Early recognition of spondyloarthritis in patients at risk

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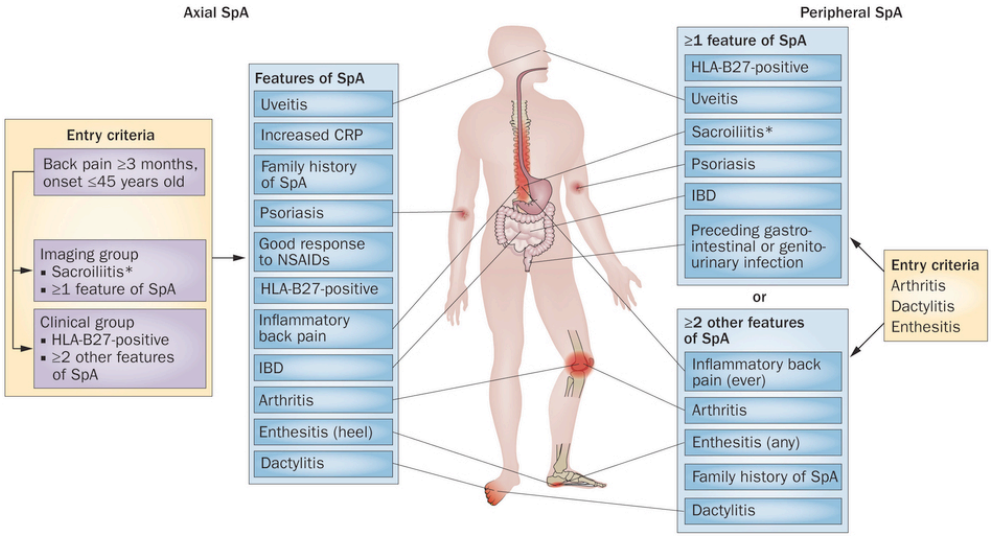
Chapter 1.

General Introduction

Spondyloarthritis

Spondyloarthritis (SpA) is an umbrella term for a group of inflammatory rheumatic diseases with signs and symptoms that have an overlapping genetic and pathophysiologic etiology.[1]

SpA can manifest itself through pain and stiffness of the joints, tendons and /or lower back. Due to inflammation of the axial skeleton, peripheral joints or entheses the main clinical manifestations are respectively sacroiliitis, arthritis, dactylitis and/or enthesitis. But also extra-articular manifestations like uveitis, psoriasis and inflammatory bowel disease (IBD) can occur. Multiple combinations of these features are possible, leading to a wide range of different phenotypes of SpA.



Van Tubergen, nat rev rheum 2015

SpA can be considered a condition in itself, but in practice several subtypes are used like ankylosing spondylitis (AS), non-radiographic axial SpA (nr-axSpA), psoriatic arthritis (PsA), SpA related to IBD (IBD-SpA), reactive arthritis (ReA) and undifferentiated SpA (uSpA).[2] Until the 1950s it was believed that there was no distinction between the different types of arthritis like rheumatoid arthritis and spondyloarthritis. Afterwards, the discussion started that SpA may be an entirely different disease than rheumatoid arthritis. In 1976, Moll & Wright were the first to describe the unified concept of SpA characterized as seronegative arthritides, with overlapping clinical, serological and radiological features.[3] After the concept of SpA was established, the development of classification criteria started. Many different sets of classification criteria for the different subtypes (i.e. ankylosing spondylitis, psoriatic arthritis) were developed over the years. For SpA in general the AMOR criteria were set up

in 1990, followed by the ESSG criteria in 1991.[4,5] The AMOR criteria consist of a scoring system of different signs and symptoms of SpA, which can contribute either 1, 2 or 3 points to the required 6 for classifying SpA.[4] To fulfil the ESSG criteria a patient must have inflammatory back pain and/or peripheral arthritis, in combination with one other SpA feature.[5] These criteria seemed to perform reasonable in different cohorts, but the main problem was the low sensitivity for early SpA. In addition, no distinction is made between axial or peripheral manifestations, which is important as these different manifestations have different epidemiology, symptoms and treatment options. Recently, the ASAS (Assessment of SpondyloArthritis international Society) group proposed another classification of SpA. These criteria do not look at the different subtypes of SpA, but focus on the predominant clinical manifestation, which can be either axial or peripheral.[6,7] Besides inflammatory axial or peripheral symptoms, patients must have other SpA features to classify as having SpA.

Ethiopathogenesis

The prevalence of SpA has been widely studied and the reported prevalences in the general population range from 0.2% in South-East Asia to 1.61% in Northern Arctic communities as demonstrated in a recent meta-analysis.[8] The prevalence of SpA is hereby comparable with the prevalence of rheumatoid arthritis. The prevalence of SpA is strongly dependent on the prevalence of HLA-B27 across the world, which partly explains the spread in prevalence. Besides this important etiological factor, several other factors like study design, population selection and the use of different classification criteria also play an important role in the spread in prevalence.

The pathophysiology of SpA is complex and has not yet been fully revealed. Although SpA can manifest in multiple forms, the genetics and pathogenesis overlap to a greater or lesser extent.[9]

Multiple factors are likely relevant in the development of SpA, among which environmental factors and genetic factors. These genetic factors contribute to a great extent to the hereditability of SpA, with studies showing contribution of these genetic factors of up to 90% of the susceptibility to ankylosing spondylitis.[10] The most well-known and important genetic factor in SpA is HLA-B27.[9] The presence of HLA-B27 differs across the world and therefore partly explains the geographic variation in SpA prevalence.[8] The link between SpA and HLA-B27 is strongest in axial SpA, demonstrated by the fact that approximately 80-90% of Northern European patients with axial SpA are HLA-B27 positive. The other way around, if a patient is HLA-B27 positive the risk of developing SpA is approximately 5-7%, HLA-B27 is therefore included in the ASAS classification criteria as well as in several referral tools for axial SpA.[11-14] However, the prevalence of HLA-B27 is lower in patients with early axial SpA and decreases towards 20% in psoriasis patients with peripheral arthritis. Besides HLA-B27, several other

potential genetic determinants have been identified, such as IL23R, IL1A, IL1R2 and ERAP1.[15] However, the contribution of these factors seems to be low and the evidence is still scarce.

Another well-established important factor in the pathogenesis of SpA is Tumor Necrosis Factor (TNF). TNF-α plays a role in the development of synovitis, but also in extra-articular manifestations like gut inflammation and psoriasis. [16-18] Over the last years, knowledge about the role of interleukin-23 (IL-23) en interleukin-17 (IL-17) has exponentially increased. [18] IL-23, which is produced by dendritic cells and macrophages, induces amongst others the production of IL-17 and IL-22.These two cytokines are physiologically important for gut homeostasis, but have a pathological role in the joint. It has been demonstrated that the link between SpA and gut inflammation works both ways. Multiple studies have demonstrated the presence of microscopic gut inflammation in patients with SpA. The other way around it also seems that the gut has an important role in the etiopathogenesis of SpA.[17]IL-17 and IL-22 are also important in the development of enthesitis and osteoproliferation.[17,18]

Risk Groups

As mentioned earlier, SpA can manifest with musculoskeletal complaints, like inflammatory back pain or arthritis. However, in some patients skin (i.e. psoriasis) or bowel (i.e. IBD) symptoms occur before the onset of musculoskeletal complaints. These groups of patients are therefore at risk of developing certain subtypes of SpA; namely psoriatic arthritis (PsA) in patients with psoriasis and IBD-associated SpA in patients with IBD. These subgroups of patients at risk are the focus of this thesis and will be described separately.

Psoriasis and Psoriatic Arthritis

Clinical Manifestations

Psoriasis is a chronic immune-mediated disease of the skin, leading to characteristic erythematous plaques.[19] It affects men and women equally and can occur at any age with peak incidence between 20-30 years of age and 50-60 years of age.[20] Psoriasis can be accompanied by a number of comorbidities, including cardiovascular disease, depression and as described in this thesis psoriatic arthritis (PsA).[21] In most cases, psoriasis precedes the development of PsA by approximately 12 years.[16]

PsA affects men and woman equally and typically presents between 30 and 50 years of age.[22] It can manifest with peripheral arthritis, but also with enthesitis or sacroiliitis.[16,22] Peripheral arthritis usually occurs in an asymmetrical distribution and mostly in the larger joints, but there is also a subtype mimicking rheumatoid arthritis with polyarthritis of the small joints.[22] Enthesitis, defined as an inflammation of the insertion of the tendon to the bone, can occur at any site were tendons attach to

the bone, but the most known location is the Achilles tendon. Another subtype of PsA is the axial subtype, with inflammation of the sacroiliac joints, like ankylosing spondylitis. It has been described that certain factors in psoriasis patients are associated with the development of PsA. These characteristics include psoriasis of the nail, scalp or intergluteal as well as certain environmental factors like infections, heavy lifting and injuries.[23,24] Over the years, multiple sets of classification criteria have been developed and used for PsA. One of the first is by Moll & Wright, who divided PsA into five clinical patterns; asymmetrical oligoarthritis, symmetrical polyarthritis, distal interphalangeal arthritis, arthritis mutilans and spinal column involvement.[25] As the pattern of involvement may change over time, this classification proved not very useful.[22] In 2006 the now widely used CASPAR criteria were introduced.[26] To fulfil these classification criteria, a patient must have inflammatory articular, entheseal or spinal disease. On top of this, at least 3 out of the following 6 points are required: the presence of psoriasis (current (2 points) or history), presence of psoriatic nail dystrophy, absence of rheumatoid factor, dactylitis (diagnosed by rheumatologist) and radiographic evidence of juxtaarticular new bone formation. The difficulty with these criteria is that the stem elements (inflammatory articular, entheseal or spinal disease) are not defined. Whereas this might be less of a problem for articular and spinal disease, the definition of inflammatory entheseal disease is not clear. Although the CASPAR criteria are widely used in research, in clinical practice the diagnosis of the rheumatologist based on clinical manifestations is still the gold standard.

Epidemiology

The estimated prevalence of psoriasis is approximately 3%, with higher prevalences in Caucasians compared to other ethnicities.[27] The prevalence of PsA in the general population is reported to range from 0.01% in the Middle East to 0.19% in Europe.[8,28] The prevalence of PsA in patients with psoriasis has also been frequently studied and ranges from 6 to 42%.[28] Most prevalence studies were performed in secondary care, whereas in a country like the Netherlands with an extensive primary health care system, the prevalence in primary care is very important, but lacking.

Burden of Disease

Numerous studies have been performed regarding the burden of disease of both psoriasis and PsA. Psoriasis negatively affects quality of life, as to be expected this quality of life depends partly on the severity of the skin involvement.[29] In addition to the risk psoriasis patients have at developing PsA, a number of other comorbidities can occur among which cardiovascular problems like hypertension, hyperlipidemia and diabetes mellitus.[30] The presence of PsA besides the psoriasis reduces the quality of life further than psoriasis alone.[22,29,31] A few studies have compared the burden of disease between

PsA, rheumatoid arthritis and axial SpA and showed comparable or worse quality of life for patients with PsA or axial SpA compared with rheumatoid arthritis.[32,33] Besides the reduced quality of life, inability to work has also been recognized as a problem in both psoriasis and PsA patients.[34-36] As PsA is an erosive disease, patients are at risk for developing serious joint damage. Over the last couple of years it has become more and more apparent that early treatment can prevent this major damage and lead to better functional outcome.[37,38] With regard to the economic burden of psoriasis and PsA, it is apparent that these diseases will be accompanied by certain costs. These costs increase with the treatment and management (including the use of biologics) of more severe disease.[39,40]

Treatment

With regard to treatment both the skin manifestations and musculoskeletal manifestations have to be taken into account. As there is a certain overlap in pathogenesis, some treatments are effective for both psoriasis and PsA. However, both manifestations of psoriatic disease also have their own specific treatments. Specific treatment for psoriasis includes topical treatment (including steroids), phototherapy and oral retinoids.[41] For severe psoriasis or psoriasis in combination with PsA, DMARDS like methotrexate and biologicals such as anti-TNF can be used. If patients suffer from comorbid psoriasis and PSA, one should attempt to use treatment modalities that address both skin and joint manifestations. The treatment recommendations for PsA are quite similar with those of psoriasis in the advanced steps, but begin with PsA specific treatment. The treatment goals in PsA are to achieve a state of minimal disease activity, maintaining functional ability and quality of life and preventing joint erosions. Treatment should be monitored regularly and adjusted where necessary, based on shared decision making with the patient.[42] The first step in PsA treatment are NSAIDs. Intra-articular corticosteroids could be used as adjunctive therapy, even as systemic corticosteroids at the lowest dose possible. In patients with many swollen joints, high levels of CRP/ESR or relevant extra-articular manifestations, NSAIDs will not be sufficient. It is therefore recommended to initiate DMARDs early on in these patients, with a preference for methotrexate in case of skin involvement.[42] If the first DMARD fails, the next step is to prescribe another DMARD before switching to biologicals. For patients with predominantly axial or entheseal disease, DMARDs have no proven efficacy. If NSAIDs fail in these patients, biologicals are the treatment of choice.

Inflammatory Bowel Disease-Spondyloarthritis

Clinical Manifestations

IBD is a chronic relapsing-remitting disease of the gastro-intestinal tract and comprises both Crohn's disease (CD) and ulcerative colitis (UC).[43] CD is characterized by transmural inflammation and can

occur in any part of the gastro-intestinal tract, from mouth to anus. UC is characterized by mucosal inflammation of the colon, usually starting in the rectum and moving up in the colon in continuity. IBD usually manifests in young adults (<30 years of age) and can be accompanied by a various extra-intestinal manifestations in multiple organ systems, among which rheumatic manifestations as IBD-SpA. As with PsA, IBD-SpA will mostly occur in patients already suffering from inflammatory bowel disease (IBD). However, the concept of IBD-SpA is not as clear as the concept of PsA. Orchard et al made a classification of two types of arthritis in patients with IBD.[44] Type 1 represents an oligoarticular arthritis, particularly affecting large joint of the lower extremities and correlates with IBD activity. Type 2 has a polyarticular, symmetrical distribution mostly affecting joints of the upper extremities and is less likely to correlate with IBD activity. Although this distinction is still used by gastroenterologists, it is not widely accepted in rheumatology.[45] Rheumatologists classify IBD-SpA according to the most predominant manifestation. As this can be either peripheral (arthritis, enthesitis, dactylitis) or axial (sacroiliitis, ankylosing spondylitis), criteria are used accordingly. In practice, this means that multiple sets of criteria are used like the ASAS criteria, the ESSG criteria and the modified New York criteria.[5-7,46]

Epidemiology

Prevalence of CD varies from 1.5 to 213 cases per 100,000 persons, whereas the prevalence of UC varies from 2.4 to 294 cases per 100,000.[47]

With regard to IBD-SpA, few population-based studies are available. Two European studies reported prevalences of 0.02 and 0.09.[48,49] The prevalence of IBD-SpA in patients with IBD has been studies more extensively, with a reported range from 2 to 46% in patients with IBD.[45,50]

Burden of Disease

Over the years the quality of life in patients with IBD has been extensively studied. While some studies show reduced quality of life[51-54], other studies show no difference between IBD patients and the reference population.[55,56] As IBD can be accompanied by a large number of extra-intestinal manifestations, which all can have impact on quality of life, it is difficult to say which causes the reduce in quality of life. Until now, the specific impact of extra-intestinal manifestations, among which the large group of rheumatic manifestations, has not been fully investigated. However, some studies have looked at the influence of musculoskeletal complaints (MSC) on quality of life and show lower scores on SF-36 and IBDQ for patients with MSC.[57,58] IBD has a negative impact on employment status, where patients with MSC experience higher work and activity impairment than IBD patients without MSC.[58,59]

With regard to economic burden, the health expenditure per IBD patient can be even greater than the costs for other chronic disease like diabetes, hypertension and COPD.[53] As IBD is a chronic disease, patients often use medication, among which the expensive biologicals, for long periods of time. In addition, a lot of IBD patients need surgery or even multiple surgeries.[53] It seems apparent that patients who also suffer from SpA, will have even higher costs as the costs for the treatment and monitoring of SpA should be added.

Treatment

As with PsA, some of the treatment for IBD will be effective for IBD-SpA as well, but both diseases also have their own treatment options. Treatment for IBD also follows a step-up strategy. First step of treatment is 5-aminosalicylic acid (mesalazine or sulfalazine) or steroids. The following steps include immunusuppressants (e.g. azathioprine, cyclosporine, methotrexate), anti-TNFα (e.g. infliximab, adalumimab) and surgery.[60,61] Although treatment for IBD has improved over the last years, surgery remains unavoidable for part of the patients. For UC patients, surgical intervention is needed in 10-30% of patients, while for patients with CD, surgery is needed in up to 80% of patients.[62] For patients with IBD-SpA it is desirable to find a treatment strategy suitable for both the IBD and the SpA.

The European Crohn's and Colitis Organisation (ECCO) recently published a guideline on extraintestinal manifestations of IBD.[63] These guidelines recommend joint management with the rheumatologist of IBD patients with axial or peripheral involvement. As with PsA, first choice of treatment would be NSAIDs. However, long-term treatment of NSAIDs should be avoided in patients with IBD as it can increase the risk for relapse of IBD. Evidence suggests that selective COX-2 inhibitors may be a better option as they do not seem to cause relapse of IBD.[50,63,64] For patients with axial involvement, biologicals (anti-TNFα) are the first choice of treatment after failure of or intolerance for NSAIDs. A lot of the treatment options for IBD are also effective in peripheral arthritis. It is therefore said that effective treatment of the IBD is often sufficient to treat peripheral arthritis. However, short-term use of systemic corticosteroids or local corticosteroids injections are advised for symptom relief. Further treatment options are DMARDs (sulfasalazine, methotrexate) and if this fails biologicals. With regard to biologicals it is recommended to preferably choose a biological with proven effectiveness for both the IBD and SpA, like infliximab and adalumimab. Etanercept is effective in SpA, but has not been found effective for IBD.[50]

Early Recognition of SpA

Early recognition of SpA is important.[65] SpA is a chronic and potentially disabling disease as it can lead to severe joint deformations if left untreated. These complications could self-evidently lead to reduced

quality of life and reduced work participation.[66,67] Over the last couple of years various effective treatments for SpA have become available. Evidence suggests that short disease duration is one of the predictors of good response to these treatments.[37,38,67] In order to achieve this early recognition, two important factors are awareness and screening.

Awareness

In order to recognize a disease like SpA early, patients at risk as well as physicians treating these patients should be aware of the increased risk of SpA. In countries with a primary healthcare system, like the Netherlands, patients who experience MSC will visit their general practitioner (GP). MSC are a very common complaint in the general population, and account for about 20% of consultations in primary care.[68,69] Some of these complaints will have an inflammatory cause, like SpA. However, the prevalence of SpA is relatively low in the general population, so GPs will not see it often in their practice. Making GPs aware of the concept of SpA, including knowledge about the patientgroups at risk (e.g. psoriasis, IBD), could aid the recognition. In the United Kingdom, which also has an extensive primary health care system, campaigns for improvement of awareness for rheumatoid arthritis have been set up.[70,71] In the Netherlands, a guideline for general practitioners has been set up to aid them in the workup of patients with inflammatory arthritis.[72] However, the focus on early recognition and awareness of SpA lags behind. As awareness and knowledge are very broad concepts, it is necessary to assess the current status of GPs to detect where the gaps are in this knowledge and awareness. The other way around, it may also be beneficial if patients with psoriasis or IBD are aware themselves that they could develop SpA. As with awareness for GPs, it needs to be assessed if patients with psoriasis and IBD are aware and in addition if increasing this awareness could really lead to decreasing delay in consulting a physician about these complaints.

Screening

Another way to aid early recognition, is screening. The concept of screening is to identify possible disease in patients without signs or symptoms. This has been widely implemented in for example oncology, with international successful screening programs for breastcancer, cervical cancer and bowel cancer. Screening becomes more and more important as a lot of diseases can be better treated or even cured in the early phases of the disease. As both PsA and IBD-SpA are in most cases preceded by psoriasis respectively IBD, implementing screening methods can be very beneficial.[16,45] Over the last years, multiple screeningtools have been developed to screen psoriasis patients for the presence of PsA.[73-76] Most of these tools were developed in secondary care settings and show moderate performance with regard to sensitivity and specificity.[77-79] With regard to the healthcare organization

in the Netherlands, it is valuable to gain insight in the performance in primary care. To date, the use of screeningtools has not been implemented in standard daily practice. In contrast with the extensive research in screening for PsA, no screeningtools have been developed to screen IBD patients for the presence of IBD-SpA.

