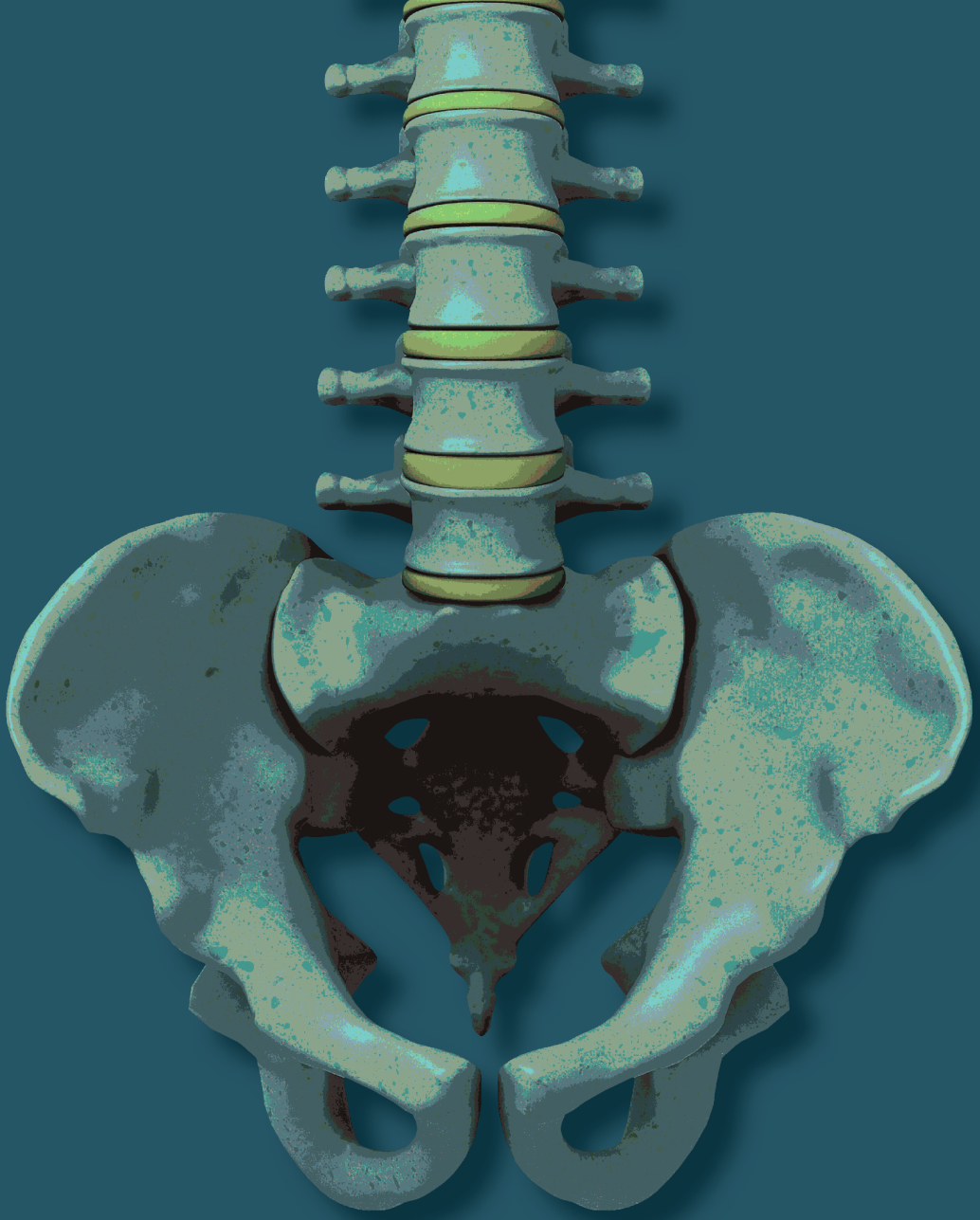

Referral Strategy for Axial Spondyloarthritis

Development, validation and impact in a chronic low back pain population

Lonneke van Hoeven

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Verwijsstrategie voor axiale spondyloartritis

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Proefschrift

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Contents

Chapter 1

Introduction, aim and outline

Chapter 1. Introduction, aim and outline

Spondyloarthritis

The term spondyloarthritis (SpA) covers a group of chronic inflammatory diseases that share clinical and genetic features. [1] Diseases within the SpA group can roughly be divided in diseases which predominantly affect the axial skeleton, and conditions wherein primarily the peripheral skeleton is involved. (Figure 1) In its current understanding, SpA encompasses the umbrella terms axial spondyloarthritis (axSpA) and peripheral spondyloarthritis. AxSpA includes non-radiographic axial spondyloarthritis (nr-axSpA) and Ankylosing Spondylitis (AS), while peripheral spondyloarthritis comprises psoriatic arthritis (PsA), reactive arthritis (ReA) and inflammatory bowel disease (IBD) associated arthritis. This thesis focuses on axSpA.

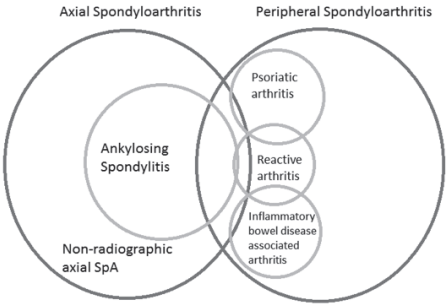


Figure 1. Current concept of spondyloarthritis. Adapted from N. Garg et al. Best Practice Clinical Rheumatology 28 (2014) 663-672[1]

Epidemiology, pathogenesis, clinical manifestations and treatment

The prevalence of axSpA varies from 0.5% to 1.5% [2, 3] and is partly explained by the geographic variation of the human leukocyte antigen (HLA)-B27. In regions were the HLA-B27 prevalence is high, axSpA is more prevalent compared to regions with a low HLA-B27 prevalence. There is one older study regarding AS prevalence in the Netherlands, this study reported an AS prevalence of 1.3% in 1988. [4] There is no recent data regarding axSpA prevalence in the Netherlands. A study in the UK in primary care patients who suffered from low back reported that up to 5%

of the CLBP complaints can be explained by AS. [5] More males are affected with AS compared to females (ratio 2:1)[6], while in nr-axSpA there is a slight trend that more females than males are affected (60% vs. 40%). [7]

Pathogenesis

The pathogenesis of axSpA is not completely elucidated. In axSpA the major sites of pathology are the entheses of the axial skeleton, opposed to the synovia of the peripheral joints as is seen in other rheumatologically disease. [8] Entheses are the sites were ligaments or tendons insert in and attach to bone. The pathological changes in the entheses include inflammation, structural damage and excessive new bone formation. New bone formation at the vertebral corners results in the formation of syndesmophytes. Bridging of syndesmophytes can lead to the classic, but rather uncommon, bamboo spine. [9] Genetic factors are important in the heritability of axSpA, the strongest association is with HLA-B27. [10] The contribution of HLA-B27 to AS heritability is estimated at 23%, so the presence of HLA-B27 alone is not sufficient for disease to occur. There are several theories how HLA-B27 induces AS, almost all related to the structural variations of the HLA-B27 molecule. The structural variations trigger inflammation causing pathways activation including activation of important mediators such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-17. There are theories that axSpA may be initiated in the gastrointestinal tract[11], supported by the finding that in approximately two-thirds of the axSpA patients a subclinical intestinal inflammation is present.

Clinical manifestations

AxSpA is characterized by chronic low back pain (CPBP) and stiffness of the axial skeleton, which is caused by inflammation of the sacroiliac joints (SI-joints) and spine. [12] Patients with axSpA usually experience the first complaints in their 2nd or 3rd decade of life, and >95% of patients are symptomatic by age 45 years. [13] In most cases (70%-80%) the CLBP is of inflammatory nature. [14] Inflammatory back pain (IBP) is characterized by an onset at a young age (before the age of 40 years), an insidious onset, improvement by movement and pain at night. More than half of the axSpA patients suffer from complaints in peripheral joints, such as peripheral arthritis, dactylitis and enthesitis. [15] The peripheral arthritis is usually oligoarticulair, asymmetrical and predominately of the lower extremities. Dactylitis

is a diffuse swelling of digits of toes or fingers, also called 'sausage digits'. Enthesitis is an inflammation of the entheses, in axSpA enthesitis of the achilles tendon is most common. Also extra-articulair manifestations, like psoriasis, inflammatory bowel disease (IBD) and uveitis, are prevalent in axSpA patients, 15%, 5% and 9% respectively [15, 16] The chronic inflammation in axSpA leads to osteoporosis in up to 56% of the patients which can cause vertebral fractures. [17] Research about the cardiovascular risk of axSpA is ongoing, but some recent studies show an increased CVD risk in axSpA patients. [18-20]

The burden of axSpA is significant for both patients and society, and similar to other rheumatic diseases like rheumatoid arthritis and psoriatic arthritis. [21] The chronic inflammation and acute clinical features cause a decreased quality of life and impaired functioning. [22, 23] AxSpA also results in substantial health care costs for patient and society. In 2009 the annual costs for one AS patients per year were €9374 in the Netherlands. [24] The largest part of these costs was related to indirect costs, which is related to loss in work productivity. The impact of axSpA on work participation is significant. AS patients have lower employment rates, in the Netherlands only 55% of the AS patients are employed. [25] Moreover AS patients are up to 3 times more likely to have work disability, and experience more absence from work than the general population. [23] Limited data is available on the burden of nr-axSpA. [22]

Treatment

The treatment of axSpA is not solely focused on improving sign and symptoms, but also on improving functioning, quality of life and prevention of structural damage as described in the guidelines for the management of axSpA. [26] Treatment of axSpA is a combination of non-pharmacological treatment (patient education, regular exercise) and pharmacological treatment. The pharmacological treatment starts with non-steroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase 2 (COX-2) inhibitors. The guidelines describe that continuous treatment with NSAIDs is preferred. The effect of the treatment is monitored by clinical parameters, laboratory tests and disease activity questionnaires like the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Patients should try at least two different NSAIDs during four weeks. If there is a persistently high disease activity despite treatment with NSAIDs, treatment with tumor necrosis

factor-alpha (TNF-α) should be given. A persistently high disease activity means a BASDAI score higher than four and a positive expert opinion based on parameters such as; elevated C-reactive protein (CRP, normal range 1-10 mg/l) or Erythrocyte Sedimentation Rate (ESR, normal range 0-15 mm Hg/min), inflammation visible on MRI, radiological progression or clinical examination.

If axSpA patients, both AS and nr-axSpA, are adequately treated a decrease in disease activity, an increase in quality of life and an improvement in work participation is observed. [27] For example in a study estimating the effect of anti-TNFα medication versus placebo the BASDAI (score 0-10, a higher score indicates a higher disease activity), improved with more than 3.0 points after the start of anti-TNFα treatment. [28] Another study which evaluated the effect of anti-TNFα treatment on work participation showed that patients with a good treatment response had significantly improved work productivity and less work impairment. [29] Recent findings show promising results of IL-17 and IL-23 blockades in the treatment of AS, efficacy of this treatment in nr-axSpA patients should be addressed in future studies. [30-32]

A predictor for favorable treatment outcome in axSpA patients is short symptom duration. [33] A short symptom duration can be achieved when patients are recognized and diagnosed as early as possible. To reach this goal is it important to understand the early disease course of axSpA.

Early disease course

The concept of early axSpA and the natural disease course are not fully understood. The natural course of axSpA is depicted by Garg et al. (Figure 2) [1] They illustrate the natural course as a river starting with a subclinical process in genetically predisposed patients, after which a patient develops the first clinical symptoms (described as inflammatory back pain). Subsequently patients can evolve to non-radiographic axSpA (nr-axSpA) or patients evolve to spontaneous remission. Some patients progress from nr-axSpA to AS, however it is not clear how many or which progress to AS. There are a few longitudinal studies investigating the progression from non-radiographic to AS. In two different studies a similar result was found; around 11% of the nr-axSpA patients developed radiographic progression over 2 years. [34, 35] One study with a longer follow up reported that 24% of the patients

progressed to AS during 10 years of follow up. [36] Predictors of radiographic progression in nr-axSpA patients are male gender and elevated CRP. [35] More long term follow up studies of patients with CLBP, inflammatory back pain or nr-axSpA are needed to completely understand the natural history of axSpA.

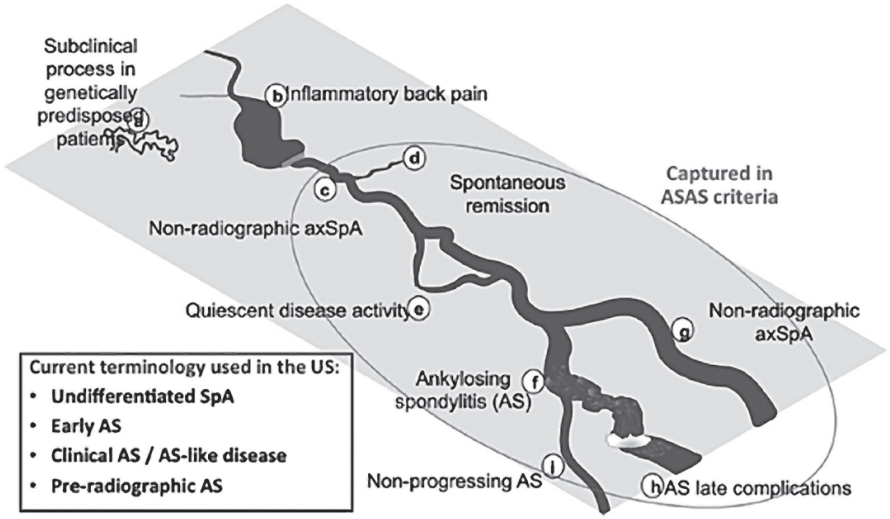


Figure 2. Clinical conceptualization of the Natural History of AxSpA. Reprinted from N. Garg et al. Best Practice Clinical Rheumatology 28 (2014) 663-672[1]

Since 1984 the modified New York (mNY) criteria have been the cornerstone of the classification of AS patients. [37] Patients fulfill these criteria when at least one clinical feature (IBP, limited spinal mobility or restricted chest expansion) was present and the radiological requirements were met. The radiological requirements are at least grade 2 bilateral sacroiliitis, or grade 3 unilateral sacroiliitis. The main limitation of the mNY criteria is their failure to identify early disease, as they require radiological changes in the SI-joints. From the moment of onset of CLBP it takes on average 6 to 8 years for sacroiliitis to appear on the X-ray. [38, 39]

Magnetic resonance imaging (MRI) provides the opportunity to detect inflammation in the SI-joints years before abnormalities are visible on radiographs. [40] This earlier detection of inflammation in the SI-joints made it possible to classify patients in an earlier course of their disease, which lead to the publication of the ASAS classification criteria for axSpA in 2009. [41] With the ASAS criteria the term non-radiographic axSpA was introduced. Nr-axSpA patients can be identified before the detection of structural changes in the SI-joints. (Figure 3)

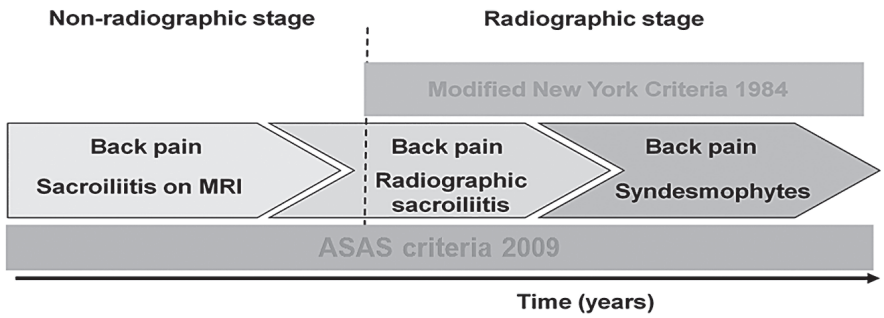


Figure 3. Axial spondyloarthritis. Adapted from Rudwaleit et al. A&R 2005;52:1000-8 [36]

Nr-axSpA patients can be classified when there is a sacroiliitis visible on the MRI and when there is at least one SpA feature present or when a patient is HLA-B27 positive and at least two other SpA features are present. (Figure 4) In AS patients structural changes are visible on the X-ray of the SI-joints. (Figure 3) The MRI of an axSpA patient is classified as positive when definite subchondral bone marrow edema highly suggestive of sacroiliitis is present. [41] Structural changes in the SI joint such as erosions and fat depositions visible on the MRI and abnormalities seen on the MRI-spine seem promising in the classification of axSpA, however they have not been incorporated into the classification criteria for axSpA yet. [42-44]

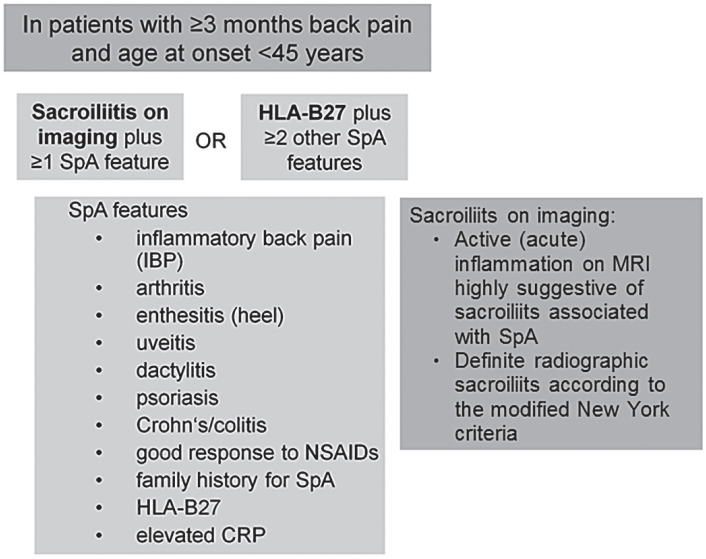


Figure 4. ASAS criteria for axSpA. Adapted from Rudwaleit et al. ARD 2011;70:25-31[41]

To support rheumatologists in early diagnosis of axSpA, the ASAS diagnostic algorithm for axSpA was published. [45] Within this algorithm referred patients follow a flowchart which incorporates imaging, clinical features and HLA-B27 testing. (Figure 6)

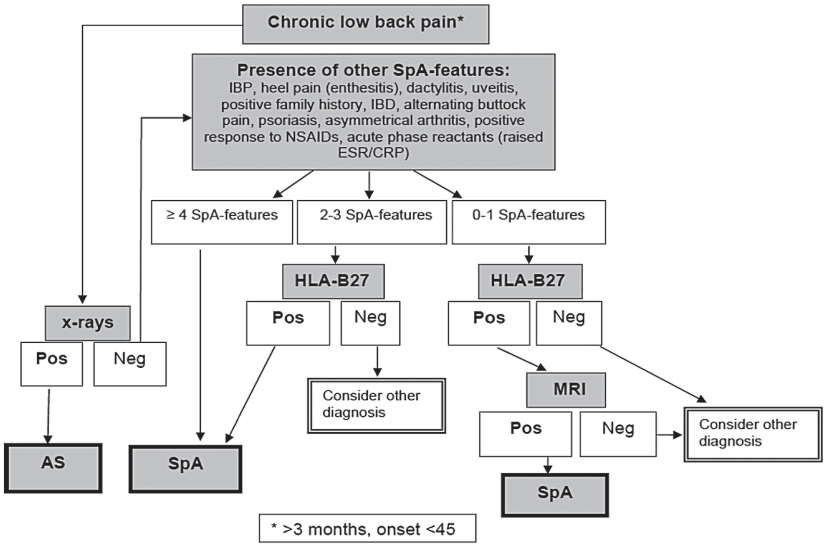


Figure 5. The ASAS diagnostic algorithm for axSpA. Reprinted from van den Berg et al. ARD 2013;72:1646-53 [45]

Early recognition

One of the reasons to develop the ASAS classification criteria for axSpA was to facilitate the identification of axSpA at an early stage, however the origin of the diagnostic delay lies in primary care. It is very difficult for primary care physicians to recognize axSpA patients. In a survey of GPs in both the Netherlands and the UK only a minority of the GPs could identify the features associated with axSpA. [46, 47] The difficulty is that not one single feature distinguishes axSpA patients from CLBP patients. Moreover CLBP is a very common complaint in primary practice, around 20% of the young adults (20-45 years) suffer from self-reported CLBP. [4, 48] In most countries CLBP patients are first seen by primary care physicians. Guidelines with red and yellow flags are used by primary care physicians to diagnose, treat and if necessary refer CLBP patients. [49] However current guidelines do not include a flag or referral recommendation specific for axSpA, which is a missed opportunity when taking into account the favorable treatment outcomes in axSpA patients

with a short symptom duration. [33] Early recognition and referral can lead to a shorter symptom duration of axSpA before treatment is started.

How can early recognition be accomplished? A review about effective referral has shown that referral from primary to secondary care can be improved by active local educational interventions involving secondary care specialists, clinical triage and by the use of structural referral sheets. [50]

In the field of rheumatoid arthritis (RA) clinical triage has been accomplished by set-up of early arthritis clinics to facilitate the early referral of patients at risk for RA. [51] Such clinics for early axSpA have been set up in Berlin, France, and in the Netherlands in Leiden and Maastricht. [15, 52-54] Those clinics describe the clinical and/or imaging characteristics of axSpA patients in an early phase of their disease. Currently there is no structural referral sheet for axSpA incorporated in the 'Nederlands Huisartsen Genootschap' (NHG) guidelines. Several referral sheets for axSpA have been published, these referral sheets were developed within rheumatology departments and have not yet been validated in primary care patients with chronic low back pain. [55-59]

Development of a referral strategy

The aim of a referral strategy is to use multiple predictors to estimate the probability or risk of a certain outcome, in this case the probability that a patient is diagnosed with axSpA. Four phases can be distinguished in the development of a referral strategy; (1) developing and internally validating a referral strategy; (2) testing in other individuals (external validation) and if necessary adjusting or updating the strategy; (3) assessing the strategy's impact on patients outcomes and decision making of the health care professional; (4) the implementation of the referral strategy in daily practice. [60].

The development of a referral strategy starts with the specification of predictors for a disease. The candidate predictors are usually acquired from previous studies. In most cases too many candidate predictors are available for one referral strategy. The candidate predictors can be reduced by looking at the applicability of the predictors, incorporating an over expensive or unavailable candidate predictor in the referral strategy is not practical. Using the candidate predictors a regression

analysis, including a backward selection method, can be performed to search for the strongest predictors. [61] To ensure the internal validity of the referral strategy a statistical method, calling bootstrapping, can be used. With bootstrapping are samples drawn with replacement from the original sample. By bootstrapping the uncertainty of the model is reduced and its corrected for optimism. [62] The performance of the strategy can be quantified by calibration and discrimination. Calibration is the agreement between the predicted and the observed outcomes and discrimination in the ability of a referral strategy to distinguish axSpA patients from CLBP patients. Discrimination is expressed in the area under the receiver operating characteristic (ROC) curve. Values for the area under the ROC curve range from 0.5 (no discrimination) to 1.0 (perfect discrimination). [63] The last step in the development of a referral strategy is providing a user friendly format of the statistical analyses. This user friendly format can have several identities, for example a score chart, a nomogram or a table.

External validation of the developed referral strategy is extremely important. If a referral strategy predicts the outcomes successfully in the development study this is not sufficient to state that the strategy is applicable in practice, even when internal validation techniques are used. When a referral strategy is applied in new individuals, the performance of this strategy is usually lower than the performance of the strategy in the development study. [64, 65] If the performance of the referral strategy is disappointing in the external validation, the strategy can be updated with the information acquired in the validation study. [64] For example it can be necessary to add an additional predictor to the referral strategy to maintain a sufficient performance. Or the cut point when a patient is referred can be adapted from for example one feature present to two features present. After external validation the generalizability of the referral strategy is increased. Therefore referral strategies should be tested or validated in new individuals before they are implemented in guidelines or applied in practice.

After external validation the impact of a referral strategy on health outcomes, cost-effectiveness, and the behavior of doctors and patients should be evaluated in a new study setting. In an impact study the intended referral strategy should be compared to usual care, to see if there is an improvement. The strongest setting of an impact study will therefore be a randomized trial. At this moment there are no impact studies of any referral strategy for axSpA.

Objective and outline thesis

In summary early recognition and diagnosing of axSpA patients is a 'hot topic' in the field of axSpA. However recent studies about the prevalence of axSpA are lacking and a validated referral strategy for axSpA applicable in primary care practice is needed.

In general terms, the four aims of this thesis are:

- The prevalence of axSpA in a primary care CLBP population.
- The development of a referral strategy for axSpA within a primary care CLBP population.
- Validation of referral strategies for axSpA within a primary care CLBP population.
- The impact of axSpA on work participation in CLBP patients and the impact of a referral strategy for axSpA on CLBP patients.

The CAse Finding Axial SPondyloArthritis studies

To address the aims of this thesis the CAse Finding Axial SPondyloArthritis (CaFaSpA) studies were set up from 2010 to 2012. The CaFaSpA 1 study was a cross-sectional study which took place in 2010 in primary care practices. Practices from greater Rotterdam in the Netherlands were personally informed about the study and invited to participate. In total 19 GP practices participated and represented a source population of approximately 12.477 patients ages 20-45 years. Potential participants with CLBP were selected from the GP database using the International Classification of Primary Care (ICPC) code L03, i.e. nonspecific low back pain excluding radiation. [66] From the source population 1106 (9%) patients were identified who had ever been registered with ICPC code L03 and they were invited to participate by letter on behalf of their GP. Potential participants could respond by reply card, telephone or e-mail. Responding participants were checked for eligibility during a telephone interview by the research assistant by

using the following inclusion criteria; current low back pain existing for >12 weeks, no trauma as cause for the back pain, no contraindication for MRI (i.e. pregnancy, claustrophobia, pacemaker) and good understanding of the Dutch language.

The CaFaSpA 2 was another cross-sectional study to validate the findings of the CaFaSpA 1 study. This study took place in 2011 and 2012 in greater Rotterdam and The Hague. Both studies had the same study design. In total 38 GP practices participated, who represented a source population of about 28.842 patients, ages 18-45 years. From the source population 2597 (9%) patients were invited to participate. The patient recruitment was the same as in the CaFaSpA 1 study. Written informed consent was obtained from all participants at the research center before any assessment was performed. Ethics approval from the St. Elisabeth Hospital in Tilburg, the Netherlands was obtained for both studies.

For both studies participants were seen in a rheumatology setting by a rheumatologist or a trained research nurse. Medical history was obtained and physical examination took place, blood was drawn for inflammatory parameters and HLA-B27 testing. All assessments followed the definitions described in the ASAS handbook. [16] An X-ray and MRI of the SI-joints were obtained from every participant. Images were read by one out of three trained readers and scored according to the ASAS definition (MRI of the SI-joints) [16] and the modified NY criteria (X-ray of the SI-joints). [37] Radiologists were blinded for clinical outcomes, laboratory data and the results of the other imaging method. Patients were identified as axSpA according the ASAS classification criteria for axSpA after evaluation of the rheumatologists and/or trained research nurse. A total of 943 CLBP patients participated in the CaFaSpA 1 and 2 studies, offering a unique opportunity to investigate the aims of this thesis.

Outline

The first part of this thesis focuses on the first aim; the prevalence of axSpA within CLBP population. **Chapter 2** will describe how many axSpA patients can be identified in a young primary care CLBP population. The validation of the prevalence of axSpA patients within another CLBP population is included in **chapter 3.**

The second part of this thesis is about the second aim; the development of the CaFaSpA referral strategy for axSpA in a CLBP population and is represented in **chapter 2.**

The third aim regarding the external validation of referral strategies for axSpA is included in the third part of this thesis, this part starts with the results of the external validation of the CaFaSpA referral strategy in **chapter 3.** Next the performance of the ASAS endorsed recommendations for referral is investigated in our cohort of CLBP patients, the results are described in **chapter 4.** A more extensive external validation of several referral strategies for axSpA is reported in **chapter 5.** This third part ends with the performance of a clinical pathway for axSpA wherein the ASAS recommendation for referral and the ASAS diagnostic algorithm are combined into one clinical pathway for axSpA. We evaluate its performance in **chapter 6.**

The fourth aim and the fourth part of this thesis investigates the impact of axSpA on work outcomes, of which the results are described in **chapter 7.** This thesis is completed by a study protocol in **chapter 8,** describing the design of an impact study which will investigates the clinical effect and cost-effectiveness of the CaFaSpA referral strategy applied in young CLBP patients.

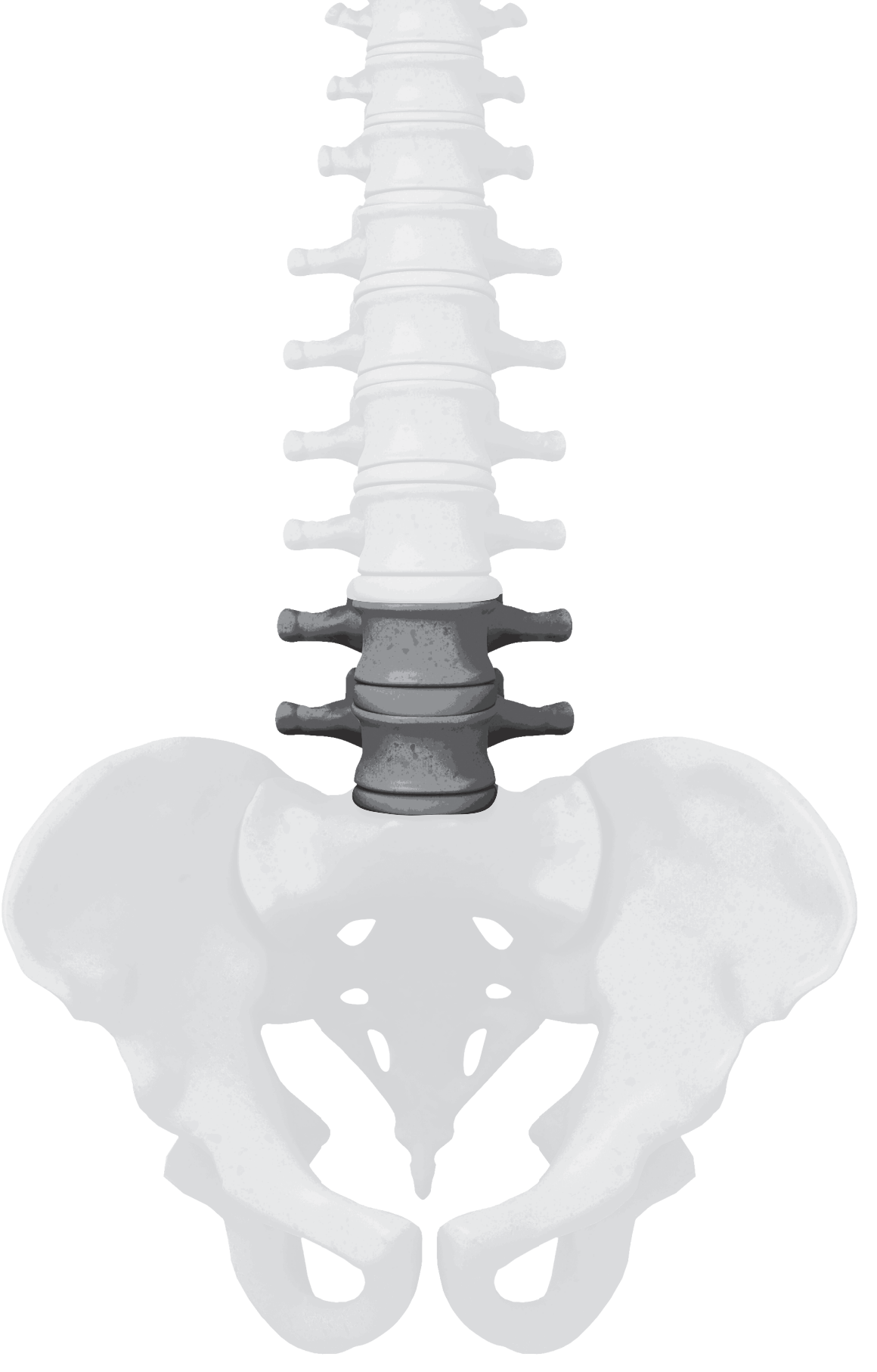
The research presented in this thesis is discussed in **chapter 9,** including the practical implications and suggestions for future research.

References

1. Garg, N., F. van den Bosch, and A. Deodhar, *The concept of spondyloarthritis: where are we now?* Best Pract Res Clin Rheumatol, 2014. **28**(5): p. 663-72.
2. Reveille, J.D., J.P. Witter, and M.H. Weisman, *Prevalence of axial spondylarthritis in the United States: estimates from a cross-sectional survey.* Arthritis Care Res (Hoboken), 2012. **64**(6): p. 905-10.
3. Stolwijk, C., et al., *Epidemiology of spondyloarthritis.* Rheum Dis Clin North Am, 2012. **38**(3): p. 441-76.
4. Urwin, M., et al., *Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation.* Ann Rheum Dis, 1998. **57**(11): p. 649-55.
5. Underwood, M.R. and P. Dawes, *Inflammatory back pain in primary care.* Br J Rheumatol, 1995. **34**(11): p. 1074-7.
6. Geuskens, G.A., et al., *Predictors of sick leave and reduced productivity at work among persons with early inflammatory joint conditions.* Scand J Work Environ Health, 2008. **34**(6): p. 420-9.
7. van Onna, M., et al., *General practitioners' perceptions of their ability to identify and refer patients with suspected axial spondyloarthritis: a qualitative study.* J Rheumatol, 2014. **41**(5): p. 897-901.
8. Benjamin, M. and D. McGonagle, *The enthesis organ concept and its relevance to the spondyloarthropathies.* Adv Exp Med Biol, 2009. **649**: p. 57-70.
9. Cawley, M.I., T.M. Chalmers, and J. Ball, *Destructive lesions of vertebral bodies in ankylosing spondylitis.* Ann Rheum Dis, 1971. **30**(5): p. 539-40.
10. Reveille, J.D., *Genetics of spondyloarthritis--beyond the MHC.* Nat Rev Rheumatol, 2012. **8**(5): p. 296-304.
11. Van Praet, L., et al., *Mucosal inflammation in spondylarthritides: past, present, and future.* Curr Rheumatol Rep, 2011. **13**(5): p. 409-15.
12. Braun, A., et al., *Identifying patients with axial spondyloarthritis in primary care: how useful are items indicative of inflammatory back pain?* Ann Rheum Dis, 2011. **70**(10): p. 1782-7.
13. Feldtkeller, E., et al., *Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis.* Rheumatol Int, 2003. **23**(2): p. 61-6.
14. Rudwaleit, M., et al., *How to diagnose axial spondyloarthritis early.* Ann Rheum Dis, 2004. **63**(5): p. 535-43.
15. http://www.nivel.nl/NZR/fysiotherapie, 2014.
16. Sieper, J., et al., *The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis.* Ann Rheum Dis, 2009. **68 Suppl 2**: p. ii1-44.
17. El Maghraoui, A., *Osteoporosis and ankylosing spondylitis.* Joint Bone Spine, 2004. **71**(4): p. 291-5.
18. Gherghe, A.M., et al., *Cardiovascular and selected comorbidities in early arthritis and early spondyloarthritis, a comparative study: results from the ESPOIR and DESIR cohorts.* RMD Open, 2015. **1**(1): p. e000128.
19. Gensler, L.S., *Axial spondyloarthritis: the heart of the matter.* Clin Rheumatol, 2015. **34**(6): p. 995-8.
20. Essers, I., et al., *Ankylosing spondylitis and risk of ischaemic heart disease: a population-based cohort study.* Ann Rheum Dis, 2014.
21. Dougados, M., et al., *Clinical presentation of patients suffering from recent onset chronic inflammatory back pain suggestive of spondyloarthritis: The DESIR cohort.* Joint Bone Spine, 2015. **82**(5): p. 345-51.
22. Boonen, A., et al., *The burden of non-radiographic axial spondyloarthritis.* Semin Arthritis Rheum, 2014.
23. Boonen, A. and S.M. van der Linden, *The burden of ankylosing spondylitis.* J Rheumatol Suppl, 2006. **78**: p. 4-11.
24. Baraliakos, X. and J. Braun, *Non-radiographic axial spondyloarthritis and ankylosing spondylitis: what are the similarities and differences?* RMD Open, 2015. **1**(Suppl 1): p. e000053.
25. Boonen, A., et al., *Work status and its determinants among patients with ankylosing spondylitis. A systematic literature review.* J Rheumatol, 2001. **28**(5): p. 1056-62.
26. Braun, J., et al., *2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis.* Ann Rheum Dis, 2011. **70**(6): p. 896-904.
27. Callhoff, J., et al., *Efficacy of TNFalpha blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis.* Ann Rheum Dis, 2014.

28. Landewe, R., et al., *Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study.* Ann Rheum Dis, 2014. **73**(1): p. 39-47.
29. van der Heijde, D., et al., *ASAS40 and ASDAS clinical responses in the ABILITY-1 clinical trial translate to meaningful improvements in physical function, health-related quality of life and work productivity in patients with non-radiographic axial spondyloarthritis.* Rheumatology (Oxford), 2015.
30. Weber, U., et al., *Candidate lesion-based criteria for defining a positive sacroiliac joint MRI in two cohorts of patients with axial spondyloarthritis.* Ann Rheum Dis, 2015. **74**(11): p. 1976-82.
31. Mattey, D.L., et al., *Association of cytokine and matrix metalloproteinase profiles with disease activity and function in ankylosing spondylitis.* Arthritis Res Ther, 2012. **14**(3): p. R127.
32. Maksymowych, W.P., et al., *Serum matrix metalloproteinase 3 is an independent predictor of structural damage progression in patients with ankylosing spondylitis.* Arthritis Rheum, 2007. **56**(6): p. 1846-53.
33. Sieper, J., et al., *Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1).* Ann Rheum Dis, 2013. **72**(6): p. 815-22.
34. Sampaio-Barros, P.D., et al., *Undifferentiated spondyloarthropathies: a 2-year follow-up study.* Clin Rheumatol, 2001. **20**(3): p. 201-6.
35. Poddubnyy, D., et al., *Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis.* Ann Rheum Dis, 2011. **70**(8): p. 1369-74.
36. Sampaio-Barros, P.D., et al., *Undifferentiated spondyloarthritis: a longterm followup.* J Rheumatol, 2010. **37**(6): p. 1195-9.
37. van der Linden, S., H.A. Valkenburg, and A. Cats, *Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria.* Arthritis Rheum, 1984. **27**(4): p. 361-8.
38. Rudwaleit, M., M.A. Khan, and J. Sieper, *The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria?* Arthritis Rheum, 2005. **52**(4): p. 1000-8.
39. Mau, W., et al., *Outcome of possible ankylosing spondylitis in a 10 years' follow-up study.* Clin Rheumatol, 1987. **6 Suppl 2**: p. 60-6.
40. Oostveen, 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**(9): p. 1953-8.
41. Rudwaleit, M., 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**(6): p. 777-83.
42. Murphy, S.E., et al., *Comparison of a Stratified Group Intervention (STarT Back) with Usual Group Care in Patients with Low Back Pain: A Non-randomised Controlled Trial.* Spine (Phila Pa 1976), 2015.
43. da Luz, M.A., Jr., et al., *Effectiveness of mat Pilates or equipment-based Pilates exercises in patients with chronic nonspecific low back pain: a randomized controlled trial.* Phys Ther, 2014. **94**(5): p. 623-31.
44. Pedersen, S.J. and W.P. Maksymowych, *Recent Advances in Imaging of the Axial Skeleton in Spondyloarthritis for Diagnosis, Assessment of Treatment Effect, and Prognostication.* Curr Rheumatol Rep, 2015. **17**(9): p. 60.
45. van den Berg, R., 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, 2012.
46. Jois, R.N., A.J. Macgregor, and K. Gaffney, *Recognition of inflammatory back pain and ankylosing spondylitis in primary care.* Rheumatology (Oxford), 2008. **47**(9): p. 1364-6.
47. Robinson, P.C., et al., *Axial spondyloarthritis: a new disease entity, not necessarily early ankylosing spondylitis.* Ann Rheum Dis, 2013. **72**(2): p. 162-4.
48. Picavet, H.S. and J.S. Schouten, *Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study.* Pain, 2003. **102**(1-2): p. 167-78.
49. Koes, B.W., et al., *An updated overview of clinical guidelines for the management of non-specific low back pain in primary care.* Eur Spine J, 2010. **19**(12): p. 2075-94.
50. Akbari, A., et al., *Interventions to improve outpatient referrals from primary care to secondary care.* Cochrane Database Syst Rev, 2008(4): p. CD005471.
51. Akkoc, N. and M.A. Khan, *Looking into the new ASAS classification criteria for axial spondyloarthritis through the other side of the glass.* Curr Rheumatol Rep, 2015. **17**(6): p. 515.

