00	.44
Rheumatoid arthritis	5 (26)	3 (16)	-2 (-10)	.69	2 (5)	5 (13)	3 (8)	0.45	.18
Gout	1 (5)	1 (5)	0 (0)	1.00	8 (20)	6 (15)	-2 (-5)	0.77	.70
Sprain	4 (21)	1 (5)	-3 (-16)	.25	6 (15)	5 (13)	-1 (-2)	1.00	.30
Skin or nail infection / insect bite	2 (11)	0 (0)	-2 (-11)	.50	3 (8)	1 (3)	-2 (-5)	0.25	.70
Trauma	0 (0)	1 (5)	1 (5)	1.00	1 (3)	1 (3)	0 (0)	1.00	.49
Other or no differential diagnosis	0 (0)	1 (5)	1 (5)	1.00	1 (3)	2 (5)	1 (2)	1.00	.71
Additional diagnostic tests									
Laboratory tests (general)	8 (42)	5 (26)	-3 (-16)	.38	17 (43)	18 (45)	1 (3)	1.00	.18
HLA-B27 test	0 (0)	0 (0)	0 (0)	NA	0 (0)	0 (0)	0 (0)	NA	1.00
IgM RF and/or ACPA test	5 (26)	2 (11)	-3 (-16)	.38	11 (28)	7 (18)	-4 (-10)	0.29	.64
Radiograph of the hand or foot	0 (0)	1 (5)	1 (5)	1.00	4 (10)	8 (20)	4 (10)	0.22	.59
Management									
NSAIDs prescribed	13 (68)	13 (68)	0 (0)	1.00	21 (53)	22 (55)	1 (3)	1.00	.86
Arranged follow-up consultation with GP (resident)	10 (53)	10 (53)	0 (0)	1.00	23 (58)	25 (63)	2 (5)	0.82	.82

SpA=spondyloarthritis; SPs=standardized patients; GP=general practitioner; HLA-B27=Human Leukocyte Antigen B27; RF=rheumatoid factor; ACPA=anti-citrullinated protein antibody; NA=not assessed. Values are expressed as number (percentage) of participants. Numbers may not add up due to rounding. NcNemar tests were used within groups and Mann-Whitney U tests were used between groups.

Table 8.4   List of diagnoses and management in patients suspected for carpal tunnel syndrome.

	GP resident (n=37)	GP (n=28)	P Value	All participants (n=65)
Number 1 diagnosis				
CTS	30 (81%)	24 (86%)	.75	54 (83%)
Osteoarthritis	1 (3%)	0 (0%)	1.00	1 (2%)
Sprain	6 (16%)	4 (14%)	1.00	6 (16%)
Additional diagnostic tests				
Radiography of the hand	0 (0%)	2 (5%)	.50	2 (3%)
EMG	3 (11%)	3 (8%)	1.00	6 (9%)
Management				
NSAIDs prescribed	3 (8%)	3 (11%)	.52	6 (9%)
Local injection with corticosteroids	2 (7%)	8 (22%)	.17	10 (15%)
Splint	7 (25%)	15 (41%)	.29	22 (34%)
Follow-up consultation with GP (resident) arranged	10 (35%)	21 (57%)	.13	31 (47%)
Referral to neurologist	1 (4%)	2 (5%)	.57	3 (5%)

CTS=carpal tunnel syndrome; EMG=electromyography; NSAIDs=non-steroidal anti-inflammatory drugs; GP=general practitioner.

Recognition and management of carpal tunnel syndrome

As expected, CTS was ranked as the no. 1 diagnosis by 54 (83%) out of 65 participants, and by 61 (90%) in their top 3 (Table 8.5). No differences between the GP and GP resident or gender of the SP regarding ranking CTS as no. 1 diagnosis were found. Also the management and follow-up of the CTS case were similar for the GP and GP resident.

Table 8.5   List of diagnoses and management in patients suspected for carpal tunnel syndrome.

	GP resident (n=37)	GP (n=28)	p Value	All participants (n=65)
Number 1 diagnosis				
CTS	30 (81%)	24 (86%)	0.75	54 (83%)
Osteoarthritis	1 (3%)	0 (0%)	1.00	1 (2%)
Sprain	6 (16%)	4 (14%)	1.00	6 (16%)
Additional diagnostic tests				
Radiography of the hand	0 (0%)	2 (5%)	0.50	2 (3%)
EMG	3 (11%)	3 (8%)	1.00	6 (9%)
Management				
NSAIDs prescribed	3 (8%)	3 (11%)	0.52	6 (9%)
Local injection with corticosteroids	2 (7%)	8 (22%)	0.17	10 (15%)
Splint	7 (25%)	15 (41%)	0.29	22 (34%)
Follow-up consultation with GP (resident) arranged	10 (35%)	21 (57%)	0.13	31 (47%)
Referral to neurologist	1 (4%)	2 (5%)	0.57	3 (5%)

CTS = carpal tunnel syndrome, EMG = electromyography, NSAIDs = non-steroidal anti-inflammatory drugs, GP = general practitioner.

DISCUSSION

In this study we showed that education is an important means to change clinicians' practice behaviour regarding recognition and referral of patients with SpA. While medical history and symptoms simulated by SPs would have acknowledged a referral to a rheumatologist, such a policy was executed by only 10% of the GPs. Specific SpA-aimed education improved this policy dramatically. The primary outcome, more than 40% improvement in (considering) referral for both axial and peripheral SpA after education, was met.

Approximately 20% of the adult population consult their GP because of musculoskeletal complaints, among which chronic low back pain is the most prevalent.[1-3,26] Although it is impossible for GPs to have considerable expertise in all areas, the high exposure to musculoskeletal disorders (MSD) warrants development of high-quality training programs aiming at gaining and maintaining sufficient expertise on MSD. Several studies, however, suggest that graduated medical students and residents lack knowledge and confidence in this respect.[27-30] Multi-faceted education interventions, including mixed interactive and didactic learning activities focussing on pertinent outcomes have shown to sustainably change physicians' behaviour.[31,32] In the present study, we also applied multi-faceted educational tools including interactive power-point presentations, case vignettes and printed materials, which may have added to a better recognition of SpA three months after the intervention. Future studies may shed light on the sustainability of education in this context.

Strengths of our study are that we have used a prospective, multicenter design and that we have included a control group for an evaluation of the effect of education. In addition, our study was conducted in primary care which is the source of most referrals of SpA to the rheumatologist. Furthermore, the SP-model has proven reliability for the assessment of physicians' knowledge and -skills in a 'genuine' clinical setting.[23-25,33,34]

Several limitations of this study require discussion. First, SPs did not truly have signs of their disease detectable at physical examination, which may have jeopardised recognition. SPs performing a role of peripheral SpA, for example, showed a photograph with dactylitis to the GP. Dactylitis is a relatively uncommon (albeit specific) manifestation of peripheral SpA. Nevertheless, one in two GPs (residents) ranked an inflammatory rheumatic disease as the diagnosis of highest likelihood in both SP encounters. This observation suggests that a knowledge deficit about peripheral SpA prevented an adequate diagnosis but not the recognition of a rheumatic

disease. While referral to a medical specialist would have been the best option here, only a minority of the patients was indeed referred.

Second, information to GPs about an SP visiting their practice may have raised arousal leading to different diagnostic behaviour. However, GP (residents) were neither aware of the specific case presentation or the purpose of the study nor were they informed about education being part of this study. In addition, participants were visited in their own practices by SPs during regular working hours. Since a previous study has failed to demonstrate a difference in performance by residents evaluating real patients and SPs [35], we believe the precautions we have taken have assured a most truthful performance of GP (residents) in daily practice.