SENSOR & AppSpA Studies

The studies that are described in this thesis used data from two large primary care projects: SENSOR (ScrEeNing arthritiS in psORiasis) and AppSpA (Awareness in Patients and Primary care physicians of SPondyloArthritis).

The SENSOR study was set up in 2013 in a primary care setting, where GPs were invited to participate. Participating GPs selected their patients with psoriasis out of their databases based on ICPC coding (International Classification of Primary Care), which is the standard for coding symptoms and diseases in primary care in the Netherlands. All patients with ICPC S91 for psoriasis were selected and invited to participate. Patients were eligible to participate if they had psoriasis, were 18 years or older and suffered from any kind of MSC. All eligible patients willing to participate, completed a set of questionnaires and were subsequently invited for clinical evaluation by a trained research assistant. Clinical evaluation focused on skin, joints, entheses and lower back. If there were indications of underlying inflammatory rheumatic disease, patients were advised to consult a rheumatologist, where a diagnosis of PsA could be considered.

The AppSpA study was set up in 2014 and also focused on primary care. This study consisted of two parts; namely a GP-part and a patient-part. The GP-part focused on awareness and knowledge of SpA and was assessed with a survey. GPs from various regions in the Netherlands were invited to participate and complete the survey. The patient part also consisted of a survey and included patients at risk for SpA, i.e. patients with psoriasis or IBD. This aim of this survey was to assess the burden of disease for psoriasis and IBD patients with and without MSC. GPs were recruited to select patients with psoriasis or IBD aged 18-55 years out of their database (ICPC S91 for psoriasis and D94 for IBD) and invite them to participate. In addition, patients were recruited via the Dutch patients' organizations for psoriasis and IBD. If patients were willing to participate they received a set of questionnaires concerning their IBD, presence of musculoskeletal complaints, quality of life and work participation.

Objective and Outline Thesis

In summary, early recognition of patients at risk for SpA is important. Since patients with musculoskeletal pain will, irrespective of having PSO or IBD, most likely visit their general practitioner for these complaints, the primary care setting seems key.

The aims of this thesis are:

- To get insight in the prevalence of PsA and ultrasound findings of enthesitis in psoriasis patients in a primary care setting
- To give an overview of the prevalence of axial and peripheral SpA in IBD patients
- To describe the burden of musculoskeletal complaints in patients with IBD
- To evaluate the awareness of SpA among GPs and patients with IBD or PSO
- To assess the optimal screening-strategy for PsA in a primary care setting

Part I. Prevalence & Burden of SpA in patients at risk

In **Chapter 2** we describe the results of a cross-sectional study estimating the prevalence of musculoskeletal complaints and PsA in primary care psoriasis patients. **Chapter 3** focuses on an important but scarcely studied part of PsA, namely enthesitis. In this study we aimed to assess the frequency of clinically relevant ultrasound inflammation at the entheses of primary care psoriasis patients.

Chapter 4 focuses on the prevalence of the various manifestations of SpA in patients suffering from IBD. We performed a systematic review and aimed to give pooled estimates for both the axial manifestations and the peripheral manifestations of SpA in IBD patients. In **Chapter 5** we looked at patients with IBD with or without musculoskeletal complaints. The aim of this study was to assess the impact of musculoskeletal complaints on quality of life and work participation in patients with IBD.

Part II. Early Recognition

The second part of this thesis focusses on early recognition of SpA in patients at risk, by means of awareness and screening. **Chapter 6** describes the current practice of Dutch GPs with regard to inflammatory musculoskeletal complaints. With this survey we aimed to gain insight in the knowledge and awareness of GPs with regard to SpA and patients with psoriasis or IBD at risk for SpA. Besides the GPs, we also looked into the awareness of the patients themselves. **Chapter 7** describes the performance of different in secondary care validated screeningtools for PsA in a primary care setting. Finally, **Chapter 8** describes the performance of a newly developed screeningtool for PsA, consisting

of the best performing items of previous screeningtools. This screeningtool was initially developed in a secondary care setting and we assess its performance in our primary care setting.

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Part I.

Prevalence and Burden of Spondyloarthritis in Patients at Risk

Chapter 2.

Prevalence of Psoriatic Arthritis in Primary Care Patients With Psoriasis

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Abstract

Objective. To estimate the prevalence of PsA in primary care patients diagnosed with psoriasis. The second objective was to estimate the prevalence of MSC in primary care psoriasis patients.

Methods. We conducted a cross-sectional study in adult primary care patients with psoriasis. Responding patients reporting pain in joints, entheses or lower back were checked on eligibility by a telephone interview and invited for clinical evaluation. During clinical evaluation skin, nails, joints and entheses were assessed. Additionally, ultrasonography of the entheses was performed by an independent trained examiner if a patient had at least one tender enthesis (LEI/MASES). A patient had PsA if fulfilling the CASPAR criteria.

Results. 2564 psoriasis patients from 97 GPs were invited. Of the 1673 responders (65.2%), 841 (50.3%) were willing to participate. 823 (32.1%) patients reported suffering from MSC of which eventually 524 were eligible and clinically evaluated. Sixty-four cases of established PsA were identified and another 17 cases of PsA were newly diagnosed, leading to a prevalence of 3.2% (95%CI 2.5%-3.9%) among primary care psoriasis patients. This would increase towards 4.6% (95% CI 3.8%-5.4%) if the PsA cases based on enthesitis are also taken into account.

Conclusion. Among psoriasis patients in primary care the prevalence of PsA is conservatively estimated to be 3.2% increasing to 4.6% if enthesitis is taken into account. The prevalence of MSC in psoriasis patients is comparable to the prevalence in general population.

Introduction

Psoriatic arthritis (PsA) is the second most frequent inflammatory arthritis for which a rheumatologist is consulted.[1] PsA is well treatable and an increasing number of studies show that early diagnosis improves the outcome substantially.[2-6] In most cases PsA is preceded by psoriasis, which affects 2-3% of the Western population.[7-9] Estimates of the prevalence of PsA among psoriasis patients are numerous and range widely (6-42%) and most data stems from secondary dermatology care.[10,11] However, most psoriasis patients at risk for PsA will visit their general practitioner (GP) first if having musculoskeletal complaints (MSC), enabling early referral if recognized timely. Therefore, prevalence data from primary care is important. To our knowledge, only two studies have reported the prevalence of PsA in primary care. Both studies were performed in the UK and report prevalences of 9.0% and 13.8%.[12,13]

The primary objective of this study was to give an estimate of the prevalence of PsA including enthesitis in primary care psoriasis patients and secondly to estimate the prevalence of MSC in psoriasis patients.

Methods

Patients

Between June 2013 and March 2014, 270 GPs from the greater Rotterdam area in the Netherlands were invited to participate, initially by a personal letter and if they did not respond by phone call. The participating GPs (n=97; 36%) selected their psoriasis patients aged 18 years and over from their databases using ICPC code S91 (International Classification of Primary Care code for psoriasis).[14] In the Netherlands, the ICPC is the standard for coding and classification of signs and symptoms in general practice. The identified psoriasis patients received an invitation from their GP asking them to participate. Patients were asked to return the reply slip, which contained two questions. The first question was if they did or did not suffer from regular joint complaints, back complaints or tendon complaints. Secondly they were asked if they wanted to participate. In the accompanying letter, patients were asked to return the reply slip, regardless of whether they wanted to participate. The patients who agreed to participate were called by a trained interviewer to verify if they had regular joint and tendon complaints or chronic low back pain (with chronic defined as more than 12 weeks and onset before the age of 45). She also verified whether they had a diagnosis of psoriasis and sufficient knowledge of the Dutch language to complete the questionnaires. Ethics approval from the Dutch Medical Ethical Committee (M12-1275) was obtained as well as written informed consent from all participating patients.

Data collection

Data was collected by self-reported questionnaires and clinical evaluation.

Questionnaires. Patients were asked to complete three questionnaires related to their complaints. Indication of inflammatory back pain was assessed by the ASAS-IBP (ASAS questionnaire on Inflammatory Back Pain)[15], which consists of five yes-no questions. To assess the presence of other MSC the PEST (Psoriasis Epidemiology Screening Tool)[16] and the EARP (Early Psoriatic Arthritis Screening Questionnaire)[17] were used. These are both validated questionnaires developed as screening tools for PsA, consisting of yes-no questions on the presence of particular features such as joint swelling and swelling of the Achilles tendon. The PEST also includes a manikin for stiff, swollen or painful joints.

Clinical Evaluation. A trained research assistant completed a detailed history, containing information about psoriasis and musculoskeletal complaints, presence of other features including dactylitis, uveitis and inflammatory bowel disease and family history. Physical examination focused on the skin, nails, joints and entheses. Psoriasis severity was scored by the psoriasis area and severity index PASI[18] This provides a quantitative assessment of psoriasis based on the amount of body surface area involved and the degree of severity of erythema, induration and scaling weighted by body area. The score ranges between 0 and 72 and a score above 10 is considered to represent moderate to severe psoriasis. The nails were visually inspected and if an abnormality was observed a photograph was taken, which was evaluated by a trained dermatologist who was unaware of clinical presentation. The joints were evaluated by manual palpation of tenderness and swelling using the 66/68 joint count.[19] The enthesis were manually evaluated for tenderness using the LEI (Leeds Enthesitis Index[20] and the MASES (Maastricht Ankylosing Spondylitis Enthesitis Score)[21]. The LEI consists of 6 entheseal sites (lateral epicondyle of the humerus, medial condyle of the femur and Achilles tendon insertion, all bilaterally) and the MASES of 13 entheseal sites (1st and 7th costochondral joint, anterior and posterior superior iliac spine, iliac crest, proximal insertion of Achilles tendon, all bilaterally and the 5th lumbar spinous processus), the score is the sum of all tender sites.

Ultrasound evaluation of the enthesis. If clinical evaluation resulted in at least one tender enthesis, patients were referred for an ultrasonographic examination by an independent trained examiner using Esaote Mylab60 (probe LA 435). The six entheses included in the MASEI (Madrid Sonographic Enthesis Index) [22] were examined bilaterally: olecranon tuberosity, superior & inferior pole of the patella, tibial tuberosity, superior pole (Achilles tendon) & inferior pole (plantar fascia) of the calcaneus plus the lateral epicondyle tendon insertions (elbow). US enthesitis was defined as the presence of power Doppler (PD) signal (<2mm of the bony cortex) or in case of the plantar fascia an increased thickness of the enthesis (>4.4mm) as PD signal cannot be obtained at the plantar fascia.[22,23]

Referral to rheumatologist

Patients were advised to consult a rheumatologist if there were indications of underlying rheumatological disease. Referral criteria were set up and these included an evident history of dactylitis or arthritis as well as current peripheral or axial manifestations. Peripheral manifestations were defined as arthritis in one or more joints upon physical examination or enthesitis at US examination. Possible axial manifestation was defined as low back pain for more than 12 consecutive weeks with an onset before the age of 45 and two or more of the following; positive ASAS-IBP questionnaire (4 out of 5 positive), positive family history of SpA, good response to NSAIDs or chronic low back pain for more than 5 years.[24]

Case definition

The diagnosis of PsA was based on the CASPAR criteria, where patients must have inflammatory articular disease in the joints, spine or entheses.[25] On top of this, at least 3 out of the following 6 points are required: the presence of psoriasis (current (2 points) or history), presence of psoriatic nail dystrophy, absence of rheumatoid factor, dactylitis (diagnosed by rheumatologist) and radiographic evidence of juxtaarticular new bone formation. The presence of peripheral arthritis and axial disease were confirmed by a rheumatologist. For enthesitis there is no commonly accepted clinical definition, which is why we decided to use a combination of clinical characteristics and positive Power Doppler signal at the enthesis (<2mm of the bony cortex).[23] Clinical characteristics included self-reported pain at the enthesis (either on PEST or EARP questionnaire or in the history) or the presence of a tender enthesis at clinical examination (LEI/MASES). We did not accept the sole presence of PD as study data suggest that PD could be present in non-clinical cases.[26-28]

Statistical Analysis

Descriptive statistics were used for the prevalence of PsA and MSC, symptom duration, medication use and other clinical features in STATA 13. Because of missing information in different phases of the patient recruitment on both the prevalence of PsA and the prevalence of MSC, sensitivity analysis was performed. We evaluated three scenarios in which we assumed what would have been the frequency of PsA and MSC as if we had have evaluated the patients that did not reply. In the first scenario, we used our observed frequency of MSC among the responders to apply to the non-responders and subsequently we applied the observed frequency of PsA within the MSC to the non-responders. In the second scenario, we used for the non-responders the MSC frequency we observed from the patients who returned their reply-slip but did not want to participate. For the frequency of PsA we made the

same assumption as in the first scenario. The third scenario equals the second with regard to the observed frequency of MSC, but the frequency of PsA was as observed among clinically evaluated patients only.

Results

Source population

In total, 97 GPs participated, representing a source population of 158 046 patients aged 18 years and over. Out of these 158 046 patients, 2647 had an ICPC code S91 for psoriasis (1.7%) (Figure 1). In the process of inviting the patients for clinical evaluation, 83 (3.1%) patients reported not having psoriasis and were excluded, so eventually we had a population of 2564 psoriasis patients (mean age 55.2 years (SD 17.5), 51.6% male). Figure 2 shows the distribution of psoriasis per age category and gender.

Figure 1. Recruitment of primary care psoriasis patients

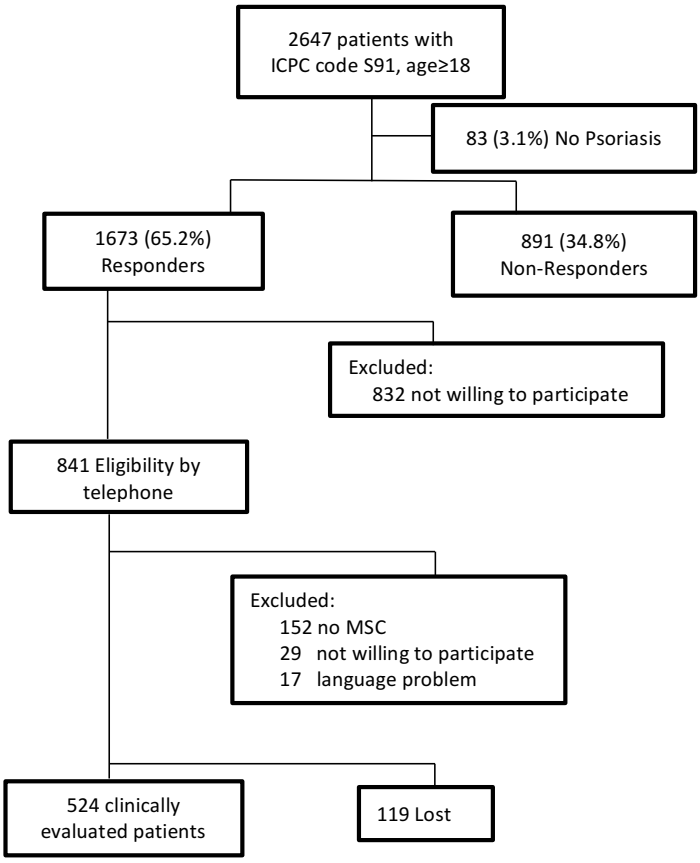
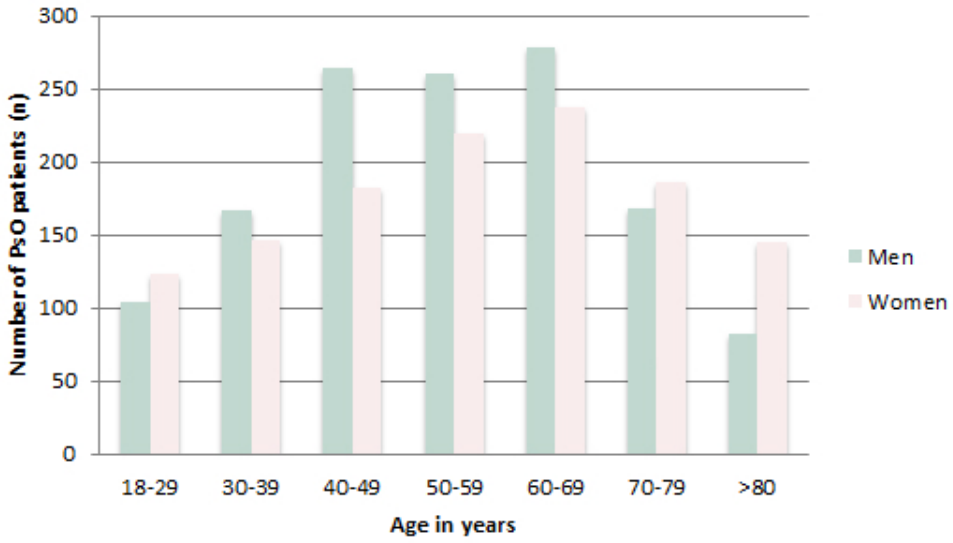


Figure 2. Distribution of psoriasis in different age groups in a primary care population (n=2564)



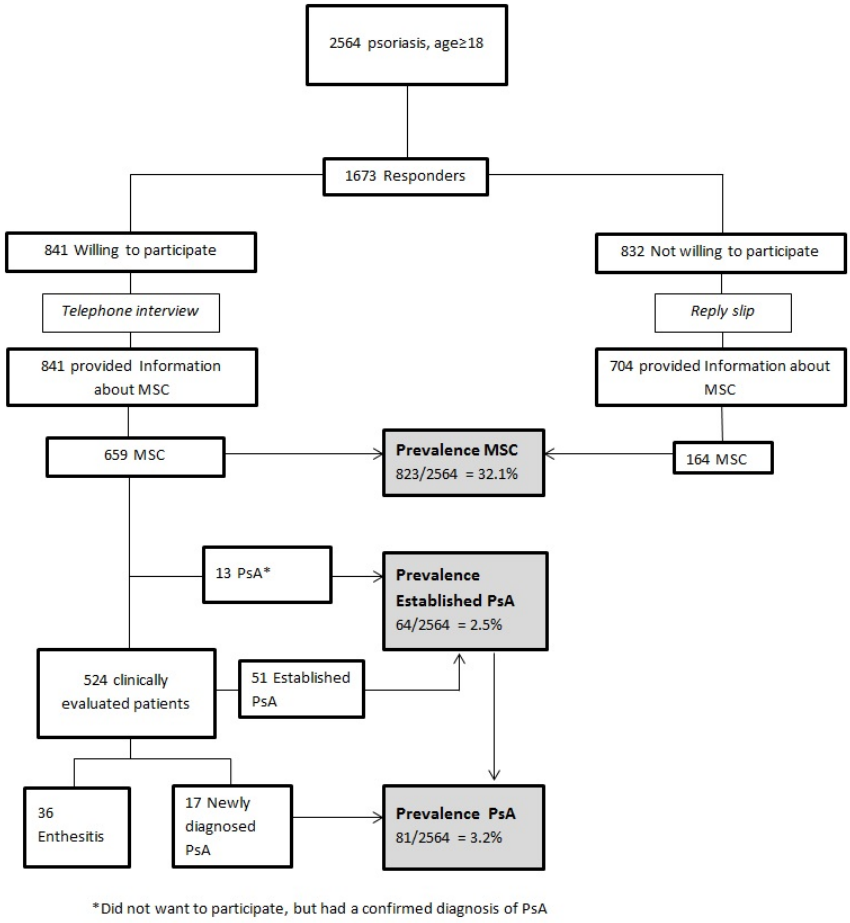
Invited patients

Of the 2564 invited psoriasis patients, 1673 returned the reply slip (65.2%). Of these 1673 responders 841 (50.3%) were willing to participate and their eligibility was verified. Regular complaints from joints, tendons and/or lower back were then mentioned by 78.4% of the patients (n=659) and subsequently invited for clinical evaluation. Of these, 524 patients were actually present at their clinical evaluation (Figure 1).