52. Poddubnyy, D., et al., *The frequency of non-radiographic axial spondyloarthritis in relation to symptom duration in patients referred because of chronic back pain: results from the Berlin early spondyloarthritis clinic.* Ann Rheum Dis, 2012. **71**(12): p. 1998-2001.
53. van den Berg, R., 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.
54. Heuft-Dorenbosch, L., et al., *Performance of various criteria sets in patients with inflammatory back pain of short duration; the Maastricht early spondyloarthritis clinic.* Ann Rheum Dis, 2007. **66**(1): p. 92-8.
55. Brandt, H.C., et al., *Performance of referral recommendations in patients with chronic back pain and suspected axial spondyloarthritis.* Ann Rheum Dis, 2007. **66**(11): p. 1479-84.
56. Poddubnyy, D., et al., *Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care.* J Rheumatol, 2011. **38**(11): p. 2452-60.
57. Sieper, J., et al., *Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study.* Ann Rheum Dis, 2012.
58. Braun, A., et al., *Optimizing the identification of patients with axial spondyloarthritis in primary care--the case for a two-step strategy combining the most relevant clinical items with HLA B27.* Rheumatology (Oxford), 2013. **52**(8): p. 1418-24.
59. Poddubnyy, D., 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**(8): p. 1483-7.
60. Moons, K.G., et al., *Risk prediction models: II. External validation, model updating, and impact assessment.* Heart, 2012. **98**(9): p. 691-8.
61. Van Houwelingen, J.C. and S. Le Cessie, *Predictive value of statistical models.* Stat Med, 1990. **9**(11): p. 1303-25.
62. Steyerberg, E.W., et al., *Internal validation of predictive models: efficiency of some procedures for logistic regression analysis.* J Clin Epidemiol, 2001. **54**(8): p. 774-81.
63. Hanley, J.A. and B.J. McNeil, *The meaning and use of the area under a receiver operating characteristic (ROC) curve.* Radiology, 1982. **143**(1): p. 29-36.
64. Toll, D.B., et al., *Validation, updating and impact of clinical prediction rules: a review.* J Clin Epidemiol, 2008. **61**(11): p. 1085-94.
65. Bleeker, S.E., et al., *External validation is necessary in prediction research:: A clinical example.* Journal of Clinical Epidemiology, 2003. **56**(9): p. 826-832.
66. Gebel, R.S., *Semi-automatic coding with ICPC: the Thesaurus, the algorithm and the Dutch subtitles.* Stud Health Technol Inform, 1997. **43 Pt A**: p. 421-5.



Chapter 2

Identifying axial Spondyloarthritis in Dutch primary care patients, ages 20-45 years, with chronic low back pain

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Abstract

Objective

To identify axial spondyloarthritis (axSpA) in Dutch primary care patients with chronic low back pain (CLBP), and to design a simple referral model for general practitioners (GP) that would identify patients at risk for axSpA.

Methods

Patients (ages 20-45 years) with CLBP were identified from GP records. Assessments included inflammatory back pain questionnaires, medical interviews, physical examinations, HLA-B27, C-reactive protein level, conventional radiography and magnetic resonance imaging. The outcome measure was axSpA defined by the Assessment of SpondyloArthritis international Society (ASAS) criteria. Multivariable regression analysis with bootstrapping was used to develop the referral model.

Results

A total of 364 patients (mean ±SD age 36.3 ±6.8 years) was recruited with a median symptom duration of 9.0 years. Eighty-six patients (24%) fulfilled the ASAS criteria for axSpA. Of all potential determinants, the ASAS inflammatory back pain questionnaire, good response to nonsteroidal anti-inflammatory drugs, family history of SpA and symptom duration were identified as most relevant for diagnosing axSpA by multivariable regression analysis related to axSpA. The shrunken regression coefficients were respectively, 1.04, 0.83, 0.73 and 0.23. The combination of these 4 items proved an useful area under the receiver operating curve of 0.75 (SE 0.03). In a simplified score model, at the suggested cut off value of 1.5, the sensitivity was 83% and specificity was 59%.

Conclusion

This study shows that 1 out of 4 primary care patients with CLBP were classified as having axSpA. A preselection in primary care based on a combination of clinical items may be useful to facilitate the identification of patients at risk of axSpA.

Introduction

Low back pain (LBP) is one of the most frequent musculoskeletal disorders affecting approximately two-thirds of adults at some point in their lives. [1, 2] The underlying cause of LBP is unknown in 85% of the patients, but the majority of acute LBP is self-limiting. [3] However, in 10-28 % of the patients the pain persists for more than 12 weeks and is classified as chronic low back pain (CLBP). [4] One of the causes of CLBP is axial Spondyloarthritis (axSpA), an inflammatory joint disease. AxSpA can be easily missed in primary care since there are no specific symptoms or referral tools by which it is discriminated from all LBP syndromes by general practioners (GPs). [5]

The Assessment of SpondyloArthritis international Society (ASAS) classification criteria made a step forward by providing new classification criteria for axSpA that will improve early diagnosis. [6] Early diagnosis may provide earlier effective treatment, leading to a reduction in disease activity and improving daily functioning including work. [7] Ideally, diagnosing axSpA early by rheumatologist needs early recognition in primary care.

However, there is limited knowledge on the prevalence of axSpA in primary care. Previous reports suggest that prevalence of axSpA in the general population will be approximately 1%, similar to that of rheumatoid arthritis. [8, 9] The prevalence of axSpA in a CLBP population is unknown, but might exceed the reported prevalence of 5-8% for Ankylosing Spondylitis (AS). [10, 11] AS is a subgroup of axSpA with definite radiographic sacroiliitis [12] and classified by the modified New York criteria. [13]

Therefore, the purpose of this study was to determine the prevalence of axSpA in in primary care patients ages 20-45 years with CLBP. The second objective was to develop a simple referral tool that might assist GPs in identifying patients at risk for axSpA, who should be referred to a rheumatologist.

Patients and Methods

Recruitment

The study recruitment started in January 2010 and lasted to July 2010. Primary care GPs from greater Rotterdam in the Netherlands were personally informed about the study and invited to participate. In total 19 GPs participated and represented a source population of approximately 12.477 patients ages 20-45 years. Potential participants with LBP were selected from the GP databases using the International Classification of Primary Care (ICPC) code L03, i.e. nonspecific LBP.[14] The ICPC is the standard for coding and classification of signs and symptoms in general practice. The Dutch ICPC is managed and maintained by the Netherlands Society of General Medical Practitioners (NHG). At present, most general practice information systems use the ICPC codes.
From all 12.477 primary care records, 1106 patients (9%) were identified who had ever been registered by the ICPC code L03 and were invited to participate by a letter on behalf of their GP. Potential participants could respond by reply card, fax, telephone or e-mail. Responding participants were checked for eligibility during a telephone interview by the research assistant by using the following inclusion criteria: current low back pain existing for >12 weeks, no trauma and no contraindications for magnetic resonance imaging (MRI; i.e. pregnancy, claustrophobia, pacemaker). Written informed consent was obtained at the research centre before any assessment was performed. Ethics approval from the Dutch Medical Ethical Committee was obtained.

Data collection

Questionnaires
Participants were asked to complete the Calin [15], Berlin [16], and ASAS [17] questionnaires on inflammatory back pain (IBP) in the waiting room, before any clinical and/or radiological evaluation. These questionnaires comprises 4 (Berlin) or 5 (Calin, ASAS) questions related to back pain. A positive Berlin questionnaire is achieved when at least 2 of 4 questions are answered positively. The ASAS and Calin questionnaires becomes positive when 4 of 5 questions are answered positively. The outcome of all IBP questionnaires are reported in a binary value, i.e. positive or negative.

Clinical evaluation

An experienced rheumatologist (AW or HH) completed a clinical history containing all potential features of axSpA, namely IBP, arthritis, family history, psoriasis, inflammatory bowel disease, dactylitis, enthesitis, uveitis anterior and a good response to nonsteroidal anti-inflammatory drugs (NSAIDs). Visual analogue scales (VAS; 0-10) of spinal pain (0= no pain, 10= extreme pain), general health (0= worst, 10= best), and fatigue (0= no fatigue, 10= extreme fatigue) over the past 7 days were completed. The rheumatologist measured chest expansion, modified Schober test, tragus-to-wall distance, lateral spinal flexion, cervical rotation and intermalleolar distance as described in the ASAS handbook. [17] Furthermore, a 44-swollen joint count [18] and skin/nail examination for psoriasis were performed.

Blood sampling

Blood was drawn for the Erythrocyte Sedimentation Rate (ESR, normal range 0-15 mm Hg/min), C-reactive protein (CPR) level (normal range 1-10 mg/l) and HLA-B27 typing.

Image evaluation

Sacroiliac joints (SIJ) were scored according to the modified New York criteria (from 0 = normal, to 4= complete fusion), using conventional pelvic radiographs in the anteroposterior view. [13] A score of 0, 1 or 2 unilateral was considered normal, while bilateral grade 2 or unilateral grade 3 or 4 was classified as positive.

The MRI of the SIJ was obtained by using a 1.5T scanner (Siemens Essenza) in semicoronal section orientation along the long axis of the sacral bone with 3 mm slices. The protocol comprised T1-weigthed turbo spin-echo sequence, T2-weigthed gradient-echo sequence and a STIR (fat suppression) sequence. A definitive diagnosis of sacroiliitis on MRI was made according to the ASAS criteria: presence of a minimum amount of bone marrow edema (1 lesion in ≥2 adjacent slices or >1 lesion in at least 1 slice). [19] Images were read by a trained radiologist blinded to the patient's identity and clinical and laboratory data. If one of the radiologists had doubts about the score, the 2 observers discussed the scan and came to a consensus.

Case definition

Patients were classified as having axSpA according to the ASAS criteria. [6] Classification can be accomplished by the imaging arm (sacroiliitis on imaging (MRI or radiography) plus ≥1 SpA feature), or the clinical arm (no sacroiliits on imaging but positive HLA-B27 plus ≥2 SpA features). The SpA features are IBP, arthritis, (heel) enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease/colitis, good response to NSAIDs, family history for SpA, HLA-B27 positive or elevated CRP level. Patients were classified as having AS according to the modified New York criteria, meaning sacroiliitis on radiographs plus at least 1 clinical feature, such as stiffness and LBP or limitation of motion of the lumbar spine. [20] Recently a distinction between radiographic and non-radiographic axSpA (nr-axSpA) is made. The term non-radiographic axSpA has been introduced to identify patients with axSpA before detection of structural changes in the SIJ. [12]

Statistical analysis

Descriptive statistics provided insight in the prevalence of axSpA, symptom duration, pain severity and other clinical features. In the development of the referral model the first step is reducing the numbers of candidate predictors. Candidate predictors were selected that are quick and easy to assess by GPs, without additional costs. If predictors addressed the same domain (e.g. Calin, Berlin and ASAS questionnaire for IBP) the strongest predictor tested in univariate logistic regression was kept.

As result 8 candidate predictors were defined, age, sex, ASAS IBP questionnaire, positive family history, good response to NSAIDs, modified Schober test, symptom duration and a predictor that included ≥1 easy to determine ASAS feature, including psoriasis, enthesitis, dactylitis, arthritis, psoriasis, inflammatory bowel disease and uveitis. This predictor was dichotomized and positive if at least 1 feature was present. Symptom duration showed a nonlinear association with the risk of axSpA; when fitted as a restricted cubic spline with 3 knots (2 df), a log transformation could well approximate the flexible spline function. We fitted a multivariable logistic regression model including the 8 candidate predictors. Afterward we used a backward stepwise procedure to select the strongest predictors (p-value 0.157). [21] The p-value of 0.157 is equal to using the Akaike Information Criterium for

predictors with 1 regression coefficient and is recommended to use in stepwise selection of predictors. [22]

We used bootstrapping to assess the internal validity; 200 bootstrap samples were drawn from the development set. Together with the internal validity, a shrinkage factor to correct for overfitting was conducted by bootstrapping. The regression coefficients of the predictors in the final model were multiplied with the shrinkage factor, to prevent too extreme predictors. [23, 24]

The performance of the final model was quantified using discrimination and calibration measures. Discrimination is the ability to discriminate axSpA from CLBP patients without axSpA and is usually quantified by the c statistics, a measure for concordance. In binary outcomes, as in our study, the c statistics is identical to the area under the receiver operating characteristics (ROC) curve. Reasonable values for the area under the ROC curve range from 0.5 (no discrimination) to 1.0 (perfect discrimination). [25] Calibration is the agreement between the predicted probabilities and the observed frequencies and was assessed graphically.

To provide a user friendly format of the prediction model, variables with similar regression coefficients were given equal points in a simple scoring system. Based on estimates of sensitivity and specificity, we determined a sensible cutoff value above which patients could be referred to the rheumatologist. The analyses were performed using Stata version 12.0 software (Stata Corporation TX, USA) and R (version 2.15.2; The R Foundation for Statistical Computing).

Results

Of the 1106 invited patients with LBP, 534 patients (48%) expressed initial interest in participating. Of these, 364 participants fulfilled the inclusion criteria and were further evaluated (Figure 1). The main reason for exclusion (n= 56, 67%) was the absence of *chronic* low back pain at the telephonic interview.

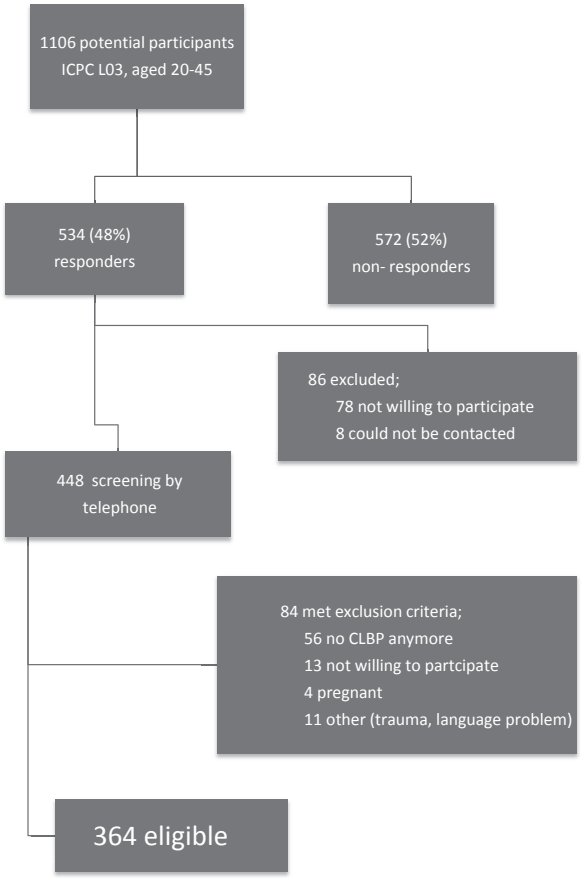


Figure 1 - Recruitment flowchart

Characteristics of the study population

More women (57%) participated and most participants were white (70%) (Table 1). The mean ± SD age was 36.3 ±6.8 years and the mean duration of LBP of 10 year (median 9.0 yrs, range 0.5-36 years). Of all participants, 289 (80%) ever used NSAIDs for their LBP. The median VAS score was 5.0 for each of the 3 measures: pain, fatigue and general health.

Table 1. Demographic and clinical characteristics of the study participants (n=364)

	Cases n=86	Non-cases n=278
Demographics		
Age (yrs), *mean (sd)*	36.6 (6.6)	36.2 (6.9)
Sex, male, *no (%)*	33 (38%)	122 (44%)
Native Dutch, *no (%)*	63 (73%)	192 (69%)
Medical history		
BMI, *mean (sd)*	28.1 (5.1)	27.1 (5.1)
Symptom duration (yrs), *mean (median)*	11.4 (10)	9.5 (7.5)
VAS pain, *mean (sd)*	4.7 (2.6)	4.9 (2.7)
genaral health		
Berlin questionnaire (positive) , *no (%)*[1]	67 (78%)	183 (64%)
Calin questionnaire (positive), *no (%)*[2]	75 (87%)	200 (72%)
ASAS questionnaire (positive), *no (%)*[3]	52 (61%)	85 (31%)
Good reaction to NSAID, *no (%)*	52 (60%)	105 (38%)
Family history positive, no (%)	17 (20%)	23 (8%)
IBD, *no (%)*	3 (3%)	3 (1%)
Uveitis, *no (%)*	3 (3%)	4 (1%)
Enthesitis, *no (%)*	8 (9%)	43 (15%)
Arthritis, *no (%)*	10 (12%)	18 (6%)
Dactylitis, *no (%)*	4 (5%)	9 (3%)
Psoriasis, *no (%)*	5 (6%)	13 (5%)
Modified Schober (Δ<5 cm), *no (%)*	38 (44%)	123 (44%)
Chest expansion (<2.5 cm), *no (%)*	9 (10%)	20 (7%)
Lateral flexion (<10 cm), *no (%)*	1 (1%)	11 (4%)
Cervical rotation (<70°), *no (%)*	6 (7%)	5 (2%)
Tragus to wall distance (>15 cm), *no (%)*	1 (1%)	14 (5%)
Intermalleolair distance (<100cm), *no (%)*	19 (22%)	60 (22%)
Blood		
CRP >10 mg/l, *no (%)*	9 (10%)	12 (4%)
HLA-B27 positive, *no (%)*	17 (20%)	3 (1%)

[1] A positive Berlin questionnaire is achieved when at least two out of four questions are present
[2] A positive Calin questionnaire is achieved when at least four out of five questions are present
[3] A positive ASAS questionnaire is achieved when at least four out of five questions are present
Abbreviations: BMI, body-mass index; VAS, visual analogue scale; NSAIDs, non-steroidal anti-inflammatory drugs; IBD, inflammatory bowel disease; CRP, C-reactive protein.

Prevalence of axial spondyloarthritis

In this cross-sectional study, the prevalence of axSpA was 24% (n=86; 95% confidence interval 19.4%-28.3%) (Table 2). The difference between women and men was not statistically significant (25% versus 21%). Among all cases, 30 (35%) subjects were classified as having radiographic axial spondyloarthritis, and 56 (65%) as having nr-axSpA. Of all 41 patients having at least bilateral grade 2 or

unilateral or bilateral grade 3 sacroiliits, only 24 fulfilled the modified New York criteria (7%), since 17 of them did not have a clinical feature as described in those criteria.

Table 2. Prevalence of axial spondyloarthritis

	Total N=364	Man N=155	Woman N=209
Axial SpA (ASAS criteria)	86 (24%)	33 (21%)	53 (25%)
MRI + ≥ 1 feature	57 (16%)	24 (16%)	33 (16%)
X-SIJ + ≥ 1 feature	30 (8%)	7 (5%)	23 (11%)
HLA-B27 + ≥ 2 features	10 (3%)	6 (4%)	4 (2%)
Ankylosing Spondylitis	24 (7%)	9 (6%)	15 (7%)

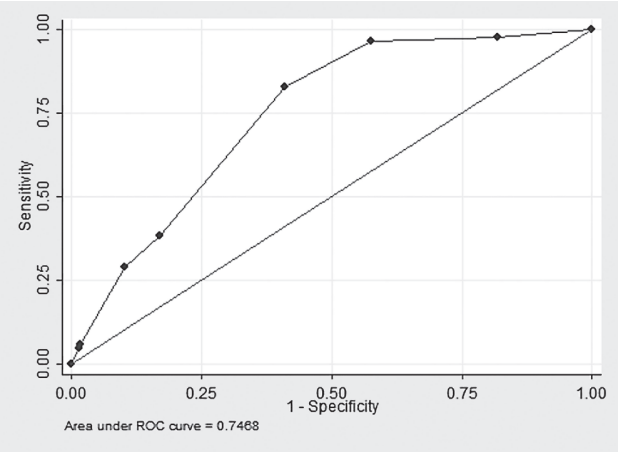
Referral model

Table 3 shows the logistic regression analysis of the 8 candidate predictors, and both odds ratio and the regression coefficients are reported. After the backward selection ASAS IBP questionnaire, NSAID response, family history of SpA and symptom duration appear to be the strongest predictors for axSpA. The shrinkage factor derived with bootstrapping was 0.84. Discriminative performance was good with a c statistics of 0.75 (SE 0.03) after correction for optimism (see also ROC curve in Figure 2A). Calibration was reasonable as shown in the calibration plot (Figure 2B).

The referral model is presented as a simple scoring system (Table 3). The predictors NSAIDs response, family history of SpA and ASAS IBP questionnaire were all assigned 1 point (based on the regression coefficients). Duration of symptoms (CLBP) >5 years was assigned 0.5 point. A cutoff value of 1.5 points in the scoring system resulted in a sensitivity of 0.83 and a specificity of 0.59. A more stringent cutoff value of 2 points corresponded to a sensitivity of 0.38, whit specificity of 0.83. A more liberal cutoff value of 1 point corresponded to a sensitivity 0.97, with a low specificity of 0.42. Regarding the screening purpose a cut off value of 1.5 may be preferred. This implies that for patients with a score of 1.5 or higher (e.g. a symptom duration longer than 5 years and a positive family history for SpA or a positive ASAS IBP questionnaire or a good reaction to NSAIDs), referral to a rheumatologist would be justified.

Figure 2 – **A**; Receiver operating characteristics curve (area under the curve 0.75, sensitivity 0.83 and specificity of 0.59) of the screening model, including nonsteroidal anti-inflammatory drugs (NSAIDs) use, positive family history of spondyloarthritis (SpA), Assessment of SpondyloArthritis international Society (ASAS) inflammatory back pain (IBP) questionnaire and symptom duration. * = cutoff value of 1.5.

B; Calibration plot of the multivariate screenings model including positive response to NSAID use, family history of SpA, the ASAS IBP questionnaire and symptom duration.



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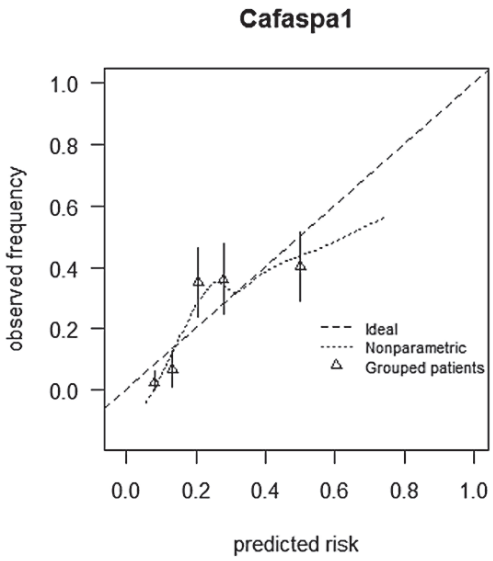


B

Table 3. Results of the initial multivariate logistic regression model and the results of the multivariate final model after backwards selection, bootstrapping and corrected for overoptimism.

	Multivariable model			Multivariable model after bootstrap	Score[&]
Demographics	*Odds ratio (95 %CI)*	*Regression coefficient*	*P-value*	*Regression coefficient**	
Age	0.98 (0.94-1.02)	-0.02	0.38	-	
Sex	1.17 (0.68-2.01)	0.16	0.58	-	
Medical history					
ASAS IBP questionnaire	3.68 (2.16-6.27)	1.30	<0.0001	1.04	1
Positive family history	2.76 (1.28-5.97)	1.01	0.01	0.83	1
Good response to NSAIDs	2.46 (1.44-4.21)	0.90	0.001	0.73	1
Log transformation of symptom duration	1.41 (0.98-2.04)	0.35	0.07	0.23	0.5
At least one of: psoriasis, enthesitis, dactylitis, arthritis, uveitis, IBD	0.88 (0.47-1.62)	-0.13	0.67	-	
Physical examination					
Modified Schober	0.75 (0.44-1.29)	0.29	0.30	-	
AUC (se)		0.76 (0.03)		0.75(0.03)§	

*Regression coefficients were updated for the shrinkage coefficient of 0.84
[&]The score was calculated by rounding the regression coefficients. The log transformation of symptom duration was transformed to a dichotomized value, symptom duration shorter of longer than 5 years. A symptom duration longer than 5 years gives a score of 0.5.
§AUC after correction for optimism

Discussion

Our results imply that CLBP in young patients is frequently caused by undiagnosed axSpA. Overall, 24% of primary care patients with CLBP, between ages 20 and 45 years, were classified for axSpA. Strikingly, none of them had ever been referred to a rheumatologist. In addition, 22% of these axSpA patients fulfilled the classification criteria for AS, the prototype subgroup of axSpA that currently has very effective treatment. [26] This study provides the first data on prevalence of axSpA in primary care practice. Additionally, within this study we set the initial steps to develop a simple referral model that might assist GPs to identify patients with CLBP who should be referred to specialized care for diagnosing and subsequent treatment of axSpA.

The high percentage of axSpA we found in primary care may raise questions as to whether our estimate is correct or flawed by selection bias. Patients were invited based on LBP ever (ICPC L03), 48% (n=534) of our target population responded to our invitation of which 364 (68%) were classified as CLBP. Given that none of the nonresponders would be classified as having axSpA, and 68% of them had CLBP, the prevalence would decrease to 11%, which is still substantial. However it is more likely that the nonresponders comprised patients who had no current LBP, as we invited patients with back pain ever and not with current back pain. We even might have missed cases because we only used L03, while patients with more widespread back pain, categorised with ICPC code L02 and/or L84 could have axSpA. Another source of selection bias could be the use of prespecified criteria that select patients toward axSpA. This was not the case since we did not use specific inclusion criteria known to be related to axSpA. As well, the selection of GPs does not create a selection bias, given that there were no particular inclusion criteria for participating GPs. One source of selection bias we could not fully exclude is selection toward more severe patients. However in our study the average VAS score for pain, fatigue and general health was lower than that of other studies in patients with CLBP. [27]

An issue that could be raised when discussing the validity of the different features of the ASAS criteria in the primary care is the potential lack of specificity of the MRI in classifying patients for axSpA. [28] This might have led to an overestimation of the prevalence in our study. This discussion was raised because subchondral bone marrow edema may be induced by different causes, including mechanical stress. However, recent published data on healthy subjects indicate that MRI has much greater diagnostic utility than has been documented previously. [29, 30] Moreover in our study only 65% of the patients were classified as having axSpA assed by MRI abnormalities, the other 35% fulfilled the criteria either via radiographic damage or the presence of HLA-B27. This underscores the fact that the ASAS workgroup proposed a classification of axSpA not based on MRI findings alone, but incorporated other clinical relevant information. [31]

Comparison to other studies on the prevalence of axSpA is difficult as we are the first ones to estimate the prevalence in primary care. However, our findings are in line with axSpA in general population ages 20-45 years [9, 32] and lower than the 35% in patients presenting to a rheumatologist, reflecting the different pretest probability of axSpA. [33, 34] A recent subanalysis that reflected the primary care setting among orthopaedic patients in Germany, confirmed our results with a

prevalence of axSpA of almost 20%. [35] For AS there is more evidence, the 7% of AS patients is in line with the 5-8% published in studies performed in primary care patients with CLBP. [5, 10]

A number of study observations are of noteworthy. First, the prevalence of HLA-B27 (6%) was lower than the expected 8% in a Dutch population. [36, 37] An explanation might be the multicultural composition of our cohort, since 30% of the participants had a nonwhite background; they originated from countries were the prevalence of HLA-B27 is known to be lower. [38, 39]

Second, most patients presented with longstanding symptoms of approximately 10 years. Only 26 CLBP patients presented with symptom duration less than 1 year. Of this 26 patients, 6 (23%) fulfilled the ASAS classification criteria for axSpA. Even for early diagnosis this would be fairly late. Since our final objective is diagnosis as early as possible, it would be very interesting to look at the performance of the referral model in the very early CLBP patient, but the number of cases are too small to make valid assumptions concerning the performance.

We aimed to investigate which patients with CLBP in primary care fulfilled axSpA criteria, and we aimed to develop a simple scoring system for GPs to refer patients at high risk for axSpA to a rheumatologist. This referral model should contain noninvasive, nonexpensive variables that are easy for GPs to perform. The strongest predictors were good response to NSAIDs, positive family history of SpA, positive ASAS IBP questionnaire and symptom duration, which is in line with observations from earlier studies. [34] The interesting difference in our study is that all data were obtained in a non-prespecified population. The cutoff value of 1.5 provides a sensitivity of 83% and a specificity of 59 %, which is powerful enough to use as a referral model, although it needs external validation in another cohort as data-driven prediction rules tend to fit the development cohort best.

For interpreting the outcome of referral models, there is always the question of what is more desirable, a high sensitivity or specificity? Choosing the highest sensitivity has the advantage to identify as many axSpA patients as possible, but the drawback is accepting a lower specificity leading to more irrelevant, and in this case expensive, diagnostic procedures. For our referral or screening model, we aimed to strike the highest sensitivity of 83%, relative to an acceptable specificity (59%) to identify primary care patients at risk of axSpA. These results have comparable accuracy; for example, screening models used nationwide for breast and cervical cancer. [40, 41] Moreover the choice for a relative high sensitivity is further supported by the fact that until now, patients with CLBP will not be referred

to a rheumatologist since this is not incorporated yet into international guidelines. [5] This was confirmed in our study; only 1 patient, of the 364 patients (0.3%), was referred to a rheumatologist.

There are some limitations to this study. First our study results are limited to the SIJ as we did not perform imaging of the lumbar and thoracic spine. This may have prevented us identifying axSpA patients who presented with spine involvement only. However, the ASAS study that was performed to validate the new axSpA criteria showed only a few patients with activity on spinal MRI and normal appearance on SIJ. [31] Another weakness of our study is the fact that all radiographs and MRIs were not scored by 2 readers as recommended for studies by the Outcome Measures in Rheumatology trials. However, we aimed in our study to get an insight in the frequency of axSpA by using the ASAS criteria in daily practice. Therefore, for scoring MRIs we used, as will be the case in daily practice, experienced skeletal radiologist. Moreover, other studies suggested that a high level of radiologic training is not required to extract pathoanatomic information from MRIs. [42] Overall axSpA is a frequent abnormality in young patients with CLBP. Until now international LBP guidelines provide no information on the risk of IBP, nor do they recommend GPs to refer patients to a rheumatologist. [43] This seems to be a missed opportunity for patients that have signs and symptoms that indicated the presence of axSpA, especially since rheumatologists have the skills to diagnose and treat axSpA based on disease activity scores that are not used in primary care. Moreover if NSAIDs, a first-choice treatment, do not reduce disease activity, the next step would be anti-tumor necrosis factor α treatment. Finally, recent studies in axSpA showed that early diagnosis and treatment will enhance patient outcome. [44] Although our results need to be confirmed in new cohorts, GPs may bear in mind the diagnosis of axSpA in CLBP patients younger than 45 years.

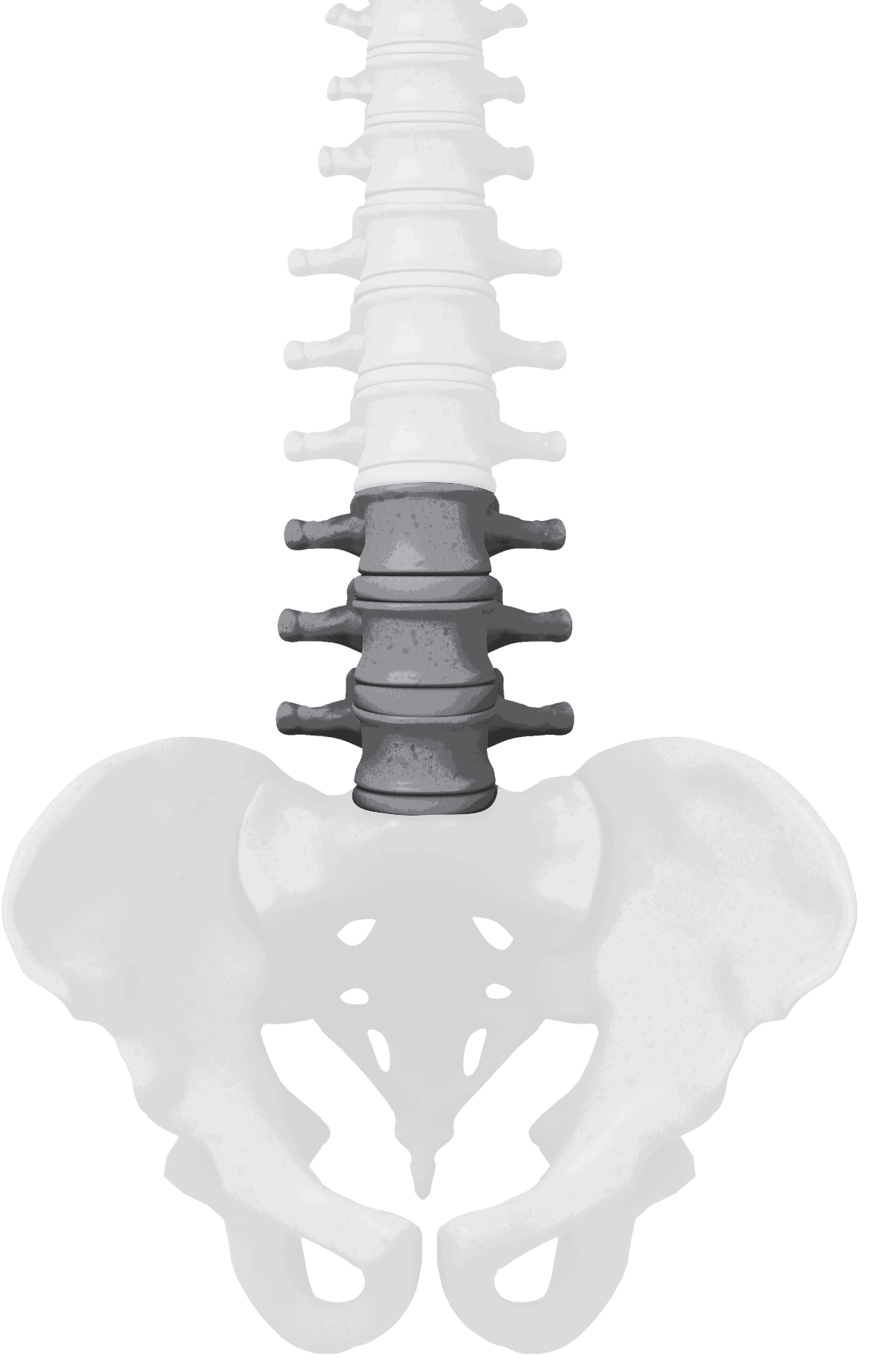
Conclusion

In conclusion, in primary care a high prevalence of undiagnosed axSpA (24%) was observed in patients between ages 20-45 years with CLBP. GPs might be aided by using a simple referral tool (i.e. good response to NSAIDs, a positive family history of SpA, symptom duration and self-reported IBP by the ASAS questionnaire) for referring patients with CLBP prone to have axSpA, to a rheumatologist. Future studies are necessary to validate both the prevalence of axSpA in primary care and the referral tool in another population.

References

1. Hoy, D., et al., *A systematic review of the global prevalence of low back pain.* Arthritis Rheum, 2012. **64**(6): p. 2028-37.
2. Walker, B.F., *The prevalence of low back pain: a systematic review of the literature from 1966 to 1998.* J Spinal Disord, 2000. **13**(3): p. 205-17.
3. Deyo, R.A., *Measuring the functional status of patients with low back pain.* Arch Phys Med Rehabil, 1988. **69**(12): p. 1044-53.
4. Freburger, J.K., et al., *The rising prevalence of chronic low back pain.* Arch Intern Med, 2009. **169**(3): p. 251-8.
5. Jois, R.N., A.J. Macgregor, and K. Gaffney, *Recognition of inflammatory back pain and ankylosing spondylitis in primary care.* Rheumatology (Oxford), 2008. **47**(9): p. 1364-6.
6. Rudwaleit, M., 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**(6): p. 777-83.
7. Sieper, J., et al., *Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1.* Ann Rheum Dis, 2013.
8. Akkoc, N., *Are spondyloarthropathies as common as rheumatoid arthritis worldwide? A review.* Current rheumatology reports, 2008. **10**(5): p. 371-8.
9. Reveille, J.D., J.P. Witter, and M.H. Weisman, *Prevalence of axial spondylarthritis in the United States: estimates from a cross-sectional survey.* Arthritis Care Res (Hoboken), 2012. **64**(6): p. 905-10.
10. Underwood, M.R. and P. Dawes, *Inflammatory back pain in primary care.* Br J Rheumatol, 1995. **34**(11): p. 1074-7.
11. O'Shea, F.D., et al., *Inflammatory and degenerative sacroiliac joint disease in a primary back pain cohort.* Arthritis care & research, 2010. **62**(4): p. 447-54.
12. Sieper, J. and D. van der Heijde, *Review: Nonradiographic axial spondyloarthritis: New definition of an old disease?* Arthritis Rheum, 2013. **65**(3): p. 543-51.
13. Goie The, H.S., et al., *Evaluation of diagnostic criteria for ankylosing spondylitis: a comparison of the Rome, New York and modified New York criteria in patients with a positive clinical history screening test for ankylosing spondylitis.* Br J Rheumatol, 1985. **24**(3): p. 242-9.
14. Gebel, R.S., *Semi-automatic coding with ICPC: the Thesaurus, the algorithm and the Dutch subtitles.* Stud Health Technol Inform, 1997. **43 Pt A**: p. 421-5.
15. Calin, A., et al., *Clinical history as a screening test for ankylosing spondylitis.* JAMA, 1977. **237**(24): p. 2613-4.
16. Rudwaleit, M., 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**(2): p. 569-78.
17. Sieper, J., et al., *The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis.* Ann Rheum Dis, 2009. **68 Suppl 2**: p. ii1-44.
18. van Riel, P.L.C.M. and D.L. Scott, *EULAR handbook of clinical assessments in rheumatoid arthritis*. 2001: Van Zuiden Communications B.V.
19. Rudwaleit, M., et al., *Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group.* Annals of the rheumatic diseases, 2009. **68**(10): p. 1520-7.
20. van der Linden, S., H.A. Valkenburg, and A. Cats, *Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria.* Arthritis Rheum, 1984. **27**(4): p. 361-8.
21. Harrell, F.E., Jr., K.L. Lee, and D.B. Mark, *Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors.* Statistics in medicine, 1996. **15**(4): p. 361-87.
22. Ambler, G., A.R. Brady, and P. Royston, *Simplifying a prognostic model: a simulation study based on clinical data.* Stat Med, 2002. **21**(24): p. 3803-22.
23. Van Houwelingen, J.C. and S. Le Cessie, *Predictive value of statistical models.* Statistics in medicine, 1990. **9**(11): p. 1303-25.