Third, one may argue that the GP (residents) suspected the SP was simulating SpA, but that they were unaware of the fact that referral would have been indicated in this case. Making a correct diagnosis was a secondary outcome in our study. Before education, only a minority of GPs correctly diagnosed axial SpA (20%) and peripheral SpA (10%). In contrast, CTS was recognised by the large majority of participants (83%), indicating that GPs have sufficient knowledge of common disorders. However, they fall short regarding SpA, which is more unfamiliar than CTS.

Fourth, we were unable to include the projected number of participants. Nevertheless, the primary outcome was met. A small sample size, however, may limit generalizability of results to a larger population.

In conclusion, recognition and referral of patients suspected for having SpA by GP (residents) is in general low, but targeted education can markedly improve this. Increased awareness of a potential underlying inflammatory condition in patients presenting with musculoskeletal complaints and timely referral may prevent a debilitating disease course in patients with SpA. Therefore, we recommend the combination of a referral tool targeted at SpA and educational activities that maximize practitioner engagement and support for practice change.

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CHAPTER 9

Summary and general discussion
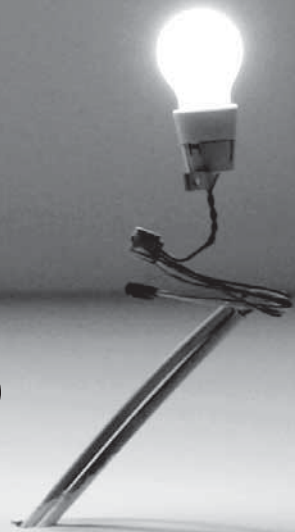
SUMMARY AND DISCUSSION OF MAIN FINDINGS

This thesis describes several studies that focus on the early identification of patients with spondyloarthritis (SpA).

As described in **Chapter 1**, major advances have been made over the last years to facilitate early diagnosis of SpA. One of the important key changes was the proposal of the Assessment of SpondyloArthritis international Society (ASAS) to revise disease nomenclature. Consistent with this proposal, SpA is now categorised into predominantly axial SpA (axSpA) and predominantly peripheral SpA.[1-4] In addition, axSpA has further been differentiated as "radiographic axial SpA" which is synonymous to ankylosing spondylitis (AS) and "non-radiographic (nr)-axSpA", in which pelvic radiographs are normal or equivocal.[1] By recognizing non-radiographic axSpA and incorporating this concept in the ASAS classification criteria for axSpA, the focus has shifted towards an earlier detection of axSpA.[1,3]

However, to achieve timely and accurate diagnosis of SpA, further research in several areas is required.

One of the challenges was aggregating the available epidemiological data in a reliable manner so that it could be used to better understand disease patterns. This information may also help to provide insight about which health care resources are needed to detect and manage SpA at an early stage.

Chapter 2 presents therefore a systematic literature review and meta-analysis on the prevalence of SpA and its subtypes. Several demographical (including geographical) and methodological variables were studied to explain variation in the prevalence of (subtypes of) SpA in the 84 studies that were included. The pooled prevalence of SpA was 0.55% (95% confidence interval (CI): 0.37-0.77) and the pooled prevalence of AS was 0.18% (95% CI: 0.15-0.23). There was however a high level of heterogeneity across studies. Substantial variation between geographic areas was found, which can partly be explained by the prevalence of HLA-B27; in populations known to have a high prevalence of HLA-B27, a higher prevalence of SpA was reported. The highest prevalence of SpA (including AS) in our review was reported in decreasing order in Northern Artic indigenous communities, North America, East Asia and Europe. Interestingly, prevalence estimates of SpA were positively related to the year of data collection. This finding might be the result of increased awareness and recognition of SpA as a separate disease entity. In addition, our study showed that the reported prevalence of SpA was highly dependent on the type of case definition that was used.

This is illustrated by a population-based study in the US.[5] The prevalence of SpA was 1.4% according to the ESSG criteria, but 0.9% according to the Amor criteria. This finding makes clear that the type of classification criteria may have an impact on the reported prevalence of (subtypes of) SpA. Consequently, the prevalence of SpA using the new classification criteria for axial and peripheral SpA may be different.

In axSpA, the development of new classification criteria was preceded by the introduction of magnetic resonance imaging (MRI) of the SIJ, with the aim to facilitate an early diagnosis of axSpA.[6] The Early SpondyloArthritis Clinic (ESpAC) was established by our group in order to better understand the role of MRI in patients suspected for axSpA. The follow-up study included three full clinical and imaging examinations performed with one year time intervals. MRIs of the sacroiliac joints (MRI-SIJ) were an integral part of this study. **Chapter 3** describes the evolution of active lesions on MRI-SIJ, suggestive for sacroiliitis, over a 2-year follow-up period. Twenty-four (35%) out of 68 patients had a positive MRI-SIJ at baseline. We found that both a positive HLA-B27 status and positive MRI-SIJ at baseline were independently associated with a persistently positive MRI-SIJ over time. A combination of a negative HLA-B27 status and a negative MRI-SIJ at baseline essentially ruled out a positive MRI over time. Especially in male HLA-B27 positive patients with a negative baseline MRI-SIJ, a follow-up MRI seems rational since a considerable proportion of these patients may develop a positive MRI over time. Our findings not only contribute to efficiently diagnose patients with axSpA but also give credit to the prominent place of MRI-SIJ in the ASAS axial SpA classification criteria.[1,7,8]

To date, active lesions (bone marrow edema (BME)) highly suggestive for sacroiliitis are required for a positive MRI-SIJ.[9] There is increasing debate, though, if structural lesions (erosions or fatty lesions) may also have an independent diagnostic value.[10] In **Chapter 4** we investigated the presence and evolution of structural changes on MRI-SIJ in patients included in the ESpAC. Subsequently, we analysed whether structural changes on either MRI or pelvic radiographs were preceded by BME on MRI at the same anatomic location. The number of erosions on MRI increased significantly during follow-up, but these new erosions were not associated with preceding BME. While the number of fatty lesions only showed a slight increase, the few new fatty lesions were associated with preceding BME. Interestingly, they occurred preferably in locations that showed resolution of BME. The relation between inflammation and structural damage on MRI in patients with axSpA had been extensively discussed over the last years.[11-18] The debate is mainly confined to the question whether inflammation and

structural damage are "coupled" or "uncoupled" processes. Earlier reports have shown conflicting results.[14-17] Our current findings support the view that fatty lesions should be seen as a repair reaction in response to inflammatory triggers.[19] Other data have suggested that fatty lesions on MRI are linked to subsequent development of syndesmophytes in the spine.[20] We did not find an association between active lesions and erosions on MRI and subsequent progression of sacroiliitis on conventional radiographs. Larger studies than ours with sequential MRI examinations over a longer follow-up period will be needed in order to be conclusive.

Different MRI techniques can be used to detect active lesions on MRI; these are short tau inversion recovery (STIR) sequence, and fat-saturated T1-weighted spin-echo sequence after administration of the contrast agent gadolinium diethylene-triaminepentaacetic acid (Gd-DTPA).[9] In **Chapter 5** we showed that the post-Gd-DTPA sequence did not have a surplus value compared with the STIR sequence in combination with pelvic radiographs. Our results were comparable to the results of the SPondyloArthritis Caught Early (SPACE)-cohort that found a 100% agreement between the STIR and post-Gd-DTPA MRI sequence both at baseline and 3-month follow-up.[21] All together, it seems as if the post-Gd-DTPA can safely be omitted. This finding increases feasibility of MRI and reduces costs regarding the use of MRI during the diagnostic work-up of patients suspected for axSpA.