Prevalence of musculoskeletal complaints

Data on the prevalence of MSC was derived from two sources. First, we had a group of 832 patients who did not want to participate. Of these patients, 128 left the question about the presence of MSC blank. Among the other 704 patients, 164 (23.3%) reported to suffer from MSC. The second source comprised the 841 patients that were interested in participating, of which during a telephone interview 659 patients reported regular suffering from MSC. Of these 659 patients, 581 (88.2%) reported regular spells of joint complaints, recurrent tendon complaints were reported by 332 patients (50.4%) and low back pain was reported by 487 patients (73.9%). In total 823 of 2564 patients reported having regular MSC, which leads to a prevalence of 32.1%, assuming no additional MSC would be found in patients that did not reply or did not provide information about the presence of MSC on the reply slip (Figure 3).

Figure 3. Flow diagram of sources used for calculating the prevalence of musculoskeletal complaints & psoriatic arthritis in a primary care psoriasis population



Clinically evaluated patients

The mean age of the 524 evaluated patients was 55.8 years (SD 13.9) and 50.0% were male. Mean psoriasis duration was 21.0±16.3 years, with 74% of the psoriasis diagnoses confirmed by a dermatologist. The remaining 26% of psoriasis cases were confirmed by the GP. During clinical evaluation 81 patients (15.5%) had nail abnormalities consistent with psoriatic nail dystrophy. Median PASI score in the study population was 2.2 (IQR 1-4). Table 1 provides the clinical details for those not suffering from PsA, established PsA, new PsA and enthesitis.

Table 1 Characteristics of the 524 participating psoriasis patients

	Axial manifestations & Peripheral Arthritis* (n=17)	Enthesitis* (n=36)	Established PsA patients* (n=51)	Psoriasis patients* (n=420)
Mean Age, years (±SD)	47.4 (10.7)	58.0 (12.3)	56.1 (14.4)	55.9 (14.0)
Male sex, n (%)	8 (47.1)	17 (47.2)	21 (41.2)	216 (51.4)
Body Mass Index, mean (±SD)	27.9 (6.2)	30.0 (4.1)	28.2 (8.3)	27.8 (4.8)
Median Psoriasis Symptom Duration, years (IQR)	15 (4-30)	20 (11-37)	20 (12-33)	15 (8-30)
Psoriasis Diagnosis by Dermatologist, n (%)	13 (76.5)	31 (86.1)	42 (82.4)	302 (71.9)
Nail psoriasis, n (%)	5 (29.4)	2 (5.6)	10 (19.6)	64 (15.2)
PASI, median (IQR)	3 (1.3-4)	3.1 (1.7-4.4)	1 (0-3)	2.2 (1-4)
Median MSC Symptom Duration, years (IQR)				
Joints	12.5 (2-23)	10 (5-25)	12 (8-20)	8 (4-14)
Lower Back	18 (9-25)	33 (14-41)	8.5 (5-18)	12 (5-25)
LEI, median (IQR)	0 (0-1)	1 (1-2)	0 (0-1)	0 (0-0)
MASES, median (IQR)	0 (0-3)	2 (0-3)	0 (0-2)	0 (0-0)

PsA=Psoriatic Arthritis, PASI=Psoriasis Area&Severity Index, MSC=musculoskeletal complaints, LEI=Leeds Enthesitis Index, MASES= Maastricht Ankylosing Spondylitis Enthesitis Score
*Axial manifestations & arthritis are the patients who were diagnosed as having PsA by the rheumatologist. Enthesitis are the patients who would have a diagnosis of PsA based on the CASPAR criteria. Established PsA are the patients already diagnosed with PsA at the beginning of the study and psoriasis patients are the patients with MSC but without PsA.

Prevalence of PsA

Established PsA

The frequency of established PsA was 2.5% (95% CI 2.0-3.2%; n=64). As with information about MSC, information about an established diagnosis of PsA was also derived from two sources. First, we had 13 patients who did not want to participate in the study but already had a confirmed diagnosis of PsA. Another 51 patients with a confirmed diagnosis of PsA did participate in the study (Figure 3).

Newly diagnosed PsA

Besides the established cases, PsA was also newly diagnosed by a rheumatologist in 17 cases. Within the PsA cases 11 patients (64.7%) presented solely with peripheral arthritis. Five cases (29.4%) of axial PsA were diagnosed and one patient (5.9%) presented with a combination of axial PsA and peripheral arthritis. Moreover, we also identified 36 cases of enthesitis, in which the inflammatory component was confirmed by US. Most of these patients refrained from further evaluation by a rheumatologist, but according to the CASPAR criteria, most of these cases will classify as PsA.

Overall prevalence & sensitivity analysis

In total we identified 81 cases of PsA, of which 17 (21%) cases were newly diagnosed. This leads to a prevalence of PsA among all 2564 primary care psoriasis patients of 3.2% (95% CI 2.5-3.9%) (Figure 3). This represents the situation in which no additional cases would be identified in the non-responders and in patients who declined participation. It is questionable whether this assumption holds true and

we therefore did a sensitivity analysis evaluating three scenarios. In the first scenario, we assumed an equal prevalence of MSC for the responders and the non-responders. Among the 1673 responders, 823 suffered from MSC, leading to a prevalence of 49.2%. The prevalence of PsA among the patients suffering from MSC was 9.8% (81 PsA cases in 823 patients with MSC). We assumed that these prevalences we observed in the responders, would also apply to the 891 non-responders. This assumption would then increase the prevalence of PsA towards 4.8% (95% CI 4.1-5.7%). In the second scenario, we used the observed frequency of MSC among the non-participants who returned their reply slip. Among the 832 patients who indicated that they did not want to participate, 704 provided information about the presence of MSC, of which 164 suffered from MSC (23.3%) (Figure 3). In this scenario, when assuming equal prevalence of PsA as in the first scenario (9.8%), the prevalence of PsA would increase towards 3.9% (95% CI 3.2-4.8%). In the third and final scenario, we used the same frequency of MSC as in the second scenario (23.3%), but varied the prevalence of PsA. We used the frequency of PsA we observed in all patients who were clinically evaluated, this leads to a prevalence of PsA of 13.0%. Applying this prevalence of PsA on the non-responders, the prevalence of PsA would increase towards 4.2% (95%CI 3.5-5.1%).

Enthesitis

111 patients were referred for US evaluation of the enthesis. In 36 cases a combination of clinical and US enthesitis was present. As the CASPAR criteria suggest that the sole presence of enthesitis is sufficient to have inflammatory articular disease, adding the patients with enthesitis would increase the prevalence to 4.6% (95% CI 3.8-5.4%). The three scenarios in the sensitivity analysis would than lead to a prevalence of 7.0 (95%CI 6.1-8.0) if assuming equal prevalences of MSC and PsA, 5.7 (95% CI 4.9-6.7%) if the MSC frequency in the non-participants would be taken into account and 6.2% (95%CI 5.3-7.2%) if varying the frequency of PsA

Discussion

In this large primary care based study we found a PsA prevalence of 3.2% (95% CI 2.5-3.9%) among 2564 psoriasis patients, of which 21% was newly diagnosed. The prevalence of musculoskeletal complaints was 32.1% (95%CI 30.3-33.9%). In these estimates we assumed that no additional cases would be found in the non-responders. This is probably a harsh assumption and we therefore did a sensitivity analysis in which the prevalence increased towards 7.0% (95%CI 6.1-8.0%) if cases would be found in the non-responders as well.

Previous literature about the prevalence of PsA in primary care is scarce.[12,13] A higher prevalence of 8.6% (95% CI 7.7-9.5%) was observed by Ogdie et al.[13] One of the explanations for this

difference could be that they based the diagnosis of PsA on medical codes in a population-based medical records database rather than clinical examination. An even higher prevalence was reported by Ibrahim et al (13.8% (95%CI 7.1-24.1%)), but this study had substantial non-response.[12] The prevalence would reduce towards 1.9% if all initial patients would be taken into account and no additional cases would be found in the non-responders. More data is available from secondary care, where PsA prevalence figures range from 6% to 42% among psoriasis patients.[10,29] This wide spread is likely to be caused by the use of many different criteria sets, self-reported patient diagnosis and diagnosis by the dermatologist.

Defining PsA has proven to be challenging due to its clinical heterogeneity. In 2006, new classification criteria were established, the CASPAR criteria.[25] Besides peripheral synovitis and axial disease, entheseal involvement was characterized as inflammatory articular disease. Enthesitis is established by manual palpation in which pain, redness and swelling are considered. No detailed definition for these features is available and according to the CASPAR criteria, left to the discretion of the treating physician. If the enthesis lies deep within the surrounding tissue, it is difficult to locate the enthesis and observe redness and swelling. Pain itself is no sign for underlying inflammation as it could be related to overuse, metabolic disease or ageing.[27] To overcome these difficulties, we chose to combine the inflammatory signs on US with clinical symptoms, as we think this is an acceptable definition for enthesitis. If positive for this definition patients classified as PsA according to the CASPAR criteria.

The prevalence of MSC among all initially invited psoriasis patients was 32.1%, running up to 49.2% among the patients returning their reply slip. These numbers fall well into the MSC estimates in the general population of 39.7%[30] and 53.9%[31] in the Netherlands. It seems that psoriasis patients do not suffer more frequently from MSC than the general population.

Our study has certain strengths and limitations. One of the strengths of this study is the large population of psoriasis patients. We invited 2564 psoriasis patients out of primary care databases and achieved a response rate of 65.2%. This is a high response rate for a primary care study, as you have to depend on the GPs in order to recruit patients. Patients are invited for the study via the GP, so you are not able to recruit patients yourself. Secondly, our study provides prevalence estimates for primary care and as mentioned before only two studies reported about the prevalence in a primary care setting thus far.[12,13] Among the limitations are misclassification of psoriasis, ethnicity, self-selection of patients, selection by MSC and missed cases. Psoriasis was identified by applying the ICPC code in the GP databases. Some misclassification (3.1%) occurred, possibly related to the GP initially considering the skin problem to be psoriasis, which then later on was changed without updating the ICPC code. Ethnic and geographic variation play a role in the prevalence of psoriasis and also in PsA

prevalence.[32] For example, 1% of the Asian psoriasis patients is affected by PsA versus 10-42% in Europe and North-America.[33] In our study population about 98% were from Caucasian origin. This should be taken into account when interpreting the results. Self-selection related to symptoms might have been an issue as we observe that the mean age of the responders was 55.8±13.9 years and people of older age tend to have more joint complaints. The ideal population would be younger, as we know that the peak incidence of PsA is between 30 and 50 years of age. It could therefore be possible that we missed some cases among the younger patients who did not participate. In addition, we only invited patients with regular spells of MSC. This might have left us with missed cases as patients could suffer from symptom-free synovitis or enthesitis. However, we think the chance of missing a substantial number of cases this way is negligible. Missed established PsA cases might be an issue, although we explicitly asked to contact us independent of symptom state.

In conclusion, we conservatively estimated the prevalence of PsA among psoriasis patients in primary care to be 3.2% increasing to 4.6% if enthesitis is taken into account. The prevalence of MSC among psoriasis patients is comparable with the prevalence of MSC in general population.

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Chapter 3.

Adding Ultrasound to Clinical Examination reduced Frequency of Enthesitis in Primary Care Psoriasis Patients with Musculoskeletal Complaints

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Abstract

Objective. Part of the psoriasis patients with musculoskeletal complaints will have inflammation of the entheses. Entheseal inflammation is difficult to assess by clinical examination only. Therefore, we aimed to determine the frequency of clinically relevant ultrasound inflammation at the most commonly assessed entheses (MASEI; Madrid Sonographic Enthesis Index) in primary care psoriasis patients with one or more tender entheses.

Methods. Adult primary care psoriasis patients with musculoskeletal complaints (tender enthesis or arthritis at physical examination) had an ultrasound examination of seven entheses according to the MASEI. Clinically relevant ultrasound inflammation was defined as active inflammation on ultrasound in combination with at least one clinical feature at the same enthesis. Active ultrasound inflammation contained positive power Doppler signal or in case of the plantar aponeurosis increased thickness. Structural changes entailed calcifications, enthesophytes, increased thickness, hypoechogeneicity indicating irregular fiber structure and erosions. Clinically, an enthesis was scored positive by a tender enthesis at clinical examination, reported pain in the history or self-reported pain in the questionnaires.

Results. Of 542 primary care psoriasis patient, 111 patients had tender entheses and/or arthritis. These patients were both clinically and ultrasonographically evaluated. Active ultrasound inflammation accompanied with pain or tenderness at the enthesis was found in 36% of the patients (n=40). Most common were inflammation at the knee (n=11) and at the plantar aponeurosis (n=10). Structural changes were observed in 95% of the psoriasis patients independent of their clinical manifestation.

Conclusion. We found concurrent presence of ultrasound inflammatory changes and clinical symptoms in 36% of the primary care psoriasis patients who had tenderness at one or more entheseal sites.

Introduction

Enthesitis is an important domain in psoriatic arthritis (PsA). Since the introduction of the CASPAR classification criteria for PsA in 2006, psoriasis patients can classify as PsA with only enthesitis as inflammatory articular involvement.[1] Increasing attention is paid to its assessment[2, 3], but up to now no consensus has been achieved on its measurements in the diagnostic setting. In both the classification criteria for PsA and spondyloarthritis (SpA), enthesitis is included. The CASPAR criteria suggest that the doctor diagnoses enthesitis as he sees fit. The ASAS criteria for peripheral SpA include only the Achilles tendon and the plantar aponeurosis without being specific which clinical characteristics need to present.[4]

Enthesitis is defined as inflammation at tendon, ligament, joint capsules or aponeurosis insertion sites to bone. Entheseal pain can be severe, disabling and continuous, and can last for several years.[5, 6] The ethiopathogenesis is poorly understood and may relate to mechanical stress on top of the immune response.[7] Clinical assessment of the entheses is difficult as inflammation is often not visible or palpable. In addition, it may be difficult to anatomically locate the enthesis if it lies deep within the surrounding tissue.[8] The location of several entheseal sites overlaps with those of the tender points of fibromyalgia.[9] Furthermore, the presence of a tender enthesis is not necessarily indicative for underlying inflammatory disease as it could be related to overuse, metabolic disease or ageing.[10] These challenges could lead to clinically false-positive patients.

To resolve the difficulties regarding clinical assessment of the entheses, inflammatory characteristics at the enthesis can be visualized by ultrasound.[11] Especially the use of the power Doppler mode improves the assessment of inflammation at the entheses.[12, 13] New data about ultrasound enthesitis emerged in patients with psoriasis, PsA and healthy controls.[14-16] So far, studies evaluated enthesitis in patients with psoriasis who were referred from the dermatologist.[16-20] A significant higher prevalence of both grayscale (GS) and power Doppler (PD) ultrasound enthesopathy was found in patients with psoriasis than in controls (patients with dermatological diseases other than psoriasis).[16-18] In patients with PsA the severity of ultrasound abnormalities was even higher than in patients with psoriasis.[20] Ultrasound abnormalities at the entheses were present in both symptomatic (true-positive) and asymptomatic (false-positive or subclinical disease) psoriasis patients which suggests single application of ultrasound is not sufficient to detect clinically relevant entheseal inflammation.[19, 21]

Little data is available on the presence of PsA in primary care psoriasis patients.[22, 23] In several countries psoriasis patients are treated by their general practitioner and this might mean that cases of PsA are missed. In addition, these studies did not include ultrasound to assess inflammation at the

entheses. In a large primary care based study the frequency of PsA in psoriasis patients was estimated to be 3.1% for arthritis and axial disease, increasing to 4.6% when enthesitis would be included.[24]
In this study we describe the frequency of ultrasound abnormalities at the entheses and its clinical information in primary care psoriasis patients who had at least one tender enthesis at clinical examination. We combined PD ultrasound and clinical information at the same enthesis to differentiate between active inflammation and other manifestations of enthesopathy.

Materials & Methods

Patients

Adult patients with psoriasis (ICPC S91) were identified from 97 general practitioners (GPs) in the Rotterdam area. These patients were invited to participate in the SENSOR study. Details of this cross-sectional study can be found in Karreman et al.[24] In brief, patients who reported regular episodes of pain in joints, entheses or the lower back were eligible and invited for clinical evaluation by a trained nurse. Patients were not recruited consecutively. Data collection included a detailed clinical examination (amongst others, swollen joint count, tender joint count, entheses evaluation), demographic characteristics and symptom history.
Written informed consent was obtained from the participants. The study was approved by the medical ethic committee of Catharina Hospital, Eindhoven, the Netherlands.

Entheses evaluation

Clinical examination

Physical examination included the 66/68 joint count for PsA and entheseal assessment following the Leeds Enthesitis Index (LEI) and the Maastricht Ankylosing Spondylitis Enthesis Score (MASES).[2, 3] Other assessments included measurement of psoriasis severity by the PASI and body mass index. If clinical examination indicated a painful enthesis on the LEI/MASES or indicated an arthritis, ultrasound examination of the entheses was performed.

Ultrasound examination

An independent ultrasound examiner blinded for the clinical details performed the ultrasound using Esoate MyLab60 (probe LA 435). The six entheses of the Madrid Sonographic Enthesis Index (MASEI)[25] and the lateral epicondyle tendon insertion (elbow) were examined. Each tendon was examined in the longitudinal plane. Knee entheses were examined with the patient in supine position and the knee flexed at 20°. The Achilles tendon and the plantar aponeurosis were examined with the patient in prone position and the feet hanging over the edge of the examination table in neutral position. To

examine the lateral aspect of the elbow, the patient was positioned with the elbow flexed, forearm extended and palm down. To examine the olecranon, the patient was asked to raise the elbow and to keep the elbow flexed (90°) with the hand palm resting on the table. According to the MASEI scoring system the following elemental lesions of enthesitis were evaluated at each site: calcifications, bursitis, erosions, PD signal in bursa or enthesis full tendon (cortical bone profile, intratendon and paratendon on the enthesis insertion) and thickness and structure.[25] Ultrasound abnormalities were divided into 'active inflammation' and 'structural change' parameters. Active inflammatory components on ultrasound included the presence of PD signal (<2mm of the bony cortex)[15] or in case of the plantar aponeurosis an increased thickness (≥4.4mm).[26] Structural changes included calcifications, erosions, structure, and increased thickness.

Self-reported pain at the entheses

Patients completed online self-reported questionnaires including the EARP[27] and PEST[28]. From the EARP questionnaire we used the question regarding the Achilles tendon. From the PEST questionnaire we used those questions regarding pain of the heel, elbows, and knees. Patient history included questions about symptom history regarding previous episodes of entheseal inflammatory complaints, which were diagnosed by a GP.

Enthesitis definition

In this study we combined data from ultrasound and clinical examination, and patient-reported questionnaires to define active inflammation at the enthesis. We defined enthesitis as active inflammation on ultrasound (presence of PD signal and/or increased thickness of the plantar aponeurosis) in combination with at least one clinical feature at the same enthesis: i) tender point LEI/MASES, ii) self-reported pain at the elbow, knee, Achilles tendon and heel from the EARP or PEST questionnaire, iii) self-reported entheseal complaints (defined as previous episodes of entheseal inflammatory complaints, diagnosed by a GP).

Statistical analysis

To determine differences in baseline characteristics and ultrasound findings between patients suspected for enthesitis and patients suspected for arthritis we used descriptive statistics. Depending on the distribution of the data we used the independent T-test or Wilcoxon-Mann-Whitney test. Frequencies were compared using a Chi-square test. Analyses were done using STATA 12.0.

Results

In total, 111 patients of the total study population with psoriasis (n=524) who reported regularly musculoskeletal complaints were evaluated by ultrasound. Of these patients, 88 patients were referred for ultrasound because they had at least one tender enthesis on the LEI/MASES. The other 23 patients were referred for suspected arthritis and also underwent an evaluation of the entheses by ultrasound. Nine (8%) patients had a confirmed diagnosis of PsA by a rheumatologist. Patient characteristics are presented in Table 1.