24. Steyerberg, E.W., et al., *Internal validation of predictive models: efficiency of some procedures for logistic regression analysis.* J Clin Epidemiol, 2001. **54**(8): p. 774-81.
25. Hanley, J.A. and B.J. McNeil, *The meaning and use of the area under a receiver operating characteristic (ROC) curve.* Radiology, 1982. **143**(1): p. 29-36.
26. Braun, J., et al., *2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis.* Annals of the rheumatic diseases, 2011. **70**(6): p. 896-904.
27. Gordon, A., et al., *Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase.* Clin Ther, 2010. **32**(5): p. 844-60.
28. De Rycke, L., et al., *'MRI-tis' in the early diagnosis of axial SpA: issues and limitations.* Nat Rev Rheumatol, 2010. **6**(11): p. 666-9.
29. Weber, U., 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**(10): p. 3048-58.
30. Aydin, S.Z., et al., *Validation of the ASAS criteria and definition of a positive MRI of the sacroiliac joint in an inception cohort of axial spondyloarthritis followed up for 8 years.* Ann Rheum Dis, 2012. **71**(1): p. 56-60.
31. van der Heijde, D., et al., *Justification for including MRI as a tool in the diagnosis of axial SpA.* Nat Rev Rheumatol, 2010. **6**(11): p. 670-2.
32. Onen, F., et al., *Prevalence of ankylosing spondylitis and related spondyloarthritides in an urban area of Izmir, Turkey.* J Rheumatol, 2008. **35**(2): p. 305-9.
33. Poddubnyy, D., et al., *Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care.* J Rheumatol, 2011. **38**(11): p. 2452-60.
34. Rudwaleit, M. and J. Sieper, *Referral strategies for early diagnosis of axial spondyloarthritis.* Nat Rev Rheumatol, 2012. **8**(5): p. 262-8.
35. Braun, A., et al., *Identifying patients with axial spondyloarthritis in primary care: how useful are items indicative of inflammatory back pain?* Ann Rheum Dis, 2011. **70**(10): p. 1782-7.
36. van der Linden, S.M., 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**(3): p. 241-9.
37. D'Amaro, J., *HLA polymorfism in the Netherlands.* 1978, Leiden University.
38. Mustafa, K.N., M. Hammoudeh, and M.A. Khan, *HLA-B27 Prevalence in Arab Populations and Among Patients with Ankylosing Spondylitis.* J Rheumatol, 2012. **39**(8): p. 1675-7.
39. Reveille, J.D., et al., *The prevalence of HLA-B27 in the US: data from the US National Health and Nutrition Examination Survey, 2009.* Arthritis Rheum, 2012. **64**(5): p. 1407-11.
40. Amir, E., et al., *Assessing women at high risk of breast cancer: a review of risk assessment models.* J Natl Cancer Inst, 2010. **102**(10): p. 680-91.
41. Priebe, A.M., *2012 cervical cancer screening guidelines and the future role of HPV testing.* Clin Obstet Gynecol, 2013. **56**(1): p. 44-50.
42. Kent, P., et al., *Inexperienced clinicians can extract pathoanatomic information from MRI narrative reports with high reproducibility for use in research/quality assurance.* Chiropr Man Therap, 2011. **19**(1): p. 16.
43. Koes, B.W., et al., *An updated overview of clinical guidelines for the management of non-specific low back pain in primary care.* Eur Spine J, 2010. **19**(12): p. 2075-94.
44. Sieper, J., et al., *Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1).* Ann Rheum Dis, 2012.



Chapter 3

External validation of a referral rule for axial spondyloarthritis in primary care patients with chronic low back pain

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Abstract

Objective: To validate and optimize a referral rule to identify primary care patients with chronic low back pain (CLBP) suspected for axial spondyloarthritis (axSpA).

Design: Cross-sectional study with data from 19 Dutch primary care practices for development and 38 for validation.

Participants: Primary care patients aged 18-45 years with CLBP existing more than three months and onset of back pain started before the age of 45 years.

Main outcome: The number of axSpA patients according to the ASAS criteria.

Methods: The referral rule (CaFaSpA referral rule) was developed using 364 CLBP patients from 19 primary care practices and contains four easy to use variables; inflammatory back pain, good response to nonsteriodal anti-inflammatory drugs, family history of spondyloarthritis and a back pain duration longer than five years. This referral rule is positive when at least two variables are present. Validation of the CaFaSpA rule was accomplished in 579 primary care CLBP patients from 38 practices from other areas. Performance of the referral rule was assessed by c-statistic and calibration plot. To fit the final referral rule the development and validation datasets were pooled leading to a total study population of 943 primary care participants.

Results: The referral rule was validated in 579 patients (41% male, mean age 36 (sd7.0). The percentage of identified axSpA patients was 16% (n=95). External validation resulted in satisfactory calibration and reasonable discriminative ability (c-statistics 0.70 [95% CI, 0.64-0.75]). In the pooled dataset sensitivity and specificity of the referral rule were 75% and 58%.

Conclusions: The CaFaSpA referral rule for axSpA consists of four easy to use predictors for primary care physicians and has a good predictive value in this validation study. The referral rule has the potential to be a screening tool for primary care by identifying CLBP patients suspected for axSpA.

Introduction

Axial spondyloarthritis (axSpA) is relative new term in the field of rheumatology. It is a chronic inflammatory joint disease, that is potentially disabling and characterized by chronic low back pain (CLBP). [1] AxSpA is associated with increased morbidity, mortality, high health care costs and reduced work productivity. [2, 3] Quality of life and work participation can be improvement with effective treatment; non-steroidal anti-inflammatory drugs (NSAIDs) and biologicals.[4] This treatment is even more effective when it is given early in the disease course [5]. Nevertheless there is a delay of 4-9 years between the first CLBP symptoms and the final diagnosis of axSpA. [6, 7] This delay can be explained by the difficulty for primary care physicians to recognize an axSpA patient in the large amount of CLBP patients seen in primary care.

Low back pain (LBP) is one of the most common health problems and it is worldwide the largest contributor to the overall amount of years lived with disability (YLDs) causing a large burden for patients, health systems and society. [8, 9] Around 10% of LBP complaints persists for more than 12 weeks and become chronic. [10] In most countries CLBP patients are first seen by their primary care physicians. Guidelines with red and yellow flags are used to diagnose, treat and if necessary refer CLBP patients. [11] These guidelines do not include a flag or referral recommendation specific for axSpA. The lack of a specifically axSpA flag is notable since a number of recent studies showed that up to 40% of the CLBP complaints, if patient are referred by pre-defined criteria, can be explained by axSpA. [7, 12-17] In addition to studying prevalence these studies also proposed different referral strategies. Referral strategies for axSpA aim to achieve earlier referral of patients suspected for axSpA by primary care physicians. However most of the published referral rules were not easy to use, costly, or developed in secondary care patients. This pre-selection of patients makes it hard to implement these referral strategies in primary care practice. Furthermore most published referral strategies are merely based on development studies so no external validation took place, an important step for deriving a clinical useful referral strategy. [18] In 2014 we published the CaFaSpA referral rule, a referral strategy for axSpA developed in primary care patients with CLBP and applicable for primary care physicians. [7] In this study we want to externally validate and optimize the performance of this CaFaSpA referral rule in another, independent population of young primary care CLBP patients.

Material and Methods

Study design and data source:

We did a cross-sectional study in a large population of primary care CLBP patients from June 2011 to June 2012, the acronym of the study was the CaFaSpA (Case Finding Axial SpondyloArthritis) study. Primary-care group practices in the Rotterdam and The Hague area in the Netherlands were informed about the study and invited to participate. In total 38 GPs participated, who represented a source population of about 28.842 patients, ages 18-45 years. Potential participants with LBP were selected from the GP databases using the International Classification of Primary Care (ICPC) code L03, standing for low back pain symptom/complaint excluding radiation. [19].
From the 28.842 primary care records, 2597 (9%) patients ages 18-45 years were identified who had ever been registered by the ICPC code L03. Those 2597 patients were invited to participate by a letter on behalf of their GP. Responding participants were checked for eligibility during a telephonic interview by a research assistant. Inclusion criteria were current low back pain existing for more than 12 weeks, good understanding of the Dutch language and no contraindications for MRI (i.e. pregnancy, claustrophobia, pacemaker). Patients were excluded if there was a explainable cause for the back pain, such as a hernia nuclei pulposi or a trauma.

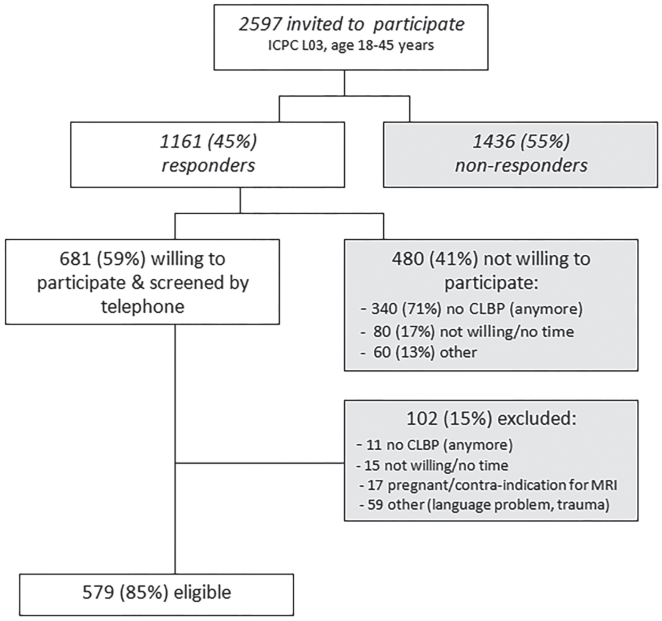
Ethics statement

Written informed consent was obtained from all participants at the research center before any assessment was performed. Ethics approval from the St. Elisabeth Hospital in Tilburg, the Netherlands was obtained (NL3571806011).

Clinical evaluation

All participants were asked to complete the ASAS [1] questionnaire on inflammatory back pain (IBP), before any clinical and/or radiological evaluation was done. This questionnaire comprised of five questions related to back pain. A positive ASAS questionnaire was achieved when four out of five questions were answered positively. The outcome the ASAS questionnaires was reported in a binary value; positive or negative. Furthermore participants completed the

Figure 1. Recruitment flowchart CaFaSpA 2 study



BASDAI [20] and ASDAS [21] questionnaire, both measure the disease activity of axSpA, a higher score indicates a higher disease activity. Also the Roland Morris disability questionnaire (RMDQ) was completed. [22] The RMDQ is a measure of disability caused by the LBP. Higher numbers on a 24-point scale reflect greater levels of disability.

Within a rheumatology setting an experienced research nurse obtained a clinical history including axSpA features, namely IBP, arthritis, psoriasis, enthesitis, dactylitis, uveitis, Crohn's disease/colitis, good reaction to non-steroidal anti-inflammatory drugs (NSAIDs) and a positive family history of SpA.

The 'red flags' used by primary care physicians, standing for typical signs or symptoms that are frequently associated with specific LBP were also checked. [23] A description of the red flags is available in the supplementary file, S1 Table 1. All assessments followed the definitions described in the ASAS handbook. [1] Statistical comparisons between clinical features of axSpA patients and CLBP patients were made by the Student t test or X^2 test, when appropriate.

Blood was drawn from all patients, irrespective of the research nurse's opinion of clinical diagnosis of axSpA or IBP, for the Erythrocyte Sedimentation Rate

(normal range 0-15 mm Hg/min), C-reactive protein (normal range 1-10 mg/l) and HLA-B27 typing.

Image evaluation

All patients underwent image evaluation by X-ray and MRI, again irrespective of the research nurse's opinion of clinical diagnosis of axSpA or IBP. Sacroiliac joints (SIJ) were scored according to the modified New York criteria (from 0 normal, to 4 complete fusion), using conventional pelvic radiographs in the anterior-posterior view. [24] A score of 0, 1 or 2 unilateral was considered normal, while bilateral grade 2 or unilateral grade 3 or 4 was classified as positive. A definitive diagnosis of sacroiliitis on MRI was made according to the ASAS criteria: presence of a minimum amount of bone marrow edema (one lesion in at least two adjacent slices or more than one lesion in at least one slice). [25] Images were read by one out of two trained radiologists, blinded for patient identity, clinical and laboratory data. If one of the radiologists doubted the score, the two observers discussed the scan and came to consensus.

Clinical outcome definition

Patients were classified as axSpA according to the ASAS criteria for axial spondyloarthritis. [25] Definite axSpA can be accomplished by the imaging arm; sacroiliitis on imaging (MRI or X-ray) plus ≥1 SpA feature, or by the clinical arm; no sacroiliitis on imaging but a positive HLA-B27 plus ≥2 SpA features. The SpA features are ASAS IBP, arthritis, (heel) enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease/colitis, good response to NSAIDs, family history for SpA, HLA-B27 positive and elevated C-reactive protein. A distinction between Ankylosing Spondylitis (AS) and non-radiographic axSpA (nr-axSpA) was made. The difference between AS and nr-axSpA is the presence of sacroiliits on plain radiographic of the sacroiliac joints (SI-joints). [1] AS comes with abnormalities on the X-ray consistent with sacroiliits, while nr-axSpA patients do not fulfill the imaging part of the modified NY criteria for AS.

Validated predictors

The CaFaSpA referral rule was previously developed with logistic regression analysis and internally validated with bootstrapping and corrected for over fitting by a shrinkage factor. [7] The rule contained four dichotomous variables, the ASAS IBP questionnaire (positive vs negative), family history for SpA (positive vs negative), good response to NSAIDs (positive vs negative), LBP duration (≤ 5years vs >5 years). The ASAS IBP questionnaire is positive if at least four out of five questions are answered with yes, a positive family history means a first or second degree family member with axSpA, psoriasis, Crohn's disease/colitis or uveitis. A good response to NSAIDs implies a clear improvement or disappearance of the low back pain, within 48 hours after the start of NSAIDs treatment.

External validation

For external validation of the referral rule, performance was assessed using discrimination and calibration measures. [26, 27] The ability to discriminate axSpA patients from CLBP patients was quantified by the c statistics, a measure for concordance. In binary outcomes, as in our model, the c statistics is identical to the area under the receiver operating characteristics (ROC) curve. Reasonable values for the area under the ROC curve range from 0.5 (no discrimination) to 1.0 (perfect discrimination). [28] Calibration is the agreement between the predicted probabilities and the observed frequencies and was assessed by estimating the calibration slope and intercept. The calibration slope is ideally 1 and reflects whether the effects of the predictors are on average correct. The calibration intercept indicates whether predictions are in general correct and is ideally 0. This intercept is assessed by fitting a logistic regression model with the linear predictor as an offset variable (setting the regression coefficients to 1). The analyses were performed using Stata version 13.0 software (Stata Corporation TX, USA) and R (version 2.15.2; The R Foundation for Statistical Computing).

Model updating

For the model updating, we decided to combine this validation dataset and the development dataset (CaFaSpA 1 study). [7] In 2014 the development study has been published which consisted of 364 CLBP patients from 19 primary care

practices who had been included from January to July 2010 from the greater Rotterdam area in the Netherlands. By combining the datasets the model is based on more patients leading to more stable predictor effects. [29] First a logistic regression analysis was performed in the combined dataset. Subsequently we tested if adding new variables to the model leaded to significant improvement of the model Chi-square, a measure for overall performance of the model.
To present the model as a referral rule, a simple scoring system was made. We rounded the regression coefficients from the logistic regression analysis of the combined model. We estimated the sensitivity and specificity for several cut points. The positive predictive value (PPV) of the chosen cut point was calculated.

Results

Out of the 2597 invited patients with low back pain, 1161 patients (44.7%) responded (Figure 1). Of these 1161 responders, 480 expressed no interest in participating and 102 did not fulfilled the inclusion criteria. Informed consent was obtained from 579 participants.

Missing values

In the following variables missing values occurred: ASAS IBP questionnaire (1.5%) and laboratory parameters (0.5%). We assumed missing data occurred at random and performed single imputation of the variables used for the external validation. [30]

Characteristics of the study population

Table 1 shows the characteristics of the total study population, subdivided in axSpA and CLBP patients. Overall more women (59%) participated, the mean age was 35.9 years (sd 7.0) and the median duration of low back pain was 7 years (interquartile range (IQR) 3-15 years). The overall prevalence of HLA-B27 was 6.2% (n=36). The median VAS pain was 5 (IQR 3-7), the median BASDAI and ASDAS were respectively, 4.2 (IQR 2.3-5.9) and 2.3 (IQR 1.6-3.0). The median RMDQ score was 7 (IQR 3-13). The results of the red flags are available in the supplementary file.

Table 1. Demographics, clinical characteristics and percentage of identified axial spondyloarthritis patients of the study participants* (n=579)

	ASAS criteria axSpA (n=95)	*Chronic low back pain (n=484)*
Age, mean ± SD years	37.3 ±6.5	35.6 ±7.1
Male sex	36 (38)	202 (42)
Caucasian	88 (93)	431 (89)
Medical history		
LBP duration, median (IQR) years	6.0 (4-14)	7.0 (3-15)
VAS pain, median (IQR)	4 (2-6)	5 (3-7)
ASAS IBP questionnaire (positive)†	46 (48)	147/475 (31)
Good reaction to NSAIDs	62 (65)	201 (42)
Family history SpA	24 (25)	56 (12)
IBD	1 (1)	11 (2)
Uveitis	5 (5)	18 (4)
Enthesitis	3 (3)	29 (6)
Arthritis	13 (14)	63 (13)
Dactylitis	5 (5)	14 (3)
Psoriasis	3 (3)	23 (5)
Blood		
CRP >10 mg/l	10 (11)	24/481 (5)
HLA-B27 positive	21 (22)	15/481 (3)
Others		
BASDAI, median (IQR)	4.2 (2.4-5.8)	4.2 (2.2-6.0)
ASDAS, median (IQR)	2.4 (1.7-3.0)	2.3 (1.6-2.9)
RMDQ, median (IQR)	6 (3-13)	7 (3-13)
Percentage axSpA		
Axial SpA	95 (16.4)	
AS	24 (25)	
Non-radiological axSpA	71 (75)	

*Values are the number (percentage) IQR = interquartile range; LBP = low back pain; VAS = visual analog scale; ASAS = Assessment of SpondyloArthritis international Society; NSAIDs = nonsteroidal anti-inflammatory drugs; IBD = Inflammatory bowel disease; CRP = C-reactive protein; SpA = spondyloarthritis; AS= Ankylosing Spondylitis† A positive ASAS questionnaire is achieved when at least 4 out of 5 questions are answered positively.

Percentage of identified axial spondyloarthritis patients

The percentage identified axSpA patients was 16.4% (n=95), 95% CI: 13.5%-19.7% (Table 1). Within the axSpA cases 24 out of 95 (25%) were classified as AS and 71 (75%) as nr-axSpA. Twelve out of the 71 nr-axSpA patients (16%) fulfilled the ASAS criteria by the clinical arm, with a positive HLA-B27 status and at least two other SpA features.

Referral rule and combining datasets

Table 2 shows the discriminative ability of the original model (c-statistic 0.70, (95%CI 0.64-0.75)). The calibration slope was 0.77 indicating that the predictor effects were on average too large. The intercept of -0.48 indicates that predictions were on average too high, which is related to the lower percentage of identified axSpA cases in the current study (16.4%), compared to CaFaSpA 1 (23.6%). The c-statistic of the combined model is 0.70, with a smaller confidence interval (95% CI 0.66-0.74).

Table 2. Performance of the referral rule in the validation data (CaFaSpA 2)

Performance	CaFaSpA 2 (n=579)
C-statistic (95% CI)	0.70 (0.64-0.75)
Calibration slope (95% CI)	0.77 (0.49-1.06)
Calibration intercept (95% CI)	-0.48 (-0.73- -0.25)

The predictor effects of the ASAS IBP questionnaire, family history and reaction to NSAIDs were similar or smaller in the validation data compared with CaFaSpA 1 (Table 3). The effect of LBP duration was not profound anymore as was also shown by the similar prevalence of axSpA in two different LBP duration groups (16.8% in LBP ≤5 years versus 16.2% in LBP >5 years).

We studied the additive effect of age and a dichotomized variable with easy to determine SpA features (arthritis, dactylitis, psoriasis, enthesitis, uveitis and inflammatory bowel disease, 0= no SpA features present and 1= ≥1 SpA feature present) in the combined data. Neither variable increased the model Chi-square significantly.

Table 3. Results of the multivariable logistic regression analyses in the validation data (CaFaSpA 2), development data (CaFaSpA 1) and the two data sets combined; odds ratio's (95% confidence interval)

Predictors	CaFaSpA 2 (n=579)	CaFaSpA 1 (n=364)	Combined data (n=943)
ASAS IBP questionnaire positive †	1.97 (1.24-3.13)	3.55 (2.10-5.99)	2.49 (1.77-3.50)
Family history for SpA positive	2.42 (1.38-4.24)	2.66 (1.27-5.57)	2.35 (1.51-3.65)
Good reaction to NSAIDs	2.56 (1.60-4.10)	2.42 (1.43-4.09)	2.39 (1.70-3.38)
LBP >5years	0.78 (0.49-1.25)	1.96 (1.11-3.47)	1.16 (0.82-1.64)

† A positive ASAS questionnaire is achieved when at least 4 out of 5 questions are answered positively
LBP = low back pain; NSAIDs = nonsteroidal anti-inflammatory drugs; SpA = spondyloarthritis

To provide a user friendly format of the prediction model, predictors with similar regression coefficients were given equal points in a simple scoring system. Figure 2 shows the combined model in this simple scoring system that can be used as a referral rule. A score of 0.5 was given to a symptom duration longer than 5 years. A positive ASAS questionnaire, a positive family history for SpA and a good reaction to NSAIDs all received one point. The cut point of 1.5 point was associated with a sensitivity of 75% and a specificity of 58% (Table 4). The yield of the referral rule expressed in the PPV is 30.2%. This means that 30.2% of the CLBP patients with a positive referral rule can be identified as axSpA.

Figure 2. Scoring system CaFaSpA referral rule; applicable in primary care patients with chronic low back pain

Patients ≥3 months back pain and age at onset <45 years	
Predictor	*Score*
Positive ASAS IBP questionnaire	1
Positive family history for SpA	1
Good reaction to NSAIDs	1
Low back pain duration >5 years	0.5
Score ≥ 1.5	→ referral to rheumatologist

IBP=inflammatory back pain; NSAIDs=nonsteriodal anti-inflammatory drugs; SpA=spondyloarthritis

Table 4. Combined model different cut points for referral rule with corresponding sensitivity and specificity

Cut point CaFaSpA referral rule	Sensitivity (%)	Specificity (%)
≥1.0	92.3	39.1
≥1.5	74.6	57.6
≥2	40.9	82.4
≥2.5	28.7	88.3

Discussion

Our validation study confirms the previously described high percentage of identified axSpA patients in primary care patients with CLBP. This finding emphasizes the need to introduce a simple referral strategy that can assist primary care physicians in the identification of patients with axSpA who should be referred

to specialized care for diagnosis and subsequently for adequate treatment. This is the first study to externally validate a referral rule for axSpA in a primary care CLBP population.

Studying the referral rule performance in an external validation is a valuable step before implementation of the referral rule in clinical practice. Many referral rules have been developed, but only few are used in daily practice. An important reason for this discrepancy is the lack of evidence for external validity. [31] Recently several referral strategies for axSpA were published [13-17, 32], but only few have been externally validated. [13, 14] Moreover there is currently no consensus about what the most appropriate referral strategy for axSpA should be. The available referral strategies for axSpA have been developed in a pre-specified CLBP population or in already referred patients, reflected by the high prevalence of axSpA found in those studies. In contract to these studies, our study population consists of unselected primary care CLBP patients. This is the main strength of our study. Our referral rule has been validated in the population wherein the rule will be used. In our study there was no selection bias for including patients and GPs. For GPs no particular inclusion criteria were used, for patients only ICPC code L03 and age between 18 and 45 years were used, no axSpA specific inclusion criteria were required. Using ICPC code L03 comes with the disadvantage that we invited patients we aren't currently suffering from low back pain. In ICPC code L03 no chronicity is included. This is confirmed by the finding that more than 70% of the non-participating responders didn't had low back pain anymore (Figure 1).

The yield of our referral rule is important, the PPV of the referral rule is 30.2%. Assuming the prior probability of axSpA in a CLBP patient is 5% [33], this gives our referral rule an advantage. Our PPV is lower than the PPV of other studies [13], but our referral rule is based on clinical parameters alone. In other studies HLA-B27 testing or imaging is included in the referral strategies, which increases the PPV. However in Dutch primary care there is very limited familiarity with interpretation of SIJ imaging, and also the costs for HLA- B27 testing makes implementation of those referral strategies difficult and makes our 'simple' referral rule very applicable in Dutch primary care.

Three predictors from the original referral rule, the ASAS IBP questionnaire, a positive family history for SpA and a good reaction to NSAIDs were also found in the current data, and similar to predictors from the SPACE, MASTER and RADAR studies. [12-14] LBP could not be identified as a predictor anymore. In this current study the proportion of LBP ≤5 years was 47%, in CaFaSpA 1 only 38%, however

this difference should not bias the effect of duration. Combining the validation and development dataset has several vital advantages, i.e. creating more stable predictor effects and more accurate predictions.

For the application of the rule we propose a cut point that is related to a relative high sensitivity (75%) with a lower specificity (58%). We believe that a relative high sensitivity and thus referring many possible axSpA patients is desirable, considering axSpA is a disease where quality of life increases after the start of treatment. [34] A lower specificity comes at the cost of referring CLBP patients who do not have axSpA, creating extra work in rheumatology practices. However taking into account the impact of axSpA on work participation [3], referring a relative small amount of false positive CLBP patients might even be cost-effective.

A point of discussion is that we used the ASAS criteria to define our outcome definition, namely axSpA. Classification and diagnostic criteria serve a different purpose. The difficulty in the field of axSpA is that there are no diagnostic criteria, there are only classification criteria. We believe that classification and diagnostic criteria have a substantial overlap, and that a diagnosis is almost equal to making a classification in an individual patient. [35] Moreover, classification criteria are more stringent than diagnostic criteria which is also illustrated by two cohorts who compared the diagnosis of a rheumatologist to the ASAS criteria. In the SPACE study were 65 patients diagnosed with axSpA or AS by a rheumatologist. Of these 65 patients were only 55 also classified by the ASAS criteria. [12] In the DECLIC study were 425 patients diagnosed as AS or axSpA, of those fulfilled 324 the ASAS criteria. [36] In both studies are the classification criteria more strict than the diagnosis by a rheumatologist. The specificity was high in both studies (SPACE study 95%, DECLIC 87%) so the fear of 'over diagnosing' a lot of patients by using the ASAS criteria, is proven not to be true by those two studies. We have chosen the ASAS criteria as outcome to identify patients as axSpA or no axSpA since this criteria are exactly defined and reproducible for readers, while the diagnosis by a rheumatologist is not. The main purpose of this article was to validate a referral strategy for axSpA in primary care, in this setting is a clear outcome definition desirable.

A remarkable finding in our study is the lower HLA-B27 prevalence (6.2%) in our study compared to other studies. [12, 13, 32] This makes a direct comparison between our study and others difficult. However, the HLA-B27 prevalence was comparable to our first large study in unselected CLBP patients [7] and to the study of Underwood [33], also performed in primary care CLBP patients. There is

no evidence that HLA-B27 prevalence is higher among CLBP patients. Therefore we believe that the HLA-B27 prevalence in our study population marks the fact that we did not select on predefined axSpA features and that our referral rule is applicable in and generalizable to all primary care CLBP patients.

Conclusion

In conclusion we provide a stable and robust referral rule that may be applicable as a screening tool in primary care. The next step in the implementation of the referral rule will be, to investigate the clinical impact on GPs behaviour and patients' outcomes.

References

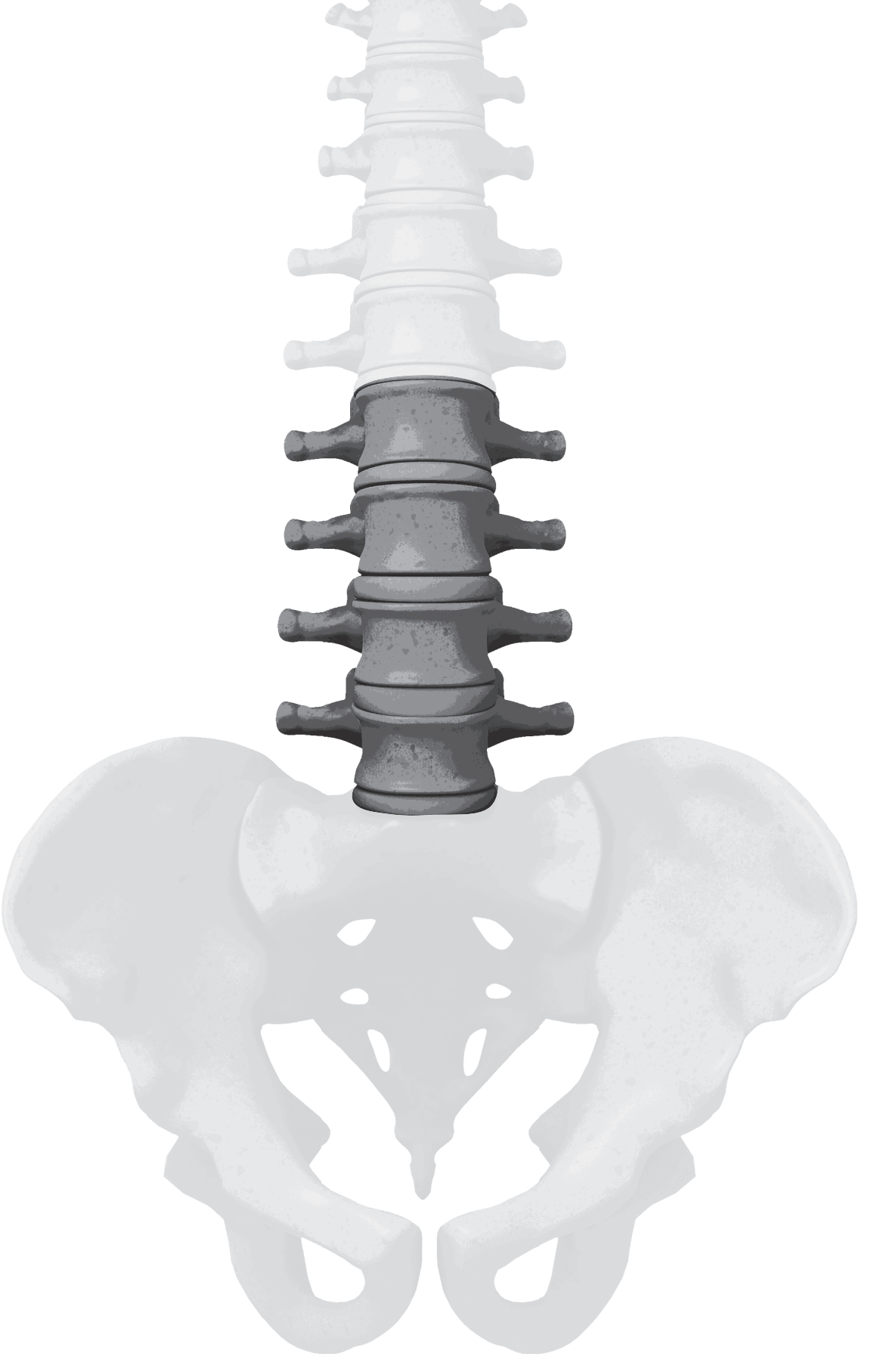
1. Sieper, J., et al., *The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis.* Ann Rheum Dis, 2009. **68 Suppl 2**: p. ii1-44.
2. van der Horst-Bruinsma, I.E., M.T. Nurmohamed, and R.B. Landewe, *Comorbidities in patients with spondyloarthritis.* Rheum Dis Clin North Am, 2012. **38**(3): p. 523-38.
3. Boonen, A. and S.M. van der Linden, *The burden of ankylosing spondylitis.* J Rheumatol Suppl, 2006. **78**: p. 4-11.
4. Callhoff, J., et al., *Efficacy of TNFalpha blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis.* Ann Rheum Dis, 2014.
5. Sieper, J., et al., *Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1).* Ann Rheum Dis, 2013. **72**(6): p. 815-22.
6. Feldtkeller, E., et al., *Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis.* Rheumatol Int, 2003. **23**(2): p. 61-6.
7. van Hoeven, L., et al., *Identifying axial spondyloarthritis in dutch primary care patients, ages 20-45 years, with chronic low back pain.* Arthritis Care Res (Hoboken), 2014. **66**(3): p. 446-53.
8. Hoy, D., et al., *The global burden of low back pain: estimates from the Global Burden of Disease 2010 study.* Ann Rheum Dis, 2014. **73**(6): p. 968-74.
9. Vos, T., et al., *Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2163-96.
10. Freburger, J.K., et al., *The rising prevalence of chronic low back pain.* Arch Intern Med, 2009. **169**(3): p. 251-8.
11. Koes, B.W., et al., *An updated overview of clinical guidelines for the management of non-specific low back pain in primary care.* Eur Spine J, 2010. **19**(12): p. 2075-94.
12. van den Berg, R., 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.
13. Sieper, J., et al., *Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study.* Ann Rheum Dis, 2012.
14. Poddubnyy, D., et al., *Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care.* J Rheumatol, 2011. **38**(11): p. 2452-60.
15. Brandt, H.C., et al., *Performance of referral recommendations in patients with chronic back pain and suspected axial spondyloarthritis.* Ann Rheum Dis, 2007. **66**(11): p. 1479-84.
16. Hermann, J., et al., *Early spondyloarthritis: usefulness of clinical screening.* Rheumatology (Oxford), 2009. **48**(7): p. 812-6.
17. Braun, J. and R. Inman, *Clinical significance of inflammatory back pain for diagnosis and screening of patients with axial spondyloarthritis.* Ann Rheum Dis, 2010. **69**(7): p. 1264-8.
18. Toll, D.B., et al., *Validation, updating and impact of clinical prediction rules: a review.* J Clin Epidemiol, 2008. **61**(11): p. 1085-94.
19. Gebel, R.S., *Semi-automatic coding with ICPC: the Thesaurus, the algorithm and the Dutch subtitles.* Stud Health Technol Inform, 1997. **43 Pt A**: p. 421-5.
20. Garrett, S., et al., *A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index.* J Rheumatol, 1994. **21**(12): p. 2286-91.
21. van der Heijde, D., et al., *ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis.* Ann Rheum Dis, 2009. **68**(12): p. 1811-8.
22. Roland, M. and R. Morris, *A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain.* Spine (Phila Pa 1976), 1983. **8**(2): p. 141-4.
23. Krismer, M., et al., *Strategies for prevention and management of musculoskeletal conditions. Low back pain (non-specific).* Best Pract Res Clin Rheumatol, 2007. **21**(1): p. 77-91.
24. Goie The, H.S., et al., *Evaluation of diagnostic criteria for ankylosing spondylitis: a comparison of the Rome, New York and modified New York criteria in patients with a positive clinical history screening test for ankylosing spondylitis.* Br J Rheumatol, 1985. **24**(3): p. 242-9.

25. Rudwaleit, M., 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**(6): p. 777-83.
26. Justice, A.C., K.E. Covinsky, and J.A. Berlin, *Assessing the generalizability of prognostic information.* Ann Intern Med, 1999. **130**(6): p. 515-24.
27. Steyerberg, E.W., et al., *Assessing the performance of prediction models: a framework for traditional and novel measures.* Epidemiology, 2010. **21**(1): p. 128-38.
28. Hanley, J.A. and B.J. McNeil, *The meaning and use of the area under a receiver operating characteristic (ROC) curve.* Radiology, 1982. **143**(1): p. 29-36.
29. Balmana, J., et al., *Prediction of MLH1 and MSH2 mutations in Lynch syndrome.* JAMA, 2006. **296**(12): p. 1469-78.
30. Marshall, A., et al., *Comparison of techniques for handling missing covariate data within prognostic modelling studies: a simulation study.* BMC Med Res Methodol, 2010. **10**: p. 7.
31. Steyerberg, E.W., et al., *Prognosis Research Strategy (PROGRESS) 3: prognostic model research.* PLoS Med, 2013. **10**(2): p. e1001381.
32. Braun, A., et al., *Optimizing the identification of patients with axial spondyloarthritis in primary care--the case for a two-step strategy combining the most relevant clinical items with HLA B27.* Rheumatology (Oxford), 2013. **52**(8): p. 1418-24.
33. Underwood, M.R. and P. Dawes, *Inflammatory back pain in primary care.* Br J Rheumatol, 1995. **34**(11): p. 1074-7.
34. Sieper, J., et al., *Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1).* Ann Rheum Dis, 2012.
35. Yazici, H., *Diagnostic versus classification criteria - a continuum.* Bull NYU Hosp Jt Dis, 2009. **67**(2): p. 206-8.
36. Molto, A., et al., *Evaluation of the validity of the different arms of the ASAS set of criteria for axial spondyloarthritis and description of the different imaging abnormalities suggestive of spondyloarthritis: data from the DESIR cohort.* Ann Rheum Dis, 2014.