At the start of this project, essential information about the use of MRI was lacking in order to recommend it in all patients with a suspicion of axSpA and a normal or equivocal pelvic radiograph. One of those questions pertained to how stable a lesion found on MRI is over time. **Chapter 6** describes the exact distribution, frequency of occurrence, and evolution over time of BME detected on MRI-SIJ in patients included in the ESpAC. Almost half of the BME lesions detected at baseline, had resolved during follow-up. Vice versa, some negative baseline MRIs had become positive over time. Both had consequences for the fulfilment of the ASAS axSpA criteria at any follow-up moment. This finding reflects a general concern inherent to diagnostic imaging in rheumatic conditions, being that imaging findings (which are inherently unreliable due to measurement error and judgement variation) become dominant over clinical findings in the process of diagnostic pattern recognition. Myopically focusing on MRI reports, for instance, could lead to a delay in the diagnosis of axSpA, if signs suggestive for sacroiliitis on MRI are absent in an otherwise clinical undisputable SpA patient. On the other hand, a focus on MRI findings could lead to a false diagnosis of SpA if too subtle and not highly suggestive lesions on MRI (the 'innocent white spots') are interpreted without the context of the clinical symptoms of a patient that actually do

not raise suspicion of SpA. The entire pattern of axSpA, including manifestations such as psoriasis, enthesitis or uveitis should therefore be taken into account. This has actually been done in the 'diagnostic algorithm' in which a thorough medical history and physical examination are prominent steps in the work-up of patients suspected for axSpA, in which imaging also plays a role.[8] MRI should only be ordered in those patients with a reasonable suspicion for SpA.

Optimizing the management of patients with SpA always starts with 'case finding'. In the Dutch healthcare setting, this usually starts in primary care. The level of knowledge and the perceptions of general practitioners (GPs) about inflammatory back pain (IBP) and axSpA, and potential barriers for referral of patients suspected for axSpA were studied in **Chapter 7**. We found that axSpA is often unrecognized in primary care, and even when recognized, it is often sub-optimally managed. In general, the level of knowledge about IBP, axSpA and the associated extra-articular manifestations is limited. GPs are aware of 'classic', but late features of axSpA, such as hyperkyphosis as seen in AS. Only half of the GPs knew, for example, that Tumor Necrosis Factor (TNF)-alpha inhibiting biologicals are a treatment option in axSpA. Improving the knowledge of GPs about the leading presenting symptoms and current treatment options of axSpA, will likely facilitate the referral of patients suspected of having axSpA.

The primary care setting itself does not facilitate the identification of patients with SpA: GPs have to deal with a broad variety of physical and psychological conditions. Chronic back pain is a common symptom in the general population and it is estimated that in only 5% of cases, axSpA is the underlying condition.[22] GPs may think that adequate recognition of axSpA is of secondary concern. However, fine-tuning the procedure in order to select those patients that may need further evaluation in secondary care is still an important step to make. A recent study has shown that 24% of primary care patients with chronic low back pain starting before the age of 45 years could be classified as having axial SpA.[23] GPs can provide 'longitudinal continuity' of care to the patient that is consistent with the patient's other needs. This means that GPs are in a unique position to recognize the pattern of symptoms suggestive for SpA (including the occurrence of SpA features over time) when a patient first seeks medical attention. In **Chapter 8** we describe the current practice performance of GPs and GP residents with regard to recognizing early axial or peripheral SpA. We used standardized patients (SPs) to demonstrate 'what is really going on' in daily clinical practice. In addition, the influence of education on this performance was investigated. In this study, 68 GP residents and their supervising GPs were included and visited by trained SPs who

simulated a case of early axial of peripheral SpA. We concluded that recognition and referral of patients suspected for SpA to the rheumatologist by GP (residents) is generally low. Providing education however markedly improved both recognition and referral of patients suspected for SpA to the rheumatologist. Education may therefore be an interesting starting point to increase awareness about SpA, paving the way to successful implementation of a referral strategy.

METHODOLOGICAL CONSIDERATIONS

The most important limitations of the studies that were described in **Chapter 2 to 8** of this thesis have already been described in the respective chapters. Two methodological considerations are highlighted and described in this section: generalizability of results (**Chapter 3 to 6**) and the use of standardized patients in outcome research (**Chapter 8**).

GENERALIZABILTY OF RESULTS

Since the main goal of research is to increase our understanding of the world around us, research results should rather be relevant when applied to other patients with a similar clinical profile. Although ESpAC is a relatively small cohort, it clearly represents a study population of high actual interest. Patients in ESpAC had IBP 2 years at most and this cohort is therefore able to provide more insight in the early stages of axSpA. Patients included in the ESpAC were recruited from the regular rheumatology outpatient clinic (60%) or by (related) medical specialties (i.e. dermatology, ophthalmology) and relatives of members of the local AS society (40%). This recruitment strategy may explain the high proportion of patients fulfilling at least one of the classification criteria for SpA (94%). In the ESpAC study, 31 (46%) out of 68 patients fulfilled the imaging arm of the ASAS criteria. Although rheumatologists often see patients referred by other medical specialists, selecting patients in this way may hamper generalizability of our results to a wider population to some extent. Our results may be restricted to patients with a clearer clinical presentation (such as "psoriasis and IBP") or those with more active disease. This means that generalization to another population, for example patients with back pain referred by GPs, should be done with caution. It is however important to note that our main research question was how BME and structural changes on MRI-SIJ, suggestive for axSpA, evolve over time. To answer this question, subject restriction by selecting patients with a high

chance of abnormalities on MRI-SIJ may have improved efficiency and internal validity. Notwithstanding, the lessons learned from ESpAC may help rheumatologists how to assess MRI-SIJ in clinical practice.

STANDARDIZED PATIENTS, EDUCATION AND OUTCOME MEASURES

In 1968, Barrows was the first to introduce SPs in order to assess the clinical performance of medical residents.[24] Since then, SPs are most commonly used for teaching communication and clinical skills.[25] The study with SPs described in this thesis, however, focused on changes in recognition of SpA and the decision to refer patients to a rheumatologist before and after education. SPs recorded several outcomes of the consultation before as well as after the educational intervention. When evaluating outcome in a study that includes an educational programme, several outcome levels can be distinguished [26]:

- *Level 1: reaction*. To what extent did the participants like the learning event? Likert scales can be used to measure the participants' level of satisfaction.
- *Level 2: learning*. To what degree did participants acquire the intended knowledge, skills and attitudes based on their participation in the leaning event? Computer tests or Objective Structured Clinical Examinations (OSCE) can be used to measure changes in for instance knowledge.
- *Level 3: behaviour*. To what degree apply participants what they learned during the training when they are back on the job? SPs that visit the GP before and after education can record changes in for instance history taking.
- *Level 4*: To what degree do *organizational changes and improvement in health* and well-being of a patient occur as a result of the learning event? Surveys and annual reports can be used to measure these changes.