Table 1 Baseline characteristics of primary care psoriasis patients (n=111)

	Suspected for enthesitis (n=88)	Suspected for arthritis (n=23)	p-value
Women (%)	57	39	0.130
Age, years (mean, sd)	54 (13)	54 (14)	0.936
LEI (median, IQR)	2 (1-4)	0 (0-1)	<0.001
MASES (median, IQR)	2 (0-4)	0 (0-1)	<0.001
MASEI (median, IQR)	7 (5-12)	10 (5-13)	0.302
Power Doppler positive, n (%)			0.626
- **1 enthesis**	14 (16)	2 (9)	
- **2 entheses**	12 (14)	3 (13)	
- **3 entheses**	3 (3)	1 (4)	

LEI = Leeds Enthesitis Index (range: 0-6); MASES = Maastricht Ankylosing Spondylitis Enthesis Score (range: 0-13); MASEI = Madrid Sonographic Enthesis Index (range: 0-136); sd = standard deviation; IQR = interquartile range

Entheses evaluation

Clinical examination

The median number of tender entheses on the LEI was 2 (IQR: 0-3). The median number of tender entheses on the MASES was 1 (IQR: 0-3). Patients suspected for enthesitis had more tender entheses on both the LEI and the MASES (median (IQR): 4 [1-7]) than patients suspected for arthritis (median (IQR): 2 [0-4]; p<0.0001). The most common tender entheses were found at the lateral epicondyle of the humerus (52%) and at the medial epicondyle of the femur (50%) [Table 3].

Ultrasound examination

In 106 (95%) patients (n=111) we detected one or more ultrasound abnormalities at the enthesis [Table 2]. There was no difference in ultrasound findings between patients suspected for enthesitis and patients suspected for arthritis.

In 50 (45%) patients we found ultrasound abnormalities indicating inflammatory disease at the enthesis [Table 3]. Thirty-five (32%) patients were PD positive on ultrasound of whom 5 (5%) also had a thickened plantar aponeurosis. Fifteen (14%) patients only had a thickened plantar aponeurosis.

Table 2 Ultrasound abnormalities at the enthesis using the MASEI score (n=111)

Insertion	PD signal	Structure	Thickness	Bursitis	Erosion	Calcification
Lateral epicondyle tendon (elbow)*	21 (19)	19 (17)	51 (46)		35 (32)	47 (42)
Triceps tendon*	0	25 (23)	18 (16)		9 (8)	26 (23)
Quadriceps tendon*	13 (12)	12 (11)	53 (48)		3 (3)	66 (59)
Proximal patella tendon*	2 (2)	4 (4)	29 (26)		2 (1)	15 (14)
Distal patella tendon*	9 (8)	3 (3)	77 (69)	1 (1)	3 (3)	23 (21)
Achilles tendon*	4 (4)	1 (1)	12 (11)	0	1 (1)	70 (63)
Plantar aponeurosis *	†	1 (1)	20 (18)		0	20 (18)

*n (%); MASEI = Madrid Sonographic Enthesis Index (range: 0-136); PD = power Doppler; † = not detectable

Positive PD signal was found most often at the lateral epicondyle of the humerus (21 patients, 19%) and at the insertion of the quadriceps tendon at the superior pole of the patella (13 patients, 12%). In 19 (17%) patients we found positive PD signal at more than one enthesis. Of note, we did not find any indication of inflammatory disease at the triceps enthesis at the olecranon.

Structural changes of the enthesis on ultrasound [Table 3] were very common. Increased thickness of the distal patella tendon at the tuberositas tibiae (69%), and calcifications at the enthesis of the quadriceps tendon (superior pole patella: 59%) and at the enthesis of the Achilles tendon (63%) were found most often. Structural changes without indication of inflammatory disease were found in 56 (50%) patients.

Self-reported pain at the entheses

In total, 105 patients (95%) reported pain at a location relevant to the enthesis: the elbow, knee, Achilles tendon, or heel. Pain in the knee was most frequently reported (71%), followed by the heel (55%) and elbow (49%). Nineteen (17%) patients reported pain at the Achilles tendon insertion.

Patients fulfilling enthesitis definition

Patients who had clinical symptoms and PD at one of their enthesis or a thickened plantar aponeurosis were classified as having ultrasound confirmed inflammatory enthesitis. Of the 50 patients

Table 3 Ultrasound and clinical findings per entheseal site (n=111)

Insertion	US inflammatory (n,%)	US structural (n,%)	Tender point (n,%)	Self-reported (n,%)
Lateral epicondyle tendon (elbow)	21 (19)	62 (56)	58 (52)	54 (49)
Triceps tendon	0	49 (44)	†	54 (49)
Quadriceps tendon	13 (12)	68 (61)	55 (50)*	79 (71)
Proximal patella tendon	2 (2)	37 (33)		
Distal patella tendon	9 (8)	74 (67)		
Achilles tendon	4 (4)	68 (61)	32 (29)	19 (17)
Plantar aponeurosis	20 (18)	16 (14)	†	61 (55)

US = ultrasound; † = not included in LEI/MASES; * = medial epicondyle femur

With ultrasound abnormalities indicating inflammatory disease, the ultrasound findings were confirmed by clinical information in 40 patients (36%). These patients were classified as having active (ultrasound confirmed inflammatory) enthesitis. Twenty-eight patients had active enthesitis at one enthesis. These were found at the knee (n=11), at the insertion of the plantar aponeurosis (n=10), at the lateral epicondyle of the humerus (n=6) and at the Achilles tendon (n=1). Ten patients had active enthesitis at two entheses, and two patients had active enthesitis at three entheses. Thirty-two cases were referred because they had at least one tender enthesis on the LEI/MASES. The other eight cases were referred for suspected arthritis.

Ten patients had inflammatory ultrasound abnormalities while they did not report clinical problems. We found a positive PD signal in five patients. The PD signal was found at the enthesis of the lateral epicondyle of the humerus (n=3), at the entheses of the knee (n=1), and in one patient both at the lateral epicondyle (humerus) and the Achilles enthesis. The plantar aponeurosis was thickened in five patients without clinical symptoms.

Figure 1 shows the distribution of the ultrasound findings, both structural changes and active inflammation combined with the clinical findings at each entheseal site.

Five patients had a painful enthesis clinically without having any ultrasound abnormalities. These patients all had a painful knee, combined with a painful enthesis at the lateral epicondyle of the humerus (n=4), with a painful heel (n=2), or a tender Achilles enthesis (n=1).

The other 56 patients had a painful enthesis with structural changes on ultrasound.

Discussion

In 36% of the primary care psoriasis patients who had tenderness at one or more entheseal sites (n=111) enthesitis was present, defined as concurrent presence of ultrasound inflammatory changes and clinical symptoms. Ultrasound assessment included five elemental lesions: the presence of calcifications, erosions, increased thickness, changes in fiber structure, and positive PD signal. We indicated the first 4 lesions as ‘structural changes’ of the enthesis which were present in 95% of the

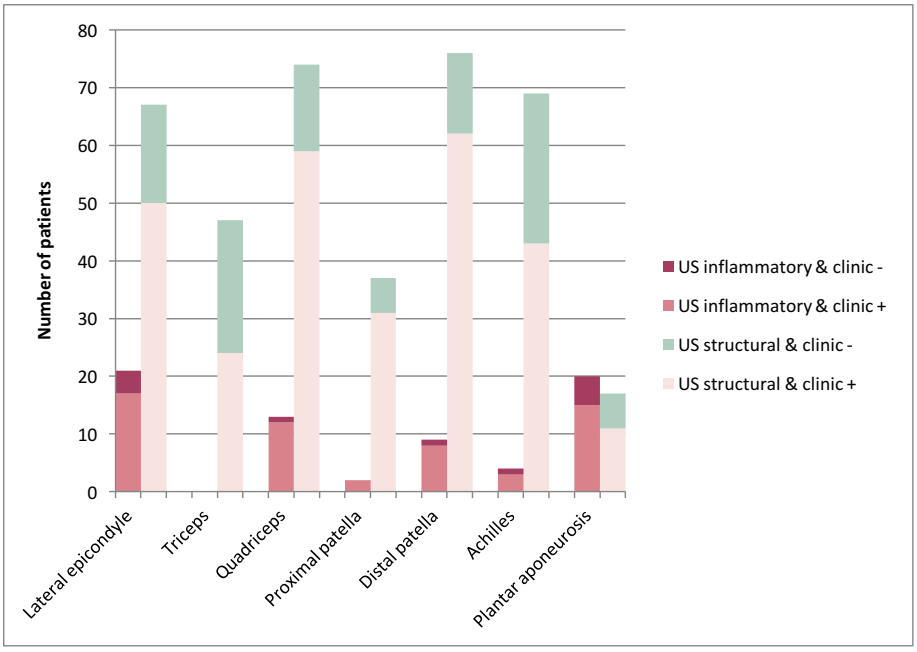

Figure 1. Distribution of the ultrasound findings, both structural changes (US structural) and active inflammation (US inflammatory), in combination with the clinical findings (- = negative; + = positive) at each entheseal site (US = ultrasound).

patients, while we named positive PD signal the 'inflammatory component', present in 32% of the patients. One exception was made for the plantar aponeurosis as ultrasound was not able to elicit any PD signal in this area. Therefore, increased thickness was chosen to assess inflammatory changes at the enthesis of the plantar aponeurosis, which was present in 18% of the patients. In total, 45% of the patients (n=50) had ultrasound inflammatory changes. Combined with clinical information at the same enthesis this led to 36% of the patients (n=40) having enthesitis. In part of our study population (9%; n=10) we found ultrasound inflammatory components, but these were not confirmed by clinical information. This could be related to subclinical disease, which could be predictive for the development of PsA in patients with psoriasis.[21, 29-31]

Considerable advances have been made in the use of ultrasound to evaluate entheses. Nevertheless, context of clinical information remains needed to differentiate between active inflammation and other manifestations of enthesopathy.[10] By adding ultrasound to the clinical evaluation of entheses we were able to visualize the presence of active inflammatory involvement of the enthesis. This could help to differentiate patients with non-inflammatory entheseal pain from patients with entheseal involvement related to inflammation, helping physicians to make informed decisions about whom to treat with anti-inflammatory drugs. First-line treatment recommendations for enthesitis in PsA

patients are NSAIDs. After insufficient response to NSAIDs, treatment can be switched to biological agents.[32, 33] Since rheumatologists are quite reserved to prescribe biologic agents to treat enthesitis, ultrasound might give more certainty for detecting inflammatory disease at tender entheses. However, further research regarding the treatment of ultrasound confirmed enthesitis is needed.

One of the difficulties we came across was the absence of general accepted definitions for both the clinical presentation as well as the ultrasound presentation of enthesitis. The OMERACT Ultrasound Task Force recently debated the latter, but they did not come to a definite conclusion what would be inflammatory.[15] The main reason for this was the discussion on entheseal thickness. Part of the ultrasound examiners felt this to belong to inflammatory changes while other examiners attributed this to structural changes. Both could be true. In the acute phase, increased thickness might be present due to inflammation as shown by McGonagle et al with soft tissue and bone edema at the plantar aponeurosis insertion on MRI appearances.[34] However, thickening could also be the result of a disorganized repair process (scar tissue) in which no inflammation is present anymore.

There are several strengths and weaknesses to discuss when interpreting the results of our study. At first, for practical reasons we choose to apply ultrasound, rather than MRI. Ultrasound was easy accessible, we could apply it to different locations at once and there were no safety issues. It has the disadvantage that it is reader dependable, which was solved by one examiner for all patients. However, ultrasound cannot depict bone edema which is also indicative for inflammatory changes like MRI does. MRI is capable of detecting soft tissue changes associated with surrounding soft tissue edema in the region adjacent to the enthesis.[10] However, application of MRI would require long acquisition time to evaluate six entheses bilaterally. There have been recent advances in whole body MRI but issues need to be solved such as field of view, image resolution for small structures and body position.[35] Secondly, patient position during the ultrasound examination of the knee entheses was not ideal. In our study maximum flexion of the knee was 20°, which could have influenced our PD signal at the entheseal level of the knee entheses. Previous studies found an severe decrease of PD signal when the knee was flexed at 30°.[36] Flexion of the knee could increase intratendinous tension, which facilitates collapse of the microvessels. Thirdly, due to the aim of our initial study, which was to estimate the prevalence of PsA in primary care psoriasis patients, we did not include control patients. However, there is a substantial body of evidence that shows the usefulness of the MASEI score in differentiating patients with PsA/SpA from healthy controls[20, 37], especially if using inflammatory changes (PD signal) rather than structural changes.[21] This stresses our choice to use a positive PD signal at the enthesis as an indication for active ultrasound enthesitis. A strength of our study is that we included primary care patients with psoriasis with musculoskeletal complaints. Most studies evaluating enthesitis with ultrasound have included psoriasis patients in secondary care referred by

the dermatologist.[16] Our study population is a different population in which it would be beneficial to screen for PsA and to improve early diagnosis of PsA.

In conclusion, enthesitis defined as concurrent presence of ultrasound inflammatory changes and clinical symptoms was present in 36% of the primary care psoriasis patients who had tenderness at one or more entheseal sites. Combining clinical data and ultrasound at the same enthesis reduced the frequency of entheseal lesions that should be evaluated by the rheumatologist compared to clinical exam only. Consensus needs to be reached to find a generally accepted definition for enthesitis which would be feasible in daily clinical work.

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Chapter 4.

The Prevalence and Incidence of Axial and Peripheral Spondyloarthritis in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

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Abstract

Background & Aims. Inflammatory Bowel Disease is a chronic disease which affects up to 0.5% of the population. Various extraintestinal manifestations occur, among which rheumatic manifestations, grouped together under the name spondyloarthritis. The objective of the systematic review and meta-analysis was to give a systematic overview of the prevalence and incidence of spondyloarthritis in patients with inflammatory bowel disease.

Methods. We systematically searched Embase, Pubmed, OvidSP, Scopus and Web-of-science databases from inception to August 2016. All articles that addressed the prevalence or incidence of the different features of spondyloarthritis in adult inflammatory bowel disease patients were included. Methodological quality was assessed using a modified quality assessment tool developed for prevalence studies.

Results. 71 studies were included reporting on the prevalence of sacroiliitis, ankylosing spondylitis, arthritis, enthesitis and dactylitis. Pooled prevalences were calculated for sacroiliitis (10%; 95% CI 8-12%), ankylosing spondylitis (3%; 95% CI 2-4%) and arthritis (13%; 95%CI 12-15%). Geographic area, setting and use of different criteria contribute to the large heterogeneity. Few estimates were available for enthesitis (prevalence range from 1 to 54%) and dactylitis (prevalence range from 0 to 6%). Only three incidence studies were identified, which report cumulative incidences from 5 to 30 years.

Conclusions. Spondyloarthritis occurs in up to 13% of patients with IBD. Ankylosing spondylitis is the least common (3%) followed by sacroiliitis (10%) and peripheral arthritis (13%).

Introduction

Inflammatory Bowel Disease (IBD) is a common chronic inflammatory disease of the gastro-intestinal tract, which encompasses both Crohn's disease (CD) and ulcerative colitis (UC). IBD can be accompanied by a number of extra-intestinal manifestations (EIM) in multiple organ systems, among which rheumatic manifestations grouped together under the name spondyloarthritis (SpA), which might affect 2-46% of IBD patients.[1-4] SpA can lead to a reduced quality of life as well as work disability, and is therefore cause of significant burden on patients as well as the society as a whole.[5-8] Without treatment, severe joint deformations can occur, both in peripheral joints and the spine. Detection of patients developing SpA is therefore important, as early and adequate treatment can prevent these complications.

In gastroenterology a distinction is made between type 1 and type 2 arthritis. Type 1 arthritis parallels IBD activity, usually affects five joints or less and tends to be self-limiting. Type 2 arthritis usually affects more than five joints and does not correlate with IBD activity.[3] Although this distinction is widely used in gastroenterology practice, it is not often used by rheumatologists. Rheumatologists tend to follow the recently developed ASAs criteria, which make a distinction between axial and peripheral manifestations.[9,10] Both axial and peripheral manifestations can occur in patients with IBD. With regard to the axial manifestations of SpA, the main symptom is chronic low back pain induced by inflammation of the sacroiliac joints, the so-called sacroiliitis (SI). Ankylosing spondylitis (AS) is the best known subtype, however it is the least frequent manifestation. In peripheral SpA, arthritis, enthesitis and dactylitis are the main symptoms. Arthritis can be observed in every peripheral joint, with a preference for the large joints. Enthesitis indicates inflammation of the tendon insertion to the bone. This can occur in every location of tendon insertions to bone, but best-known locations are the Achilles heel and the fascia plantaris. Dactylitis is a less common manifestation of SpA and indicates the presence of inflammation of an entire digit, the so called sausage-fingers or –toes. Patients with IBD are at increased risk for developing SpA but prevalence estimates based on the recently accepted definition of axial and peripheral joint manifestations are lacking. In this systematic review, we summarize the prevalence and incidence of the various axial and peripheral joint manifestations of SpA in patients with IBD. Secondly, we perform a meta-analysis to estimate the point prevalence of SI, AS and peripheral arthritis in patients with IBD.

Methods

This systematic review was reported in accordance with the PRISMA guidelines.[11]

Literature Search

In collaboration with a medical librarian a search strategy was developed. Medline, Embase, Web of Science and Pubmed as publisher were searched to identify relevant studies from database inception to August 2016. Keywords included terms and synonyms for all joint manifestations of spondylarthropathies, inflammatory bowel disease (including Crohn's disease and ulcerative colitis), incidence and prevalence. The full search strategy is available in supplemental file S1.

Selection of studies

Inclusion of studies was based on a two-stage process; first, titles and abstracts were screened for eligibility followed by retrieval of full-text articles to further check the eligibility criteria. One investigator (MK) screened all articles for eligibility on title and abstract and subsequently the full text of all articles that had passed the first eligibility screening. Studies were eligible if they (i) were written in Dutch or English language, (ii) had an observational design and (iii) described the prevalence of axial manifestations (SI, AS) or peripheral joint manifestations (arthritis, enthesitis or dactylitis) in patients diagnosed with IBD. Studies were excluded if they were only published as conference abstract or contained no original data. The reference section in review articles and original studies were searched for additional studies.

Data Extraction

Data was extracted by one investigator (MK) according to a pre-defined data form. The following information was extracted: setting (population based, secondary care, tertiary care (university hospital)), type of study, study population, number of IBD patients participating, mean age and percentage women of IBD patients, criteria for establishment of IBD, disease duration of IBD, case definition of axial and peripheral joint manifestations of SpA, outcome measurement, outcome assessor and number of cases of different SpA manifestations.

Assessment of methodological quality

MK assessed all and AW or JL each assessed half of the papers for methods of data collection by a quality list, comprising six yes-no questions. The quality list was based on a recently developed quality assessment tool for prevalence studies, slightly adjusted for our situation.[12] We included the questions about representativeness of the sample for the target population, appropriate recruitment of the study participants, adequate sample size calculation and if the data analysis was conducted with sufficient coverage of the identified sample. With regard to case ascertainment, we included questions about whether objective, standard criteria were used for the establishment of a case and if the condition was measured reliably (meaning by a qualified outcome assessor). The full quality

assessment tool with instructions how we applied the tool can be found in supplemental file S2. All papers were discussed between MK and AW or JL and disagreements were resolved by consensus.

Pooling of data

A meta-analysis was performed for the prevalence of the axial manifestations AS and SI and for the peripheral manifestation arthritis in patients with CD and UC. For the peripheral manifestations enthesitis and dactylitis too few studies were available for pooling, so these were described narratively.

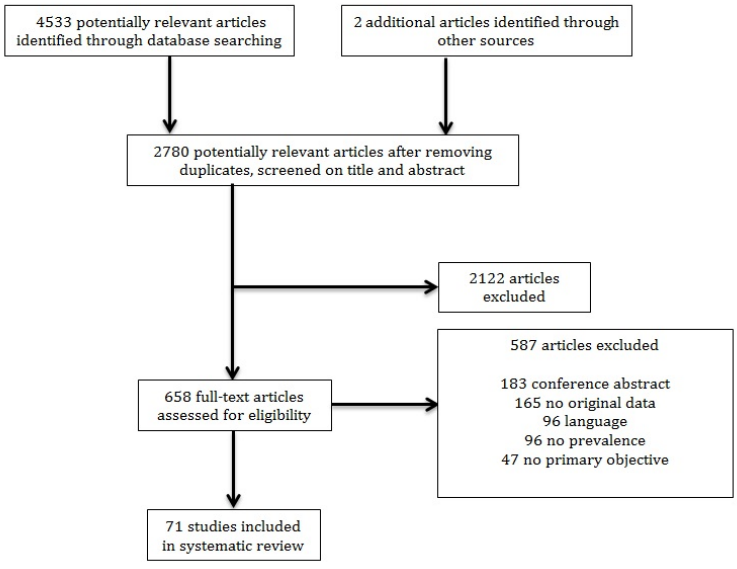
Meta-analysis was performed using the 'metaprop' command in Stata 13, using a random effects model.[13] I^2 was used to calculate the between-study heterogeneity. Meta-analysis according to different subgroups was performed to explore possible sources of heterogeneity.

