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Diagnosis and classification of axial spondyloarthritis : imaging and non-imaging features

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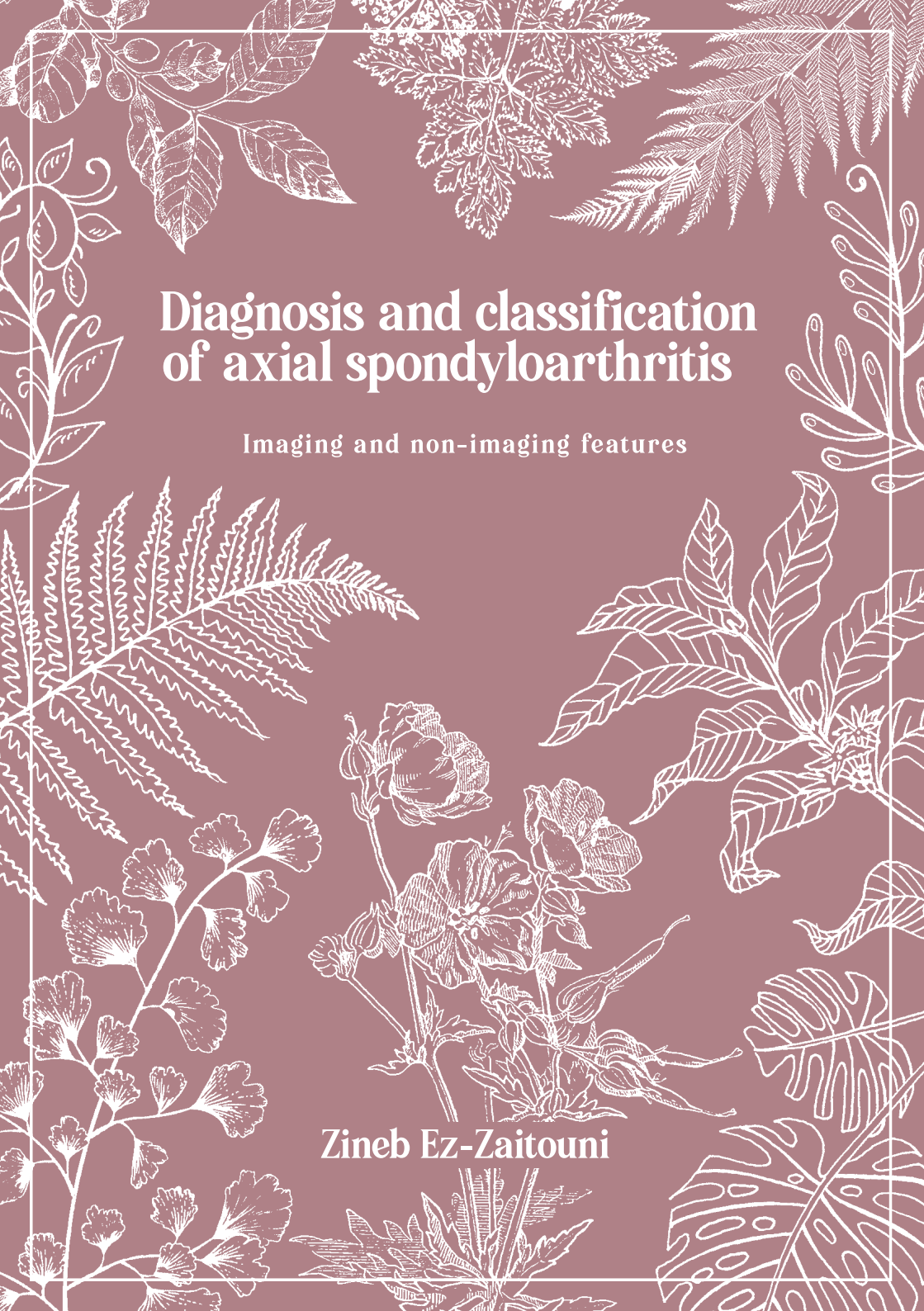


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The background of the cover is a dense, intricate botanical illustration in a light beige or cream color, set against a solid dark teal background. The illustration features a variety of plants, including ferns with delicate, feathery fronds, broad-leafed plants with serrated edges, and several flowering plants with detailed petals and stems. The overall style is reminiscent of traditional botanical woodcut prints or detailed line art.

Diagnosis and classification of axial spondyloarthritis

Imaging and non-imaging features

Zineb Ez-Zaitouni

**DIAGNOSIS AND CLASSIFICATION
OF AXIAL SPONDYLOARTHRITIS**
IMAGING AND NON-IMAGING FEATURES

Zineb Ez-Zaitouni

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**DIAGNOSIS AND CLASSIFICATION
OF AXIAL SPONDYLOARTHRITIS**
IMAGING AND NON-IMAGING FEATURES

Proefschrift

Ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
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Prof. dr. M. Boers (Amsterdam UMC, locatie VUmc)

**'SUCCESS ISN'T ABOUT HOW MUCH MONEY YOU MAKE,
IT'S ABOUT THE DIFFERENCE YOU MAKE IN PEOPLE'S LIVES'**

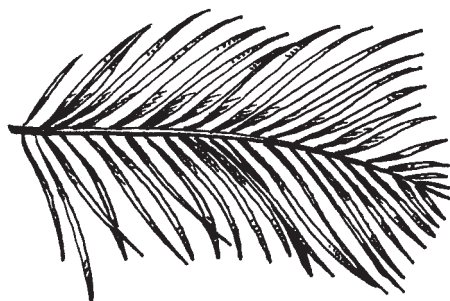
- Michelle Obama, September 4, 2012 -

Aan mijn ouders

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General introduction



GENERAL INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease which is characterized by inflammation and frequently structural damage in the sacroiliac joints and/or spine. Patients typically present during young adulthood (typically before the age of 45) with chronic back pain (at least three months' duration) – often of inflammatory character – and spinal stiffness. AxSpA is frequently split into two subtypes: (1) non-radiographic axSpA, in which patients have clinical signs and symptoms of axSpA but without sacroiliitis on radiographs; and (2) radiographic axSpA (i.e. Ankylosing Spondylitis (AS)), in which patients have the abovementioned clinical presentation in combination with definite sacroiliitis on radiographs.¹ Patients with axSpA may have several so called spondyloarthritis (SpA) features, although this varies strongly across patients. These SpA features include elevated acute phase reactants (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), Human Leukocyte Antigen B27 (HLA-B27), sacroiliitis on imaging (radiography and magnetic resonance imaging (MRI) of the sacroiliac joints), inflammatory back pain (IBP), good response to non-steroidal anti-inflammatory drugs (NSAIDs), positive family history of SpA, peripheral arthritis, dactylitis, enthesitis, acute anterior uveitis, inflammatory bowel disease (IBD), and psoriasis.²⁻¹¹

The timely recognition of axSpA – especially in an early disease stage – is challenging as the disease is heterogeneous in its presentation and diagnostic criteria including a formal gold standard for diagnosis are lacking. The diagnosis of axSpA is therefore usually made after a thorough diagnostic work-up which includes a clinical assessment of all typical SpA features, laboratory tests (HLA-B27 and acute phase reactants), and imaging findings (sacroiliitis on radiographs or MRI) while excluding other more likely causes of chronic back pain.^{3, 12-16} An important tool in assisting clinicians with the (early) diagnosis of axSpA and increasing diagnostic confidence is the modified Berlin algorithm.¹⁷ This algorithm was developed to minimize the number of unnecessary diagnostic tests in chronic back pain patients eventually leading to fewer costs for patients and for the health care system. The algorithm combines multiple clinical and laboratory indices of patients with chronic back pain (duration of at least three months) with an age of onset ≤ 45 years to advise rheumatologists in their next diagnostic step after initial radiography. In the absence of radiographic sacroiliitis the algorithm, depending on the number of SpA features present in a patient, guides the diagnostician with regard to which patients require subsequent testing, such as determining HLA-B27 and/or performing an MRI of the sacroiliac joints (MRI-SI). Importantly, the diagnostic algorithm is an aid and does not suffice to make a definite diagnosis in an individual patient.

Next to this diagnostic tool for axSpA several classification criteria sets have been developed for the purpose of conducting clinical trials or cohort studies. In 2009, the Assessment of Spondyloarthritis international Society (ASAS), an international group of experts in the field of SpA, developed new classification criteria covering the full spectrum of axSpA.¹⁸ These classification criteria combine clinical, laboratory, and imaging features for classification of axSpA patients. However, it is important to note that these classification criteria should only be applied to patients in whom a diagnosis of axSpA has already been established. Classification criteria are used for research purposes (i.e. creating a homogenous group of patients) with a clear dichotomous (yes or no) result. This is in contrast to clinical diagnosis making, where differential diagnoses have to be considered and negative findings are also taken into account in the diagnostic work-up.

One of the most important aspects in the (early) diagnosis (and classification) of axSpA is the use of imaging (conventional radiography and MRI) to assess active inflammation and/or structural damage highly suggestive of axSpA. For several years clinicians, have relied on radiography of the sacroiliac joints (X-SI) to detect sacroiliitis.¹ However, an important disadvantage of X-SI is that it only captures structural damage (i.e. erosions, sclerosis, and ankylosis), which usually takes months to years to develop.^{19, 20} Furthermore, not all patients will develop structural bone lesions in the sacroiliac joints or spine, which jeopardises the early detection of axSpA patients. MRI-SI can be used to visualize both inflammation and structural damage and can therefore be used to detect axSpA in patients who have not (yet) developed radiographic sacroiliitis.²¹⁻²⁴ There have been studies investigating the presence of spinal inflammatory and structural lesions (i.e. fatty lesions, erosions, and syndesmophytes) on MRI in axSpA patients.²⁵⁻²⁷ However, currently only radiographic sacroiliitis and sacroiliitis on MRI based on inflammation are considered in the ASAS classification criteria for axSpA. Information on the use of structural lesions on MRI-SI and spinal (inflammatory and structural) lesions on MRI in axSpA diagnosis and classification is still limited.

Outline of this thesis

The continued challenge of early diagnosis of axSpA in patients presenting with chronic back pain has led to the research presented in this thesis.

In general terms, the aims of this thesis were as follows:

1. To gain better insight into how a diagnosis of early axSpA is made in common clinical practice.
2. To assess the potential value of adding spine MRI to the classification criteria for axSpA.
3. To evaluate the role of imaging findings in early axSpA diagnosis and classification.

To address the aims of this thesis data from two cohorts were used: The Spondyloarthritis Caught Early (SPACE) and DEvenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohorts.

The SPACE cohort is an ongoing observational study which was initiated in 2009 at the Leiden University Medical Center (LUMC, the Netherlands). Patients with a minimum age of 16 years referred to Rheumatology outpatient clinics with short term chronic back pain (of unknown origin) for at least three months but not longer than two years, and age at onset of back pain <45 years, were included. In addition to not meeting the minimum age and duration of back pain criteria, the presence of other painful conditions not associated with axSpA that could interfere with the evaluation of disease activity, or any reason invalidating the informed consent or limiting the ability of the subject to comply with the protocol requirements, led to exclusion. Patients had been recruited from multiple rheumatology centres in Europe; the Netherlands (Leiden, Amsterdam and Gouda), Norway (Oslo), Italy (Padova), Portugal (Lisbon) and Sweden (Göteborg, Malmö, Falun, Skövde, Västerås, Huddinge, Stockholm). A detailed description of the SPACE cohort has been published elsewhere.²⁸

DESIR is a longitudinal cohort for which the inclusion period was between December 2007 and April 2010 in 25 participating centres in France. Patients between 18 and 50 years old with inflammatory back pain (thoracic, lumbar or buttock region) according to the Calin or Berlin criteria, persisting for at least three months but not longer than three years, were included.^{2,4} Moreover, the symptoms had to be highly suggestive of axSpA according to the treating rheumatologist expressed in a score of five or more on a numerical rating scale from zero to ten. Exclusion criteria were (1) the presence of a clearly defined spinal disease, (2) history of treatment with any biological drug, (3) corticosteroid intake of a dose higher than 10 mg prednisone per day and unstable intake for at least 4 weeks prior to baseline, and (4) history or current disorders which might interfere with the validity of the informed consent and/or prevent an optimal compliance of the patient to the cohort (e.g. alcoholism, psychological disorders). A detailed description of the DESIR cohort has also been published before.²⁹

As part of both study protocols patients underwent a full diagnostic work-up to assess disease characteristics and the presence of all SpA features, however small but important differences exist between the two cohorts. The SPACE cohort is a multicentre, multinational study whilst the DESIR cohort is a strictly French cohort with multiple participating centres across the country. Furthermore, the SPACE cohort includes patients with chronic back pain of short duration (between three months and two years), and with an age of onset <45 years. DESIR,

however, included patients between the ages of 18 and 50 years with IBP (between three months and three years) and a substantial suspicion of axSpA (measured by the physician's level of confidence in diagnosis of at least five on a zero to ten scale).

The first aim of this thesis focuses on getting better insight into how chronic back pain patients are diagnosed with axSpA in clinical practice. Since the development of the ASAS classification criteria for axSpA, and the lack of diagnostic criteria, experts have raised concerns about 'overdiagnosis' when using the classification criteria as a checklist in the diagnosis of chronic back pain patients. In **Chapter 2** we investigated in the SPACE cohort whether the presence of multiple SpA features in a chronic back pain patient always leads to axSpA diagnosis, and looked into the agreement between the rheumatologist's diagnosis and ASAS classification. An important question is what the alternative diagnoses were in the patients who were not diagnosed with axSpA but who did have at least four SpA features. In **Chapter 3** we briefly discuss the clinical characteristics of these patients and their alternative diagnosis. The diagnosis of axSpA is complex and is therefore accompanied by a certain diagnostic uncertainty. It is unclear whether the development of SpA features over time may possibly lead to more confidence in diagnosis. Therefore, we investigated diagnostic uncertainty in patients with recent onset CBP at baseline and after one-year follow-up in **Chapter 4**. In addition, we systematically investigated SpA feature accrual in one year and the influence on diagnosis and level of certainty. One of the SpA features which can be assessed in chronic back pain patients is a positive family history of SpA (i.e. the presence of AS, acute anterior uveitis, reactive arthritis, IBD, and psoriasis in first- or second-degree relatives). The definition of a positive family history was constructed by a panel of SpA experts, but was never validated. **Chapter 5** discusses the usefulness of the current definition in identifying axSpA in both the SPACE and DESIR cohorts.

MRI is an important tool in the assessment of inflammation in both clinical practice for diagnosis and in scientific studies for classification using the ASAS criteria. The ASAS classification criteria have only incorporated inflammatory lesions according to a specific definition on MRI and structural lesions on radiography in the sacroiliac joints to define positive imaging. Several studies however have shown that spinal inflammatory lesions occur in chronic back pain patients either together with abnormalities in the SI joints or independently. **Chapter 6** focuses on the second aim of this thesis, which is to evaluate the additional value of MRI-spine, with the use of different definitions of a positive MRI-spine, as an imaging criterion in the ASAS classification criteria in both SPACE and DESIR.

The last part of this thesis describes the influence of imaging and its interpretation in the diagnosis and classification of chronic back pain patients. Previous studies have already shown that the interpretation of sacroiliac joint imaging may result in different interpretations in a significant number of patients. In **Chapter 7** we investigated the influence of different readings by local assessors and central readers on the classification of chronic back pain patients in the SPACE cohort. The aim was to validate the findings of the DESIR cohort on this topic. From previous work in the SPACE cohort it is known that rheumatologists highly value the presence of HLA-B27 and sacroiliitis on imaging when making a diagnosis of axSpA. However, there is limited knowledge on how imaging is used in the diagnostic process of axSpA, and – more specifically – to what extent rheumatologists are influenced by imaging results in diagnosing chronic back pain patients. **Chapter 8** finally looks into the impact of sacroiliac imaging on axSpA diagnosis and the diagnostic confidence of rheumatologists. **Chapter 9** consists of a summary and a general discussion on the findings of this thesis with future perspectives for clinical practice and research. A summary in Dutch is provided in **Chapter 10**.

REFERENCES

1. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.
2. Calin A, Porta J, Fries JF, *et al.* Clinical history as a screening test for ankylosing spondylitis. *Jama* 1977;237:2613-4.
3. Rudwaleit M, van der Heijde D, Khan MA, *et al.* How to diagnose axial spondyloarthritis early. *Ann Rheum Dis* 2004;63:535-43.
4. Rudwaleit M, Metter A, Listing J, *et al.* Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum* 2006;54:569-78.
5. Rojas-Vargas M, Munoz-Gomariz E, Escudero A, *et al.* First signs and symptoms of spondyloarthritis--data from an inception cohort with a disease course of two years or less (REGISPONSER-Early). *Rheumatology (Oxford)* 2009;48:404-9.
6. Rudwaleit M, Haibel H, Baraliakos X, *et al.* The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum* 2009;60:717-27.
7. Sieper J, Rudwaleit M, Baraliakos X, *et al.* The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;68 Suppl 2:ii1-44.
8. Braun J, Inman R. Clinical significance of inflammatory back pain for diagnosis and screening of patients with axial spondyloarthritis. *Ann Rheum Dis* 2010;69:1264-8.
9. Rudwaleit M, van der Heijde D, Landewe R, *et al.* The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011;70:25-31.
10. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, *et al.* Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:65-73.
11. de Winter JJ, van Mens LJ, van der Heijde D, *et al.* Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. *Arthritis Res Ther* 2016;18:196.
12. Tuite MJ. Sacroiliac joint imaging. *Semin Musculoskelet Radiol* 2008;12:72-82.
13. Mitra R. Osteitis Condensans Ilii. *Rheumatol Int* 2010;30:293-6.
14. van Tubergen A, Weber U. Diagnosis and classification in spondyloarthritis: identifying a chameleon. *Nat Rev Rheumatol* 2012;8:253-61.
15. Salaffi F, De Angelis R, Carotti M, *et al.* Fibromyalgia in patients with axial spondyloarthritis: epidemiological profile and effect on measures of disease activity. *Rheumatol Int* 2014;34:1103-10.
16. Slobodin G, Lidar M, Eshed I. Clinical and imaging mimickers of axial spondyloarthritis. *Semin Arthritis Rheum* 2017.
17. van den Berg R, de Hooze M, Rudwaleit M, *et al.* ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. *Ann Rheum Dis* 2013;72:1646-53.

18. Rudwaleit M, van der Heijde D, Landewe R, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-83.
19. Bennett AN, McGonagle D, O'Connor P, *et al.* Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. *Arthritis Rheum* 2008;58:3413-8.
20. Dougados M, Sepriano A, Molto A, *et al.* Sacroiliac radiographic progression in recent onset axial spondyloarthritis: the 5-year data of the DESIR cohort. *Ann Rheum Dis* 2017.
21. Landewe RB, Hermann KG, van der Heijde DM, *et al.* Scoring sacroiliac joints by magnetic resonance imaging. A multiple-reader reliability experiment. *J Rheumatol* 2005;32:2050-5.
22. Bennett AN, Rehman A, Hensor EM, *et al.* Evaluation of the diagnostic utility of spinal magnetic resonance imaging in axial spondylarthritis. *Arthritis Rheum* 2009;60:1331-41.
23. Rudwaleit M, Jurik AG, Hermann KG, *et al.* Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis* 2009;68:1520-7.
24. Weber U, Lambert RG, Ostergaard M, *et al.* The diagnostic utility of magnetic resonance imaging in spondylarthritis: an international multicenter evaluation of one hundred eighty-seven subjects. *Arthritis Rheum* 2010;62:3048-58.
25. Baraliakos X, Landewe R, Hermann KG, *et al.* Inflammation in ankylosing spondylitis: a systematic description of the extent and frequency of acute spinal changes using magnetic resonance imaging. *Ann Rheum Dis* 2005;64:730-4.
26. Hermann KG, Baraliakos X, van der Heijde DM, *et al.* Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. *Ann Rheum Dis* 2012;71:1278-88.
27. de Hooze M, van den Berg R, Navarro-Compan V, *et al.* Patients with chronic back pain of short duration from the SPACE cohort: which MRI structural lesions in the sacroiliac joints and inflammatory and structural lesions in the spine are most specific for axial spondyloarthritis? *Ann Rheum Dis* 2015.
28. van den Berg R, de Hooze M, van Gaalen F, *et al.* Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. *Rheumatology (Oxford)* 2013;52:1492-9.
29. Dougados M, d'Agostino MA, Benessiano J, *et al.* The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. *Joint Bone Spine* 2011;78:598-603.

Presence of multiple spondyloarthritis (SpA)-features is important but not sufficient for a diagnosis of axial spondyloarthritis: data from the Spondyloarthritis Caught Early (SPACE)-cohort.



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Ann Rheum Dis, 2017. 76(6): p. 1086-1092.

ABSTRACT

Objectives

Concerns have been raised about overdiagnosis of axial spondyloarthritis (axSpA). We investigated whether patients with chronic back pain (CBP) of short duration and multiple SpA-features are always diagnosed with axSpA by the rheumatologist, and to what extent fulfilment of the ASAS axSpA criteria is associated with an axSpA diagnosis.

Methods

Baseline data from 500 patients from the SPondyloArthritis Caught Early (SPACE)-cohort which includes CBP patients (≥ 3 months, ≤ 2 years, onset < 45 years) were analysed. All patients underwent full diagnostic work-up including MRI-SI and X-SI. For each patient, the total number of SpA-features excluding sacroiliac imaging and HLA-B27 status was calculated.

Results

Before sacroiliac imaging and HLA-B27 testing, 32% of patients had ≤ 1 SpA-feature, 29% had 2 SpA-features, 16% had 3 SpA-features and 24% had ≥ 4 SpA-features. A diagnosis of axSpA was made in 250 (50%) of the patients: 24% with ≤ 1 SpA-feature, 43% with 2 SpA-features, 62% with 3 SpA-features and 85% with ≥ 4 SpA-features. Of the 230 patients with a positive ASAS classification 40 (17.4%) did not have a diagnosis of axSpA. HLA-B27 positivity (OR 5.6; 95% CI 3.7 to 8.3) and any (MRI-SI and/or X-SI) positive imaging (OR 34.3; 95% CI 17.3 to 67.7) were strong determinants of an axSpA diagnosis

Conclusion

In this cohort of CBP patients, neither the presence of numerous SpA-features nor fulfilment of the ASAS classification criteria did automatically lead to a diagnosis axSpA. Positive imaging was considered particularly important in making a diagnosis of axSpA.

INTRODUCTION

Axial spondyloarthritis (axSpA) has a heterogeneous clinical presentation and does not have a single pathognomonic feature that distinguishes the disease from other conditions with similar symptoms.^{1, 2} Therefore, it is a challenge to identify axSpA early in patients with chronic back pain (CBP). In daily rheumatologic practice, a diagnosis of axSpA is generally made in patients with CBP on the basis of a combination of symptoms from medical history, physical examination, laboratory investigations, and findings on imaging.^{3, 4}

In 2009 the Assessment of SpondyloArthritis international Society (ASAS) developed classification criteria for axSpA. The criteria combine information from several sources such as medical history, physical examination, laboratory testing, and imaging.⁵ In a secondary or tertiary care setting the fulfilment of the ASAS-criteria is strongly associated with a clinical diagnosis of axSpA at the group level, but the criteria cannot be used for diagnosing axSpA in individual patients.^{6, 7} Classification criteria can only be applied in patients in whom a diagnosis of axSpA has been established (not vice versa).⁸⁻¹⁰ The recognition of axSpA therefore requires the physician's knowledge about SpA, as well as expertise in aggregating information obtained during the diagnostic work-up and a differential diagnosis.

In order to assist physicians in the diagnosis of axSpA the ASAS modified Berlin algorithm has been developed, which can be applied in CBP patients with age of onset <45 years (**Figure 1**). As a first step the algorithm advises a radiograph of the sacroiliac joints (X-SI) in all patients. According to the algorithm CBP patients with indisputable radiographic sacroiliitis may be readily diagnosed with axSpA. Patients without clear sacroiliitis on radiographs are subsequently stratified according to the number of spondyloarthritis (SpA)-features they have after patient history, physical examination and measuring C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). A important feature of the algorithm is that it allows a diagnosis of axSpA in patients with ≥ 4 SpA-features without further imaging (MRI of the sacroiliac joints (MRI-SI)) or HLA-B27 testing. Moreover, HLA-B27 positive patients with normal radiographs and 2 or 3 SpA-features may also be diagnosed with axSpA without performing MRI-SI. Van den Berg et al. have already shown that an axSpA diagnosis according to the modified Berlin algorithm is not necessarily the same as an expert's (i.e. rheumatologist's) clinical diagnosis, so false-positive and false-negative diagnoses may occur if the algorithm is followed blindly.¹¹ Therefore, it should be stressed again that the ASAS modified Berlin algorithm is only a tool in aiding rheumatologists in diagnosing axSpA and can and should not replace a differential diagnostic procedure in patients with CBP.

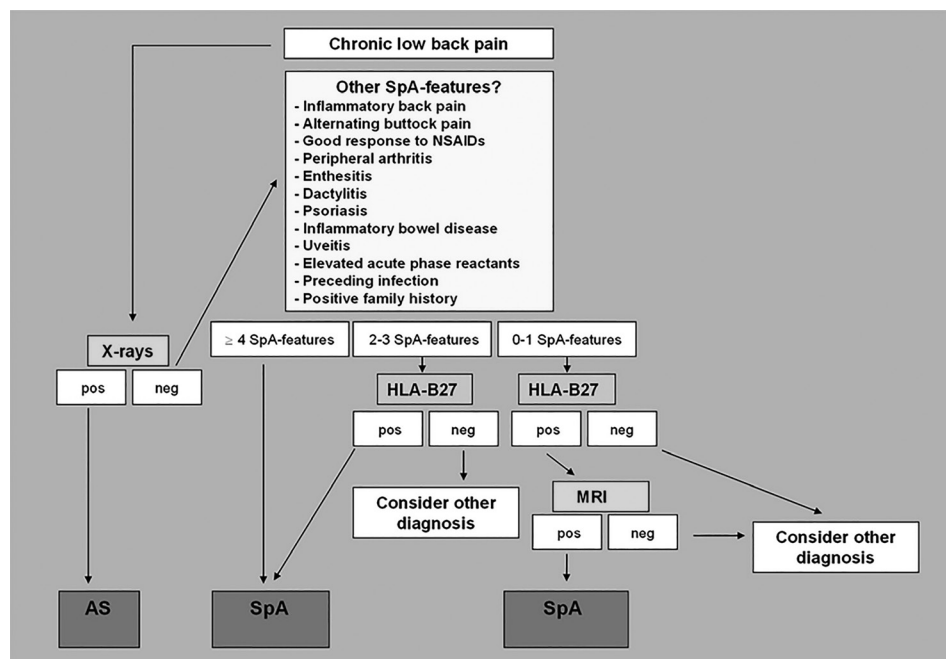


Figure 1 ASAS modification of the Berlin algorithm* for diagnosing axial spondyloarthritis. *Adapted from:* van den Berg R et al. Ann Rheum Dis 2013;72;1646-53 (with permission). *Rudwaleit M et al. Ann Rheum Dis 2004;63:535-43.

Nevertheless, several concerns have been raised about the risk of overdiagnosis of axSpA when the diagnosis is made by counting the number of SpA-features without paying attention to an alternative diagnosis that may be more likely.¹² Similarly, the use of ASAS classification as diagnostic criteria may lead to misdiagnosis. These issues are of particular concern in patients with non-inflammatory conditions in whom overdiagnosis may inappropriately lead to the start of anti-inflammatory treatments that will not be effective but are associated with side-effects and costs. Concerns like these have contributed to the United States Food and Drug Administration (FDA) formal disapproval of adalimumab and certolizumab for the treatment of non-radiographic axSpA in the United States, while both drugs have been approved by the European Medicines Agency (EMA) for this indication in the European Union.¹³

The diagnostic process of early axSpA in patients presenting with CBP is not well studied. Cohort studies typically include patients with an established diagnosis of axSpA. The multicenter SPondyloArthritis Caught Early (SPACE)-cohort is a study that has included

patients presenting with CBP but without a formal diagnosis who have been referred to a rheumatologist. Consequently, the SPACE-cohort contains patients with and without a diagnosis of axSpA.

The main objectives of our study were to investigate 1) which SpA-features contribute most to a diagnosis of axSpA; 2) if the presence of multiple SpA-features automatically leads to a diagnosis of axSpA in patients presenting with CBP; and 3) how positive classification according to the ASAS-criteria relates to a diagnosis of axSpA.

METHODS

Study design and population

The SPACE-cohort is a prospective multicenter study, which was initiated in January 2009. The study has been described elsewhere.¹⁴ In brief, patients with CBP (≥ 3 months and ≤ 2 years) of unknown origin and age of onset < 45 years were included. Patients were recruited for the study from five different rheumatology outpatient clinics in the Netherlands (Amsterdam, Gouda, Leiden), Norway (Oslo) and Italy (Padua).

Approval for the study was obtained from all local medical ethics committees. All patients provided written informed consent. Data of 157 patients from the LUMC in Leiden have previously been published as part of the validation of the modified Berlin algorithm.

Imaging of the sacroiliac joints

Plain radiographs of the pelvis (X-SI) were performed in anteroposterior view. MRI-SI were also performed: the acquired sequences were coronal oblique T1-weighted turbo spin echo (TSE) and short tau inversion recovery (STIR) with a slice thickness of 4 mm. Each center interpreted the radiographs and MRI-SI on the presence of sacroiliitis using global assessment as part of routine clinical practice (local reading) with radiologists specifically asked whether there was evidence of sacroiliitis.

Clinical measurements

Patients underwent a full diagnostic work-up including the assessment of SpA-features according to the ASAS-criteria: CRP and ESR, HLA-B27, imaging (X-SI and MRI-SI), and the actual presence or a history of all other SpA-features: inflammatory back pain (IBP), good response to non-steroidal anti-inflammatory drugs (NSAIDs), positive family history

of SpA, peripheral arthritis, dactylitis, enthesitis, acute anterior uveitis, inflammatory bowel disease (IBD), psoriasis. Rheumatologists provided a diagnosis of axSpA based on all collected information, including imaging and HLA-B27 status. In case of 'no axSpA' rheumatologists were asked to provide a most likely alternative diagnosis. In addition, rheumatologists were requested to provide a level of confidence about the diagnosis on a 11-point numerical rating scale (NRS) ranging from 0 (not confident at all) to 10 (very confident) after imaging was performed. Independently of the clinical diagnosis the ASAS axSpA classification criteria were used to classify patients using the local imaging results. The rheumatologists were not formally informed about the patients' classification status at the time of diagnosis.

Statistical analysis

For the present analyses baseline data were available (n=522). Patients with missing values for ≥ 1 SpA-feature, including imaging and HLA-B27 status, and those with missing information on clinical diagnosis, were excluded from the analyses (n=22). Total number of SpA-features was determined without taking HLA-B27 and imaging into account. Next, patients were stratified according to the number of SpA-features present: ≤ 1 feature, 2 features, 3 features, and ≥ 4 features. Patient characteristics are presented for the total patient group and for each subgroup as mean $\pm$ SD or number (%). The rheumatologist's diagnosis was the main outcome. Sensitivity and specificity were calculated to assess the agreement between the clinical diagnosis and the ASAS axSpA classification criteria. Where zeroes caused problems with computation of odds ratios or their standard errors, 0.5 were added to all cells. Multivariable logistic regression analysis was performed to assess independent determinants of clinical diagnosis. Data analysis was performed using STATA SE V.14. *P* values less than 0.05 were considered significant.

RESULTS

A total of 500 patients with CBP of short duration and complete data were analysed. Of these patients 37% were male, mean age (SD) was 29.3 (8.3) years and mean symptom duration (SD) was 13.4 (7.4) months (Table 1). Of all patients, 159 (32%) had ≤ 1 feature, 143 (29%) had 2 features, 79 (16%) had 3 features and 119 (24%) had ≥ 4 features. Age at onset of back pain, sex, and disease duration were similar across subgroups. Of the 159 patients in the ≤ 1 SpA-feature subgroup 24% was diagnosed with axSpA; for patients with 2 SpA-features this was 43%, for patients with 3 SpA-features 62%, and for patients with ≥ 4 SpA-features this was 85%. When stratifying for each participating center the same trend - higher percentages of diagnosis with increasing numbers of features - in clinical diagnosis was observed (supplementary data Table S1).

In patients with ≤ 1 SpA-feature 9/159 (6%) had radiographic sacroiliitis and 26/159 (16%) had a positive MRI-SI (Table 2). Of the patients with normal radiographs 99/150 (66%) had neither a positive MRI-SI nor HLA-B27 and only 2/99 (2%) were diagnosed with axSpA (both CBP patients had 1 SpA-feature which were IBP and positive family history, respectively). In total, 38/159 (24%) patients were diagnosed with axSpA. One patient with radiographic sacroiliitis was not diagnosed with axSpA. When the ASAS axSpA classification criteria were applied, 5 patients without a diagnosis of axSpA fulfilled the ASAS-criteria. In addition, 13 patients with an axSpA diagnosis did not fulfil the ASAS classification criteria.