The majority of studies that report on educational program innovations focus on changes in knowledge, skills and attitudes (level 2).[26] Our study also assessed the changes in practice behaviour (level 3). The advantage of collecting data on practice behaviour is that it offers information about what actually happens in clinical practice. The SP method is valid, but thorough selection and training of the SP is a prerequisite. In addition, SP visits have proven to be accurate and reliable in collecting information.[27-30] In a review of Rethans et al. it was concluded that both intra-SP reliability and inter-SP reliability are 0.85 or more, which indicates an excellent agreement.[27] An important limitation regarding the use of SPs in our study is the fact

that the SP visit was restricted to one (first) consultation. Especially in the case of rare or chronic conditions, GPs may unfold diagnostic and therapeutic interventions in several consultations. To overcome this limitation, we included in the medical history of the SP that complaints were present for more than one year, multiple visits with other GPs had taken place and physiotherapy or swimming were unsuccessful. Overall, the use of SPs seems an excellent method to assess the effect of education on practice performance. When taking the right precautions, it seems that SPs can also be used for less straightforward medical problems, such as we did in the case of SpA.

IMPLICATIONS FOR CLINICAL PRACTICE

Improving evidence-based care of patients suffering from SpA is the ultimate goal of research in the SpA-field.

New insights about the epidemiology of SpA, as described in this thesis, suggest that spondyloarthritis is as prevalent as rheumatoid arthritis.[31] The actual prevalence of SpA is important for implementing standards of care for patients with SpA (including efforts to diagnose the disease earlier), and for decision makers when allocating resources to research and healthcare. Knowledge about (variation in) prevalence contributes to plan optimal quality of care within the limits of available health care resources.

The introduction of MRI to diagnose sacroiliitis at an early stage has already shown to be highly useful to both rheumatologists and patients. For rheumatologists, the introduction of MRI helps to improve the diagnostic approach of a highly prevalent clinical problem. When rheumatologists have a real suspicion of an inflammatory back problem in a patient after careful evaluation, conventional pelvic radiographs often fail to show radiographic sacroiliitis. The findings described in this thesis may guide rheumatologists to correctly assess the value of MRI in these day-to-day clinical cases. For instance, in an HLA-B27 positive male patient with a negative MRI-SIJ, a second MRI can be considered in case of persisting complaints since a reasonable percentage of these patients will develop active lesions on MRI over time.

For patients, early diagnosis is important since the pain and physical limitations associated with axSpA may have important socio-economic consequences, such as decreased work participation.[32] Substantial diagnostic delay can have an adverse impact on several outcomes, including physical functioning and quality of life.[33] Last but not least, patients with nr-axSpA who have objective measures of inflammation (elevated C-reactive protein and active lesions on MRI) have a similar response to

treatment as compared to patients with established AS, emphasizing the need for early and correct diagnosis.[34,35] Early diagnosis might facilitate early initiation of effective treatment, thereby diminishing the burden of disease for patients and possibly avoid long term costs of work disability for society.[36]

Optimization of the diagnostic and management process by the rheumatologist is important, but decreasing the diagnostic delay in primary care is equally essential. The greater part of the diagnostic delay pertains to primary care.[37,38] It is therefore important to communicate new disease concepts, in particular those with implications for primary care, to the GP. Our data have shown that educating GP residents about SpA increases the number of referrals to the rheumatologist. Postgraduate training of GPs in rheumatology seems a feasible approach to improve the care for patients with SpA and deserves greater priority.

FUTURE PERSPECTIVES

A definite diagnosis of axSpA remains a challenge in daily practice due to the heterogeneous clinical picture of the disease. Although MRI has undoubtedly facilitated an early diagnosis of axSpA, several research questions remain unsolved. First, although MRI is widely accepted as imaging technique to detect sacroiliitis at an early stage, the specificity and predictive value of these active MRI lesions on the long-term needs to be further validated in prospective studies.[39] Second, further clarification of the potential contribution of structural changes on MRI in relation to classification and diagnosis of axSpA is needed. Several studies suggest that structural damage on MRI, especially erosions, may be helpful in establishing an early diagnosis of axSpA.[40,41] Detection of erosions on MRI-SIJ is more challenging than detection of BME, since the spectrum of appearance of erosions is more heterogeneous.[42,43] Further defining the characteristics of erosions and their role in further improving the diagnostic utility of MRI is needed. Third, the link between active and structural lesions on MRI and bone formation on conventional radiographs, needs to be further elucidated. Inflammation might be the first step in the domino-effect leading to bone formation.[44] However, inflammation and bone formation might also be (partly) uncoupled processes. New therapeutic options should then also need to target pathways of bone-formation.[11] Prospective (longitudinal) cohorts are necessary to provide more insight into the predictive potential of MRI and may ultimately guide the rheumatologist in clinical decision-making.

With regard to improving referral of patients suspected for axial and peripheral SpA to specialist services, it is important that GPs are both informed and motivated to incorporate the latest insights about SpA into their daily work practices.[43] Much attention has been given to referral strategies, but lack of knowledge about SpA and absence of incentives for change may prevent successful implementation of any referral strategy. Therefore, a targeted educational activity should not only include increase knowledge about SpA, but also create commitment among GPs to change the quality of care for this relatively young patient group.[45-47] More research is necessary in order to develop and test educational activities that can ultimately be used to successfully implement referral strategies in primary care.

OVERALL CONCLUSIONS

This thesis shows that the predictive potential of MRI-SIJ in patients with early IBP is high with regard to the presence or absence of active lesions, especially in combination with other parameters such as HLA-B27 and gender. Signs of BME on MRI seem a trigger for reparative processes such as fatty lesions, which strengthen ideas about the need for early anti-inflammatory treatment. Early initiation of treatment can only start after timely referral of patients suspected of SpA by GPs. To achieve timely referral, it is important that GPs and rheumatologists learn from each other. Both have complementary skills that are necessary to ensure high-quality care for patients throughout their disease trajectory. Knowing is half the battle.

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Samenvatting in het Nederlands

INLEIDING

Spondyloartritis (SpA) is een verzamelnaam voor een aantal inflammatoire reumatische aandoeningen van het bewegingsapparaat met verwante klinische kenmerken, genetische aanleg en familiair optreden. Tot de groep van SpA behoren onder andere ankyloserende spondylitis (AS), arthritis psoriatica, reactieve artritis en enteropathische artritis.[1] Typisch voor SpA is dat ook extra-articulaire manifestaties (aandoeningen in andere organen dan het skelet) deel kunnen uitmaken van het ziektebeeld.[2]

Tegenwoordig wordt de groep van SpA ook wel ingedeeld in axiale SpA en perifere SpA. Bij axiale SpA staan symptomen van het axiale skelet op de voorgrond, met als overheersende symptoom inflammatoire rugpijn veroorzaakt door sacro-iliitis (ontsteking van het heiligbeen) en/of spondylitis (ontsteking van de wervellichamen). De bekendste vorm van axiale SpA is de aandoening AS, oftewel de ziekte van Bechterew.[2] Bij perifere SpA staan artritis, enthesitis (inflammatie op de plaats waar pees aan bot vastzit) en dactylitis (worstvormig gezwollen teen of vinger) op de voorgrond.[2] In totaal krijgt 40-50% van de patiënten met SpA tijdens het beloop van de ziekte een extra-articulaire manifestatie, zoals acute uveitis anterior (regenboog-vliesontsteking), inflammatoire darmziekten en psoriasis.[3] SpA begint meestal op jongvolwassen leeftijd. Aanvang van de eerste klachten na het 45e levensjaar is zeldzaam.[4]