Results

Search Results

The search resulted in 4533 publications (Figure 1). After removing duplicates 2780 publications remained and were screened on title and abstract. Eventually 658 publications were found eligible for full-text review, after which 71 publications were included. These 71 publications reported on the prevalence of the different axial and peripheral joint manifestations of SpA in either CD or UC. Seven studies did not specify the type of inflammatory bowel disease and are described as unspecified IBD. The characteristics of the included studies are shown in table 1.

Figure 1. Flow diagram of study selection



Risk of Bias

A complete overview of the assessment of methodological quality can be found in supplementary file S2. In table 2 the different items of the quality list are shown with the percentage of studies that scored positive on this item. The majority of studies had a sample representative of the target population (63.4%) and most studies recruited their patients in an appropriate way (90.1%), meaning consecutive, at random or all patients were selected for the study. None of the studies reported a sample size calculation while a slight majority did conduct an adequate data-analysis (59.2%). With regard to case-ascertainment, in 56.3% objective standard criteria were used and in 46.5% of the studies the condition, meaning SpA, was measured reliably.

Table 2 Risk of Bias Assessment

	% Positive
Was the sample representative of the target population?	63.4
Were study participants recruited in an appropriate way?	90.1
Was the sample size adequate?	0
Was the data analysis conducted with sufficient coverage of the identified sample?	59.2
Were objective, standard criteria used for the measurement of the condition?	56.3
Was the condition measured reliably?	46.5

Prevalence of Axial involvement

Fifty-nine studies (125 estimates) reported the prevalence of axial SpA in patients with IBD.[14-66]

Sacroiliitis

The prevalence of SI in patients with IBD was described in 41 studies (59 estimates) (see supplemental file S3).[16-18,21-26,28,30-32,34,35,37-40,42,43,45-49,51,52,55,57-62,65,67-71]. The pooled prevalence of SI in IBD patients is estimated to be 10% (95%CI 8-12%), with an I^2 of 94.3%. The prevalence of SI is higher in patients with CD (13%, 95%CI 1-17%) than in patients with UC (7%, 95%CI 4-11%).

As there was considerable heterogeneity in the observed prevalence between studies, we explored the variability by a meta-analysis of subgroups according to different demographical and study characteristics (Figure 2). Higher prevalences were observed in European and studies (11%; 95%CI 8-15% and11%; 95%CI 7-16%), compared to North-America (7%; 95%CI 2-14%) and South-America (5%; 95%CI 2-9%). With regard to mean age, the prevalence seemed highest in the three studies for age category 20-30 years of age with 16% (95%CI 8-27%). In the age group 30-40 years the prevalence dropped towards 9% (95%CI 5-14%), to rise again slightly in the age groups of 40-50 years and 50-60

years. Studies were performed in different settings, resulting in higher prevalences of SI in tertiary care (15%; 95%CI 1-22%) compared to secondary care (7%; 95%CI 5-11%) and population based studies (3%; 95% CI 1-7%). The use of clinical evaluation also resulted in a higher prevalence (15%, 95%CI 10-21%) than studies using case records or a self-reported diagnosis as outcome. The use of different imaging techniques to establish a SI did not seem to have much influence on the prevalence estimates, with an estimate of 12% (95%CI 8-16%) when using X-ray, 15% (95%CI 5-29%) when using CT and 10% (95%CI 6-14%) when using MRI.

When making the distinction between subclinical SI (i.e. no pain or stiffness) and clinical SI, the prevalence differed slightly. The prevalence of subclinical SI was estimated to be 11% (95%CI 7-17%) in 12 studies (18 estimates).[21,24,31,32,34,35,38,40,45,46,51,62] The prevalence of clinical SI was estimated to be 8% (95%CI 6-10%).[16-18,22-26,28,30,32,34,37-40,42,43,47-49,52,55,57-62,65,67-71]

Ankylosing Spondylitis

The prevalence of AS in IBD patients was described in 43 studies (64 estimates) (see supplemental file S3). The pooled prevalence of AS was 3% (95%CI 2-4%) with considerable heterogeneity (I^2=81.9%). Patients with CD had a slightly higher prevalence of AS than patients with UC; 4% (95%CI 3-5%) compared to 2% (95%CI 1-3%).

To look into potential explanations for the heterogeneity, the prevalence estimates for AS are shown in figure 3 according to several demographical and study characteristics. For geographic area, the prevalence of AS in IBD patients was highest in Europe with 3% (95% CI 3-4%) and North-America (3%, 95%CI 2-5%). The prevalence was slightly lower in South-America and Asia with 2% (95%CI 0-5%/1-3% respectively). For the mean age of the study population, patients of younger age (age group 20-30) had a slightly higher prevalence of AS, based on two estimates (4%,95%CI 3-6%), compared to older age groups (3%,95%CI 2/1%-5/% respectively). Study characteristics like setting, outcome measurement and case ascertainment seemed to influence the reported prevalences. The differences are small, with slightly higher prevalences in tertiary care setting, diagnoses based on clinical evaluation and the use of the recommended (modified) New York criteria to diagnose AS.

Figure 2. Meta-analysis of the Prevalence of Sacroiliitis in IBD Patients

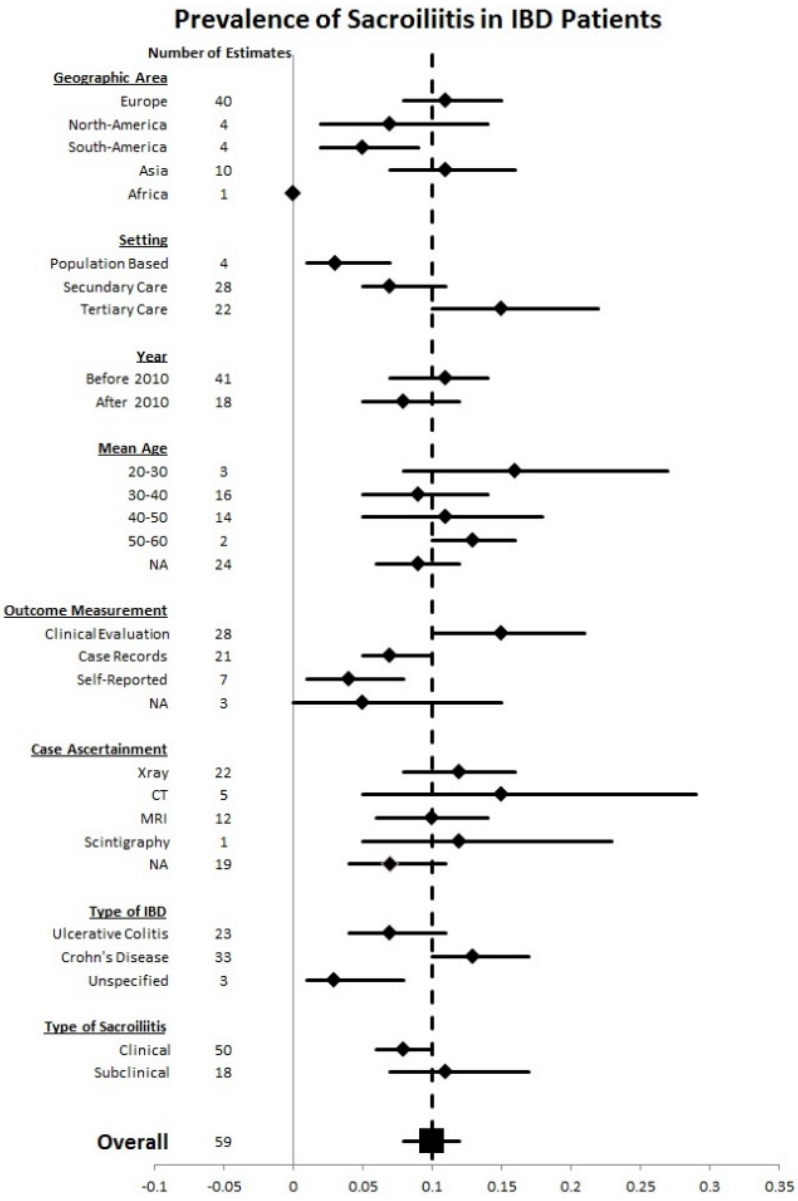
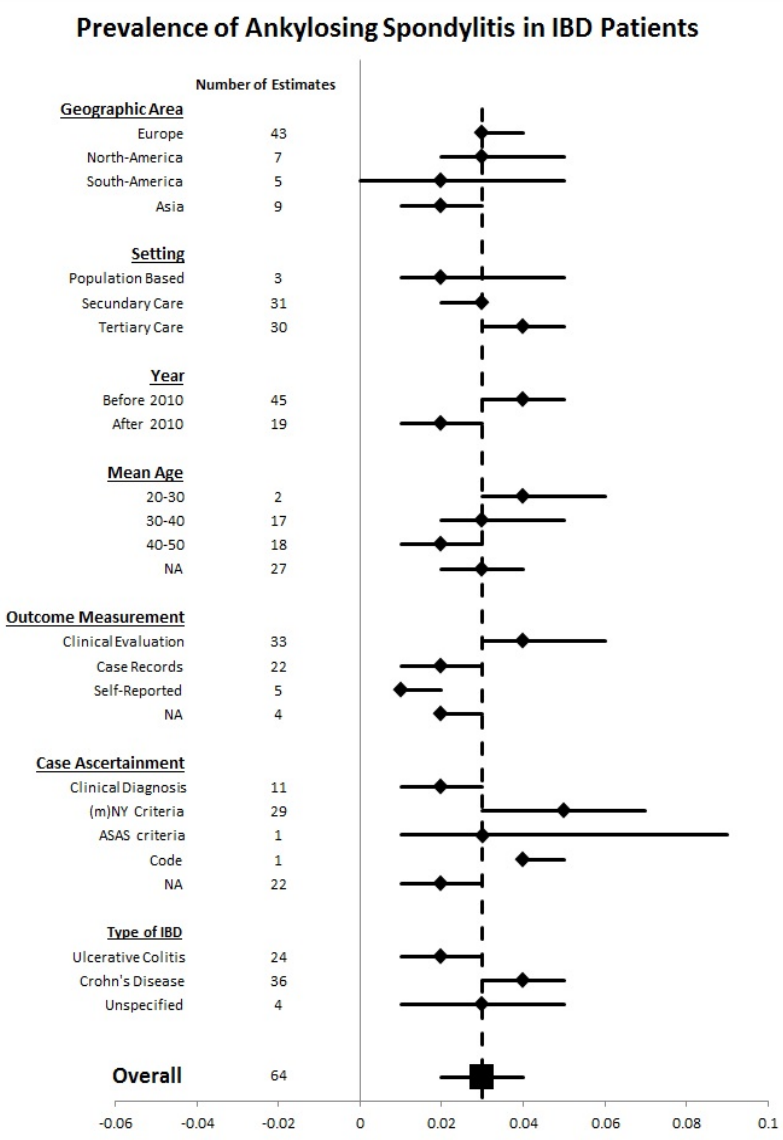


Figure 3. Meta-analysis of the Prevalence of Ankylosing Spondylitis in IBD Patients



Unspecified Axial Involvement

Six studies (9 estimates) did not specify the type of axial involvement, in these studies the prevalence ranged from 1 to 16%.[14,15,33,36,53,72] One recent study (2 estimates) used the new ASAS criteria to diagnose axial spondyloarthritis. Since axial spondyloarthritis can be diagnosed without abnormalities on imaging (which are required for diagnosing AS), these estimates are higher at 18% for UC and 19% for CD.

Prevalence of Peripheral Involvement

One hundred and three estimates from 52 studies were available for the prevalence of peripheral joint manifestations of SpA in IBD patients (see supplemental file S3).

Arthritis

The pooled prevalence of peripheral arthritis (79 estimates) was 13% (95%CI 12-15%) with a high heterogeneity (I^2=92.3%).[14-16,18,20,22-27,29,30,32-34,36-38,41,42,44,45,47-53,55,56,58,60-67,69-78] Forty estimates were available for CD and 37 for UC, while two studies did not specify the type of IBD. The prevalence was highest in this unspecified IBD with 17% (95%CI 14-20%), followed by CD (15%,95%CI 12-18%) and UC (12%,95%CI 9-15%).

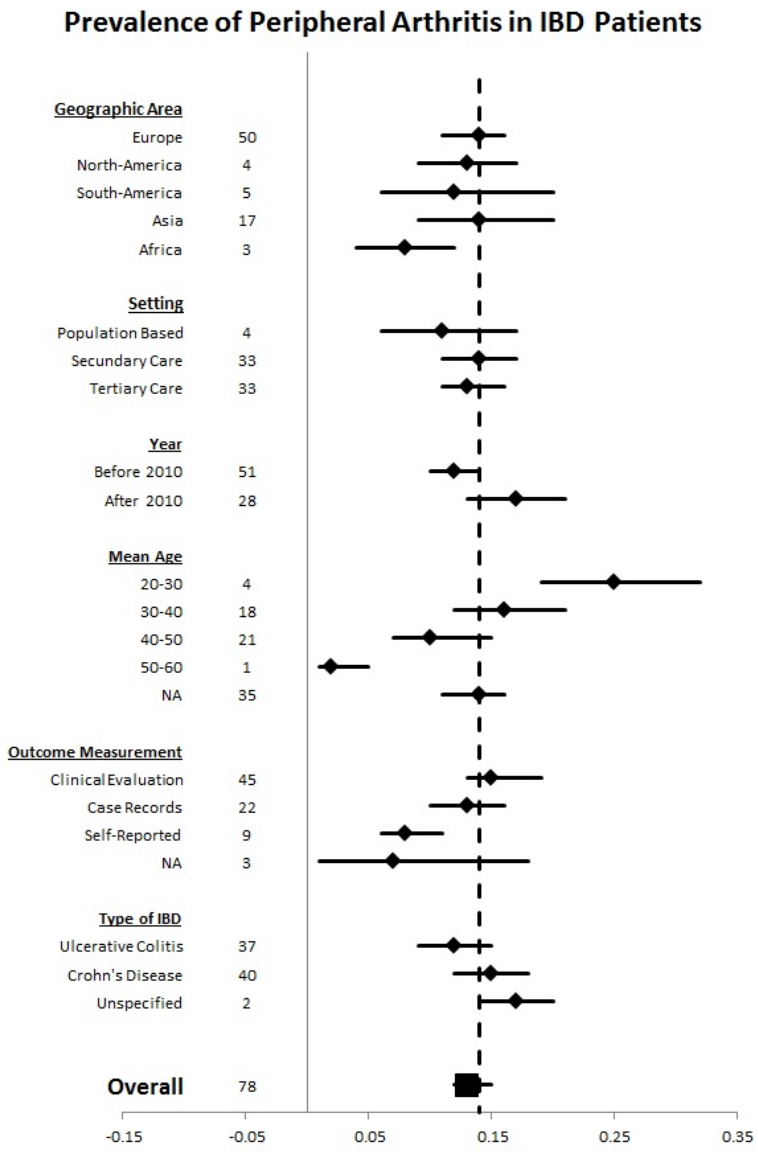
Figure 4 shows the estimates according to several subgroups that might explain the heterogeneity. With regard to geographic area, the prevalence seemed comparable among the different continents. Most studies were available from Europe (14%, 95% CI 11-16%) and Asia (14%, 95%CI 9-20%), followed by North- & South-America (13%, 95%CI 9-17% and 12%, 95% CI 6-20% respectively). The prevalence of arthritis in IBD seemed to be decreasing with increasing age. The prevalence in the youngest age group of 20-30 years was 25% (95%CI 19-32%), while the prevalence in the age group of 50-60 years was 2% (95%CI 1-5%). Estimates from tertiary care were slightly higher compared with secondary care and population based studies, but the difference is negligible. In the majority of studies clinical evaluation was used as an outcome measurement and this led to the highest prevalence estimate with 15% (95%CI 13-19%).

Enthesitis

The prevalence of enthesitis was reported in eight studies (14 estimates); six from Europe[20,24,44,45,55,62], one from South-America[34] and one from Asia[15]. The reported prevalence ranged from 1% (95%CI 0-6%) to 54% (95%CI 42-65%). Three estimates were available from Turkey and these were considerably higher than the other estimates with 20% (95%CI 13-28%), 46% (95%CI 35-58%) and 54% (95%CI 42-65%).[20,62] The estimates from the other countries ranged from 1% (95%CI 0-6%) in Kuwait to 0.15%

(95%CI 7-27%) in a combined study from Italy and the Netherlands.[15,55] With regard to setting or type of IBD, the differences in prevalence were negligible.

Figure 4. Meta-analysis of Peripheral Arthritis in IBD patients



Dactylitis

For the prevalence of dactylitis ten estimates from six studies were available.[15,24,44,45,55,79] The reported prevalence were all quite low with a range from 0 in CD patients in Kuwait[15] and Belgium[24] to 5% (95%CI 2-10%) in CD patients in Norway[44]. The range in UC patients was reported to be from 2% (95%CI 0-7%) to 4% (95%CI 1-15%). Two studies did not specify the type of IBD and reported prevalences of 4% (95% CI 3-7%)[45] and 6% (95% CI 3-11%)[79]. Geographic area or setting did not seem to influence the prevalence when looking at the available estimates.

Incidence

Three studies that report incidence figures were identified.[80-82] All were performed in North-America and using database records.

In CD patients, the cumulative incidence of SpA according to the ASAS criteria increased from 0.67 (95%CI 0.35-0.97) at 10 years towards 0.19 (95%CI 0.11-0.26%) at 30 years. The 5-year cumulative incidence of AS was 0.02 and of peripheral arthritis 0.009.

In UC patients, the cumulative incidence at 10 years according to the ASAS criteria was 0.48 (95%CI 0.02-0.07) increasing towards 0.22 (95%CI 0.04-0.29) at 30 years. The 5-year cumulative incidence for AS was 0.03 and of peripheral arthritis 0.05.

Discussion

In this systematic review we calculated the pooled prevalences of SpA manifestations in IBD patients. The pooled prevalence of SI was 10% (95%CI 8-12%) and for its subtype AS it was 3% (95%CI 3-4%). The pooled prevalence of peripheral arthritis was 13% (95%CI 12-15%). The prevalence of AS, SI and peripheral arthritis was higher in patients with CD than in patients with UC. This difference in prevalence estimates has been described before.[2,4,83] For the prevalence of enthesitis and dactylitis fewer estimates were available. The prevalence of enthesitis had a wide range from 1% (95%CI 0-6%) to 54% (95%CI 42-65%) with outliers in two studies from Turkey. The prevalence of dactylitis was relatively low between 0 and 5% (95%CI 2-10%). Only three studies reported the cumulative incidence of SpA in IBD patients.

As the heterogeneity between the different studies was high, these estimates should be interpreted with caution. Geographic area, setting and case ascertainment seemed to contribute to this large heterogeneity in prevalence estimates.