In patients with 2 SpA-features 16/143 (11%) had radiographic sacroiliitis and 35/143 (24.5%) patients had a positive MRI-SI. Of the patients with normal radiographs 70/127 (55%) had neither a positive MRI-SI nor HLA-B27 and 11/127 (9%) were diagnosed with axSpA. In total, 62/143 (43%) patients were diagnosed with axSpA. All patients with radiographic sacroiliitis were diagnosed with axSpA. When the ASAS axSpA classification criteria were applied, 22 patients without a diagnosis of axSpA fulfilled the ASAS-criteria and 11 patients with an axSpA diagnosis did not fulfil the ASAS-criteria and.

In patients with 3 SpA-features 5/79 (6%) had radiographic sacroiliitis and 29/79 (38%) had a positive MRI-SI. Of the patients with normal radiographs 29/74 (39%) had neither a positive MRI-SI nor HLA-B27 and 8/74 (11%) were diagnosed with axSpA. In total, 49/79 (62%) patients were diagnosed with axSpA. All patients with radiographic sacroiliitis were diagnosed with axSpA. When the ASAS axSpA classification criteria were applied, 9 patients without a diagnosis of axSpA fulfilled ASAS-criteria and 8 patients with an axSpA diagnosis did not fulfil the ASAS-criteria.

In patients with ≥ 4 SpA-features 28/119 (24%) had radiographic sacroiliitis and 47/119 (40%) had a positive MRI-SI. Of the 91 patients with normal radiographs 42 (46%) had neither a positive MRI-SI nor HLA-B27 and 28/91 (31%) were diagnosed with axSpA. In total, 101/119 (85%) patients were diagnosed with axSpA. Again, all patients with radiographic sacroiliitis (28/28) were diagnosed with axSpA. Remarkably, 18/119 patients (15%) with ≥ 4 SpA-features but with negative imaging were not given the diagnosis axSpA, 4 of whom were HLA-B27 positive. When the ASAS axSpA classification criteria were applied, 4 patients without a diagnosis of axSpA fulfilled ASAS-criteria and 28 patients with an axSpA diagnosis did not fulfil the ASAS-criteria. Moreover, patients with ≥ 4 features not diagnosed with axSpA were mostly given the diagnosis non-specific back pain and degenerative disc disease (data not shown). In these patients the most common SpA-features were a positive family history for SpA (67%), good response to NSAIDs (82%), and IBP (94%).

Table 1 Baseline characteristics of patients with chronic back pain in the SPACE-cohort and stratified by total number of SpA-features after medical history taking, physical examination and measurement of acute phase reactants but before HLA-B27 testing and imaging.

Characteristic	All patients, <i>n</i> =500	Patients with ≤1 features, <i>n</i> =159
Age, years	29.3 (8.3)	29.7 (8.8)
Symptom duration, months	13.4 (7.4)	12.9 (7.3)
Male	185 (37)	51 (32)
IBP	329 (66)	43 (27)
Good response to NSAIDs ^a	208 (42)	13 (8)
Positive family history SpA ^b	206 (41)	26 (16)
Peripheral arthritis [‡]	74 (15)	2 (1)
Dactylitis [‡]	26 (5)	0 (0)
Enthesitis [‡]	108 (22)	4 (3)
Anterior uveitis [‡]	38 (8)	2 (1)
IBD [‡]	35 (7)	8 (5)
Psoriasis [‡]	57 (11)	2 (1)
Elevated CRP (mg/L) / ESR (mm) ^c	132 (26)	12 (8)
HLA-B27 positive	198 (40)	36 (23)
Imaging^o		
X-SI positive **	58 (12)	9 (6)
MRI-SI positive **	146 (29)	33 (21)
Diagnosis axSpA ^d	250 (50)	38 (24)

Results are presented as mean ± SD or number (%). [‡] Past or present condition, either confirmed or diagnosed by a physician. IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis; IBD, inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leucocyte antigen B27; ^oAccording to global assessment radiologist (local reading). ** X-SI, radiograph of sacroiliac joints;

Patients with 2 features, <i>n</i> =143	Patients with 3 features, <i>n</i> =79	Patients with ≥ 4 features, <i>n</i> =119
28.8 (8.3)	29.1 (8.0)	29.5 (7.9)
14.6 (7.7)	13.3 (7.0)	12.7 (7.4)
56 (39)	24 (30)	54 (45)
103 (72)	71 (90)	112 (94)
50 (35)	47 (60)	98 (82)
57 (40)	43 (54)	80 (67)
15 (11)	11 (14)	46 (39)
1 (1)	3 (4)	22 (19)
12 (8)	15 (19)	77 (65)
9 (6)	6 (8)	21 (18)
7 (5)	7 (9)	13 (11)
7 (5)	8 (10)	40 (34)
25 (18)	26 (33)	69 (58)
65 (46)	41 (52)	56 (47)
16 (11)	5 (6)	28 (24)
37 (26)	29 (37)	47 (40)
62 (43)	49 (62)	101 (85)

MRI-SI, magnetic resonance imaging of sacroiliac joints. AxSpA, axial spondyloarthritis. ^a Back pain not present anymore or is much better 24–48 hours after a full dose of NSAID. ^b Presence in first- or second degree relatives of any of the following: ankylosing spondylitis, psoriasis, acute anterior uveitis, reactive arthritis, or inflammatory bowel disease. ^c Values greater than the upper limit of normal. ^d Diagnosis based on information after full diagnostic work-up: medical history, physical examination, imaging, and laboratory testing.

Table 2 Diagnosis and classification of patients ($n=500$) with ≤ 1 , 2, 3 and ≥ 4 spondyloarthritis (SpA)-features after medical history taking, physical examination and measurement of acute phase reactants, followed by sacroiliac imaging and HLA-B27 testing.

Number of SpA-features	X-SI status	HLA-B27/MRI status
0-1 <i>n</i> = 159	X-SI+ <i>n</i> = 9	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-
	X-SI- <i>n</i> = 150	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-
Mean level of confidence regarding diagnosis (SD)		
2 <i>n</i> = 143	X-SI+ <i>n</i> = 16	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-
	X-SI- <i>n</i> = 127	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-
Mean level of confidence regarding diagnosis (SD)		
3 <i>n</i> = 79	X-SI+ <i>n</i> = 5	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-
	X-SI- <i>n</i> = 74	HLA-B27+/MRI+
		HLA-B27+/MRI-
		HLA-B27-/MRI+
		HLA-B27-/MRI-

Rheumatologist SpA diagnosis	Rheumatologist SpA diagnosis	ASAS axSpA classification	ASAS axSpA classification
<u>yes</u>	<u>no</u>	<u>yes</u>	<u>no</u>
4		4	
1	1	2	
1		1	
2		2	
6	1	7	
7	16		23
15	6	14	7
2	97		99
6.9 (2.3)	7.5 (2.4)		
14		14	
1		1	
1		1	
15		15	
15	20	35	
5	2	7	
11	59		70
7.6 (1.9)	6.7 (2.3)		
3		3	
1		1	
1		1	
17		17	
11	9	20	
8		8	
8	21		29

Rheumatologist SpA diagnosis <u>yes</u>	Rheumatologist SpA diagnosis <u>no</u>	ASAS ax SpA classification <u>yes</u>	ASAS axSpA classification <u>no</u>
8.0 (1.9)	7.1 (2.0)		
15		15	
8		8	
5		5	
16		16	
21	4	25	
8		8	
28	14		42
8.0 (2.0)	7.3 (1.7)		

ASAS axSpA criteria, Assessment of SpondyloArthritis international Society criteria for axial spondyloarthritis. Mean level of confidence regarding diagnosis: 0 (not confident at all) through 10 (very confident).

Overall, the mean levels of confidence (SD) regarding a diagnosis of axSpA and no axSpA were 7.7 (2.0) and 7.2 (2.3), respectively. Mean levels of confidence of axSpA diagnosis for the different patient subgroups rose with the presence of more SpA-features; ≤ 1 feature, mean 6.9 (2.3); 2 features, mean 7.6 (1.9); 3 features, mean 8.0 (1.9); ≥ 4 features, mean 8.0 (2.0) (Table 2).

With the clinical diagnosis of the rheumatologist as the gold standard, sensitivity and specificity of the ASAS classification criteria for axSpA were 76% (190/250) and 84% (210/250), respectively (Table 3).

In univariable analysis, HLA-B27 positivity and any positive imaging were associated with an axSpA diagnosis (OR 5.6, 95% CI 3.7 to 8.3 and OR 34.3, 95% CI 17.3 to 67.7 respectively). These associations were similar across subgroups (Table 4 and 5). In multivariable logistic regression analysis with clinical diagnosis as the dependent variable and SpA-features from the ASAS-criteria as independent variables HLA-B27 and positive imaging were both independent determinants of diagnosis (data not shown).

Table 3 Concordance between clinical axSpA diagnosis and meeting the ASAS classification criteria for axSpA in CBP patients with the physician’s diagnosis as the gold standard in the SPACE-cohort ($n=500$). Sensitivity 76% (190/250) and specificity 84% (210/250). Positive predictive value (PPV): 190/230 (83%), negative predictive value (NPV): 210/270 (78%).

ASAS classification criteria	Clinical axSpA diagnosis		
	Yes	No	Total
Yes	190	40	230
No	60	210	270
Total	250	250	500

Table 4 Concordance between clinical axSpA diagnosis and presence of HLA-B27 for all patients and stratified for total number of SpA-features.

All patients		Clinical axSpA diagnosis	
HLA-B27 positive	Yes	No	Total
	Yes	147	51
	No	103	199
	Total	250	500
OR (95% CI)		5.6 (3.7-8.3)	
≤1 feature		Clinical axSpA diagnosis	
HLA-B27 positive	Yes	No	Total
	Yes	18	18
	No	20	103
	Total	38	121
OR (95% CI)		5.2 (2.3-11.6)	
2 features		Clinical axSpA diagnosis	
HLA-B27 positive	Yes	No	Total
	Yes	45	20
	No	17	61
	Total	62	81
OR (95% CI)		8.1 (3.8-17.1)	
3 features		Clinical axSpA diagnosis	
HLA-B27 positive	Yes	No	Total
	Yes	32	9
	No	17	21
	Total	49	30
OR (95% CI)		4.4 (1.7-11.7)	
≥4 features		Clinical axSpA diagnosis	
HLA-B27 positive	Yes	No	Total
	Yes	52	4
	No	49	14
	Total	101	18
OR (95% CI)		3.7 (1.1-12.1)	

HLA-B27, human leucocyte antigen B27; axSpA, axial spondyloarthritis; OR = odds ratio; 95% CI = 95% confidence interval.

Table 5 Concordance between clinical axSpA diagnosis and any positive imaging (MRI-SI and/or X-SI) for all patients and stratified for total number of SpA-features.

All patients		Clinical axSpA diagnosis	
Any positive imaging		Yes	No
Yes	147	10	157
No	103	240	343
Total	250	250	500
OR (95% CI)		34.3 (17.3-67.7)	
≤1 feature		Clinical axSpA diagnosis	
Any positive imaging		Yes	No
Yes	29	8	37
No	9	113	122
Total	38	121	159
OR (95% CI)		45.5 (16.1-128.3)	
2 features		Clinical axSpA diagnosis	
Any positive imaging		Yes	No
Yes	36	2	38
No	26	79	105
Total	62	81	143
OR (95% CI)		54.7 (12.3-243)	
3 features		Clinical axSpA diagnosis	
Any positive imaging		Yes	No
Yes	30	0 *	30
No	19	30	49
Total	49	30	79
OR (95% CI)		95.4 (5.5-1652.2)	
≥4 features		Clinical axSpA diagnosis	
Any positive imaging		Yes	No
Yes	52	0 *	52
No	49	18	67
Total	101	18	119
OR (95% CI)		39.2 (2.3-668.8)	

axSpA, axial spondyloarthritis; X-SI, radiograph of sacroiliac joints; MRI-SI, magnetic resonance imaging of sacroiliac joints; OR, odds ratio; 95% CI, 95% confidence interval. * For computation of odds ratios in case of zeroes, 0.5 were added to all cells.

DISCUSSION

Prompted by concerns regarding overdiagnosis of axSpA we investigated whether in patients referred with recent onset CBP and a suspicion of axSpA, the presence of several SpA-features suffices for a diagnosis of axSpA. While, as expected, an increasing number of SpA-features was associated with an increased likelihood of axSpA diagnosis this association was not absolute. Numerous patients with multiple SpA-features did not get a diagnosis of axSpA. Among them are half of the HLA-B27 positive patients with 3 SpA-features but without imaging abnormalities. This example clearly shows that a clinical diagnosis is based on more than simply a sum of features.

In this cohort the ASAS classification criteria had an overall sensitivity and specificity of 76% and 84%, respectively. This is comparable to those found in the original ASAS-cohort. In line with the finding that patients with multiple SpA-features are not always diagnosed with axSpA 17% of patients that on paper met the ASAS classification criteria, which requires presence of at least two SpA-features, were not diagnosed with axSpA.

An important finding is the prominent -if not dominant- role of imaging and HLA-B27 testing in diagnosing axSpA in rheumatology clinics. The statistically stronger association between positive imaging and axSpA diagnosis as compared to HLA-B27 and axSpA diagnosis (or any other SpA-feature) should be interpreted with caution. The prevalence of axSpA in this cohort of patients specifically referred to the rheumatologist (50%) is much higher than the prevalence of axSpA in unselected CBP patients, and we do not know which screening tools were applied to select patients for referral. In our cohort X-SI was positive in only a minority of patients whilst an analysis of 204 referral letters indicated that HLA-B27 positivity was mentioned four times more often than a positive MRI-SI as a reason for referral (unpublished data). This difference in absolute prevalence implies that the impact of different ORs (OR=5.6 for HLA-B27 and OR=35 for imaging) may be far more similar than the ORs suggest.

Nevertheless, our findings stress the dominance of imaging in establishing an axSpA diagnosis and add to the importance of a proper interpretation of the images.¹⁵⁻¹⁷

At first sight, some of the diagnoses may raise suspicion. For instance, a diagnosis of axSpA may not be expected in HLA-B27 negative patients that have normal imaging tests, and only a few other SpA-features. In such patients, a diagnosis may still be justifiable because of features or symptoms that are not part of the ASAS-criteria, e.g. buttock pain, IBP according

to Calin or Berlin criteria, presence of structural (but not active) lesions on MRI-SI or spinal inflammatory lesions, even though the latter two manifestations are rare in the absence of bone marrow edema on MRI-SI.¹⁸

Furthermore, differences in the interpretation of imaging may also have contributed to unexpected diagnoses. Even though the assessment of the radiologist was used for the analyses, the rheumatologist has provided the diagnosis and may -based on the clinical symptoms- have overruled the radiologist's report, for instance by taking structural lesions or spinal inflammatory lesions into account.^{18, 19}

A possible limitation of this study is that the clinical diagnosis - as is usual in clinical practice - was provided by only one rheumatologist. Each rheumatologist may consider different features, apart from positive imaging and presence of HLA-B27, being most informative for axSpA diagnosis. Even though this was not assessed it is conceivable this might have influenced the diagnosis. Future studies should definitely assess interobserver variance in clinical diagnosis.

The ASAS modified Berlin algorithm can be used by rheumatologists in the clinical decision making process when diagnosing CBP patients. But blindly applying the ASAS modified Berlin algorithm will also result in false-positive and false-negative diagnoses. As has become clear in our study, in patients without radiographic sacroiliitis but with multiple SpA-features (and/or presence of HLA-B27), the algorithm immediately leads to an axSpA diagnosis, while in clinical practice this is not always clear. In 15% of the patients with ≥ 4 SpA-features and 13% of the HLA-B27 positive patients with 2-3 SpA-features that should have a clinical diagnosis of axSpA according to the algorithm, such a diagnosis was not confirmed by the clinician.

While the SPACE-cohort is running in different countries and settings (academic and non-academic), we did not find an important center effect. In all centers the likelihood of axSpA diagnosis similarly increased by an increasing number of SpA-features, which adds to the credibility of our data. Nevertheless, patients were diagnosed by hospital-based rheumatologists with an expertise in diagnosing patients with axSpA, and results of this study cannot be extrapolated to different clinical settings such as primary care and common rheumatology practices or those of other medical specialities.

In conclusion, in clinical practice the mere presence of SpA-features does not automatically result in a clinical diagnosis of axSpA. Furthermore, this study confirms that the ASAS modified

Berlin algorithm could be used as a guidance tool but that a thorough diagnostic work-up with ample consideration for alternative diagnoses is still mandatory. Preferably, all information including imaging of sacroiliac joints and presence of HLA-B27 should be available to the rheumatologist to come to a final diagnosis.

REFERENCES

1. Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis Rheum* 2005;52:1000-8.
2. Rudwaleit M, van der Heijde D, Khan MA, *et al.* How to diagnose axial spondyloarthritis early. *Ann Rheum Dis* 2004;63:535-43.
3. van Tubergen A, Weber U. Diagnosis and classification in spondyloarthritis: identifying a chameleon. *Nat Rev Rheumatol* 2012;8:253-61.
4. Sieper J, Rudwaleit M, Baraliakos X, *et al.* The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;68 Suppl 2:ii1-44.
5. Rudwaleit M, van der Heijde D, Landewe R, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-83.
6. Rudwaleit M, Landewe R, van der Heijde D, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009;68:770-6.
7. Sepriano A, Landewe R, van der Heijde D, *et al.* Predictive validity of the ASAS classification criteria for axial and peripheral spondyloarthritis after follow-up in the ASAS cohort: a final analysis. *Ann Rheum Dis* 2016;75:1034-42.
8. Braun J, Baraliakos X, Kiltz U, *et al.* Classification and diagnosis of axial spondyloarthritis--what is the clinically relevant difference? *J Rheumatol* 2015;42:31-8.
9. Rudwaleit M, van der Heijde D, Landewe R, *et al.* The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011;70:25-31.
10. Molto A, Paternotte S, Comet D, *et al.* Performances of the Assessment of SpondyloArthritis International Society axial spondyloarthritis criteria for diagnostic and classification purposes in patients visiting a rheumatologist because of chronic back pain: results from a multicenter, cross-sectional study. *Arthritis Care Res (Hoboken)* 2013;65:1472-81.
11. van den Berg R, de Hooge M, Rudwaleit M, *et al.* ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. *Ann Rheum Dis* 2013;72:1646-53.
12. Berthelot JM, Le Goff B, Maugars Y. Overdiagnosing early spondyloarthritis: what are the risks? *Joint Bone Spine* 2013;80:446-8.
13. Deodhar A, Reveille JD, van den Bosch F, *et al.* The concept of axial spondyloarthritis: joint statement of the spondyloarthritis research and treatment network and the Assessment of SpondyloArthritis international Society in response to the US Food and Drug Administration's comments and concerns. *Arthritis Rheumatol* 2014;66:2649-56.
14. van den Berg R, de Hooge M, van Gaalen F, *et al.* Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. *Rheumatology (Oxford)* 2013;52:1492-9.

15. Deodhar A. Editorial: Sacroiliac Joint Magnetic Resonance Imaging in the Diagnosis of Axial Spondyloarthritis: “A Tiny Bit of White on Two Consecutive Slices” May Be Objective, but Not Specific. *Arthritis Rheumatol* 2016;68:775-8.
16. van Gaalen FA, Bakker PA, de Hooze M, *et al.* Assessment of sacroiliitis by radiographs and MRI: where are we now? *Curr Opin Rheumatol* 2014;26:384-8.
17. Lambert RG, Bakker PA, van der Heijde D, *et al.* Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. *Ann Rheum Dis* 2016.
18. de Hooze M, van den Berg R, Navarro-Compan V, *et al.* Patients with chronic back pain of short duration from the SPACE cohort: which MRI structural lesions in the sacroiliac joints and inflammatory and structural lesions in the spine are most specific for axial spondyloarthritis? *Ann Rheum Dis* 2016;75:1308-14.
19. van den Berg R, Lenczner G, Thevenin F, *et al.* Classification of axial SpA based on positive imaging (radiographs and/or MRI of the sacroiliac joints) by local rheumatologists or radiologists versus central trained readers in the DESIR cohort. *Ann Rheum Dis* 2015;74:2016-21.

SUPPLEMENTARY MATERIAL

Table S1. Diagnosis of axSpA in participating centers for all patients and stratified for total number of SpA-features.

	All patients n=250	≤1 features, n=38
Diagnosis axSpA per center		
1. Leiden (n _{total} =298)	119 (39.9)	23/123 (18.7)
2. Padova (n _{total} =50)	50 (100)	0 (0)
3. Oslo (n _{total} =87)	53 (60.9)	9/18 (50)
4. Amsterdam (n _{total} =42)	19 (45.2)	6/14 (42.9)
5. Gouda (n _{total} =23)	9 (39.1)	0/4 (0)

Diagnosis based on information after full diagnostic work-up: medical history, physical examination, imaging, and laboratory testing. Patient data available from the following centers: Leiden University Medical Center (LUMC), Leiden, the Netherlands;

2 features, n=62	3 features, n=49	≥4 features, n=101
44/99 (44.4)	24/40 (60)	28/36 (77.7)
0 (0)	6/6 (100.0)	44/44 (100.0)
13/23 (56.5)	13/21 (61.9)	18/25 (72.0)
3/14 (21.4)	3/7 (42.9)	7/7 (100)
2/7 (28.6)	3/5 (60.0)	4/7 (57.1)

University of Padova, Padova, Italy; Diakonhjemmet hospital, Oslo, Norway; Academic Medical Center, Amsterdam, The Netherlands; Groene Hart ziekenhuis, Gouda, the Netherlands.

Alternative diagnoses in chronic back pain patients not diagnosed with axial spondyloarthritis: data from the SPACE cohort.



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We recently published a study investigating whether the mere presence of multiple spondyloarthritis (SpA) features is sufficient for an axial spondyloarthritis (axSpA) diagnosis.¹ Patients (n=500) with chronic back pain (CBP) suspected of axSpA were stratified according to their number of SpA features into four subgroups: ≤ 1 , 2, 3 and ≥ 4 SpA features based on medical history taking, physical examination and measurement of acute phase reactants, but before sacroiliac imaging and HLA-B27 testing. In total, 24% (38/159), 43% (62/143), 62% (49/79), and 85% (101/119) of CBP patients with ≤ 1 , 2, 3 and ≥ 4 SpA features respectively were diagnosed with axSpA. In particular, HLA-B27 positivity and imaging findings highly suggestive of axSpA were strongly associated with an axSpA diagnosis. So although the likelihood of axSpA diagnosis increased with an increasing number of SpA features, not all patients with multiple SpA features were diagnosed as having axSpA.

In the News and Views section of *Nature Reviews Rheumatology*, Braun and Kiltz raised the question what diagnoses were made in CBP patients who were *not* diagnosed with axSpA. This information was not provided in the manuscript.² The question is relevant since we agree with these authors that it is unlikely that a patient with 4 or more SpA features does not have SpA. This reasoning follows the modified Berlin algorithm in which patients with CBP and ≥ 4 SpA features are readily diagnosed with axSpA.³

In our study, rheumatologists were first asked to provide a diagnosis (i.e. presence of axSpA yes/no). In all patients this question was answered with 250 patients diagnosed with axSpA after full diagnostic work-up. Secondly, in case of 'no axSpA' rheumatologists were requested to provide a most likely alternative diagnosis.

In 76% (189/250) of patients who were not diagnosed as having axSpA, the alternative diagnosis for the chronic back pain was recorded in the study database. Across all subgroups based on the number of SpA features most common diagnoses were nonspecific back pain, mechanical back pain, degenerative disc disease, and (fibro)myalgia (Table 1). Not surprisingly, in these patients almost no positive imaging (sacroiliitis on either radiographs or MRI) was observed and HLA-B27 positivity was infrequent.¹ Especially in the 18 patients not diagnosed with axSpA, but with at least 4 SpA features, none of the patients had imaging abnormalities suggestive of axSpA on MRI or radiography and only 4 of them were HLA-B27 positive. The most frequent SpA features in these patients were: IBP (16/18), a positive family history of SpA (16/18), a good response to NSAIDs (11/18), elevated CRP or ESR (8/18) and enthesitis (8/18). Overall, these findings show that rheumatologists in clinical practice rightly dispute a diagnosis of axSpA even when there is a high number of SpA features, especially when imaging is normal and patients are negative for HLA-B27.

Table 1 Alternative diagnoses in CBP patients **not diagnosed with axSpA** (n=250) stratified by total number of SpA features after medical history taking, physical examination and measurement of acute phase reactants but before HLA-B27 testing and imaging.

Number of SpA features ^y	Alternative diagnoses	N (%)
0-1 <i>n</i> =121	Nonspecific back pain	32 (26)
	Mechanical back pain	5 (4)
	IBP	4 (3)
	Degenerative disc disease/HNP ^a	14 (12)
	Myalgia	17 (14)
	Fibromyalgia	8 (7)
	Hypermobility syndrome	3 (2)
	Other*	12 (10)
	Missing diagnosis	29 (24)
2 <i>n</i> =81	Nonspecific back pain	15 (19)
	Mechanical back pain	8 (9)
	IBP	3 (4)
	Degenerative disc disease/HNP ^a	9 (11)
	Myalgia	14 (17)
	Fibromyalgia	4 (5)
	Hypermobility syndrome	1 (1)
	Other**	12 (15)
3 <i>n</i> =30	Missing diagnosis	16 (20)
	Nonspecific back pain	6 (20)
	Mechanical back pain	3 (10)
	IBP	1 (3)
	Degenerative disc disease/HNP ^a	3 (10)
	Myalgia	2 (7)
	Fibromyalgia	3 (10)
	Hypermobility syndrome	0 (0)
	Other***	2 (7)
	Missing diagnosis	10 (33)

Table 1 Continued.

Number of SpA features [‡]	Alternative diagnoses	N (%)
≥ 4 <i>n</i> =18	Nonspecific back pain	4 (22)
	Mechanical back pain	0 (0)
	IBP	1 (6)
	Degenerative disc disease/HNP ^a	4 (22)
	Myalgia	1 (6)
	Fibromyalgia	0 (0)
	Hypermobility syndrome	1 (6)
	Other****	1 (6)
	Missing diagnosis	6 (33)

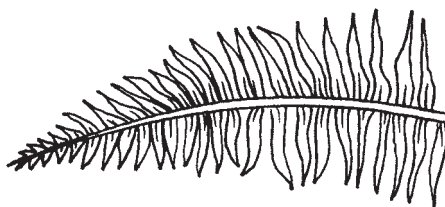
[‡] Total patient group: 0-1 SpA feature, *n*=159; 2 SpA features, *n*=143; 3 SpA features, *n*=79; ≥ 4 SpA features, *n*=119. CBP, chronic back pain; axSpA, axial spondyloarthritis; SpA, spondyloarthritis.

^a Herniated Nucleus Pulposus. *Arthralgia, *n*=1; local pain syndrome, *n*=1; Diffuse idiopathic skeletal hyperostosis (DISH), *n*=1; ileitis condensans, *n*=1; osteoarthritis, *n*=2; Tarlov cyst, *n*=1; undifferentiated arthritis, *n*=1; uterus myomatosus, *n*=1. **Arthritis, *n*=3; functional complaints, *n*=2; osteoarthritis, *n*=2; pelvic instability, *n*=1; uterus myomatosus, *n*=1; tendinopathy, *n*=2. *** Undifferentiated oligoarthritis, *n*=1; tendinopathy, *n*=1. **** Osteoarthritis, *n*=1.

REFERENCES

1. Ez-Zaitouni Z, Bakker PAC, van Lunteren M, *et al.* Presence of multiple spondyloarthritis (SpA) features is important but not sufficient for a diagnosis of axial spondyloarthritis: data from the SPondyloArthritis Caught Early (SPACE) cohort. *Ann Rheum Dis* 2017;76:1086-92.
2. Braun J, Kiltz U. Spondyloarthropathies: How should axial spondyloarthritis be diagnosed? *Nat Rev Rheumatol* 2017;13:264-6.
3. van den Berg R, de Hooze M, Rudwaleit M, *et al.* ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. *Ann Rheum Dis* 2013;72:1646-53.

Diagnostic uncertainty is common in patients with chronic back pain suspected of axial spondyloarthritis but is reduced by one-year follow-up.



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Submitted

ABSTRACT

Objectives

To investigate diagnostic uncertainty in patients suspected of axial spondyloarthritis (axSpA).

Methods

SPACE is an inception cohort of chronic back pain (CBP) patients (≥ 3 months, ≤ 2 years, onset < 45 years) suspected of axSpA. Baseline and one-year visits, both including sacroiliac MRI and radiography, were analysed. Diagnosis was provided by the treating rheumatologist with level of confidence ≤ 6 defined as uncertain.

Results

At baseline, 127/245 (52%) patients were diagnosed as axSpA, 46 (19%) as no axSpA, and 72 patients (29%) had an uncertain diagnosis. Of the 72 patients with an uncertain diagnosis at baseline, at one year 17 (24%) received a diagnosis of axSpA, in 29 (40%) axSpA was excluded (no axSpA), and in 26 (36%) the diagnosis remained uncertain. In the patients with an uncertain baseline diagnosis 39/72 (54%) had gained at least one SpA feature after one-year follow-up with a good response to NSAIDs (21%), and elevated CRP/ESR (15%) being the two most commonly gained features. Sacroiliac MRI became positive in 11% of these patients. At year one, 112/127 (88%) of patients with axSpA and 37/46 (80%) of patients with no axSpA had an unchanged diagnosis. Over one year, the percentage of patients with an uncertain diagnosis decreased from 72/245 (29%) to 47/245 (19%).

Conclusion

Diagnostic uncertainty is common in CBP patients suspected of having axSpA. Nevertheless, despite the limited accrual of SpA features, the overall decrease in uncertain diagnoses after one year justifies an expert approach of “wait and see” in cases of diagnostic uncertainty.

INTRODUCTION

In spite of the efforts to facilitate earlier diagnosis, it is unclear if the reported diagnostic delay in axial spondyloarthritis (axSpA) has improved during the past decade.¹⁻⁵ After relying on conventional imaging of the sacroiliac joints for many years, magnetic resonance imaging (MRI) was introduced as an imaging tool for the early recognition of axSpA. Not all patients develop structural bone damage (i.e. radiographic sacroiliitis) and it may take months to years before this occurs. MRI, however, can depict both inflammation and structural damage and is therefore potentially useful in the diagnostic work-up of early onset chronic back pain (CBP) patients with a suspicion of axSpA. Since a positive MRI of the sacroiliac joints was considered specific for axSpA it was added as an imaging criterion to the Assessment of Spondyloarthritis international Society (ASAS) classification criteria for axSpA.⁶ However, several studies have shown that inflammation in the sacroiliac joints can also occur in healthy individuals.⁷⁻⁹

Next to optimizing the use of imaging in the diagnostic process of (early) axSpA several studies have been conducted with the aim to help clinicians in diagnosing CBP patients with axSpA. The modified Berlin algorithm is a tool to assist clinicians in diagnosing patients presenting with CBP as axial spondyloarthritis.¹⁰ The algorithm is based on the number of spondyloarthritis (SpA) features and its use may result in extra diagnostic confidence.

AxSpA is a heterogeneous disease and may present with very different signs and symptoms. There is no single feature that reliably distinguishes axSpA from other conditions with CBP. In daily practice, a diagnosis of axSpA is usually based on a combination of signs and symptoms, imaging and laboratory testing. However, axSpA is a chronic disease and patients may develop additional SpA features over time so in patients where a certain diagnosis cannot be made, despite a full diagnostic work-up, a 'wait and see policy' has been recommended.^{11, 12}

However, it is not known to what extent follow-up suffices to accrue a sufficient number of SpA features to reliably make a diagnosis of axSpA. We have recently shown already that repeating sacroiliac MRI after three months or one year is not useful.¹³ However, this study did not consider the development of other SpA features. In this study, we investigated if diagnostic uncertainty in patients with recent onset CBP improves after one-year follow-up. In addition, we systematically investigated SpA feature accrual in one year.

PATIENTS AND METHODS

Study design and population

The SPACE cohort is an ongoing multinational study of which the details have been published before.¹⁴ In summary, patients with chronic back pain (duration of ≥ 3 months but < 2 years) of unknown origin and age of onset between 16 and 45 years are included. Patients are recruited from several rheumatology outpatient clinics in Europe. Patients signed informed consent before participation in the study and approval for the study was obtained from all local medical ethics committees.

Clinical assessments

All patients underwent a full work-up at baseline and one year follow-up, including physical examination, imaging of the sacroiliac joints (magnetic resonance imaging (MRI-SI) and radiographs (X-SI)), laboratory testing (acute phase reactants and HLA-B27), and assessment of all other SpA features: inflammatory back pain (IBP), good response to NSAIDs, positive family history of SpA, peripheral arthritis, dactylitis, heel enthesitis, acute anterior uveitis, inflammatory bowel disease (IBD), and psoriasis all according the definitions of the ASAS SpA criteria.⁶

Imaging assessments

Plain radiographs of the pelvis were performed in anteroposterior view. MRI acquired sequences were coronal oblique T1-weighted TSE and STIR with a slice thickness of 4 mm. The presence of sacroiliitis (yes/no) on radiographs and MRI of the sacroiliac joints was interpreted by the participating centres using global assessment as part of routine clinical practice (local reading).