Supplementary file

Table 1. Description of characteristics for red flags of (sub)acute low back pain in 579 primary care chronic low back patients

Description of red flag	Total (n=579)	<5 years LBP (n=270)	≥5 years LBP (n=309)	axSpA (n=95)
Age at onset back pain <20 years	175 (30.2%)	40 (14.8%)	135 (43.7%)	21 (22.1%)
Unexplained fever	14 (2.4%)	7 (2.6%)	7 (2.3%)	1 (1.1%)
Unbearable pain	48 (8.3%)	26 (9.6%)	22 (7.2%)	7 (7.4%)
Unexplained weight loss	18 (3.1%)	10 (3.7%)	8 (2.6%)	0
Previous history of cancer	16 (2.8%)	6 (2.2%)	10 (3.2%)	2 (2.1%)
Feeling unwell	122 (21.1%)	57 (21.1%)	65 (21.0%)	21 (22.1%)
Longer than 2 months use of pain medication	35 (6.0%)	16 (5.9%)	19 (6.2%)	8 (8.4%)
Constant pain	205 (35.4%)	94 (34.8%)	111 (35.9%)	35 (36.8%)
Not able to bend over	80 (13.8%)	35 (13.0%)	45 (14.6%)	13 (13.7%)
Significant motor weakness or sensory deficit	225 (38.9%)	102 (37.8%)	123 (39.8%)	40 (42.1%)
Loss of bladder control	56 (9.7%)	26 (9.6%)	30 (9.7%)	9 (9.5%)
Loss of sensation in the buttocks	73 (12.6%)	32 (11.9%)	41 (13.3%)	13 (13.7%)
Number of flags present				
0 red flags present	120 (20.7%)	74 (27.4%)	46 (14.9)	23 (24.2)
1 red flag present	177 (30.6%)	83 (30.7%)	94 (30.4)	23 (24.2)
≥2 red flags present	282 (48.7%)	113 (41.9%)	169 (54.7%)	49 (51.6)



Chapter 4

Evaluating the ASAS recommendations for early referral of axial spondyloarthritis in chronic low back pain patients; is one parameter present sufficient for primary care practice?

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New diagnostic tools and effective treatment for axial spondyloarthritis (axSpA) became available in the last decade. This has raised the need for adequate referral strategies for patients with low back pain suspected of axSpA. However, there is no agreement on which referral strategy is best. Recently the Assessment of SpondyloArthritis international Society (ASAS) group has published recommendations for the early referral for suspected axSpA. [1] (Box 1) Nonetheless, some critical remarks can be made regarding these recommendations.

Box 1. The ASAS-endorsed recommendations for early referral of patients suspected for having axial spondyloarthritis by primary care physicians or non-rheumatologists [1]

Patients with CLBP (duration ≥3 months) with back pain onset before 45 years of age should be referred to a rheumatologist if at least one of the following parameters is present:

- Inflammatory back pain*
- HLA-B27 positivity
- Sacroiliitis on imaging, if available (on X-rays or MRI)†
- Peripheral manifestations (arthritis, enthesitis and/or dactylitis)‡
- Extra-articulair manifestations (psoriasis, inflammatory bowel disease and or/uveitis)‡
- Positive family history for spondyloarthritis‡
- Good response to non-steroidal anti-inflammatory drugs‡
- Elevated acute phase reactants§

*Any set of criteria, preferably ASAS definition of inflammatory back pain.[2] † Only if imaging is available, not recommended as routine screening parameter. ‡ According to the definition applied in the classification criteria for axial spondyloarthritis. [2] §C-reactive protein serum concentration or erythrocyte sedimentation rate above upper normal limit after exclusion of other causes for elevation.

First, the recommendations have been developed using a Delphi process and final voting, but they have not been tested in daily practice yet. Testing in daily practice is important since it provides measures to determine the accuracy of the recommendations, such as sensitivity and specificity. Second, no primary care specialists were involved in this Delphi process, which is remarkable as the recommendations are intended to use in primary care. Finally, it is not clear if the chosen cut point for referral, that is, at least one parameter present in patients with low back pain aged <45 years, is the optimal cut point for primary care practice. To find the optimal cut point not only a high sensitivity or specificity, but also an acceptable level of positive predictive value (PPV) is essential. The PPV is important for daily practice; it is the proportion of patients with a positive referral recommendation who actually have axSpA. [3]

The two recently published CaFaSpA (CAse Finding Axial SPondyloArthritis) studies provide a large cohort of young primary care patients (18-45 years) with chronic low back pain (CLBP) [4, 5]. The cohort consists of 941 Dutch patients (58% female, mean age 36.0 years), who had CLBP for at least 3 months and age of back pain onset <45 years. All patients underwent a complete diagnostic work-up which included; standardized history, physical examination, HLA-B27, C reactive protein, erythrocyte sedimentation rate, X-ray and MRI of the sacroiliac joints. AxSpA was defined by the ASAS criteria. [2]

One-hundred-eighty-one (19%) of the 941 CLBP patients were identified as having axSpA. Using the ASAS recommendations 800 of the 941 patients would be referred to the rheumatologist, resulting in a sensitivity of 100%, specificity of 19% and PPV of 23%. (Table 1) This means that all axSpA cases are detected by the ASAS recommendations. However, more than 80% of the referred patients do not have axSpA, which is undesirable. Using a cut point of at least two parameters also results in a sensitivity of 100% but the specificity increases to 60% and the PPV to 38%.

Table 1. The performance of the ASAS recommendation in a primary care CLBP population (N=941) calculated per number of SpA parameters present in a patient

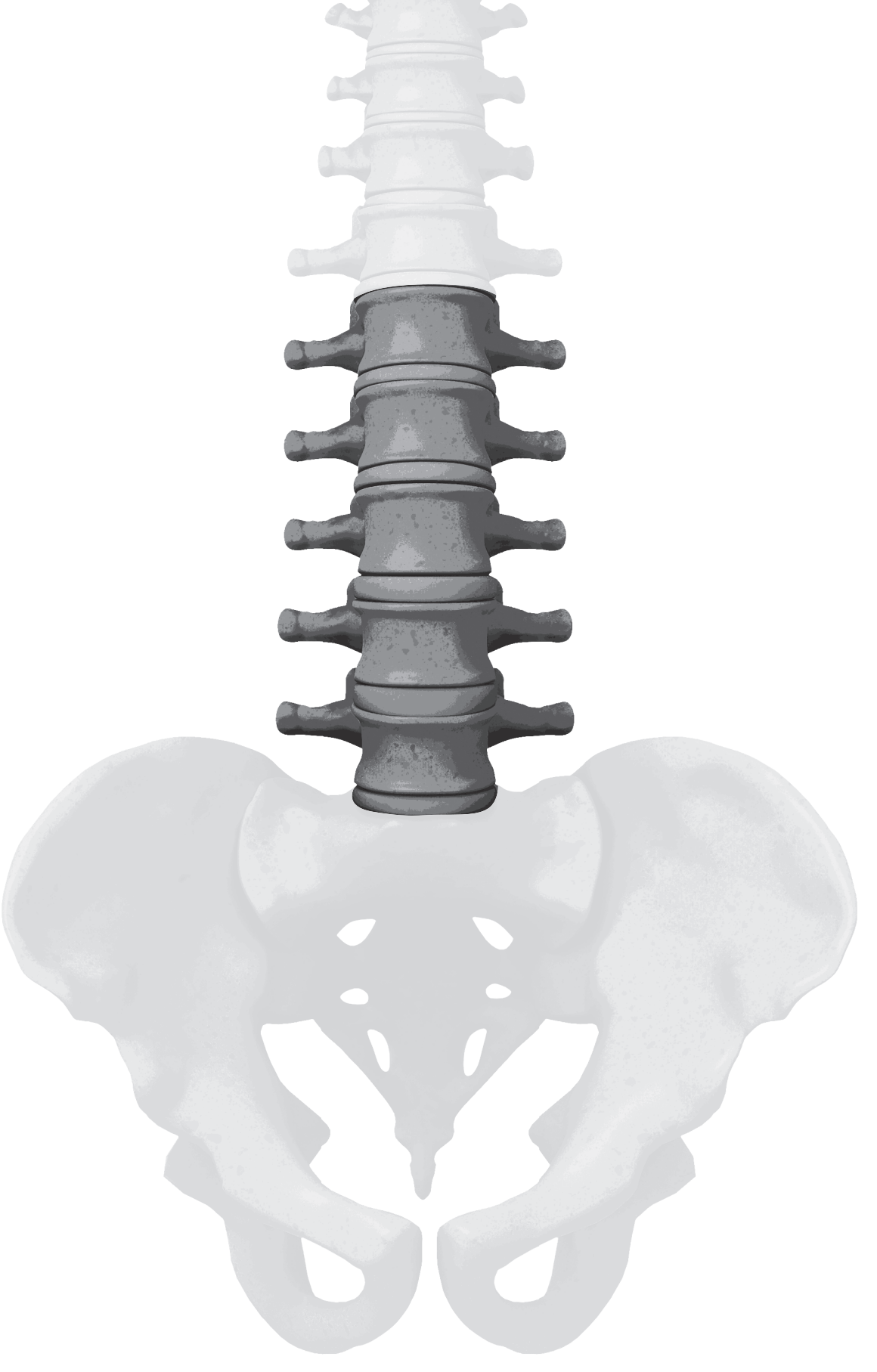
Number of parameters present*	Sensitivity (%)	Specificity (%)	PPV (%)
≥1	100.0	18.6	22.6
≥2	100.0	60.1	37.6
≥3	66.9	86.5	54.0
≥4	30.4	96.5	67.0
≥5	9.4	98.8	65.4
≥6	2.8	99.6	62.5

Parameters as described by the ASAS recommendations; inflammatory back pain; HLA-B27 positivity; sacroiliitis on imaging (X-ray or MRI); peripheral manifestations (arthritis, enthesitis, dactylitis); extra-articulair manifestation (psoriasis, inflammatory bowel disease, uveitis); positive family history for SpA; good response to NSAIDs; elevated acute phase reactants (ESR or CRP).

We believe that these findings are valid as they were assessed in a large primary care CLBP population, in which, information of all referral parameters was available. Assuming a prior probability of 5% of axSpA in a CLBP population [6], the probability of having axSpA increases to 23% if there is one parameter of the ASAS recommendations present. Using the cut point of two parameters present the probability of axSpA increases to 38%; therefore, it seems more appropriate to use the cut point of two parameters in daily practice. For a more widespread validation of referral strategies for axSpA prospective follow-up cohorts should be set up, where the real impact of referral strategies on patients should be investigated.

References

1. Poddubnyy, D., et al., *Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis.* Ann Rheum Dis, 2015.
2. Rudwaleit, M., 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**(6): p. 777-83.
3. Altman, D.G. and J.M. Bland, *Diagnostic tests 2: Predictive values.* BMJ, 1994. **309**(6947): p. 102.
4. van Hoeven, L., et al., *Identifying axial spondyloarthritis in dutch primary care patients, ages 20-45 years, with chronic low back pain.* Arthritis Care Res (Hoboken), 2014. **66**(3): p. 446-53.
5. van Hoeven, L., et al., *External Validation of a Referral Rule for Axial Spondyloarthritis in Primary Care Patients with Chronic Low Back Pain.* PLoS One, 2015. **10**(7): p. e0131963.
6. Underwood, M.R. and P. Dawes, *Inflammatory back pain in primary care.* Br J Rheumatol, 1995. **34**(11): p. 1074-7.



Chapter 5

External validation of referral strategies for axial spondyloarthritis in patients with chronic low back pain; the search for the optimal referral strategy in primary care

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Submitted

Abstract

Objective: To externally validate referral strategies for axial spondyloarthritis (axSpA) in a primary care cohort of young (18-45 years) patients with chronic low back pain (CLBP) and to examine which referral strategy is advisable for primary care practice.

Methods: The following referral strategies were externally validated; Berlin, MASTER, RADAR, 2-step, CaFaSpA and the new ASAS recommendations. The strategies were validated in a large Dutch primary care population of unselected CLBP patients (CLBP ≥3 months, back pain onset <45 years). Patients underwent a diagnostic work-up which included; standardized history, physical examination, HLA-B27, CRP, ESR, conventional X-ray and MRI of the sacroiliac joints. AxSpA was defined by the ASAS criteria. Performance of referral strategies was assessed by sensitivity, specificity and positive predictive value (PPV).

Results: 941 primary care CLBP patients were used (58% female, mean age 36.0 years), of these patients 181 (19%) were identified as axSpA. Almost all referral strategies had a good discriminative performance. The MASTER referral strategy had the most balanced sensitivity (96%), specificity (82%) and the highest PPV (55%). The new ASAS recommendations (using all eight referral parameters) had a perfect sensitivity (100%), but the lowest specificity (19%) and the lowest PPV (23%).

Conclusion: Referral strategies including costly procedures like imaging and HLA-B27 had the best PPV, sensitivity and specificity. However imaging and HLA-B27 are not always available in a primary care setting. The optimal strategy for primary care depends on budget, available resources and knowledge of axSpA in primary care.

Introduction

Axial spondyloarthritis (axSpA) is a chronic condition associated with a high burden of illness, expressed in reduced quality of life, impaired physical functioning and work disability. [1, 2] The prevalence of axSpA in young patients with chronic low back pain (CLBP) is 20-40%. [3] [4-9] Early recognition of axSpA is an important goal to achieve, as effective treatment for axSpA is available. [10] However a recent study showed that there is still an average diagnostic delay of 8.5 years. [11] To achieve early recognition, it is necessary that primary care physicians can identify potential axSpA patients early in their primary care practice. CLBP is the first symptom in the majority of axSpA patients, which hampers early identification of axSpA. CLBP is a very common complaint in primary care [12] and no specific signs or symptoms for axSpA are described in the current CLBP guidelines for primary care physicians. [13]

Recently the Assessment of SpondyloArthritis international Society (ASAS) workgroup proposed referral recommendations for axSpA to achieve early recognition in primary care [14], furthermore several other referral strategies have been proposed in recent years. [3, 5-9] Almost all referral strategies have been developed in a pre-specified CLBP populations or in already referred patients. These pre-selection of patients leads to a higher probability that a patient will actually be diagnosed with axSpA compared to unselected primary care CLBP patients. Only one strategy, the Case Finding Axial SpondyloArthritis (CaFaSpA) strategy, was developed and validated in primary care patients with CLBP. [3, 9]

Furthermore, not all components of the referral models are easy to use in primary care and/or are costly. For example HLA-B27 and imaging are not always available due to high costs or the incapability of a primary care physician to interpret the findings of the MRI or X-ray of the sacroiliac joints (SI-joints). It is important to test the referral strategies in a population in which the strategies will also be applied, a primary care CLBP population.

The aim of this study is to validate referral strategies for axSpA in unselected young primary care patients with CLBP and secondly to discuss the most suitable referral strategy for primary care practice.

Material and Methods

Study population

Patients from both CaFaSpA (Case Finding Axial SpondyloArthritis) cohorts were included. These cohorts consisted of patients that participated in two cross-sectional studies that took place in the South-Western part of the Netherlands. The first study (CaFaSpA 1, n=364) was performed in 2010 and designed to develop a referral strategy for axSpA. [9] The validation study (CaFaSpA 2, n=579) was performed in 2011-2012. [3] Both studies had the exact same study design. Complete and detailed data collection of the CaFaSpA cohort had been described before. [3, 9]

Patients (18-45 years) were selected using ICPC code L03 (nonspecific low back pain) from primary care records and invited to participate. Patients already diagnosed with ankylosing spondylitis (AS) or axSpA were not invited. Inclusion criteria were current low back pain existing for more than 12 weeks, no trauma as cause for the back pain, good understanding of the Dutch language and no contraindications for MRI (i.e. pregnancy, claustrophobia, pacemaker). Written informed consent was obtained from all study participants at the research center before any assessment was performed. Ethics approval from the St. Elisabeth Hospital in Tilburg, the Netherlands was obtained for both studies.

Participating patients were examined by rheumatologists or a trained research assistant , i.e. medical history and physical examination including the presence of SpA-features, such as inflammatory back pain (IBP), both sides buttock pain, arthritis, psoriasis, enthesitis, dactylitis, uveitis, Crohn's disease/colitis (IBD), good reaction to non-steroidal anti-inflammatory drugs (NSAIDs), and a positive family history of SpA. All assessments followed the definitions described in the ASAS handbook. [15]

Blood was drawn to determine HLA-B27 positivity, C-reactive protein (normal range 1-10 mg/l) and Erythrocyte Sedimentation Rate (normal range 0-15 mm Hg/min). An X-ray and magnetic resonance imaging (MRI) of the SI-joints was obtained. Images were read by one out of three trained readers (HW, AW and FN), and scored according to the ASAS definition (MRI-SIJ) [15] and the modified New

York criteria. [16] Radiologists were blinded for clinical outcomes, laboratory data and the results of the other imaging method.

Patients were identified as axSpA according to the ASAS criteria for axSpA after evaluation of the rheumatologist and/or a trained research assistant. [17] The ASAS criteria introduced a new subdomain of axSpA, the non-radiographic axSpA (nr-axSpA) patient. This new term made it possible to identify axSpA patients before the detection of structural changes on the sacroiliac joints.

Referral strategies

We only externally validated referral strategies of which we had information on all individual referral parameters and that we could test in our study population. All described referral strategies are applicable in patients with chronic back pain (duration >3 months) and back pain onset before 45 years of age. Figure 1 shows the parameters that are included in the referral strategies. The referral strategies are listed by year of publication.

Figure 1. Referral parameters included in different referral strategies for axial spondyloarthritis

Referral parameter		*Imaging†*	*HLA-B27*	*IBP$*	*Positive family history[ƒ]*	*Good response NSAIDs*	*EAM[£]*	*Elevated CRP/ESR‡*	*Peripheral manifestations[@]*	*Both sides buttock pain*	*Psoriasis*	*Improvement by movement*	*LBP duration ≥5 years*
Strategy	Refer if												
Berlin	≥1	■	■	■									
MASTER	≥2	■	■	■	■	■							
RADAR	≥2	■	■	■	■	■	■						
2-step	≥2		■							■	■	■	
CaFaSpA	≥2			■	■	■							■
ASAS	≥1	■	■	■	■	■	■	■	■				

CRP=C-reactive protein; ESR=; IBP=Inflammatory back pain; EAM= Extra-articular manifestations; NSAIDs= non-steriodal anti-inflammatory drugs; LBP=low back pain.
†Imaging, sacroiliits on X-ray or MRI; $IBP is per referral strategy different defined; ƒ Depending on referral strategy family history for ankylosing spondylitis or spondyloarthritis; £EAM include uveitis, psoriasis and inflammatory bowel disease; ‡elevated CRP/ESR; @Peripheral manifestation include arthritis, enthesitis or dactylitis

The oldest strategy is the Berlin strategy, their strategy consist of three parameters; IBP, HLA-B27 positivity and imaging (sacroiliitis on X-ray or MRI). [5] A referral is advised if at least one of the three parameters is present. From the MASTER study we validated the more comprehensive strategy consisting of five parameters, a referral to the rheumatologists is advised when at least two parameters are present. [6] Also the more comprehensive strategy from the RADAR study was validated, consisting of six parameters. A referral to the rheumatologists is advised when at least two parameters are present. [7] The next strategy is the 2-step strategy of Braun et al. [8] The first step in this strategy is to refer patients when there are two of the following three parameters present in a patient; both sides buttock pain ,

improvement by movement or psoriasis. When there are less than two parameters present the second step is to determine HLA-B27, when HLA-B27 is positive a referral to the rheumatologists is advised. Subsequently a non-invasive strategy was published, the CaFaSpA referral strategy, a referral is recommended when at least two parameters are present. [3, 9] All referral parameters are noninvasive (IBP, positive family history, good reaction to NSAIDs and duration of CLBP >5 years), no additional blood tests or imaging are necessary. This strategy was developed within the CaFaSpA cohort and is already externally validated in a primary care setting. We included the CaFaSpA strategy in the comparison of the referral strategies but no external validation of this CaFaSpA strategy takes place in this study. And finally the newest referral strategy is the ASAS recommendation for early referral. [14] These recommendations were achieved within the ASAS workgroup as a result of a Delphi process and final voting. This is an extensive referral strategy which includes eight referral parameters, having one parameter present is sufficient for a referral to the rheumatologist. We tested the complete strategy with all eight parameters.

We uses the ASAS definition to assess IBP: at least four out of five parameters present; (1) age at onset ≤40 years; (2) insidious onset; (3) improvement with exercise; (4) no improvement with rest; and (5) pain at night (with improvement upon getting up). This definition is also recommended to use by the ASAS workgroup. [17] Family history for SpA was positive if a first of second degree family member had ankylosing spondylitis, psoriasis, uveitis anterior or IBD.

Statistical analysis

In order to assess the performance of the strategies in an unselected CLBP population we calculated the number of referred patients, sensitivity, specificity and positive predictive value (PPV) at the suggested cut off point for each referral strategy. The PPV indicates the proportion of patients with axSpA from those who should be referred according to the strategy. [18] To investigate the strength of the individual parameters included in the referral strategies we performed a univariate logistic regression analysis with axSpA as outcome and the different parameters as single covariates. The analyses were performed using STATA version 13.0 software (Stata Corporation TX, USA).

Results

Study cohort

In total 943 CLBP patients were included (58% female, mean age 36.0 years sd ±6.9). For the performance of the referral strategies 941 (99.8%) complete cases were analyzed. The characteristics of the study population are presented in Table 1. In total 181 patients (19%) fulfilled the ASAS classification criteria for axSpA. Among all SpA cases, 54 (30%) were classified as ankylosing spondylitis (AS) by the modified New York criteria [16] and 127 (70%) as non-radiographic axSpA.

Table 1. Demographics and clinical characteristics in chronic low back pain, ankylosing spondylitis and non-radiographic axial spondyloarthritis patients

	Unspecified chronic low back pain (n=762)	*Ankylosing Spondylitis (n=54)*	*Non-radiographic axial spondyloarthritis (n=127)*
Age, mean ±SD years	35.8 ±7.0	37.7 ±6.5	36.6 ±6.5
Male sex, n (%)	323 (43)	13 (24)	55 (43)
Medical history			
LBP duration, median (IQR) years	7.0 (3-15)	10.0 (4-20)	8.0 (4-15)
VAS pain, median (IQR)	5.0 (3-7)	5.0 (2-7)	4.0 (3-6)
ASAS IBP questionnaire (positive)†, n (%)	233 (31)	28 (52)	70 (55)
Good reaction to NSAIDs, n(%)	305 (40)	35 (65)	79 (62)
Familiy history for SpA, n (%)	79 (10)	13 (24)	28 (22)
IBD, n (%)	14 (2)	1 (2)	3 (2)
Uveitis, n (%)	22 (3)	4 (7)	4 (3)
Enthesitis, n (%)	72 (9)	5 (9)	6 (5)
Arthritis, n (%)	81 (11)	5 (9)	18 (14)
Dactylitis, n (%)	23 (3)	2 (4)	7 (6)
Psoriasis, n (%)	36 (5)	4 (7)	4 (3)
Both sides buttock pain, n(%)	489 (66)	35 (65)	95 (75)
Blood∞			
ESR >15 mm/hg, n (%)	137 (19)	18 (33)	27 (21)
CRP >10 mg/l, n (%)	36 (5)	8 (15)	11 (9)
HLA-B27 positive, n (%)	18 (2)	4 (7)	34 (27)
Imaging			
Sacroiliitis, X-ray, n (%)	22 (3)	54 (100)	0 (0)
Sacroiliitis, MRI, n (%)	42 (6)	19 (35)	105 (83)
Number of SpA features present			
0, n (%)	223 (29)	0 (0)	0(0)
1, n (%)	279 (37)	21 (39)	45 (35)
2, n (%)	173 (23)	21 (39)	46 (36)
3, n (%)	60 (8)	4 (7)	23 (18)
≥4, n (%)	25 (3)	8 (15)	13 (10)

IQR = interquartile range, SD = standard deviation
LBP = low back pain; VAS = visual analog scale; ASAS = Assessment of SpondyloArthritis international Society; NSAIDs = nonsteriodal anti-inflammatory drugs; IBD = Inflammatory bowel disease; CRP = C-reactive protein; SpA = spondyloarthritis; MRI = magnetic resonance imaging
† A positive ASAS IBP questionnaire is achieved when at least 4 out of 5 questions are answered positively.
∞ In the unspecified CLBP group were four missing blood samples (n=756)

Performance of referral strategies

The ASAS recommendations and the Berlin strategy had the maximum sensitivity of 1.0, this means that zero axSpA patients are missed when this strategy is applied (Table 2). The two-step model had the lowest sensitivity of 0.69, this means that more than 30% of axSpA patients are missed by this referral strategy. The highest specificity was found in the MASTER (82%) and RADAR (78%) strategies. The ASAS recommendation had the lowest specificity, 19%, this means that more than 80% of the patients are unnecessarily referred to the rheumatologist. The MASTER strategy had the highest PPV (55%) meaning that 55% of the patients with a positive referral strategy are actually diagnosed with axSpA. The ASAS recommendation had the lowest PPV, 23%.

Table 2. Performance of several referral strategies for axial spondyloarthritis tested in primary care patients (18-45 years) with chronic low back pain (n=941)

Referral strategy	*No. of referred patients*	*Sensitivity*	*Specificity*	*PPV*
Berlin	485 (52%)	100% (181/181)	60% (456/760)	37% (181/485)
Master	312 (33%)	96% (173/181)	82% (621/760)	55% (173/312)
RADAR	343 (36%)	97% (175/181)	78% (592/760)	51% (175/343)
2-step	476 (51%)	69% (124/181)	54% (408/760)	26% (124/476)
CaFaSpA	457 (49%)	75% (135/181)	58% (438/760)	30% (135/457)
ASAS recommendation (all 8 parameters)	800 (85%)	100% (181/181)	19% (141/760)	23% (181/800)

In Table 3 is shown that X-ray, MRI and HLA-B27 have the highest odds ratios of all the different referral parameters and are the strongest predictors in referring the 'true' axSpA patient to the rheumatologist. However also non-invasive parameters such as IBP, positive family history, good response to NSAIDs, both sided buttock pain, improvement by movement and a LBP duration of >5 years are statistically significant and thus predictive in referring the 'true' axSpA patient to the rheumatologist.

Table 3. Univariate logistic regression of all referral parameters included in the different referral strategies for axial spondyloarthritis

	Axial spondylo-arthritis (n=181)		*Chronic low back pain (n=760)*		*Odds ratio (95% CI)*
Referral parameter	n	%	n	%	
X-ray					
Sacroiliits	54	30	22	3	14.3 (8.4-24.2)
MRI					
Sacroiliits	124	67	42	6	37.2 (23.9-57.8)
HLA-B27					
Positive	38	21	18	2	10.9 (6.0-19.6)
Inflammatory back pain*					
Present	98	54	223	29	2.7 (1.9-3.7)
Positive family history					
Present	41	23	79	10	2.5 (1.7-3.8)
Good response to NSAIDs					
Present	114	63	305	40	2.5 (1.8-3.5)
EAM					
Present	19	10	69	9	1.2 (0.7-2.0)
Elevated CRP/ESR					
Present	51	28	153	20	1.6 (1.1-2.3)
Peripheral manifestation					
Present	40	22	152	20	1.1 (0.8-1.7)
Both sides buttock pain					
Present	127	70	476	63	1.4 (1.0-2.0)
Psoriasis					
Present	8	4	36	5	0.9 (0.4-2.0)
Improvement by movement					
Present	141	78	491	65	1.9 (1.3-2.8)
LBP duration >5 years					
Present	113	62	419	55	1.4 (1.0-1.9)

*= ASAS definition of inflammatory back pain; Positive family history= first of second degree family member with ankylosing spondylitis, psoriasis, uveitis or IBD; NSAIDs= non-steriodal anti-inflammatory drugs; EAM=extra-articulair manifestation, includes uveitis, psoriasis or inflammatory bowel disease; Peripheral manifestation= arthritis, enthesitis or dactylitis; LBP= low back pain

Discussion

To our knowledge this is the first study to externally validate referral strategies for axSpA in an unselected primary care CLBP population. Strategies which included imaging, HLA-B27 and IBP had the highest PPV, sensitivity and specificity. However the optimal referral strategy does not solely depend on good statistical performance but also on the primary care setting, the availability of imaging and HLA-B27 assessment in primary care and the knowledge of axSpA of the primary care physician. If imaging and HLA-B27 are available, the MASTER strategy is the most favorable strategy. When imaging and HLA-B27 are not accessible, then the CaFaSpA strategy is the most suitable strategy. This strategy includes parameters without additional costs such as IBP, family history and good response to NSAIDs and is easy to interpret by primary care physicians.

The performance of the strategies in our cohort compared to the performance of the strategies in their original studies showed some discrepancies. The two-step referral strategy reported a sensitivity of 80% and specificity of 75%. [8] In our cohort are both sensitivity (69%) and specificity (54%) lower. The lower sensitivity can be explained by differences in the study populations. In the original two-step study 36% of the patients had axSpA compared to 19% in our study. [8] Consequently 30% of the patients were HLA-B27 positive in the original study, compared to 6% in our study. The influence of disease incidence on sensitivity and specificity is a well-known phenomenon. [19, 20] The Berlin strategy reported a higher PPV in their original study (63%) [5], than we found (37%). This can be explained by the differences in prevalence of axSpA. [18] In the original study of the Berlin strategy was the prevalence of axSpA 45% given the predictive power of the strategy, a positive referral strategy was associated with 63% axSpA. In our study the axSpA prevalence of 19% was increased to 37% with a positive Berlin referral strategy. The MASTER and RADAR studies reported only sensitivity and specificity for individual referral parameters, not for their complete strategies. This makes it difficult to compare as we evaluated the complete strategy, not individual parameters. The ASAS recommendations, using all eight parameters, have a perfect sensitivity (100%), however the specificity is low, only 19%. With such a low specificity more than 80% of the referrals are unnecessarily, leading to undesirable high costs in secondary care. We investigated the performance of the ASAS recommendations using at least two parameters present as cut point for referral instead of the

proposed one parameter. [21] This again results in a sensitivity of 100%, but the specificity increases to 60% and the PPV increases to 38%. Using the cut point of at least two parameters present seems more useful in our CLBP population considering fewer patients are unnecessarily referred to the rheumatologist while maintaining a perfect sensitivity. The high sensitivity of the strategy can be explained by the comparability between the ASAS recommendations and our outcome, the ASAS classification criteria. [17]

The main strength of this study is the population in which the referral strategies were tested, an independent population of nearly 1000 unselected primary care CLBP patients. This is directly comparable to the population in which the referral strategies will be used. Patients in our study were only selected based on current low back pain existing for more than 12 weeks, no axSpA specific features were used and patients who were already diagnosed with AS or axSpA were not invited to participate. Another strength of our cohort is the completeness of our data. All the various referral parameters used by the strategies are known in our cohort, leading to a unique opportunity to simultaneously test the different referral strategies.

A point of discussion is that we used the ASAS classification criteria to define our outcome definition, namely axSpA. We are aware that classification and diagnostic criteria serve a different purpose. The difficulty in the field of axSpA is that there are no diagnostic criteria, there are only classification criteria. We believe that classification and diagnostic criteria have a substantial overlap, and that a diagnosis is almost equal to making a classification in an individual patient. [22] We have chosen the ASAS criteria as outcome as these criteria are clearly defined and reproducible for readers, while the diagnosis by a rheumatologist is not. The main purpose of this article was to validate referral strategies for axSpA in primary care, in this setting a clear definition of outcome is desirable.

A remarkable finding is the prevalence of AS cases (6%) in our CLBP population, Underwood et al, who investigated the prevalence of AS in a primary care cohort of CLBP patients, found similar results. [23] Moreover this finding confirms our belief that we didn't 'overdiagnose' a lot of patients by using the ASAS criteria as definition of outcome. Another point is interest is the relative low prevalence of HLA-B27 (6%) in our CLBP patients. However there is no evidence that the prevalence of HLA-B27

is higher among CLBP patient and the HLA-B27 prevalence in the Dutch general population is 7%. [24] We believe that this finding only confirms the unselected nature of our CLBP cohort.

A potential weakness of our cohort is the cross-sectional nature of our data. The ideal study design to evaluate referral strategies would be a prospective cluster-randomized trial with as intervention various referral strategies and as outcome a diagnosis of axSpA. To the best of our knowledge we are not aware of such a trial to test the optimal referral strategy. These cross-sectional data are second best and at this moment the only available data to validate referral strategies.

The choice of the optimal referral strategy for axSpA in primary care is challenging. Purely looking at the statistical performance, strategies that include imaging, HLA-B27 and IBP (Berlin, MASTER and RADAR) have the best PPV, sensitivity and specificity. If the aim for a referral strategy is to avoid missing any axSpA patient the strategy with the highest sensitivity is desirable, if the aim is to avoid unnecessary costs the strategy with the highest specificity is suitable.

However we believe that beside the statistical performance also the primary care setting is relevant. Primary care settings differ per country, in the Netherlands the primary care physician is the gatekeeper of the health care system. Patients are not allowed to go to the rheumatologist without a referral from their primary care physician. Therefor is it desirable that Dutch primary care physicians already use validated referral strategies, to ascertain that only patients with a definite suspicion of axSpA are referred to the more expensive secondary care.

The differences in primary care settings per country also means that there are differences in resources and diagnostic tools available in primary care. For example imaging and HLA-B27 are not always accessible in a primary care setting [13] sometimes due to high costs, sometimes due to unavailability of MRI. In the Netherlands a MRI of the SI-joints is not available for primary care physicians. Taking this into account, it leads to the conclusion that all strategies which include imaging are not optimal to use in a Dutch primary care setting.

And finally it's likely that there are differences between primary care providers in interpreting medical history, IBP questions and physical examination of

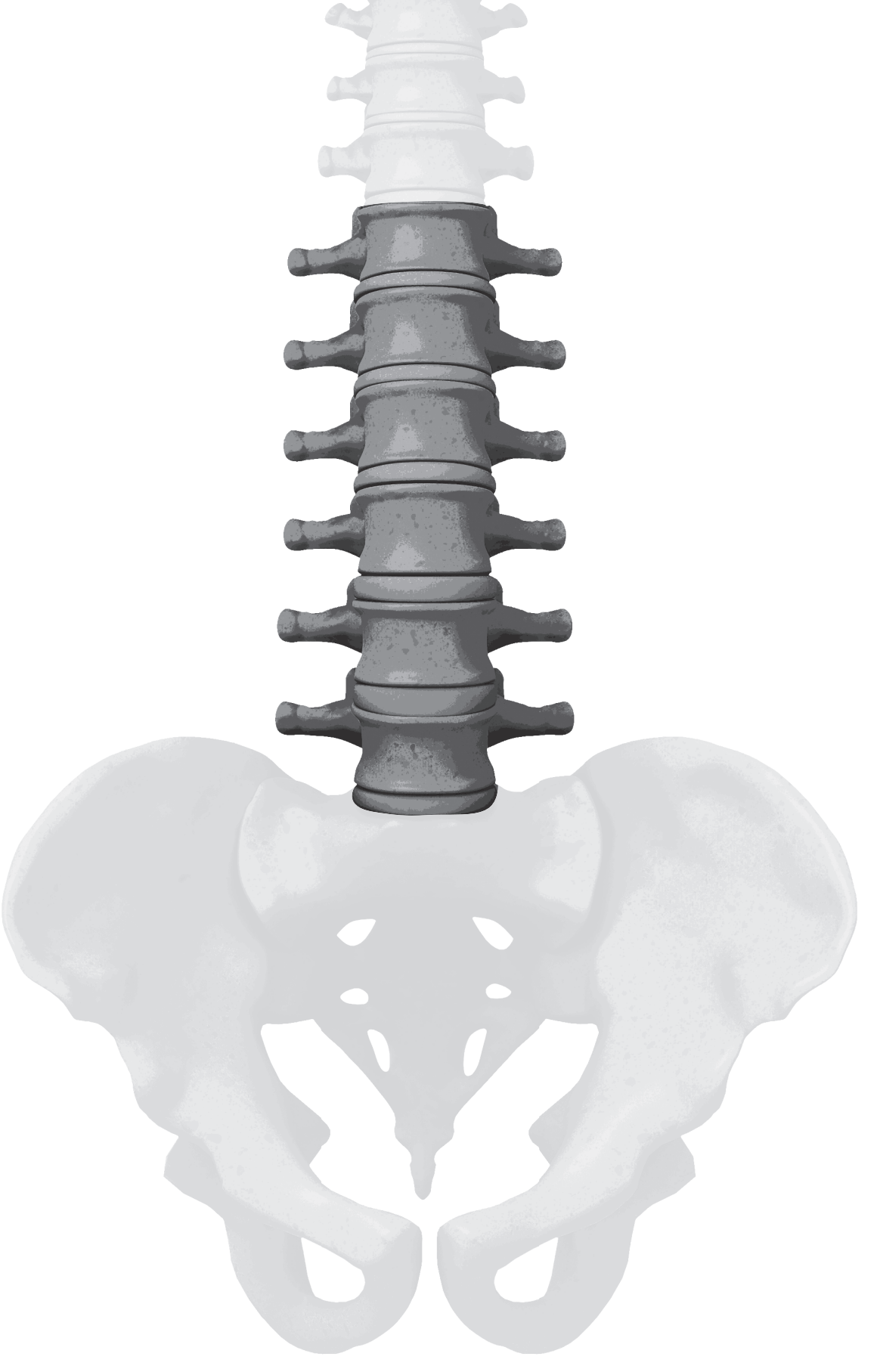
patients suspected of axSpA. This differences emphasize that is important to use a simple, straightforward referral strategy. By the CaFaSpA referral strategy we have developed a easy to use and interpret strategy. A correct interpretation of subjective clinical parameters as IBP and a good reaction to NSAIDs is simplified by using the ASAS IBP questionnaire which consist of five simple questions that should be answered with yes or no and the clear definition of a good response to NSAIDs as described in the methods section. [15] Nevertheless it would be necessary to educate primary care physicians about the referral of suspected axSpA patients to enhance the implementation of a referral strategy in daily practice. [25]

Conclusion

In conclusion, the optimal strategy for primary care depends not only on the statistical performance but also on the budget, resources available and knowledge of axSpA in primary care. This will differ by country and by primary care setting. Strategies that include costly procedures like imaging and HLA-B27 have the best performance. However non-invasive referral strategies have a reasonable performance in identifying potential axSpA patients and are easier to use and to implement in primary care.