Bij axiale SpA en in het bijzonder type AS kan uiteindelijk een klassiek radiologisch beeld met ankylosering van de sacro-iliacale gewrichten op een bekkenfoto zichtbaar worden.[1] In de wervelkolom kunnen syndesmofyten ontstaan door verbening van intervertebrale ligamenten.[1] Dit leidt uiteindelijk in het meest gevorderde stadium tot volledige ankylose van de wervelkolom, een zogeheten bamboo spine. Wanneer er geen of slechts dubieuze afwijkingen zichtbaar zijn op een conventionele bekkenfoto, kan men besluiten een Magnetic Resonance Imaging (MRI) van de sacro-iliacale gewrichten te maken. Op de MRI kunnen voor sacro-iliitis kenmerkende afwijkingen worden gezien, bijvoorbeeld subchondraal beenmergoedeem. Indien de patiënt een afwijkende MRI heeft in combinatie met een ander SpA kenmerk, dan wordt dit 'niet-röntgenologische axiale SpA' genoemd.[5,6] Bij een aantal patiënten met niet-röntgenologische axiale SpA is sacro-iliitis op een MRI (nog) niet aantoonbaar. Deze patiënten worden op basis van genetische aanleg (humaan leukocytenantigeen B27 (HLA-B27)) en minimaal twee andere kenmerkende SpA-manifestaties ook gerekend tot de groep van niet-röntgenologische axiale SpA.

Bij patiënten met axiale SpA duurt het gemiddeld negen jaar na het ontstaan van de eerste rugklachten voordat de diagnose wordt gesteld.[4] Een belangrijke reden hiervoor is dat afwijkingen op een conventionele bekkenfoto, wat voorheen als een vereiste gold voor het stellen van de diagnose ankyloserende spondylitis, slechts laat in het ziekteproces zichtbaar worden. De MRI kan hier uitkomst bieden, omdat op de MRI vaak wel afwijkingen typisch voor sacro-iliitis worden gezien.[6] Daarnaast heeft men lang gedacht dat axiale SpA een typische mannenziekte was. In de literatuur zijn man-vrouwverhoudingen beschreven van 8:1 à 10:1. Er blijkt echter sprake te zijn geweest van onderdiagnose bij vrouwen. Bij vrouwen ziet men minder structurele schade op een conventionele bekkenfoto.[7] Tegenwoordig wordt verondersteld dat de prevalentie van axiale SpA in mannen en vrouwen gelijk is.

Eerder onderzoek heeft laten zien dat een goede en tijdige behandeling van SpA uiteindelijk leidt tot een verbetering van verschillende uitkomstmaten, waaronder de mate van ziekteactiviteit, arbeidsproductiviteit en kwaliteit van leven.[8-10] De huisarts is een sleutelfiguur wanneer het gaat om de herkenning en vroege verwijzing van patiënten met klachten die zouden kunnen wijzen op SpA. De afgelopen jaren zijn verschillende strategieën ontwikkeld die een snelle verwijzing van patiënten met SpA mogelijk zouden moeten maken.[11-15] Huisartsen hebben echter moeite met het herkennen van het ziektebeeld.[16] Slechte herkenning kan er toe leiden dat de verwijsstrategieën niet goed worden toegepast in de huisartsenpraktijk. Educatie specifiek gericht op SpA zou de kennis, herkenning en daardoor verwijzing van patiënten naar de reumatoloog mogelijk kunnen verbeteren.

De onderzoeken zoals beschreven in dit proefschrift richten zich op de vroege herkenning van SpA.

DEEL I: DE EPIDEMIOLOGIE VAN SPONDYLOARTRITIS

In **hoofdstuk 1** wordt beschreven dat er de afgelopen jaren veel is verbeterd ten aanzien van de mogelijkheden om SpA eerder te diagnosticeren. Een belangrijke verandering is de ontwikkeling van nieuwe naamgeving door de Assessment in SpondyloArthritis international Society (ASAS).[17-20] Momenteel wordt onderscheid gemaakt tussen axiale SpA en perifere SpA. Axiale SpA wordt verder onderverdeeld in 'röntgenologische axiale SpA' ofwel AS en 'niet-röntgenologische axiale SpA', een aandoening waarbij geen of onvoldoende afwijkingen op een röntgenfoto aanwezig

zijn.[17] Door niet-röntgenologische axiale SpA als zodanig te erkennen en op te nemen in de ASAS axiale SpA classificatiecriteria, heeft de focus zich de afgelopen jaren verlegd richting vroege herkenning van axiale SpA.[17,19]

Ondanks (of door) deze ontwikkelingen, bleef verder onderzoek op het gebied van SpA nodig. Zo is het belangrijk om betrouwbare epidemiologische gegevens te verzamelen over het wereldwijd voorkomen van (de verschillende subtypes van) SpA. Deze gegevens kunnen worden gebruikt om meer inzicht te krijgen in welke maatregelen en middelen nodig zijn om patiënten met SpA tijdig op te kunnen sporen en te behandelen. In **hoofdstuk 2** wordt een systematisch literatuuronderzoek en meta-analyse naar de prevalentie van (subtypes van) SpA gepresenteerd. In totaal werden 84 studies geïdentificeerd. Verschillende demografische (waaronder ook geografische) en methodologische variabelen werden bestudeerd om te achterhalen of zij een deel van de variatie in prevalentie tussen de verschillende studies konden verklaren. De gepoolde populatieprevalentie van SpA was 0.55% (95% betrouwbaarheidsinterval (BI) 0.37-0.77); de gepoolde populatieprevalentie van AS was 0.18% (95% BI 0.15-0.23). Tussen de geïncludeerde studies werd echter een hoge heterogeniteit gevonden. De variatie in prevalentie tussen de verschillende wereldregio's kon deels worden verklaard door de bekende variatie in de prevalentie van HLA-B27 tussen deze regio's. In populaties waar de prevalentie van HLA-B27 hoog is, werd een hoge prevalentie van SpA gevonden. De hoogste prevalenties van SpA (inclusief AS) werden in afnemende volgorde gevonden bij inheemse bevolkingsgroepen die leven in het Arctisch gebied, Noord-Amerika, Oost-Azië en Europa. Een andere interessante bevinding was dat de prevalentie van SpA hoger was in studies van meer recente datum. Wellicht is deze stijging in prevalentie door de jaren heen te verklaren door het feit dat SpA inmiddels beter wordt herkend. Daarnaast was prevalentie afhankelijk van de manier waarop SpA werd gedefinieerd. Dit wordt mooi geïllustreerd in een populatiestudie uit de Verenigde Staten.[21] De prevalentie van SpA was 1.4% wanneer de ESSG criteria werden gehanteerd en 0.9% wanneer de Amor criteria werden gehanteerd. Dit verschil in prevalentie maakt duidelijk dat het type classificatiecriteria uiteindelijk invloed kan hebben op de gerapporteerde prevalentie van (subtypes van) SpA. Het is daarom te verwachten dat door het toepassen van de nieuwe ASAS axiale en perifere SpA classificatiecriteria, de prevalentie van SpA wederom beïnvloed kan worden en/of andere patiënten geïdentificeerd zullen worden.