Diagnosis

At baseline and after one-year follow-up rheumatologists were asked to provide a diagnosis based on all collected information, including imaging (local reading) and HLA-B27 status. Rheumatologists were asked to provide a most likely alternative diagnosis in case of 'no axSpA'. Regardless of the diagnosis (i.e. axSpA or no axSpA) rheumatologists were requested to state a level of confidence regarding the diagnosis on a numerical rating scale ranging from 0 (not confident at all) to 10 (very confident). Patients were labelled according to the following diagnosis groups with arbitrary cut-off values: (1) axSpA diagnosis with a level of confidence (LoC) ≥ 7 , (2) no axSpA diagnosis with a LoC ≥ 7 , and (3) axSpA or no axSpA diagnosis with a LoC ≤ 6 ('no certain diagnosis' group).

Data analysis

Patients with baseline and one-year follow-up visits were analysed. The used database was locked in March 2016. Descriptive analyses were performed on the total patient group with visits at both time points and with available diagnosis. Total number of SpA features was determined after the full work-up, but without taking HLA-B27 and sacroiliac imaging into account. Furthermore, for the purpose of this study, SpA features were considered positive according to the principle of “once a feature always a feature”. This implies that patients can only gain but not lose features over time. For example, a patient with a positive sacroiliac MRI at baseline remained MRI positive even if the repeated sacroiliac MRI was not positive at one-year follow-up. Patient characteristics are presented for all defined diagnosis subgroups as frequencies (%) for categorical variables or as means and standard deviations ($\pm$ SD) for continuous variables. Data analysis was performed using Stata SE V.14 (StataCorp LP, College Station, (TX, USA)).

RESULTS

After database lock 257 patients with baseline and one-year follow-up visits were available. A total of 245 patients with CBP of short duration and complete information on diagnosis and corresponding LoC at both baseline and one-year follow-up were analysed. Of these, 38% were male, mean age (SD) was 30.6 (7.8) years, and mean symptom duration was 13.1 (7.1) months. Mean number of SpA features (SD) at baseline was 2.9 (1.6) and approximately half of the patients ($n=121$, 49%) gained ≥ 1 SpA feature after one year (Table 1). At baseline, 173 patients already had a certain diagnosis (LoC ≥ 7): 127 (52%) of them were diagnosed with axSpA and 46 (19%) were definitely considered not having axSpA but another diagnosis. In 72 (29%) patients a diagnosis could not be established with sufficient certainty (i.e. LoC ≤ 6) (Table 2). The mean (SD) LoC was 8.6 (1.0) in the axSpA group, 7.9 (0.7) in the non-axSpA group and 4.5 (1.5) in the uncertain diagnosis group.

AxSpA diagnosis at baseline

Of the 127 patients at baseline with a diagnosis of axSpA, 112 (88%) were still diagnosed as such after one year (Table 3). In 3 (2%) axSpA patients rheumatologists changed the diagnosis to no axSpA, and in 12 (10%) patients the LoC regarding the axSpA diagnosis decreased to ≤ 6 . After one year, in the axSpA diagnosis group the most frequently gained SpA features were ‘good response to NSAIDs’ (+29%), ‘elevated CRP/ESR’ (+12%), and ‘sacroiliitis on imaging’ (+6% and +11% for sacroiliitis on MRI and radiographs, respectively) (supplementary table

S1). Within the group of patients who changed from axSpA diagnosis to no axSpA ($n=3$) or uncertain diagnosis ($n=12$) feature gain after one year was limited (supplementary table S1). In the group of patients with axSpA the mean number of SpA features rose with 0.9 after one year.

Table 1 Baseline demographic and clinical characteristics of CBP patients suspected of having axSpA, $n=245$.

Characteristic	Baseline
Male, n (%)	94 (38)
Age at baseline (years), mean (SD)	30.6 (7.8)
Symptom duration (months), mean (SD)	13.1 (7.2)
IBP, n (%)	188 (78)
Good response to NSAIDs, n (%) [‡]	115 (48)
Positive family history of SpA, n (%)	123 (50)
Past history or current symptoms	
Peripheral arthritis, n (%)	46 (19)
Dactylitis, n (%)	22 (9)
Enthesitis, n (%)	63 (26)
AAU, n (%)	24 (10)
IBD, n (%)	19 (8)
Psoriasis, n (%)	34 (14)
Elevated CRP/ESR, n (%)	74 (30)
Number of SpA features, mean (SD) [°]	2.9 (1.6)
Presence of 2 or more SpA features, n (%)	205 (84)
HLA-B27 positive, n (%)	131 (53)
Sacroiliitis radiographs, n (%) [‡]	39 (16)
Sacroiliitis MRI, n (%) ^{‡‡}	90 (38)
Mean (SD) LoC 'axSpA diagnosis'	8.6 (1.0)
Mean (SD) LoC 'no axSpA diagnosis'	7.9 (0.7)
Mean (SD) LoC 'no certain diagnosis'	4.5 (1.5)

IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis; AAU, acute anterior uveitis; IBD, inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging; LoC, level of confidence regarding diagnosis on a 1 to 10 scale with 1 implying little certainty and 10 implying great certainty about diagnosis. [°]Total number of SpA features after medical history taking, physical examination and measurement of acute phase reactants but before HLA-B27 testing and imaging. *axSpA diagnosis defined as LoC ≥ 7 , $n=127$; no axSpA defined as LoC ≥ 7 , $n=46$, and no certain diagnosis defined as any diagnosis (axSpA or no axSpA) with a LoC ≤ 6 , $n=72$. n/a, not applicable. [‡] $n=242$ CBP patients, ^{‡‡} $n=236$ CBP patients. n/a, not applicable.

Table 2 Baseline characteristics of CBP patients stratified according to certain and uncertain axSpA diagnosis using the arbitrary cut of level of confidence ≥ 7 , $n = 245$.

Characteristics	Certain diagnosis (level of confidence ≥ 7)	Certain diagnosis (level of confidence ≥ 7)	Uncertain diagnosis* (level of confidence ≤ 6)
	axSpA n = 127	no axSpA n = 46	axSpA/no axSpA n = 72
Age (years), mean $\pm$ SD	30.3 (7.7)	31.0 (7.8)	31.0 (8.2)
Male, n (%)	59 (46)	11 (24)	24 (33)
IBP, n (%)	104 (82)	36 (78)	48 (67)
Good response to NSAIDs, n (%)	66 (53)	24 (53)	25 (35)
Positive family history of SpA, n (%)	57 (45)	25 (54)	41 (57)
Past history or current symptoms			
Peripheral arthritis, n (%)	30 (24)	2 (4)	14 (19)
Dactylitis, n (%)	18 (14)	0 (0)	4 (6)
Enthesitis, n (%)	43 (34)	7 (15)	13 (18)
AAU, n (%)	16 (13)	2 (4)	6 (8)
IBD, n (%)	10 (8)	3 (7)	6 (8)
Psoriasis, n (%)	26 (20)	4 (9)	4 (6)
Elevated CRP/ESR, n (%)	53 (42)	8 (17)	13 (18)
Mean (SD) number of SpA features ^o	3.3 (1.7)	2.4 (1.0)	2.4 (1.3)
Presence of 2 or more SpA features, n (%)	122 (96)	38 (83)	55 (76)
HLA-B27 positive, n (%)	88 (69)	9 (20)	34 (47)
Sacroiliitis MRI, n (%) [‡]	82 (67)	0 (0)	8 (12)
Sacroiliitis radiography, n (%)	36 (29)	1 (2)	2 (3)

*No certain diagnosis defined as any diagnosis (axSpA or no axSpA) with a level of confidence (LoC) ≤ 6 . SpA features in this case are accumulated according to the principle of “once a feature always a feature”. AxSpA, axial spondyloarthritis; IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis; AAU, acute anterior uveitis; IBD, inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging. ^oTotal number of SpA features after medical history taking, physical examination and measurement of acute phase reactants but before HLA-B27 testing and imaging. Level of certainty regarding diagnosis on a 1 to 10 scale with 1 implying little certainty and 10 implying great certainty about diagnosis. n/a, not applicable. [‡] $n = 123$ for patients with axSpA diagnosis, $n = 68$ for patients with no certain diagnosis.

No axSpA diagnosis at baseline

Of the 46 patients who were not diagnosed as having axSpA, 37 (80%) patients remained as ‘no axSpA’ after one-year follow-up (Table 3). In 9 (20%) patients the LoC changed to ≤6. Remarkably, none of the patients ‘without axSpA’ changed into an axSpA diagnosis. In the no axSpA diagnosis group the most frequently gained SpA features after one year were: ‘IBP’ (+14%), ‘good response to NSAIDs’ (+10%), and ‘elevated CRP/ESR’ (+10%). Within the group of patients with an uncertain diagnosis (n=9) ‘elevated CRP/ESR’ was the most frequently acquired feature (+45%) (supplementary table S2). Most common diagnoses within the group of patients without axSpA were ‘non-specific back pain’, ‘(fibro)myalgia’ and ‘degenerative disc disease’.

Uncertain diagnosis at baseline

Of the 72 patients with uncertain diagnosis (i.e. LoC ≤6 for either axSpA or no axSpA), 17 (24%) patients were diagnosed with axSpA after one-year follow-up (LoC ≥7) (Table 4). In 29 (40%) patients rheumatologists changed their initial diagnosis to no axSpA with a LoC ≥7, and in 26 (36%) patients the LoC regarding diagnosis remained ≤6. In the patients diagnosed with axSpA after one year ‘IBP’ (+17%), ‘good response to NSAIDs’ (+30%), and ‘sacroiliitis on MRI’ (+24%) were the most prevalent SpA features gained. Although patients in the no axSpA and the uncertain diagnosis groups frequently gained new SpA features (‘good response to NSAIDs’ (+14% and +23% respectively), ‘elevated CRP/ESR’ (+11% and +31%), and ‘sacroiliitis on MRI’ (+7% and +8%)), they remained in the ‘no axSpA’ or ‘uncertain diagnosis’ groups.

The mean (SD) diagnostic confidence increased at one-year follow-up: 8.8 (1.0) (vs. baseline 8.6 (1.0)) in the axSpA group, 8.3 (1.0) (vs. baseline 7.9 (0.7)) in the no axSpA group and in the uncertain diagnosis group the LoC was 4.7 (1.4) (vs baseline 4.5 (1.5)).

Table 3 Diagnosis at baseline and after one-year follow-up in patients with chronic back pain suspected of axSpA.

Diagnosis at baseline	Diagnosis at follow-up			Total
	AxSpA	No axSpA	No certain diagnosis*	
AxSpA	112	3	12	127
No axSpA	0	37	9	46
No certain diagnosis*	17	29	26	72
Total	129	69	47	245

* No certain diagnosis defined as any diagnosis (axSpA or no axSpA) with a level of confidence (LoC) ≤6. AxSpA, axial spondyloarthritis.

Table 4 Feature gain of baseline ‘no certain diagnosis’ patients at one-year follow-up stratified for their follow-up diagnosis status (n=72).

Feature gain	Diagnosis at one-year follow-up			
	All patients n=72	axSpA n=17	No axSpA n=29	No certain diagnosis* n=26
IBP, n (%)	+10 (14)	+3 (17)	+1 (3)	+6 (23)
Good response to NSAIDs, n (%)	+15 (21)	+5 (30)	+4 (14)	+6 (23)
Positive family history of SpA, n (%)	+2 (3)	0 (0)	+1 (3)	+1 (4)
Past history or current symptoms				
Peripheral arthritis, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Dactylitis, n (%)	+1 (1)	+1 (6)	0 (0)	0 (0)
Enthesitis, n (%)	+4 (6)	+1 (6)	+2 (7)	+1 (4)
AAU, n (%)	+1 (1)	0 (0)	+1 (3)	0 (0)
IBD, n (%)	+2 (3)	+1 (6)	0 (0)	+1 (4)
Psoriasis, n (%)	+2 (3)	0 (0)	+1 (3)	+1 (4)
Elevated CRP/ESR, n (%)	+11 (15)	0 (0)	+3 (11)	+8 (31)
Number of SpA features gained, mean °	+0.7	+0.7	+0.5	+0.9
Sacroiliitis MRI, n (%)	+8 (11)	+4 (24)	+2 (7)	+2 (8)
Sacroiliitis radiography, n (%)	0 (0)	0 (0)	0 (0)	0 (0)

* No certain diagnosis defined as any diagnosis (SpA or no SpA) with a level of confidence (LoC) ≤6. SpA features in this case are accumulated according to the principle of “once a feature always a feature”. AxSpA, axial spondyloarthritis; IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis; AAU, acute anterior uveitis; IBD, inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging. °Total number of SpA features after medical history taking, physical examination and measurement of acute phase reactants but before HLA-B27 testing and imaging. Level of certainty regarding diagnosis on a 1 to10 scale with 1 implying little certainty and 10 implying great certainty about diagnosis. n/a, not applicable.

DISCUSSION

In this study we have evaluated the evolution of diagnostic uncertainty in CBP patients with a suspicion of axSpA in relation to the accrual of SpA features during one-year follow up. In only about 1% of patients with axSpA at baseline rheumatologists changed a diagnosis from axSpA into 'no axSpA' or in an 'uncertain diagnosis'. Interestingly, none of the patients with 'no axSpA' at baseline were diagnosed as axSpA at follow-up. Nevertheless, in some of these cases rheumatologists were less certain about 'no axSpA'. We found that standardized follow-up led to a decrease of patients with uncertain diagnosis, however, despite an extensive work-up some uncertainty regarding the diagnosis remained at follow-up. Remarkably, around two-third of patients with an uncertain diagnosis at baseline received a definite diagnosis (either 'no axSpA' or 'axSpA') after one-year follow-up. In addition, approximately half of the patients had developed at least one new SpA feature after one year but this did in most instances not lead to a change in diagnosis or level of certainty.

In all diagnosis subgroups the most frequently acquired SpA features were 'good response to NSAIDs', 'IBP', 'positive family history of SpA', and 'elevated acute phase reactants'. Most of these are relatively subjective SpA features and reporting may differ between the baseline and follow-up visits. For example, patients may have had a better understanding of their symptoms after their visit to the rheumatologist thus leading to a positive answer at follow-up. The acquisition of these features may not really reflect a newly developed SpA feature, but rather a better comprehension of the SpA feature in question. Although half of the patients acquired at least one SpA feature, it did not lead to major diagnosis changes. A possible explanation is that rheumatologists may base their diagnosis and their diagnostic certainty on different SpA features. Certain SpA features may bear more "weight" when considering an axSpA diagnosis. For example, rheumatologists may mistrust the feature 'good response to NSAIDs' when considering a diagnosis of axSpA but may put more weight on 'inflammation on MRI-SI'. These relative differences could not be assessed in this study and should be evaluated in future research on the diagnostic process of early axSpA.

An important limitation of this study is that there is no gold standard for diagnosing axSpA and that rheumatologists might base their diagnosis on different considerations, which may have influenced the diagnostic LoCs. In addition, patients were not necessarily seen by the same rheumatologist at follow-up, which might have influenced the LoCs because of inter-observer variability. Moreover, patients were diagnosed by hospital-based rheumatologists with

an affinity for axSpA, and as such, findings from this study cannot be extrapolated to different clinical settings such as primary care and common rheumatology practices or those of other medical specialities. A strength of the study, however, is that all patients received the same protocolized work-up at baseline and one-year follow-up.

Another aspect -as often in daily practice- is that differences may be attributed to different levels of clinical expertise. A more experienced rheumatologist may feel more confident in diagnosing axSpA, thus giving a higher validation, than one with less experience. We have, however, not made this distinction in our study as these data are not available. Furthermore, the cut-off value for the level of confidence to stratify the different diagnosis groups was chosen arbitrarily as it is unclear what defines an uncertain or definite diagnosis. It is plausible that the number of diagnosis changes after one-year follow-up is different with another cut-off value.

As earlier mentioned, diagnostic uncertainty in this study was defined arbitrarily by choosing a cut-off value of the LoC regarding diagnosis. There is, however, no clear definition of diagnostic uncertainty nor a scientific method to measure diagnostic uncertainty in daily clinical practice.^{15, 16} In this study we have shown that diagnostic uncertainty is quite common in CBP patients suspected of axSpA. Arguably, this diagnostic uncertainty is multifactorial. AxSpA has a heterogeneous clinical presentation in CBP patients and remains difficult to diagnose, even after excluding all other differential diagnoses. In addition, diagnostic criteria do not exist and recognition of axSpA may also depend on the clinician's experience (i.e. the ability of pattern recognition) in axSpA. Although follow-up in the SPACE cohort is performed according to a standard protocolized work-up, diagnostic uncertainty (outside of a research cohort context) may lead to over-testing and thus excessive use of health care resources. Diagnostic uncertainty is inherent to the practise of medicine. From the data of this study we may conclude that at baseline rheumatologists formed a hypothesis rather than a definite diagnosis which may evolve over time. Future research should focus on the clinical reasoning of axSpA diagnosis to truly identify what makes an axSpA diagnosis according to rheumatologists and which patients might benefit from regular outpatient visits.

In conclusion, diagnostic uncertainty is common in CBP patients suspected of axSpA and persists in a substantial number of patients after one-year follow-up. Nevertheless, despite the limited accrual of SpA features, the overall decrease in number of patients with an uncertain diagnosis after one year favours the experts' recommendation of pursuing a "wait and see approach" in cases of diagnostic uncertainty.

REFERENCES

1. Feldtkeller E, Khan MA, van der Heijde D, *et al.* Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int* 2003;23:61-6.
2. Salvadorini G, Bandinelli F, Delle Sedie A, *et al.* Ankylosing spondylitis: how diagnostic and therapeutic delay have changed over the last six decades. *Clin Exp Rheumatol* 2012;30:561-5.
3. Sorensen J, Hetland ML. Diagnostic delay in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: results from the Danish nationwide DANBIO registry. *Ann Rheum Dis* 2015;74:e12.
4. Sykes MP, Doll H, Sengupta R, *et al.* Delay to diagnosis in axial spondyloarthritis: are we improving in the UK? *Rheumatology (Oxford)* 2015;54:2283-4.
5. Masson Behar V, Dougados M, Etcheto A, *et al.* Diagnostic delay in axial spondyloarthritis: A cross-sectional study of 432 patients. *Joint Bone Spine* 2017;84:467-71.
6. Rudwaleit M, van der Heijde D, Landewe R, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-83.
7. Weber U, Maksymowych WP. Sensitivity and specificity of magnetic resonance imaging for axial spondyloarthritis. *Am J Med Sci* 2011;341:272-7.
8. de Winter J, de Hooze M, van de Sande M, *et al.* Magnetic Resonance Imaging of the Sacroiliac Joints Indicating Sacroiliitis According to the Assessment of SpondyloArthritis international Society Definition in Healthy Individuals, Runners, and Women With Postpartum Back Pain. *Arthritis Rheumatol* 2018;70:1042-8.
9. Weber U, Jurik AG, Zeiden A, *et al.* Frequency and Anatomic Distribution of Magnetic Resonance Imaging Features in the Sacroiliac Joints of Young Athletes: Exploring “Background Noise” Toward a Data-Driven Definition of Sacroiliitis in Early Spondyloarthritis. *Arthritis Rheumatol* 2018;70:736-45.
10. van den Berg R, de Hooze M, Rudwaleit M, *et al.* ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. *Ann Rheum Dis* 2013;72:1646-53.
11. Deodhar A, Mease PJ, Reveille JD, *et al.* Frequency of axial spondyloarthritis diagnosis among patients seen by United States rheumatologists for evaluation of chronic back pain. *Arthritis Rheumatol* 2016.
12. Diagnosis and differential diagnosis of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults. [<https://www.uptodate.com/contents/diagnosis-and-differential-diagnosis-of-axial-spondyloarthritis-ankylosing-spondylitis-and-nonradiographic-axial-spondyloarthritis-in-adults>]
13. Bakker PAC, Ramiro S, Ez-Zaitouni Z, *et al.* Is it Useful to Repeat Magnetic Resonance Imaging of the Sacroiliac Joints After Three Months or One Year in the Diagnosis of Patients With Chronic Back Pain and Suspected Axial Spondyloarthritis? *Arthritis Rheumatol* 2019;71:382-91.

14. van den Berg R, de Hooze M, van Gaalen F, *et al.* Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. *Rheumatology (Oxford)* 2013;52:1492-9.
15. Simpkin AL, Schwartzstein RM. Tolerating Uncertainty - The Next Medical Revolution? *N Engl J Med* 2016;375:1713-5.
16. Bhise V, Rajan SS, Sittig DF, *et al.* Defining and Measuring Diagnostic Uncertainty in Medicine: A Systematic Review. *J Gen Intern Med* 2018;33:103-15.

SUPPLEMENTARY MATERIAL

Table S1. Feature gain of baseline axSpA patients at one-year follow-up stratified for their follow-up diagnosis status (n=127).

<u>Feature gain</u>	Diagnosis at one-year follow-up		
	axSpA n=112	No axSpA n=3	no certain diagnosis* n=12
IBP, n (%)	+12 (11)	0	0
Good response to NSAIDs, n (%)	+33 (29)	+2 (67)	+7 (59)
Positive family history of SpA, n (%)	+5 (4)	0	+1 (8)
Past history or current symptoms			
Peripheral arthritis, n (%)	+4 (3)	0	+1 (8)
Dactylitis, n (%)	+8 (7)	0	0
Enthesitis, n (%)	+5 (4)	0	+1 (8)
AAU, n (%)	+2 (2)	0	+1 (8)
IBD, n (%)	+1 (1)	0	0
Psoriasis, n (%)	+6 (5)	0	0
Elevated CRP/ESR, n (%)	+14 (12)	0	0
Number of SpA features, mean °	+0.9	+0.7	+0.9
Presence of 2 or more SpA features, n (%)	+12 (11)	+2 (67)	0
HLA-B27 positive, n (%)	n/a	n/a	n/a
Sacroiliitis MRI, n (%) [‡]	+9 (6)	0	+1 (8)
Sacroiliitis radiography, n (%)	+13 (11)	0	0

* No certain diagnosis defined as axSpA diagnosis with a level of confidence (LoC) ≤ 6 or no axSpA diagnosis with LoC ≤ 6 . SpA features in this case are accumulated according to the principle of “once a feature always a feature”. AxSpA, axial spondyloarthritis; IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis; AAU, acute anterior uveitis; IBD, inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging. °Total number of SpA features after medical history taking, physical examination and measurement of acute phase reactants but before HLA-B27 testing and imaging. LoC, Level of certainty regarding diagnosis on a 1 to 10 scale with 1 implying little certainty and 10 implying great certainty about diagnosis. n/a, not applicable. [‡] n=108 for axSpA patients with LoC ≥ 7 .

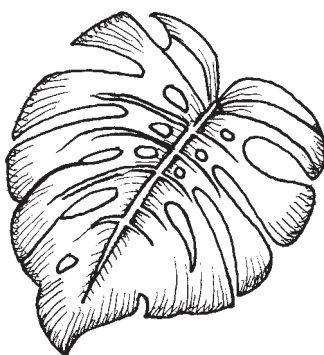
Table S2. Feature gain of baseline ‘no axSpA’ patients (LoC>6) at one-year follow-up stratified for their follow-up diagnosis status (n=46).

<u>Feature gain</u>	Diagnosis at one-year follow-up		
	axSpA n=0	No axSpA n=37	No certain diagnosis* n=9
IBP, n (%)	-	+5 (14)	+1 (11)
Good response to NSAIDs, n (%)	-	+4 (10)	0
Positive family history of SpA, n (%)	-	0	+1 (11)
Past history or current symptoms			
Peripheral arthritis, n (%)	-	0	0
Dactylitis, n (%)	-	+1 (3)	0
Enthesitis, n (%)	-	+1 (3)	0
AAU, n (%)	-	0	0
IBD, n (%)	-	0	0
Psoriasis, n (%)	-	0	0
Elevated CRP/ESR, n (%)	-	+4 (10)	+4 (45)
Number of SpA features, mean °	-	+0.4	+0.6
Presence of 2 or more SpA features, n (%)	-	+2 (5)	+1 (11)
HLA-B27 positive, n (%)	n/a	n/a	n/a
Sacroiliitis MRI, n (%)	-	0	0
Sacroiliitis radiography, n (%)	-	0	0

* No certain diagnosis defined as axSpA diagnosis with a level of confidence (LoC) ≤ 6 or no axSpA diagnosis with LoC ≤ 6 . SpA features in this case are accumulated according to the principle of “once a feature always a feature”. AxSpA, axial spondyloarthritis; IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis; AAU, acute anterior uveitis; IBD, inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging. °Total number of SpA features after medical history taking, physical examination and measurement of acute phase reactants but before HLA-B27 testing and imaging. Level of certainty regarding diagnosis on a 1 to 10 scale with 1 implying little certainty and 10 implying great certainty about diagnosis. n/a, not applicable.

Is the current ASAS expert definition of a positive family history useful in identifying axial spondyloarthritis?

Results from the SPACE and DESIR cohorts.



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ABSTRACT

Background

The Assessment of SpondyloArthritis international Society (ASAS) definition of a positive family history (PFH) of spondyloarthritis (SpA) includes the following diseases in first- or second-degree relatives: ankylosing spondylitis (AS), acute anterior uveitis (AAU), reactive arthritis (ReA), inflammatory bowel disease (IBD), and psoriasis. However, it is not known if a PFH for each of these diseases contributes to making a diagnosis of axSpA, sacroiliitis on imaging or fulfilling the ASAS criteria in patients presenting with chronic back pain (CBP). Therefore, the aim was to assess which SpA diseases in family members are associated with HLA-B27 and axial spondyloarthritis (axSpA) in CBP patients.

Methods

CBP patients suspected of axSpA from the SPACE (n=438) and the DESIR (n=647) cohort were asked about the presence of SpA diseases in first- or second-degree relatives (AS, AAU, ReA, IBD, and psoriasis). The associations between a PFH and HLA-B27, sacroiliitis on imaging (MRI or radiographs), axSpA diagnosis, and ASAS classification in CBP patients were assessed.

Results

In the SPACE and the DESIR cohort, a PFH of AS (odds ratio (OR) 5.9 (3.5-9.9) and OR 3.3 (2.1-5.2)) and a PFH of AAU (OR 9.8 (3.3-28.9) and OR 21.6 (2.9-160.1)) were significantly associated with presence of HLA-B27. Furthermore, in both cohorts a PFH of AS and a PFH of AAU were positively associated with fulfilment of the ASAS criteria, but not with sacroiliitis on imaging. In SPACE but not in DESIR a PFH of AAU was positively associated with axSpA diagnosis. In both cohorts, a PFH of ReA, IBD, or psoriasis was not positively associated with HLA-B27 positivity, sacroiliitis on imaging, axSpA diagnosis or meeting the ASAS criteria for axSpA.

Conclusions

In our cohorts, a PFH of AS or AAU is useful for case-finding of axSpA as this is correlated with HLA-B27 carriership. However, as a PFH of ReA, IBD, or psoriasis does not contribute to identifying axSpA in CBP patients, these data suggest that the widely used ASAS definition of a PFH of SpA should be updated.

BACKGROUND

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease mainly involving the spine and sacroiliac joints. Genetic risk factors play a role in axSpA with human leukocyte antigen B27 (HLA-B27) by far the strongest genetic risk factor for disease.¹ A positive family history (PFH) of SpA has been reported in up to 40% of ankylosing spondylitis (AS) patients and the risk to develop AS in HLA-B27 positive first-degree relatives of HLA-B27 positive AS patients has been estimated to be 16 times higher than that of HLA-B27 positive individuals in the general population.²⁻⁵ As a result, familial aggregation of SpA is considered a risk indicator for the presence of axSpA in patients with chronic back pain (CBP) and is part of several SpA classification criteria sets.⁶⁻⁸

In the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA, a PFH of SpA is defined as the presence of any of the following diseases in first- or second-degree relatives: AS, acute anterior uveitis (AAU), reactive arthritis (ReA), inflammatory bowel disease (IBD), and psoriasis.⁸ This PFH definition is also recommended in diagnosing axSpA, and is incorporated in several referral strategies for CBP patients used by non-rheumatologists.^{9, 10}

However, only three of these diseases have a documented HLA-B27 association (i.e. AS, AAU, ReA) and two are not HLA-B27 associated (i.e. IBD, psoriasis).¹¹⁻¹³ So, even though a PFH of SpA is a common finding in axSpA patients, it is unknown whether a PFH of each of these diseases contributes equally well to making a diagnosis of axSpA in patients presenting with CBP.

In this study, we present data from two unique early axSpA cohorts: the multinational multicenter SPondyloArthritis Caught Early (SPACE) cohort and the French multicenter DEvenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort. In these cohorts of CBP patients with a suspicion of axSpA we have investigated which of the SpA diseases present among family members were associated with HLA-B27, sacroiliitis on imaging, a clinical diagnosis of axSpA, and meeting the ASAS classification criteria for axSpA.

METHODS

Patient cohorts

The SPACE cohort is a prospective study which includes patients with short term CBP (≥ 3 months, ≤ 2 years, and an onset < 45 years) at a minimum age of 16 years from five Rheumatology outpatient clinics in the Netherlands, Norway, and Italy. DESIR is a prospective longitudinal cohort running in 25 centers in France (clinicaltrials.gov NCT01648907). Patients between the ages of 18 and 50 years with inflammatory back pain (IBP) according to the Calin¹⁴ or Berlin¹⁵ criteria, persisting ≥ 3 months but < 3 years, were included. In addition, the treating rheumatologist had to have a substantial suspicion of axSpA (level of confidence ≥ 5 on a 0-10 rating scale, where 0=not confident and 10=very confident). A detailed description of both cohorts is provided elsewhere.^{16, 17} Both studies were approved by local medical ethics committees. All participants provided written informed consent beforehand.

Clinical data collection

All patients underwent a diagnostic work-up according to a fixed protocol which includes physical examination, laboratory assessments (HLA-B27, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)), and magnetic resonance imaging (MRI) as well as radiographs of sacroiliac joints. The presence and history of clinical SpA features were assessed: inflammatory back pain (IBP), good response to non-steroidal anti-inflammatory drugs (NSAIDs), peripheral arthritis, dactylitis, enthesitis, AAU, IBD, and psoriasis. Patients were inquired about the presence of any of the following SpA diseases in first- or second-degree relatives: AS, AAU, ReA, IBD, and psoriasis. For each SpA disease possible answers were “yes”, “no” or “unknown/uncertain”. A PFH was defined as the presence of ≥ 1 SpA related disease in first- (mother, father, sister, brother, daughter, son) or second-degree relatives (aunt, uncle, niece, nephew, grandmother, and grandfather) reported by the patient.⁸

In the SPACE cohort, axSpA was diagnosed by the treating rheumatologist. In the DESIR cohort axSpA diagnosis was defined as the level of confidence regarding diagnosis of ≥ 8 on a 0–10 numerical rating scale (where 0=not confident at all and 10=very confident). The ASAS axSpA classification criteria were used to classify patients.

Data analysis

Baseline demographic and clinical characteristics are presented using descriptive statistics for both the SPACE and DESIR cohorts. The association between each PFH disease and HLA-B27 in patients was assessed using the Chi-squared test. Similar analyses

were performed for the assessment of the association between each PFH disease and a clinical diagnosis of axSpA, sacroiliitis on imaging (defined as either sacroiliitis on MRI, radiographs or on both modalities by local reading), and the fulfilment of the ASAS axSpA classification criteria. Statistical testing was performed using Stata SE v.14 (StataCorp LP, College Station, Texas, USA).

RESULTS

For the current analyses, 438 patients from the SPACE cohort and 647 patients from the DESIR cohort with complete data at baseline were used (Table 1). Several baseline characteristics differed between the two cohorts, mainly reflecting differences in inclusion criteria. In both cohorts, the distribution of all PFH diseases (AS, AAU, ReA, IBD, and psoriasis) in first- or second-degree relatives were similar.

In both the SPACE and DESIR cohort, any PFH, a PFH of AS, and a PFH of AAU were significantly associated with HLA-B27 in CBP patients (Table 2). In multivariable analyses, a PFH of AS or AAU were independently associated with HLA-B27 positivity (data not shown). However, in neither cohort a PFH of ReA, IBD, or psoriasis was associated with HLA-B27 positivity.

To investigate whether the presence of any of the PFH diseases in relatives is associated with sacroiliitis, a clinical diagnosis of axSpA or a positive ASAS classification similar analyses were performed. In both cohorts, neither 'any PFH' nor a separate PFH disease were associated with sacroiliitis (see online Supplementary Table S1). In SPACE but not in DESIR a PFH of AAU was positively associated with axSpA diagnosis (see online Supplementary Table S2). While a PFH of AS or AAU had a significant positive association with fulfilment of the ASAS criteria, such an association was not found for a PFH of ReA, IBD or psoriasis in the SPACE and DESIR cohorts (Table 3).