References

1. Boonen, A. and S.M. van der Linden, *The burden of ankylosing spondylitis.* J Rheumatol Suppl, 2006. **78**: p. 4-11.
2. Boonen, A., et al., *The burden of non-radiographic axial spondyloarthritis.* Semin Arthritis Rheum, 2014.
3. van Hoeven, L., et al., *External Validation of a Referral Rule for Axial Spondyloarthritis in Primary Care Patients with Chronic Low Back Pain.* PLOS ONE, 2015. **10**(7): p. e0131963.
4. van den Berg, R., 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.
5. Brandt, H.C., et al., *Performance of referral recommendations in patients with chronic back pain and suspected axial spondyloarthritis.* Ann Rheum Dis, 2007. **66**(11): p. 1479-84.
6. Poddubnyy, D., et al., *Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care.* J Rheumatol, 2011. **38**(11): p. 2452-60.
7. Sieper, J., et al., *Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study.* Ann Rheum Dis, 2012.
8. Braun, A., et al., *Optimizing the identification of patients with axial spondyloarthritis in primary care--the case for a two-step strategy combining the most relevant clinical items with HLA B27.* Rheumatology (Oxford), 2013. **52**(8): p. 1418-24.
9. van Hoeven, L., et al., *Identifying axial spondyloarthritis in dutch primary care patients, ages 20-45 years, with chronic low back pain.* Arthritis Care Res (Hoboken), 2014. **66**(3): p. 446-53.
10. Sieper, J., et al., *Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1).* Ann Rheum Dis, 2013. **72**(6): p. 815-22.
11. Sykes, M.P., et al., *223. Delay to Diagnosis in Axial Spondyloarthritis: Are we Improving?* Rheumatology, 2014. **53**(suppl 1): p. i143.
12. Picavet, H.S. and J.S. Schouten, *Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study.* Pain, 2003. **102**(1-2): p. 167-78.
13. Koes, B.W., et al., *An updated overview of clinical guidelines for the management of non-specific low back pain in primary care.* Eur Spine J, 2010. **19**(12): p. 2075-94.
14. Poddubnyy, D., et al., *Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis.* Ann Rheum Dis, 2015.
15. Sieper, J., et al., *The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis.* Ann Rheum Dis, 2009. **68 Suppl 2**: p. ii1-44.
16. Goie The, H.S., et al., *Evaluation of diagnostic criteria for ankylosing spondylitis: a comparison of the Rome, New York and modified New York criteria in patients with a positive clinical history screening test for ankylosing spondylitis.* Br J Rheumatol, 1985. **24**(3): p. 242-9.
17. Rudwaleit, M., 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**(6): p. 777-83.
18. Altman, D.G. and J.M. Bland, *Diagnostic tests 2: Predictive values.* BMJ, 1994. **309**(6947): p. 102.
19. Ransohoff, D.F. and A.R. Feinstein, *Problems of spectrum and bias in evaluating the efficacy of diagnostic tests.* N Engl J Med, 1978. **299**(17): p. 926-30.
20. Mulherin, S.A. and W.C. Miller, *Spectrum bias or spectrum effect? Subgroup variation in diagnostic test evaluation.* Ann Intern Med, 2002. **137**(7): p. 598-602.
21. van Hoeven, L., et al., *Evaluating the ASAS recommendations for early referral of axial spondyloarthritis in patients with chronic low back pain; is one parameter present sufficient for primary care practice?* Ann Rheum Dis, 2015.
22. Yazici, H., *Diagnostic versus classification criteria - a continuum.* Bull NYU Hosp Jt Dis, 2009. **67**(2): p. 206-8.
23. Underwood, M.R. and P. Dawes, *Inflammatory back pain in primary care.* Br J Rheumatol, 1995. **34**(11): p. 1074-7.



Chapter 6

Combining the ASAS referral recommendation and ASAS diagnostic algorithm to identify axial spondyloarthritis in chronic low back pain patients

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Abstract

Objectives: Early recognition and diagnoses of axial spondyloarthritis (axSpA) is important. To achieve this goal, the ASAS recommendation for referral of axSpA and the ASAS diagnostic algorithm have been developed. It would be interesting to combine the referral recommendation and the algorithm into one clinical pathway for axSpA and to investigate its performance in a CLBP population.

Methods: A large Dutch primary care population of unselected CLBP patients (CLBP ≥3 months, back pain onset <45 years) was used to evaluate the clinical pathway. Patients underwent a diagnostic work-up which included; standardized history, physical examination, HLA-B27, CRP, ESR, conventional X-ray and MRI of the sacroiliac joints. Performance of the clinical pathway was assessed by the number of referred patients, positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity, with the number of identified axSpA patients as outcome.

Results: In total were 941 CLBP patients included (58% female, mean age 36.0 years), of these patients were 181 (19%) identified as axSpA. The clinical pathway referred 800 of the 941 CLBP patients and showed a PPV of 53%, NPV of 89%, sensitivity of 56% and specificity of 88%.

Conclusion: The practical value of a clinical pathway for axSpA by combining the ASAS recommendation for referral and the ASAS diagnostic algorithm is modest, especially the large number of unnecessarily referrals will hamper implementation of the clinical pathway in primary care practice. The number of unnecessarily referrals might be reduced by using more strict referral criteria.

Introduction

Axial spondyloarthritis (axSpA) is a disabling inflammatory joint disease with chronic low back pain (CLBP) as main symptom. [1] Patients with axSpA respond better on their treatment when given in an early phase of their disease. [2] Therefore timely recognition and consequently timely diagnosing are the ultimate goals for rheumatologists nowadays. To achieve this the Assessment of SpondyloArthritis international Society (ASAS) published recommendations for both timely referral and subsequently diagnosing of axSpA patients. [3, 4]

The ASAS referral recommendation is applicable in all patients with CLBP (duration ≥3 months) with back pain onset before 45 years of age. [3] CLBP patients should be referred to the rheumatologists if at least one parameter is present. The eight different parameters vary from sacroiliitis on imaging to a good reaction to non-steriodal anti-inflammatory drugs (NSAIDs).

The subsequent ASAS diagnostic algorithm should be applied in all referred CLBP patients. Within the algorithm follow CLBP patients a flowchart wherein imaging, clinical features and HLA-B27 testing are incorporated. [4]

The ASAS referral recommendation and subsequently the ASAS diagnostic algorithm can be combined into one clinical pathway to recognize and diagnose those patients with axSpA as early and effective as possible. However until now this clinical pathway has not been validated in daily practice. Therefor it would be interesting to investigate the performance of the axSpA clinical pathway in a CLBP population.

Methods

CaFaSpA cohort

For this study all patients from the CaFaSpA (Case Finding Axial SpondyloArthritis) cohort were included. This cohort consisted of primary care CLBP patients that participated in two cross-sectional studies that were performed to investigate the prevalence of axSpA and secondly to develop and externally validate a referral strategy for axSpA. Both studies had the exact same study design. Complete and detailed data collection of the CaFaSpA cohort had been described before. [5, 6]

Patients (18-45 years) were selected by ICPC code L03 (nonspecific low back pain) from GP records and invited to participate. Patients who were already diagnosed with Ankylosing Spondylitis (AS) or axSpA were not invited. Inclusion criteria were current low back pain existing for more than 12 weeks, no trauma as cause for the back pain, good understanding of the Dutch language and no contraindications for MRI (i.e. pregnancy, claustrophobia, pacemaker). Written informed consent was obtained from all participants at the research center before any assessment was performed. Ethics approval from the Medical Ethical Committee from the St. Elisabeth Hospital in Tilburg, the Netherlands was obtained for both studies.

Participating patients were examined by a rheumatologist or experienced research nurse, i.e. medical history and physical examination, including the presence of SpA-features. All assessments followed the definitions described in the ASAS handbook. [7] Blood was drawn to determine HLA-B27 positivity, C-reactive protein (normal range 1-10 mg/l) and Erythrocyte Sedimentation Rate (normal range 0-15 mm Hg/min). All patients underwent image evaluation by X-ray and MRI. Sacroiliac joints were scored according to the modified New York criteria, using conventional pelvic radiographs in the anterior-posterior view. [8] A definitive diagnosis of sacroiliitis on MRI was made according to the ASAS MRI criteria; presence of a minimum amount of bone marrow edema (one lesion in at least two adjacent slides or more than one lesion in at least one slice). [1] Images were read by one out of three trained radiologists, blinded for patient' identity, clinical and laboratory data.

Patients were identified as axSpA according to the ASAS criteria for axSpA after evaluation of the rheumatologists and/or trained research nurse. [1]

ASAS referral recommendation

The ASAS referral recommendation has been developed by using information form literature, a Delphi process and final voting. [3]The recommendation is applicable in patients with CLBP (duration ≥3 months) with back pain onset before 45 years of age. (Figure 1) Patients should be referred if at least one of the following parameters is present; inflammatory back pain (IBP), HLA-B27 positivity, sacroiliitis on imaging, if available (X-rays or MRI), peripheral manifestations (arthritis, enthesitis and/or dactylitis), extra-articulair manifestations (psoriasis, inflammatory bowel disease and/or uveitis), positive family history for spondyloarthritis, good response to non-steroidal anti-inflammatory drugs (NSAIDs) and elevated acute phase reactants.

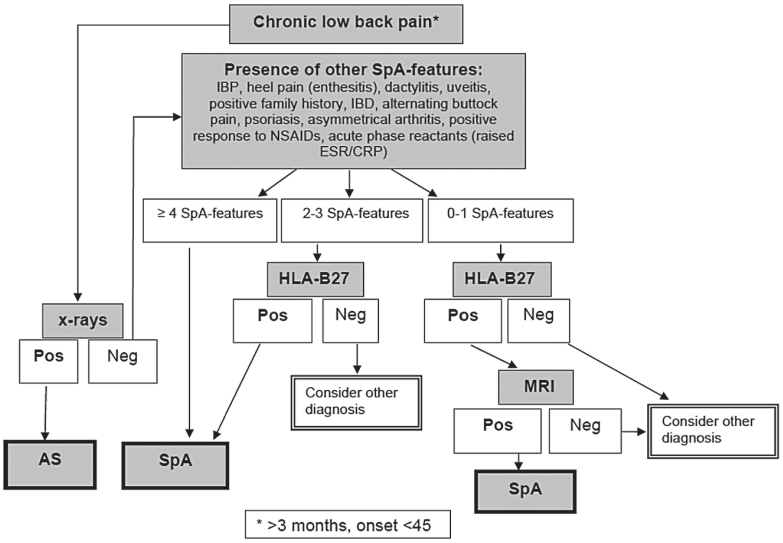
Figure 1. ASAS endorsed recommendation for early referral of patients suspected for having axial spondyloarthritis by primary care physicians or non-rheumatologists.

The ASAS-endorsed recommendations for early referral of patients suspected for having axial spondyloarthritis by primary care physicians or non-rheumatologists
Patients with CLBP (duration ≥3 months) with back pain onset before 45 years of age should be referred to a rheumatologist if at least one of the following parameters is present:
▪ Inflammatory back pain*
▪ HLA-B27 positivity
▪ Sacroiliitis on imaging, if available (on X-rays or MRI)†
▪ Peripheral manifestations (arthritis, enthesitis and/or dactylitis)‡
▪ Extra-articulair manifestations (psoriasis, inflammatory bowel disease and or/uveitis)‡
▪ Positive family history for spondyloarthritis‡
▪ Good response to non-steroidal anti-inflammatory drugs‡
▪ Elevated acute phase reactants§
*Any set of criteria, preferably ASAS definition of inflammatory back pain. † Only if imaging is available, not recommended as routine screening parameter. ‡ According to the definition applied in the classification criteria for axial spondyloarthritis. §C-reactive protein serum concentration or erythrocyte sedimentation rate above upper normal limit after exclusion of other causes for elevation.

ASAS diagnostic algorithm

The ASAS diagnostic algorithm is a modification of the original Berlin algorithm and it is validated in two different cohorts, the SPondyloArthritis Caught Early (SPACE) cohort and the Assessment of SpondyloArthritis international Society (ASAS) axSpA criteria validation cohort. The entry criterion of the ASAS diagnostic algorithm is the onset of CLBP before the age of 45 and CLBP present for more than three months. (Figure 2) According to the ASAS diagnostic algorithm [4] patients can be identified in four different ways; (1) by a sacroiliitis on X-ray (2) if ≥4 clinical SpA-features are present, (3) 2-3 clinical SpA features present and a positive HLA-B27 or (4) 0-1 clinical SpA features present with positive HLA-B27 and sacroiliits visible on MRI. (Figure 2)The SpA features included in the algorithm are; IBP, heel pain (enthesitis), dactylitis, uveitis, positive family history for SpA, inflammatory bowel disease, alternating buttock pain, psoriasis, asymmetrical arthritis, positive response to NSAIDs, acute phase reactants (raised ESR/CRP).

Figure 2. ASAS diagnostic algorithm. AS, ankylosing spondylitis; SpA, spondyloartritis; HLA-B27, Human Leukocyte Antigen. Adapted from van den Berg et al. [4]



Clinical pathway

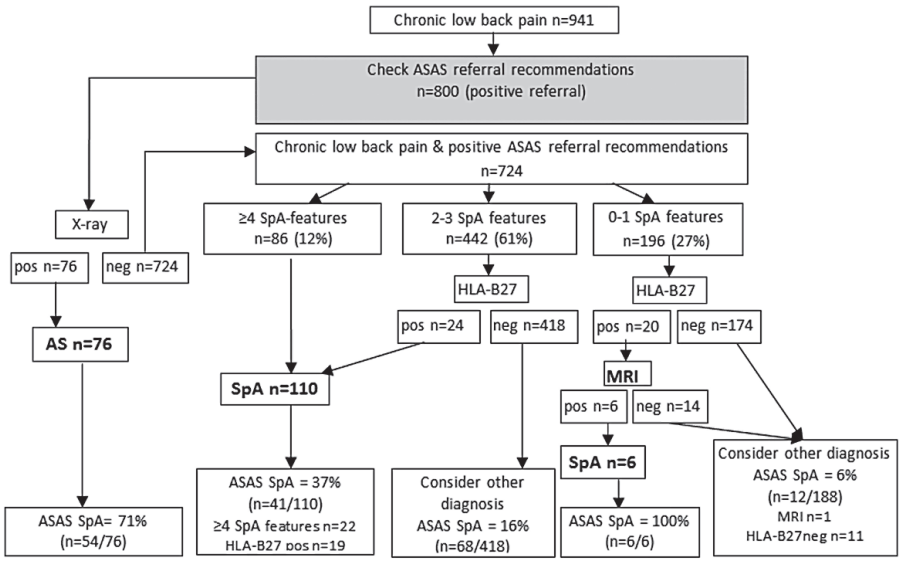
We combined the ASAS recommendation for referral and the ASAS diagnostic algorithm into a clinical pathway for axSpA.(Figure 3) When a CLBP patient should be referred according to the ASAS recommendation for referral, this patients enters the ASAS diagnostic algorithm.

Statistical analysis

The performance of the clinical pathway in a primary care CLBP population was assessed by calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Sensitivity and specificity are important measures of the diagnostic accuracy of a test, however they do not help the clinician in estimating the probability of axSpA in individual patients. The PPV is the percentage patients with a positive test result who can be identified as axSpA. For example, if the PPV of a test is 60%, this means that 60% of the patients with a positive test can be identified as diseased. The NPV is the percentage patients with a negative test result who do not have axSpA. We also calculated the percentages of the false positive patients (erroneously diagnosed as axSpA) and false negative patients

(true axSpA patients that were missed by the clinical pathway). The analyses were performed using Stata version 13.0 software (Stata Corporation TX, USA).

Figure 3. The clinical pathway for axSpA. First the ASAS recommendation for early referral are applied in chronic low back pain (CLBP) patients. If patients are referred by the ASAS recommendation they enter the ASAS algorithm. AS, ankylosing spondylitis; SpA, spondyloartritis; HLA-B27, Human Leukocyte Antigen; ASAS SpA, patients having axial spondyloartritis according to the ASAS classification criteria.



Results

CaFaSpA cohort

In total 943 CLBP patients were included (58% female, mean age 36.0 years sd ±6.9). For the performance of the algorithm 941 complete cases (99.8%) were analyzed, as the number of missing's was minimal, no imputation took place. The characteristics of the study population are presented in Table 1. In total 181 (19%) axSpA patients were identified. Among all new axSpA cases, 54 (30%) patients were classified as AS by the modified New York criteria [8] and 127 (70%) as non-radiographic axSpA.

Table 1. Demographics and clinical characteristics in study participants; axSpA versus CLBP

	CaFaSpA cohort	
	axSpA (n=181)	*CLBP (n=762)*
Age, mean ±SD years	36.9 ±6.5	35.8 ±7.0
Male sex, n (%)	68 (38)	323 (43)
Medical history		
LBP duration, median (IQR) years	8.0 (4-15)	7.0 (3-15)
VAS pain, median (IQR)	4.0 (2-6)	5.0 (3-7)
ASAS IBP questionnaire (positive)†, n (%)	98 (54)	233 (31)
Good reaction to NSAIDs, n (%)	114 (63)	305 (40)
Familiy history for SpA, n (%)	41 (23)	79 (10)
IBD, n (%)	4 (2)	14 (2)
Uveitis, n (%)	8 (4)	22 (3)
Enthesitis, n (%)	11 (6)	72 (9)
Arthritis, n (%)	23 (13)	81 (11)
Dactylitis, n (%)	9 (5)	23 (3)
Psoriasis, n (%)	8 (4)	36 (5)
Alternating buttock pain, n (%)	130 (72)	489 (66)
Blood		
ESR >15 mm/hg	45 (25)	137 (19)
CRP >10 mg/l	19 (10)	36 (5)
HLA-B27 positive	38 (21)	18 (2)
Imaging		
Sacroiliitis, X-ray	54 (30)	22 (3)
Sacroiliitis, MRI	124 (69)	42 (6)
Number of SpA features present		
0, n (%)	0 (0)	223 (29)
1, n (%)	66 (36)	279 (37)
2, n (%)	67 (37)	173 (23)
3, n (%)	27 (15)	60 (8)
≥4, n (%)	21 (12)	25 (3)

IQR = interquartile range, SD = standard deviation
LBP = low back pain; VAS = visual analog scale; ASAS = Assessment of SpondyloArthritis international Society; NSAIDs = nonsteriodal anti-inflammatory drugs; IBD = Inflammatory bowel disease; CRP = C-reactive protein; SpA = spondyloarthritis; MRI = magnetic resonance imaging
† A positive ASAS IBP questionnaire is achieved when at least 4 out of 5 questions are answered positively.
∞ In the unspecified CLBP group were four missing blood samples (n=756)

Performance of clinical pathway for axSpA

Based on the ASAS recommendation 800 (85%) of the 941 primary care CLBP patients would be referred to the rheumatologist. Subsequently 800 CLBP patients entered the diagnostic algorithm, the flowchart of the CLBP patients in the clinical pathway is represented in Figure 3.

By the clinical pathway are 192 (76 + 110 + 6) CLBP patients identified as axSpA. Of those 192 identified patients are 101 true axSpA cases, resulting in a PPV of 53% (101/192) (Table 2). There are 749 patients with a negative clinical pathway, of those are 669 non-axSpA cases, giving a NPV of 89% (669/749).

Table 2. *A) Number of axSpA patients identified by the clinical pathway* versus axSpA patients (ASAS criteria as reference standard) B) Performance measures of the clinical pathway for axSpA*

A) Clinical pathway for axSpA

	Reference standard ASAS criteria		
	axSpA cases	*non-axSpA cases*	***Total***
Clinical pathway positive	101	91	**192**
Clinical pathway negative	80	669	**749**
Total	**181**	**760**	**941**

B) Performance measures of the clinical pathway for axSpA

	PPV (%)	*NPV (%)*	*Sensitivity (%)*	*Specificity (%)*	*False negative (%)*	***False positive (%)***
Clinical pathway	**53**	**89**	**88**	**56**	**44**	**12**

*The clinical pathway for axSpA consists of the ASAS endorsed recommendation for referral and the ASAS diagnostic algorithm

In our cohort are in total 181 axSpA patients, of those were 101 patients identified by the clinical pathway as axSpA leading to a sensitivity of 56% (Table 2). Of the 760 non-axSpA patients, 669 patients (specificity 88%) were correctly identified as non-axSpA by the clinical pathway.

In total were 80 axSpA patients missed by the clinical pathway (Figure 3), resulting in a false negative percentage of 44% (80/181) (Table 2). All these false negative patients were HLA-B27 negative, but had sacroiliitis on the MRI and at least 1 SpA feature, (68 patients had 2-3 features, 12 patients had 0-1 features) (Figure 3). The most common features in the missed axSpA patients were a good reaction to NSAIDs (n=47), IBP (n=41), elevated CRP or ESR (n=20) and positive family history (n=11).

Another 91 patients were erroneously identified (i.e. false positive= 12%, (91/760)) as axSpA by the clinical pathway. (Table 2) Seventy percent (64/91) of the erroneously identified patients had ≥4 SpA features, but were HLA-B27 negative and didn't had sacroiliitis on neither the X-ray or the MRI. In these erroneously identified patients were the most common features alternating buttock pain (n=59), a good reaction to NSAIDS (n=55), IBP (n=43) and positive family history (n=32). Another 24% (22 of the 91) of the erroneously identified patients had a sacroiliits on X-ray, but no clinical SpA features. The remaining five erroneously identified patients can

be explained by the discrepancy between the SpA features used by the diagnostic algorithm and the ASAS criteria. Both alternating buttock pain and elevated ESR, are not included as SpA feature in the ASAS axSpA criteria, but are included as SpA features in the diagnostic algorithm.

Discussion

We combined the ASAS recommendation for referral and the ASAS diagnostic algorithm into one clinical pathway for axSpA and investigated its performance in a CLBP population. The relative high PPV and NPV, respectively 53% and 89% are promising. For rheumatologists in daily practice is the PPV an important outcome measure, a PPV of 53% means that more than half of the CLBP patients with a positive outcome after following the clinical pathway will be identified as axSpA. The NPV of 89% implies that the vast majority of the patients with a negative clinical pathway are non-axSpA patients. However despite the high PPV and NPV the practical value of this clinical pathway seems limited and costly. The main disadvantage of using the clinical pathway is that a huge number of CLBP patients who do not have axSpA will be referred to the rheumatologist. According to the clinical pathway, 85% (800 of 941) of the CLBP patients should be referred to the rheumatologists, while only 19% (181 of 941) of the CLBP patients will be identified as axSpA.

Comparing our results to other studies is challenging, as we are the first to validate a complete clinical pathway for axSpA. But if we compare our the results separately to the ASAS recommendation and the ASAS algorithm, we can draw some conclusions. Focusing on the referral recommendation, only our own study about the performance of the ASAS recommendation in the CaFaSpA cohort reports clinical data. [9] We describe that the sensitivity of the referral recommendation is very high (100%), at the cost of a very low specificity (19%). Meaning that more than 80% of the referred patients do not have axSpA, which is undesirable. The same trend is observed in the current study, a lot of patients are unnecessarily referred to the rheumatologist. No other studies with clinical data of the ASAS recommendation are published yet.

The sensitivity of the ASAS algorithm was 90% in both the SPACE and the ASAS cohort, and the specificity was respectively 84% and 83%. [4] The specificity of the algorithm is comparable in our study (88%), but the sensitivity is considerably lower (44%). We believe that this difference can be explained by the inequalities in the recruitment of patients. The recruitment of patients in the SPACE cohort took place by the general practioners and by specialists in secondary care such as the ophthalmologist and the gastroenterologists. [10] In the ASAS cohort patients were recruited from rheumatologist practices. [1] In contrast to our cohort which completely consist of primary care CLBP patients. A preselection of patients leads to a higher probability of diagnosing patients with axSpA and subsequently to a higher sensitivity of the algorithm. [11]

There a number of strengths in our study, first of all the completeness of our data by which we can test both the ASAS referral recommendation and the ASAS algorithm within one cohort. Secondly the size of our cohort, nearly 1000 CLBP patients who all underwent a diagnostic work-up including MRI for axSpA, providing a unique opportunity to investigate the performance of the axSpA clinical pathway. And finally all patients in our cohort are primary care CLBP patients, no preselection on SpA features was used. This unselected CLBP population provides insight in the application of the ASAS referral recommendation and ASAS algorithm in daily practice. The unselected nature of our cohort is emphasized by our relative low percentage of axSpA cases (19%), versus 41% [10] or 61% [1] in preselected cohorts. Moreover is our percentage HLA-B27 positivity (6%), comparable with the HLA-B27 prevalence in the general population (7%). [12]

One limitation of the present study that we have to discuss is the fact that we used the ASAS criteria for axSpA to define our reference standard in the CaFaSpA cohort. We are aware that these classification criteria are different from a diagnosis by the rheumatologist. The difficulty in the field of rheumatology irrespective of axSpA is that there are no diagnostic criteria, even for rheumatoid arthritis there are only classification criteria. Two studies in secondary care compared the diagnosis of a rheumatologists to the ASAS classification criteria. In the DECLIC study 425 patients were diagnosed with axSpA by a rheumatologists, only 324 (76%) fulfilled the ASAS criteria.[13] In the SPACE study is also a comparison between the rheumatologists and the criteria, 65 patients were diagnosed by a rheumatologist and only 55 (85%) fulfilled the criteria. [10] Those studies illustrate that the criteria

are more strict than the rheumatologist. Besides this, the specificity in both studies (DECLIC 87%, SPACE 95%) was high, so the fear of 'over diagnosing' many patients by using the ASAS criteria seems not to be true. Also were our patients judged on the presence of SpA features by either an experienced rheumatologist (AW or KH) or by a well trained and experienced research nurse, no simple 'checkbox' approach was used. We have chosen for the ASAS criteria as outcome since the criteria are exactly defined and reproducible for research, while the diagnosis of a rheumatologists is not. It is desirable to have a clearly defined reference standard.

The practical value of the clinical pathway seems limited, the PPV is promising but the number of referred CLBP patients is high. Referring 800 out of 941 young CLBP patients to the rheumatologists is an undesirable situation. The number of rheumatologists to see all these referred CLBP patients is insufficient and it is likely that the health care costs for axSpA will become unacceptable, as a large amount of patients would undergo costly diagnostic procedures, such as X-ray, HLA-B27 testing and MRI.

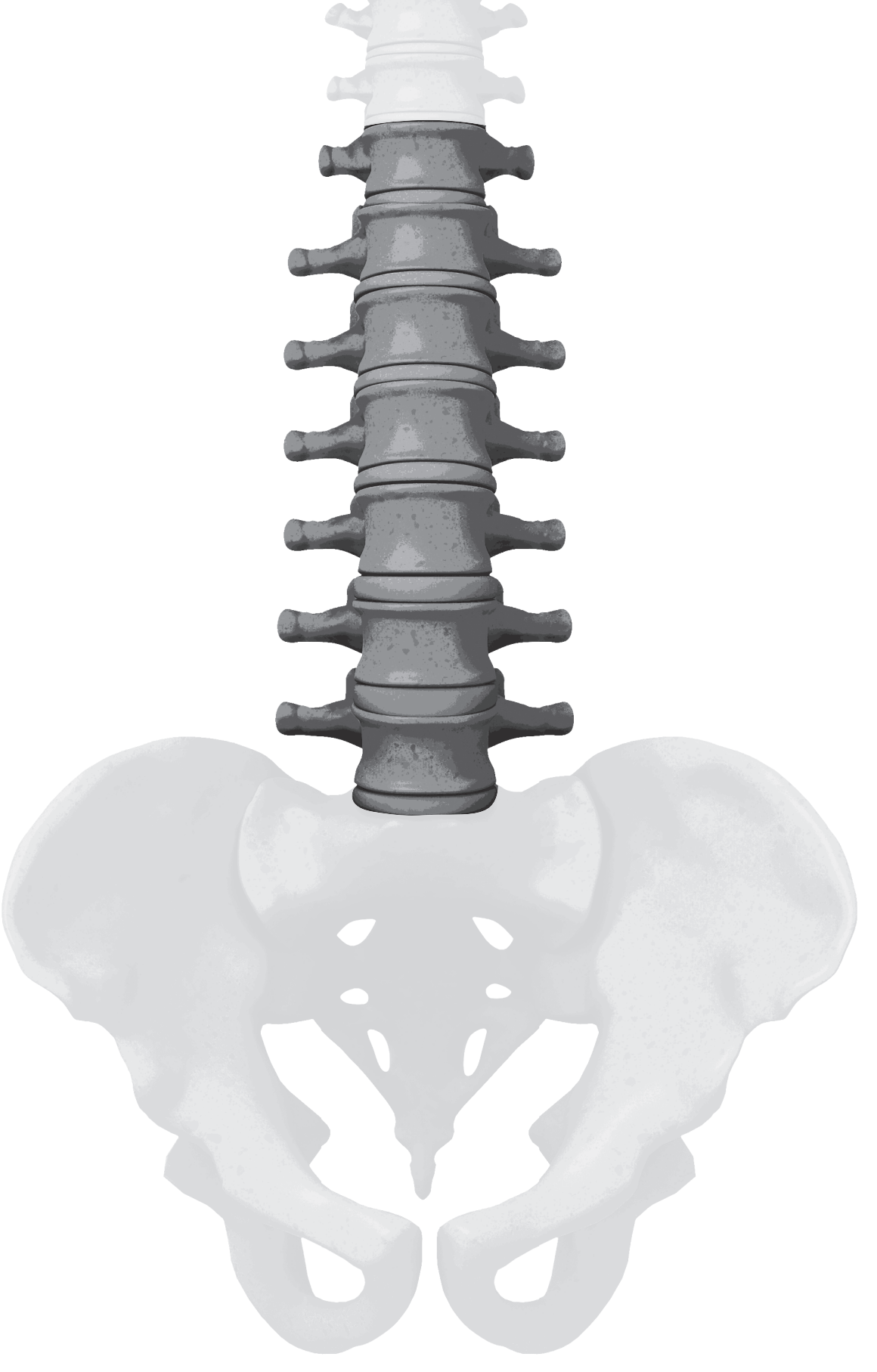
One solution to make the ASAS clinical pathway more applicable in practice is to make stricter requirements in the referral of CLBP patients. As we recently reported, adapting the ASAS recommendation by referring a patient if at least two parameters are present instead of one, seems more appropriate to use in daily practice. [9] Preceding the ASAS algorithm with the adapted referral recommendation, gives a sensitivity of the clinical pathway of again 56%, the specificity and PPV slightly increases to respectively 90% and 58%, and most important almost half of the patients are referred compared to the original clinical pathway (484 vs. 800).

Another potential solution to increase the sensitivity of the ASAS algorithm can be the suggestion already mentioned by van den Berg et al. [4]; "in the group of patients with 2-3 SpA features but with negative HLA-B27 a MRI should be considered." Especially since all our false negative patients with 2-3 SpA features (n=68) did have a sacroiliitis on the MRI. Less false negative patients will lead to a higher sensitivity, in our case with 68 less false negative patients will the sensitivity increase to 93% ((101+68)/181). However some caution regarding the sacroiliitis on MRI must be taken into account, several studies have shown that in up to 20% of the healthy population also a sacroiliitis is seen on MRI [14].

In conclusion; the practical value of a clinical pathway for axSpA by combining the ASAS referral recommendation and the ASAS diagnostic algorithm is modest, especially the large number of unnecessarily referrals will hamper implementation of the clinical pathway in daily practice. The large number of unnecessarily referrals might be reduced by using more strict criteria for referral. We suggest to perform further diagnostic studies in prospective cohorts of young primary care CLBP patients who are followed up for the development of axSpA, testing the more strict referral criteria, and to investigate if the introduction of a clinical pathway leads to earlier recognition and diagnoses of axSpA.

References

1. Rudwaleit, M., 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**(6): p. 777-83.
2. Sieper, J., et al., *Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1).* Ann Rheum Dis, 2013. **72**(6): p. 815-22.
3. Poddubnyy, D., et al., *Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis.* Ann Rheum Dis, 2015.
4. van den Berg, R., 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, 2012.
5. van Hoeven, L., et al., *External Validation of a Referral Rule for Axial Spondyloarthritis in Primary Care Patients with Chronic Low Back Pain.* PLoS One, 2015. **10**(7): p. e0131963.
6. van Hoeven, L., et al., *Identifying axial spondyloarthritis in dutch primary care patients, ages 20-45 years, with chronic low back pain.* Arthritis Care Res (Hoboken), 2014. **66**(3): p. 446-53.
7. Sieper, J., et al., *The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis.* Ann Rheum Dis, 2009. **68 Suppl 2**: p. ii1-44.
8. Goie The, H.S., et al., *Evaluation of diagnostic criteria for ankylosing spondylitis: a comparison of the Rome, New York and modified New York criteria in patients with a positive clinical history screening test for ankylosing spondylitis.* Br J Rheumatol, 1985. **24**(3): p. 242-9.
9. van Hoeven, L., et al., *Evaluating the ASAS recommendations for early referral of axial spondyloarthritis in patients with chronic low back pain; is one parameter present sufficient for primary care practice?* Ann Rheum Dis, 2015.
10. van den Berg, R., 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.
11. Bandolier, *How good is that test? II. Available at http://www.medicine.ox.ac.uk/bandolier/band27/b27.2.html.* Accessed 2 November 2015
12. van Gaalen, F., et al., *Is HLA-B27 Increased in Patients Diagnosed with Undifferentiated Arthritis? Results from the Leiden Early Arthritis Cohort.* J Rheumatol, 2014. **41**(10): p. 1948-51.
13. Molto, A., 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**(9): p. 1472-81.
14. Pedersen, S.J., U. Weber, and M. Ostergaard, *The diagnostic utility of MRI in spondyloarthritis.* Best Pract Res Clin Rheumatol, 2012. **26**(6): p. 751-66.



Chapter 7

Work-outcome in yet undiagnosed patients with non-radiographic axial spondyloarthritis and ankylosing spondylitis patients; results of a study among patients with chronic low back pain

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Submitted

Abstract

Objective: To understand the impact of yet undiagnosed non-radiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS) on work outcomes in a cohort of patients with chronic low back pain (CLBP).

Methods: Data was used from a primary care CLBP cohort that was established to understand the prevalence of nr-axSpA and AS. Clinical characteristics comprised measures of back pain (visual analogue scale), inflammation (C-reactive protein) and physical functioning (Roland Morris Disability Questionnaire (RMDQ)). Worker outcomes comprised a question on employment and the Work Productivity and Activity Impairment (WPAI) questionnaire, distinguishing absenteeism, presenteeism, and overall work impairment in those employed and activity impairment in all patients. For each disease subgroup employment ratio compared to general population was assessed by indirect standardization. Factors associated with work productivity were explored by zero inflated negative binomial (ZINB) regression models.

Results: 579 CLBP patients were included (41% male, mean age 36 years), of whom 71 (12%) were identified as nr-axSpA and 24 (4%) as AS. The standardized employment ratios were 0.89 (95% CI 0.84-0.94), 0.97 (95% CI 0.85-1.09) and 0.81 (95% CI 0.56-1.06) for CLBP, nr-axSpA and AS patients respectively. Scores of the WPAI subdomains were not significantly different between CLBP and nr-axSpA or AS patients. The ZINB models showed significant associations between VAS pain and RMDQ and work productivity.

Conclusion: The impact of yet undiagnosed nr-axSpA and AS on work outcomes is substantial but was not significantly different from CLBP patients. Variables significantly associated with work productivity were VAS pain and RMDQ.

Introduction

Low back pain (LBP) is a major health and societal problem affecting more than 80% of the adults at some point in their lives. [1] Between 10 and 28% of the LBP complaints persist for more than 12 weeks and becomes chronic. [2] A study has shown that up to 24% of the CLBP complaints in young adults can be explained by axial spondyloarthritis (axSpA). [3] AxSpA is an auto-inflammatory disease of the spine that is potentially treatable. Two subtypes of axSpA can be distinguished; in *non-radiographic axSpA* (nr-axSpA) either sacroiliitis is visible on the MRI or HLA-B27 is positive, and in addition one or two so-called 'SpA features' are present. [4] In those with *radiographic axSpA* structural changes are visible on the X-ray of the SI-joint and this subtype corresponds to what is commonly known as ankylosing spondylitis (AS).

Although the new classification criteria for axSpA were developed to enhance early recognition and subsequently provide earlier and better treatment, the profile of those in whom the diagnosis of axSpA is wrongly missed is not completely elucidated. This is important, as it could provide insight into the reversible burden of the disease when diagnosis would have made earlier. Several studies report an overall comparable clinical burden between AS and nr-axSpA patients [5, 6], but these patients were not necessarily wrongly missed but referred in prospective settings.

Clinical burden of a chronic inflammatory disease can be expressed in terms of disease activity and impaired function, but also in work participation. The impact of undiagnosed axSpA on the patients' capacity to work is important from the perspective of the patient and their families, as well as from the societal perspective when calculating indirect costs when determining the economic burden of a disease and possible return on invest by case finding strategies for axSpA patients. Moreover, such data can help to understand the level of support patients with axSpA might need to help them to remain active in labor force and safeguard career perspective.

Some data about the impact of AS and axSpA on work participation is already available. A review on work outcomes in AS indicates that patients with longstanding disease incur up to three times more frequently official work

disability, and a substantial part of work loss was already present at the time of diagnosis. [7] Also a recent study in early axSpA patients reported that after only 5 years of diagnosis, already 19% of patients with axSpA was not employed because of axSpA. [8] And in those working, sick leave was reported in 28% and 48% of the patients reported reduced productivity at work. Recent literature supports the suggestion that early recognition of axSpA might prevent adverse work outcomes. A recent medication trial in nr-axSpA patients showed an improvement in worker productivity of 9.6h/week in the nr-axSpA patients who had a good response to their treatment (assuming a 40 hours work week). [9]

The aim of this study is to investigate work outcomes in yet undiagnosed nr-axSpA and AS patients among a cohort of CLBP patients. The specific aims are to compare employment of patients with AS, nr-axSpA and CLBP with the general population, to explore whether these diagnostic groups differ in sick leave and at-work productivity, and which demographic and disease characteristics contributed to sick leave and at-work productivity.

Material and Methods

Study population

All patients from the second cross-sectional Case Finding Axial SpondyloArthritis (CaFaSpA 2) study were included. [10] The study was performed in 2011 and 2012 in the South-western part of the Netherlands. Ethics approval from the Medical Ethical Committee from the St. Elisabeth Hospital in Tilburg, the Netherlands was received. Written informed consent was obtained from all participants at the research center, before any assessment was performed.

CLBP patients ages 18-45 years were selected by ICPC code L03 (nonspecific low back pain) from GP records and invited to participate if the CLBP complaints were present for at least 3 months. Participating patients were examined by a rheumatologists or an experienced research nurse, i.e. medical history and physical examination, including the presence of SpA-features. All assessments and definitions adhered to the descriptions in the ASAS handbook. [11] Blood was drawn to determine HLA-B27 positivity, C-reactive protein (CRP, normal range 1-10 mg/l) and Erythrocyte Sedimentation Rate (ESR, normal range 0-15 mm Hg/

min). X-ray and magnetic resonance imaging (MRI) of the sacroiliac joints (SIJ) were obtained from all patients. A definitive diagnosis of sacroiliitis was made according to the ASAS MRI criteria [4] or the modified New York criteria for the X-ray [12] by one out of three trained radiologist, who were blinded for clinical outcomes, laboratory data and the results of the other imaging method. The primary outcome of this study was to identify new axSpA patients by the ASAS classification criteria. [4] All newly identified axSpA patients were not seen by a rheumatologist yet.

To assess disease severity patients completed the Bath AS Disease Activity Index (BASDAI) [13], Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) [14], a visual analogue scale (VAS) for pain (range 0-10) and the Roland Morris Disability Questionnaire (RMDQ) score [15]. The RMDQ was developed to measure limitations in physical functioning in CLBP patients. It consists of questions about impairment and limitations in different activities due to low back pain complaints. Patients indicate if a question is applicable to them (score=1) or not (score=0). The score can range from 0 to 24 and a higher score indicates a higher level of disability.