DEEL II: HET GEBRUIK VAN MRI BIJ HET OPSPOREN VAN VROEGE SPONDYLOARTRITIS

Bij axiale SpA werd de ontwikkeling van nieuwe classificatiecriteria voorafgegaan aan de introductie van de MRI van de sacro-iliacale gewrichten. Door de MRI te gebruiken, wordt het mogelijk de diagnose axiale SpA eerder te stellen.[22] Op een MRI kunnen immers, in tegenstelling met conventionele röntgenfoto's, ook kenmerken van ontstekingsactiviteit worden gezien, zoals beenmergoedeem. Verder kunnen ook structurele veranderingen worden gezien zoals erosies, vervetting van het beenmerg en ankylose.[6] Een MRI van de sacro-iliacale gewrichten wordt positief bevonden voor sacro-iliitis wanneer minstens één inflammatoire laesie (beenmergoedeem) aanwezig is op twee opeenvolgende MRI-sneden, of wanneer twee laesies aanwezig zijn op één MRI-snede.[6] De Early SpondyloArthritis Clinic (ESpAC) werd door onze onderzoeksgroep opgezet om meer inzicht te krijgen in de rol van MRI bij patiënten met symptomen suggestief voor axiale SpA. De twee jaar durende follow-up studie bestond uit drie evaluaties met tussenpozen van telkens één jaar. Elke evaluatie bestond onder meer uit een uitgebreid klinisch onderzoek en beeldvorming. MRI-scans van de sacro-iliacale gewrichten maakten een belangrijk onderdeel uit van deze studie. **Hoofdstuk 3** beschrijft de ontwikkeling van ontstekingsactiviteit op de MRI van de sacro-iliacale gewrichten, suggestief voor sacro-iliitis, gedurende een twee jaar durende follow-up periode. Op baseline hadden 24 (35%) van de 68 geïncludeerde patiënten een positieve MRI van de sacro-iliacale gewrichten. Zowel de aanwezigheid van HLA-B27 als een positieve MRI op baseline, waren onafhankelijk geassocieerd met een positieve MRI tijdens de follow-up periode. Bij afwezigheid van HLA-B27 en een negatieve MRI op baseline, was de ontwikkeling een positieve MRI tijdens follow-up zeer onwaarschijnlijk. Enkel bij HLA-B27 positieve mannen met een negatieve MRI kan het zinvol zijn de MRI te herhalen. Een aanzienlijk deel van deze patiënten ontwikkelde namelijk alsnog een positieve MRI tijdens de follow-up periode. Onze resultaten laten zien hoe patiënten met klachten verdacht voor axiale SpA op efficiënte wijze het diagnostisch traject kunnen doorlopen. Daarnaast ondersteunen onze bevindingen het feit dat de MRI inmiddels een prominente plaats heeft gekregen in de ASAS axiale SpA classificatiecriteria.[17,23,24]

Op dit moment wordt alleen ontstekingsactiviteit (beenmergoedeem) meegenomen bij de beoordeling of een MRI van de sacro-iliacale gewrichten al dan niet positief is. Er is momenteel echter een discussie gaande of structurele afwijkingen (erosies of beenmergvervetting) ook niet een onafhankelijke diagnostische waarde hebben.[25] In **hoofdstuk 4** onderzochten we de aanwezigheid en ontwikkeling van structurele

afwijkingen op een MRI van de sacro-iliacale gewrichten bij patiënten die zijn geïncludeerd in de ESpAC. Daarnaast werd gekeken of structurele afwijkingen op zowel de MRI als conventionele bekkenfoto vooraf werden gegaan door beenmergoedeem op de MRI op dezelfde locatie. Hoewel het aantal erosies op MRI tijdens follow-up toenam, werd er geen associatie met beenmergoedeem op dezelfde locatie een jaar daarvoor gevonden. Ondanks dat er slechts een lichte toename werd gevonden in de gebieden met beenmergvervetting, werd er wel een associatie met beenmergoedeem op dezelfde locatie in het voorafgaande jaar gevonden. Een interessante bevinding was dat beenmergvervetting met name werd gezien op locaties waar beenmergoedeem was verdwenen. De relatie tussen ontstekingsactiviteit en structurele schade op MRI bij patiënten met axiale SpA is de laatste jaren volop bediscussieerd.[26-33] De discussie richt zich met name op de vraag of ontstekingsactiviteit en structurele schade 'in relatie tot elkaar staan' of 'los van elkaar staan'. Eerder onderzoek laat tegenstrijdige resultaten zien.[29-32] Onze bevindingen ondersteunen de theorie dat beenmerg-vervetting mogelijk een herstelreactie is op eerder aanwezige ontsteking.[34] Ander onderzoek heeft aangetoond dat beenmergvervetting is geassocieerd met ontwikkeling van syndesmofieten (benige vergroeiing) in de wervelkolom.[35] Wij vonden geen associatie tussen ontstekingsactiviteit op MRI enerzijds en ontwikkeling van erosies op MRI of ankylose op de bekkenfoto anderzijds. Grotere studies dan ESpAC met meerdere MRI's en röntgenfoto's over een langere follow-up periode kunnen hierover uitsluitsel geven.

Om ontstekingsactiviteit op de MRI te kunnen vaststellen, kunnen verschillende MRI-sequenties worden gebruikt. Dit zijn de short tau inversion recovery (STIR) sequentie en de T1-gewogen spin-echo sequentie met onderdrukking van het vetsignaal na toediening van het contrastmiddel gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA).[6] In **hoofdstuk 5** lieten we zien dat de post-Gd-DTPA-sequentie geen toegevoegde waarde heeft boven de STIR-sequentie in combinatie met de conven-tionele bekkenfoto. Onze resultaten komen overeen met die van het SPondyloArthritis Caught Early (SPACE)-cohort, waar zowel op baseline als na drie maanden een volledige overeenkomst werd gezien tussen de STIR- en post-Gd-DTPA-sequentie.[36] Het lijkt er dus op dat de post-Gd-DTPA-sequentie kan worden overgeslagen terwijl de diagnostische waarde van de MRI behouden blijft. Deze bevinding leidt tot een kostenbesparing en vergroot daarmee de toepasbaarheid van de MRI wanneer patiënten verdacht voor axiale SpA tijdens het diagnostisch traject een MRI moeten ondergaan.

Bij aanvang van dit promotieonderzoek was er nog veel onduidelijkheid omtrent de toepasbaarheid van MRI. De aanbeveling dat alle patiënten met klachten verdacht voor axiale SpA en een negatieve bekkenfoto een MRI zouden moeten ondergaan, kon nog niet hard worden gemaakt. Een belangrijke vraag was of beenmergoedeem op MRI stabiel aanwezig blijft over de tijd. In **hoofdstuk 6** onderzochten we daarom de verdeling, frequentie van voorkomen en de ontwikkeling over de tijd van beenmerg-oedeem op een MRI van de sacro-iliacale gewrichten bij patiënten geïncludeerd in de ESpAC. Bijna de helft van de lokalisaties met beenmergoedeem dat op baseline werd vastgesteld, verdween tijdens follow-up. Omgekeerd werden er nieuwe lokalisaties met beenmergoedeem op een aantal MRI's tijdens follow-up vastgesteld, terwijl de voorafgaande MRI op baseline negatief was. In beide gevallen had dit gevolgen voor het al dan niet voldoen aan de ASAS axiale SpA classificatiecriteria. Dit laat zien dat het toepassen van beeldvormende technieken om een reumatische aandoening te diagnosticeren ook beperkingen met zich meebrengt. Bevindingen bij beeldvorming zijn immers altijd onderhevig aan meetfouten van beoordelaars en variatie tussen beoordelaars; beeldvorming moet daarom geen belangrijkere rol toebedeeld krijgen dan de bevindingen tijdens anamnese en klinisch onderzoek. 'Blindstaren' op een MRI-uitslag kan bijvoorbeeld leiden tot een vertraging in het stellen van de diagnose van axiale SpA, wanneer cruciale bevindingen op MRI tijdelijk afwezig zijn bij een patiënt die wel past in het klinisch profiel. Omgekeerd, een MRI-uitslag kan ook leiden tot een fout-positieve diagnose van SpA, wanneer aan subtiele en weinig suggestieve laesies op MRI ('onschuldige witte plekjes') veel waarde wordt gehecht terwijl de klinische symptomen van de patiënt hier eigenlijk geen aanleiding toe geven. Alle manifestaties die worden gezien bij axiale SpA moeten daarom in overweging worden genomen bij de beoordeling van een patiënt, waaronder bijvoorbeeld psoriasis, enthesitis of uveitis. Dit gegeven komt eveneens terug in een recent ontwikkeld 'diagnostisch algoritme' waarin een gedegen anamnese en lichamelijk onderzoek onmisbare stappen zijn bij de beoordeling van een patiënt met verdenking op axiale SpA.[24] Alleen wanneer er voldoende verdenking is op axiale SpA, kan aanvullende beeldvorming worden aangevraagd.