In addition, the relative contribution of HLA-B27 was investigated among patients who were classified according to the ASAS criteria. A total of 203 (46%) patients from the SPACE cohort and 410 (63%) patients from the DESIR cohort fulfilled the ASAS criteria for axSpA, and 156 (77%) and 347 (85%) patients were HLA-B27 positive, respectively (Table 4). A PFH was reported more frequently in HLA-B27 positive patients than in HLA-B27 negative patients meeting the ASAS classification criteria (SPACE 45% vs 7% and DESIR 35% vs 6%).

Table 1 Baseline characteristics and clinical features of CBP patients in the SPACE (n=438) and DESIR cohorts (n=647).

Characteristic	SPACE n = 438	DESIR n = 647
Age, years	31.3 (8.3)	33.6 (8.6)
Symptom duration, months	13.4 (7.4)	18.1 (10.5)
Male	165 (38)	305 (47)
IBP	286 (66)	647 (100)*
Good response to NSAIDs ^a	181/420 (43)	515/643 (80)
<i>Past history or current symptoms</i>		
Peripheral arthritis	64 (15)	363 (56)
Dactylitis	24 (6)	83 (13)
Enthesitis	89 (20)	312 (48)
AAU	34 (8)	51 (8)
IBD	34 (8)	23 (4)
Psoriasis	51 (12)	97 (15)
Elevated CRP (mg/L) / ESR (mm) ^b	123 (28)	254 (39)
HLA-B27 positive	174/436 (40)	376/646 (58)
Sacroiliitis, radiography [‡]	48/434 (11)	172 (27)
Sacroiliitis, MRI [‡]	135/431 (31)	207/636 (33)
ASAS criteria for axSpA	203 (46)	410/634 (65)
Any positive family history ^c	185 (42)	249 (39)
PFH of AS	90 (21)	127 (20)
PFH of AAU	27 (6)	29 (5)
PFH of ReA	14 (3)	6 (1)
PFH of IBD	33 (8)	32 (5)
PFH of Psoriasis	83 (19)	129 (20)
<i>Total number of SpA diseases in first- or second-degree relatives</i>		
Number of patients with 1 disease	135 (73)	189 (76)
Number of patients with 2 diseases	39 (21)	47 (19)
Number of patients with ≥3 diseases	11 (6)	13 (5)

Unless specified otherwise, results are presented as mean ± SD or number (%). * Inclusion criterion. CBP, chronic back pain; IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis; AS, ankylosing spondylitis; AAU, acute anterior uveitis; ReA, reactive arthritis; IBD, inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leucocyte antigen B27; ASAS axSpA criteria, Assessment of Spondyloarthritis international Society criteria for axial Spondyloarthritis; PFH, positive family history. [‡]Imaging based on local reading. MRI, magnetic resonance imaging of sacroiliac joints. ^aBack pain not present anymore or is much better 24–48 hours after a full dose of NSAID. ^bValues greater than the upper limit of normal. ^cPresence in first- or second-degree relatives of any of the following: AS, AAU, ReA, IBD, or psoriasis.

Table 2 Association of family history manifestations with HLA-B27 in CBP patients in the SPACE (n=438) and DESIR cohorts (n=647).

SPACE*				
	HLA-B27+ n= 174	HLA-B27- n= 262	OR (95% CI)	P- value
Any PFH	97	87	2.5 (1.7-3.8)	<0.001
AS	65	24	5.9 (3.5-9.9)	<0.001
AAU	23	4	9.8 (3.3-28.9)	<0.001
ReA	5	9	0.8 (0.3-2.5)	0.745
IBD	12	21	0.9 (0.4-1.8)	0.666
Psoriasis	34	48	1.1 (0.6-1.8)	0.750

HLA-B27, human leukocyte antigen B27; CBP, chronic back pain; Any PFH, any family history manifestation in first- or second-degree relatives; AS, ankylosing spondylitis; AAU, acute anterior uveitis;

Table 3 Association of family history manifestations with the fulfilment of ASAS axSpA criteria in the SPACE cohort and DESIR cohorts.

Fulfilment of ASAS axSpA criteria				
	SPACE		DESIR	
	OR (95% CI)	P- value	OR (95% CI)	P- value
Any PFH	2.1 (1.4-3.1)	<0.001	1.3 (1.0-1.9)	0.091
AS	3.3 (2.0-5.3)	<0.001	2.1 (1.3-3.3)	<0.001
AAU	7.4 (2.5-21.7)	<0.001	5.0 (1.5-16.7)	0.009
ReA	0.6 (0.2-1.9)	0.421	0.3 (0.05-1.5)	0.132
IBD	1.1 (0.5-2.2)	0.798	0.8 (0.4-1.6)	0.521
Psoriasis	1.2 (0.8-2.0)	0.388	1.2 (0.8-1.8)	0.464

Any PFH, any family history manifestation in first- or second-degree relatives; AS, ankylosing spondylitis; AAU, acute anterior uveitis; ReA, reactive arthritis; IBD, inflammatory bowel disease; OR, odds ratio; 95% CI, 95% confidence interval.

DESIR**			
HLA-B27+	HLA-B27-		
n= 376	n= 270	OR (95% CI)	P- value
158	91	1.4 (1.0-2.0)	0.032
100	27	3.3 (2.1-5.2)	<0.001
28	1	21.6 (2.9-160.1)	0.003
1	5	0.1 (0.01-1.2)	0.075
17	15	0.8 (0.4-1.6)	0.551
69	60	0.8 (0.5-1.2)	0.225

ReA, reactive arthritis; IBD, inflammatory bowel disease; OR, odds ratio; 95% CI, 95% confidence interval. * 2 patients with unknown HLA-B27 status; **1 with patient unknown HLA-B27 status.

Table 4 PFH diseases in first- or second-degree relatives of CBP patients meeting the ASAS axSpA criteria, stratified according to HLA-B27 status.

Positive family history	SPACE cohort		DESIR cohort	
	n= 201*		n= 409**	
	HLA-B27+	HLA-B27-	HLA-B27+	HLA-B27-
Any PFH	90 (45%)	14 (7%)	145 (35%)	24 (6%)
AS	59 (29%)	2 (1%)	92 (23%)	5 (1%)
AAU	22 (11%)	1 (1%)	26 (6%)	0 (0)
ReA	4 (1%)	1 (1%)	1 (0.2%)	1 (0.2%)
IBD	11 (6%)	5 (3%)	14 (3%)	5 (1%)
Psoriasis	32 (16%)	9 (5%)	65 (16%)	20 (5%)

ASAS axSpA criteria, Assessment of Spondyloarthritis international Society criteria for axial Spondyloarthritis; HLA-B27, human leucocyte antigen B27; Any PFH, any family history manifestation in first- or second-degree relatives; AS, ankylosing spondylitis; AAU, acute anterior uveitis; ReA, reactive arthritis; IBD, inflammatory bowel disease.*203 patients fulfilled ASAS-criteria, 2 with unknown HLA-B27 status; **410 patients fulfilled ASAS-criteria, 1 with unknown HLA-B27 status.

DISCUSSION

To our knowledge, this is the first study to investigate the usefulness of the separate SpA diseases in a PFH as defined for the ASAS classification criteria. In two independent cohorts of predominantly Caucasoid Europeans, we found that in CBP patients suspected of axSpA a PFH of ReA, IBD or psoriasis were neither associated with HLA-B27 positivity, nor with sacroiliitis, a diagnosis of axSpA or fulfilment of the ASAS criteria. In contrast, a PFH of AS or AAU was strongly correlated with HLA-B27 carriership.

IBD and psoriasis are generally not HLA-B27 associated diseases, but ReA has been reported to be associated with HLA-B27 in a secondary care setting, although in population-based studies the prevalence of HLA-B27 in ReA was comparable to that of the general population.^{12, 18} A possible explanation for the absence of the association between ReA and HLA-B27 in our study is that the (self)reported prevalence of ReA in family members of patients in the SPACE and DESIR cohort was low, suggesting underreporting.

It is important to emphasize that the current study is done in patients with predominantly axial symptoms. Although only a PFH of AS or AAU have shown to be independently associated with HLA-B27, this does not mean that a PFH of the other SpA diseases is always irrelevant.¹⁹ For example, presence of psoriasis in relatives could be relevant in a patient with peripheral symptoms suspected of psoriatic arthritis.²⁰

A strength of this study is the use of two large early axSpA cohorts in which all patients were assessed following a similar protocol which allowed for replication of findings. Strikingly similar prevalences of PFH were found in both cohorts which adds to the credibility of the data. The major limitation of this study, however, is that the diagnosis in relatives (the PFH) is solely based on patients' information which may have led to either under- or overestimation of a PFH. However, this is similar to most clinical settings in which PFH is mostly based on self-reporting too. Moreover, subdividing a PFH into five different diseases meant that a PFH of for instance AAU or ReA was uncommon.

CONCLUSIONS

In conclusion, in our two cohorts a PFH of ReA, IBD, and psoriasis does not contribute to diagnosing axSpA in CBP patients suspected of axSpA. A PFH of AS or AAU may be useful in case-finding in low prevalence settings, such as general practice, as these are correlated with HLA-B27 carriership. When replicated, preferably in other regions of the world in patients with a different genetic background, it is justified to remove a PFH of ReA, IBD, and psoriasis from the current ASAS definition of a positive PFH relevant for axSpA.

REFERENCES

1. Schlosstein L, Terasaki PI, Bluestone R, *et al.* High association of an HL-A antigen, W27, with ankylosing spondylitis. *N Engl J Med* 1973;288:704-6.
2. Bedendo A, Glorioso S, Pasini CV, *et al.* A family study of ankylosing spondylitis. *Rheumatology International* 1984;5:29-32.
3. van der Linden SM, Valkenburg HA, de Jongh BM, *et al.* The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. *Arthritis Rheum* 1984;27:241-9.
4. Said-Nahal R, Miceli-Richard C, Berthelot JM, *et al.* The familial form of spondylarthropathy: a clinical study of 115 multiplex families. Groupe Francais d'Etude Genetique des Spondylarthropathies. *Arthritis Rheum* 2000;43:1356-65.
5. Brown MA, Kennedy LG, MacGregor AJ, *et al.* Susceptibility to ankylosing spondylitis in twins: the role of genes, HLA, and the environment. *Arthritis Rheum* 1997;40:1823-8.
6. Amor B, Dougados M, Mijiyawa M. [Criteria of the classification of spondylarthropathies]. *Rev Rhum Mal Osteoartic* 1990;57:85-9.
7. Dougados M, van der Linden S, Juhlin R, *et al.* The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991;34:1218-27.
8. Rudwaleit M, van der Heijde D, Landewe R, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-83.
9. Poddubnyy D, van Tubergen A, Landewe R, *et al.* Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis. *Ann Rheum Dis* 2015;74:1483-7.
10. van den Berg R, de Hooge M, Rudwaleit M, *et al.* ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. *Ann Rheum Dis* 2013;72:1646-53.
11. Reveille JD. Genetics of spondyloarthritis--beyond the MHC. *Nat Rev Rheumatol* 2012;8:296-304.
12. Aho K, Ahvonen P, Lassus A, *et al.* HL-A antigen 27 and reactive arthritis. *Lancet* 1973;2:157.
13. Wakefield D, Chang JH, Amjadi S, *et al.* What is new HLA-B27 acute anterior uveitis? *Ocul Immunol Inflamm* 2011;19:139-44.
14. Calin A, Porta J, Fries JF, *et al.* Clinical history as a screening test for ankylosing spondylitis. *Jama* 1977;237:2613-4.
15. Rudwaleit M, Metter A, Listing J, *et al.* Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum* 2006;54:569-78.
16. van den Berg R, de Hooge M, van Gaalen F, *et al.* Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. *Rheumatology (Oxford)* 2013;52:1492-9.

17. Dougados M, d'Agostino MA, Benessiano J, *et al.* The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. *Joint Bone Spine* 2011;78:598-603.
18. Leirisalo-Repo M, Hannu T, Mattila L. Microbial factors in spondyloarthropathies: insights from population studies. *Curr Opin Rheumatol* 2003;15:408-12.
19. Rudwaleit M, van der Heijde D, Khan MA, *et al.* How to diagnose axial spondyloarthritis early. *Ann Rheum Dis* 2004;63:535-43.
20. Reich K, Kruger K, Mossner R, *et al.* Epidemiology and clinical pattern of psoriatic arthritis in Germany: a prospective interdisciplinary epidemiological study of 1511 patients with plaque-type psoriasis. *Br J Dermatol* 2009;160:1040-7.

SUPPLEMENTARY MATERIAL

Table S1. Association of family history manifestations with any positive imaging (sacroiliitis on MRI or radiographs) in the SPACE cohort and DESIR cohorts.

Sacroiliitis on imaging (local reading)				
	SPACE		DESIR	
	OR (95% CI)	P- value	OR (95% CI)	P- value
Any PFH	0.9 (0.6-1.3)	0.597	0.9 (0.7-1.3)	0.753
AS	0.8 (0.5-1.4)	0.452	1.0 (0.7-1.5)	0.928
AAU	1.7 (0.8-3.8)	0.164	1.2 (0.6-2.6)	0.566
ReA	0.2 (0.02-1.2)	0.075	0.8 (0.1-4.2)	0.749
IBD	0.8 (0.4-1.7)	0.530	0.7 (0.3-1.5)	0.318
Psoriasis	0.9 (0.6-1.6)	0.851	0.9 (0.6-1.4)	0.652

Any PFH, any family history manifestation in first- or second-degree relatives; AS, ankylosing spondylitis; AAU, acute anterior uveitis; ReA, reactive arthritis; IBD, inflammatory bowel disease; OR, odds ratio; 95% CI, 95% confidence interval.

Table S2. Association of family history manifestations with clinical diagnosis in the SPACE cohort and DESIR cohorts.

Clinical axSpA diagnosis				
	SPACE		DESIR*	
	OR (95% CI)	P- value	OR (95% CI)	P- value
Any PFH	1.5 (1.0-2.2)	0.053	1.0 (0.7-1.4)	0.900
AS	1.3 (0.8-2.1)	0.282	1.2 (0.8-1.7)	0.461
AAU	3.4 (1.3-8.6)	0.010	1.4 (0.7-3.0)	0.350
ReA	0.2 (0.1-0.9)	0.035	1.1 (0.2-5.7)	0.870
IBD	1.0 (0.5-2.1)	0.960	1.0 (0.5-2.1)	0.982
Psoriasis	1.6 (1.0-2.6)	0.064	0.9 (0.6-1.3)	0.526

*Diagnosis defined as level of confidence of axSpA diagnosis ≥ 8 . Any PFH, any family history manifestation in first- or second-degree relatives; AS, ankylosing spondylitis; AAU, acute anterior uveitis; ReA, reactive arthritis; IBD, inflammatory bowel disease; OR, odds ratio; 95% CI, 95% confidence interval.

The yield of a positive MRI of the spine as imaging criterion in the ASAS classification criteria for axial spondyloarthritis.

Results from the SPACE and DESIR cohorts.



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ABSTRACT

Objectives

To assess the prevalence of spinal inflammation on MRI in patients with chronic back pain (CBP) of maximally three years duration, and to evaluate the yield of adding a positive MRI-spine as imaging criterion to the ASAS classification criteria for axSpA.

Methods

Baseline X-SI, MRI-SI, and MRI-spine were scored by ≥ 2 experienced central readers per modality in the SPACE and DESIR cohorts. Inflammation suggestive of axSpA was assessed in the entire spine. A positive MRI-spine was defined by the presence of ≥ 5 inflammatory lesions. Alternative less strict definitions were also tested.

Results

In this study 541 and 650 CBP patients from the SPACE and DESIR cohorts were included. Sacroiliitis on X-SI and MRI-SI was found in 40/541(7%) and 76/541(14%) patients in SPACE, and in DESIR in 134/650(21%) and 231/650(36%) patients, respectively. In SPACE and DESIR, a positive MRI-spine was seen in 4/541(1%) and 48/650(7%) patients. Of the patients without sacroiliitis on imaging, 3/447(1%) (SPACE) and 8/382(2%) (DESIR) patients had a positive MRI-spine. Adding positive MRI-spine as imaging criterion led to new classification in only one patient in each cohort, as the other patients already fulfilled the clinical arm. Other definitions of a positive MRI-spine yielded similar results.

Conclusion

In two cohorts of CBP patients with a maximum symptom duration of three years, a positive MRI-spine was rare in patients without sacroiliitis on MRI-SI and X-SI. Addition of MRI-spine as imaging criterion to the ASAS axSpA criteria had a low yield of newly classified patients and is therefore not recommended.

INTRODUCTION

Magnetic resonance imaging (MRI) has become of great interest as a diagnostic tool in the evaluation of patients suffering from chronic back pain (CBP) suspected of axial spondyloarthritis (axSpA).¹⁻⁸ For years, clinicians (and researchers) relied on conventional imaging of the sacroiliac joints (X-SI) to detect abnormalities suggestive of axSpA.⁹ However, X-SI only captures structural damage, which generally takes months to years to develop, leaving aside that not all patients will develop structural bone damage in the axial skeleton. This jeopardises the early recognition of patients with axSpA. MRI, however, can visualize both inflammation and structural damage, and therefore may help in recognizing axSpA patients that do not (yet) have radiographic sacroiliitis.

The Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA comprise a criteria set combining the information obtained from patient history taking, physical examination, laboratory testing, and imaging (X-SI and MRI of the sacroiliac joints).¹⁰ A pivotal aspect of these criteria is the “two arms” concept, commonly referred to as the ‘imaging arm’ and the ‘clinical arm’. According to the ASAS classification criteria, CBP patients with the onset of back pain <45 years of age are classified via the imaging arm when 1) radiographic sacroiliitis plus ≥ 1 spondyloarthritis (SpA)-feature is present or 2) sacroiliitis on MRI plus ≥ 1 additional SpA-feature is present also defined as ‘positive MRI’. Currently, a positive MRI in the ASAS classification criteria is solely based on the presence of inflammatory lesions in the sacroiliac joints and positive findings are defined according to the ASAS definition: 1 bone marrow edema (BME) lesion highly suggestive of axSpA present on ≥ 2 consecutive slices, or ≥ 2 BME lesions highly suggestive of axSpA on a single slice.^{11, 12}

Several studies have shown that besides inflammation on MRI of the sacroiliac joints (MRI-SI), inflammatory lesions in the spine on MRI (MRI-spine) may also occur.^{8, 13} Remarkably, in one study spinal inflammation - in the absence of sacroiliitis on MRI - was observed in about half of the patients with longer disease duration.¹⁴ A consensus definition for a positive MRI-spine was developed by the ASAS/Outcome Measures in Rheumatology (OMERACT) MRI working group.⁸ In this consensus definition a positive MRI-spine is described as the presence of ≥ 3 inflammatory lesions in the vertebrae, whereas each lesion needs to be present on ≥ 2 consecutive slices. De Hooge *et al* recently proposed a cut-off value of ≥ 5 inflammatory lesions that defines a positive MRI-spine with higher specificity of $\geq 95\%$ (i.e. <5% patients without axSpA with a positive MRI-spine).¹⁵

The main objectives of this study were to evaluate the presence of spinal inflammatory lesions on MRI in patients with a maximum CBP duration of 3 years in two different cohorts, the SPondyloArthritis Caught Early (SPACE) cohort and the DEvenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort. In addition, we assessed the added value of spinal inflammatory lesions on MRI, represented in various definitions of a positive MRI-spine, as imaging criterion in the ASAS classification criteria for axSpA.

METHODS

Cohorts and clinical assessments

For this analysis baseline data from the SPACE and the DESIR cohorts were used which have been described in detail before.^{16,17} In summary, SPACE is an ongoing observational cohort in which patients with a minimum age of 16 years with short term CBP (≥ 3 months, ≤ 2 years, and an onset < 45 years) are included. Patients are recruited from multiple Rheumatology centres in Europe; the Netherlands, Norway, Italy, and Sweden. The clinical database used for the current study was locked on September 30th 2016.

DESIR is a longitudinal cohort for which the inclusion period was from December 2007 until April 2010 in 25 centres in France. Patients aged 18-50 years with inflammatory back pain (IBP) according to the Calin¹⁸ or Berlin¹⁹ criteria, persisting ≥ 3 months but < 3 years, suggestive of axSpA according to the treating rheumatologist, were included. The clinical database used for the current study was locked on April 30th 2015.

As part of both study protocols and to determine fulfilment of the ASAS-criteria, presence of all SpA-features was assessed. These include Human Leukocyte Antigen B27 (HLA-B27), positive family history of SpA, IBP, psoriasis, peripheral arthritis, dactylitis, heel enthesitis, acute anterior uveitis, inflammatory bowel disease (IBD), good response to non-steroidal anti-inflammatory drugs (NSAIDs), elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), sacroiliitis on X-SI and MRI-SI, all according to the published definitions. In both cohorts informed consent forms from all study participants as well as approval from all local medical ethical committees were obtained beforehand.

Imaging

Detailed descriptions of the applied scoring methods in both cohorts have been published previously. In brief, all available baseline imaging modalities were scored by experienced

central readers. In the SPACE cohort each imaging modality was scored by three central readers. In the DESIR cohort each imaging modality was scored by two central readers and an adjudicator in case of disagreement. The readers were blinded for all clinical and laboratory data as well as the other imaging modalities, and the various modalities were scored separately.

Imaging assessments

Sacroiliac joints were evaluated on pelvic radiographs using the mNY criteria in which sacroiliitis is defined as grade ≥ 2 bilaterally or grade 3–4 unilaterally.⁹ MRI-SI and MRI-spine were performed on a 1T-1.5T scanner. For both modalities, Short Tau Inversion Recovery (TR2500–4000/TE600) and T1-weighted Turbo Spin-Echo (TR500–700/TE10–55) sequences were acquired. MRI-SI were performed in coronal oblique plane and MRI-spine in sagittal plane with a slice thickness of 4 mm. Readers provided an overall judgement on a positive MRI-SI (yes/no) according to the ASAS definition.¹¹ X-SI and MRI-SI were considered positive if ≥ 2 readers agreed.

MRI-spine

In the SPACE cohort, a positive MRI-spine was defined by the presence of ≥ 5 corner BME lesions highly suggestive of axSpA each visible on ≥ 2 consecutive slices and if ≥ 2 readers agreed.¹⁵ A positive MRI-spine was also defined by the ASAS consensus definition (≥ 3 corner BME lesions on ≥ 2 consecutive slices) and if ≥ 2 readers agreed.⁸

In addition, spinal inflammation suggestive of axSpA was scored according to the Spondyloarthritis Research Consortium of Canada (SPARCC) method. Presence of BME was marked on three consecutive sagittal slices per vertebral unit (VU).²⁰ In case of BME lesions on more than three slices, the three most affected consecutive slices were selected. The 23 VUs each are divided into 4 quadrants and assessed for the presence (score of 1) or absence (score of 0) of inflammatory lesions (maximum possible score 276). In addition, for each VU a score of 1 could be assigned to the presence of an “intense” signal (maximum possible score of 69), defined as a signal as intense as a blood vessel, and a “deep” lesion (maximum possible score of 69), defined as a homogeneous, unequivocal increase in STIR signal extending at least 1 cm from the vertebral end plate. In total, the maximum possible total SPARCC-score is 414. We tested two additional definitions of a positive MRI-spine using the SPARCC-score (including intensity and depth of a lesion). The first, in which a positive MRI-spine was defined by a SPARCC-score ≥ 5 by ≥ 2 readers, and the second, in which a positive MRI-spine was defined by a mean SPARCC-score ≥ 5 of all 3 readers. All four of the described definitions of a positive MRI-spine (i.e. ≥ 5 BME lesions on ≥ 2 consecutive

slices; ≥ 3 BME lesions on ≥ 2 consecutive slices (ASAS definition); SPARCC score ≥ 5 by ≥ 2 readers, and mean SPARCC score ≥ 5 of 3 readers) were applied to assess the added value of a positive MRI-spine in the ASAS classification criteria.

In the DESIR cohort spinal inflammation suggestive of axSpA was scored according to the Berlin method.²¹ In total, the maximum possible total Berlin-score is 69. Additionally, the 23 VUs were each divided into 4 quadrants and assessed for the presence (score of 1) or absence (score of 0) of inflammatory lesions. Inflammatory lesions were scored when present on ≥ 2 consecutive slices. When central readers disagreed on the presence of inflammation, an adjudicator provided scores for all 23 VUs. A positive MRI-spine was defined by the presence of ≥ 5 corner inflammatory lesions and if ≥ 2 readers agreed. A positive MRI-spine was also defined by the ASAS consensus definition (i.e. ≥ 3 inflammatory lesions) and when ≥ 2 readers agreed. Only these two definitions were used to assess the additional value of a positive MRI-spine in the ASAS classification criteria, as the SPARCC method was not applied.

Data analysis

Baseline demographic and clinical characteristics are presented using descriptive statistics for both the SPACE and DESIR cohort (reported in this order). Results are presented as mean and standard deviation (SD) or numbers and percentages (%). Agreement (Cohen's kappa, κ) between readers regarding a positive MRI-SI and MRI-spine was calculated.

Stata 14 (StataCorp. College Station (TX, USA)) was used for data analysis.

RESULTS

For 541/639 and 650/708 patients from the SPACE and DESIR cohorts complete scores of MRI-SI, MRI-spine, X-SI, and clinical data were available for analyses. Of these, 34% and 46% were male, mean symptom duration (SD) was 13.0 (7.1) and 18.2 (10.5) months, and mean age was 29.1 (8.4) and 33.7 (8.7) years (Table 1), respectively.

Interreader reliability The agreement between the readers in the SPACE and DESIR cohorts regarding a positive MRI-spine according to the ASAS definition was $\kappa=0.66$ and $\kappa=0.58$, respectively. Interreader agreement for a positive MRI-spine according to the cut-off of ≥ 5 BME lesions in SPACE was $\kappa=0.60$ and in DESIR $\kappa=0.49$. For MRI-SI the reliability between the readers in the SPACE cohort was $\kappa=0.76$ and in the DESIR cohort $\kappa=0.73$.

Table 1 Baseline clinical and demographic characteristics of patients with CBP suspected of axSpA in the SPACE and DESIR cohorts.

	SPACE n=541	DESIR n=650
Male	186 (34)	301 (46)
Age (years) at onset of back pain	29.1 (8.4)	33.7 (8.7)
Symptom duration, months	13.0 (7.1)	18.2 (10.5)
HLA-B27 positive	211 (39)	381 (59)
Number of SpA-features, mean (SD)	2.4 (1.6)	4.0 (1.4)
IBP	358 (66)	650 (100)*
Good response to NSAIDs ^a	217/521 (42)	518 (80)
Positive family history of SpA ^b	235 (43)	248 (38)
Peripheral arthritis	76 (14)	366 (56)
Dactylitis	28 (5)	82 (13)
Enthesitis	105 (19)	322 (50)
Acute anterior uveitis	42 (8)	55 (8)
IBD	35 (6)	29 (4)
Psoriasis	57 (11)	103 (16)
Elevated CRP/ESR	138 (26)	257 (40)
ASAS axSpA classification	207 (38)	411 (63)
Imaging arm (with/without clinical arm)		
Sacroiliitis on MRI (mNY-MRI+)	53 (10)	115 (21)
Sacroiliitis on radiograph (mNY+MRI+/MRI-)	39 (7)	121 (21)
Clinical arm only	115 (21)	175 (31)

Results are presented as mean ($\pm$ SD) or number (%). CBP, chronic back pain; axSpA, axial spondyloarthritis; HLA-B27, human leukocyte antigen B27; IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis; IBD, inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ASAS, Assessment of Spondyloarthritis international Society. mNY, modified New York; MRI, magnetic resonance imaging. * Inclusion criterion. ^aBack pain not present anymore or is much better 24–48 hours after a full dose of NSAID.

^b Patient reported presence in first- or second-degree relatives of any of the following: ankylosing spondylitis, acute anterior uveitis, reactive arthritis, IBD, or psoriasis.

In both cohorts, the majority of patients did not show abnormalities on MRI-SI, MRI-spine, and X-SI (444/541 (82%) and 374/650 (58%), SPACE and DESIR respectively) (Table 2). In total, 40/541 (7%) and 134/650 (21%) patients in the SPACE and DESIR cohorts had radiographic sacroiliitis (Figure 1). Of the remaining patients without radiographic sacroiliitis, 447/501 (89%) and 382/516 (74%) in SPACE and DESIR had no evidence of inflammation on MRI-SI. In both cohorts, an isolated positive MRI-spine (without sacroiliitis on either MRI-SI or X-SI), applying the cut-off of ≥ 5 BME lesions, was found in 3/447 (1%) and 8/382 (2%) patients (Table 2).

Table 2 Cross-tabulations of baseline sacroiliac imaging (MRI-SI and X-SI) and MRI-spine of CBP patients suspected of axSpA in the SPACE (n=541) and DESIR cohorts (n=650).

SPACE			
MRI of the Spine, cut-off ≥ 5 BME lesions	Any SI-imaging (MRI-SI/X-SI)		
	Positive	Negative	Total
Positive	1	3	4
Negative	93	444	537
Total	94	447	541
DESIR			
MRI of the Spine, cut-off ≥ 5 BME lesions	Any SI-imaging (MRI-SI/X-SI)		
	Positive	Negative	Total
Positive	40	8	48
Negative	228	374	602
Total	268	382	650

SI, sacroiliac joints; MRI, magnetic resonance imaging; X, radiography; CBP, chronic back pain; axSpA, axial spondyloarthritis; BME, bone marrow edema.

Two of the three patients in the SPACE cohort with a positive MRI-spine (definition of ≥ 5 BME lesions) but without sacroiliitis on MRI-SI and X-SI, already fulfilled the clinical arm of the ASAS-criteria, were male and their mean (SD) number of SpA-features was 3.5 (0.7) (Table 3). When hypothetically adding a positive MRI-spine as imaging criterion to the ASAS-criteria for axSpA, the remaining patient could be additionally classified via the imaging arm. Therefore, 447 MRIs of the spine have to be performed to additionally classify this single patient. This patient was a male with one SpA-feature (i.e. good response to NSAIDs).

In the DESIR cohort eight patients had a positive MRI-spine (definition of ≥ 5 BME lesions) without having any signs of inflammation or structural damage suggestive of axSpA on MRI-SI and X-SI (Figure 1). As patients within the DESIR cohort are included until the age of 50 and the ASAS-criteria are, in principle, to be applied to CBP patients ≤ 45 years, we report this

separately. In total, 7 out of 8 patients already fulfilled the clinical arm of the ASAS-criteria: 6/8 patients ≤ 45 years and 1/8 > 45 years (Table 3). Of these seven patients, one was male and the mean (SD) number of SpA-features was 3.7 (2.0). When hypothetically adding a positive MRI-spine as imaging criterion to the ASAS-criteria for axSpA, the remaining patient could be additionally classified via the imaging arm. Therefore, 382 MRI of the spine have to be performed to additionally classify this single patient. This was a HLA-B27 negative male patient with the following 6 SpA-features: positive family history of SpA, IBP, good response to NSAIDs, heel enthesitis, IBD, and peripheral arthritis.

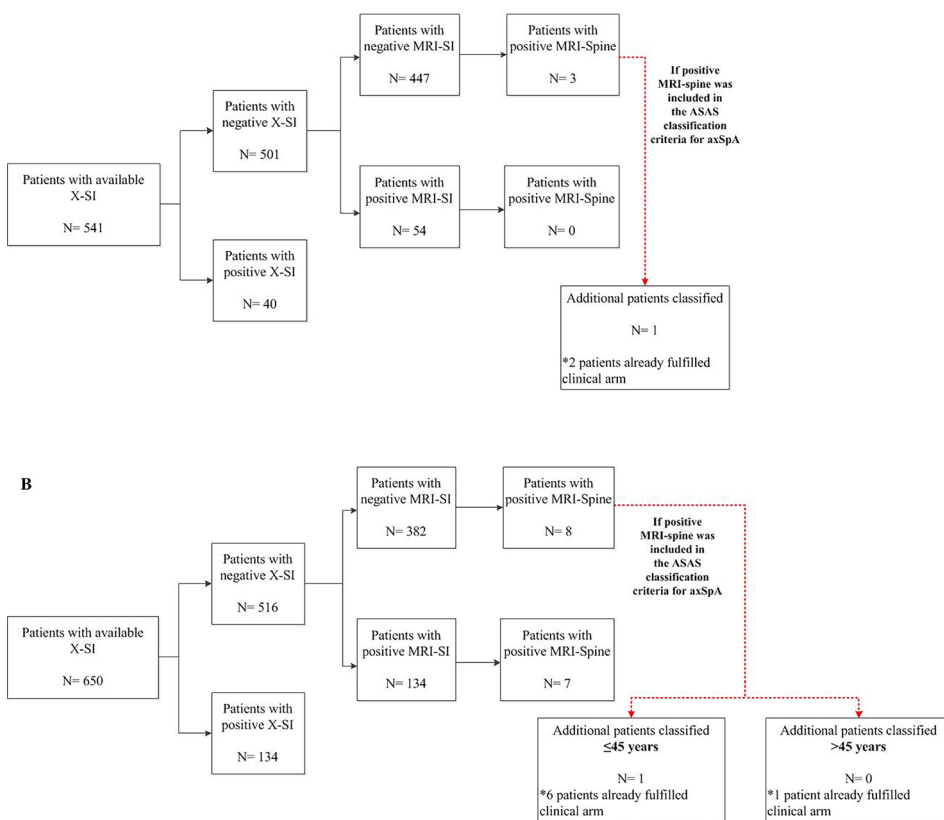


Figure 1 ASAS classification of CBP patients with negative MRI-SI and positive MRI-spine defined by ≥ 5 inflammatory lesions, and the effect of adding positive MRI-spine as an imaging criterion to the ASAS axSpA criteria on classification of patients. **A.** Additional classification of CBP patients in the SPACE cohort. **B.** Additional classification of CBP patients in the DESIR cohort. ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; CBP, chronic back pain; SPACE, SPondyloArthritis Caught Early.