Prevalence estimates of AS were higher if case ascertainment was done by using validated criteria. As only a slight majority (60%) of studies used validated criteria for diagnosing AS, a lot of studies will underestimate the prevalence of AS in IBD. The same applies for studies performed in

secondary care, which seem to estimate a lower prevalence of the different SpA manifestations than studies in tertiary care. This could imply that tertiary care centers are more focused on joined care between gastroenterologists and rheumatologists to enhance recognition of SpA in IBD patients. Geographic area also contributes to the heterogeneity and prevalences for axial manifestations (SI&AS) are highest in Europe and North-America. This is in line with the estimates for SpA in general.[84,85] Clinical evaluation as an outcome measurement led to higher prevalence estimates compared to self-reported diagnosis or case records. This might suggest that our estimates are an underestimation, as in other types of arthritis it has been shown that the prevalence of self-reported diagnosis is higher than could be objectified via case records or specialists.[86,87]

As shown, there was large variety in methodological quality of studies. Most studies included their participants adequately, but merely 65% selected a sample representative of the target population. The results of these studies therefore have poor external validity. Even though the quality of the included studies differed widely, we chose not to pool on the quality in the meta-analysis as it has been shown before that the quality is highly dependent on the quality assessment tool you choose.[88]

When discussing the results of our study, several strengths and limitations should be taken into account. Although some narrative reviews about the prevalence of rheumatic manifestations in IBD patients have been published[2-4,83,89], the strength of this study is that it is the first systematically performed review and it includes a meta-analysis. We set up an extensive search strategy in collaboration with an experienced librarian in order to identify as many relevant studies as possible. We also included a risk of bias assessment to give an indication of the methodological quality of the included studies. Furthermore, we are the first to make the distinction between axial and peripheral manifestations of SpA, as recommended by the widely used ASAS criteria.[9,10] Regarding the limitations, we only included studies that were available in the English language so we cannot rule out missing certain studies. Secondly, only one author performed the screening of the papers and the data extraction. Ideally, this would have been done independently by two authors. However, we discussed beforehand with all authors which papers to include and which not. In addition, the author who performed the screening was very liberal and in case of any doubt, the paper was discussed with one of the other authors until consensus was reached. Thirdly, we used a risk of bias tool especially developed for prevalence studies, but left some items out as these did not seem to apply to our selected studies. We left out items about the description of study subjects and setting as we gathered this information in the data-extraction. Items about the definition of subgroups and differences between subgroups were also left out, as we only looked at prevalence in the complete groups. As we do not take the quality into account when pooling the results, we do not think leaving out these items

will influence our results. For the pooled estimates of SI and AS, we cannot rule out that a certain overlap between these two manifestations occurred. Some papers described very accurately if patients only suffered from SI or AS, but in the majority of studies it was unclear whether the patients with AS were a subset of the patients with SI or if they were completely separated in establishing the cases. It is therefore possible that the prevalence of SI is slightly overestimated.

Based on this meta-analysis the prevalence of peripheral arthritis is around 13%. This means that one in every eight patients will develop SpA. The prevalence for axial involvement in slightly lower with 10% for SI (i.e. one in every ten patients) and 3% for AS (i.e. one in every thirty-three patients). Gastroenterologists, especially in secondary care, should pay attention to their IBD patients with musculoskeletal complaints since they are common and might cause significant impact on quality of life, even in the absence of inflammation.[8] IBD patients are prone to develop SpA and should be recognized early as the benefits of early treatment are well established.[90,91]

In conclusion, we calculated pooled prevalences for SI (10%), its subtype AS(3%) and peripheral arthritis(13%) in patients with IBD. It seems that there is room for improvement in gastroenterology, especially in secondary care, with regard to recognition of SpA manifestations in IBD patients.

Table 1 Study Characteristics of Included Studies

	Setting	Study Design	No of IBD patients	Mean age population (years)	% women	Disease Duration (months)	Outcome	Case Definition Axial	Axial n(%)	AS n(%)	SI n(%)	Imaging SI	Arthritis n(%)	Enthesitis n(%)	Dactylitis n(%)
IBD															
Bernstein, 2001, Canada [19]	PB	RS	4454	NA	NA	NA	CR	Code		182 (4.1)					
Beslek, 2009, Turkey [20]	TC	CS	122	44.1	53.3	61	CR	(m)NY		10 (8.2)			19 (15.6)	24 (19.7)	
Gotler, 2015, Israel [68]	SC	RS	286	29.3	49	151.2	CR	ASAS			26 (9.1)	MRI			
Kamo, 2015, Japan [79]	SC	CS	137	45	40.9	122.4	SR								8 (5.8)
Nguyen, 2006, US/ Canada [39]	SC	RS	1106	36.1	51.9	NA	CR	Clinical		14 (1.3)	23 (2.1)	NA			
Palm, 2001, Norway [44]	SC	CS	521	39	53.0	73	CE	(m)NY		7 (1.3)	(0)				
Palm, 2002, Norway [45]	SC	CS	406	NA	NA	NA	CE	(m)NY			5 (1.2)	NA	69 (17)	26 (6.4)	18 (4.4)
CD															
Al-Jarallah, 2012, Kuwait [14]	TC	CS	81	29.6	33.3	NA	CE	Clinical	8 (9.9)				29 (35.8)		
Al-Jarallah, 2013, Kuwait [15]	TC	CS	85	29.6	NA	NA	CE	Clinical	10 (11.8)				25 (29.4)	1 (1.2)	0 (0)
Ansell BM, 1964, Canada [16]	SC	CS	91	NA	59.3	94.8	CE	NA		5 (5.5)	18 (19.8)	Xray	10 (11)		
Bandyopadhyay, 2015, India [67]	SC	CS	62	NA	34	NA	CE	ASAS	12 (19.4)		13 (21)	MRI	15 (24.2)		
Barreiro-De Acosta, 2007, Spain [18]	TC	CS	173	36	59	90	CE	Clinical		4 (2.3)	12 (6.9)	Xray	31 (17.9)		
Bruining, 2008, US [21]	SC	RS	357	NA	51	NA	CR	NA			8 (2.2)	CT			
Christodoulou, 2002, Greece [22]	TC	RS	37	40.2	40.5	7.8	SR	NA			6 (16.2)	NA	2 (5.4)		
Davis, 1978, Canada [23]	SC	CS	60	36	50	96	CE	(m)NY		3 (5)	7 (11.7)	Scinti-graphy	4 (6.7)		
De Vlam, 2000, Belgium [24]	TC	CS	78	NA	68	127.8	CE	(m)NY		7 (9)	27 (34.6)	Xray	7 (9)	6 (7.7)	0 (0)

Table 1 continues

Table 1 Study Characteristics of Included Studies

	Setting	Study Design	No of IBD patients	Mean age population (years)	% women	Disease Duration (months)	Outcome	Case Definition Axial	Axial n(%)	AS n(%)	SI n(%)	Imaging SI	Arthritis n(%)	Enthesitis n(%)	Dactylitis n(%)
Dekker Saeys, 1978, Netherlands [25]	TC	CS	51	37.2	58.8	NA	CE	(m)NY		2 (3.9)	8 (15.7)	Xray	6 (11.8)		
D'Inca, 2009, Italy [26]	SC	CS	266	41	47.7	126	CE	(m)NY		5 (1.9)	15 (5.6)	MRI	9 (3.4)		
Fatemi, 2016, Iran [74]	TC	CS	96	40.6	52.1	80.4	CE	Clinical		2 (2.1)			5 (5.2)		
Fielding, 1986, Ireland [28]	SC	CS	72	30.5	51.4	NA	SR	NA			1 (1.4)	NA			
Greenstein, 1976, US [29]	SC	RS	498	NA	NA	NA	CR	NA		19 (3.8)			84 (16.9)		
Haslock, 1973, UK [30]	TC	CS	116	NA	50	152.4	CE	(m)NY		8 (6.9)	19 (16.4)	Xray	24 (20.7)		
Hwangbo, 2010, Korea [31]	SC	CS	81	28.8	27.2	32.1	CR	(m)NY			17 (21)	CT			
Indiveri, 2010, South-Africa [75]	TC	RS	43	NA	69.8	NA	CR						3 (7)		
Isene, 2015, Norway, Denmark et al [69]	PB	FU	364	42.4	NA	NA	CR	NA		6 (1.6)	8 (2.2)	NA	33 (9.1)		
Karmiris, 2016, Greece [70]	TC	CS	1001	NA	NA	NA	CR	Clinical		34 (3.4)	70 (7)	MRI	155 (15.5)		
Lakatos, 2003, Hungary [33]	SC	FU	254	NA	50.8	110.4	CE	Clinical	26 (10.2)				37 (14.6)		
Lanna, 2008, Brasil [34]	TC	CS	71	39.4	59.2	63.3	CE	(m)NY		8 (11.3)	10 (14.1)	Xray	14 (19.7)	5 (7)	
Leclerc-Jacob, 2014, France [35]	TC	RS	131	NA	NA	NA	CR	Other			23 (17.6)	MRI			
Liu, 2016, China [92]	TC	RS	194	NA	NA	NA	CR	(m)NY		8 (4.1)					
Maeda, 1994, Japan [36]	SC	FU	203	NA	30	52.8	CE	NA	3 (1.5)				21 (10.3)		
Mocelin, 2015, Brasil [72]	TC	CS	100	41.9	60	NA	CE	ASAS	2 (2)	3 (3)			1 (1)		
Modena, 1988, Italy [37]	SC	CS	51	NA	47.1	NA	CE	(m)NY		5 (9.8)	6 (11.8)	Xray	10 (19.6)		
Münch, 1986, Germany [38]	SC	FU	167	25	62.3	76.8	CE	(m)NY		15 (9)	35 (21)	Xray	34 (20.4)		

Table 1 continues

Table 1 Study Characteristics of Included Studies

	Setting	Study Design	No of IBD patients	Mean age population (years)	% women	Disease Duration (months)	Outcome	Case Definition Axial	Axial n(%)	AS n(%)	SI n(%)	Imaging SI	Arthritis n(%)	Enthesitis n(%)	Dactylitis n(%)
Orchard, 1998, UK [41]	TC	CS	483	NA	58.2	NA	SR	(m)NY		6 (1.2)			49 (10.1)		
Orchard, 2009, UK [40]	TC	CS	44	36.2	75	96	CR	(m)NY		5 (11.4)	17 (38.6)	MRI			
Ott, 2014, Germany [71]	PB	FU	161	NA	55.9	NA	SR	Clinical			16 (9.9)	MRI	26 (16.1)		
Ozdil, 2003, Turkey [42]	TC	RS	105	37.4	55.2	32.4	NA	NA		5 (4.8)	8 (7.6)	NA			
Palm, 2001, Norway [44]	SC	CS	168	39	53.0	73	CE	(m)NY					24 (14.3)	6 (3.6)	9 (5.4)
Palm, 2002, Norway [45]	SC	CS	133	NA	NA	NA	CE	(m)NY		8 (6)					
Paparo, 2012, Italy [46]	SC	RS	221	50.2	48.4	NA	CR	Other			53 (24)	CT			
Peeters, 2008, Belgium [47]	TC	CS	251	35	40	NA	CE	(m)NY		16 (6.4)	49 (19.5)	Xray	72 (28.7)		
Pezerovic, 2013, Croatia [48]	SC	RS	31	NA	NA	NA	CR	NA		4 (12.9)	3 (9.7)	NA	8 (25.8)		
Queiro, 2000, Spain [51]	SC	FU	35	35.9	57.1	81.6	CE	(m)NY		1 (2.9)	8 (22.9)	Xray	10 (28.6)		
Repiso, 2006, Spain [53]	SC	RS	157	41.15	43.3	NA	CR	NA	9 (5.7)				9 (5.7)		
Ricart, 2004, US [54]	SC	CS	243	NA	48	NA	SR	NA		9 (3.7)					
Salvarani, 2001, Italy+Netherlands[55]	SC	CS	59	NA	NA	NA	CE	(m)NY		3 (5.1)	3 (5.1)	Xray	6 (10.2)	9 (15.3)	1 (1.7)
Singh, 2015, India[93]	SC	FU	303	NA	NA	NA	NA	NA		10 (3.3)					
Steer, 2003, UK [57]	SC	CS	134	NA	52.9	NA	CE	(m)NY		9 (6.7)	31 (23.1)	CT			
Suh, 1998, Korea [58]	TC	RS	52	34	40.4	NA	CR	NA		1 (1.9)	4 (7.7)	Xray	5 (9.6)		
Teh, 1987, Singapore [59]	SC	RS	9	30.5	44.4	NA	CR	NA			1 (11.1)	NA			
Torres, 2012, Puerto-Rico [60]	SC	CS	336	30.9	41	NA	CR	NA		1 (0.3)	13 (3.9)	NA	62 (18.5)		
Tozun, 2009, Turkey [61]	SC	CS	216	37.4	44	NA	SR	NA		3 (1.4)	5 (2.3)	NA	24 (11.1)		

Table 1 continues

Table 1 Study Characteristics of Included Studies

	Setting	Study Design	No of IBD patients	Mean age population (years)	% women	Disease Duration (months)	Outcome	Case Definition Axial	Axial n(%)	AS n(%)	SI n(%)	Imaging SI	Arthritis n(%)	Enthesitis n(%)	Dactylitis n(%)
Turkcapar, 2006, Turkey [62]	TC	CS	78	40.91	64.1	52.29	CE	(m)NY		9 (11.5)	48 (61.5)	NA	12 (15.4)	42 (53.8)	
Vavricka, 2011, Switzerland [63]	SC	CS	580	41	54	132	CE	Clinical		33 (5.7)			193 (33.3)		
Veloso, 1996, Portugal [64]	TC	FU	449	29.4	56.1	54	CE	Clinical		14 (3.1)			91 (20.3)		
Wagtmans, 2001, Netherlands [65]	TC	RS	541	NA	50.8	NA	CR	Clinical		20 (3.7)	23 (4.3)	NA	77 (14.2)		
Yi, 2012, China [66]	SC	RS	153	33.64	62.1	20.67	CR	Clinical		1 (0.7)			7 (4.6)		
Yuksel, 2011, Turkey [77]	SC	CS	120	NA	43.3	6.22	CE						34 (28.3)		
Zippi, 2014, Italy [78]	SC	RS	216	NA	39.4	NA	CR	NA		5 (2.3)			66 (30.6)		
UC															
Al-Jarallah, 2012, Kuwait [14]	TC	CS	44	37.6	61.4	NA	CE	Clinical	7 (15.9)				22 (50)		
Al-Jarallah, 2013, Kuwait [15]	TC	CS	45	37.6	NA	NA	CE	Clinical	5 (11.1)				16 (35.6)	6 (13.3)	2 (4.4)
Al-Shamali, 2003, Kuwait [73]	TC	CS	90	NA	56	NA	SR	NA					8 (8.9)		
Bandyopadhyay, 2015, India [67]	SC	CS	58	NA	29	NA	CE	ASAS	9 (15.5)		11 (19)	MRI	12 (20.7)		
Bardazzi, 1997, Italy [17]	SC	CS	68	48.5	41.2	NA	CE	(m)NY			9 (13.2)	Xray			
Christodoulou, 2002, Greece [22]	TC	RS	215	54.1	42.3	8.2	SR	NA			9 (4.2)	NA	5 (2.3)		
De Vlam, 2000, Belgium [24]	TC	CS	25	NA	52	107	CE	(m)NY		3 (12)	6 (24)	Xray	3 (12)	1 (4)	1 (4)
Dekker Saeys, 1978, Netherlands [25]	TC	CS	58	42.1	58.6	NA	CE	(m)NY		2 (3.4)	7 (12.1)	Xray	8 (13.8)		
D'Inca, 2009, Italy [26]	SC	CS	385	44	44.2	138	CE	(m)NY		4 (1)	8 (2.1)	MRI	15 (3.9)		
Dorofeyev, 2009, Ukraine [27]	TC	CS	319	43.2	53.9	NA	NA	NA		8 (2.5)			48 (15)		
Fatemi, 2016, Iran [74]	TC	CS	177	41.4	56.5	94.8	CE	Clinical		0 (0)			7 (4)		

Table 1 continues

Table 1 Study Characteristics of Included Studies

	Setting	Study Design	No of IBD patients	Mean age population (years)	% women	Disease Duration (months)	Outcome	Case Definition Axial	Axial n(%)	AS n(%)	SI n(%)	Imaging SI	Arthritis n(%)	Enthesitis n(%)	Dactylitis n(%)
Greenstein, 1976, US [29]	SC	RS	202	NA	NA	NA	CR	NA		8 (4)			27 (13.4)		
Hwangbo, 2010, Korea [31]	SC	CS	82	42.7	46.3	18.0	CR	(m)NY			10 (12.2)	CT			
Indiveri, 2010, South-Africa [75]	TC	RS	80	NA	52.5	NA	CR						8 (10)		
Isene, 2015, Norway, Denmark et al [69]	PB	FU	781	47.7	NA	NA	CR	NA		8 (1)	12 (1.5)	NA	43 (5.5)		
Karmiris, 2016, Greece [70]	TC	CS	859	NA	NA	NA	CR	Clinical		5 (0.6)	16 (1.9)	MRI	66 (7.7)		
Kochhar, 1991, India [32]	SC	CS	150	NA	47.3	NA	CE	(m)NY			21 (14)	Xray	16 (10.7)		
Lakatos, 2003, Hungary [33]	SC	FU	619	NA	48.8	134.4	CE	Clinical	20 (3.2)				30 (4.8)		
Lanna, 2008, Brasil [34]	TC	CS	59	40.9	59.3	54	CE	(m)NY		0 (0)	2 (3.4)	Xray	7 (11.9)	2 (3.4)	
Leclerc-Jacob, 2014, France [35]	TC	RS	55	NA	NA	NA	CR	Other			8 (14.5)	MRI			
Orchard, 1998, UK [41]	TC	CS	976	NA	50.4	NA	SR	(m)NY		9 (0.9)			59 (6)		
Ott, 2014, Germany [71]	PB	FU	96	NA	47.9	NA	SR	Clinical			3 (3.125)	MRI	15 (15.6)		
Ozdil, 2004, Turkey [42]	TC	RS	116	36	55.2	51.8	NA	NA			14 (12.1)	NA	2 (1.7)		
Palm, 2001, Norway [44]	SC	CS	353	46	50.1	74	CE	(m)NY					38 (10.8)	17 (4.8)	9 (2.5)
Palm, 2002, Norway [45]	SC	CS	273	NA	NA	NA	CE	(m)NY		7 (2.6)					
Pezerovic, 2013, Croatia [48]	SC	RS	119	NA	NA	NA	CR	NA		4 (3.4)	3 (2.5)	NA	24 (20.2)		
Pokharna, 2004, India [49]	SC	CS	46	NA	37.0	57.6	CE	(m)NY			0 (0)	Xray	1 (2.2)		
Pongprasobchai, 2001, Thailand [50]	TC	RS	40	NA	52.5	NA	CR	NA		1 (2.5)	(0)		2 (5)		
Queiro, 2000, Spain [51]	SC	FU	27	40.9	48.1	84	CE	(m)NY		1 (3.7)	7 (25.9)	Xray	9 (33.3)		

Table 1 continues

Table 1 Study Characteristics of Included Studies

	Setting	Study Design	No of IBD patients	Mean age population (years)	% women	Disease Duration (months)	Outcome	Case Definition Axial	Axial n(%)	AS n(%)	SI n(%)	Imaging SI	Arthritis n(%)	Enthesitis n(%)	Dactylitis n(%)
Rajput, 1992, South-Africa [52]	TC	NA	64	NA	50	NA	NA	NA			0 (0)	Xray	4 (6.3)		
Salvarani, 2001, Italy+Netherlands[55]	SC	CS	98	NA	NA	NA	CE	(m)NY		2 (2)	2 (2)	Xray	11 (11.2)	6 (6.1)	2 (2)
Scarpa, 1992, Italy [56]	TC	CS	79	38.72	30.4	NA	CE	(m)NY		20 (25.3)			23 (29.1)		
Singh, 2015, India [93]	SC	FU	1146	NA	NA	NA	NA	NA		25 (2.2)					
Suh, 1998, Korea [58]	TC	RS	77	38.5	55.8	NA	CR	NA		0 (0)	4 (5.2)	Xray	15 (19.5)		
Teh, 1987, Singapore [76]	SC	RS	61	38.2	50.8	NA	CR						4 (6.6)		
Torres, 2012, Puerto-Rico [60]	SC	CS	299	40.3	56	NA	CR	NA		2 (0.7)	8 (2.7)	NA	48 (16.1)		
Tozun, 2009, Turkey [61]	SC	CS	661	42.6	43	NA	SR	NA		6 (0.9)	4 (0.6)	NA	37 (5.6)		
Turkcapar, 2006, Turkey [62]	TC	CS	84	42	61.9	57.36	CE	(m)NY		7 (8.3)	48 (57.1)	NA	12 (14.3)	39 (46.4)	
Vavricka, 2011, Switzerland [63]	SC	CS	370	42	48	108	CE	Clinical		6 (1.6)			79 (21.4)		
Veloso, 1996, Portugal [64]	TC	FU	343	36.4	50.7	52.8	CE	NA		10 (2.9)			38 (11.1)		
Yuksel, 2011, Turkey [77]	SC	CS	237	NA	41.8	7.06	CE						32 (13.5)		
Zippi, 2014, Italy[78]	SC	RS	595	NA	48.6	NA	CR	NA		8 (1.3)			161 (27.1)		

IBD=Inflammatory Bowel Disease, CD=Crohn's Disease, UC=Ulcerative Colitis, NA=Not Available, PB=Population Based, SC=Secondary Care, TC=Tertiary Care, RS=Retrospective, CS=Cross-sectional, FU=Prospective Follow-up, CR=Case Records, SR=Self-Reported, CE=Clinical Evaluation, (m)NY= (modified) New York Criteria, ASAS=Assessment of Spondyloarthritis International Society, AS=Ankylosing Spondylitis, SI=Sacroiliitis

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Supplemental File S1 Search strategy

Embase	2236	2208
Medline (OvidSP)	1028	114
Web-of-science	1059	323
Cochrane	10	0
Google scholar	200	133
Total	**4533**	**2778**

Embase

(spondyloarthropathy/de OR spondylarthritis/de OR arthropathy/de OR (spondyloarthr* OR spondylarthr* OR arthropath* OR ((spondyl* OR enteropath*) NEXT/1 arthr*) OR ((extra-intestinal OR extra-bowel OR extraintestin* OR rheumat* OR arthrit* OR articul*) NEAR/3 (manifestation* OR disorder* OR site* OR complicat* OR symptom* OR involv*))):ab,ti) AND ('inflammatory bowel disease'/de OR 'Crohn disease'/de OR 'colon Crohn disease'/de OR 'ulcerative colitis'/de OR ((inflammat* NEAR/3 bowel) OR crohn* OR (ulcerat* NEAR/3 colit*) OR ibd OR ibds):ab,ti) AND (epidemiology/de OR epidemiology:lnk OR prevalence/de OR incidence/exp OR comorbidity/de OR (prevalen* OR inciden* OR frequen* OR epidemiol* OR comorbid* OR occuren* OR coexist*):ab,ti)

Medline (OvidSP)

(spondyloarthropathies/ OR spondylarthritis/ OR (spondyloarthr* OR spondylarthr* OR arthropath* OR ((spondyl* OR enteropath*) ADJ arthr*) OR ((extra-intestinal OR extra-bowel OR extraintestin* OR rheumat* OR arthrit* OR articul*) ADJ3 (manifestation* OR disorder* OR site* OR complicat* OR symptom* OR involv*))).ab,ti.) AND (exp "Inflammatory Bowel Diseases"/ OR ((inflammat* ADJ3 bowel) OR crohn* OR (ulcerat* ADJ3 colit*) OR ibd OR ibds).ab,ti.) AND (epidemiology/ OR epidemiology.xs. OR "Epidemiologic Factors"/ OR prevalence/ OR incidence/ OR comorbidity/ OR (prevalen* OR inciden* OR frequen* OR epidemiol* OR comorbid* OR occuren* OR coexist*).ab,ti.)