Socio-economic status and worker productivity

All participants completed questions about their highest achieved educational level; low (elementary school), medium (high school) and high (university), current work status (employed, or not employed), and the number of working days and working hours per week in those employed. To assess whether a patient was work-disabled or not work-disabled, we asked the patient is there was an official disapproval of the insurance company doctors. Answers on an open question about occupation were classified into manual (administrative, scientific and managerial professions) and non-manual (industrial, commercial, servicing, transportation and agricultural) jobs.

Finally, the Work Productivity and Activity Impairment (WPAI) questionnaire was completed, which evaluates four subdomains; absenteeism, presenteeism, work impairment and activity impairment due to back problems in past 7 days. [16] The subdomains are all expressed in percentages; absenteeism (% work time lost), presenteeism (% productivity loss at work), work impairment (absenteeism and presenteeism combined) and activity impairment (% activity loss). Higher percentages indicates worse outcomes.

Statistical analyses

The ASAS criteria were used to classify patients as having nr-axSpA, AS or not fulfilling the criteria (CLBP). Socio-demographic and clinical characteristics were summarized as mean and standard deviation (SD) or as median and interquartile range (IQR) and compared between subgroups by using unpaired t-test or Wilcoxon rank sum test for continuous variables and χ^2 or Fisher exact test for categorical data.

Indirect standardization was used to calculate employment ratios for the total population and each disease subgroup (AS, nr-axSpA and CLBP), in comparison to the general Dutch population. Employment data from the general Dutch population was provided by the Dutch Centraal Bureau voor Statistiek (CBS). [17] Poisson 95% confidence intervals (CI) for standardized proportions were calculated.

Scores on the WPAI are presented first as proportion of patients with any (>0%) absenteeism, presenteeism, work or activity impairment and next as the average % absenteeism, presenteeism, work and activity impairment. Absenteeism, presenteeism and activity impairment are calculated only in employed patients, activity impairment in all patients. Differences between subgroups in proportion of patients with any restriction was tested using Chi-square and Fisher exact test. Differences between subgroups in the level of restriction in each subdomain of the WPAI were tested using Wilcoxon rank sum test.

To investigate which factors are associated with each of the four domains of worker productivity, zero inflated negative binomial (ZINB) models were used. Zero inflated models were needed to adjust for the excess zeros in productivity outcomes (absenteeism: 87 %; presenteeism: 50%; work impairment: 39%; activity impairment: 32% of all observations). Zero inflated binomial models assume that the zeros can result from two different processes; [18] the 'certain zeros' (or always zeros) which are accounted for in the zero inflated logistic part and the 'possible zeros' that are accounted for in the count part. As in the count part the values are over dispersed (i.e. the variance was much larger than the mean), the negative binomial distribution was preferred and to fit the four subdomains of the WPAI zero-inflated models were used. [19]

To create the multivariable ZINB models four different steps were taken. In *step 1* gender and age were included in both the binomial and count part of the ZINB model. In the *second step* all the candidate covariates (disease: CLBP, nr-axSpA or AS; education level: low, intermediate, high; occupation: manual vs. non-manual; duration of low back pain (years); VAS pain; CRP, RMDQ, ASDAS-CRP and BASDAI) were tested univariate in both the binomial and count part of the ZINB. All variables that were significant at $p<0.20$ were considered for multivariable analyses in *step 3*. However ASDAS-CRP and BASDAI were not validated in CLBP patients, and as a moderate correlation was seen between VAS pain and BASDAI it was decided to take CRP, VAS pain and RMDQ into the multivariable model. In *step* 4, the model was repeated with the covariates with $p<0.05$ in the multivariable analysis.

A ZINB provides regression coefficients for both the logistic and the count part separately. A positive coefficient in the zero inflated (logistic) part of the ZINB means that an increase of that variable leads to a higher likelihood of resulting in a 'certain zero'. A negative coefficient in the count part of the ZINB means that an increase of that variable leads to a smaller change of scoring a zero in the outcome (i.e. subdomain of the WPAI).

The analyses were performed using STATA version 13.0 software (Stata Corporation TX, USA).

Results

CaFaSpA cohort

The enrollment of patients in the CaFaSpA 2 study is previously described. [10] Overall 2597 patients with CLBP of 38 primary care practices were invited to participate. 1161 (45%) patients responded to the invitation of which 480 expressed no interest in participation and 102 did not fulfil the inclusion criteria. In total were 579 CLBP patients included in this study. The median duration of low back pain was 7 years (IQR 3-15 years), 41% of the patients were male and the mean age was 36.0 years (sd 7.0) (Table 1). In total 95 (16.4%) patients could be classified as axSpA. Of those 95, 24 (25%) fulfilled classification criteria for AS and 71 (75%) for nr-axSpA. The majority (59 out of 71) of the patients in the nr-axSpA group was

classified based on MRI abnormalities. In the AS group was the percentage women higher (75%) compared to the nr-axSpA (58%) and CLBP group (58%), although this difference was not statistically significant (p=0.10). Of the three subgroups, patients with AS (8%) are less highly educated compared to patients with CLBP (21%) and nr-axSpA (24%). The percentage of patients with a manual occupation is the highest in the nr-axSpA patients (46%) compared to AS (29%) and CLBP (37%).

Table 1. Demographics and clinical characteristics in study participants (n=579)

Age, mean (sd) years ‡	*CLBP (n=484)*	*Nr-axSpA (n=71)*	*AS (n=24)*
	35.6 (7.1)	36.8 (6.6)	38.6 (5.8)
Male sex, n (%)	202 (42)	30 (42)	6 (25)
LBP duration, mean (sd) years	9.2 (7.7)	9.6 (7.4)	9.3 (9.9)
Disease activity			
VAS pain, median (IQR) ±	5 (3-7)	4 (2-5)	4.5 (2-7)
BASDAI, median (IQR)	4.2 (2.3-6)	3.9 (2.4-5.4)	5.3 (2.9-6.6)
ASDAS-CRP, median (IQR) §	2.3 (1.6-2.9)	2.3 (1.6-2.9)	2.8 (2.1-3.5)
RMDQ, median (IQR) [5]	7 (3-13)	6 (3-9)	12 (5-17)
*Educational level**			
Low (elementary school) (%)	177 (38)	29 (41)	11 (46)
Medium (high school)(%)	194 (41)	24 (34)	11 (46)
High (university) (%)	101 (21)	17 (24)	2 (8)
Work status			
Employed, n (%)	342 (72.2)	55 (77.5)	15 (62.5)
Disability pension, n (%)	8 (1.7)	2 (2.8)	0 (0)
Number of hours working per week, mean(sd) †	33.1 (9.4)	34.6 (8.6)	27.9 (12.4)
Occupation in employed patients†			
Manual, n (%)	124 (37)	24 (46)	4 (29)
Non-manual, n (%)	208 (63)	28 (54)	10 (71)

IQR = interquartile range; * Total number of questionnaires about educational level: CLBP n=472 (12 missing), nr-axSpA n=70 (1 missing); † Total number of questionnaires about occupation and working hours in employed patients: CLBP n=332 (10 missing), AS n=14 (1 missing), nr-axSpA n=52 (3 missing)
‡ p=0.04 for CLBP vs AS § p=0.01 for CLBP vs AS
± p=0.04 for CLBP vs nr-axSpA [5] p=0.03 for CLBP vs AS

Work status

In total 342 out of 579 (72.4%) participants (ages 18-45 years) were employed. After adjusting for age, the likelihood of being employed was 0.92 (95% CI 0.86-0.99) and 0.88 (95%CI 0.81-0.94) for man and woman respectively, compared with the Dutch general population. The age adjusted ratio's for employment in CLBP, nr-axSpA and AS patients were 0.89 (95% CI 0.84-0.94), 0.97 (95% CI 0.85-1.09) and 0.81 (95% CI 0.56-1.06) respectively. There were no patients with a disability pension in the

newly identified AS group, while eight (1.7%) in the CLBP group and two (2.8%) in the newly identified nr-axSpA group.

Work Productivity and Activity Impairment (WPAI) questionnaire

Of the 342 employed CLBP patients, 318 (93%) completed the WPAI questionnaire, and these proportions were 14/15 (93%) in AS and 48/55 (87%) in the nr-axSpA patients. Of the employed AS patients was 14% absent from work in the past 7 days, while this percentage was 10% and 12% in employed nr-axSpA and CLBP patients respectively (Table 2). Presenteeism was the most prevalent in CLBP patients (59%), but the percentage presenteeism was the highest in the AS group, 59%. No significant differences in all four sub scores between CLBP and nr-axSpA or CLBP and AS patients were found.

Table 2. Worker productivity assessed by the WPAI for employed patients with CLBP, nr-axSpA and AS (18-45 years)†

	CLBP (n=318)	*Nr-axSpA (n=48)*	*AS (n=14)*
Absenteeism			
Absenteeism present, n (%; (95% CI))	38 (12; (8-16))	5 (10; (4-23))	2 (14; (2-43))
Absenteeism, mean % (sd)	53 (31)	47 (43)	54 (59)
Presenteeism			
Presenteeism present, n (%; (95% CI))	188 (59; (53-64))	23 (47; (34-61))	7 (53; (27-79))
Presenteeism, mean % (sd)	45 (28)	46 (32)	59 (34)
Work impairment			
Work impairment present, n (%; (95% CI))	197 (62; (56-67))	25 (52; (37- 67))	8 (57; (29-82))
Work impairment, mean % (sd)	49 (30)	48 (33)	62 (36)
*Activity impairment**			
Activity impairment present, n(%; (95% CI))	322 (68; (63-72))	45 (63; (51-75))	19 (79; (58-93))
Activity impairment, mean % (sd)	51 (27)	49 (28)	56 (34)

WPAI= Worker Productivity and Activity Impairment Questionnaire; CLBP= chronic low back pain; nr-axSpA= non-radiographic axial spondyloarthritis; AS= Ankylosing Spondylitis
† No significant differences in all four sub scores between CLBP and nr-axSpA or CLBP and AS patients were found.
*Calculated in all patients, not only in the employed patients (CLBP=474, nr-axSpA=71, AS=24)

Zero inflated negative binomial models

Results of the age and gender adjusted univariable regression can be found in the ine Supplementary file, while the final multivariable model is presented in Table 3. In the final model VAS pain and RMDQ were independently associated with the logistic part of each of the four domains of the WPAI. For the count part of the

model, VAS pain and RMDQ were independently associated with presenteeism, work and activity impairment. This means that patients with pain and functional limitations are unlike to have no restrictions in worker productivity (so unlikely to belong to the zero inflated part) and that increased pain and functional limitations are associated with more presenteeism, overall work impairment and activity impairment, but no absenteeism. In addition, lower education was associated to the likelihood as well as level of overall work impairment and with the level of presenteeism, and longer disease duration was associated with a decreased likelihood of work impairment.

As an example of the interpretation of the output of the ZINB model; for activity impairment the 'inflated' (logit) model predicting the 'certain zeros' indicates that if a patient was to increase his VAS pain score by one point, the odds that he will belong in the 'certain zero' group (have no activity impairment) would be a factor of exp(-0.261)= 0.770. In other words, the higher a patients VAS score the less likely the patients is a certain zero (have no activity impairment). On the other hand, the 'count' part, indicates that one point increase in the VAS pain would increase activity impairment by a factor exp(0.079)= 1.082. Thus, the higher a patients VAS score, the more activity impairment is present.

Table 3. Final results of the ZINB regression model testing associations between demographical and clinical parameters and the WPAI subdomains corrected for age and gender*

	Absenteeism		*Presenteeism*		*Work impairment*		*Activity impairment*	
Parameter	Count	Logistic	Count	Logistic	Count	Logistic	Count	Logistic
Education level†								
Intermediate			0.100 (0.195)		-0.051 (0.578)	0.844 (0.004)		
High			-0.228 (0.015)		-0.252 (0.017)	0.716 (0.029)		
Duration of LBP (yrs)						0.043 (0.012)		
VAS pain		-0.190 (0.008)	0.081 (0.000)	-0.165 (<0.001)	0.079 (<0.001)	-0.324 (<0.001)	0.079 (<0.001)	-0.261 (<0.001)
RMDQ		-0.188 (<0.001)	0.048 (<0.001)	-0.005 (0.744)	0.058 (<0.001)	-0.152 (<0.001)	0.044 (<0.001)	-0.106 (<0.001)

*Only the significant regression coefficients are showed, the p-value is between the brackets. The logistic part of the ZINB model is generated for the 'certain zero' cases, predicting whether or not a patient would be in this group. At the same time the count part of the model is predicting the counts for those patients who are not certain zeros.
ZINB= zero inflated negative binomial; WPAI= Worker Productivity and Activity Impairment Questionnaire; LBP= low back pain; VAS = visual analogue scale; RDMQ = Roland Morris Disability Questionnaire

Discussion

To our knowledge this is the first study investigating the impact of yet undiagnosed nr-axSpA and AS on work outcomes within a group of CLBP patients. The employment rate among our CLBP patients was, as anticipated, lower than expected compared to the Dutch population of the same age and gender, and the lower employment rate was more pronounced in the AS patients, although not significantly different. In addition AS patients reported the highest values of absenteeism, presenteeism, work and activity impairment although the differences with CLBP and nr-axSpA patients were not significant, likely due to the low number of AS patients in the study population. Pain and functional limitations were associated with higher likelihood to have any work impairment. Pain by itself was associated with the level of presenteeism, overall work impairment and activity impairment.

A comprehensive comparison with existing literature is difficult as this is the first study addressing patients with previously unrecognized axSpA. Further, there is only limited literature concerning work outcomes in nr-axSpA patients [20], and last but not least data on employment and sick leave are country specific as the socio-economic environment plays an important role. [21] Notwithstanding, a comparison that can be made involves a recent study in Dutch early axSpA patients (defined based on the ESSG criteria) which evaluates problems in work participation. This study showed a remarkable high percentage of employed axSpA patients namely 81%. [8] This employment rate is even higher than the employment rate of the Dutch general population in 2014, which was 74.8% in the age category of 15 to 45 years. [17] An explanation of this high employment rate can be the high percentages of males in this study, which was 69% or relative low median BASDAI score (3.0) which was reported by the participants.

Focusing on the variables which are associated with work productivity in axSpA patients, they are reported equally within different studies and setting. Several studies reported that variables measuring pain, disease activity and physical functioning are associated with reduced work productivity. [8, 22-24] This association is not only found in axSpA but also in other rheumatic conditions such as rheumatoid arthritis. [25]

The strength is of this study is our study population, providing an unique opportunity to investigate yet undiagnosed nr-axSpA and AS patients and compare their outcomes to the outcomes in CLBP patients. Moreover are none of the nr-axSpA and AS patients diagnosed or treated by a rheumatologist for their disease, so there is no treatment bias in the impact of the disease on work outcomes. Also is this the first study describing work productivity in nr-axSpA patients outside a medication trial. And finally the use of the ZINB models to asses associations with work productivity, this is a very elegant statistical technique using at the same time a logistic and a count model, creating an optimal fit for our data with excessive zero's. [19]

Limitations of our study are that we didn't include coping in our analyses, therefor is it unclear to which extent coping plays a role in the self-reported questionnaire such as the VAS pain and RMDQ. Not all participants answered the questions about work outcomes, however the response rate of those questionnaires was 92% and there were no difference in patients characteristics between the responders and non-responders. Another potential limitation is that it is unclear why the nr-axSpA and AS patients have not been recognized by their primary care physicians and referred to a rheumatologist. Is this because their primary care physician had limited knowledge about axSpA and didn't recognized those patients or because the patient had experienced little symptoms from their disease so far? The second reasons seems not to be true as the median BASDAI score is 3.9 and 5.2 in the nr-axSpA and AS patients, respectively. And finally the group of AS patients is small, only 24 patients, making it hard to find significant differences between the AS, nr-axSpA and CLBP groups.

On this line it should be noted that a high percentage women was found in our AS sample (75%), no other AS cohorts report such a high percentage. A possible explanation can be that we used a different approach of including patients in our study, we only selected on age and the presence of CLBP. Subsequently all patients were examined for the presence of axSpA, while in most other cohorts patients are already selected by predefined features specific for axSpA and the change that males will be included in such a cohort is higher. On the other hand is this finding an indication that at this moment more females with AS are missed by primary care physicians, indicating an opportunity to educate primary care physicians more thoroughly about axSpA.

It is important to conduct research about work productivity, absenteeism and presenteeism as they can be indicators for future work disability. [26] Our results show that there are significant associations between patients reported outcomes measurements (PROMs) such as pain and functional limitations and work productivity, but no associations between more objective variables such as age, gender, disease (CLBP, nr-axSpA, or AS), manual occupation and work productivity. Leading to the cautious conclusion that the impact on work productivity is not disease related but related to the degree of pain and physical limitations a patient experiences. This finding is encouraging as we known from previous studies that adequately treating both AS and nr-axSpA patients leads to an improvement in PROMs. [27] Moreover after start of treatment not only an improvement in work participation, but also in unpaid work is reported in both AS and nr-axSpA patients. [9, 28] These findings emphasize that is important and useful to early recognize and referrer patients suspected of axSpA to a rheumatologist.

Conclusion

In conclusion, our findings demonstrate that the impact of yet undiagnosed nr-axSpA and AS is substantial although the outcomes in work productivity were not significantly different from CLBP patients. Variables associated with reduced work productivity were mainly PROMs such as VAS pain and functional limitations measured by the RMDQ. Early recognition and subsequently adequate treatment of yet undiagnosed nr-axSpA and AS patients can potentially lead to maintaining an optimal work productivity in nr- axSpA and AS patients and a reduction in indirect costs.

References

1. Hoy, D., et al., *A systematic review of the global prevalence of low back pain.* Arthritis Rheum, 2012. **64**(6): p. 2028-37.
2. Freburger, J.K., et al., *The rising prevalence of chronic low back pain.* Arch Intern Med, 2009. **169**(3): p. 251-8.
3. van Hoeven, L., et al., *Identifying axial spondyloarthritis in dutch primary care patients, ages 20-45 years, with chronic low back pain.* Arthritis Care Res (Hoboken), 2014. **66**(3): p. 446-53.
4. Rudwaleit, M., 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**(6): p. 777-83.
5. Poddubnyy, D., et al., *The frequency of non-radiographic axial spondyloarthritis in relation to symptom duration in patients referred because of chronic back pain: results from the Berlin early spondyloarthritis clinic.* Ann Rheum Dis, 2012. **71**(12): p. 1998-2001.
6. Kiltz, U., et al., *Do patients with non-radiographic axial spondylarthritis differ from patients with ankylosing spondylitis?* Arthritis Care Res (Hoboken), 2012. **64**(9): p. 1415-22.
7. Boonen, A. and S.M. van der Linden, *The burden of ankylosing spondylitis.* J Rheumatol Suppl, 2006. **78**: p. 4-11.
8. van der Weijden, M.A., A. Boonen, and I.E. van der Horst-Bruinsma, *Problems in work participation and resource use should not be underestimated in patients with early spondyloarthritis.* J Rheumatol, 2014. **41**(12): p. 2413-20.
9. van der Heijde, D., et al., *ASAS40 and ASDAS clinical responses in the ABILITY-1 clinical trial translate to meaningful improvements in physical function, health-related quality of life and work productivity in patients with non-radiographic axial spondyloarthritis.* Rheumatology (Oxford), 2015.
10. van Hoeven, L., et al., *External Validation of a Referral Rule for Axial Spondyloarthritis in Primary Care Patients with Chronic Low Back Pain.* PLoS One, 2015. **10**(7): p. e0131963.
11. Sieper, J., et al., *The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis.* Ann Rheum Dis, 2009. **68 Suppl 2**: p. ii1-44.
12. Goie The, H.S., et al., *Evaluation of diagnostic criteria for ankylosing spondylitis: a comparison of the Rome, New York and modified New York criteria in patients with a positive clinical history screening test for ankylosing spondylitis.* Br J Rheumatol, 1985. **24**(3): p. 242-9.
13. Bonisch, A. and I. Ehlebracht-Konig, *[The BASDAI-D--an instrument to defining disease status in ankylosing spondylitis and related diseases]*

Der BASDAI-D--ein Fragebogen zur Erfassung der Krankheitsaktivitat bei Spondylitis ankylosans und verwandten Erkrankungen. Z Rheumatol, 2003. **62**(3): p. 251-63.

14. Machado, P., et al., *Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores.* Ann Rheum Dis, 2011. **70**(1): p. 47-53.
15. Roland, M. and R. Morris, *A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain.* Spine (Phila Pa 1976), 1983. **8**(2): p. 141-4.
16. Reilly, M.C., et al., *Validity, reliability and responsiveness of the Work Productivity and Activity Impairment Questionnaire in ankylosing spondylitis.* Rheumatology (Oxford), 2010. **49**(4): p. 812-9.
17. CBS, *www.statline.cbs.nl.* 2014.
18. Yau, K.K.W., K. Wang, and A.H. Lee, *Zero-Inflated Negative Binomial Mixed Regression Modeling of Over-Dispersed Count Data with Extra Zeros.* Biometrical Journal, 2003. **45**(4): p. 437-452.
19. Greene, W.H., *Accounting for excess zeros and sample selection in Poisson and negative binomial regression models.* 1994.
20. Boonen, A., et al., *The burden of non-radiographic axial spondyloarthritis.* Semin Arthritis Rheum, 2014.
21. Wynne-Jones, G., et al., *Absence from work and return to work in people with back pain: a systematic review and meta-analysis.* Occup Environ Med, 2014. **71**(6): p. 448-56.
22. Haglund, E., et al., *Work productivity in a population-based cohort of patients with spondyloarthritis.* Rheumatology (Oxford), 2013. **52**(9): p. 1708-14.

23. Boonen, A., et al., *Impact of ankylosing spondylitis on sick leave, presenteeism and unpaid productivity, and estimation of the societal cost.* Ann Rheum Dis, 2010. **69**(6): p. 1123-8.
24. Boonen, A., et al., *Employment, work disability, and work days lost in patients with ankylosing spondylitis: a cross sectional study of Dutch patients.* Ann Rheum Dis, 2001. **60**(4): p. 353-8.
25. Geuskens, G.A., et al., *Predictors of sick leave and reduced productivity at work among persons with early inflammatory joint conditions.* Scand J Work Environ Health, 2008. **34**(6): p. 420-9.
26. Mau, W., et al., *Employment across chronic inflammatory rheumatic diseases and comparison with the general population.* J Rheumatol, 2005. **32**(4): p. 721-8.
27. Callhoff, J., et al., *Efficacy of TNFalpha blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis.* Ann Rheum Dis, 2015. **74**(6): p. 1241-8.
28. Barkham, N., et al., *Double-blind placebo-controlled trial of etanercept in the prevention of work disability in ankylosing spondylitis.* Ann Rheum Dis, 2010. **69**(11): p. 1926-8.

Supplementary file by article 'Work-outcome in previously undiagnosed patients with non-radiographic axial spondyloarthritis and ankylosing spondylitis patients; results of a study among patients with chronic low back pain'

Table 1. Modelling steps to create per subdomain of the WPAI a zero inflated negative binomial (ZINB) regression model to explore associations between WPAI subdomains and demographical and clinical variables *

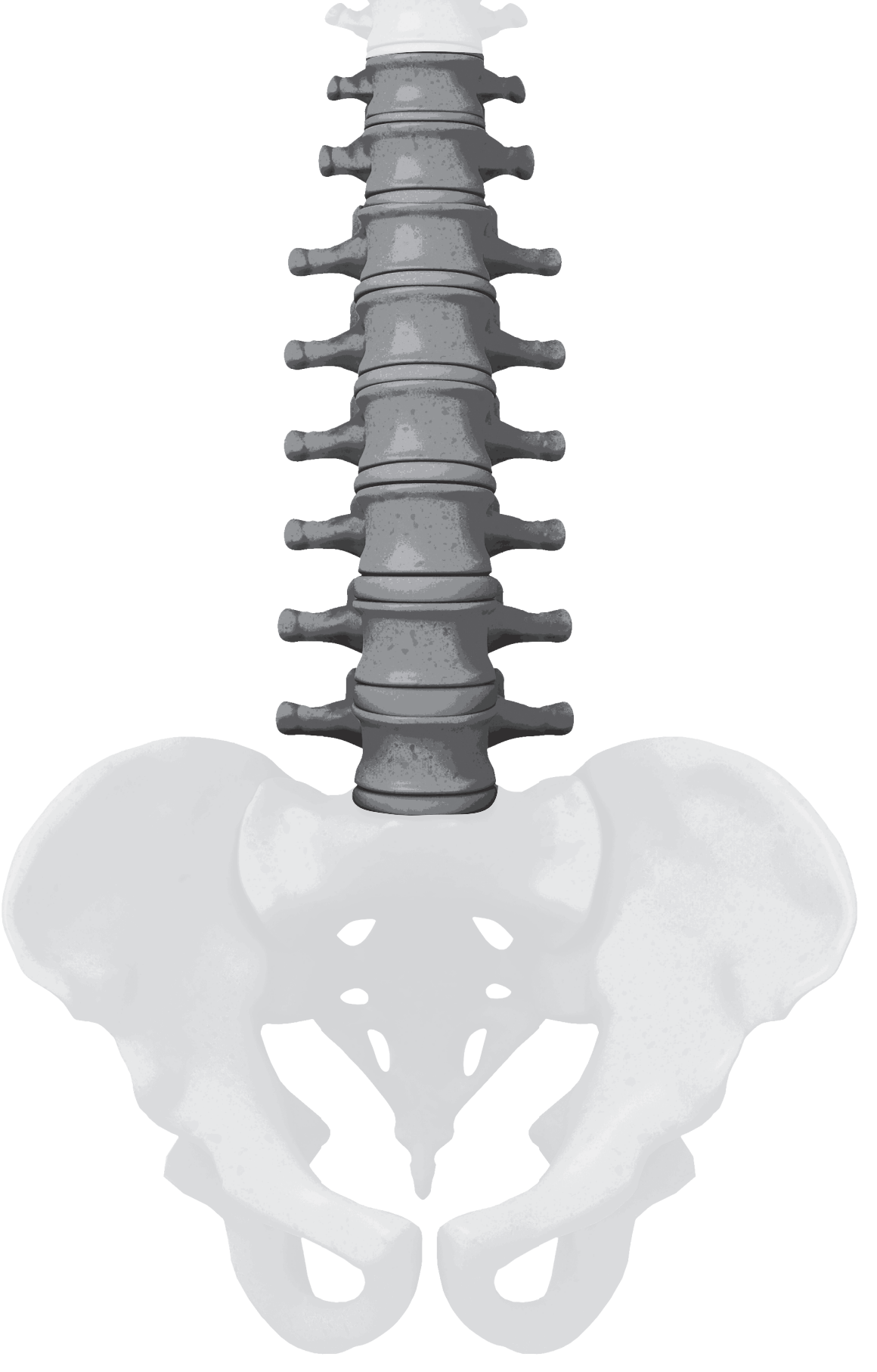
Step 2: Univariate analyses with candidate covariates corrected for gender and age. Covariates with p <0.20 are maintained in the multivariate model (step 3)								
	Absenteeism		Presenteeism		Work Impairment		Activity impairment	
Variable	**Binomial**	**Logit**	**Binomial**	**Logit**	**Binomial**	**Logit**	**Binomial**	**Logit**
Disease‡								
Nr-axSpA	-0.366 (0.313	0.254 (0.612)	-0.021 (0.869)	**0.341 (0.186)**	-0.012 (0.934)	**0.407 (0.194)**	-0.034 (0.725)	0.221 (0.411)
AS	-0.113 (0.826)	-0.093 (0.905)	**0.281 (0.112)**	-0.448 (0.303)	0.248 (0.324)	0.229 (0.682)	0.086 (0.554)	- 0.441 (0.396)
Education level§								
Intermediate	-0.195 (0.438)	**0.927 (0.009)**	**-0.180 (0.043)**	0.095 (0.620)	-0.118 (0.263)	**0.839 (0.001)**	**-0.139 (0.049)**	**0.494 (0.020)**
High	-0.243 (0.392)	**0.873 (0.036)**	**-0.361 (0.001)**	0.285 (0.213)	**-0.363 (0.003)**	**0.884 (0.003)**	**-0.142 (0.098)**	**0.635 (0.010)**
Manueel occupation‡	0.205 (0.372)	**0.904 (0.006)**	**-0.173 (0.062)**	**0.509 (0.019)**	**-0.156 (0.105)**	**0.661 (0.004)**	-0.067 (0.414)	0.134 (0.538)
Duration LBP	0.005 (0.686)	**0.041 (0.081)**	0.005 (0.367)	0.015 (0.205)	0.000 (0.901)	**0.023 (0.113)**	-0.000 (0.828)	**0.023 (0.067)**
Vas pain	-0.003 (0.949)	**-0.305 (<0.001)**	**0.116 (<0.001)**	**-0.171 (<0.001)**	**0.105 (<0.001)**	**-0.338 (<0.001)**	**0.116 (<0.001)**	**-0.317 (<0.001)**
ASDAS-CRP	-0.136 (0.399)	**-1.056 (<0.001)**	**0.292 (<0.001)**	**-0.507 (<0.001)**	**0.269 (<0.001)**	**-.0898 (<0.001)**	**0.304 (<0.001)**	**-0.746 (<0.001)**
BASDAI	-0.290 (0.582)	**-0.375 (<0.001)**	**0.117 (<0.001)**	**-0.164 (<0.001)**	**0.113 (<0.001)**	**-0.342 (<0.001)**	**0.111 (<0.001)**	**-0.354 (<0.001)**
RMDQ	**0.036 (0.094)**	**-0.204 (<0.001)**	**0.059 (<0.001)**	**-0.031 (0.029)**	**0.066 (<0.001)**	**-0.124 (<0.001)**	**0.056 (<0.001)**	**-0.137 (<0.001)**
CRP	-0.012 (0.660)	-0.010 (0.770)	0.004 (0.635)	**-0.046 (0.036)**	-0.001 (0.933)	-0.026 (0.323)	-0.000 (0.983)	0.022 (0.296)

*The estimated regression coefficients are given, the p-value is between the brackets. The logit model of the ZINB is generated for the 'certain zero' cases, predicting whether or not a patient would be in this group. At the same time a negative binomial model is generated predicting the counts for those patients who are not certain zeros.
‡ CLBP as reference, nr-axSpA coded as 1, AS coded as 2; §Low education level as reference, intermediate level coded as 1, high level coded as 2; LBP= low back pain; VAS = visual analogue scale; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score with c-reactive protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; RDMQ = Roland Morris Disability Questionnaire; CRP = C-reactive protein

Step 3. Multivariate analyses with significant and applicable covariates corrected for gender and age.† Covariates with p<0.05 are maintained for step 4

	Absenteeism		Presenteeism		Work Impairment		Activity impairment	
Variable	**Binomial**	**Logit**	**Binomial**	**Logit**	**Binomial**	**Logit**	**Binomial**	**Logit**
Disease‡								
Nr-axspa			0.179 (0.155)	0.239 (0.467)		0.156 (0.663)		
AS			0.012 (0.956)	0.231 (0.711)		0.216 (0.747)		
Education level§								
Intermediate		0.606 (0.144)	-0.082 (0.371)		-0.062 (0.505)	**0.820 (0.007)**	-0.051 (0.381)	0.231 (0.326)
High		0.309 (0.563)	**-0.223 (0.047)**		**-0.290 (0.011)**	0.489 (0.164)	-0.067 (0.337)	0.303 (0.269)
Manueel occupation		0.571 (0.152)	0.020 (0.819)	0.404 (0.095)	0.053 (0.541)	0.537 (0.051)		
Duration LBP		0.053 (0.057)				**0.047 (0.008)**		
Vas pain		**-0.219 (0.004)**	**0.095 (<0.001)**	**-0.323 (<0.001)**	**0.082 (<0.001)**	**-0.340 (<0.001)**	**0.080 (<0.001)**	**-0.267 (<0.001)**
RMDQ	0.044 (0.054)	**-0.172 (<0.001)**	**0.052 (<0.001)**	**-0.092 (0.003)**	**0.058 (<0.001)**	**-0.090 (<0.001)**	**0.044 (<0.001)**	**-0.104 (<0.001)**
CRP				-0.057 (0.072)				

*The estimated regression coefficients are given, the p-value is between the brackets. The logit model of the ZINB is generated for the 'certain zero' cases, predicting whether or not a patient would be in this group. At the same time a negative binomial model is generated predicting the counts for those patients who are not certain zeros.
† BASDAI and ASDAS-CRP were excluded after step 2 as both are not validated to use in CLBP patients.
‡ CLBP as reference, nr-axSpA coded as 1, AS coded as 2; §Low education level as reference, intermediate level coded as 1, high level coded as 2; LBP = low back pian; VAS = visual analogue scale; RDMQ = Roland Morris Disability Questionnaire; CRP = C-reactive protein



Chapter 8

A cluster randomized controlled trial to evaluate a referral strategy for axial spondyloarthritis in young primary care patients with chronic low back pain; an impact study

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Submitted

Abstract

Background: Axial spondyloarthritis (axSpA) is a disabling inflammatory joint disease with chronic low back pain (CLBP) as leading symptom. Recognizing axSpA in the large amount of CLBP patients is difficult for general practioners (GP). This evaluation aims to assess the effect of a referral strategy for axSpA in young primary care patients with CLBP by comparing the use of the strategy with usual care.

Methods/Design: This study entails a clinical effect, process and cost evaluation using a cluster randomized controlled trial with GP as clusters. GPs throughout the Netherlands are invited to participate and randomized to either the intervention or the control group. Patients from participating GPs are invited to participate if they have ever been registered with low back pain, without radiation (ICPC L03) and aged 18-45 years. To be included in the study, patients need to have current low back pain and chronic low back pain (>12 weeks). In the intervention arm a referral strategy for axSpA will be applied in CLBP patients, in the control arm care as usual will be provided for CLBP patients. The referral strategy consists of four easy to use variables. All are questions about the back pain complaints of the patients. Data is prospectively collected in an online database at baseline (T0), 4 months (T1), 12 months (T2) and 24 months (T3). Patient outcomes (e.g. pain scores, quality of life) as well as process measures (e.g. number of axSpA diagnoses by rheumatologists) will be measured. Our primary outcome is the Roland Morris Disability Questionnaire after 4 months, secondary outcomes are pain and quality of life. Costs will be assessed before and after the use of the referral strategy, to estimate if the use of the strategy will lead to a reduction in health care costs and improvement in work participation.

Discussion: It is anticipated that using the axSpA referral strategy for primary care CLBP patients will result in more (correct) diagnoses of axSpA by the rheumatologists, will increase the quality of life of CLBP patients and will be cost-effective. Ultimately, the results of this study may contribute to the national implementation of the axSpA referral strategy to identify timely CLBP patients with axSpA.

Trial registration: NCT01944163 (Clinicaltrials.gov)

Background

Low back pain (LBP) is one of the most common musculoskeletal disorders affecting up to 85% of the adults at some point in their lives. [1] In 10-28% of the patients the pain persists for more than 12 weeks and becomes chronic. [2] On top of the high prevalence, LBP is the leading cause of years lived with disability (YLD). The YLD of low back pain is higher than the YLD of e.g. major depressive disorders, anemia, chronic obstructive pulmonary disease and diabetes. [3]

One of the possible causes of chronic low back pain (CLBP) is axial spondyloarthritis (axSpA) which is a heterogeneous inflammatory joint disease. Two recent studies showed a prevalence of axSpA among young (18-45 years) CLBP patients between 16% and 24%. [4, 5] Recently the focus of axSpA is on early diagnosis considering treatment is more effective in patients with short symptom duration. [6] For an early diagnosis of axSpA by rheumatologists, early recognition in primary care is important. However recognition of axSpA is difficult because specific signs or symptoms do not exist. [7] Moreover, in the current CLBP guidelines for GPs no referral guidelines for axSpA are included. [8]

Within the field of rheumatology several models to identify patients at high risk for axSpA have been published, these models combine multiple predictors, such as clinical symptoms, patients' characteristics and test results to estimate the probability of the disease. Almost all published referral models are tested in a pre-selected population with a high prior probability of axSpA. Only one referral strategy is developed and externally validated in a primary care CLBP population, the CaFaSpA referral rule. [4, 5] This low cost referral rule is easy to use and consists of four variables, all variables are questions. The GP can ask these questions while taking a patient's history.

After development and external validation of a referral rule the next step before application in daily practice is to investigate the impact of the referral rule. [9, 10] Since the CaFaSpA referral rule can identify axSpA patients, it is worthwhile to perform an impact analysis to determine its effect in primary care.

Objective of the evaluation: This study entails a clinical effect, process and cost evaluation of using the axSpA referral strategy for primary care CLBP patients.

The study aims to determine to what extent use of the rule, in comparison with usual care, leads to more diagnoses of axSpA and improved quality of life in CLBP patients. Second, health care costs and work participation will be compared before and after the application of the referral strategy.

Methods

Design: The study uses a cluster randomized controlled trial design which is carried out in the primary care setting in the Netherlands. Sixty primary care practices will be randomized to either the intervention or the control (usual care) group. Each cluster contains the GPs from one practice and their included patients.

General practices: GPs at the surrounding areas of participating Dutch rheumatologists will be invited to participate by an invitation letter. Two weeks after this invitation letter a member our research team will call the GP to assure if the GP was interested in participating. The only exclusion criteria for GPs is not using the ICPC coding system for their patients, as patients will be selected from the GP practice using the ICPC system.

Recruitment of patients and eligibility criteria: Patients will be recruited from participating practices by searching their records for patients with ICPC L03 and aged between 18 and 45 years. The recruitment of patients is the same for GPs randomized to the intervention as for GPs randomized to the control group. All selected patients will receive a letter from their GP briefly explaining the study and asking the patient to respond using the attached return form. If the patient does not respond to the invitation within 4 weeks, a second invitation letter will be sent.

The inclusion criteria are:

- Age 18-45 years
- Ever registered with low back pain, without radiation (ICPC L03)
- Current low back pain
- ≥12 weeks low back pain

The exclusion criteria are:

- A clear explanation for the back pain (like a trauma, hernia nuclei pulposi or malignancy)
- Mentally incompetent
- No understanding of the Dutch language (written)

Patients who agree to participate sign a consent form, thereafter they will be called by a research assistant to confirm the inclusion criteria. The research assistant will register the answers to the CaFaSpA referral rule of the participant. After this telephone contact the patient will receive online questionnaires per email concerning their back pain. If email contact it is not possible, the patient will receive the questionnaires by post.

Those who do not wish to participate will be registered by gender, date of birth and the reason for not participating, such as no current low back pain, no time, etc.

Randomisation, allocation procedure and blinding: Primary care practices are randomly allocated to either the intervention or the control group. Randomisation is stratified for number of GPs working in the primary care practice (one or two vs more than two) to ensure similar number of patients in both groups. The block randomisation schedule is computer generated and administrated by an independent person, who is not involved in patient care. It is impossible to blind patients or GPs for allocation. If a patient receives the advice of a referral to the rheumatologist, both the patient and the GP are actively involved in this referral. Also the outcome assessment is not blinded, as patients assess the outcomes themselves by filling in questionnaires. Blinded analyses of the data will take place when possible.