Table 3 Baseline clinical characteristics and disease activity of CBP patients additionally classified according to the ASAS axSpA criteria by baseline presence of sacroiliitis on MRI and spinal inflammation defined by ≥ 5 inflammatory lesions.

SPACE	Imaging arm n=1	Clinical arm n=2
Male, n (%)	1 (100)	2 (100)
HLA-B27 positive, n (%)	0	2 (100)
Number of SpA features	1	3.5 (0.7)
SPARCC spine score, 0-414	13.3	14 (2.4)
<i>Disease activity</i>		
BASDAI ^y	3.4	2.9 (0)
CRP ≥ 5 mg/l, n (%)	0	1 (50)
CRP, mg/l	3	30 (41)
ASDAS-CRP ^{yy}	2.4	4.1 (0)
DESIR	Imaging arm n=1	Clinical arm* n=7
Male, n (%)	1 (100)	1 (14)
HLA-B27 positive, n (%)	0	7 (100)
Number of SpA features	6	3.7 (2)
Berlin spine score, 0-69	9.5	8.5 (2)
<i>Disease activity</i>		
BASDAI	2.9	5 (1.4)
CRP ≥ 5 mg/l, n (%)	0	2 (29)
CRP, mg/l	4	5.3 (4.2)
ASDAS-CRP	1.8	2.8 (0.8)

Unless stated otherwise, results are presented as mean $\pm$ SD (range). CBP, chronic back pain; axSpA, axial spondyloarthritis; MRI-SI, magnetic resonance imaging sacroiliac joints; HLA-B27, Human Leukocyte Antigen B27; SpA-features, total number of spondyloarthritis features without taking imaging and HLA-B27 into account; SPARCC, Spondyloarthritis Research Consortium of Canada; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; NRS, numerical rating scale; CRP, C-reactive protein; ASDAS, Ankylosing Spondylitis Disease Activity Score. ^{yy}n=1 for patients already fulfilling the clinical arm. ^{yy}n=1 for patients already fulfilling the clinical arm. *Patients already fulfilling the clinical arm of the ASAS-criteria, 1/7 patients was >45 years of age.

Alternative definitions of a positive MRI-spine

SPARCC-score

Two other definitions of a positive MRI-spine were tested in the SPACE cohort using the SPARCC-score (Table 4). When a positive MRI-spine was defined as a SPARCC-score of ≥ 5 by ≥ 2 central readers, a total of 21/447 (5%) patients without sacroiliitis on MRI-SI and X-SI had a positive MRI-spine (see online **supplementary Figure S1**). Eight patients (38%) already fulfilled the clinical arm and when adding MRI-spine to the ASAS-criteria, 13/21 (62%) patients could be additionally classified via the imaging arm. Of these 13 patients almost half had ≥ 2 SpA-features. Most frequently reported SpA-features were good response to NSAIDs, positive family history of SpA, and IBP (data not shown). When a positive MRI-spine was defined as a mean SPARCC-score ≥ 5 of all 3 readers, a total of 13/447 (3%) patients had a positive MRI-spine (see online **supplementary Figure S2**). Of these, 7/13 (54%) already fulfilled the clinical arm and the remaining six (46%) patients could be additionally classified via the imaging arm when adding positive MRI-spine to the ASAS-criteria. Half of these patients had ≥ 2 SpA-features and positive family history of SpA and IBP were amongst the frequent features (data not shown).

ASAS consensus definition

According to the ASAS consensus definition (≥ 3 spinal inflammatory lesions on ≥ 2 consecutive slices) 5/447 (1%) patients from the SPACE cohort and 25/382 (7%) patients from the DESIR cohort had a positive MRI-spine without sacroiliitis on MRI-SI and X-SI (Table 4). Of these, 3/5 (60%) patients and 18/25 (72%) patients (16 patients ≤ 45 years and 2 patients > 45 years) already fulfilled the clinical arm (see online **supplementary Figure S3**). The addition of a positive MRI-spine as a criterion in the ASAS-criteria would have resulted in the additional classification of 2/5 (40%) and 7/25 (28%) patients (6 patients ≤ 45 years and 1 patient > 45 years) for SPACE and DESIR, respectively.

Table 4 Patients additionally classified through positive MRI-spine according to 4 different definitions, and diagnosis of axSpA in the SPACE and DESIR cohorts.

SPACE	SPARCC-score ≥5, ≥2 readers n=21
Already classified by clinical arm	8 (38%)
axSpA diagnosis	7/8
Additionally classified by imaging arm	13 (62%)
axSpA diagnosis	5/13
DESIR	SPARCC-score ≥5, ≥2 readers n/a
Already classified by clinical arm*	-
axSpA diagnosis [‡]	-
Additionally classified by imaging arm*	-
axSpA diagnosis [‡]	-

MRI, magnetic resonance imaging; axSpA, axial spondyloarthritis; HLA-B27, Human Leukocyte Antigen B27; SPARCC, Spondyloarthritis Research Consortium of Canada;

DISCUSSION

In patients with CBP of a maximum duration of 3 years and suspected of axSpA from two different cohorts (SPACE and DESIR), the overall prevalence of spinal inflammation is low. In addition, spinal inflammation in the absence of sacroiliitis on MRI-SI and X-SI occurred in a very small proportion of patients. Consequently, adding a positive MRI-spine (represented in various definitions) as an imaging criterion to the ASAS-criteria resulted in a very low percentage of newly classified patients. Considering the number of MRI-spine needed to additionally classify a few patients, the longer scanning time for the patient and higher costs, we conclude that the yield of adding MRI-spine to the ASAS-criteria is unacceptably low in relation to the number of MRI-spine needed to be performed in patients with early disease.

Multiple studies assessed the presence of spinal inflammation in different patient groups (e.g. nonradiographic axSpA), however, to the best of our knowledge this is the first study to report on the value of a positive MRI-spine in classifying patients according to the ASAS-criteria using different definitions in patients with recent onset CBP. Our findings are in line with a recent study by Weber *et al* in which they state that the combination of MRI-spine and MRI-SI has little incremental value compared to MRI-SI alone.²² Using global assessment in

SPARCC-score ≥ 5 , mean of 3 readers n=13	≥ 3 BME lesions, ≥ 2 consecutive slices n=5	≥ 5 BME lesions, ≥ 2 consecutive slices n=3
7 (54%)	3 (60%)	2 (67%)
7/7	3/3	2/2
6 (46%)	2 (40%)	1 (33%)
2/6	1/2	0
SPARCC-score ≥ 5 , mean of 3 readers n/a	≥ 3 BME lesions, ≥ 2 consecutive slices n= 25	≥ 5 BME lesions, ≥ 2 consecutive slices n= 8
-	18 (72%)	7 (88%)
-	13/18	5/7
-	7 (28%)	1 (12%)
-	3/7	1/1

BME, bone marrow edema; n/a, not assessed. *Classification for all patients <50 years. † Diagnosis based on rheumatologist's level of confidence regarding axSpA diagnosis ≥ 8 .

patients with nonradiographic axSpA and normal MRI-SI, approximately 20% of MRI-spine were judged as being consistent with axSpA. However, reading of MRI-spine in nonspecific back pain patients and healthy controls yielded similar percentages.

In the SPACE and DESIR cohorts, the majority of patients with only spinal inflammation (≥ 5 BME lesions and normal MRI-SI and X-SI) already fulfilled the clinical arm of the ASAS-criteria (2/3 and 6/7, respectively). The remaining patients, hypothetically classified via the imaging arm solely because of a positive MRI-spine, can either be misclassified or truly 'missed' cases. We did not formally investigate the role of MRI-spine in diagnosis making in routine clinical practice and this may still be considered as an imaging tool in the differential diagnosis of CBP patients or in the confirmation of the diagnosis in specific patients.

This study has several strengths. Two independent early axSpA cohorts were examined in which CBP patients have been assessed according to a similar standardized protocol. Both cohorts were rather complete in terms of images being present and scored by multiple readers, and the findings in both cohorts were similar providing credit to the robustness of our data. Furthermore, the observation that in both cohorts several definitions of a positive MRI-spine in the ASAS-criteria for axSpA yielded comparable misclassifications strengthens the validity of the findings.

It can be seen as a limitation that we only used patients with short symptom duration. Consequently, the results can only be extrapolated to this group of patients. However, we feel that this is the most applicable group to test the usefulness of MRI-spine as part of the ASAS classification criteria as abnormalities on imaging of the sacroiliac joints are more likely to become positive with longer symptom duration. Moreover, our data are very much in line with the data from Weber *et al* in a study with more established disease.

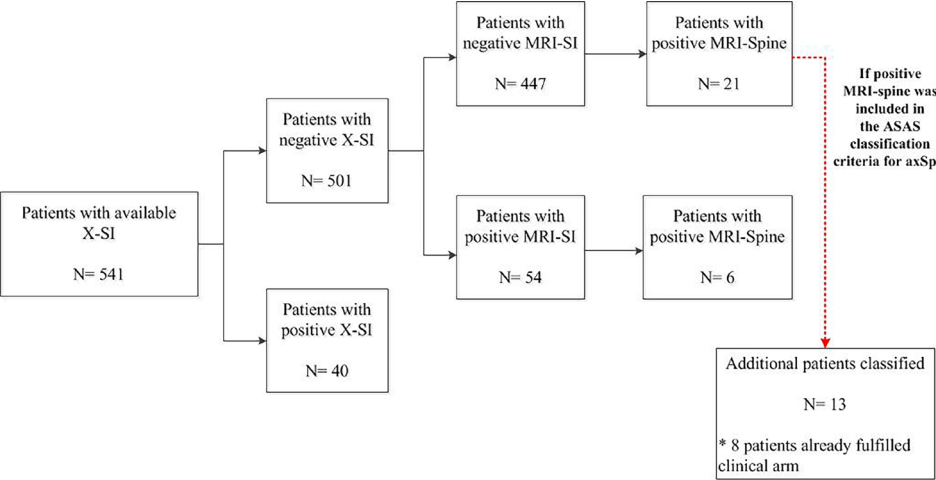
In summary, in both the SPACE and the DESIR cohorts a positive MRI-spine in CBP patients suspected of early axSpA was infrequent. Furthermore, spinal inflammation in the absence of sacroiliitis was observed in very few patients. In this early disease stage, the addition of a positive MRI-spine as imaging criterion to the ASAS classification criteria for axSpA yielded a very low number of newly classified patients in both cohorts. Therefore, the use of MRI-spine is not recommended in the classification of CBP patients suspected of axSpA.

REFERENCES

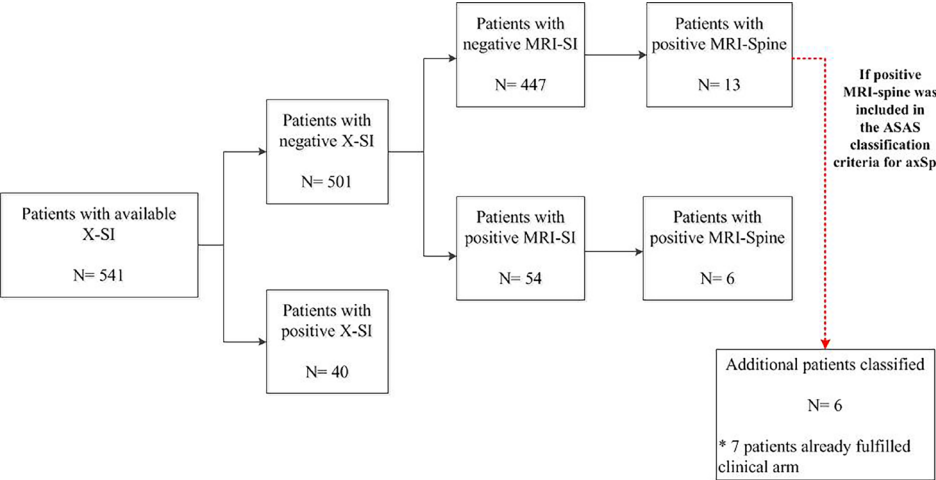
1. Bollow M, Enzweiler C, Taupitz M, *et al.* Use of contrast enhanced magnetic resonance imaging to detect spinal inflammation in patients with spondyloarthritis. *Clin Exp Rheumatol* 2002;20:S167-74.
2. Braun J, Baraliakos X, Golder W, *et al.* Analysing chronic spinal changes in ankylosing spondylitis: a systematic comparison of conventional x rays with magnetic resonance imaging using established and new scoring systems. *Ann Rheum Dis* 2004;63:1046-55.
3. Rudwaleit M, van der Heijde D, Khan MA, *et al.* How to diagnose axial spondyloarthritis early. *Ann Rheum Dis* 2004;63:535-43.
4. Hermann KG, Althoff CE, Schneider U, *et al.* Spinal changes in patients with spondyloarthritis: comparison of MR imaging and radiographic appearances. *Radiographics* 2005;25:559-69; discussion 69-70.
5. Landewe RB, Hermann KG, van der Heijde DM, *et al.* Scoring sacroiliac joints by magnetic resonance imaging. A multiple-reader reliability experiment. *J Rheumatol* 2005;32:2050-5.
6. Bennett AN, Rehman A, Hensor EM, *et al.* Evaluation of the diagnostic utility of spinal magnetic resonance imaging in axial spondylarthritis. *Arthritis Rheum* 2009;60:1331-41.
7. Weber U, Lambert RG, Ostergaard M, *et al.* The diagnostic utility of magnetic resonance imaging in spondylarthritis: an international multicenter evaluation of one hundred eighty-seven subjects. *Arthritis Rheum* 2010;62:3048-58.
8. Hermann KG, Baraliakos X, van der Heijde DM, *et al.* Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. *Ann Rheum Dis* 2012;71:1278-88.
9. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.
10. Rudwaleit M, Landewe R, van der Heijde D, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009;68:770-6.
11. Lambert RG, Bakker PA, van der Heijde D, *et al.* Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. *Ann Rheum Dis* 2016.
12. Rudwaleit M, Jurik AG, Hermann KG, *et al.* Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis* 2009;68:1520-7.
13. Baraliakos X, Landewe R, Hermann KG, *et al.* Inflammation in ankylosing spondylitis: a systematic description of the extent and frequency of acute spinal changes using magnetic resonance imaging. *Ann Rheum Dis* 2005;64:730-4.
14. van der Heijde D, Sieper J, Maksymowych WP, *et al.* Spinal inflammation in the absence of sacroiliac joint inflammation on magnetic resonance imaging in patients with active nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2014;66:667-73.

15. de Hooge M, van den Berg R, Navarro-Compan V, *et al.* Patients with chronic back pain of short duration from the SPACE cohort: which MRI structural lesions in the sacroiliac joints and inflammatory and structural lesions in the spine are most specific for axial spondyloarthritis? *Ann Rheum Dis* 2015.
16. Dougados M, d'Agostino MA, Benessiano J, *et al.* The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. *Joint Bone Spine* 2011;78:598-603.
17. van den Berg R, de Hooge M, van Gaalen F, *et al.* Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. *Rheumatology (Oxford)* 2013;52:1492-9.
18. Calin A, Porta J, Fries JF, *et al.* Clinical history as a screening test for ankylosing spondylitis. *Jama* 1977;237:2613-4.
19. Rudwaleit M, Metter A, Listing J, *et al.* Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum* 2006;54:569-78.
20. Maksymowych WP, Inman RD, Salonen D, *et al.* Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. *Arthritis Rheum* 2005;53:502-9.
21. Braun J, Baraliakos X, Golder W, *et al.* Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. *Arthritis Rheum* 2003;48:1126-36.
22. Weber U, Zubler V, Zhao Z, *et al.* Does spinal MRI add incremental diagnostic value to MRI of the sacroiliac joints alone in patients with non-radiographic axial spondyloarthritis? *Ann Rheum Dis* 2015;74:985-92.

SUPPLEMENTARY MATERIAL

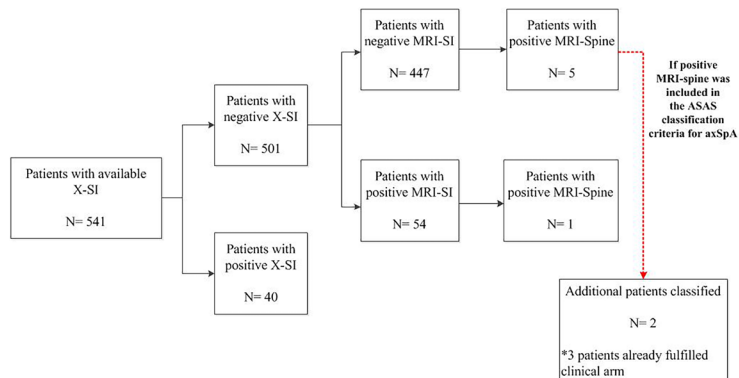


Supplementary figure S1 ASAS classification of CBP patients with negative MRI-SI and positive MRI-spine defined by a SPARCC score ≥ 5 by at least 2 readers, and the effect of adding positive MRI-spine as an imaging criterion to the ASAS axSpA criteria on classification of patients in the **SPACE cohort**.

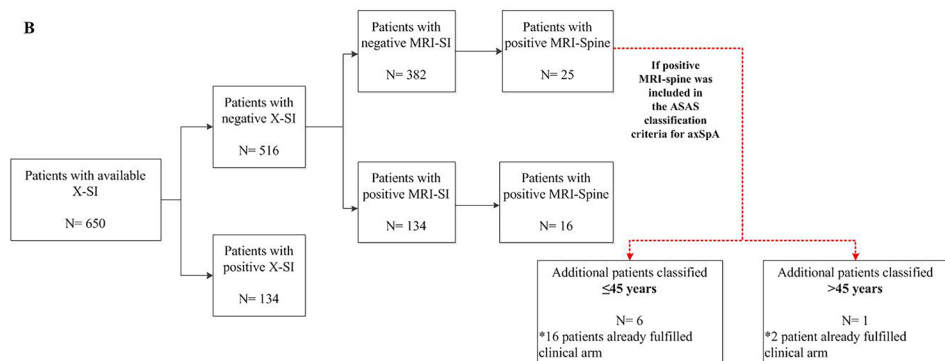


Supplementary figure S2 ASAS classification of CBP patients with negative MRI-SI and positive MRI-spine defined by a mean SPARCC-score ≥ 5 of all 3 readers, and the effect of adding positive MRI-spine as an imaging criterion to the ASAS axSpA criteria on classification of patients in the **SPACE cohort**.

A

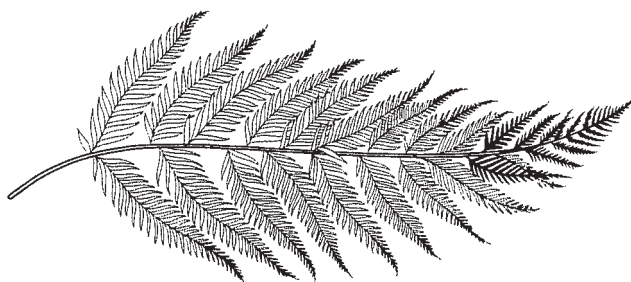


B



Supplementary figure S3 ASAS classification of CBP patients with negative MRI-SI and positive MRI-spine defined by ≥ 3 inflammatory lesions, and the effect of adding positive MRI-spine as an imaging criterion to the ASAS axSpA criteria on classification of patients. **A.** Additional classification of CBP patients in the **SPACE** cohort. **B.** Additional classification of CBP patients in the **DESIR** cohort.

The influence of discrepant imaging judgements on the classification of axial spondyloarthritis is limited: A replication in the SpondyloArthritis Caught Early (SPACE) cohort.



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Sacroiliitis on imaging is important in the diagnosis and classification of axial spondyloarthritis (axSpA) patients. In the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA, sacroiliitis is defined as either radiographic sacroiliitis (X-SI) according to the modified New York (mNY) criteria or active inflammation on magnetic resonance imaging (MRI-SI) highly suggestive of axSpA (ASAS definition).¹⁻⁴ According to the ASAS-criteria chronic back pain patients are classified via the imaging arm when sacroiliitis on MRI-SI or X-SI plus ≥ 1 spondyloarthritis (SpA)-feature is present, or via the clinical arm where ≥ 2 SpA-features in addition to HLA-B27 have to be present.

While local clinicians can interpret imaging of the sacroiliac joints in the context of clinical information, central readers of research studies are not aware of the clinical data. If local and central readers disagree about the presence of sacroiliitis, a patient may be erroneously classified. The clinical arm of the ASAS-criteria may substitute for discrepant reads, so that the effect of discrepant reads on classification may be mitigated: In the DEvenir des Spondylarthropathies Indifférenciées Récentes (DESIR)-cohort, local and central readers disagreed in 28% of the cases, but this led to a change in classification in only 7.9% of patients.^{5,6}

This is a replication study in the SpondyloArthritisCaughtEarly (SPACE)-cohort.⁷ In SPACE patients with chronic back pain (≥ 3 months and ≤ 2 years, onset < 45 years) are assessed following a fixed protocol. Patients with complete imaging were included in this analysis. Local assessors interpreted MRI-SI and X-SI (sacroiliitis yes/no) as part of routine clinical practice. Three central readers, blinded for all clinical and laboratory data as well as other imaging modalities, scored each imaging modality. Positive X-SI was defined according to the mNY criteria and positive MRI-SI was defined by the ASAS definition.

MRI-SI and X-SI were available for 513 patients. MRI-SI results were discordant in 81/513 (16%) patients and X-SI results were discordant in 55/513 (11%) patients between local assessors and central readers (Table 1). In 17% of patients local assessors and central readers disagreed either about sacroiliitis on MRI-SI or on X-SI. With central reading as external standard, the false-positive rate for MRI-SI was 48% and for X-SI 60% ('local overcall'). In 52/513 (10%) patients discrepant reading resulted in a different classification of axSpA: 46 patients that did not classify as axSpA after central reading were classified as axSpA after local assessment and 6 patients classified as axSpA after central reading were not after local assessment (Table 2). When fulfilment of the imaging arm was required (irrespective of the clinical arm), the discordance increased to 16% (82/513).

We confirmed the findings in the DESIR-cohort that the classification of axSpA was rather insensitive to differences between local and central reading. DESIR is performed in multiple French centres and SPACE includes patients from multiple European sites. Our results add to the strength of the conclusion that the ASAS classification criteria are rather robust against discrepant reading results of images of the sacroiliac joints due to the incorporation of the clinical arm.

Table 1 Cross-tabulation of MRI-SI and X-SI reading by central readers and local assessors in the SPACE cohort (*n*=513).

MRI-SI central reading			
MRI-SI local assessment	Positive	Negative	Total
Positive	85	78	163
Negative	3	347	350
Total	88	425	513

X-SI central reading			
X-SI local assessment	Positive	Negative	Total
Positive	26	39	65
Negative	16	432	448
Total	42	471	513

MRI-SI, magnetic resonance imaging sacroiliac joints. Positive predictive value (PPV): 85/163 (52%), negative predictive value (NPV): 347/350 (99%). Concordance positive MRI-SI: 85/513 (17%).
X-SI, radiography sacroiliac joints. PPV: 26/65 (40%), NPV: 432/448 (96%). Concordance positive X-SI: 26/513 (5%).

Table 2 Concordance between central reading and local assessment of imaging according to the classification of CBP patients using the ASAS axSpA criteria in the SPACE cohort (*n*=513).

		Central reading		
		No SpA	Clinical arm only	MRI positive only
Local assessment	Classification			
	No SpA	256	n/a	2
	Clinical arm only	n/a	79	n/a
	MRI positive only	32	n/a	17
	mNY positive only	8	n/a	0
	Both arms (clinical arm and MRI positive)	0	18	n/a
	Both arms (clinical arm and mNY positive)	0	2	n/a
	Clinical arm, MRI and mNY positive	0	8	n/a
	MRI and mNY positive	6	n/a	5
	Total	302	107	24

CBP, chronic back pain; ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; SPACE, SpondyloArthritis Caught Early; MRI, magnetic resonance imaging; mNY, modified New York; n/a, not applicable (fulfilment of the clinical arm does not depend on (different) reading of imaging).

mNY positive only	Both arms (clinical arm and MRI positive)	Both arms (clinical arm and mNY positive)	Clinical arm, MRI and mNY positive	MRI and mNY positive	Total
4	0	0	0	0	262
n/a	<i>1</i>	<i>1</i>	0	n/a	81
2	n/a	n/a	n/a	1	52
2	n/a	n/a	n/a	0	10
n/a	27	2	6	0	53
n/a	0	0	0	0	2
n/a	10	5	15	0	38
2	0	0	0	2	15
10	38	8	21	3	513

For 52/513 (10%) patients different reading resulted in a different classification of axSpA (grey boxes). If hypothetically fulfilment of the imaging arm was required (irrespective of the clinical arm), 30 more patients (in italic and bold) would be discordant (82/513, 16%).

REFERENCES

1. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.
2. Lambert RG, Bakker PA, van der Heijde D, *et al.* Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. *Ann Rheum Dis* 2016.
3. Rudwaleit M, Landewe R, van der Heijde D, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009;68:770-6.
4. Rudwaleit M, Jurik AG, Hermann KG, *et al.* Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis* 2009;68:1520-7.
5. Dougados M, d'Agostino MA, Benessiano J, *et al.* The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. *Joint Bone Spine* 2011;78:598-603.
6. van den Berg R, Lenczner G, Thevenin F, *et al.* Classification of axial SpA based on positive imaging (radiographs and/or MRI of the sacroiliac joints) by local rheumatologists or radiologists versus central trained readers in the DESIR cohort. *Ann Rheum Dis* 2015;74:2016-21.
7. van den Berg R, de Hooze M, van Gaalen F, *et al.* Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. *Rheumatology (Oxford)* 2013;52:1492-9.

Imaging of the sacroiliac joints is important for diagnosing early axial spondyloarthritis but not all-decisive.



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ABSTRACT

Objectives

To evaluate the contribution of the results of sacroiliac imaging on diagnosis and on the level of confidence in diagnosis in patients presenting with chronic back pain (CBP) and suspected of having axial spondyloarthritis (axSpA).

Methods

Data from 513 patients from the SPondyloArthritisCaughtEarly (SPACE) cohort with CBP (≥ 3 months, ≤ 2 years, onset < 45 years) were analysed after full diagnostic work-up. Rheumatologists were asked not only to provide a diagnosis before- and after the imaging results had been provided to them, but also to provide the level of confidence (LoC) of this diagnosis on an 11-point numerical scale.

Results

Before imaging, 317/513 patients were diagnosed with axSpA. Of these patients, 178/317 (56%) did not have signs of sacroiliitis on either MRI or radiography, which led to the rheumatologist refuting the initial diagnosis of axSpA in 81/178 (46%) patients. Of the 196/513 patients without axSpA before imaging, 35/196 (18%) had signs of sacroiliitis on imaging. Subsequently, 28/35 (80%) patients were diagnosed with axSpA. Overall, imaging was incongruent with the diagnosis before imaging in 213 patients. This led to a change in diagnosis in 109/213 (51%), which corresponds to 21% (109/513) of all patients in the cohort. In general, diagnostic confidence increased by having imaging results available (from 6.2 to 7.4, $p < 0.001$).

Conclusions

In patients with chronic back pain suspected of having axSpA sacroiliac imaging adds to the confidence in the final diagnosis. However, the number of changes in diagnosis suggests that imaging is important but not all-decisive in early axSpA diagnosis.

INTRODUCTION

The diagnosis of axial spondyloarthritis (axSpA) in patients presenting with chronic back pain (CBP) is a known challenge in clinical practice as there is a broad spectrum in clinical presentations.¹ Rheumatologists may use information acquired from several sources such as a patient's medical history, physical examination, laboratory tests, and imaging (radiography and/or magnetic resonance imaging of sacroiliac joints) to make a diagnosis.²⁻⁴

Several decades ago, conventional radiography was introduced as an imaging tool to detect sacroiliitis.⁵ However, pelvic radiographs can only detect structural changes such as erosions and sclerosis. Furthermore, in early axSpA radiography of the sacroiliac joints may not show structural abnormalities which can remain absent for many years after disease onset.⁶ In recent years, magnetic resonance imaging (MRI) has become an important instrument in the visualisation of both inflammation and structural damage in CBP patients especially without radiographic sacroiliitis.⁷⁻¹¹

Imaging of the sacroiliac joints plays a pivotal role in the early recognition of axSpA.^{12, 13} We have recently shown that in CBP patients suspected of axSpA positive imaging of the sacroiliac joints is highly associated with a diagnosis of axSpA (odds ratio 34.3; 95% confidence interval 17.3 to 67.7).¹⁴

Unfortunately, recognition of sacroiliitis on radiographs can be difficult. For example, it has been shown that agreement on radiographic sacroiliitis between readers is low and that this does not improve after training.¹⁵ Moreover, bone marrow oedema on MRI suggestive of axSpA may not always be due to axSpA.¹⁶ Therefore, some axSpA experts have expressed their concerns about relying solely on imaging, which may lead to incorrect diagnoses of axSpA. In turn, this may lead to unnecessary exposure to anti-inflammatory drugs with potentially severe side effects.^{17, 18}

Given these controversies, surprisingly little is known about how rheumatologists actually integrate sacroiliac imaging results in their diagnostic work-up of CBP patients suspected of having axSpA. Therefore, the main objectives of this study were to study the contribution of sacroiliac imaging to the rheumatologist's diagnosis, and to quantify the contribution of sacroiliac imaging to diagnostic certainty.

METHODS

Study design and population

The data used for the current study were obtained from the SPondyloArthritis Caught Early (SPACE) cohort. The SPACE cohort is a prospective multicentre study, which has been initiated in January 2009. A detailed description of the study design has been published previously.¹⁹

Briefly, patients with chronic back pain (≥ 3 months and ≤ 2 years) of unknown origin and age of onset < 45 years were recruited and included from multiple European rheumatology centres in the Netherlands, Norway, Italy, and Sweden. The clinical database used for the current study was locked on January 11th 2017. Approval for the study was obtained from all local medical ethics committees and patients provided written informed consent before participation.

Clinical assessments and measurements

All patients were examined according to a standardized full work-up including the assessment of the presence and history of clinical SpA features according to the Assessment of SpondyloArthritis international Society (ASAS) definitions³: C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR), human leukocyte antigen B27 (HLA-B27), inflammatory back pain (IBP), good response to non-steroidal anti-inflammatory drugs (NSAIDs), positive family history of SpA, peripheral arthritis, dactylitis, heel enthesitis, acute anterior uveitis, inflammatory bowel disease (IBD), and psoriasis.

Imaging of the sacroiliac joints

Plain radiographs of the pelvis (X-SI) were performed in anteroposterior view. MRI of sacroiliac joints (MRI-SI) was performed in coronal oblique T1-weighted turbo spin echo (TSE) and short tau inversion recovery (STIR) with a slice thickness of 4 mm. Interpretation of the radiographs and MRI of the sacroiliac joints (sacroiliitis yes/no) was done by each participating centre as part of routine clinical practice (local reading). Patients were classified according to the ASAS classification criteria for which data from central reading in the SPACE cohort was used.²⁰

Diagnosis

During the diagnostic work-up, rheumatologists were asked to provide a diagnosis twice (axSpA, yes/no): (1) based only on information available after medical history, physical examination, and laboratory testing, but before taking sacroiliac imaging into account (“Diagnosis before imaging”), and (2) based on all previously collected information but after taking sacroiliac imaging into account (“Diagnosis after imaging”). In case of ‘no axSpA’,

rheumatologists were asked to provide the most likely alternative diagnosis. In addition, rheumatologists were requested to provide a level of confidence (LoC) regarding their diagnosis (axSpA or no axSpA) on an 11-point numerical rating scale ranging from 0 (not confident at all) to 10 (very confident).

Data analysis

For the present study baseline patients with complete information on sacroiliac imaging (both MRI and radiography) and diagnosis were analysed. Descriptive statistics were used to define patient characteristics for the total patient group, for each diagnosis subgroup (axSpA vs no axSpA), and for each imaging subgroup (i.e. sacroiliitis positive and negative) as means and standard deviations (SD) for continuous variables or frequencies (%) for categorical variables. Chi-square and unpaired *t* tests were used to compare variables between groups. The paired *t* test was used to compare the level of confidence regarding diagnosis before and after imaging within each diagnosis subgroup according to their imaging status. Total number of SpA features was calculated including HLA-B27 status, but without taking imaging of the sacroiliac joints into account. Any positive imaging was defined as either a negative X-SI but positive MRI-SI (X-SI-/MRI-SI+), a positive X-SI but negative MRI-SI (X-SI+/MRI-SI-), or sacroiliitis on both modalities (X-SI+/MRI-SI+). The rheumatologist's diagnosis and the LoC regarding diagnosis were the main outcomes. Data analysis was performed using Stata SE v.14 software (StataCorp LP, College Station, (TX, USA)).