DEEL III: HERKENNING VAN SPONDYLOARTRITIS IN DE HUISARTSENPRAKTIJK

De reumatoloog is mede dankzij de MRI in staat gesteld de diagnose SpA in een eerder stadium te stellen. Patiënten met een verdenking op SpA moeten hiervoor wel eerst

tijdig naar de reumatoloog verwezen worden. Het optimaliseren van de zorg rondom patiënten met SpA begint dus altijd met zogenaamde 'case finding'. Dit proces start meestal in de eerste lijn. In **hoofdstuk 7** werden zowel het kennisniveau als de percepties van huisartsen over inflammatoire rugpijn en axiale SpA bestudeerd. Daarnaast werd gekeken welke potentiële barrières een tijdige verwijzing van patiënten met mogelijk axiale SpA verhinderen. We toonden aan dat axiale SpA vaak niet goed in de eerste lijn wordt herkend. Zelfs wanneer het wel wordt herkend, dan is de zorg rondom deze patiënten vaak suboptimaal. In het algemeen was de kennis omtrent inflammatoire rugpijn, axiale SpA en extra-articulaire manifestaties beperkt. Huisartsen herkenden veelal slechts de 'klassieke', maar langetermijngevolgen van axiale SpA, zoals bijvoorbeeld een kyfose die wordt gezien bij AS. Slechts de helft van de geïnterviewde huisartsen wist dat Tumor Necrosis Factor (TNF)-alpha blokkerende biologicals, een erkende en effectieve behandeling bij een specifieke groep van patiënten met bij axiale SpA, een behandeloptie zijn bij deze patiëntengroep. Vergroten van kennis bij huisartsen aangaande de symptomen en behandeling van axiale SpA, zal waarschijnlijk de verwijzing van patiënten met klachten verdacht voor axiale SpA bevorderen.

In de dagelijkse praktijk moet de huisarts adequaat kunnen anticiperen op velerlei lichamelijke en psychische klachten waar patiënten zich mee presenteren. Herkenning van patiënten met SpA in de huisartsenpraktijk kan lastig zijn. Chronische rugpijn is immers een veelvoorkomend symptoom in de algemene populatie en is voor patiënten ook vaak een reden om de huisarts te bezoeken. Slechts in 5% van de gevallen is axiale SpA de onderliggende oorzaak.[37] Het finetunen van de procedure om de patiënten te selecteren die wel dienen te worden verwezen naar de tweedelijn, is echter een belangrijke nog te maken stap. Een recente studie heeft laten zien dat bijna een kwart van de patiënten met chronische rugpijn die ontstond voor de leeftijd van 45 jaar geclassificeerd kon worden met axiale SpA nadat de huisarts deze patiënten had verwezen naar de reumatoloog.[38]

De huisarts is onmisbaar bij het herkennen van patiënten met SpA. Huisartsen verkeren in een unieke positie: ze kunnen 'longitudinale continue zorg' leveren in overeen-stemming met overige behoeften van een patiënt. Dit betekent dat ze in staat zijn om het patroon kenmerkend voor axiale SpA, bijvoorbeeld achtereenvolgens optreden van psoriasis en rugpijn, als eerste te herkennen wanneer een patiënt de praktijk bezoekt.

In **hoofdstuk 8** onderzochten we in hoeverre huisartsen en huisartsen in opleiding (HAIO) vroege axiale en perifere SpA herkennen en verwijzen. We maakten gebruik van simulatiepatiënten om te onderzoeken 'hoe het er in de praktijk echt aan toe gaat'.

Daarbij keken we ook naar de invloed van educatie op de mate van herkenning en uiteindelijk verwijzing. In totaal werden 68 huisartsen en HAIO's bezocht door simulatiepatiënten die waren getraind om een casus van vroege axiale dan wel perifere SpA te simuleren. We bevestigden dat zowel de herkenning als verwijzing van patiënten met klachten suggestief voor SpA slechts beperkt was. Educatie verbeterde duidelijk de herkenning en verwijzing van patiënten naar de reumatoloog. Het geven van onderwijs lijkt daarmee een belangrijke kans om de kennis wat betreft SpA te verbeteren, waardoor een succesvolle implementatie van een verwijsstrategie dichterbij komt.

PERSPECTIEF

In **hoofdstuk 9** werden bevindingen uit dit proefschrift samengevat en enkele methodologische aspecten verder bediscussieerd. Ten eerste werd stilgestaan bij de generaliseerbaarheid van de resultaten die zijn verkregen uit het ESpAC-onderzoek. Patiënten die werden geïncludeerd in de ESpAC waren reeds verdacht op het hebben van SpA en waren verwezen door de reumatoloog of door medisch specialisten die extra-articulaire manifestaties van SpA behandelen (waaronder dermatologen, oogartsen). Veel patiënten in ESpAC presenteerden zich dus met duidelijke klachten, zoals bijvoorbeeld 'inflammatoire rugpijn in combinatie met psoriasis of uveitis'. Door patiënten langs deze route te includeren is het waarschijnlijk dat sommige bevindingen niet meteen te generaliseren zijn naar patiënten met een minder duidelijk klinisch beeld, bijvoorbeeld patiënten met uitsluitend inflammatoire rugpijn in de huisartsenpraktijk. Daarentegen, onze primaire onderzoeksvraag was hoe afwijkingen op de MRI verdacht voor sacro-iliitis zich over de tijd ontwikkelen. Het includeren van patiënten met een hoge 'pakkans' vergroot dan de efficiëntie en interne validiteit.

Ten tweede werden de voor- en nadelen van het gebruik van simulatiepatiënten in onderzoek besproken. Door simulatiepatiënten in te zetten waren wij in staat te kijken of educatie uiteindelijk ook een gedragsverandering in gang zet. Dit gaat dus verder dan het afnemen van een toets na een educatiemoment. Onze resultaten laten zien dat simulatiepatiënten ook ingezet kunnen worden bij meer ingewikkelde medische problemen zoals bijvoorbeeld SpA. Er zijn dan wel meer voorbereidingsmaatregelen nodig. Specifiek in ons onderzoek was het bijvoorbeeld belangrijk om een goede voorgeschiedenis op te stellen en een nauwkeurige beschrijving te geven van de reeds ondernomen stappen, zoals het effect van eerder ontvangen fysiotherapie op de klachten.