Intervention: The intervention is the application of the CaFaSpA referral rule by GPs in young primary care patients with CLBP.[4] [5] (Box 1) If the referral rule is positive, a referral to the rheumatologist will be advised. This advice will be send to the patient and the patients' GP by post.

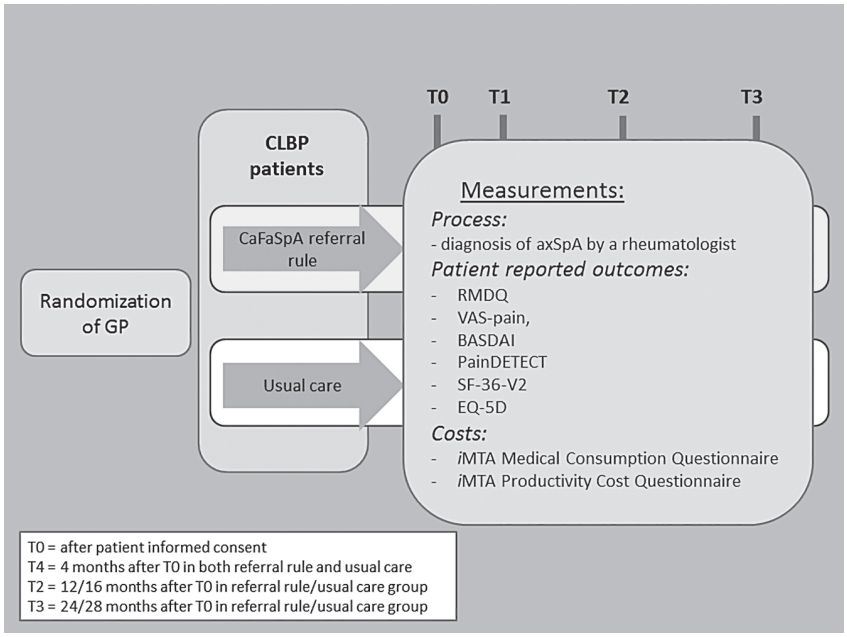
Box 1. The CaFaSpA referral strategy
Applicable in patients ≥3 months back pain and age at onset <45 years
Inflammatory back pain
Inflammatory back pain is considered present if at least four questions are answered with yes - Age at onset <40 years - Insidious onset - Improvement with exercise - No improvement with rest - Pain at night (with improvement upon getting up)
Positive family history
A positive family history is considered present if there is a first or second degree family member with axial spondyloarthritis, Crohn's disease, psoriasis or uveitis anterior
Good reaction to NSAIDs
A good reaction to NSAIDs is present when a patients reports a relieve in pain perception within 48 hours after receiving a non-steroidal anti-inflammatory drug
CLBP ≥5 years
A long low back duration is present if the duration of the back pain is 5 years or longer
If at least two out of the four referral parameters is present → a referral to the rheumatologist is advised

Control group: Participating patients of the control group are also called by our research assistant to check the inclusion criteria and to register the answers to the CaFaSpA referral rule. No active advice regarding a referral takes place. If control group patients choose to go to their GP, they will be treated according to the Dutch College of General Practice guidelines for the management of low back pain. [11]

To increase the feasibility of our study we decided to communicate the outcome of the referral rule to the control group after 4 months. Therefore after 4 months (primary outcome time point) the CLBP patients in the control group and their GPs will receive a letter containing the outcome of the referral rule and an advice to refer or not refer the patient. After receiving the outcome of the referral rule the patients of the control group will be followed for two years, data will be collected after 1 and 2 years of exposure to the referral rule, this will be sixteen and twenty-eight months after inclusion of the study. (Figure 1)

Data collection: Data collection of patient outcomes are at baseline (T0) (directly after inclusion of a patient in the study), after 4 months (T1), after 12 or 16 months (T3) and after 24 or 28 months (T4). (Figure 1) At each time point patients will automatically receive an email with a link to online questionnaires.

Figure 1: Flowchart of the IMPACT study



Outcome measures: The primary clinical outcome is the score on the Roland Morris Disability Questionnaire (RMDQ) after 4 months. [12] The RMDQ has a scale of 0 to 24. A higher score indicates a more severe disability score.

Process

- Diagnosis of axial spondyloarthritis made by rheumatologists The diagnosis of axSpA by a rheumatologist is verified by hospital records.

Patient reported outcomes

- Pain measured by the Visual Analogue Scale (VAS) pain [13]
- Health related quality of life measured by the SF-36 version 2 and EQ-5D. [14, 15]
- Disease activity for axSpA, measured by the BASDAI. [16]
- Neuropathic components related to back pain measured by the painDETECT [17]

Costs

- Loss of work-productivity measured by work participation (*i*MTA Productivity Cost Questionnaire iPCQ))[18]
- Health care resources use measured by the *i*MTA Medical consumption questionnaire [19]

Compliance: The compliance of patients is optimized by sending up to three reminders emails, asking the patient to fill out the online questionnaires. If the patient still has not completed the questionnaires the research assistant will contact the patient by telephone and the questionnaires are sent to the patient by post.

Sample size: For the power calculation we assumed a difference of 2.5 points on the RMDQ at four months between the referral rule and usual care group. These 2.5 points are the clinically significant difference, found in previous studies. [20, 21] The SD of the RMDQ is 6.0 based on data observed in the previous CaFaSpA 2 study. [4] Detection of this 2.5 point improvement in a randomized trial would require 180 patients per group, using a two-sided α of 0.05 and power of 0.80. (Figure 2A)

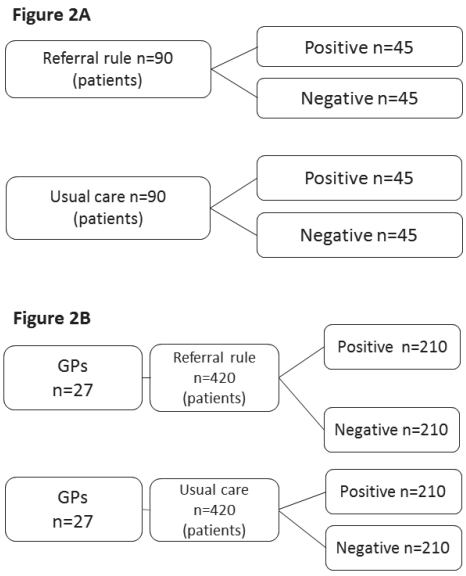
Patient with a negative result of referral strategy (no referral to the rheumatologists) in the intervention group will receive the same treatment as the usual care group. Therefore, the effect of the referral strategy can only be assessed in patients with a positive result of the referral strategy. From the previous CaFaSpA studies we know that around 50% of the participating patients will have a positive result. Therefore 360 patients (180 x2)would be required for 80% power.

Further, the sample size was adjusted for cluster randomization based on an intra-cluster correlation coefficient of 0.05 and an average cluster size of 16. [22] [23] The average cluster size is based on data of the CaFaSpA 1 and 2 studies, with on average 16 participating patients per GP. With these findings we can calculate the design effect; design effect= 1 +(16-1) * 0.05 = 1.75

Multiplying 360 patients by the design effect of 1.75 implies that a total of 630 patients must be included in this study. If a lost to follow up of 25% is taken into account 840 patients need to be enrolled. Assuming 16 CLBP patients per GP, implies that 54 GPs (840/16) need to be randomized. (Figure 2B)

We expect that 16 patient per GP practice will participate, if the number of participating patients per practice is smaller, for example only 6, this will lead to a smaller design effect (1.25) and a total of only 600 patients should be enrolled to create sufficient power.

Figure 2: A. Crude sample size calculation
B. Sample size calculation taking clustering into account (ICC of 0.05)



Data analysis: Effects at 4 months and the process evaluation will be analysed according to the intention-to-treat principle. The baseline characteristics of the patients will be summarized by randomisation group, reported as mean (standard deviation) or median (interquartile range) for continuous variables and count (percent) for categorical variables.

As this is a cluster-randomized trial mixed effect regression analysis will be used to compare the mean RMDQ score after four months between the intervention and usual care group. Fixed effects include allocation group and result of the referral strategy (referral y/n). As the effect of the referral strategy is expected in the subgroup of patient with a referral advice, an interaction term between allocation group and result of the referral strategy will also be included. A random intercept will be included adjusting for clustering. [24, 25] This random intercept stand for the effect of different primary care practices (i.e. clusters).

For the secondary outcomes we will again use a mixed effect regression analysis to estimate the effect of the use of the referral strategy after 4 months on process level (i.e. the number of axSpA diagnoses by a rheumatologists), pain (VAS pain),

quality of life (SF-36 version 2 and EQ-5D) and disease activity (BASDAI). We will use linear regression for continuous outcomes and logistic regression for dichotomous outcomes. Similar to the primary outcome analysis an interaction term and random intercept will be used to take into account interaction between allocation group and referral strategy and clustering. We intended to assess the effect of using the referral strategy also at 12 and 24 months. However, patients in the control group receive also an advice based on the referral rule after 4 months. Contrast between the intervention and control group is no longer present. Therefore, individual trajectories will be modeled using random effect regression with patient outcome as the dependent variable and time as covariate and a random intercept for patient.

For the cost evaluation we will compare costs before and after the application of the referral strategy. We will consider costs of provided health care and costs due to loss of work-productivity. In order to calculate costs, the volume of care will be linked to the actual, integrated cost prices per medical service. [26]

A p-value of <0.05 will be considered statistically significant. Statistical analyses will be undertaken with STATA.

Patient advisory board: When designing the IMPACT study, we consulted several members of the 'Stichting Bechterew in Beweging', all suffering from Ankylosing Spondylitis. We asked their opinion about our study and how to improve it, for example they helped by improving the quality of the patient information letter sent to potential participants.

Ethics approval: Ethics approval has been gained from the medical ethics committee (Toetsingscommissie Wetenschapelijk Onderzoek Rotterdam) of the Maasstad Hospital in Rotterdam the Netherlands in April 2014. The investigators will ensure that the trial will be conducted in compliance with this protocol.
Patient consent: All patients provide written informed consent after receiving a patient information leaflet and before any questions concerning the IMPACT study are asked.
Sponsor: Investigator driven study, no sponsor present.
Funding: The Dutch Institute of Rheumatology (TDIOR BV), Rotterdam, the Netherlands

Discussion

This evaluation aims to assess the effects on patient outcomes, processes and costs of a referral strategy for axSpA in young primary care patients with CLBP by comparing the use of the strategy with usual care. The study started in July 2014 and the first results are expected in May 2016.

There are only a very few impact studies in the field of prognostic research. In a recent review there were 61 development studies and only 2 (3%) of them also had an impact evaluation [27], an essential step to asses clinical effectiveness and costs.

The main strength of this study is that it provides information on the process outcome (referral to the rheumatologists and result of the diagnostic process) and on the patient outcomes (pain and quality of life). The combination of process and patients outcomes allows for a better interpretation of findings. An effect in process does not necessarily results in improved patient outcomes. Possible absence of effect in patient outcomes, on the other hand, may be the result of insufficient improvement in the process. Further, the study measures the impact of a validated referral strategy. The referral strategy has already shown to discriminating axSpA patients from other CLBP patients. [4] We have chosen to only test the impact of the CaFaSpA referral strategy as this is the cheapest and the most feasible strategy for primary care of all proposed referral strategies for axSpA.

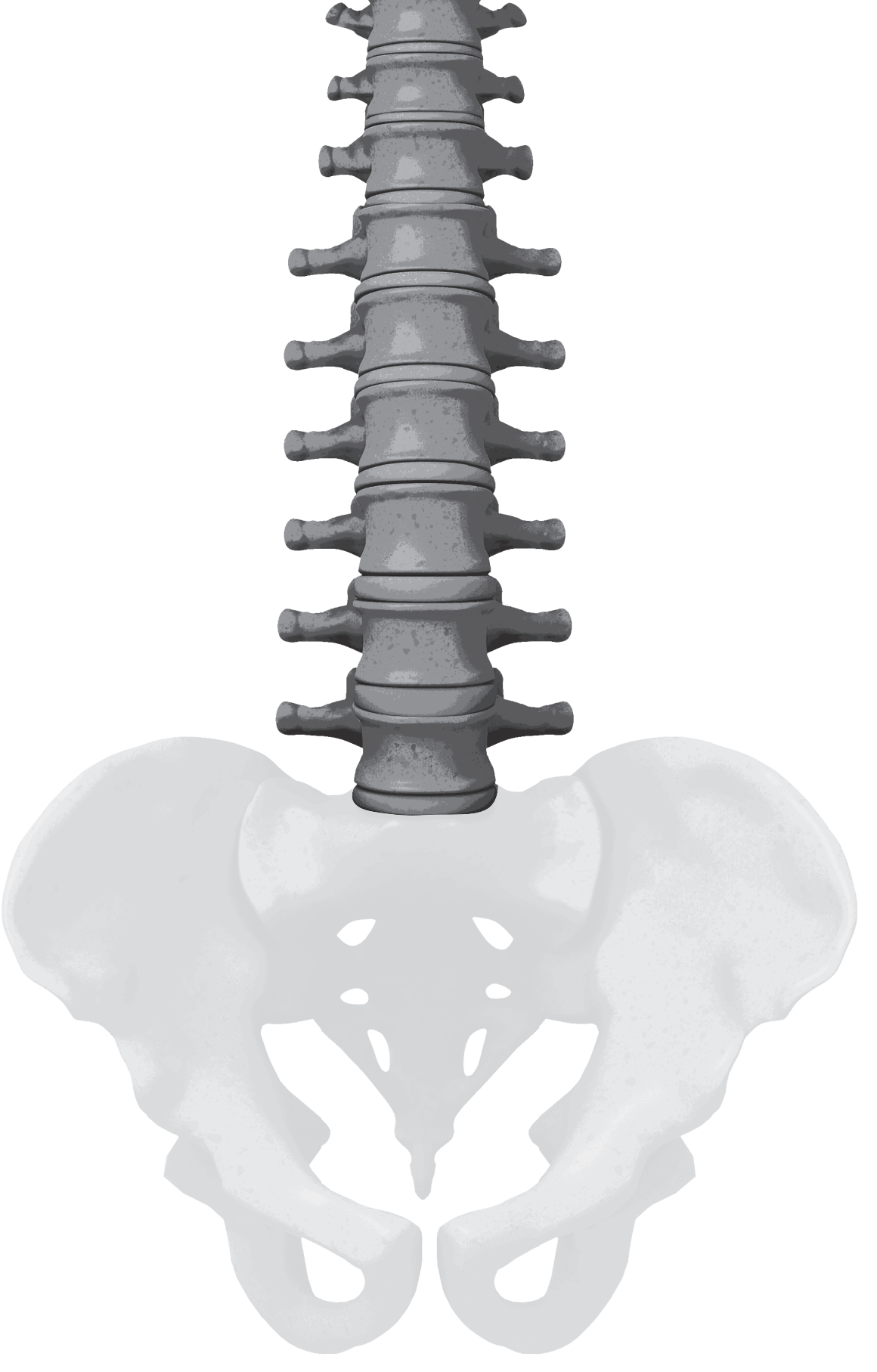
A weakness of the study is that the contrast between intervention and control groups disappears after 4 months, as patients of the control group are also provided with the advice of the referral strategy. Nevertheless our primary outcome is assessed before the outcome of the referral strategy is provided in the control group and we expect that 4 months is a sufficient period to achieve a substantial improvement in the primary outcome by using the referral strategy in the intervention group. For other outcomes, a before after design within patients is acceptable as the back pain complaints are chronic. Another potential weakness is that patients are selected by a registry, rather than actively care seeking patients. This can lead to a lower participation rate of the invited patients and a potential selection bias of only severe cases of low back pain. However in the prior CaFaSpA studies, the same approach to select participants by the GP register was conducted

and this didn't result in a more severe low back pain study population. [4, 5] In both CaFaSpA studies was the VAS pain comparable with other low back pain cohorts.

If this study succeeds in demonstrating an impact of applying the referral strategy for axSpA in young CLBP patients, the potential benefit may be substantial. The care provided to CLBP patients can be improved, it will be easier for GPs to refer the CLBP patient with a high risk for axSpA to the rheumatologist. And an earlier diagnosis of axSpA has favorable outcomes, as several studies have shown that an effective treatment in axSpA patients results in a lower disease activity, improved quality of life and enhanced work participation. [28, 29] And finally the gain for society; CLBP is a great socio-economic burden for society. When one of the causes for CLBP is recognized earlier and subsequently diagnosed and treated in an earlier stage this can lead to decreased sick leave due to back pain and increased work productivity.

References

1. Hoy, D., et al., *A systematic review of the global prevalence of low back pain.* Arthritis Rheum, 2012. **64**(6): p. 2028-37.
2. Freburger, J.K., et al., *The rising prevalence of chronic low back pain.* Arch Intern Med, 2009. **169**(3): p. 251-8.
3. Vos, T., et al., *Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2163-96.
4. van Hoeven, L., et al., *External Validation of a Referral Rule for Axial Spondyloarthritis in Primary Care Patients with Chronic Low Back Pain.* PLOS ONE, 2015. **10**(7): p. e0131963.
5. van Hoeven, L., et al., *Identifying axial spondyloarthritis in dutch primary care patients, ages 20-45 years, with chronic low back pain.* Arthritis Care Res (Hoboken), 2014. **66**(3): p. 446-53.
6. Sieper, J., et al., *Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1).* Ann Rheum Dis, 2013. **72**(6): p. 815-22.
7. Jois, R.N., A.J. Macgregor, and K. Gaffney, *Recognition of inflammatory back pain and ankylosing spondylitis in primary care.* Rheumatology (Oxford), 2008. **47**(9): p. 1364-6.
8. Koes, B.W., et al., *An updated overview of clinical guidelines for the management of non-specific low back pain in primary care.* Eur Spine J, 2010. **19**(12): p. 2075-94.
9. Reilly, B.M. and A.T. Evans, *Translating clinical research into clinical practice: impact of using prediction rules to make decisions.* Ann Intern Med, 2006. **144**(3): p. 201-9.
10. Moons, K.G., et al., *Risk prediction models: II. External validation, model updating, and impact assessment.* Heart, 2012. **98**(9): p. 691-8.
11. lagerugpijn, N.-S.A., 2005.
12. Roland, M. and R. Morris, *A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain.* Spine (Phila Pa 1976), 1983. **8**(2): p. 141-4.
13. Price, D.D., et al., *The validation of visual analogue scales as ratio scale measures for chronic and experimental pain.* Pain, 1983. **17**(1): p. 45-56.
14. Ware, J.E., Jr., *SF-36 health survey update.* Spine (Phila Pa 1976), 2000. **25**(24): p. 3130-9.
15. Sullivan, P.W. and V. Ghushchyan, *Preference-Based EQ-5D index scores for chronic conditions in the United States.* Med Decis Making, 2006. **26**(4): p. 410-20.
16. Bonisch, A. and I. Ehlebracht-Konig, *[The BASDAI-D--an instrument to defining disease status in ankylosing spondylitis and related diseases] Der BASDAI-D--ein Fragebogen zur Erfassung der Krankheitsaktivitat bei Spondylitis ankylosans und verwandten Erkrankungen.* Z Rheumatol, 2003. **62**(3): p. 251-63.
17. Freynhagen, R., et al., *painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain.* Curr Med Res Opin, 2006. **22**(10): p. 1911-20.
18. C. Bouwmans, L.H.-v.R., M. Koopmanschap, M. Krol, H. Severens, W. Brouwer, *Handleiding iMTA Productivity Cost Questionnaire (iPCQ).* Rotterdam; iMTA, Erasmus University 2013.
19. C. Bouwmans, L.H.-v.R., M. Koopmanschap, M. Krol, H. Severens, W. Brouwer, *Handleiding iMTA Medical Cost Questionnaire (iMCQ).* Rotterdam; iMTA, Erasmus University, 2013.
20. Hill, J.C., et al., *Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial.* Lancet, 2011. **378**(9802): p. 1560-71.
21. Ostelo, R.W., et al., *Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change.* Spine (Phila Pa 1976), 2008. **33**(1): p. 90-4.
22. Killip, S., Z. Mahfoud, and K. Pearce, *What is an intracluster correlation coefficient? Crucial concepts for primary care researchers.* Ann Fam Med, 2004. **2**(3): p. 204-8.
23. Campbell, M.K., et al., *Analysis of cluster randomized trials in primary care: a practical approach.* Fam Pract, 2000. **17**(2): p. 192-6.
24. Vickers, A.J. and D.G. Altman, *Statistics notes: Analysing controlled trials with baseline and follow up measurements.* BMJ, 2001. **323**(7321): p. 1123-4.
25. Bouwmeester, W., et al., *Prediction models for clustered data: comparison of a random intercept and standard regression model.* BMC Med Res Methodol, 2013. **13**: p. 19.
26. Rutten FFH, v.I.B., van Ommen R, van Hout BA, Huijsman R, *Kostenberekening bij gezondheidszorgonderzoek; richtlijnen voor de praktijk.* Utrecht: STG/Jan van Arkel, 1994.
27. Steyerberg, E.W., et al., *Prognosis Research Strategy (PROGRESS) 3: Prognostic Model Research.* PLoS Med, 2013. **10**(2): p. e1001381.
28. Dougados, M., et al., *Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial.* Arthritis Rheumatol, 2014. **66**(8): p. 2091-102.
29. Sieper, J., et al., *Impact of certolizumab pegol on patient-reported outcomes in patients with axial spondyloarthritis.* Arthritis Care Res (Hoboken), 2015.



Chapter 9

General discussion

General discussion

In the past decade, major progress has been made in the recognition, classification and treatment of axial spondyloarthritis (axSpA). More knowledge about the early disease course has been acquired and to facilitate early identification of axSpA, several referral strategies applicable in patients suspected for axSpA have been published. Nevertheless, the majority of research in the early disease course and referral strategies comes from research in secondary care, while in the Netherlands all patients with musculoskeletal or low back pain complaints are first seen in primary care. Little is known about axSpA in primary care, in this thesis we aim to provide more insight in the following unresolved topics:

- The prevalence of axSpA in a primary care chronic low back pain (CLBP) population
- The development of a referral strategy for axSpA within a primary care CLBP population
- Validation of referral strategies for axSpA within a primary care CLBP population
- The impact of axSpA on work participation in CLBP patients and the impact of a referral strategy for axSpA on CLBP patients.

To answer these questions we used data from the CAse Finding Axial SPondyloArthritis (CaFaSpA) studies. These studies comprised of young (18-45 years) primary care CLBP patients. All patients were examined for the presence of axSpA as underlying cause for their back pain complaints. We have determined the prevalence of axSpA within a young primary care CLBP population. Subsequently a referral strategy for axSpA is developed and validated in a primary care CLBP population. And finally we have investigated the impact of axSpA on work participation in CLBP and we are examining the impact of a referral strategy for axSpA on CLBP patients.

In this chapter three methodological considerations of our findings are highlighted and described; the generalizability of our results, our case definition and the statistical groundwork of the development and validation of a referral strategy. The

thesis ends with the clinical applicability of our findings and recommendations for future research.

Generalizability

The main goal of research is to increase knowledge about a disease and subsequently improve the care provided to patients. To improve the care provided to patients is it necessary to implement research findings in daily practice. To achieve implementation it is crucial that research findings are generalizable to other populations of patients. In the following part the generalizability of the research findings in this thesis are discussed.

At first is it necessary to assess whether our study population is flawed by selection or whether our study population is comparable to the population in which our research findings can be implemented. Patients in the CaFaSpA studies were selected using only two criteria; the presence of CLBP for at least 12 weeks (using the ICPC code L03) and age between 18 and 45 years. [1, 2] The exclusion criteria were limited; contraindications for MRI, no understanding of the Dutch language and an explainable cause for the back pain, such as trauma. Also the selection of general practioners (GP) does not create a selection bias, given that there were no particular inclusion criteria for participating GPs. These limited inclusion and exclusion criteria support the generalizability of our results.

To investigate whether there was a selection in the patients who participated in the CaFaSpA studies the patients' characteristics should be inspected. At first the male-female ratio, around 40% of our participants in the CaFaSpA studies were male. This ratio is comparable with other studies in CLBP patients, in general there is a predominance of females with CLBP. [3, 4] Secondly, the average VAS score for pain and fatigue in our studies was comparable to the VAS score in other studies in CLBP patients, excluding the selection bias towards more severe CLBP patients in the CaFaSpA studies. [3, 5] Thirdly, the HLA-B27 prevalence in the CaFaSpA studies was 6%, which is close to the reported HLA-B27 prevalence of 7% in the Netherlands. [6] There are no indications that patients with CLBP have a higher HLA-B27 prevalence compared to the general population. This statement was supported by a Swedish study where the HLA-B27 prevalence in the general population was 16% and 17% in their selected CLBP population. [7]

A second element of the generalizability of our findings is a comparison with other studies. An important part in this comparison is to explain potential differences. For example the prevalence of identified axSpA patients (19%) within CLBP patients is lower in the CaFaSpA studies than the prevalence of identified axSpA patients in the SPACE study (38%) [8] and several German studies (35%-41%) [9-12]. The difference in prevalence can be explained by the difference in participants' selection, the SPACE and the German studies selected participants who were already referred with a suspicion of axSpA, while the participants of the CaFaSpA studies only had CLBP, a suspicion of axSpA was not required. The differences in participants' selection should be taken into account for the generalizability of the research findings.

Comparing the CaFaSpA referral strategy to other referral strategies for axSpA (Berlin, MASTER, RADAR, 2-step and ASAS recommendations) there is one obvious difference. With the exception of the CaFaSpA referral strategy, all referral strategies include invasive and expensive referral features such as MRI, X-ray or HLA-B27. [9-13] And although these features are not an absolute requirement for referral, it is a big hurdle for the implementation and generalizability of those strategies in primary care practice in the Netherlands. Not all GPs are equally skilled in interpreting X-ray or MRI images of the sacroiliac joints (SI-joints), moreover there is limited accessibility for GPs to order an MRI of the SI-joints and there is no budget to test HLA-B27 in a large amount of CLBP patients. Secondly when referral strategies are developed in a preselected population with a nonrealistic high prevalence of a disease, it limits the generalizability of this strategy in for example a primary care population where the prevalence of the disease will be much lower. The CaFaSpA strategy has been developed and validated in the population in which it is intended to be used, a primary care CLBP population. Moreover the CaFaSpA strategy consist of features all of which can be incorporated into a patients history, no additional blood or imaging tests are necessary, increasing the implementability of this strategy in Dutch primary care.

Case definition

Another methodological consideration we want to highlight is our case definition. In both CaFaSpA studies we used the ASAS criteria as outcome to define our axSpA cases. [14] It can be argued whether using these criteria is appropriate. The

ASAS criteria were published as classification criteria and not as diagnostic criteria. The purpose of diagnostic criteria is to help clinicians make a diagnosis, while the purpose of classification criteria is to differentiate patients with a specific disease from patients without this disease. [15] The characteristics of diagnostic criteria is that they should be sensitive, as many patients with the disease as possible should be identified in an early disease stage. In a later stage the clinician can judge if a patient actual has the disease or not. In contrast to classification criteria which are characterized by a high specificity to create homogenous group of patients that can be used for research purposes.

The ASAS criteria were published in 2009 and since then several studies have investigated the validity and diagnostic performance of the ASAS criteria. In these studies the diagnosis of the rheumatologists was used as 'golden standard'. In the SPACE study 65 patients were diagnosed as axSpA by a rheumatologist, 55 of these were classified as axSpA by the ASAS criteria, giving a sensitivity of 85%. [8] In the DECLIC study 425 patients were diagnosed as axSpA and 324 of those fulfilled the ASAS criteria (sensitivity 76%). [16] In both studies the specificity of the ASAS criteria was high (SPACE 95%, DECLIC 87%), suggesting that the fear of 'overdiagnosing' many patients by using the ASAS criteria is proven to be unfounded.

Another potential drawback of using the ASAS criteria as outcome is that a classification is highly dependent on abnormalities seen on MRI. Bone marrow edema is not specific for SI-joints inflammation, it is also seen in up to 20% of the healthy volunteers or patients with mechanical back pain. [17] However the criteria partly solve this problem as MRI sacroiliitis is not the only feature necessary to classify a patient, as also at least one clinical SpA feature must be present for the classification of a patient. On top of that several studies regarding the diagnostic utility of the MRI in axSpA have been published. [18] Updating the definition of a 'positive' MRI for sacroiliitis is a hot topic. In future years it will become clear whether this definition will be updated with the presence of structural abnormalities and whether abnormalities seen on the MRI of the spine will be included in the definition of a positive MRI. [17, 19]

The big advantage of using the ASAS criteria as outcome is that the criteria are defined and reproducible for others, while the diagnosis by a rheumatologist is not. Furthermore all patients included in the CaFaSpA cohort are examined by an

experienced rheumatologists or trained research nurse and all clinical assessments followed the definitions described in the ASAS handbook. [20] The radiologists were blinded for patient identity, clinical and laboratory data, when scoring the X-ray or MRI of a patient. To classify patients we did not use a 'ticking the boxes' approach, but made a considered decision using the ASAS criteria as a clearly case definition. As the main purpose of this thesis was to develop and validate a referral strategy a well-defined and reproducible outcome was desirable.

The statistical groundwork of the development and validation of a referral strategy

The third accentuated methodological consideration is the statistical groundwork of prediction models. More and more information about prediction modelling has become available in the recent years. However not all this knowledge is used in the development of referral strategies for axSpA.

The optimal way to test the generalizability of a referral strategy is to externally validate the strategy in a new independent population. Generalizability of a referral strategy can be improved by using standardized statistical techniques to develop a referral strategy such as logistic and Cox regression modelling. [21] The CaFaSpA referral strategy is the only referral strategy in the field of axSpA which has used regression techniques to test which referral features are the strongest in distinguishing axSpA patients from CLBP patients. The other referral strategies for axSpA (Berlin, MASTER, RADAR, 2-step and ASAS recommendations) have not used these techniques. [9-13] It is important in the development phase of a referral strategy to correct for statistical overfitting. In the CaFaSpA 1 study overfitting was corrected by a shrinkage factor which was conducted by bootstrapping. This internal validation technique makes the referral strategy more generalizable to other populations.

The CaFaSpA referral strategy is the only referral strategy for axSpA which has undergone external validation using the appropriate statistical techniques as discrimination, calibration and updating. The external validation of other referral strategies for axSpA is limited. The Berlin strategy has been validated in the MASTER and RADAR studies, and the performance of the MASTER and RADAR strategies has been tested in different populations, however the efficacy of these

strategies was only measured by the proportion of referred patients in which axSpA was diagnosed, sensitivity and specificity. Discrimination and calibration are lacking and none of the other referral strategies have used updating techniques to improve the generalizability of their strategy.

Finally the clinical effect and cost-effectiveness of the CaFaSpA referral strategy is currently investigated by the IMPACT study. The protocol of this study is described in chapter eight. Results of this study will give more insight in whether a CLBP patient is better off when the CaFaSpA referral strategy is applied, whether the referral strategy is cost-effective and whether it changes decision making by GPs. If the results are in favor of the CaFaSpA referral strategy, generalizability of the strategy is proven and implementation of this strategy can be started throughout the Netherlands.

Implications for clinical practice

With the findings of this thesis new insights have been provided regarding axSpA prevalence in a primary care CLBP population. This is a valuable finding as previous to our studies only the prevalence of Ankylosing Spondylitis among CLBP patients was known. [22] The prevalence of axSpA among CLBP patients is important as policymakers use prevalence estimates in the allocation of resources for research and healthcare.

Now that the magnitude of axSpA in primary care has been determinate, the diagnostic delay in axSpA should be reduced. Early recognition and referral are important as short symptom duration is an important predictor for a favorable treatment outcome. [23] Several studies have already shown that when axSpA patients are adequately treated a decrease in disease activity, an increase in quality of life and improvement in work participation is observed. [24] To reduce diagnostic delay in axSpA, GPs should be educated about early recognition and referral of patients with suspected axSpA. [25] A helpful tool for GPs in the early recognition of axSpA is the CaFaSpA referral strategy. This strategy consists of questions that can all be asked during the patients history, no additional tests such as HLA-B27 testing or imaging are required, making implementation of the CaFaSpA referral strategy in daily practice easier.

Recommendations for future research

The prevalence of axSpA within primary care CLBP patients has been determinate and a referral strategy for axSpA has been developed and validated. However this referral strategy is not yet used in daily practice. The recommendations for future research are focused on the implementation of a referral strategy for axSpA.

It will be challenging to develop a referral strategy for axSpA that is applicable in all the different primary settings around the world. Primary care settings differ in available resources (whether or not a X-ray, MRI or HLA-B27 testing is available), budget and knowledge how to interpret clinical and imaging findings regarding axSpA. In the Netherlands there is limited availability of an MRI of the SI-joints for GPs and the budget for X-ray and HLA-B27 testing is restricted. Ideally the non-invasive and cheap CaFaSpA referral strategy should be tested against both the current referral guidelines used by Dutch GPs as well as an invasive referral strategy which includes imaging and HLA-B27 testing. Ideally the design of the study would be a cluster randomized trial in which one group of GPs uses the CaFaSpA referral strategy, one uses the current referral guidelines and the third group of GPs uses the invasive strategy. Outcomes should be measured by improvement in patient reported outcomes, but also cost-effectiveness, applicability and how the GPs experienced the use of a standardized referral strategy. Also the long term outcomes of using referral strategies should be investigated. At this moment there are no follow up studies of patients who were included in a referral strategy study, it is unclear if these patients are still seen by a rheumatologist and if they are receiving treatment for their disease.

Our second recommendation for future research is related to GPs. Two studies of van Onna et al. showed that knowledge of axSpA and its early recognition is limited in GPs, and that knowledge can be improved by targeted education of the GPs. [25, 26] Even if the optimal referral strategy for axSpA is obtained, the GP remains the gatekeeper whether or not a patient is referred to secondary care. Therefore more effort should be put into educating GPs about axSpA and the importance of early recognition and referral. However the optimal way to educate GPs is not clear. An opportunity for targeted education of GPs would be when the implementation of a referral strategy for axSpA is at hand. At that moment referral of potential axSpA patients would be an actual issue and directly applicable.

To guarantee successful implementation of a referral strategy it is recommended to study the optimal implementation technique. Is this by a paper card where the referral strategy is printed on which GPs can use during their consultation, or by a digital application, such as a pop-up with the referral strategy when the GP register that a patient has CLBP. Another idea is that all CLBP patients from one practice receive an appointment by the practice nurse who screens all CLBP patients for the presence of axSpA and refers patients who are suspected for axSpA to the rheumatologist. Such a setting with the practice nurse as a screening moment is already successfully used in the Netherlands for the screening for cardiovascular diseases and chronic obstructive pulmonary disease.

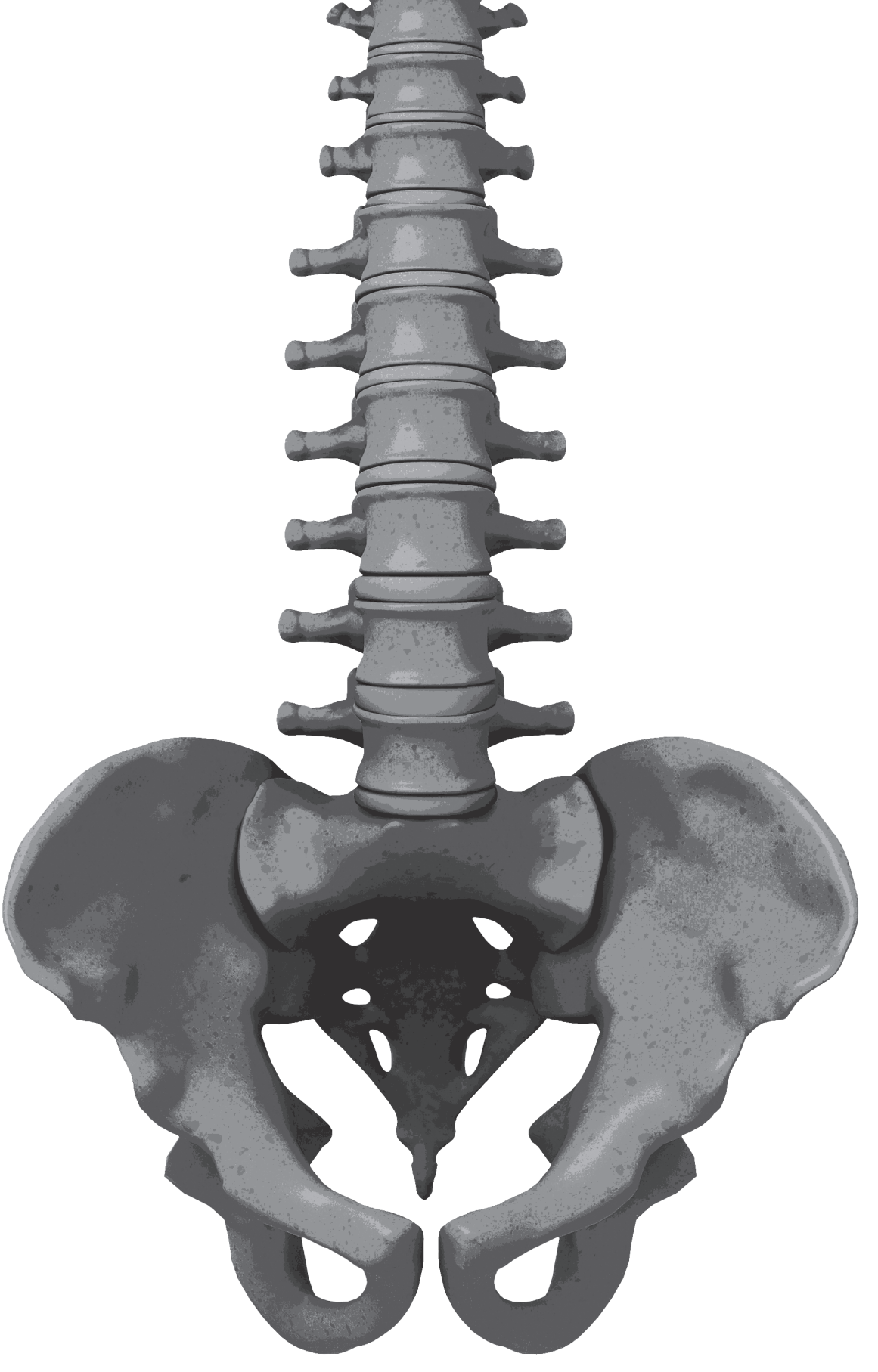
Another suggestion for further research is to educate not only GP but also physiotherapists. In the Netherlands many patients with CLBP complaints are seen by a physiotherapist, without the interposition of a GP. [27] It would be interesting to set up a pilot study whether a physiotherapist can effectively use referral strategies for axSpA.