RESULTS

Baseline data of 583 CBP patients were available. A total of 70 (12%) patients were excluded because of incomplete or missing data regarding diagnosis or sacroiliac imaging. Baseline characteristics of these patients were similar to the remaining 513 patients with complete data (not shown). Of these 513 CBP patients suspected of having axSpA, 188 (37%) patients were male, mean age (SD) was 31.0 (8.2) years, mean symptom duration was 13.3 (7.0) months, and 210 (41%) patients were HLA-B27 positive (Table 1).

In all patients, rheumatologists provided a diagnosis before- and after taking sacroiliac imaging into account (Figure 1). Before imaging, 317 (62%) patients were diagnosed with axSpA (Table 2). Most common diagnoses in the 196 patients without axSpA were 'nonspecific back pain', 'degenerative disc disease', and 'mechanical back pain' (data not shown). Diagnostic confidence was moderate in patients with- and without an axSpA diagnosis before imaging (mean (SD) LoC

‘axSpA’ 6.6 (1.9) and mean LoC ‘no axSpA’ 5.6 (2.0), respectively). Patients diagnosed with axSpA before imaging were more often male (41% vs 29%) and were more often HLA-B27 positive (53% vs 22%) compared to patients who were not diagnosed with axSpA before imaging. As expected, the mean (SD) number of SpA features was twice as high for axSpA patients compared to the patients not diagnosed with axSpA (3.1 (1.7) and 1.5 (1.0), respectively).

Table 1 Baseline characteristics of CBP patients suspected of axSpA in the SPACE cohort, n= 513.

Characteristic	
Male	188 (37)
Age, years, mean (SD)	31.0 (8.2)
Symptom duration, months, mean (SD)	13.3 (7.0)
Number of SpA features incl. HLA-B27, mean (SD)	2.9 (1.8)
HLA-B27 positive *	210 (41)
IBP	346 (68)
Peripheral arthritis	78 (15)
Dactylitis	28 (5)
Enthesitis	106 (21)
Acute anterior uveitis	38 (7)
IBD	35 (7)
Psoriasis	58 (11)
Good response to NSAIDs **	216 (43)
Positive family history of SpA	222 (43)
Elevated CRP/ESR	147 (29)

Values are listed as n (%), unless otherwise stated.. CBP, chronic back pain; axSpA, axial spondyloarthritis; HLA-B27, human leukocyte antigen B27; IBP, inflammatory back pain; DMARD, disease modifying drug; NSAIDs, non-steroidal anti-inflammatory drugs; IBD, inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; * n=510 patients for HLA-B27, ** n=499 patients for good response to NSAIDs.

In total, 317/513 (62%) of CBP patients were initially diagnosed with axSpA, and this figure decreased to 269/513 (52%) patients with a final diagnosis of axSpA after imaging. Of these 269 axSpA patients, 55% were male, 59% were HLA-B27 positive, 62% had positive imaging, and the mean number of SpA features was 3.2 (1.7). A total of 172/269 (64%) patients fulfilled the ASAS classification criteria (52% male, 87% HLA-B27 positive, and mean number of SpA features 3.2 (1.5)). Overall, the mean diagnostic confidence increased by having imaging results available (from 6.2 to 7.4, $p<0.001$). This increase in diagnostic confidence was observed in both axSpA patients (from 7.1 (1.7) to 7.7 (2.1), $p<0.001$) and ‘non-axSpA’ patients (from 5.7 (2.0) to 7.5 (2.3), $p<0.001$).

Table 2 Clinical features of CBP patients stratified for diagnosis **before** taking sacroiliac imaging results into account.

Characteristic	Diagnosis <u>before</u> imaging of sacroiliac joints	
	AxSpA n=317	No axSpA n=196
LoC regarding diagnosis, mean (SD)	6.6 (1.9)	5.6 (2.0)
Male	131 (41)	57 (29)
Number of SpA features incl. HLA-B27, mean (SD)	3.6 (1.7)	1.7 (1.1)
HLA-B27 positive	168 (53) *	42 (22)
IBP	253 (80)	93 (48)
Peripheral arthritis [‡]	68 (22)	10 (5)
Dactylitis [‡]	27 (9)	1 (1)
Enthesitis [‡]	92 (29)	14 (7)
Acute anterior uveitis [‡]	32 (10)	6 (3)
IBD [‡]	26 (8)	9 (5)
Psoriasis [‡]	48 (15)	10 (5)
Good response to NSAIDs ^{‡‡}	176 (57) **	40 (21) ***
Positive family history of SpA ^{‡‡‡}	160 (50)	62 (32)
Elevated CRP/ESR	107 (34)	40 (20)

Values are listed as n (%), unless otherwise stated. LoC, level of confidence regarding diagnosis: 0 (not confident at all) through 10 (very confident); axSpA, axial spondyloarthritis; HLA-B27, human leukocyte antigen B27; IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; IBD, inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. [‡] Past or present condition, either confirmed or diagnosed by a physician. ^{‡‡} Back pain not present anymore or is much better 24–48 hours after a full dose of NSAID. ^{‡‡‡} Presence in first- or second-degree relatives of any of the following: ankylosing spondylitis, acute anterior uveitis, reactive arthritis, psoriasis, or inflammatory bowel disease. * n=315 for patients with axSpA diagnosis before imaging, ** n=310 for patients with axSpA diagnosis before imaging, *** n=189 for patients without axSpA diagnosis before imaging.

Of the 317 patients who were diagnosed with axSpA before imaging, 139 (44%) had positive imaging (Table 3). In these 139 patients, sacroiliitis was seen in 85 (61%) patients only on MRI-SI, in 10 (7%) patients only on X-SI, and in 44 (32%) patients on both modalities (X-SI+/MRI-SI+). After imaging, the axSpA diagnosis was maintained in all of these 139 patients and the mean LoC in the diagnosis of axSpA increased significantly (from 7.4 (1.8) to 8.6 (1.7), $p<0.001$).

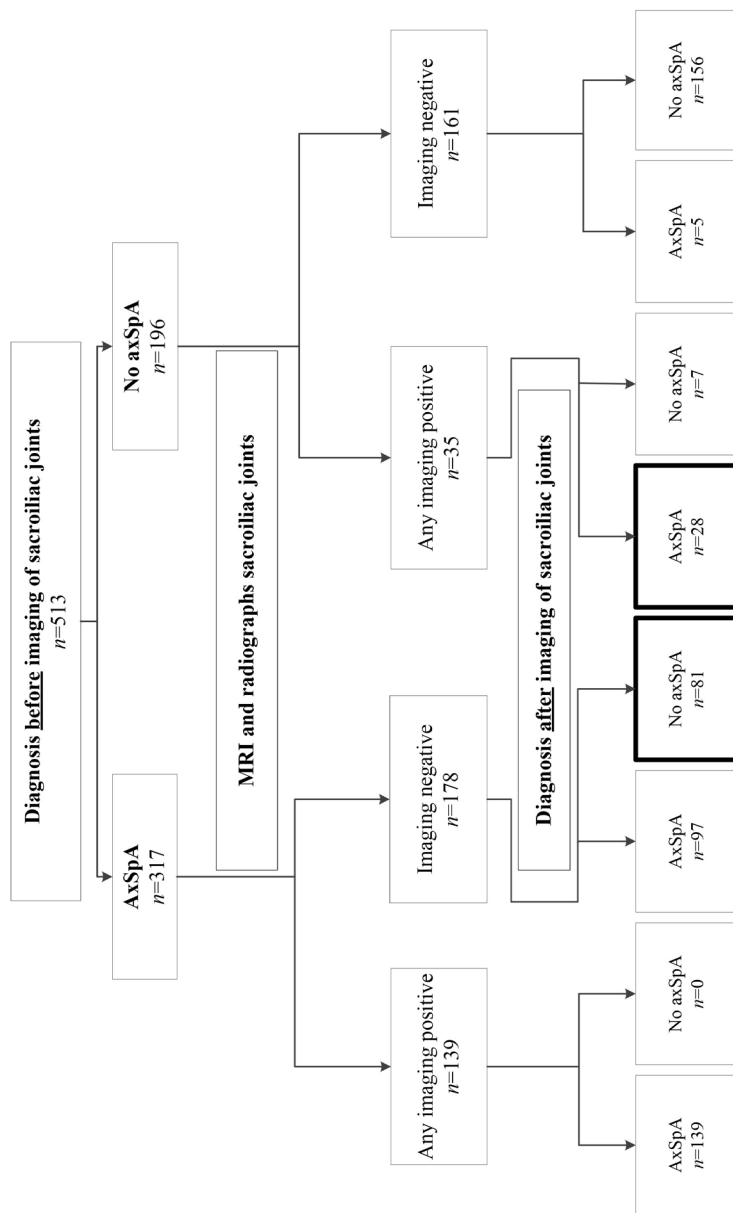


Figure 1 Rheumatologist's diagnosis before and after considering imaging of sacroiliac joints, n=513. axSpA, axial spondyloarthritis; MRI, magnetic resonance imaging; any positive imaging defined as sacroiliitis on MRI and/or radiographic sacroiliitis; imaging negative defined as no abnormalities on MRI and radiographs of sacroiliac joints. Boxes in bold represent patients with a change in diagnosis due to imaging results discordant with the diagnosis before imaging.

Of the 317 patients who were diagnosed with axSpA before imaging, 178 (56%) had negative imaging. In 97/178 patients the diagnosis axSpA was maintained. In these patients, the LoC in the diagnosis somewhat decreased (from 6.7 (1.6) to 6.4 (2.1), $p=0.06$). In 81/178 patients with negative imaging the diagnosis was changed to “no axSpA” after imaging. In these patients the LoC increased significantly after imaging (from 5.1 (1.7) to 6.4 (2.0), $p<0.001$). By comparison, the 97/178 patients diagnosed with axSpA after imaging had a higher number of SpA features (excluding imaging and HLA-B27) than the 81/178 patients without axSpA (mean 3.5 (1.6) vs 2.2 (1.2), $p<0.001$). Moreover, these 97 axSpA patients were also more often HLA-B27 positive than the 81 patients without axSpA (53% vs 33%, $p=0.010$).

Of the 196 patients not diagnosed with axSpA before imaging, 35 (18%) had positive imaging (Table 4). In these 35 patients, sacroiliitis was seen in 24 (68%) patients only on MRI-SI, in 2 (6%) patients only on X-SI, and in 9 (26%) patients on both modalities (X-SI+/MRI-SI+). In 28 of these 35 patients (80%) with sacroiliitis the diagnosis was changed into axSpA (18/28 (64%) patients only MRI-SI+, 1/28 (4%) only X-SI+, and 9/28 (32%) MRI-SI+/X-SI+). The mean LoC in diagnosis increased significantly following imaging (from 4.7 (2.0) to 7.6 (2.3), $p<0.001$). In 7 of the 35 patients with positive imaging (20%) the diagnosis ‘no axSpA’ remained unchanged (6/7 (86%) patients were MRI-SI+ and one (14%) patient was X-SI+). In these 7 patients, the mean LoC in diagnosis remained the same after imaging (LoC from 5.0 (1.3) to 5.0 (2.3)). By comparison, the 28/35 patients diagnosed with axSpA after imaging had a higher number of SpA features than the 7/35 patients without axSpA (mean 1.6 (0.9) versus 1.0 (0.8), $p=0.10$). Moreover, these 28 patients diagnosed with axSpA were also more often HLA-B27 positive than the 7 patients without axSpA (48% vs 29%, $p=0.35$).

Of the 196 patients not diagnosed with axSpA before imaging, 161 (82%) had negative imaging. Despite having negative imaging, the diagnosis changed to axSpA after imaging in 5/196 patients (3%). In these 5 patients, LoC in diagnosis increased (from 5.0 (1.9) to 6.4 (1.9), $p=0.43$). In 156/161 (97%) patients with negative imaging the diagnosis “no axSpA” remained unchanged. The LoC in diagnosis increased after imaging (from 5.8 (2.0) to 7.6 (2.2), $p<0.001$). By comparison, the 5/161 patients diagnosed with axSpA after imaging had a higher number of SpA features than the 156/161 patients without axSpA (mean 1.8 (0.8) versus 1.4 (1.0), $p=0.43$). Moreover, these 5 axSpA patients were also more often HLA-B27 positive than the 156 patients without axSpA (40% vs 16%, $p=0.16$).

Table 3 Diagnosis and imaging status after sacroiliac imaging in patients with axSpA diagnosis **before** sacroiliac imaging.

<i>Imaging status</i>
Only MRI-SI+
Only X-SI+
MRI-SI+/X-SI+
LoC regarding diagnosis before imaging , mean (SD)
LoC regarding diagnosis after imaging , mean (SD)
<i>Imaging status</i>
Only MRI-SI+
Only X-SI+
MRI-SI+/X-SI+
<i>Clinical features</i>
Male
Number of SpA features °, mean (SD)
HLA-B27 positive
Values are listed as n (%), unless otherwise stated.LoC, level of confidence regarding diagnosis: 0 (not confident at all) through 10 (very confident); MRI-SI, magnetic resonance imaging of sacroiliac joints; X-SI, radiographs of sacroiliac joints. axSpA, axial spondyloarthritis; HLA-B27, human leukocyte antigen B27.

AxSpA diagnosis before imaging n=317			
Any imaging positive n=139		Negative imaging n=178	
	85 (61)		n/a
	10 (7)		n/a
	44 (32)		n/a
Diagnosis after imaging		Diagnosis after imaging	
AxSpA n=139	No axSpA n=0	AxSpA n=97	No axSpA n=81
7.4 (1.8)	-	6.7 (1.6)	5.1 (1.7)
8.6 (1.7) ^a	-	6.4 (2.1) ^b	6.4 (2.0) ^c
85 (61)	-	n/a	n/a
10 (7)	-	n/a	n/a
44 (32)	-	n/a	n/a
71 (51)	-	32 (33)	28 (35)
3.4 (1.7)	-	3.5 (1.6)	2.2 (1.2)
90 (66) [*]	-	51 (53)	27 (33)

^aTotal number of SpA features after medical history taking, physical examination and measurement of acute phase reactants but before HLA-B27 testing and imaging. ^{*} n=137 for patients with axSpA diagnosis before and after imaging. ^a mean difference 1.2, 95% Confidence Interval (CI) 0.9 to 1.6, *p*-value <0.001; ^b mean difference -0.3, 95% CI -0.5 to 0.01, *p*-value=0.06; ^c mean difference 1.3, 95% CI 0.7 to 1.8, *p*-value <0.001. n/a, not applicable.

Table 4 Diagnosis and imaging status after sacroiliac imaging in patients without axSpA diagnosis before sacroiliac imaging.

Imaging status Only MRI-SI+ Only X-SI+ MRI-SI+/X-SI+
LoC regarding diagnosis before imaging, mean (SD) LoC regarding diagnosis after imaging, mean (SD) Imaging status Only MRI-SI+ Only X-SI+ MRI-SI+/X-SI+ Clinical features Male Number of SpA features °, mean (SD) HLA-B27 positive

Values are listed as n (%), unless otherwise stated.LoC, level of confidence regarding diagnosis: 0 (not confident at all) through 10 (very confident); MRI-SI, magnetic resonance imaging of sacroiliac joints; X-SI, radiographs of sacroiliac joints. axSpA, axial spondyloarthritis; HLA-B27, human leukocyte antigen B27.

No axSpA diagnosis before imaging n=196			
Any imaging positive n=35		Negative imaging n=161	
	24 (68)		n/a
	2 (6)		n/a
	9 (26)		n/a
Diagnosis after imaging		Diagnosis after imaging	
AxSpA n=28	No axSpA n=7	AxSpA n=5	No axSpA n=156
4.7 (2.0)	5.0 (1.3)	5.0 (1.9)	5.8 (2.0)
7.6 (2.3) ^a	5.0 (2.3) ^b	6.4 (1.9) ^c	7.6 (2.2) ^d
18 (64)	6 (86)	n/a	n/a
1 (4)	1 (14)	n/a	n/a
9 (32)	-	n/a	n/a
15 (54)	2 (29)	2 (40)	38 (24)
1.6 (0.9)	1 (0.8)	1.8 (0.8)	1.4 (1.0)
13 (48)	2 (29)	2 (40)	25 (16)

^aTotal number of SpA features after medical history taking, physical examination and measurement of acute phase reactants but before HLA-B27 testing and imaging. ^a mean difference 2.9, 95% CI 1.6 to 4.2, *p*-value <0.001; ^b mean difference 0; ^c mean difference 1.4, 95% CI -3.1 to 5.9, *p*-value=0.43; ^d mean difference 1.8, 95% CI 1.5 to 2.1, *p*-value <0.001. n/a, not applicable.

In the entire cohort, the diagnosis changed in 21% (109/513) of the CBP patients following imaging. In patients with imaging results that were discordant with their primary diagnosis (n=213 (178+35)) the diagnosis changed in 109 (51%) patients (**Figure 1**, boxes in bold). This change of diagnosis more often pertained to patients in whom a clinical diagnosis was suspected but imaging was negative (81/109 (74%)) than in patients in whom a clinical diagnosis of axSpA was not suspected but imaging was positive (28/109 (26%)).

DISCUSSION

This study was performed to investigate the contribution of sacroiliac imaging to the rheumatologist's diagnosis and its respective confidence. We have shown that the rheumatologist's confidence in the diagnosis of patients with chronic back pain suspected of having axSpA increases after the results of sacroiliac imaging are taken into account. However, the number of changes in diagnosis after imaging implies that imaging is indeed an important but not the all-decisive factor in axSpA diagnosis.

Prior to imaging the physician's confidence in diagnosis was already moderate to high in most patients, which corroborates the value of medical history taking, physical examination and laboratory tests in the diagnostic work-up of axSpA. Congruent imaging results significantly increased the diagnostic confidence of rheumatologists except in axSpA patients (before- and after imaging) without sacroiliitis. In general, these findings are in line with results from an international survey conducted amongst rheumatologists throughout the world illustrating the value rheumatologists place on imaging in the diagnostic work-up of patients suspected of axSpA.²¹

Nevertheless, there were patients diagnosed as "no axSpA" before imaging in which a positive imaging result did not influence the final diagnosis. A few patients were not diagnosed with axSpA after imaging, even though they had sacroiliitis (n=6 for MRI-SI and n=1 for X-SI). These patients had only few other SpA features and rheumatologists remained uncertain about the diagnosis (mean LoC 5.0). Apparently, the diagnosing rheumatologist considered the observed lesions -in combination with the clinical presentation- not sufficiently specific for an axSpA diagnosis, which is an indication that rheumatologists do not necessarily find that imaging is the dominant feature in establishing a diagnosis of axSpA. An even smaller number of patients (n=5) without a diagnosis of axSpA before imaging and without signs of sacroiliitis were still diagnosed with axSpA after imaging. Since these 5 patients have a low number of

SpA features, it is difficult to understand these diagnoses. Moreover, our findings also stress the importance of imaging in rejecting an axSpA diagnosis as in 81/178 (46%) patients with axSpA before imaging the diagnosis was dismissed when imaging turned out to be negative. This study has several limitations. First, rheumatologists were asked to provide CBP patients with a diagnosis before- and after taking imaging into account. We cannot, however, rule out the possibility that rheumatologists may have already looked at the imaging results before filling out the diagnosis in the case report form. However, this does not explain why change in diagnosis still occurred. More importantly, the overall diagnostic confidence clearly increased after taking imaging results into account, which most likely would not have happened (or to a lesser extent) if rheumatologists had indeed looked at the imaging results before filling out the diagnosis “Before imaging”. Although in line with clinical practice, the fact that each patient was diagnosed by one rheumatologist and the imaging was read by one radiologist) might be regarded as a limitation. Furthermore, the rheumatologist may also have used information from other sources such as spinal imaging in the diagnostic process, which may have (additionally) contributed to the LoC regarding the diagnosis. In addition, due to the high overlap of positive imaging (i.e. X-SI+/MRI-SI+) we cannot elaborate on the individual value of each modality (X-SI or MRI-SI) on the final diagnosis and the diagnostic confidence.

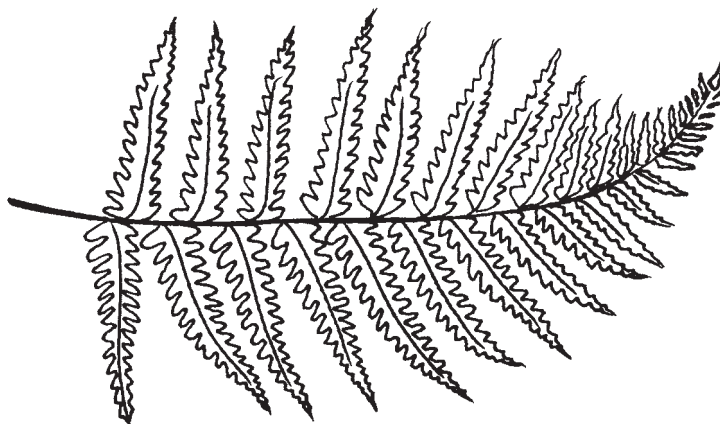
In conclusion, in chronic back pain patients suspected of having axSpA sacroiliac imaging increases diagnostic confidence. However, the number of changes in diagnosis suggests that imaging is important but not all-decisive in the early diagnosis of axSpA.

REFERENCES

1. Dougados M, Baeten D. Spondyloarthritis. *Lancet* 2011;377:2127-37.
2. Rudwaleit M, van der Heijde D, Khan MA, *et al.* How to diagnose axial spondyloarthritis early. *Ann Rheum Dis* 2004;63:535-43.
3. Rudwaleit M, van der Heijde D, Landewe R, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-83.
4. van Tubergen A, Weber U. Diagnosis and classification in spondyloarthritis: identifying a chameleon. *Nat Rev Rheumatol* 2012;8:253-61.
5. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.
6. Oostveen J, Prevo R, den Boer J, *et al.* Early detection of sacroiliitis on magnetic resonance imaging and subsequent development of sacroiliitis on plain radiography. A prospective, longitudinal study. *J Rheumatol* 1999;26:1953-8.
7. Braun J, Baraliakos X, Golder W, *et al.* Analysing chronic spinal changes in ankylosing spondylitis: a systematic comparison of conventional x rays with magnetic resonance imaging using established and new scoring systems. *Ann Rheum Dis* 2004;63:1046-55.
8. Landewe RB, Hermann KG, van der Heijde DM, *et al.* Scoring sacroiliac joints by magnetic resonance imaging. A multiple-reader reliability experiment. *J Rheumatol* 2005;32:2050-5.
9. Rudwaleit M, Jurik AG, Hermann KG, *et al.* Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis* 2009;68:1520-7.
10. Weber U, Lambert RG, Ostergaard M, *et al.* The diagnostic utility of magnetic resonance imaging in spondylarthritis: an international multicenter evaluation of one hundred eighty-seven subjects. *Arthritis Rheum* 2010;62:3048-58.
11. Lambert RG, Bakker PA, van der Heijde D, *et al.* Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. *Ann Rheum Dis* 2016.
12. Mandl P, Navarro-Compan V, Terslev L, *et al.* EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. *Ann Rheum Dis* 2015;74:1327-39.
13. Baraliakos X, Maksymowych WP. Imaging in the diagnosis and management of axial spondyloarthritis. *Best Pract Res Clin Rheumatol* 2016;30:608-23.
14. Ez-Zaitouni Z, Bakker PA, van Lunteren M, *et al.* Presence of multiple spondyloarthritis (SpA) features is important but not sufficient for a diagnosis of axial spondyloarthritis: data from the SPondyloArthritis Caught Early (SPACE) cohort. *Ann Rheum Dis* 2017.
15. van Tubergen A, Heuft-Dorenbosch L, Schulp G, *et al.* Radiographic assessment of sacroiliitis by radiologists and rheumatologists: does training improve quality? *Ann Rheum Dis* 2003;62:519-25.
16. Baraliakos X, Hermann KG, Braun J. Imaging in axial spondyloarthritis: diagnostic problems and pitfalls. *Rheum Dis Clin North Am* 2012;38:513-22.

17. Deodhar A, Reveille JD, van den Bosch F, *et al.* The concept of axial spondyloarthritis: joint statement of the spondyloarthritis research and treatment network and the Assessment of SpondyloArthritis international Society in response to the US Food and Drug Administration's comments and concerns. *Arthritis Rheumatol* 2014;66:2649-56.
18. Deodhar A. Sacroiliac Joint Magnetic Resonance Imaging in the Diagnosis of Axial Spondyloarthritis: "A Tiny Bit of White on Two Consecutive Slices" May Be Objective, but Not Specific. *Arthritis Rheumatol* 2016;68:775-8.
19. van den Berg R, de Hooze M, van Gaalen F, *et al.* Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. *Rheumatology (Oxford)* 2013;52:1492-9.
20. Ez-Zaitouni Z, Bakker PA, van Lunteren M, *et al.* The yield of a positive MRI of the spine as imaging criterion in the ASAS classification criteria for axial spondyloarthritis: results from the SPACE and DESIR cohorts. *Annals of the Rheumatic Diseases* 2017.
21. van der Heijde D, Sieper J, Elewaut D, *et al.* Referral patterns, diagnosis, and disease management of patients with axial spondyloarthritis: results of an international survey. *J Clin Rheumatol* 2014;20:411-7.

Summary and general discussion



SUMMARY AND GENERAL DISCUSSION

All studies described in this thesis cover various aspects of the diagnostic work-up of patients with chronic back pain suspected of having axial spondyloarthritis (axSpA) and the diagnosis and classification (according to the ASAS classification criteria) of axSpA. Moreover, these studies are centralized around the same objective, being the early recognition and diagnosis of axSpA.

The following topics were addressed. First, the diagnostic process in chronic back pain patients and the final diagnosis of axSpA were elaborately evaluated in a secondary/tertiary care setting. Second, the use and potential added value of spinal MRI for the classification of axSpA (according to the ASAS criteria) was tested. Finally, we focus on the diagnostic process again and evaluated the role of imaging findings as a whole in the diagnosis and classification of (early) axSpA: We investigated the use of sacroiliac imaging in clinical practice for diagnosing axSpA, but also the influence of different readings by local assessors and central readers on the classification of axSpA.

All studies presented in this thesis were performed in two cohorts: the DEvenir des Spondyloarthropathies Indifférenciées Récentes (DESIR)¹ and the SpondyloArthritis Caught Early (SPACE)² cohorts. These cohorts were collected with more or less similar study protocols as all patients underwent a full (fixed) diagnostic work-up at pre-defined time points to assess disease characteristics and the presence of all SpA features. However, there are also important differences between the two cohorts. The SPACE cohort is a multicentre, multinational (the Netherlands, Norway, Sweden, Italy) observational study, whilst the DESIR cohort is a national French observational cohort with multiple (25) participating centres across the country. Furthermore, the SPACE cohort includes patients with a minimum age of 16 years who had chronic back pain of short duration (between three months and two years), and with an age of onset before 45 years. DESIR, however, included patients between the ages of 18 and 50 years with chronic *inflammatory* back pain (IBP, duration between three months and three years) and a substantial suspicion of axSpA (measured by a physician's level of confidence in a diagnosis of at least five on a zero to ten scale). In SPACE all patients with chronic back pain (and not only those with IBP) can be included, regardless of an existing suspicion of axSpA. In addition, inclusion of patients in DESIR is now closed (inclusion took place between December 2007 and April 2010), whilst SPACE is an ongoing cohort study still actively recruiting patients. For this thesis, however, only baseline and one-year follow-up data from the SPACE cohort and only baseline data from the DESIR cohort were used.

In this final chapter we summarize the main findings of the studies presented in this thesis. Thereafter, we will discuss future perspectives and devise research questions that may further our knowledge of axSpA.

Diagnosis of axSpA

The timely recognition of axSpA – especially in an early disease stage – is challenging as the disease is heterogeneous in its presentation and confirmatory signs or symptoms, in analogy to for instance urate crystals in the joint in patients with gout, are lacking. An important phase in the diagnostic process of patients with continuous chronic back pain is the collection of information regarding a patient's present status and rheumatologic history. Patients should be inquired about past or present conditions that are relevant to axSpA (i.e. SpA features). Inflammatory back pain (IBP) is a common feature and has several definitions.³⁻⁵ However, in this thesis IBP is deemed 'positive' or present when at least four of the following characteristics are present: an onset before the age of 40 years, an insidious onset, improvement with exercise, no improvement with rest, and pain at night, i.e. fulfilment of the ASAS criteria for IBP.⁶ Furthermore, patients may complain about heel pain suggestive of enthesitis, peripheral arthritis, or swollen and painful toes or fingers suggestive of dactylitis.⁷⁻¹⁰ The concurrent presence or history of extra-articular manifestations, being acute anterior uveitis, inflammatory bowel disease (IBD), and psoriasis also increases the likelihood of axSpA.^{11,12} In addition, a positive family history of SpA (i.e. the presence of AS, psoriasis, acute anterior uveitis, reactive arthritis, or IBD in first- or second-degree relatives) and a good response (i.e. relief of pain symptoms) to non-steroidal anti-inflammatory drugs (NSAIDs) are considered useful characteristics in the diagnostic assessment of CBP patients.¹³ Next to interviewing the patient, a thorough physical examination is required to objectively assess the presence of the aforementioned clinical features. Importantly, there is no single laboratory test to diagnose axSpA. However, the presence of human leukocyte antigen-B27 (HLA-B27) and/or an elevated acute phase reactant (C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)) that cannot be explained by another condition, may further point to a diagnosis of axSpA. Finally, characteristic findings on radiographs or MRI of the sacroiliac (SI) joints may frequently be seen.

Neither a formal diagnostic standard for axSpA nor diagnostic criteria exist, so all signs and symptoms of axSpA presented by patients – either present or absent – should be appreciated and weighted in an aggregated manner (full clinical context) by the diagnostician in a rather intuitive process of pattern recognition.^{14, 15} This implies that the assessing rheumatologist has broad expertise in diagnosing axSpA and its differential diagnoses, that he knows about

types and has access to relevant laboratory tests and imaging. A previously discussed tool, the modified Berlin algorithm, is an example of how a decision tool can support clinicians in such a process, but should not be followed blindly.

If the algorithm would be used strictly as a means to diagnose axSpA, it would result in approximately 10 percent false-positive cases but 10 percent of cases will be missed (false-negative cases) when compared against the rheumatologist's (i.e. expert's) diagnosis.¹⁶

The ASAS classification criteria for axSpA are frequently used to define patients for inclusion in studies. As the classification criteria were developed in a controlled setting with an artificially high prevalence of axSpA, experts have repeatedly warned against the use of these *classification* criteria for *diagnosing* axSpA.¹⁷ Still, as diagnosing axSpA early remains a continuous challenge, concerns about inappropriate use of the ASAS classification criteria in clinical practice remain. The classification criteria have been developed with the diagnosis of a clinical 'expert panel' as the external standard in the absence of a real gold standard. Expert opinion includes patient characteristics and symptoms at presentation that are combined with results from selected laboratory tests and imaging findings. The underlying process is that of 'pattern recognition' in which physicians (i.e. rheumatologists) conscientiously (or unconscientiously) use their clinical experience to try and put all the 'pieces of the (axSpA) puzzle' together. The application of the classification criteria to diagnose axSpA in clinical practice scenarios with low pre-test probability may lead to significant *overcall*. And especially in low prevalence settings and in circumstances with little experience with axSpA, such as primary care settings, it is tempting to use classification criteria to make a diagnosis. As a complicating factor, there is a thin line between classification and diagnosis since most clinical, laboratory and imaging results are used in both classification and diagnosis of axSpA. Nevertheless, the classification criteria should be used in patients *already* diagnosed with axSpA. And part of this diagnostic process also includes the exclusion of other, more likely diagnoses.

As said, the sheer counting of SpA features – i.e. *ticking boxes of features and symptoms* – whilst neglecting more likely alternative diagnoses (differential diagnosis) may easily lead to *overdiagnosis* of axSpA, which may in turn invoke inappropriate medical treatment.¹⁷⁻¹⁹ Concerns raised by experts of misdiagnosis and in particular *overdiagnosis* have led to the research in **Chapter 2**. In this chapter – bearing the aforementioned concerns in mind – we investigated whether the presence of multiple SpA features in a chronic back pain patient has always led to axSpA diagnosis. We have studied which SpA features contributed most to an axSpA diagnosis and we assessed the agreement between the rheumatologist's diagnosis

and the ASAS classification criteria in the SPACE cohort. In this study 500 patients, after undergoing a full diagnostic protocol, were stratified according to the number of SpA features: 159 (32%) had less than or equal to one feature, 143 (29%) had two features, 79 (16%) had three features and 119 (24%) had four or more features. Half of the total study population was diagnosed with axSpA, and the likelihood of an axSpA diagnosis was generally conditional upon the number of SpA features. Still, numerous patients with multiple SpA features were not diagnosed with axSpA. These findings show that making a clinical diagnosis of axSpA is more than a simple summation of SpA features. Overdiagnosis merely based on the presence of multiple SpA features is a concern but likely did not occur frequently in centres participating in the SPACE cohort in which experts judged the diagnosis.