Ten slotte werden er aanbevelingen gedaan voor de klinische praktijk en verder onderzoek. Met de introductie van de MRI van de sacro-iliacale gewrichten is de reumatoloog in staat gesteld om patiënten met SpA eerder een diagnose te kunnen geven en hierdoor, indien nodig, tijdig te starten met een behandeling. Het onderzoek beschreven in dit proefschrift kan reumatologen helpen hoe ze de MRI in de dagelijkse praktijk kunnen inzetten. Meer onderzoek is echter nodig om onder andere de diagnostische waarde van structurele veranderingen op een MRI vast te stellen.

Snel instellen van een behandeling leidt mogelijk tot minder werkverzuim en arbeidsongeschiktheid. Om het gunstige effect van een vroege diagnose op de verschillende uitkomstmaten optimaal te benutten, is het wel belangrijk dat patiënten ook snel worden verwezen. Wij hebben laten zien dat educatie aan huisartsen hierbij kan helpen. Meer onderzoek is nodig om te kijken welke onderwijsactiviteiten bijdragen aan een succesvolle verwijsstrategie is. Bij het bewerkstelligen van dit doel is het belangrijk te realiseren dat reumatologen en huisartsen hierbij van elkaar kunnen leren. Beide medische disciplines vullen elkaar mooi aan wanneer het gaat om het leveren van kwalitatief goede zorg voor patiënten met SpA.

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Valorisation addendum

VALORISATION ADDENDUM

Valorisation refers to the process of how academic research can be utilized and translated to clinical and societal benefit. The relevance of the research presented in this thesis is described in the section below.

Part I: epidemiology of spondyloarthritis

Quantification of the burden of rheumatic conditions is important for raising awareness among health care professionals, setting research priorities and initiating a policy debate.[1] Rheumatic conditions have major impact on the individual patient, but also on society. Also in the case of spondyloarthritis (SpA), important decreases in almost all aspects of health related quality of life are reported. The onset at a relatively young age, before the fourth decade, adds to the years lived in disability for an individual.[2] As a consequence of decreased functioning, SpA has an adverse impact on the patient and family by reduced participation in social roles.[3,4] The indirect costs related to SpA are four times as high as the direct costs, reflecting the important impact of the disease on work participation in terms of sick leave, disability pensions and early retirement.[5] To extrapolate how this individual burden would affect society, appropriate data on the epidemiology are warranted. In this thesis, we found that the global prevalence of SpA was 0.55% (95% Confidence Interval (CI): 0.37-0.77). This prevalence is comparable to that of rheumatoid arthritis. Substantial variation across geographic regions was however found. For instance, the prevalence of SpA in East Asia was 0.79% (CI: 0.48-1.18). The study described in this thesis adds to the available evidence on epidemiology of rheumatic diseases that can contribute to prioritize research, but also to inform health care systems at the country level, when allocating budgets to improve diagnosis, treatment and prevention of work disability.[1,6-8]

Part II: the use of MRI in early detection of axial spondyloarthritis

The introduction of MRI for detecting active sacroiliitis has revolutionized the diagnosis of axial SpA (axSpA), making an early diagnosis possible. This thesis showed that a positive MRI is a reliable finding: a positive MRI at baseline was strongly associated with a positive MRI of the sacroiliac joints (MRI-SIJ) over time, particularly in HLA-B27 positive patients. This is important for clinicians, because it suggests that a diagnosis of axSpA incorporating a positive MRI is robust and credible. Furthermore, the post-gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) MRI sequence can be safely omitted, which increases the feasibility of MRI, since it saves time and reduces costs.

Further, in axSpA it is a challenge to identify the appropriate target for treatment: should it be disease activity, prevention or delay in progression of structural damage, or both? In this thesis, we focused on the relation between inflammation and development of structural damage (erosions and fatty lesions) on MRI. We have shown that fatty lesions on MRI-SIJ preferably develop after bone marrow edema (BME) has subsided. Other studies have suggested that fatty lesions at vertebral edges predict the development of new syndesmophytes.[9] BME may therefore be the first domino that sets off the chain that leads to development of fatty lesions and eventually new bone formation (syndesmophytes).[10,11] The true relation between BME and new bone formation still needs to be disentangled in further research. This thesis has contributed in one of the many steps to unravel the relation between inflammation and structural damage on MRI in order to enable identification of different treatment targets.

Part III: early identification of spondyloarthritis in primary care

Musculoskeletal disorders (MSD) are among the most common reasons for consulting a GP and have a major impact on healthcare resources.[12] The Global Burden of Disease 2010 study found that MSD, including rheumatic disorders, were the second main contributor to the number of years lived with disability.[1] Part of this burden is avoidable. The importance of MSD as major cause of (avoidable) disability, however, seems insufficiently acknowledged by GPs.[13,14] Training in rheumatology is rarely mandatory in general practice training programs, despite the large number of patients that present themselves in primary care with rheumatic disorders.[15] Nonetheless, it seems that musculoskeletal conditions are not a priority in primary care.[16,17]

Making a diagnosis of axSpA is often delayed up to 10 years or longer, suggesting that opportunities for early recognition and referral have been missed in primary care.[18,19] Several referral strategies that promote early referral of axSpA have been developed, but successful implementation may be hampered by ineffective referral patterns due to lack of knowledge about axSpA.[20-23] From this thesis, we learned that there is room for improvement with regard to the level of knowledge of GPs about their ability to identify and refer patients with suspected axSpA. Changing clinical practice behavior and assessing such change is a real challenge. The evidence that educational interventions may actually change anything is limited.[24] Lack of time and resources often contribute to failure of the education intervention.[24] This thesis shows that the use of standardized patients (SPs), is a feasible and informative approach to assess the impact of an educational intervention. More importantly, a multi-faceted educational program can play a key role in improving disease recognition

and referral of patients suspected for SpA. This important finding may further improve timely diagnosis and initiation of treatment of patients with SpA.

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Curriculum Vitae

CURRICULUM VITAE

Marloes van Onna werd op 2 augustus 1982 geboren in Beuningen. Na het behalen van haar gymnasiumdiploma aan het Kandinsky College in Nijmegen, studeerde zij van 2000 tot 2002 Gezondheidswetenschappen aan de universiteit van Maastricht. In 2002 besloot zij Geneeskunde te gaan studeren, omdat zij bij nader inzien toch geen 'onderzoeker' maar 'dokter' wilde worden. Tijdens een keuze-coschap Reumatologie en Maag-, Darm- en Leverziekten in Gent en vervolgens een wetenschappelijke stage op de afdeling Reumatologie in het Maastricht Universitair Medisch Centrum (MUMC) werd haar interesse voor de Reumatologie gewekt. Ze behaalde haar artsenbul in 2008 cum laude.

In 2009 begon zij aan haar vooropleiding Interne Geneeskunde in het MUMC (opleider: Prof. dr. C. Stehouwer). In hetzelfde jaar startte zij eveneens met het onderzoek welk uiteindelijk heeft geresulteerd in dit proefschrift. De resultaten zoals beschreven in dit proefschrift werden gepresenteerd op verschillende nationale en internationale congressen. De vervolgopleiding tot reumatoloog werd in 2012 voortgezet in zowel het MUMC als het Zuyderland Ziekenhuis in Heerlen (opleiders: Prof. dr. S. van der Linden, Dr. D. Vosse en Dr. R. Peeters).

Sinds 2015 werkt zij als staflid Reumatologie in het MUMC.