Our final recommendation is outside of the scope of this thesis but connects to the discussion about our outcome definition and the use of classification and diagnostic criteria in the field of rheumatology. There is a lack of diagnostic criteria in almost all rheumatological diseases, in most cases there are only classification criteria available. It would be interesting to observe the inter-observer variation in the assessment of rheumatological diseases. Do rheumatologists use the classification criteria in daily practice as a guideline to diagnose patients or do rheumatologists use other features or combinations of features to diagnose rheumatological diseases and does this differ per country?

References

1. van Hoeven, L., et al., *Identifying axial spondyloarthritis in dutch primary care patients, ages 20-45 years, with chronic low back pain.* Arthritis Care Res (Hoboken), 2014. **66**(3): p. 446-53.
2. van Hoeven, L., et al., *External Validation of a Referral Rule for Axial Spondyloarthritis in Primary Care Patients with Chronic Low Back Pain.* PLoS One, 2015. **10**(7): p. e0131963.
3. Murphy, S.E., et al., *Comparison of a Stratified Group Intervention (STarT Back) with Usual Group Care in Patients with Low Back Pain: A Non-randomised Controlled Trial.* Spine (Phila Pa 1976), 2015.
4. da Luz, M.A., Jr., et al., *Effectiveness of mat Pilates or equipment-based Pilates exercises in patients with chronic nonspecific low back pain: a randomized controlled trial.* Phys Ther, 2014. **94**(5): p. 623-31.
5. Gordon, A., et al., *Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase.* Clin Ther, 2010. **32**(5): p. 844-60.
6. van Gaalen, F., et al., *Is HLA-B27 Increased in Patients Diagnosed with Undifferentiated Arthritis? Results from the Leiden Early Arthritis Cohort.* J Rheumatol, 2014. **41**(10): p. 1948-51.
7. Bakland, G., et al., *Assessment of SpondyloArthritis International Society criteria for axial spondyloarthritis in chronic back pain patients with a high prevalence of HLA-B27.* Arthritis Care Res (Hoboken), 2013. **65**(3): p. 448-53.
8. van den Berg, R., 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.
9. Brandt, H.C., et al., *Performance of referral recommendations in patients with chronic back pain and suspected axial spondyloarthritis.* Ann Rheum Dis, 2007. **66**(11): p. 1479-84.
10. Sieper, J., et al., *Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study.* Ann Rheum Dis, 2012.
11. Poddubnyy, D., et al., *Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care.* J Rheumatol, 2011. **38**(11): p. 2452-60.
12. Braun, A., et al., *Optimizing the identification of patients with axial spondyloarthritis in primary care--the case for a two-step strategy combining the most relevant clinical items with HLA B27.* Rheumatology (Oxford), 2013. **52**(8): p. 1418-24.
13. Poddubnyy, D., 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**(8): p. 1483-7.
14. Rudwaleit, M., 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**(6): p. 777-83.
15. van Tubergen, A. and U. Weber, *Diagnosis and classification in spondyloarthritis: identifying a chameleon.* Nat Rev Rheumatol, 2012. **8**(5): p. 253-61.
16. Molto, A., 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**(9): p. 1472-81.
17. Weber, U., et al., *Candidate lesion-based criteria for defining a positive sacroiliac joint MRI in two cohorts of patients with axial spondyloarthritis.* Ann Rheum Dis, 2015. **74**(11): p. 1976-82.
18. Pedersen, S.J., U. Weber, and M. Ostergaard, *The diagnostic utility of MRI in spondyloarthritis.* Best Pract Res Clin Rheumatol, 2012. **26**(6): p. 751-66.
19. Weber, U., et al., *Diagnostic utility of candidate definitions for demonstrating axial spondyloarthritis on magnetic resonance imaging of the spine.* Arthritis Rheumatol, 2015. **67**(4): p. 924-33.
20. Sieper, J., et al., *The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis.* Ann Rheum Dis, 2009. **68 Suppl 2**: p. ii1-44.
21. Steyerberg, E.W., et al., *Prognosis Research Strategy (PROGRESS) 3: Prognostic Model Research.* PLoS Med, 2013. **10**(2): p. e1001381.

22. Underwood, M.R. and P. Dawes, *Inflammatory back pain in primary care.* Br J Rheumatol, 1995. **34**(11): p. 1074-7.
23. Sieper, J., et al., *Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1).* Ann Rheum Dis, 2013. **72**(6): p. 815-22.
24. Callhoff, J., et al., *Efficacy of TNFalpha blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis.* Ann Rheum Dis, 2014.
25. van Onna, M., et al., *Education improves referral of patients suspected of having spondyloarthritis by general practitioners: a study with unannounced standardised patients in daily practice.* RMD Open, 2015. **1**(1): p. e000152.
26. van Onna, M., et al., *General practitioners' perceptions of their ability to identify and refer patients with suspected axial spondyloarthritis: a qualitative study.* J Rheumatol, 2014. **41**(5): p. 897-901.
27. http://www.nivel.nl/NZR/fysiotherapie, 2014.



Summary

The studies described in this thesis cover the findings of the CAse Finding Axial SPondyloArthritis (CaFaSpA) studies. Axial spondyloarthritis (axSpA) is a chronic, inflammatory disease affecting the axial skeleton and it is characterized by chronic low back pain (CLBP) and stiffness of the axial skeleton. At this moment there is an average diagnostic delay of 8.5 years between the start of the symptoms and the diagnosis axSpA. A missed opportunity as effective treatment for axSpA is available. The aim of the CaFaSpA studies was to establish the prevalence of axSpA within a young CLBP population and to develop and validate a referral strategy for axSpA which can be used by primary care physicians. A validated referral strategy for axSpA can be used to achieve the goal of early recognition and referral of axSpA patients to rheumatologists.

The thesis is divided in four parts; at first the prevalence of axSpA within a young CLBP population is established, the second part describes the development of a referral strategy for axSpA, the third part covers the external validation of referral strategies for axSpA and the fourth part evaluates the impact of axSpA on work participation and the impact of a referral strategy for axSpA on young patients with CLBP and whether this referral strategy will be cost-effective.

Prevalence

Chapter 2 describes the prevalence of axSpA within a group of young (20-45 years) CLBP patients in primary care. All study participants were part of the CaFaSpA 1 study, in total 19 primary care practices and 364 CLBP patients participated. All study participants had low back pain for at least 12 weeks and none of them had a diagnosis explaining their back pain complaints. Everybody was examined by a rheumatologist, a medical history and physical examination including the SpA features took place. Blood was drawn to determine HLA-B27 positivity, C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR). An X-ray and magnetic resonance imaging (MRI) of the sacro-iliac joints (SIJ) was obtained from every patient and scored by an experienced radiologist.

Of the 364 CLBP patients were 86 (23.6%) identified as axSpA, by using the ASAS criteria. To validate this remarkable high prevalence, the CaFaSpA 2 study was set up. For this study 579 CLBP primary care patients from 38 primary care practices from

another region were included as described in **chapter 3**. All patients were aged between 18 and 45 years and all had low back pain for at least 12 weeks. Equally to the first study were all patients examined for the presence of SpA features, blood was drawn for HLA-B27, CRP and ESR and an X-ray and MRI of the SIJ were obtained from every patient. Within the CaFaSpA 2 study were 95 (16.4%) out of 579 CLBP patients identified as axSpA.

Development

The second part of this thesis is described in **chapter 2.** Besides the prevalence of axSpA among young CLBP patients also the development of the CaFaSpA referral strategy for axSpA is described. The referral strategy is developed to be used by primary care physicians. The referral strategy supports primary care physicians in recognizing and referring patients suspected of axSpA to the rheumatologist. In the development of the referral strategy we first selected candidate referral items that were quick and easy to asses by primary care physicians without additional costs. Referral items as X-ray, MRI and HLA-B27 were ruled out as they are too expensive or too complicated to be used by primary care physicians. A multivariable logistic regression model was fitted and a backward stepwise procedure was used to select the strongest predictors. Finally four referral items were selected, if there are at least two of those referral items present in a patient a referral to the rheumatologists is advised. The four referral items are a good reaction to non-steriodal anti-inflammatory drugs (NSAIDs), a positive family history of SpA, a positive ASAS inflammatory back pain (IBP) questionnaire and a CLBP duration longer than 5 years. The performance of this referral strategy is good, with a sensitivity of 83% and a specificity of 59%.

External validation

The third part of this thesis focuses on the optimal referral strategy for axSpA. External validation of a referral strategy is important as the generalizability of the strategy is evaluated, an inevitable step before the implementation of a referral strategy in daily practice.

In **chapter 3** the external validation of the CaFaSpA referral strategy is described. The referral strategy was validated in 579 young CLBP patients from the CaFaSpA 2 study and resulted in satisfactory calibration and discriminative ability. The sensitivity and specificity were 75% and 58%.

Beside the CaFaSpA referral strategy several other referral strategies for axSpA are recently published. The ASAS recommendations for the early referral of axSpA are evaluated in **chapter 4**. These recommendations have been developed using a literature search, a Delphi process and final voting, but they have not been tested in daily practice yet. The strategy can be applied by patients with CLBP (duration ≥3 months) with back pain onset before 45 years of age and patients should be referred if there is at least one of the eight referral items present. The referral items are IBP, HLA-B27 positivity, sacroiliitis on imaging (X-ray or MRI), peripheral manifestations (arthritis, enthesitis and/or dactylitis), extra-articulair manifestations (psoriasis, inflammatory bowel disease and/or uveitis), positive family history for spondyloarthritis, good response to NSAIDs and elevated acute phase reactants (CRP or ESR). We have tested this strategy in the total CaFaSpA population consisting of 941 CLBP patients ages 18-45 years.

The ASAS recommendations are excellent in recognizing axSpA patients, all patients with axSpA are identified by this strategy. However the downside of this strategy is that to identify all axSpA patients many patients are unnecessary referred to the rheumatologist. To identify all 181 axSpA patients, this strategy refers 800 of the total 941 CLBP patients to the rheumatologist. It is questionable if it is desirable to refer so many CLBP patients to the rheumatologist for a diagnostic work up. In this chapter we suggest to change the cut point of referring a patient from one item present to at least two items present. With this cut point are all axSpA patients still identified, but instead of 800 only 484 patients are referred to the rheumatologist. In **chapter 5** a more extensive comparison is made between six different referral strategies for axSpA. The aim of this study was to evaluated referral strategies for axSpA in unselected young primary care patients with CLBP and secondly to discuss the most suitable referral strategy for primary care. The following referral strategies were evaluated; Berlin, MASTER, RADAR, 2-step, CaFaSpA and the new ASAS recommendations. The strategies were validated in the total CaFaSpA population of 941 CLBP patients ages 18-45 years. Almost all referral strategies had a good discriminative performance. The MASTER strategy had the most balanced sensitivity (96%), specificity (82%) and the highest positive predictive value (PPV, 55%). The conclusion of this chapter is that referral strategies which include costly procedures like imaging and HLA-B27 had the best PPV, sensitivity and specificity. However the availability of imaging and HLA-B27 in a primary care setting differ per country. The optimal strategy for primary care depends on budget, available resources and knowledge of axSpA in primary care.

Chapter 6 is the last chapter of the third part of this thesis. Within this chapter a clinical pathway to early recognize and diagnose axSpA patients is described. For this clinical pathway we have combined the ASAS recommendations for referral and the ASAS diagnostic algorithm for axSpA. The ASAS diagnostic algorithm is a helpful tool for rheumatologists to diagnose axSpA patients earlier, within the diagnostic algorithm are imaging, clinical features and HLA-B27 testing incorporated. The first step of the clinical pathway is the application of the ASAS recommendations for referral, if there is at least one parameter present in a CLBP patients age 18-45 years, the next step is to follow the flowchart of the diagnostic algorithm. Again is the total CaFaSpA population of 941 CLBP patients used to test the clinical pathway. The practical value of this clinical pathway is modest, especially the large number of unnecessarily referrals will hamper implementation of this clinical pathway in daily practice.

Impact

The last part of this thesis focuses on the impact of axSpA on patients and the impact of a referral strategy for axSpA on CLBP patients. In **chapter 7** the impact of yet undiagnosed non-radiographic axSpA (nr-axSpA) and Ankylosing Spondylitis (AS) on work outcomes within the CaFaSpA cohort is evaluated. The specific aims were to compare employment of patients with AS, nr-axSpA and CLBP with the general population, to explore whether there these diagnostic groups differ in sick leave and at-work productivity, and which demographic and disease characteristics contributed to sick leave and at-work productivity. It was found that the impact of yet undiagnosed nr-axSpA and AS is substantial although the outcomes in work productivity were not significantly different from CLBP patients. Variables associated with reduced work productivity were mainly patient reported outcome measures (PROMs) such as Visual Analogue Scale (VAS) pain and functional limitations measured by the Roland Morris Disability Questionnaire (RMDQ). We believe that early recognition and subsequently adequate treatment of yet undiagnosed nr-axSpA and AS patients can potentially lead to maintaining an optimal work productivity in nr- axSpA and AS patients and a reduction in indirect costs.

In **chapter 8** the study protocol for an impact analysis about the clinical application of the CaFaSpA referral strategy is described. This evaluation aims to assess the clinical effect, process and costs of the referral strategy for axSpA in young primary care patients with CLBP by comparing the use of the referral strategy with usual

care. The study design is a cluster randomized trial with GPs as clusters. Patients from participating GPs are included in the study if they have current low back pain for more than 12 weeks and if they are aged between 18 and 45 years. In the intervention arm the CaFaSpA referral strategy will be applied, while in the control arm care as usual will be provided to CLBP patients. Data is prospectively collected in an online database at baseline , after 4 months, after 12 months and after 24 months. Patient outcomes (e.g. pain scores, quality of life, work productivity) as well as process outcomes (e.g. number of axSpA diagnosis by rheumatologists) will be measured. Costs will be assessed before and after the use of the referral strategy, to estimate if the use of the strategy will lead to a reduction in health care costs and improvement in work participation. It is anticipated that using the axSpA referral strategy for primary care CLBP patients will result in more (correct) diagnoses of axSpA by the rheumatologists, will increase the quality of life of CLBP patients and will be cost-effective. Ultimately, the results of this study may contribute to the national implementation of the axSpA referral strategy to identify timely CLBP with axSpA.

In **chapter 9** our results are summarized and discussed. The discussion focuses on three methodological considerations; the generalizability of our results, our case definition of axSpA and the statistical groundwork of the development and validation of a referral strategy. The thesis ends with the clinical applicability of our findings and recommendations for future research.

Samenvatting

In dit proefschrift worden de resultaten weergegeven die zijn gevonden in de CaFaSpA (CAse Finding Axial SPondyloArthritis) studies. Axiale spondyloartritis (axSpA) is een inflammatoire, reumatische aandoening van het bewegingsapparaat met chronische lage rugklachten als voornaamste en meest voorkomend symptoom. Op dit moment bestaat er een vertraging van acht jaar tussen de start van de symptomen en de uiteindelijke axSpA diagnose. Terwijl er een effectieve behandeling voor axSpA beschikbaar is op het moment dat een axSpA patiënt door een reumatoloog wordt behandeld.

Het doel van de CaFaSpA studies was het vaststellen van de prevalentie van axSpA in een chronische lage rugklachten populatie en het ontwikkelen en valideren van een verwijsstrategie voor axSpA welke toegepast kan worden door huisartsen. Met een toepasbare verwijsstrategie komt het doel van vroege herkenning en verwijzing van axSpA patiënten dichterbij, vermindert de vertraging tussen start van symptomen en diagnose en kunnen axSpA patiënten eerder worden behandeld.

In **hoofdstuk 1** wordt een overzicht gegeven van het ziektebeeld axSpA. De prevalentie, de klinische kenmerken, het ontstaan en de impact van het ziektebeeld worden besproken. Daarna wordt er ingezoomd op het vroege ziektebeloop, hoe meer kennis over dit begin van het ziekteverloop heeft geleid tot het ontwikkelen van nieuwe criteria voor axSpA. Vervolgens wordt het belang van vroege herkenning van axSpA toegelicht, maar ook waarom het moeilijk is om vroege herkenning te bereiken. Dit hoofdstuk sluit af met de methodologische uitleg over het ontwikkelen van een verwijsstrategie voor axSpA.

Het proefschrift is in vier gedeeltes onderverdeeld. Het eerste gedeelte beschrijft hoe vaak axSpA voorkomt bij jonge mensen met chronische lage rugklachten en het tweede gedeelte gaat over het ontwikkelen van een verwijsstrategie voor axSpA patiënten. Vervolgens gaat het derde gedeelte over het extern valideren van verwijsstrategieën voor axSpA. En het laatste gedeelte beschrijft de impact van axSpA op werkparticipatie en de impact van een verwijsstrategie voor axSpA op patiënten en of deze strategie kosteneffectief is.

In het eerste gedeelte van dit proefschrift bestuderen wij hoe vaak axSpA voorkomt bij jonge patiënten met chronische lage rugklachten. De eerste studie die we hiervoor hebben uitgevoerd is beschreven in **hoofdstuk 2.** In deze studie (CaFaSpA 1) hebben wij bij 19 verschillende huisartspraktijken in totaal 364 patiënten tussen de 18 en 45 jaar met chronische lage rugklachten geselecteerd. Voor al deze patiënten was de oorzaak van hun rugklachten onbekend. Alle patiënten zijn onderzocht door een reumatoloog, de reumatoloog heeft onderzocht of de rugklachten verklaard konden worden door axSpA. Naast een vraaggesprek en lichamelijk onderzoek hebben wij van alle patiënten een röntgenfoto en MRI scan van hun sacro-iliacale gewricht gemaakt en is er bij alle patiënten bloed geprikt om de ontstekingsparameters (CRP en BSE) en HLA-B27 te bepalen. Van de 364 patiënten zijn er 86 (23.6%) geïdentificeerd als axSpA. Om te controleren of deze uitkomst valide was, hebben wij een jaar later dezelfde studie, in een andere regio, nog een keer uitgevoerd. In **hoofdstuk 3** is deze studie (CaFaSpA 2) uitgewerkt. Voor deze studie hebben wij 579 nieuwe patiënten uit 38 verschillende huisartspraktijken geselecteerd. Deze patiënten hadden eveneens chronische lage rugklachten en waren tussen de 18 en 45 jaar. De patiënten zijn, net zoals in de eerste studie, onderzocht op het voorkomen van axSpA middels een vraaggesprek, lichamelijk onderzoek, röntgenfoto's, MRI en bloedonderzoek. In deze studie zijn 95 (16.4%) van de 579 patiënten geïdentificeerd als axSpA.

Voor het tweede gedeelte van dit proefschrift gaan we terug naar **hoofdstuk 2.** Naast het voorkomen van axSpA bij jonge patiënten met chronische lage rugklachten beschrijven we in dit hoofdstuk ook de ontwikkeling van een verwijsstrategie voor axSpA. Deze verwijsstrategie is ontwikkeld als hulpmiddel voor huisartsen. Met de strategie willen wij huisartsen ondersteunen in het gericht doorverwijzen van patiënten met een verdenking op axSpA. Voor het ontwikkelen van de verwijsstrategie hebben wij eerst gekeken naar voor huisartsen uitvoerbare items die we kunnen opnemen in de verwijsstrategie. Bij deze overweging vallen dure en complexe items zoals een MRI scan, een röntgenfoto en het bepalen van HLA-B27 in het bloed af. Na deze praktische overweging bleven er zeven verschillende 'kandidaat' items over. Met deze items hebben we een statistische techniek, namelijk een logistische regressie met backward selection en bootstrapping uitgevoerd. Uit deze logistische regressie kwamen vier items naar voren die het best kunnen voorspellen welke patiënt als oorzaak voor zijn of haar rugklachten een axSpA heeft. Indien er bij een chronische lage rugklachten patiënt

tussen de 18 en 45 jaar minimaal twee van de hierna genoemde items aanwezig zijn, is het risico op axSpA aanzienlijk verhoogd en geven wij het advies om de patiënt door te verwijzen naar de reumatoloog. Deze vier items zijn; inflammatoire lage rugklachten, een goede reactie op anti-ontstekingsmedicijnen (NSAIDs), een positieve familie anamnese voor spondyloarthropathieën en een duur van rugklachten langer dan 5 jaar.

Het derde gedeelte van het proefschrift richt zich op de vraag wat de optimale verwijsstrategie voor axSpA is. Net zoals bij het bepalen hoe vaak een ziektebeeld voorkomt, moeten ook de uitkomsten van de verwijsstrategie gecontroleerd worden in een nieuwe, onafhankelijke studiepopulatie. De validatie van de verwijsstrategie is beschreven in **hoofdstuk 3.** In de 579 nieuwe chronische lage rugklachten patiënten laat onze verwijsstrategie nogmaals zien dat het goed in staat is om patiënten met niet specifieke lage rugklachten te onderscheiden van patiënten met axSpA.

Naast onze eigen gevalideerde verwijsstrategie zijn er wereldwijd ook andere verwijsstrategieën voor axSpA beschreven. Deze strategieën gaan wij extern valideren in onze CaFaSpA onderzoekpopulatie. In **hoofdstuk 4** testen wij de recent gepubliceerde ASAS verwijsstrategie. ASAS staat voor the Assessement of SpondyloArthritis international Society en bestaat uit een groep van internationale experts op het gebied van axSpA. De verwijsstrategie die zij presenteren is gebaseerd op literatuuronderzoek en een Delphi proces. Deze strategie is nog door niemand in de praktijk getest. De strategie kan toegepast worden bij jonge patiënten met chronische lage rugklachten en een patiënt moet doorverwezen worden naar de reumatoloog als er minimaal één van de in totaal acht verschillende verwijsitems aanwezig is. Wij hebben deze strategie getest in de onderzoekspopulatie die we in de CaFaSpA 1 en CaFaSpA 2 studie hebben samengesteld, samen zijn dit 941 chronische lage rugklachten patiënten. Het blijkt dat de ASAS verwijsstrategie heel goed in is om alle patiënten met axSpA te herkennen. In onze groep wordt geen enkele patiënt met axSpA gemist, dit is een zeer goed resultaat. Echter is de keerzijde dat er heel veel patiënten naar de reumatoloog moeten worden doorverwezen om geen enkele patiënt te missen. In totaal werden er bij deze strategie 800 van de 941 patiënten doorverwezen terwijl er maar 181 van 800 doorgestuurde patiënten gediagnosticeerd werd met axSpA. Het is de vraag of het doorverwijzen van zoveel patiënten naar de reumatoloog een wenselijke situatie

is. In hetzelfde artikel geven we de suggestie dat wanneer het afkappunt om een patiënt door te verwijzen naar de reumatoloog van minimaal één item aanwezig wordt verhoogd naar minimaal twee items aanwezig hoopvolle resultaten geeft. Nog steeds is de strategie in staat alle patiënten met axSpA te herkennen, maar in plaats van 800 worden er maar 484 patiënten doorverwezen naar de reumatoloog.

In **hoofdstuk 5** maken we een grotere vergelijking tussen verschillende verwijsstrategieën voor axSpA. In totaal vergelijken we zes verschillende strategieën in deze studie. Als onderzoekspopulatie gebruiken we weer de 941 patiënten uit de CaFaSpA 1 en CaFaSpA 2 studie. Het doel van deze studie was om de verschillende strategieën met elkaar te vergelijken in één onderzoekspopulatie en om een advies te kunnen geven betreffende de beste strategie voor de huisarts. Als we naar de statistische uitkomsten van deze studie kijken, zien we dat de vier strategieën die afbeeldend onderzoek (röntgenonderzoek of MRI) in hun strategie hebben de beste resultaten geven. Deze strategieën zijn het best in het herkennen van de axSpA patiënten en verwijzen het minst onnodig patiënten door naar de reumatoloog (met hierbij als uitzondering de eerder genoemde ASAS verwijsstrategie, bij deze strategie worden veel patiënten onnodig doorverwezen). Het nadeel van deze strategieën is dat afbeeldend onderzoek voor een Nederlandse huisarts niet altijd beschikbaar is en dat de praktische toepasbaarheid van deze verwijsstrategieën beperkt is.

De laatste studie behorend bij het derde gedeelte van het proefschrift is beschreven in **hoofdstuk 6**. Hierin wordt een klinisch zorgpad voor axSpA beschreven. Naast dat er verschillende verwijsstrategieën voor axSpA zijn beschreven is er ook voor reumatologen een diagnostisch hulpmiddel om patiënten zo vroeg mogelijk te diagnosticeren, namelijk het ASAS diagnostisch algoritme. Wij hebben gekeken wat de resultaten zijn wanneer wij de ASAS verwijsstrategie en het ASAS diagnostisch algoritme achter elkaar toepassen. In theorie sluiten deze twee op elkaar aan maar of dit in de praktijk ook zo is, is niet bekend. De statistische resultaten zijn hoopgevend, echter het grote nadeel is opnieuw dat er veel patiënten die geen axSpA blijken te hebben wel door de ASAS verwijsstrategie worden doorverwezen en vervolgens kostbare diagnostische testen ondergaan in het ASAS diagnostisch algoritme.

Het laatste gedeelte van het proefschrift gaat over de impact van axSpA op patiënten en de impact van een verwijsstrategie voor axSpA op jonge patiënten met chronische lage rugklachten. In **hoofdstuk 7** onderzoeken wij wat de impact is van axSpA op arbeidsparticipatie. In het verleden zijn gegevens verzameld over arbeidsparticipatie in patiënten met Ankylosing Spondylitis (AS). AS is een subtype van axSpA, een andere subtype van axSpA is de niet radiografische axSpA (nr-axSpA). Van dit laatste ziektebeeld en de relatie met arbeidsparticipatie zijn maar weinig gegevens bekend. Hetgeen wat wij nu weten over arbeidsparticipatie en axSpA is merendeels verzameld in patiënten met axSpA die al lang bekend zijn met hun ziektebeeld. Hoe is de arbeidsparticipatie in tot nu toe niet gediagnosticeerde axSpA patiënten? Vaak hebben nieuw gediagnosticeerde axSpA patiënten al wel jaren chronische lage rugklachten. Zit er dan een verschil in arbeidsparticipatie tussen patiënten met chronische lage rugklachten, AS of nr-axSpA? Deze vragen konden wij met de populatie uit de CaFaSpA 2 studie beantwoorden. Wij beschrijven dat patiënten die nieuw gediagnosticeerd zijn met AS minder vaak betaald werk hebben, maar dat er geen significante verschillen zijn tussen werkproductiviteit in CLBP, nr-axSpA en AS patiënten. Daarnaast blijkt dat meer pijn en een vermindering van het functioneren geassocieerd zijn met een verminderde werkproductiviteit. Dit zijn hoopvolle resultaten, wanneer axSpA patiënten worden behandeld voor hun ziekte geeft dit een verbetering van de pijnklachten en het fysiek functioneren. Als alle nieuw gediagnosticeerde axSpA patiënten optimaal worden behandeld zou dit kunnen leiden tot een behoud van arbeidsparticipatie.

Als laatste vraag bleef over wat de impact van een verwijsstrategie voor axSpA op patiënten met chronische lage rugklachten is. Zoals in de introductie van dit proefschrift is beschreven, bestaat het toepassen van een verwijsstrategie uit vier verschillende fases. Het ontwikkelen en valideren van een verwijsstrategie hebben we beschreven in hoofdstuk 2 en 3. Voordat we deze strategie kunnen gaan toepassen bij huisartsen in Nederland moeten we de impact van de verwijsstrategie gaan onderzoeken. Hoe wij deze impact studie hebben opgezet, waar rekening mee moet worden gehouden en wat de te verwachte resultaten zijn, is beschreven in een studieprotocol in **hoofdstuk 8**.

Hoofdstuk 9 bediscussieert de bevindingen van dit proefschrift. Dit hoofdstuk richt zich op de generaliseerbaarheid van onze resultaten, de keuze van de

uitkomstmaat en de statistische onderbouwing voor het ontwikkelen en valideren van een verwijsstrategie. De generaliseerbaarheid van de uitkomsten worden doorgenomen en bediscussieerd. De bevindingen uit de CaFaSpA studies zijn te generaliseren naar andere jonge, chronische lage rugklachten patiënten in Nederland. Vervolgens worden er verschillende voor en tegenargumenten voor onze uitkomstmaat besproken. Daarna nemen we de statische principes door met betrekking tot het ontwikkelen en valideren van een verwijsstrategie en hoe deze principes in de CaFaSpA studies zijn toegepast. Dit hoofdstuk wordt afgesloten met een discussie over de praktische toepasbaarheid van de uitkomsten van het proefschrift en aanbevelingen voor verder onderzoek naar de vroege herkenning en verwijzing van axSpA.

Dankwoord

En dan is daar het laatste en meest gelezen hoofdstuk van je proefschrift, het dankwoord. Het schrijven van het dankwoord betekent dat de rit erop zit, 'het' is af! Wat waren de afgelopen jaren leuk! En wat heb ik gedurende deze periode veel moois meegemaakt en veel mensen mogen ontmoeten. Ook is een dankwoord het moment om iedereen te bedanken die gedurende mijn promotieperiode hierbij betrokken is geweest.

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Zonder deelnemende patiënten en in mijn geval ook deelnemende huisartsen is het uitvoeren van wetenschappelijk onderzoek onmogelijk. Dus allen dank voor jullie deelname, tijd en moeite die jullie in het onderzoek hebben gestoken.

Beste Angelique, ik had mij geen betere co-promotor kunnen wensen! Vanaf het moment dat ik bij het CaFaSpA 1 onderzoek ben betrokken, ben je voor mij een voorbeeld geweest. Ik heb veel bewondering voor hoe jij je werk als arts uitvoert,

maar zeker ook hoe je hiernaast verschillende succesvolle onderzoekslijnen hebt opgezet, management taken uitvoert en daarnaast betrokken bent bij familie en vrienden. Door jouw vertrouwen, coaching en begeleiding ben ik van een geneeskunde student uitgegroeid tot een volwaardig onderzoekster en ik weet zeker dat ik daardoor ook een betere arts zal zijn. Bedankt voor alle leerzame, leuke en gezellige momenten. Ik hoop dat we in de toekomst nog veel samen mogen blijven werken.

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coschap ;)), samen promoveren, samen een vrijgezellenfeest hebben, samen de voorpret van trouwen beleven en samen aan de opleiding tot reumatoloog beginnen. Als je zoveel dingen deelt dan kan het niet anders dan dat je naar elkaar toegroeit en elkaar feilloos aan gaat voelen. Ik voel mij dan ook vereerd dat jij tijdens mijn verdediging naast mij wil staan. En als ik het niet meer weet dan weet ik zeker dat jij het probleemloos van mij over kan nemen. Ik hoop dat we nog veel meer mooie momenten samen mogen beleven!

Esther wat een luxe dat wij een eigen postdoc op onze kamer hadden, je levens- en werkervaring zijn heel waardevol geweest en fijn dat ik altijd stoom bij je af mocht blazen. Myrthe, de best geklede promovenda van de afdeling. Ik bewonder je opgewektheid en efficiënte manier van werken, dank voor al je Brabantse gezelligheid. Annelieke, met je nuchterheid en praktische manier van zaken aanpakken ben je een hele fijne collega. Hilal, je vrolijkheid was aanstekelijk en onnavolgbaar, overigens net zoals de uitgebreidheid van je kledingkast ;). Jenny dank voor je waardevolle advies en dat je er altijd was om vragen te beantwoorden. Martijn je kon bij jou altijd terecht voor een statistiek vraag, dank hiervoor. En lieve meiden, geniet allemaal van de aankomende babyboom! Reumatologen en overige promovendi van het Erasmus MC dank voor jullie waardevolle aanvullingen tijdens de wekelijke research besprekingen. Joyce bedankt voor je praktische hulp.

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het altijd mogelijk hebben gemaakt dat ik verder kon leren. Dankzij jullie hebben ik geleerd wat discipline is en dat als je hard werkt alles mogelijk is. Zusjes, fijn dat jullie m'n zusjes zijn. Kim je enthousiasme werkt aanstekelijk en Anouk van jouw relaxedheid kan ik nog veel leren. Lieve Henk en Rita, ik ben er superblij mee dat jullie mijn schoonouders zijn. Jullie huis voelt echt als een tweede huis en jullie interesse in wat ik doe is fijn. Marjolein, een derde zusje erbij is erg gezellig en ik vind het altijd fijn om met jou over het ziekenhuis te praten. Ik hoop dat je je plekje op de CCU hebt gevonden. Overige familie en schoonfamilie, dank voor alle gezellig momenten gedurende m'n promotie, deze afleiding is heel belangrijk geweest. Oma's wat ben ik blij dat jullie beiden bij dit bijzondere moment aanwezig mogen zijn. Ik heb enorm veel bewondering en respect voor jullie.

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Lonneke

Curriculum vitae

Lonneke van Hoeven werd op 5 juni 1988 in Rotterdam geboren. Zij groeide op in Rotterdam en Barendrecht en haalde in 2006 haar gymnasium diploma aan de Christelijke Scholengemeenschap Calvijn te Rotterdam. Gedurende haar middelbare school periode had zij al interesse in wetenschappelijk onderzoek, haar profielwerkstuk was onderdeel van het Junior Science project, een samenwerkingsproject met het Erasmus MC.

Na de middelbare school is zij direct begonnen met haar Geneeskunde opleiding aan de Erasmus Universiteit in Rotterdam. Gedurende deze opleiding kreeg ze de mogelijkheid om in 2010, in het kader van haar keuzeonderzoek, mee te werken aan de CaFaSpA 1 studie. Een unieke en mooie gelegenheid om kennis te maken met wetenschappelijk onderzoek onder supervisie van Dr. A.E.A.M. Weel. Na dit keuzeonderzoek volgden twee jaar coschappen waarna zij in 2012 haar Geneeskunde studie cum laude heeft afgerond.

De CaFaSpA 1 studie bleek een opzet te zijn naar een volledig promotietraject welke in 2012 is begonnen. Haar promotie is een samenwerking tussen de afdelingen Reumatologie van het Erasmus MC (Prof.dr. J.M.W. Hazes), het Maasstadziekenhuis (Dr. A.E.A.M. Weel) en the Dutch Institute of Rheumatology (TDIOR). Tijdens haar promotie heeft zij in 2015 de master Clinical Epidemiology aan de NIHES (Netherlands Institute of Health Science) met goed gevolg afgerond. Op 1 mei 2015 is Lonneke getrouwd met Bart Lubbers. Sinds 1 december 2015 is zij begonnen met haar vooropleiding Interne Geneeskunde in het Maasstadziekenhuis te Rotterdam (opleider: Dr. M.A. van den Dorpel) in het kader van haar opleiding tot reumatoloog aan het Erasmus MC (opleider: Dr. R.J.E.M. Dolhain).

PhD portfolio: summary of PhD training and teaching

Name:	Lonneke van Hoeven
Erasmus MC Department:	Reumatology
Research School:	Netherlands Institute for Health Science (NIHES)
PhD period:	August 2012 – November 2015
Promotor:	Prof. dr. J.M.W. Hazes
Copromotor:	Dr. A.E.A.M. Weel

PhD training	Year	Workload (ECTS)
General academic skills		
Good Clinical Practice (GCP)	2012	0.5
Biomedical English Writing and Communication	2014	4.0
Master of Science Clinical Epidemiology	2013-2015	70 (total)
Core curriculum:		
Study Design	2014	4.3
Biostatistical Methods I: Basic Principles	2013	5.7
Clinical Epidemiology	2014	5.7
Methodologic Topics in Epidemiological Research	2014	1.4
Biostatistical Methods II: Classical Regression Models	2013	4.3
In depth courses:		
Repeated Measurements in Clinical Studies	2014	1.4
Advanced Topics in Decision-making in Medicine	2014	1.9
Advanced Topics in Clinical Trials	2015	1.9
Advanced Analysis of Prognosis Studies	2013	0.9
Quality of Life Measurement	2014	0.9
Health Services: Research and Practice	2014	0.9
Courses for the Quantitative Research	2013	1.4
Erasmus Summer Programme		
Principles in Research Medicine	2013	0.7
Clinical Decision Analysis	2013	0.7
Methods of Public Health Research	2013	0.7
Health Economics	2013	0.7
Primary and Secondary Prevention Research	2014	0.7

PhD training	Year	Workload (ECTS)
History of Epidemiologic Ideas	2014	0.7
Markers and Prognostic Research	2013	0.7
The Practice of Epidemiologic Analysis	2013	0.7
Causal Mediation Analysis	2014	0.7
Research		
Development Research Proposal	2015	2.5
Oral Research Presentation	2015	1.4
Research Period	2015	29.6
(Inter)national Conferences		
American College of Rheumatology Annual Meeting, Atlanta, USA [oral presentation]	2010	2.0
Nederlandse Vereniging voor Reumatologie (NVR) Najaarsdagen, Papendal, the Netherlands [attendence]	2012	0.5
European Congress of Rheumatology (EULAR), Madrid, Spain [two poster presentations]	2013	1.0
Nederlandse Vereniging voor Reumatologie (NVR) Najaarsdagen, Papendal, the Netherlands [one oral presentation, one poster presentation]	2013	2.0
American College of Rheumatology Annual Meeting, San Diego, USA [oral presentation]	2013	2.0
European Congress of Rheumatology (EULAR), Paris, France [three poster presentations]	2014	1.0
Nederlandse Vereniging voor Reumatologie (NVR) Najaarsdagen, Papendal, the Netherlands [one oral presentation, one poster presentation]	2014	2.0
9th International Congress on Spondyloarhtropathies, Gent, Belgium [three poster presentations]	2014	1.0
European Congress of Rheumatology (EULAR), Rome, Italy [one poster presentation, one poster presentation in tour]	2015	1.0
Nederlandse Vereniging voor Reumatologie (NVR) Najaarsdagen, Papendal, the Netherlands [two oral presentations, one poster presentation]	2015	2.0

PhD training	Year	Workload (ECTS)
Seminars and workshops		
Department Journal Club (attendance & presentations)	2012-2015	1.0
Cicero meetings	2012-2015	1.0
VENA workshops	2013-2015	1.0
Teaching		
Supervising two 2nd years medical student 'how to write a systematic review'	2012	1.0
Teaching course 'Kritisch lezen' to 1st years medical student	2012-2013	1.0
Lecturing refresher courses about axial spondyloarthritis to general practioners throughout the Netherlands	2012-2014	2.0
Working group on Diagnostic test in the Epidemiology Course for 4th year medical student	2013-2014	1.0
SPORT-refresher courses for reumaverpleegkundigen about axial spondyloarthritis	2013-2014	1.0
Teaching course 'Klinisch redeneren' to 1st and 3rd years medical students	2013-2015	2.0
Basis Kwalificatie Onderwijs (BKO) deelcertificaat (Teach the Teacher I and workshop 'Individuele Begeleiding')	2015	1.5
Other		
Study management of CaFaSpA 1 and IMPACT study	2010, 2013-2015	
Award for best poster presentation 'Wetenschapsdag' Maasstadziekenhuis	2014	
Organizing the annual PhD day for all PhD students in the Erasmus MC	2015	
Travel grants Reumafonds and EULAR	2013-2015