There were also encouraging findings showing that rheumatologists are not blindly guided by classification criteria. HLA-B27 negative patients without imaging abnormalities (either radiography or MRI of sacroiliac joints) and few other SpA features could still receive a diagnosis of axSpA without classifying as axSpA. A potential explanation for these diagnoses is that other features or symptoms (not part of the ASAS classification criteria), such as alternating buttock pain or the presence of spinal inflammatory lesions, were rated as relevant features for a diagnosis of axSpA. In addition, rheumatologists may have based their diagnosis on their own interpretation of the imaging in combination with the clinical picture. Another interesting question raised in this study was *which* SpA features were most contributory to axSpA diagnosis. In both univariable and multivariable analyses we found that 'HLA-B27 positivity' and 'any positive imaging' (i.e. either sacroiliitis on a radiograph or MRI) were independent determinants of an axSpA diagnosis. Especially positive imaging of the sacroiliac joints was a dominant feature. These results underline the importance of proper interpretation of imaging or new imaging modalities (discussed later) in the diagnostic process of axSpA. With the concern of just '*ticking boxes*' for axSpA diagnosis in mind, we have also looked at the relation between axSpA diagnosis and classification according to the ASAS axSpA criteria. For this, the diagnosis of the treating rheumatologist was used as a gold standard to test the performance of the ASAS axSpA classification criteria. The ASAS classification criteria had an overall sensitivity and specificity of 76% and 84%, respectively. These results were a bit worse than those published in a recent systematic literature review and meta-analysis in which the performance of the ASAS axSpA criteria was summarized.²⁰ A sensitivity of 82% and a specificity of 88% were reported, which is indeed in line with the aforementioned conclusion that not all patients with a diagnosis of axSpA are classified as such, and vice versa.

The differentiation of the signs and symptoms of axSpA from other conditions which may also present with CBP is important in the diagnosis of axSpA. In addition, some conditions may well co-exist with axSpA. The differential diagnosis for axSpA includes among others mechanical back pain, osteitis condensans ilii, sacroiliac joint infection, diffuse idiopathic skeletal hyperostosis (DISH), degenerative disc disease, and fibromyalgia.²¹⁻²⁴ During follow-up, the clinical presentation of CBP patients might change, which can result in the rheumatologist either refuting the initial diagnosis –axSpA or an alternative diagnosis – or getting increased confidence in the initial diagnosis. In **Chapter 3** we further elaborate on the findings in **Chapter 2**, mainly on the clinical characteristics and alternative diagnoses of patients who were not diagnosed with axSpA, especially in those with four or more SpA features who are considered as having axSpA by the Berlin algorithm. This study was prompted by the comments of Braun *et al.* in Nature Reviews in which they state that it is unlikely that a patient with four or more SpA features does not have SpA.²⁵ In the SPACE cohort rheumatologists are asked to provide a clinical diagnosis (axSpA or no axSpA). In case of ‘no axSpA’ rheumatologists were requested to provide a better alternative diagnosis. In all patient categories (those with no- or only with one- SpA features versus those with two, three, and four or more SpA features) the most frequent alternative diagnoses were expectedly non-specific back pain, mechanical back pain, degenerative disc disease, and (fibro)myalgia. None of the 18 patients with four or more SpA features had imaging abnormalities suggestive of axSpA and only four of them were HLA-B27-positive. Furthermore, they had SpA features that are considered less specific, such as IBP, a positive family history for SpA, and a good response to NSAIDs. These findings reassuringly suggest that – although an axSpA diagnosis is likely in the presence of a high number of SpA features – rheumatologists may still discard the diagnosis when they think there are not enough arguments in favour of a diagnosis.

As mentioned before, the definite diagnosis of axSpA is preceded by an elaborate work-up of imaging, physical examination, and laboratory testing. However, despite this extensive diagnostic approach, uncertainty regarding the diagnosis (diagnostic uncertainty) is not uncommon. In **Chapter 4** we looked into diagnostic uncertainty at baseline and after one-year follow-up, and at the possible influence of SpA feature accrual on diagnosis. An important finding of this study was that diagnostic uncertainty was common, however standardized (one-year) follow-up led to a decrease of patients with uncertain diagnosis. Importantly, some uncertainty regarding the diagnosis remained at follow-up. Almost half of the patients had developed at least one SpA feature after one year, but this did in most cases not lead to changes in diagnosis or level of certainty. These results may reflect certain aspects of clinical reasoning in daily rheumatologic practice. First, the finding that the acquisition of new SpA

features after one year did not necessarily lead to a switch of diagnosis can be the result of rheumatologists ‘weighing’ SpA features in importance. Positive imaging suggestive of axSpA might be considered a ‘stronger’ SpA feature than ‘good response to NSAIDs’. Second, rheumatologists may base their diagnosis and level of certainty on other features than the SpA features defined in the ASAS axSpA criteria. The definition ‘diagnostic uncertainty’ was construed by an arbitrarily chosen cut-off value as there is no clear definition nor a way to scientifically measure diagnostic uncertainty. An interesting conclusion we may draw from our data is that at baseline rheumatologists hypothesize about the possible diagnosis which can be influenced by newly acquired information of or from the patient. Diagnostic uncertainty is not necessarily a ‘bad thing’ albeit that excessive use of health care resources in the pursuit of a diagnosis should be avoided. Therefore, in cases with diagnostic uncertainty a “wait and see approach” is justified.

One of the commonly present SpA features is a positive family history. The definition of a positive family history, as is used in daily clinical practice as well as in research studies, has once been constructed by a panel of SpA experts, but was never validated. **Chapter 5** discusses the usefulness of the current definition of a positive family history (PFH) as it is considered a risk factor for axSpA, and whether the five diseases that comprise a PFH contribute equally well to diagnosing axSpA. For this study data from both the SPACE and DESIR cohorts were used. In both cohorts a PFH was defined according to the definition used in the ASAS classification criteria: the presence of ankylosing spondylitis (AS), acute anterior uveitis (AAU), reactive arthritis, inflammatory bowel disease (IBD), and psoriasis in first- or second-degree relatives (first-degree: mother, father, sister, brother, daughter, son); second-degree: aunt, uncle, niece, nephew, grandmother, and grandfather).⁵ Overall, the most common diseases among first- or second-degree relatives were AS and psoriasis, followed by IBD, AAU, and reactive arthritis. In both univariable and multivariable analyses a PFH of AS or AAU was independently associated with HLA-B27 positivity. These results were expected since AS and AAU have a known association with HLA-B27.²⁶⁻²⁸ Furthermore, AAU showed an association with axSpA diagnosis in SPACE only. In addition, there was no association of PFH with sacroiliitis on imaging. We also looked at the relative contribution of HLA-B27 among patients who were classified according to the ASAS axSpA criteria. The majority of these patients were HLA-B27 positive. Interestingly, a PFH was more often reported in HLA-B27 positive patients compared to HLA-B27 negative patients. We concluded that a PFH of AS or AAU may be useful for case-finding in low prevalence settings as they are correlated with HLA-B27 carriage. However, a PFH of reactive arthritis, IBD, and psoriasis does not contribute to diagnosing axSpA in CBP patients suspected of axSpA. A recent study by van Lunteren *et al.* replicated

this finding in the ASAS cohort. They expanded their research question to ethnicity and degree of family relationship (i.e. first or second degree relatives), and found that a PFH of AS was positively associated in all patient subgroups, but that there was no association between a PFH of AAU, ReA, IBD or psoriasis with HLA-B27 carriership.²⁹ These findings are well in line with ours in that a PFH of AS, and possibly of AAU, may ‘track’ patients who are at risk of having axSpA. These patients should subsequently be typed for HLA-B27. Furthermore, these findings underscore calls that the current definition of a PFH for this specific population should be amended.

Use of imaging in the diagnosis of axSpA

One of the most important aspects in the (early) diagnosis (and classification) of axSpA is the use of imaging (conventional radiography and MRI of the sacroiliac joints) to assess active inflammation and/or structural changes highly suggestive of axSpA. An important limitation is that patients may have symptoms long before abnormalities (i.e. sacroiliitis) are detected on radiographs.^{5, 10, 30} Another important consideration is that not all patients with axSpA will develop structural lesions in the sacroiliac joints or the spine. MRI was introduced to overcome some of these issues in an early disease phase, since MRI may visualize both structural and inflammatory lesions in the sacroiliac joints and the spine.³¹⁻³⁴ The introduction of MRI has spearheaded the distinction of a fairly new disease entity called ‘non-radiographic axSpA’. Numerous studies have investigated this imaging modality in axSpA during the past decade.³⁵ ASAS has developed several recommendations on how to best perform an MRI of the sacroiliac joints and a definition for a positive MRI.^{14, 33} Because of the widespread use of sacroiliac imaging, a correct interpretation of the imaging by either an experienced rheumatologist or a radiologist is of crucial importance. There are several concerns, however, regarding the use of sacroiliac imaging. The recognition of sacroiliitis on radiographs is unreliable, regardless of the experience or training of the assessor(s).^{36, 37} Inaccurate readings (i.e. false-positive or false-negative for sacroiliitis) may lead to wrong diagnoses, especially if a diagnosing physician would rate the importance of abnormal imaging higher than the presence or absence of clinical symptoms. Subsequently, such falsely diagnosed patients may be enrolled in clinical trials or other types of clinical research, since they may erroneously classify as positive using the ASAS classification criteria. We do not have much insight into the extent to which rheumatologists are led by imaging findings in diagnosing their patients with axSpA.

The ASAS experts, who have developed the ASAS classification criteria for axSpA, did not include spinal inflammatory lesions on MRI (MRI-spine) as an imaging criterion in the classification of axSpA.⁵ However, several studies have shown that spinal inflammatory lesions

may occur, even in the absence of sacroiliitis on MRI.³⁸⁻⁴⁰ Given these observations, it was of interest to investigate whether MRI-spine should have a place as an element in the ASAS classification criteria. A consensus definition for a positive MRI-spine (i.e. three or more spinal inflammatory lesions) had already been developed by the ASAS/Outcome Measures in Rheumatology (OMERACT) MRI working group.³⁹ A positive MRI-spine is defined as the presence of ≥ 3 inflammatory lesions in the vertebrae on ≥ 2 consecutive slices. Recently, a new cut-off value (the 'rule of five') for spinal inflammatory lesions - positive MRI-spine defined as ≥ 5 inflammatory lesions - was proposed by the Hooge *et al.* that had a higher specificity ($> 95\%$).⁴¹ In **Chapter 6** we wanted to investigate whether it is useful to add a positive MRI-spine as an imaging criterion in the ASAS classification criteria for axSpA. Baseline data from both the SPACE and DESIR cohorts were used and several definitions of a positive MRI-spine were applied: (1) the ASAS consensus definition (≥ 3 spinal inflammatory lesions); (2) 'rule of five' - ≥ 5 spinal inflammatory lesions; (3) SPARCC-score of ≥ 5 by at least two readers (not available in DESIR); (4) and SPARCC-score of ≥ 5 by the mean of three readers (not available in DESIR). The majority of chronic back pain patients did not have any imaging abnormalities suggestive of axSpA. An isolated positive MRI-spine according to the 'rule of five' definition was found in only 1% and 2% of patients in the SPACE and DESIR cohorts, respectively. Almost all patients already had fulfilled the ASAS-criteria through the clinical arm. In both cohorts only one patient could additionally be classified as having axSpA by a putative MRI-spine-enriched imaging arm. This implies that a huge number of MRI-spine have to be performed needlessly in order to additionally classify one patient. We arrived at similar conclusions when using the other definitions for a positive MRI-spine. Therefore, the use of MRI-spine in the *classification* of axSpA is not recommended. An important side note is that this study focused on the effect of adding MRI-spine to the ASAS classification criteria. We did not formally assess the role of MRI-spine for an axSpA diagnosis in routine clinical practice. Obviously, MRI-spine may still be valuable for excluding other diseases with chronic back pain (differential diagnosis). We have also not investigated if MRI-spine is of added value in establishing the *activity* of the disease, for instance for monitoring purposes. This remains to be investigated.

In daily clinical practice the diagnosis of axSpA relies on local reading of images, usually in the clinical context, by either the radiologist and/or rheumatologist. In contrast, research studies use (blinded) centralized readers who have been trained and calibrated well. In **Chapter 7** we replicated a previously performed study in DESIR to investigate whether reading discrepancies between local assessors and central readers influenced the classification of chronic back pain patients in the SPACE cohort.⁴² In our study we confirmed that local assessors and central readers did not agree on the presence of sacroiliitis on MRI in 81/513 (16%) of patients. For

sacroiliitis on radiographs this rate of disagreement was 55/513 (11%) patients. Discrepant read-results led to a different classification in 52/513 (10%) patients, which is not negligible but also not of major impact. With central reading as external standard we found that local assessors tended to overrate the presence of sacroiliitis leading to a certain false-positive rate ('local overcall'). These findings were essentially similar to those reported in DESIR and add to the conclusion that the ASAS classification criteria are reasonably robust against differences invoked by local versus central readers. That read-discrepancy did not have a greater impact is mainly due to the inclusion of the *clinical arm*, which mitigates a wrong classification based on the imaging arm only.

Chapter 8 is the last chapter addressing the use of imaging in clinical practice, particularly sacroiliac imaging, in the SPACE cohort. Moreover, the effects of imaging results on the diagnosis and diagnostic confidence of rheumatologists were studied here. According to a fixed protocol rheumatologists were asked to provide a diagnosis *before* and *after* imaging results were known, and a corresponding level of confidence regarding this diagnosis. Sacroiliac imaging was interpreted by local assessors (rheumatologists & radiologists). Before imaging results were known to rheumatologists more than half of the patients (62%) had already been diagnosed with axSpA. As we have shown before in **Chapter 3** most common diagnoses in the patients *not* diagnosed with axSpA were non-specific back pain, degenerative disc disease or mechanical back pain. Expectedly, axSpA patients were more often male, HLA-B27 positive, and had more SpA features than patients without axSpA. Both in the groups with and without the diagnosis of axSpA, the mean (SD) level of confidence (LoC) was moderate at best (axSpA LoC 6.6 (SD 1.9), no axSpA LoC 5.6 (2.0)). After studying the results of the imaging, rheumatologists refuted the previous axSpA diagnosis in a number of cases. In total, after studying the results of imaging, 109/513 (21%) patients were assigned a different diagnosis, but the level of confidence regarding their (new) diagnosis markedly increased. Our findings suggest that imaging results play an important role in the diagnostic considerations of rheumatologists and increase the confidence in a diagnosis, regardless of the imaging outcome (positive or negative). This observation is in line with the conclusion of **Chapter 2**, namely that there is a strong relation between sacroiliitis on imaging and an axSpA diagnosis. In addition, imaging results increase their level of confidence with which they conclude to a certain diagnosis.

Future perspectives for research and implications of findings

A clear challenge in Rheumatology is making an appropriate diagnosis of axSpA early in patients presenting with chronic back pain. The timely presentation of patients to the rheumatologist is dependent on primary care physicians and other workers in primary health

care (physiotherapists and others). Although not covered in this thesis, an early identification and timely referral of chronic back pain patients is pivotal. Increasing awareness of the existence of axSpA may guide patient and doctor toward a timely diagnosis. This thesis has provided elements that may be of help in this regard. An important limitation of our studies, however, is that the conclusions cannot be extrapolated to primary care and common Rheumatology practice without further consideration since they have been derived from researching the SPACE and DESIR cohorts. These are cohorts with a far higher prevalence of axSpA than any clinical setting. It would be interesting to analyse how an axSpA diagnosis is made in settings with a lower prior probability, whether the modified Berlin diagnostic algorithm has indeed a place in the diagnostic process and whether the number of present SpA features dictates the diagnosis.

We have seen that positive imaging and the presence of HLA-B27 often drive a diagnosis of axSpA by rheumatologists in clinical practice. Which SpA features were considered most important for a diagnosis by rheumatologists, however, was not assessed. It is, for instance, very likely that rheumatologists weigh different SpA features differently and this may have (had) impact on the final diagnosis. Analysing such 'heterogeneity amongst diagnosticians' may give us better insight into how a diagnosis of axSpA is made and what it means. Such a process may even lead to considering other or new features or symptoms in diagnosing axSpA.

As we try to be more efficient in our daily clinical practice we wondered whether several aspects of the current definition of a positive family history (PFH) are relevant for case-finding (or axSpA diagnosis). Of note, a PFH is usually patient-reported which may both lead to an underestimation (patients cannot remember) or to an overestimation (patients misinterpret chronic back pain in a family member as a symptom of axSpA). Further clinical research is needed here in order to better diagnose axSpA. In addition, the current definition of a PFH (in this specific population) in the classification criteria deserves reconsideration and possibly modification. Ultimately, an interesting topic for future clinical research will be to investigate if certain combinations of SpA features point to axSpA with higher likelihood than others. Altogether, this may lead to earlier and more appropriate diagnosis and treatment of axSpA in different clinical settings.

The use of conventional radiography and MRI for an axSpA diagnosis (and subsequent classification) remains a point of debate. An important remaining question is when to use which modality and whether it does make a difference for the early recognition of axSpA. There have been recent studies assessing the course and progression of imaging abnormalities as well

as the development of new lesions over time. Ideally, in a few years we may predict which patients will develop structural bone lesions or permanent damage. Such a risk-stratification may lead to an individualized treatment plan (*personalized medicine*) and follow-up for each patient. Both cohorts used in this thesis (SPACE and DESIR) have longitudinal data and may help – in time – provide us with the answers.

Final comments on this thesis

In this thesis the focus was on diagnosing axSpA early using clinical features as well as imaging modalities. We have studied multiple elements diagnosing axSpA among patients presenting with chronic back pain. We have emphasized two main themes: (1) the importance of clinical SpA features; and (2) the contribution of imaging to an axSpA diagnosis and classification. We have learned how rheumatologists use imaging results in their diagnostic considerations and thereby have helped reduce certain fears regarding the way diagnosis is made in clinical practice. We have shown that the use of MRI-spine in classification is not efficient. The common thread in all of the studies in this thesis is that axSpA diagnosis is the interaction between the clinical aspects of chronic back pain and imaging findings highly suggestive of axSpA. Clinicians should be aware of mindlessly ‘stacking up’ SpA features in chronic back pain patients in order to avoid unnecessary (biologic) treatment. Additional studies are needed to investigate the numerous phenotypes of axSpA and to predict in which chronic back pain patient axSpA diagnosis is likely. Overall, we hope the studies reported in this thesis will contribute to a better understanding of how we diagnose axSpA in daily clinical practice as this is likely an important step towards improving long term outcomes of patients with axSpA.

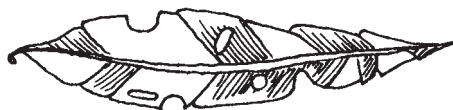
REFERENCES

1. Dougados M, d'Agostino MA, Benessiano J, *et al.* The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. *Joint Bone Spine* 2011;78:598-603.
2. van den Berg R, de Hooge M, van Gaalen F, *et al.* Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. *Rheumatology (Oxford)* 2013;52:1492-9.
3. Calin A, Porta J, Fries JF, *et al.* Clinical history as a screening test for ankylosing spondylitis. *Jama* 1977;237:2613-4.
4. Rudwaleit M, Metter A, Listing J, *et al.* Inflammatory back pain in ankylosing spondylitis: a re-assessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum* 2006;54:569-78.
5. Rudwaleit M, van der Heijde D, Landewe R, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-83.
6. Braun J, Inman R. Clinical significance of inflammatory back pain for diagnosis and screening of patients with axial spondyloarthritis. *Ann Rheum Dis* 2010;69:1264-8.
7. de Winter JJ, van Mens LJ, van der Heijde D, *et al.* Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. *Arthritis Res Ther* 2016;18:196.
8. Rudwaleit M, Haibel H, Baraliakos X, *et al.* The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum* 2009;60:717-27.
9. Rudwaleit M, van der Heijde D, Landewe R, *et al.* The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011;70:25-31.
10. Rojas-Vargas M, Munoz-Gomariz E, Escudero A, *et al.* First signs and symptoms of spondyloarthritis--data from an inception cohort with a disease course of two years or less (REGISPONSER-Early). *Rheumatology (Oxford)* 2009;48:404-9.
11. Stolwijk C, Essers I, van Tubergen A, *et al.* The epidemiology of extra-articular manifestations in ankylosing spondylitis: a population-based matched cohort study. *Ann Rheum Dis* 2015;74:1373-8.
12. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, *et al.* Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:65-73.
13. Rudwaleit M, van der Heijde D, Khan MA, *et al.* How to diagnose axial spondyloarthritis early. *Ann Rheum Dis* 2004;63:535-43.
14. Sieper J, Rudwaleit M, Baraliakos X, *et al.* The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;68 Suppl 2:ii1-44.
15. van Tubergen A, Weber U. Diagnosis and classification in spondyloarthritis: identifying a chameleon. *Nat Rev Rheumatol* 2012;8:253-61.

16. van den Berg R, de Hooge M, Rudwaleit M, *et al.* ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. *Ann Rheum Dis* 2013;72:1646-53.
17. Braun J, Baraliakos X, Kiltz U, *et al.* Classification and diagnosis of axial spondyloarthritis--what is the clinically relevant difference? *J Rheumatol* 2015;42:31-8.
18. Aggarwal R, Ringold S, Khanna D, *et al.* Distinctions between diagnostic and classification criteria? *Arthritis Care Res (Hoboken)* 2015;67:891-7.
19. Landewe RBM. Overdiagnosis and overtreatment in rheumatology: a little caution is in order. *Ann Rheum Dis* 2018;77:1394-6.
20. Sepriano A, Landewe R, van der Heijde D, *et al.* Predictive validity of the ASAS classification criteria for axial and peripheral spondyloarthritis after follow-up in the ASAS cohort: a final analysis. *Ann Rheum Dis* 2016;75:1034-42.
21. Tuite MJ. Sacroiliac joint imaging. *Semin Musculoskelet Radiol* 2008;12:72-82.
22. Mitra R. Osteitis Condensans Ilii. *Rheumatol Int* 2010;30:293-6.
23. Salaffi F, De Angelis R, Carotti M, *et al.* Fibromyalgia in patients with axial spondyloarthritis: epidemiological profile and effect on measures of disease activity. *Rheumatol Int* 2014;34:1103-10.
24. Slobodin G, Lidar M, Eshed I. Clinical and imaging mimickers of axial spondyloarthritis. *Semin Arthritis Rheum* 2017.
25. Braun J, Kiltz U. Spondyloarthropathies: How should axial spondyloarthritis be diagnosed? *Nat Rev Rheumatol* 2017;13:264-6.
26. Aho K, Ahvonen P, Lassus A, *et al.* HL-A antigen 27 and reactive arthritis. *Lancet* 1973;2:157.
27. Wakefield D, Chang JH, Amjadi S, *et al.* What is new HLA-B27 acute anterior uveitis? *Ocul Immunol Inflamm* 2011;19:139-44.
28. Reveille JD. Genetics of spondyloarthritis--beyond the MHC. *Nat Rev Rheumatol* 2012;8:296-304.
29. van Lunteren M, Sepriano A, Landewe R, *et al.* Do ethnicity, degree of family relationship, and the spondyloarthritis subtype in affected relatives influence the association between a positive family history for spondyloarthritis and HLA-B27 carriership? Results from the worldwide ASAS cohort. *Arthritis Res Ther* 2018;20:166.
30. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.
31. Landewe RB, Hermann KG, van der Heijde DM, *et al.* Scoring sacroiliac joints by magnetic resonance imaging. A multiple-reader reliability experiment. *J Rheumatol* 2005;32:2050-5.
32. Bennett AN, Rehman A, Hensor EM, *et al.* Evaluation of the diagnostic utility of spinal magnetic resonance imaging in axial spondylarthritis. *Arthritis Rheum* 2009;60:1331-41.
33. Rudwaleit M, Jurik AG, Hermann KG, *et al.* Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis* 2009;68:1520-7.
34. Weber U, Lambert RG, Ostergaard M, *et al.* The diagnostic utility of magnetic resonance imaging in spondylarthritis: an international multicenter evaluation of one hundred eighty-seven subjects. *Arthritis Rheum* 2010;62:3048-58.

35. Braun J, Baraliakos X, Buehring B, *et al.* Imaging of axial spondyloarthritis. New aspects and differential diagnoses. *Clin Exp Rheumatol* 2018;36 Suppl 114:35-42.
36. van Tubergen A, Heuft-Dorenbosch L, Schulpen G, *et al.* Radiographic assessment of sacroiliitis by radiologists and rheumatologists: does training improve quality? *Ann Rheum Dis* 2003;62:519-25.
37. van den Berg R, Lenczner G, Feydy A, *et al.* Agreement between clinical practice and trained central reading in reading of sacroiliac joints on plain pelvic radiographs. Results from the DESIR cohort. *Arthritis Rheumatol* 2014;66:2403-11.
38. Baraliakos X, Landewe R, Hermann KG, *et al.* Inflammation in ankylosing spondylitis: a systematic description of the extent and frequency of acute spinal changes using magnetic resonance imaging. *Ann Rheum Dis* 2005;64:730-4.
39. Hermann KG, Baraliakos X, van der Heijde DM, *et al.* Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. *Ann Rheum Dis* 2012;71:1278-88.
40. van der Heijde D, Sieper J, Maksymowych WP, *et al.* Spinal inflammation in the absence of sacroiliac joint inflammation on magnetic resonance imaging in patients with active nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2014;66:667-73.
41. de Hooze M, van den Berg R, Navarro-Compan V, *et al.* Patients with chronic back pain of short duration from the SPACE cohort: which MRI structural lesions in the sacroiliac joints and inflammatory and structural lesions in the spine are most specific for axial spondyloarthritis? *Ann Rheum Dis* 2015.
42. van den Berg R, Lenczner G, Thevenin F, *et al.* Classification of axial SpA based on positive imaging (radiographs and/or MRI of the sacroiliac joints) by local rheumatologists or radiologists versus central trained readers in the DESIR cohort. *Ann Rheum Dis* 2015;74:2016-21.

Nederlandse samenvatting



NEDERLANDSE SAMENVATTING

De studies beschreven in dit proefschrift omvatten aspecten van de diagnostiek bij patiënten met chronische rugpijn (CBP) die verdacht worden van axiale spondylartritis (axSpA) én de diagnose en classificatie (volgens de ASAS classificatie criteria) van axSpA. Deze studies zijn gecentreerd rondom hetzelfde doel, namelijk de vroege herkenning en diagnose van axSpA. Dit proefschrift behandelt een aantal onderwerpen. Eerst wordt het diagnostische proces en de uiteindelijke diagnosestelling bij patiënten met chronische rugpijn geëvalueerd. Vervolgens is naar de toegevoegde waarde van de MRI van de wervelkolom bij de classificatie van axSpA (met gebruik van de ASAS classificatie criteria) gekeken. Daarna gaan we in op het gebruik van beeldvormend onderzoek (en de bevindingen) bij de diagnose en classificatie van (vroege) axSpA.

Voor dit proefschrift zijn data gebruikt van twee prospectieve cohortstudies: het DEvenir des Spondyloarthropathies Indifférenciées Récentes (DESIR) cohort en het SpondyloArthritis Caught Early (SPACE) cohort. Deze twee cohorten vertonen gelijkenis op meerdere punten, zoals een volledig gestandaardiseerde diagnostische opzet en vooraf gedefinieerde tijdstippen. Echter, er zijn ook een paar belangrijke verschillen te noemen. Het SPACE cohort is een ‘multinational’ cohortstudie in vier Europese landen (Nederland, Noorwegen, Zweden en Italië), terwijl DESIR alleen patiënten binnen Frankrijk includeert. In SPACE worden alle patiënten van 16 jaar en ouder met chronische rugpijn (≥ 3 maanden en ≤ 2 jaar, aanvang < 45 jaar) gerekruteerd en geïncludeerd. De patiënten in DESIR zijn 18-50 jaar oud én hebben inflammatoire rugpijn (IBP met een duur van ≥ 3 maanden en < 3 jaar), waarbij de betrokken reumatoloog een waarschijnlijkheid voor axSpA van minimaal 50% heeft afgegeven. Het SPACE cohort is een doorlopende cohort studie met actieve inclusie van patiënten. De inclusie van patiënten in DESIR is inmiddels gesloten, echter wordt wel naar een follow-up van 10 jaar gestreefd. Voor dit proefschrift zijn alleen de baseline en 1-jaarsdata van beide cohorten gebruikt.

Diagnose axSpA

De tijdige herkenning van axSpA, zeker in een vroege fase van de ziekte, is tot op heden een uitdaging gebleken vanwege de heterogeniteit van de ziekte en de afwezigheid van echte diagnostische criteria. Een belangrijk aspect van het diagnostische proces in patiënten met chronische rugpijn is de anamnese. De behandelend arts dient te vragen naar kenmerken van - of ziektebeelden die relevant kunnen zijn voor - axSpA, ook wel SpA kenmerken genoemd. Een veelvoorkomend symptoom (c.q. SpA kenmerk) is inflammatoire rugpijn (IBP). IBP kent

meerdere definities, echter ten behoeve van dit proefschrift hebben wij de ASAS-definitie van IBP gebruikt. Volgens deze definitie is er sprake van IBP indien er minstens 4 van de volgende kenmerken aanwezig zijn: rugpijn in de ochtend, vermindering van rugpijn bij beweging, geen verbetering bij rust, nachtelijke rugpijn, een geleidelijke aanvang van de rugpijn en een leeftijd bij aanvang rugpijn van <40 jaar. Patiënten kunnen eveneens klagen over enthesitis (ontstoken peesaanhechtingen), perifere artritis (ontstoken gewrichten) of dactylitis (gezwollen en pijnlijke vingers of tenen). Extra-articulaire manifestaties (aandoeningen buiten het bewegingsapparaat), zoals uveitis, inflammatoire darmziekten (de ziekte van Crohn of colitis ulcerosa) en psoriasis, verhogen de kans op het hebben van axSpA (in patiënten met chronische rugpijn). Tevens behoren een positieve familieanamnese voor SpA bij eerste- en tweedegraads familieleden en een goede respons op non-steroïdale anti-inflammatoire geneesmiddelen (NSAIDs) ook tot de SpA kenmerken. Een gedegen lichamelijk onderzoek is een andere pijler in het diagnostische proces van de patiënt met chronische rugpijn. Aanvullende diagnostiek in de vorm van laboratoriumonderzoek (ontstekingsparameters en HLA-B27 (humaan leukocyten antigeen B27)) en beeldvormend onderzoek van de sacroiliacaal (SI) gewrichten kan eveneens bijdragen aan de diagnose.

Aangezien er geen diagnostische criteria voor axSpA bestaan dienen de symptomen van patiënt en de bevindingen bij het lichamelijk onderzoek en aanvullende diagnostiek in de volledige klinische context te worden geplaatst (patroonherkenning). Dit betekent dat de behandelend reumatoloog ruime ervaring moet hebben opgedaan in het herkennen van axSpA en gedegen kennis moet hebben van de uitgebreide differentiaaldiagnose van chronische rugpijn. Het Berlijn-algoritme is een goed voorbeeld van een beslissingsboom waarin de clinicus begeleid kan worden in het diagnostische proces van patiënten met chronische rugpijn. Voorzichtigheid is echter wel geboden bij het gebruik van dit algoritme. Het blindelings volgen van het algoritme leidt namelijk tot ongeveer 10% fout-positieve diagnoses en 10% fout-negatieve diagnoses.

De ASAS classificatie criteria voor axSpA worden gebruikt om patiënten voor wetenschappelijke studies te includeren. Deze classificatie criteria zijn ontwikkeld in een gecontroleerde setting, waarbij de axSpA prevalentie duidelijk hoger is dan in de algemene populatie. Derhalve is binnen de axSpA onderzoeksgemeenschap meermalen gewaarschuwd tegen het gebruik van deze classificatie criteria om de diagnose axSpA te stellen. Desondanks blijven er zorgen bestaan over het oneigenlijke gebruik van de classificatie criteria voor de diagnosestelling in de dagelijkse praktijk. Een ander relevant aspect is dat de classificatie criteria zijn ontwikkeld door een 'expert panel' van reumatologen die als externe standaard (in afwezigheid van een

gouden standaard) fungeerde. Een ‘expert opinion’ houdt in dat alle klinische relevante informatie wordt gecombineerd en afgewogen om tot een eventuele diagnose te komen. Het onderliggende proces is wederom patroonherkenning waarin behandelend artsen (in dit geval reumatologen) hun klinische ervaring gebruiken om tot een diagnose te komen. Heel belangrijk in dit proces is ook het uitsluiten van andere, meer waarschijnlijke diagnoses. De applicatie van de classificatie criteria in situaties waarin reeds een lage ‘*pre-test probability*’, ofwel een lage vooraf-kans, kan leiden tot significante *overdiagnose*. Zeker als er weinig ervaring is met axSpA, zoals in een huisartsenpraktijk, kan het verleidelijk zijn om de classificatie criteria te gebruiken. Een complicerende factor is dat er een dunne scheidslijn bestaat tussen classificatie en diagnose daar de meeste klinische-, laboratorium- en beeldvormend onderzoeksuitslagen zowel bij de classificatie als bij de diagnostiek van axSpA worden gebruikt. Desalniettemin dienen de classificatie criteria slechts te worden gebruikt bij patiënten met de diagnose axSpA, waarbij andere minder waarschijnlijke diagnoses zijn geëxcludeerd.