Cochrane

((spondyloarthr* OR spondylarthr* OR arthropath* OR ((spondyl* OR enteropath*) NEXT/1 arthr*) OR ((extra-intestinal OR extra-bowel OR extraintestin* OR rheumat* OR arthrit* OR articul*) NEAR/3 (manifestation* OR disorder* OR site* OR complicat* OR symptom* OR involv*))):ab,ti) AND (((inflammat* NEAR/3 bowel) OR crohn* OR (ulcerat* NEAR/3 colit*) OR ibd OR ibds):ab,ti) AND ((prevalen* OR inciden* OR frequen* OR epidemiol* OR comorbid* OR occuren* OR coexist*):ab,ti)

Web-of-science

TS=(((spondyloarthr* OR spondylarthr* OR arthropath* OR ((spondyl* OR enteropath*) NEAR/1 arthr*) OR ((extra-intestinal OR extra-bowel OR extraintestin* OR rheumat* OR arthrit* OR articul*) NEAR/3 (manifestation* OR disorder* OR site* OR complicat* OR symptom* OR involv*)))) AND (((inflammat* NEAR/3 bowel) OR crohn* OR (ulcerat* NEAR/3 colit*) OR ibd OR ibds)) AND ((prevalen* OR inciden* OR frequen* OR epidemiol* OR comorbid* OR occuren* OR coexist*)))

Google scholar

Spondyloarthropathy|spondylarthritis|"extraintestinal|rheumatic|articular|arthritic manifestations|symptoms|involvement" crohn|"ulcerative colitis|ibd epidemiology|epidemiological|prevalence|incidence|comorbidity|frequency

Supplemental file S2 Risk of bias assessment

Risk of Bias Assessment Instructions

		YES	NO
1.	Was the sample representative of the target population?	The sample was representative of the target population. Selected patients are representative of an IBD population. No pre-selection took place in selecting the patients based on for example work. The center from which the IBD patients were recruited should me mentioned	Sample was not representative.
2.	Were study participants recruited in an appropriate way?	Patients were recruited from an appropriate source and were "randomly" invited for the study (all patients OR consecutive patients OR random patients)	Patients were not recruited from an appropriate source and no random selection was used to recruit patients
3.	Was the sample size adequate/ Was sample size calculation performed?	Sample size calculation was performed and it was reported if this target was reached	No sample size calculation
4.	Was the data analysis conducted with sufficient coverage of the identified sample?	Non-response was described AND a comparison between the responders and non-responders was performed. If retrospective design, answer is yes	No information about response percentages was given or no comparison between responders and non-responders was made.
5.	Were objective, standard criteria used for the measurement of the condition?	Criteria were used for the diagnosis of SpA (for example (modified) New York criteria, ESSG criteria) OR A detailed description of how a case (for example sacroillitis) was defined is included in the manuscript. OR In case of use of ICD codes, a validation/ check was performed	No criteria were used and no description of how a case was defined is included in the manuscript.
6.	Was the condition measured reliably?	Outcome assessor was qualified to use the case definition criteria (for example; medical specialist, trained research nurse)	Outcome assessor was not qualified to use the case definition criteria or it was not mentioned who defined a case.

Overview of the Risk of Bias Assessment per study

		Item on Risk of Bias Assessment						
Author	**Journal**	**1**	**2**	**3**	**4**	**5**	**6**	**Total Score**
Al-Jarallah	Inflammatory Bowel Diseases; 2012, 18(9): 1655-1662	0	1	0	0	1	0	**2**
Al-Jarallah	Int J Rheum Dis; 2013, 16(2): 134-138	0	1	0	1	1	0	**3**
Al-Shamali	Digestion; 2003, 67(4): 218-224	1	1	0	1	0	0	**3**
Ansell BM	Annals of the Rheumatic Diseases; 1964:	1	1	0	0	0	0	**2**
Arora	Dig Dis Sci; 2010, 55(6): 1689-1695	1	1	0	1	0	0	**3**
Bandyopadhyay	Indian J Gastroenterol; 2015, 34(5): 387-394	1	1	0	0	1	1	**4**
Bardazzi	Ital J Gastroenterol Hepatol; 1997, 29(6): 520-524	0	1	0	0	1	1	**3**
Barreiro-De Acosta	Eur J Gastroenterol Hepatol; 2007, 19(1): 73-78	0	1	0	1	1	1	**4**
Bernstein	Am J Gastroenterol; 2001, 96(4): 1116-1122	1	1	0	1	1	0	**4**
Beslek	Rheumatol Int; 2009, 29(8): 955-957	0	0	0	0	1	1	**2**
Bruining	Inflammatory Bowel Dis; 2008, 14(12): 1701-1706	1	1	0	1	0	1	**4**
Christodoulou	Dig Liver Dis; 2002, 34(11): 781-786	0	1	0	1	0	1	**3**
Davis	ARTHRITIS RHEUM; 1978, 21(2): 234-7	0	1	0	0	1	0	**2**
De Vlam	J Rheumatol; 2000, 27(12): 2860-2865	0	1	0	0	1	1	**3**
Dekker Saeys	Annals of the Rheumatic Diseases; 1978, 37(1): 33-35	1	1	0	1	1	1	**5**
D'Inca	Dig Liver Dis; 2009, 41(8): 565-569	1	1	0	0	1	1	**4**
Dorofeyev	Dig Dis; 2009, 27(4): 502-510	0	0	0	0	0	0	**0**
Fatemi	J Res Med Sci; 2016, 21(3):	0	1	0	1	0	1	**3**
Fielding	AM J GASTROENTEROL; 1986, 81(7): 524-528	1	1	0	1	0	0	**3**
Gotler	J. Magn. Reson. Imaging; 2015, 42(1): 121-127	0	1	0	1	1	1	**4**
Greenstein	MEDICINE; 1976, 55(5): 401-412	1	1	0	1	1	0	**4**
Haslock	MEDICINE; 1973, 52(3): 217-225	1	1	0	0	0	0	**2**
Hwangbo	Gut Liver; 2010, 4(3): 338-344	0	1	0	1	1	1	**4**
Indiveri	S Afr Gastroenterol Rev; 2010, 8(3): 6-18	0	1	0	1	0	0	**2**
Isene	Scand J Gastroenterol; 2015, 50(3): 300-305	1	1	0	0	0	1	**3**
Kamo	Mod Rheumatol; 2015, 25(3): 435-437	1	1	0	0	0	0	**2**
Karmiris	J Crohn's Colitis; 2016, 10(4): 429-436	0	1	0	1	0	0	**2**
Kochhar	Indian J Gastroenterol; 1991, 10(3): 88-89	1	1	0	1	1	0	**4**
Lakatos	World J Gastroenterol; 2003, 9(10): 2300-2307	1	1	0	0	1	1	**4**
Lanna	Clin Rheumatol; 2008, 27(4): 503-509	1	1	0	0	1	1	**4**
Leclerc-Jacob	Aliment Pharmacol Ther; 2014, 39(9): 957-962	1	1	0	1	1	1	**5**
Liu	Medicine (Baltimore); 2016, 95(28): e4267	0	1	0	1	1	1	**4**

Table continues

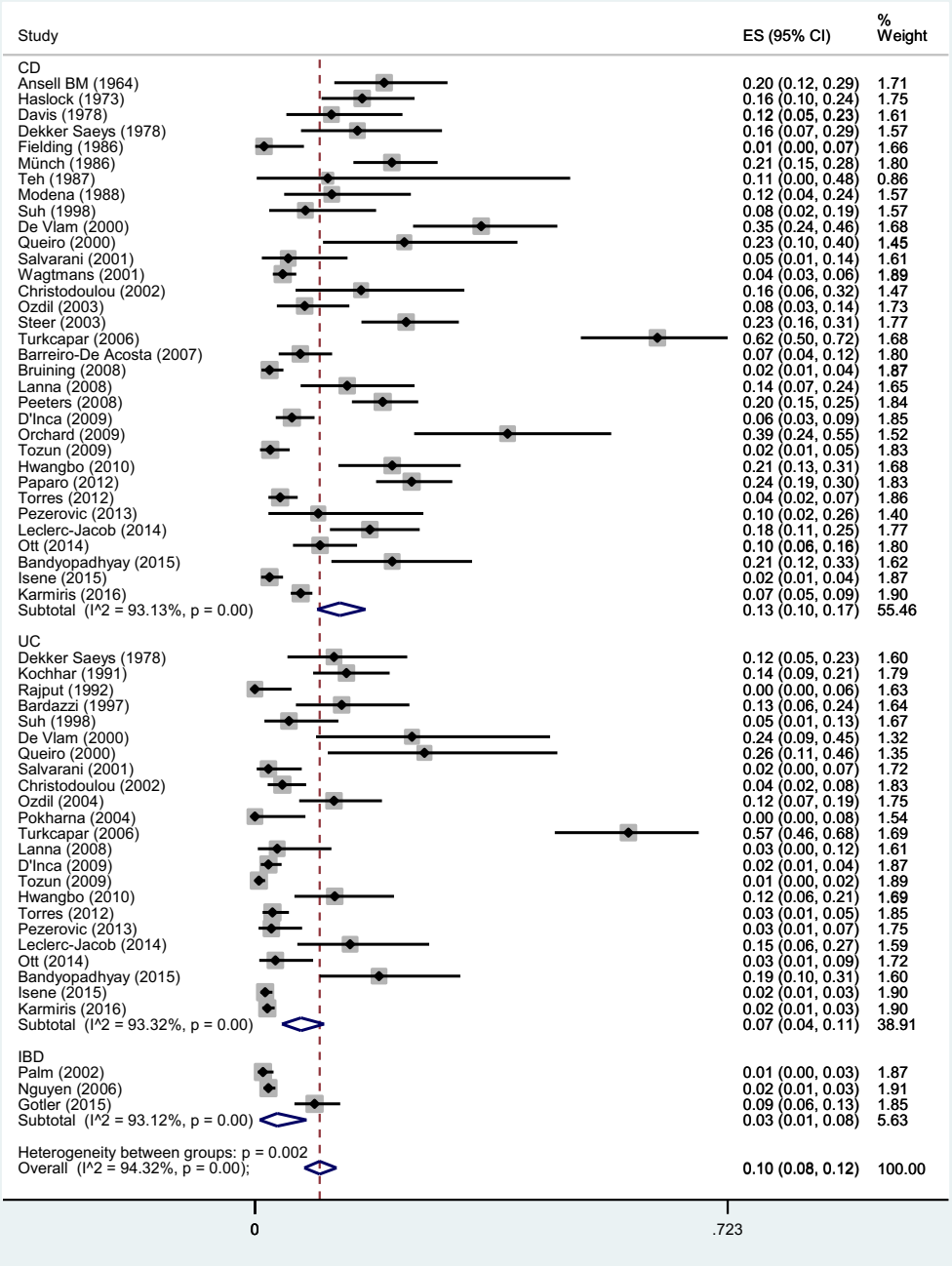
Maeda	J GASTROENTEROL; 1994, 29(5): 577-582	1	0	0	1	0	0	**2**
Mocelin	Digestion; 2015, 91(4): 303-306	0	1	0	0	1	1	**3**
Modena	CLIN EXP RHEUMATOL; 1988, 6(3): 221-225	1	1	0	0	1	1	**4**
Münch	Hepato- …; 1986:	1	1	0	0	1	1	**4**
Nguyen	Am J Gastroenterol; 2006, 101(5): 1012-1023	0	1	0	0	1	0	**2**
Orchard	GUT; 1998:	1	1	0	1	1	0	**4**
Orchard	Aliment Pharmacol Ther; 2009, 29(2): 193-197	1	1	0	1	1	1	**5**
Ott	World J Gastroenterol; 2014, 20(34): 12269-12276	1	1	0	0	0	0	**2**
Ozdil	Hepatogastroenterology; 2003, 50 Suppl 2	0	0	0	1	0	0	**1**
Ozdil	Hepato-Gastroenterology; 2004, 51(57): 768-770	0	1	0	1	0	0	**2**
Palm	Rheumatology; 2001, 40(11): 1256-1261	1	1	0	0	1	1	**4**
Palm	J Rheumatol; 2002, 29(3): 511-515	1	1	0	0	1	1	**4**
Paparo	Abdom Imaging; 2012, 37(3): 326-337	0	1	0	1	1	1	**4**
Peeters	J Gastroenterol Hepatol; 2008, 23(1): 132-137	0	0	0	0	1	1	**2**
Pezerovic	Coll Antropol; 2013, 37(3): 919-927	0	1	0	1	0	0	**2**
Pokharna	Indian J Gastroenterol; 2004, 23(3): 89-90	1	1	0	1	1	0	**4**
Pongprasobchai	J Med Assoc Thailand; 2001, 84(9): 1281-1288	1	1	0	1	0	0	**3**
Queiro	Clin Rheumatol; 2000, 19(6): 445-449	1	1	0	1	1	1	**5**
Rajput	S AFR MED J; 1992, 81(5): 245-248	1	1	0	0	0	0	**2**
Repiso Ortega	Rev Esp Enferm Dig; 2006, 98(7): 510-517	1	1	0	1	0	0	**3**
Ricart	Inflammatory Bowel Diseases; 2004, 10(3): 207-214	1	1	0	0	0	0	**2**
Salvarani	Scand J Gastroenterol; 2001, 36(12): 1307-1313	1	1	0	0	1	1	**4**
Scarpa	J RHEUMATOL; 1992, 19(3): 373-377	1	1	0	1	1	1	**5**
Shivashankar	J Rheumatol; 2012, 39(11): 2148-2152	1	1	0	1	1	1	**5**
Shivashankar	J Rheumatol; 2013, 40(7): 1153-1157	1	1	0	1	1	1	**5**
Singh	Indian J Gastroenterol; 2015,	1	1	0	1	0	0	**3**
Steer	Journal of Rheumatology; 2003, 30(3): 518-522	1	1	0	1	1	1	**5**
Suh	J Korean Med Sci; 1998, 13(1): 39-43	0	1	0	1	1	0	**3**
Teh	Ann Acad Med Singap; 1987, 16(3): 480-487 (CD)	0	1	0	1	0	0	**2**
Teh	Ann Acad Med Singap; 1987, 16(3): 474-479 (UC)	1	1	0	1	0	0	**3**
Torres	Intern J Inflamm; 2012,	1	0	0	1	0	0	**2**
Tozun	J Clin Gastroenterol; 2009, 43(1): 51-57	1	1	0	0	0	0	**2**
Turkcapar	Rheumatol Int; 2006, 26(7): 663-668	0	1	0	0	1	1	**3**
Vavricka	Am J Gastroenterol; 2011, 106(1): 110-119	1	1	0	0	1	0	**3**
Veloso	J CLIN GASTROENTEROL; 1996, 23(1): 29-34	1	1	0	0	1	0	**3**

Table continues

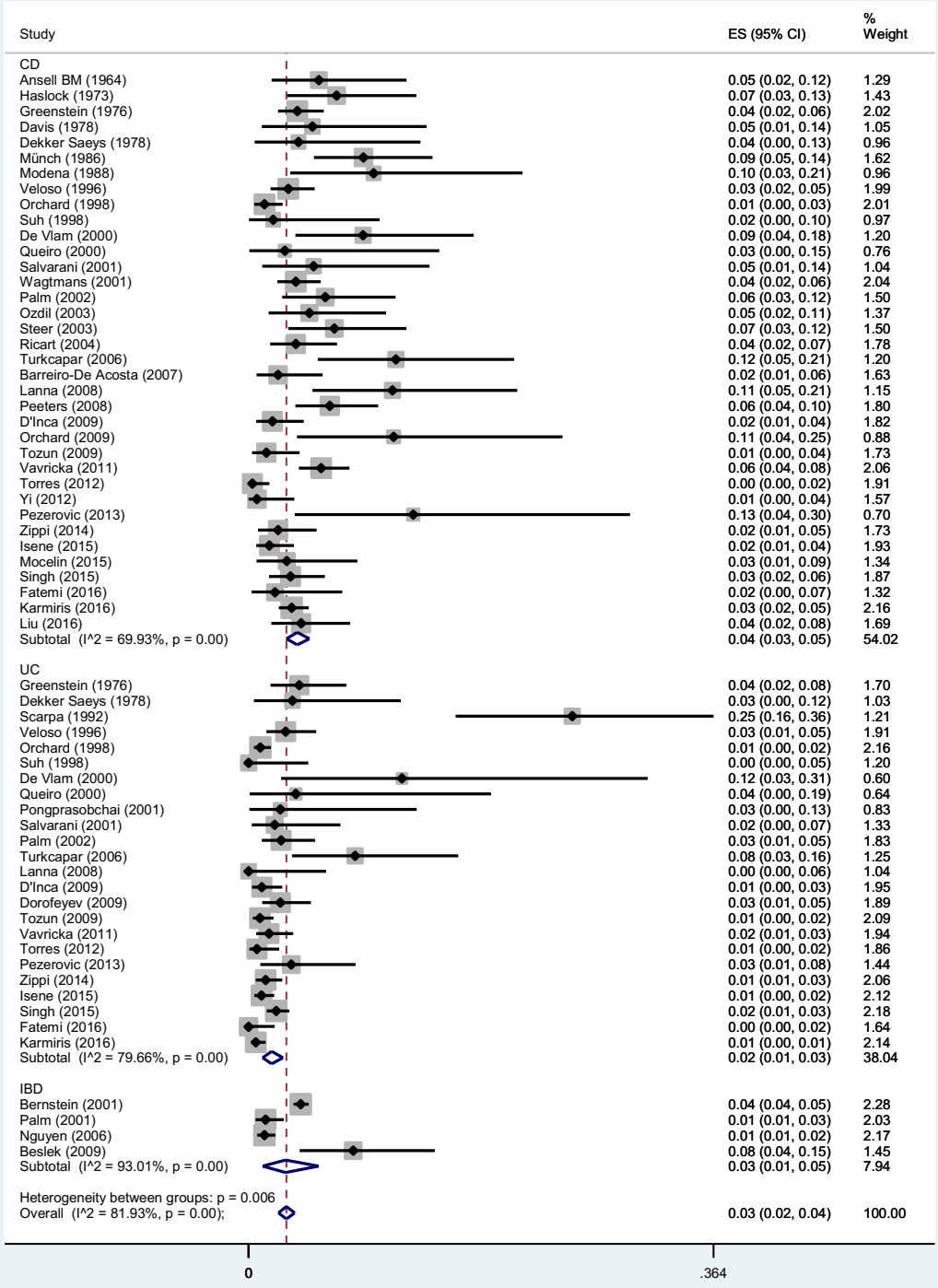
Wagtmans	Am J Gastroenterol; 2001, 96(5): 1541-1546	0	0	0	1	0	0	**1**
Yi	Eur J Gastroenterol Hepatol; 2012, 24(12): 1424-1429	1	1	0	1	0	0	**3**
Yuksel	Dig Dis Sci; 2011, 56(1): 183-187	1	1	0	1	0	1	**4**
Zippi	World J Gastroenterol; 2014, 20(46): 17463-17467	1	1	0	1	0	0	**3**