Zoals eerder besproken, kan het optellen van SpA kenmerken en het negeren van andere meer waarschijnlijke diagnoses leiden tot aanmerkelijke overdiagnose van axSpA, mogelijk leidend tot foutieve behandeling. De geuite zorgen over verkeerde diagnoses dan wel overdiagnose van axSpA hebben geleid tot het onderzoek in hoofdstuk 2. In dit hoofdstuk hebben wij onderzocht of de aanwezigheid van meerdere SpA kenmerken inderdaad automatisch leidt tot de diagnose axSpA. Eveneens werd onderzocht welke SpA kenmerken het meest bijdragen aan de diagnose axSpA en de overeenkomst tussen de diagnose van de reumatoloog en de ASAS classificatie criteria in het SPACE cohort. Er werden in totaal 500 patiënten geanalyseerd en gestratificeerd naar het aantal aanwezige SpA kenmerken: 159 (32%) patiënten hadden geen of maximaal 1 SpA kenmerk, 143 (29%) hadden 2 SpA kenmerken, 79 (16%) 3 SpA kenmerken en 119 (24%) minimaal 4 SpA kenmerken. De helft van de studiepopulatie had axSpA en de kans op de diagnose axSpA was in het algemeen gecorreleerd aan het aantal aanwezige SpA kenmerken. Echter, een deel van de patiënten met meerdere SpA kenmerken hadden geen diagnose axSpA. Deze bevindingen laten zien dat de diagnose axSpA niet alleen wordt bepaald door het aantal aanwezige SpA kenmerken. Overdiagnose is een reële zorg, maar heeft zich zeer waarschijnlijk niet vaak voorgedaan in het SPACE-cohort waar experts de diagnose hebben gesteld.

Enkele bevindingen in deze studie lieten eveneens zien dat reumatologen zich niet blindelings laten leiden door de classificatie criteria. HLA-B27 negatieve patiënten zonder afwijkingen op beeldvormend onderzoek (MRI of röntgenonderzoek van de SI-gewrichten) met enkele SpA kenmerken konden ook de diagnose axSpA krijgen zónder aan de classificatie criteria

van axSpA te voldoen. Een mogelijke verklaring voor deze diagnoses is dat andere kenmerken of symptomen (niet in de ASAS criteria geïncorporeerd), zoals alternerende bilpijn of de aanwezigheid van inflammatoire laesies in de wervelkolom, zijn meegenomen in de diagnosestelling. In aanvulling hierop kunnen reumatologen hun diagnose hebben gebaseerd op hun eigen interpretatie van het verrichte beeldvormend onderzoek in combinatie met de klachtenpresentatie. Een andere interessante onderzoeksvraag was welke SpA kenmerken het meeste bijdragen aan een axSpA diagnose. Zowel in uni- als multivariabele analyses waren de aanwezigheid van HLA-B27 en positief beeldvormend onderzoek (sacroiliitis op röntgen of MRI) onafhankelijke determinanten van axSpA diagnose. Met name positief beeldvormend onderzoek bleek een dominant kenmerk te zijn. Deze resultaten onderschrijven nogmaals het belang van correcte interpretatie van de verschillende modaliteiten in het diagnostisch proces. In deze studie werd ook gekeken naar de relatie tussen axSpA diagnose en de ASAS classificatie criteria voor axSpA. De diagnose van de reumatoloog werd als gouden standaard gebruikt. De classificatie criteria hadden een sensitiviteit van 76% en een specificiteit van 84%. Deze resultaten verschillen enigszins met de waarden uit andere studies, maar zijn wel in overeenstemming met de conclusie dat niet alle patiënten met axSpA voldoen aan de classificatie criteria en vice versa.

Het stellen van de diagnose axSpA bij patiënten met chronische rugpijn is een proces waarin de differentiaaldiagnose een belangrijke rol speelt. De differentiaaldiagnose voor axSpA omvat onder andere mechanische rugpijn, osteitis condensans ilii, DISH (diffuse idiopathic skeletal hyperostosis), degeneratieve discopathie en fibromyalgie. Tijdens de follow-up van patiënten kan de klinische presentatie veranderen hetgeen weer kan leiden tot het veranderen van de initieel gestelde diagnose of juist tot een toename van het vertrouwen in de gestelde diagnose. In **hoofdstuk 3** gaan we verder in op de bevindingen in **hoofdstuk 2**, in het bijzonder kijken we naar de alternatieve diagnoses bij patiënten met meerdere SpA kenmerken die volgens het Berlijn algoritme (naar verwachting) wél axSpA hebben. Deze aanvulling is gekomen na een commentaar van Braun *et al.* in Nature Reviews waarin zij beweren dat het onwaarschijnlijk is dat een patiënt met 4 of meer SpA kenmerken géén axSpA heeft. In het SPACE-cohort worden reumatologen gevraagd een diagnose te geven (axSpA of geen axSpA). Indien een patiënt geen axSpA heeft, wordt om een (meest waarschijnlijke) alternatieve diagnose gevraagd. In alle patiëntgroepen (0-1, 2, 3 en 4 SpA kenmerken) waren de meest voorkomende alternatieve diagnoses aspecifieke rugpijn, mechanische rugpijn, degeneratieve discopathie en fibromyalgie. Geen van de 18 patiënten met 4 of meer SpA kenmerken had afwijkingen op beeldvormend onderzoek en maar 4 waren HLA-B27 positief. De meest voorkomende SpA kenmerken waren IBP, een positieve

familieanamnese en een goede respons op NSAIDs, die alle als minder specifiek worden beschouwd. De (geruststellende) conclusie die hieruit getrokken kan worden, is dat een hoog aantal SpA kenmerken alleen niet voldoende is voor de diagnose axSpA.

Ondanks de uitgebreide diagnostische *work-up* in de diagnosestelling van axSpA is er vaak onzekerheid over de diagnose (diagnostische onzekerheid). **Hoofdstuk 4** behandelt de diagnostische onzekerheid op baseline en na 1 jaar follow-up, en de mogelijke invloed daarop van een toename van SpA kenmerken. Een belangrijke bevinding van deze studie is dat diagnostische onzekerheid normaal is. Hoewel enige diagnostische onzekerheid tijdens follow-up blijft bestaan, leidt gestandaardiseerde follow-up wel tot een afname van patiënten met een onzekere diagnose. Ongeveer de helft van de patiënten ontwikkelde minimaal één nieuw SpA kenmerk na 1 jaar follow-up, maar dit leidde in de meeste gevallen niet tot een verandering van diagnose of niveau van zekerheid. Deze resultaten geven enig inzicht in het klinisch redeneren in de dagelijkse praktijk. De bevinding dat toename van het aantal SpA kenmerken bij follow-up niet noodzakelijkerwijs leidt tot diagnoseverandering kan het resultaat zijn van het ‘wegen’ van de verschillende SpA kenmerken door reumatologen. Oftewel, de reumatoloog vindt sacroiliitis op beeldvormend onderzoek een zwaarder wegend SpA kenmerk dan een goede respons op NSAIDs. Ten tweede is het mogelijk dat reumatologen hun diagnose alsmede de zekerheid omtrent de diagnose baseren op andere kenmerken dan die zijn gedefinieerd in de ASAS criteria. Het is belangrijk te vermelden dat de term ‘diagnostische onzekerheid’ is gebaseerd op een arbitrair gekozen afkapwaarde, gezien er geen definitie is van diagnostische onzekerheid. Wellicht stellen reumatologen een eerste werkhypothese (diagnose) op, die dan na verloop van tijd kan veranderen bij het beschikbaar komen van nieuwe informatie. Een afwachtend beleid is in deze gerechtvaardigd, ook al om overdiagnostiek te voorkomen.

Een van de frequent voorkomende SpA kenmerken is een positieve familieanamnese voor SpA. De definitie voor een positieve familieanamnese (PFH) is door een expert panel opgesteld maar nooit gevalideerd. In **hoofdstuk 5** wordt het nut van een positieve familieanamnese bij de diagnose van axSpA behandeld. Een positieve familieanamnese voor SpA wordt in het algemeen beschouwd als een risicofactor voor axSpA. In de SPACE en DESIR cohorten werd de volgende definitie aangehouden: de aanwezigheid van ankyloserende spondylitis (AS/Bechterew), acute uveitis anterior (AAU), reactieve artritis, IBD, en psoriasis in eerste- of tweedegraads familieleden (eerstegraads: moeder, vader, zus, broer, zoon, dochter; tweedegraads: oom, tante, neef, nicht, grootvader, grootmoeder). Zowel in eerste- als tweedegraads familieleden waren AS en psoriasis de meest voorkomende aandoeningen, gevolgd door IBD, AAU en reactieve artritis. Zowel uni- als multivariabele analyses laten een onafhankelijk verband tussen een

PFH voor AS en AAU met de aanwezigheid van HLA-B27 zien. Deze resultaten waren min of meer verwacht gezien de bekende associatie van AS en AAU met HLA-B27. Alleen in het SPACE cohort werd een associatie tussen AAU en axSpA diagnose gevonden. Sacroiliitis op beeldvormend onderzoek liet echter geen associatie met een PFH zien. In aanvulling hierop werd de relatieve bijdrage van HLA-B27 onderzocht bij patiënten die waren geclassificeerd volgens de ASAS classificatie criteria. De meerderheid van deze patiënten waren HLA-B27 positief. Een interessante bevinding was dat een PFH vaker werd gerapporteerd bij HLA-B27 positieve patiënten dan bij HLA-B27 negatieve patiënten. Wij concludeerden dat een PFH voor AS of AAU een nuttig signaal kan zijn bij ‘*case-finding*’ in een omgeving met een lage kans op axSpA gezien de correlatie met HLA-B27 dragerschap. Een PFH voor reactieve artritis, IBD of psoriasis draagt niet bij aan de diagnosestelling. Deze bevindingen zijn gerepliceerd in een studie door van Lunteren *et al.* Zij hebben eveneens gekeken naar etniciteit en de bijdrage van familiegraad, waarbij een PFH voor AS bij alle patiëntengroepen een positieve associatie liet zien met HLA-B27 dragerschap. Een PFH voor AS of AAU kan gebruikt worden bij de opsporing van patiënten met een hogere kans op axSpA. Tevens pleiten deze bevindingen voor een herziening van de huidige definitie van een PFH binnen deze populatie.

Het gebruik van beeldvormend onderzoek voor axSpA diagnose

Een van de meest cruciale aspecten bij de (vroege) diagnose (en classificatie) van axSpA is het gebruik van beeldvormend onderzoek (conventionele radiografie en MRI van de SI-gewrichten) om inflammatie en/of structurele afwijkingen die suggestief zijn voor axSpA te identificeren. Een belangrijke beperking is dat patiënten al lang klachten kunnen hebben vóórdat zij afwijkingen (sacroiliitis) op röntgenfoto's krijgen. Ten tweede ontwikkelen lang niet alle axSpA patiënten afwijkingen in de SI-gewrichten of wervelkolom. De MRI bracht verandering in de diagnostiek van de vroege fase van axSpA waarbij vooral ontsteking te zien is. MRI is in staat zowel structurele afwijkingen als ontstekingslaesies in de SI-gewrichten en de wervelkolom af te beelden. Hiermee werd ook de nieuwe ziekte entiteit ‘non-radiografische axSpA’ bepaald. Het gebruik van MRI bij axSpA is de afgelopen 10 jaar frequent onderzocht, en diverse aanbevelingen ten aanzien van het gebruik en de interpretatie zagen het licht. De toename van het gebruik van beeldvormend onderzoek onderschrijft het belang van correcte interpretatie van de bevindingen door een reumatoloog of radioloog. Het (toenemend) gebruik van beeldvormend onderzoek roept ook enkele zorgen en bezwaren op. Ten eerste is sacroiliitis op röntgenfoto's lastig te herkennen en is de interpretatie ervan onbetrouwbaar, ongeacht ervaring en training van de *lezers*. Onjuiste interpretaties kunnen leiden tot verkeerde diagnoses (fout-positief of fout-negatief), zeker wanneer de behandelend arts afwijkingen op beeldvormend onderzoek belangrijker acht dan de klinische verschijnselen van de patiënt.

Eveneens kan een onjuiste interpretatie in klinische trials leiden tot verkeerde classificatie. Helaas is er weinig bekend over in welke mate reumatologen worden geleid door bevindingen op beeldvormend onderzoek voor de diagnose axSpA.

In de ontwikkeling van de ASAS classificatie criteria werden inflammatoire laesies in de wervelkolom op MRI (MRI-rug) niet meegenomen als criterium voor een positieve uitslag. Desondanks hebben meerdere studies laten zien dat spinale inflammatoire laesies wel degelijk kunnen voorkomen zonder sacroiliitis op MRI. Derhalve werd in **hoofdstuk 6** onderzocht of een positieve MRI-wervelkolom (inflammatoire laesies suggestief voor axSpA) een toegevoegde waarde heeft als criterium voor MRI-positiviteit in de ASAS classificatie criteria. Baseline data van de SPACE en DESIR cohorten werden gebruikt voor deze onderzoeksvraag. Verschillende definities voor een positieve MRI-wervelkolom werden gebruikt: (1) ASAS consensus definitie (≥ 3 spinale inflammatoire laesies); (2) 'regel van vijf' - ≥ 5 spinale inflammatoire laesies; (3) SPARCC-score van ≥ 5 door minstens 2 lezers (niet in DESIR); (4) en SPARCC-score van ≥ 5 berekend uit het gemiddelde van 3 lezers (niet in DESIR). De meerderheid van de patiënten met chronische rugpijn had geen afwijkingen op beeldvormend onderzoek. Een geïsoleerde positieve MRI-wervelkolom volgens de 'regel van vijf' definitie werd respectievelijk in slechts 1% en 2% van de patiënten in de SPACE- en DESIR-cohorten gevonden. Echter, bijna alle patiënten voldeden reeds aan de klinische arm van de classificatie criteria. In beide cohorten zou maar 1 patiënt aanvullend worden geclassificeerd als axSpA door de positieve MRI-wervelkolom. Dit suggereert dat een groot aantal MRI's van de wervelkolom verricht moeten worden om één patiënt extra te classificeren. Dezelfde conclusies werden getrokken met gebruik van de overige definities van een positieve MRI-rug. Derhalve ontraden wij het gebruik van een MRI-wervelkolom bij de *classificatie* van axSpA. Een belangrijke kanttekening is dat in deze studie de rol van de MRI-wervelkolom alleen bij de classificatie van axSpA is getoetst en niet bij het stellen van de diagnose. Een MRI-wervelkolom kan zeker nuttig zijn voor het excluderen van andere oorzaken van chronische rugpijn. Of de MRI-wervelkolom kan worden ingezet voor de evaluatie van ziekteactiviteit dient nog te worden onderzocht.

In de dagelijkse praktijk wordt voor de diagnose axSpA veelal de interpretatie van beeldvormend onderzoek van de radioloog gebruikt dan wel de eigen interpretatie in de klinische context. Dit is in tegenstelling tot de vele studies waarbij geblindeerde 'centrale' lezers worden gebruikt die vooraf worden getraind en gekalibreerd. **Hoofdstuk 7** is een replicatiestudie waarin is gekeken in hoeverre discrepanties in interpretatie van het verricht beeldvormend onderzoek (MRI-SI en X-SI) tussen lokale lezers (radiologen) en centrale lezers van invloed waren op de classificatie van patiënten in het SPACE-cohort. Deze studie liet zien dat in 16% van de gevallen er

onenigheid was over de interpretatie van de MRI-SI, terwijl dit 11% was voor de X-SI. In 10% van de patiënten leidde deze discrepantie in de beoordeling tot een andere classificatie van patiënten. Met de uitslag van centrale lezers als gouden standaard werd geconcludeerd dat lokale lezers de neiging hebben vaker sacroiliitis te rapporteren (fout-positieven). Deze bevindingen zijn in essentie in overeenstemming met de bevindingen in het DESIR-cohort en bevestigen dat de ASAS classificatie criteria redelijk robuust zijn tegen discrepanties die optreden bij beoordelingen van MRI's en röntgenfoto's door lokale en centrale lezers, mede omdat de klinische arm helpt om foute classificaties te voorkomen.

Hoofdstuk 8 is het laatste hoofdstuk waarin het gebruik van beeldvormend onderzoek, met name van de SI-gewrichten, in de dagelijkse praktijk wordt behandeld. Eveneens worden de effecten op de diagnose en de diagnostische zekerheid onderzocht. In het SPACE-onderzoek worden reumatologen gevraagd een diagnose te geven vóór en ná de interpretatie van de bevindingen bij beeldvormend onderzoek. Ten tweede wordt gevraagd een score te geven voor de mate van diagnostische zekerheid (hoe hoger de score, des te zekerder is de reumatoloog van zijn diagnose). Beeldvormend onderzoek werd geïnterpreteerd door lokale lezers (reumatologen of radiologen). Voordat de bevindingen van beeldvormend onderzoek bekend waren, had ruim de helft van de patiënten een diagnose axSpA (62%). Zoals reeds beschreven in **hoofdstuk 3** waren de meest frequente diagnoses bij patiënten die geen axSpA bleken te hebben aspecifieke rugpijn, degeneratieve discopathie of mechanische rugpijn. De ruime meerderheid van de patiënten met axSpA had het mannelijk geslacht, was HLA-B27 positief en had meer SpA kenmerken dan de patiënten zonder axSpA. Bij zowel de axSpA patiënten als de patiënten zonder axSpA bleek de gemiddelde mate van diagnostische zekerheid (op een schaal van 0 tot 10) onder reumatologen matig (axSpA: 6.6 (SD 1.9), geen axSpA 5.6 (2.0)). Na het bekend worden van de bevindingen bij beeldvormend onderzoek werd in een aantal gevallen de diagnose axSpA verworpen: 21% van de patiënten een andere diagnose toebedeeld na de interpretatie van deze bevindingen, en de mate van diagnostische zekerheid steeg. Deze resultaten bevestigen dat beeldvormend onderzoek zeker een belangrijke rol speelt bij de diagnostische overwegingen van de reumatoloog en ook leidt tot een toename van diagnostische zekerheid. Dit gegeven komt overeen met de bevindingen in **hoofdstuk 2**, waarin de correlatie tussen sacroiliitis op beeldvormend onderzoek en axSpA diagnose is aangetoond.

Toekomstperspectieven

Een belangrijke uitdaging in de Reumatologie is de tijdige en juiste diagnose van axSpA in patiënten met chronische rugpijn. De juiste verwijzing van patiënten naar de reumatoloog is sterk afhankelijk van huisartsen en andere zorgverleners in de eerstelijnszorg. Alhoewel niet

specifiek besproken in dit proefschrift is een vroege identificatie en verwijzing cruciaal. Een belangrijk aspect is de bewustwording van zowel patiënt als dokter van het bestaan van axSpA en de daarbij horende symptomen. Dit proefschrift biedt enkele handvatten hiervoor. Een belangrijke beperking van onze studies is dat de getrokken conclusies niet zomaar vertaald kunnen worden naar de huisartsenpraktijk of naar andere eerstelijns zorgomgevingen. De onderzochte cohorten, SPACE en DESIR, zijn cohorten met veel hogere prevalenties van axSpA dan wordt gevonden in de gewone bevolking. Enkele belangrijke onderzoeksvragen zijn derhalve hoe de diagnose axSpA het best wordt gesteld in situaties waarbij er een lage voorafkans op axSpA is, of het Berlijn algoritme inderdaad een plek heeft en houdt bij het diagnosticeren van axSpA en of het aantal aanwezige SpA kenmerken voldoende betrouwbaar de diagnose axSpA dicteert. Dit proefschrift heeft laten zien dat afwijkend beeldvormend onderzoek en de aanwezigheid van HLA-B27 zeer vaak de drijvende factoren achter een diagnose van axSpA zijn. Echter, welk specifieke SpA kenmerk door reumatologen als meest belangrijk wordt beschouwd is niet onderzocht. Zeer waarschijnlijk zijn er verschillen tussen reumatologen. Inzicht in de mate van heterogeniteit tussen behandelend artsen kan ons helpen te begrijpen hoe de diagnose axSpA gesteld wordt.

De zoektocht naar meer efficiëntie in de dagelijkse praktijk heeft geleid tot het opnieuw evalueren van de definitie van een positieve familieanamnese voor SpA. Het is belangrijk te begrijpen dat een positieve familieanamnese een subjectief (*patient-reported*) kenmerk is en onderhevig aan foutieve interpretaties van de klachten en symptomen van familieleden, hetgeen kan leiden tot een overschatting zowel als een onderschatting (geen herinnering, geen contact met familie). Aanvullend onderzoek is dan nodig om de diagnose axSpA te kunnen stellen. De huidige definitie van een positieve familieanamnese verdient naar onze mening herziening. Het uiteindelijke doel van de verrichte studies is om een eerdere en accuratere diagnose van axSpA te kunnen stellen. Een belangrijk onderwerp van toekomstig onderzoek is het identificeren van combinaties van SpA kenmerken die leiden tot een hogere kans op het hebben van axSpA. Al met al zou dit kunnen leiden tot een betere vroegdiagnostiek en behandeling.

Het gebruik van conventioneel beeldvormend onderzoek en MRI voor de diagnose axSpA (en classificatie) blijft een punt van discussie. Een belangrijke vraag is wanneer welke modaliteit dient te worden gebruikt en of dit inderdaad verschil maakt voor vroege herkenning van axSpA. Recente studies beschrijven zowel het beloop als de progressie van afwijkingen op beeldvormend onderzoek over de tijd. Idealiter kan men over enkele jaren voorspellen welke patiënten structurele laesies of permanente schade zullen ontwikkelen. Deze ‘risico-stratificatie’ kan leiden tot een geïndividualiseerd behandelplan en follow-up voor elke patiënt.

Tot slot

In dit proefschrift werd de nadruk gelegd op de (vroeg) diagnose van axSpA door middel van het gebruik van zowel klinische kenmerken als beeldvormend onderzoek. We hebben meerdere aspecten van de diagnose axSpA bestudeerd met twee hoofdthema's: (1) het belang van klinische SpA kenmerken; en (2) de bijdrage van beeldvormend onderzoek voor de diagnose en classificatie van axSpA. De resultaten van de studies geven inzicht in hoe reumatologen beeldvormend onderzoek gebruiken bij hun diagnostische overwegingen. We hebben aangetoond dat het gebruik van de MRI-wervelkolom bij de classificatie van axSpA zinvol noch efficiënt is. De rode draad in dit proefschrift is dat een diagnose axSpA de uitkomst is van het wegen van klinische argumenten en afwijkingen gevonden bij beeldvormend onderzoek. We hebben ook geleerd dat clinici voorzichtig moeten zijn met het zo maar optellen van klinische SpA kenmerken om tot een diagnose van axSpA te komen. Enkele onbeantwoorde onderzoeksvragen zijn welke fenotypen er bestaan binnen axSpA en hoe axSpA het beste te voorspellen is bij patiënten die zich presenteren met chronische rugpijn.

Wij hopen dat de studies in dit proefschrift zullen leiden tot meer inzicht in de diagnose axSpA en (uiteindelijk) tot betere lange-termijn uitkomsten bij patiënten met axSpA.

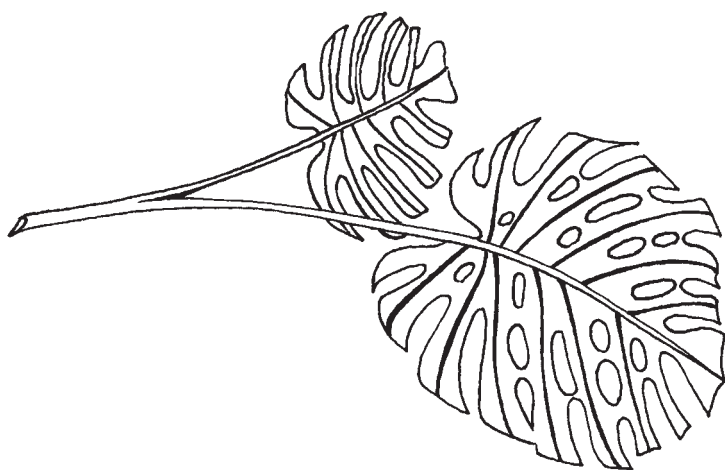
Appendix

LIST OF PUBLICATIONS

CURRICULUM VITAE

DANKWOORD

LIST OF PUBLICATIONS



LIST OF PUBLICATIONS

1. Bakker, P.A., Ez-Zaitouni, Z., van Lunteren, M., van den Berg, R., De Hooge, M., Fagerli, K.M., Landewe, R., van Oosterhout, M., Ramonda, R., Reijnierse, M., van der Heijde, D., and van Gaalen, F.A., *Are Additional Tests Needed to Rule Out Axial Spondyloarthritis in Patients Ages 16-45 Years With Short-Duration Chronic Back Pain and Maximally One Spondyloarthritis Feature?* Arthritis Care Res (Hoboken), 2016. 68(11): p. 1726-1730.
2. Rubio Vargas, R., van den Berg, R., van Lunteren, M., Ez-Zaitouni, Z., Bakker, P.A., Dagfinrud, H., Ramonda, R., Landewe, R., Molenaar, E., van Gaalen, F.A., and van der Heijde, D., *Does body mass index (BMI) influence the Ankylosing Spondylitis Disease Activity Score in axial spondyloarthritis?: Data from the SPACE cohort.* RMD Open, 2016. 2(1): p. e000283.
3. Aizenberg, E., van den Berg, R., Ez-Zaitouni, Z., van der Heijde, D., Reijnierse, M., Dzyubachyk, O., and Lelieveldt, B.P.F., *Computer-aided evaluation of inflammatory changes over time on MRI of the spine in patients with suspected axial spondyloarthritis: a feasibility study.* BMC Med Imaging, 2017. 17(1): p. 55.
4. Ez-Zaitouni, Z., Bakker, P.A., van Lunteren, M., de Hooge, M., van den Berg, R., Reijnierse, M., Fagerli, K.M., Landewe, R.B., Ramonda, R., Jacobsson, L.T., Saraux, A., Lenczner, G., Feydy, A., Pialat, J.B., Thevenin, F., van Gaalen, F.A., and van der Heijde, D., *The yield of a positive MRI of the spine as imaging criterion in the ASAS classification criteria for axial spondyloarthritis: results from the SPACE and DESIR cohorts.* Ann Rheum Dis, 2017. 76(10): p. 1731-1736.
5. Ez-Zaitouni, Z., Bakker, P.A.C., van Lunteren, M., Berg, I.J., Landewe, R., van Oosterhout, M., Lorenzin, M., van der Heijde, D., and van Gaalen, F.A., *Presence of multiple spondyloarthritis (SpA) features is important but not sufficient for a diagnosis of axial spondyloarthritis: data from the SPondyloArthritis Caught Early (SPACE) cohort.* Ann Rheum Dis, 2017. 76(6): p. 1086-1092.
6. Ez-Zaitouni, Z., Hilken, A., Gossec, L., Berg, I.J., Landewe, R., Ramonda, R., Dougados, M., van der Heijde, D., and van Gaalen, F., *Is the current ASAS expert definition of a positive family history useful in identifying axial spondyloarthritis? Results from the SPACE and DESIR cohorts.* Arthritis Res Ther, 2017. 19(1): p. 118.

7. van Lunteren, M., **Ez-Zaitouni, Z.**, Fongen, C., Landewe, R., Ramonda, R., van der Heijde, D., and van Gaalen, F.A., *Disease activity decrease is associated with improvement in work productivity over 1 year in early axial spondyloarthritis (SPondyloArthritis Caught Early cohort)*. Rheumatology (Oxford), 2017. 56(12): p. 2222-2228.
8. Bakker, P.A., van den Berg, R., Hooge, M., van Lunteren, M., **Ez-Zaitouni, Z.**, Fagerli, K.M., Landewe, R., van Oosterhout, M., Ramonda, R., Reijnierse, M., van Gaalen, F.A., and van der Heijde, D., *Impact of replacing radiographic sacroiliitis by magnetic resonance imaging structural lesions on the classification of patients with axial spondyloarthritis*. Rheumatology (Oxford), 2018.
9. **Ez-Zaitouni, Z.**, Landewe, R., van Lunteren, M., Bakker, P.A., Fagerli, K.M., Ramonda, R., Jacobsson, L.T.H., van der Heijde, D., and van Gaalen, F.A., *Imaging of the sacroiliac joints is important for diagnosing early axial spondyloarthritis but not all-decisive*. Rheumatology (Oxford), 2018.
10. **Ez-Zaitouni, Z.**, Landewe, R.B.M., van der Heijde, D., and van Gaalen, F.A., *Alternative diagnoses in patients with chronic back pain not diagnosed with axial spondyloarthritis: data from the SPACE cohort*. Ann Rheum Dis, 2018. 77(6): p. e34.
11. **Ez-Zaitouni, Z.**, van Lunteren, M., Bakker, P.A.C., van den Berg, R., Reijnierse, M., Fagerli, K.M., Landewe, R.B.M., Ramonda, R., Jacobsson, L.T.H., van Gaalen, F.A., and van der Heijde, D., *The influence of discrepant imaging judgements on the classification of axial spondyloarthritis is limited: a replication in the SpondyloArthritis Caught Early (SPACE) cohort*. Ann Rheum Dis, 2018. 77(1): p. e1.
12. van Lunteren, M., **Ez-Zaitouni, Z.**, de Koning, A., Dagfinrud, H., Ramonda, R., Jacobsson, L., Landewe, R., van der Heijde, D., and van Gaalen, F.A., *In Early Axial Spondyloarthritis, Increasing Disease Activity Is Associated with Worsening of Health-related Quality of Life over Time*. J Rheumatol, 2018.
13. van Lunteren, M., Scharloo, M., **Ez-Zaitouni, Z.**, de Koning, A., Landewe, R., Fongen, C., Ramonda, R., Kaptein, A.A., van Gaalen, F.A., and van der Heijde, D., *The impact of illness perceptions and coping on the association between back pain and health outcomes in patients suspected of axial spondyloarthritis: data from the SPACE cohort*. Arthritis Care Res (Hoboken), 2018.

14. Bakker, P.A., Ramiro, S., Ez-Zaitouni, Z., van Lunteren, M., Berg, I.J., Landewe, R., Ramonda, R., van Oosterhout, M., Reijnierse, M., van Gaalen, F.A., and van der Heijde, D., *Is it useful to repeat MRI of the sacroiliac joints after three months or one year in the diagnostic process of patients with chronic back pain suspected of axial spondyloarthritis?* Arthritis Rheumatol, 2018.



DIAGNOSIS AND CLASSIFICATION OF AXIAL SPONDYLOARTHRITIS *IMAGING AND NON-IMAGING FEATURES*

1. A clinical diagnosis of axial spondyloarthritis is more than the sum of spondyloarthritis features; it requires the skill of pattern recognition. (*this thesis*)
2. Sacroiliitis on MRI or radiographs and HLA-B27 positivity are determinants of axial spondyloarthritis diagnosis. (*this thesis*)
3. A family history of ankylosing spondylitis or acute anterior uveitis is useful in identifying chronic back pain patients at increased risk of suffering from axial spondyloarthritis. (*this thesis*)
4. Diagnostic uncertainty is inherent to rheumatology since patients may present with heterogeneous disease manifestations and unequivocal diagnostic tests are lacking. (*this thesis*)
5. Since information obtained on MRI of the spine is not of additional diagnostic value MRI-spine should also not be added as an imaging criterion to the ASAS classification criteria for axial spondyloarthritis. (*this thesis*)
6. Rheumatologists have stronger belief in the results of imaging than in the information obtained by history and physical examination. (*this thesis*)
7. Our curricula should recognize diagnosis as dynamic and evolving — an iterative process that accounts for multiple, changing perspectives. We can speak about “hypotheses” rather than “diagnoses,” thereby changing the expectations of both patients and physicians and facilitating a shift in culture. (*Simpkin AL et al. N Engl J Med 2016; 375:1713-5*)
8. In rheumatology ‘earlier’ (diagnosis) is not always necessarily ‘better’, ‘more’ (treatment) is not automatically ‘more effective’, and ‘increased sensitivity’ (of diagnostic tests) is not synonymous to ‘better yield’. We need to better distinguish ‘disease’ from the ‘risk of disease’. (*after Landewé RBM. Ann Rheum Dis 2018;77:1394-6*)
9. Because of the wide range of clinical phenotypes that constitute SpA the expert opinion of a rheumatologist will remain the crucial step in recognition of this disease. (*after van Tubergen et al. Nat Rev Rheumatol 2012;8:253-61*)
10. Unmet needs for new and accessible targeted therapies, disease prevention and ultimately cure remain a priority in rheumatology. (*after Winthrop KL et al. Ann Rheum Dis 2019;78:872-8*)
11. Je kunt beter iets dan niets opschrijven.
12. Wie groot wil zijn, blijft het beste klein.