Supplemental file S3 Individual Forestplots

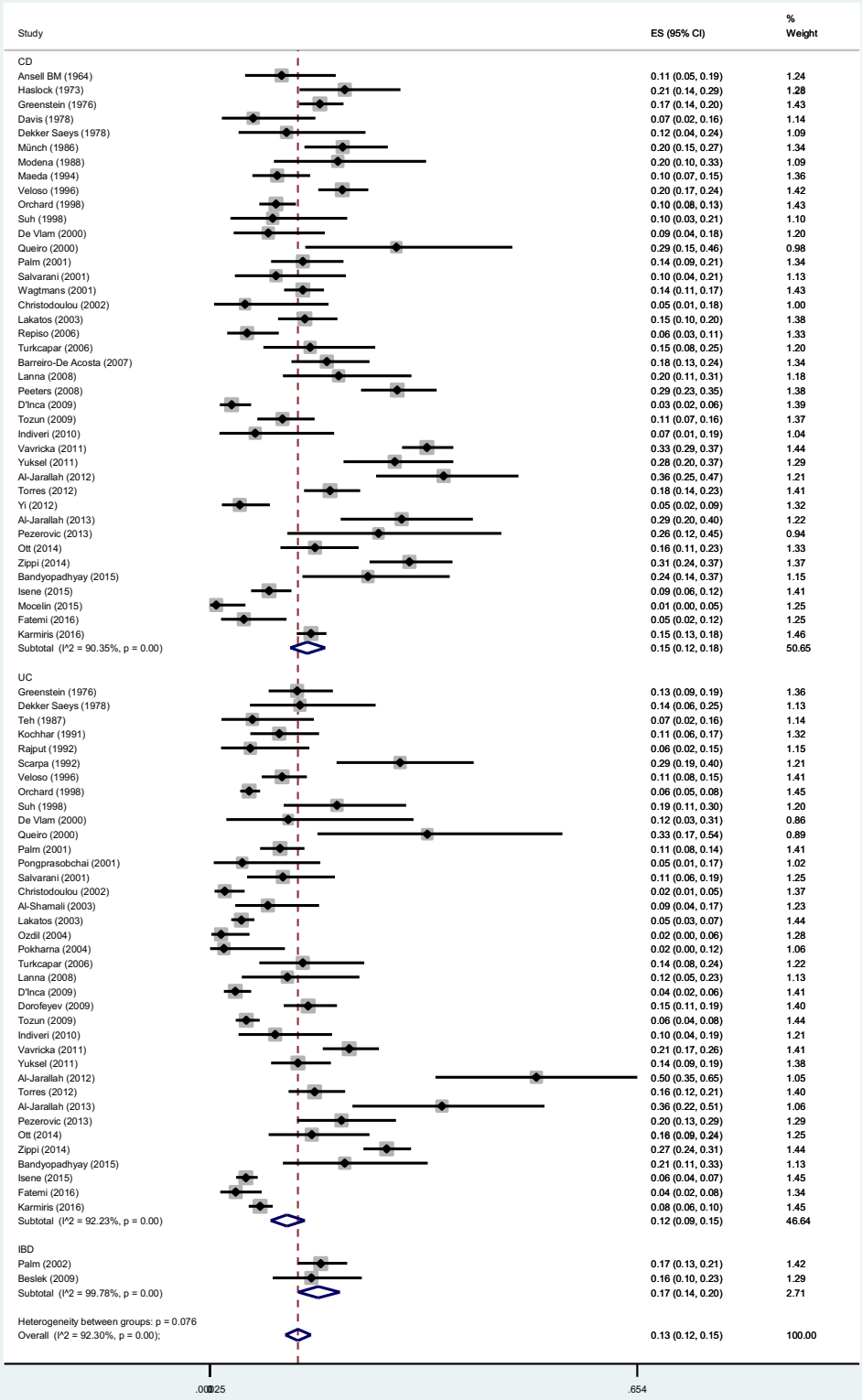
Forestplot of the prevalence of Sacroiliitis of all included studies



Forestplot of the prevalence of Ankylosking Spondylitis of all included studies



Forestplot of the prevalence of Peripheral Arthritis of all included studies



Chapter 5.

Musculoskeletal Complaints cause Significant Burden in Patientswith Inflammatory Bowel Disease: A Survey among Patients

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A.E.A.M. Weel

Submitted

Abstract

Background. Musculoskeletal complaints (MSC) are the most frequent extra-intestinal manifestation of inflammatory bowel disease (IBD). The aim of this study was to assess the influence of MSC on quality of life, disability and work participation in patients with IBD.

Methods. A cross-sectional survey was set up among IBD patients 18-55 years of age selected from primary care databases and via the patient organization. Participating patients completed a set of questionnaires including questions about their IBD, the presence of MSC (joint, tendon or lower back), disability (HAQ, RMDQ), quality of life (IBDQ, SF-36) and work participation and productivity.

Results. 338 IBD patients completed the questionnaires (45.6% Crohn's disease (CD), 45.0% ulcerative colitis (UC)). Mean age was 42.3±9.3 years and 25.4% were male. MSC were very common with a prevalence of 81.1%, with higher percentages for CD patients compared to UC patients. IBD patients with MSC had significantly lower quality of life on both the IBDQ and the SF-36. With regard to work status and productivity, IBD patients with MSC were more often unemployed and work-disabled and reported lower work productivity compared to IBD patients without MSC. Activity impairment in daily life was also higher for patients with MSC.

Conclusion. MSC are a very common extra-intestinal manifestation of IBD and cause significant burden, both in quality of life as on work status and productivity. Reduced quality of life in IBD patients seems to be influenced explicitly by MSC.

Introduction

Inflammatory Bowel Disease (IBD) is a chronic inflammatory disease of the intestines, comprising both Crohn's disease (CD) and ulcerative colitis (UC). IBD often manifests at young age and it can be accompanied by a number of extra-intestinal manifestations which have a significant impact on health related quality of life (HRQoL).[1-4] Musculoskeletal complaints (MSC) are the most common extra-intestinal manifestation and could be caused by the underlying inflammatory rheumatic disease called spondyloarthritis (SpA).[5,6] SpA is an umbrella term for a group of rheumatic manifestations with the same pathophysiological mechanisms like IBD but also psoriasis, ankylosing spondylitis and uveitis.[7] SpA is divided into axial or peripheral manifestations according to the recent and widely used criteria from the ASAS group.[8,9] Back pain is the predominant symptom in axial disease whereas peripheral disease is characterized by arthritis, enthesitis or dactylitis. The prevalence of axial manifestations in IBD is estimated to be around 11%, while peripheral manifestations like arthritis are slightly more common with an estimated prevalence of 14%.[10] Detection of patients developing SpA is important as early and adequate treatment can reduce pain, stiffness and functional impairment but also prevent late complications like severe joint deformations.[11,12] IBD and SpA both have a significant impact on health related quality of life (HRQoL).[1-3,13] Less is known however about the impact of these MSC complaints on patients with IBD. Because we wanted to assess this impact in a real life unselected population of IBD patients, we selected patients from a primary care setting. The objective of this study therefore was to assess the burden of MSC (from health related quality of life to functional ability and work participation) in IBD patients from primary care.

Materials & Methods

Patients

Between December 2014 and August 2015, 81 GPs from the Southwest of the Netherlands were recruited to participate in our study. These GPs selected all their IBD patients aged 18 to 55 years from their databases using ICPC code D94 (international Classification of Primary Care code for IBD, including CD, UC and undifferentiated IBD). ICPC is the standard for coding and classification of signs and symptoms in general practice in the Netherlands. All identified IBD patients received an invitation, including a reply slip, from their GP asking them to participate in this study. The invitation explained that this was a study to assess the prevalence and burden of musculoskeletal complaints in patients with IBD and consisted solely of a set of questionnaires. In addition, we reached out to the patient organization for IBD in the Netherlands (CCUVN, approximately 5400 members) asking for their help in recruiting patients. They placed information about this study on their website as well as an announcement in their newsletter, which was distributed via e-mail.

If patients agreed to participate, they received an e-mail with a link to a set of questionnaires, which could be completed online. If patients did not have access to internet or preferred to complete the questionnaires on paper, they received the questionnaires on paper. The questionnaires included questions about IBD (such as type of IBD, characteristics and current treatment), about musculoskeletal complaints, quality of life and work participation.

This study was exempted from medical ethical approval by the medical ethical committee of the Erasmus University Medical Centre as patients only had to complete a set of questionnaires (MEC-2014-269). All patients signed the reply slip when they agreed to participate.

Musculoskeletal Complaints

With regard to musculoskeletal complaints, patients were asked if they suffered regularly from joint, tendon and/or lower back complaints. For each of the three domains of MSC, the duration of the complaints was asked, as well as medication use and pain in the preceding 7 days (VAS scale 0-100, where 0 indicates no pain and 100 indicates worst pain imaginable). If patients suffered from lower back complaints, they also completed the Assessment of SpondyloArthritis International Society questionnaire on Inflammatory Back Pain (ASAS-IBP).[14] This questionnaire consists of 5 yes/no questions and is positive when 4 or more questions are answered positively. All patients were asked if they ever visited a rheumatologist and if so which diagnosis was made.

Functional Ability

Patients with joint and/or tendon complaints completed the HAQ (Health Assessment Questionnaire) to assess functional ability.[15] It contains questions on different domains like dressing, getting up, eating, walking, personal hygiene, reaching, grip and activity. The score for the HAG ranges from 0 to 3, where higher scores indicate more disability.

Patients who indicated to have complaints of the lower back, completed the RMDQ (Roland Morris Disability Questionnaire).[16] This questionnaire measures limitations in physical functioning in patients with low back pain. It has a score from 0-24, where a higher score represents more severe disability.

Health Related Quality of Life (HRQoL)

Patients completed the IBDQ and SF-36 to assess HRQoL.

IBDQ (Inflammatory Bowel Disease Questionnaire) is the most widely used and validated disease-specific quality of life questionnaire for patient with IBD.[17-19] It consists of 32 questions and the responses are graded on a 7 point Likert scale, giving a possible score range from 32 to 224, where a higher score represents better HRQoL. The questionnaire can be subdivided in four different domains:

bowel symptoms (10 questions, score 0-70), systemic symptoms (5 questions, score 0-35), social function (5 questions, score 0-35) and emotional function (12 questions, score 0-84). The individual scores for the different domains are calculated as average scores per domain.

SF-36 (Short Form 36) is a widely used questionnaire on general HRQoL with high validity and reliability.[20] It consists of 36 questions and the score is presented in the following 8 domains: physical functioning, role physical (limitations due to physical problems), bodily pain, vitality, social functioning, role emotional (limitations due to emotional problems), mental health and general health. The score on all eight separate domains is compared with the scores from the background population in the Netherlands.[21] Scores may range from 0-100, where a higher score indicates a better HRQoL.

Education and Work Status

All patients answered questions about their highest completed educational level; low (elementary school), medium (high school) or high (university). Current work status (employed or not employed) and work-disability were also asked for and compared with the general Dutch population.[22] To assess the impact of MSC on work participation, we used the WPAI (Work Productivity and Activity Impairment) questionnaires.[23] The WPAI measures 4 different domains related to work and activity over the past seven days, namely absenteeism (% work time lost), presenteism (% productivity loss at work), work impairment (combination of absenteeism and presenteism) and activity impairment (% activity loss in general, not necessarily work related). Patients were asked to complete these questions separately for impairment caused by their IBD, joint complaints, tendon complaints or lower back complaints.

Statistical Analysis

Descriptive statistics were used to describe patient characteristics and outcomes in STATA 14. Statistically significant differences for HAQ, IBDQ and SF-36 between patients with and without MSC were tested with the Wilcoxon rank sum test. A p-value below 0.05 was considered as statistically significant.

Results

Participants

In total, 535 patients with IBD aged 18-55 years of age (37.9% male) were selected out of the databases of the 81 participating GPs. In the process of inviting the patients to participate, 23 (4.3%) reported not to have IBD, so eventually 512 IBD patients selected by the GP were eligible to

participate. Of these patients, 292 (57.0%) responded to the invitation, of whom 273 were willing to participate (Figure 1). Via the patient organization another 120 IBD patients (17.5% male) responded on the advertisement and wanted to participate. In total, 393 IBD patients were willing to participate, of whom 338 completed the set of questionnaires.

Figure 1. Flowchart of Patients' Inclusion

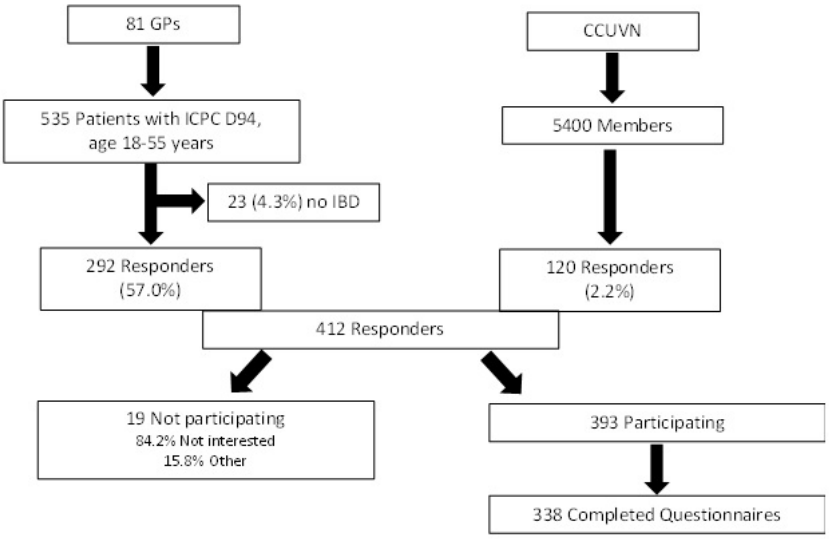

Table 1 provides an overview of the clinical characteristics for the total group of IBD patients and separately for CD and UC patients. Of the participants, 45.6% suffered from CD while 45.0% suffered from UC. The remaining 9.4% suffered from unspecified IBD. Mean age of the participants was 42.3 years (SD 9.3), with 25.1% being male (Table 1). Median duration of IBD was 10 years (IQR 5-18). With regard to medication, the majority (around 70%) used some kind of medication for their IBD with mesalazine and immunosuppressants being used most often. Approximately 25% of patients underwent surgery for their bowel disease, patients with CD considerably more often than patients with UC.

Table 1 Baseline Characteristics

	Total	Crohn's Disease	Ulcerative Colitis
No of Patients, n (%)[#]	338	154 (45.6)	152 (45.0)
Age, mean (SD)	42.3 (9.3)	41.7 (9.7)	42.5 (9.0)
Male sex, n (%)	85 (25.1)	32 (20.8)	44 (28.9)
Dutch nationality, n (%)	333 (98.5)	153 (99.4)	148 (97.4)
Median duration IBD, years (IQR)	10 (5-18)	12 (7-21)	9 (4-15)
Level of Education			
Low, n (%)	32 (9.5)	10 (6.5)	17 (11.3)
Intermediate, n (%)	175 (52.1)	81 (52.9)	75 (49.7)
High, n (%)	129 (38.4)	62 (40.5)	59 (39.1)
Medication IBD, n (%)			
None	94 (27.8)	41 (26.6)	41 (27.0)
Mesalazine	119 (35.2)	27 (17.5)	83 (54.6)
Corticosteroids	41 (12.1)	22 (14.3)	14 (9.2)
Immunosuppressants[$]	99 (29.3)	59 (38.3)	35 (23.0)
Anti-TNF*	69 (20.4)	44 (28.6)	17 (11.2)
Other	16 (4.7)	8 (5.2)	5 (3.3)
Bowel surgery, n (%)			
None	245 (72.5)	84 (54.5)	135 (88.8)
Partial resection	61 (18.0)	57 (37.0)	3 (2.0)
Stoma	17 (5.0)	7 (4.5)	8 (5.3)
Pouch	9 (2.7)	0	3 (2.0)
Other	6 (1.8)	6 (3.9)	3 (2.0)

[#] The remaining 32 patients suffered from unclassified IBD and were disregarded for the scope of this study. [$] azathioprine, thioguanine & methotrexate. *Adalumimab & Infliximab

Presence of Musculoskeletal Complaints

Out of the total of 338 IBD patients, 274 (81.1%) indicated to suffer from any kind of MSC; either joint, tendon or lower back (Figure 2). This percentage was higher for patients with CD than for patients with UC. About one third (33.9%) of the patients visited a rheumatologist for these complaints, 36 (10.7%) were diagnosed with an inflammatory rheumatological disease, again slightly more patients with CD compared with UC (Table 2).

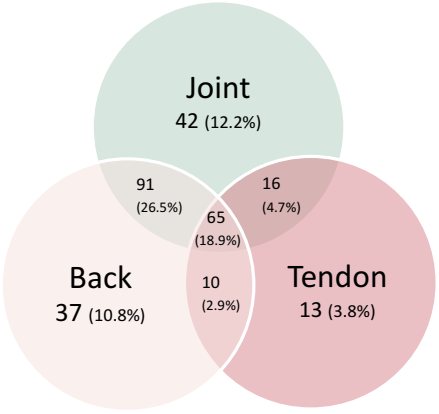

Table 2 Characteristics of Musculoskeletal Complaints in patients with IBD

	IBD (n=338)	CD (n=154)	UC (n=152)
Musculoskeletal Complaints, n (%)	274 (81.1)	133 (86.4)	114 (75.0)
Rheumatological Diagnosis, n (%)	36 (10.7)	20 (13.0)	11 (7.2)
Joint complaints			
No of Patients, n (%)	214 (63.3)	109 (70.8)	81 (53.3)
Duration of complaints, median (IQR) years	7 (3-15)	7 (3-13)	6 (2-15)
Pain in preceding week, mean (SD)	43.4 (24.7)	44.6 (24.7)	41.3 (25.2)
HAQ score, median (IQR)	0.38 (0.13-0.63) (n=127)	0.5 (0.13-0.75) (n=72)	0.13 (0-0.5) (n=45)
Medication use, n (%)	110 (51.4)	54 (40.6)	42 (51.9)
Paracetamol, n (%)	79 (71.8)	40 (74.1)	30 (71.4)
NSAIDs, n (%)	29 (26.4)	11 (20.4)	12 (28.6)
Morphinomimetics, n (%)	28 (25.5)	19 (35.2)	5 (11.9)
Tendon Complaints			
No of Patients, n (%)	104 (30.8)	43 (27.9)	47 (30.9)
Duration of complaints, median (IQR) years	4 (2-10)	5 (1-15)	3 (2-8)
Pain in preceding week, mean (SD)	42.8 (25.9)	48.1 (24.7)	39.7 (25.7)
HAQ score, median (IQR)	0.13 (0-0.25) (n=21)	0 (0-0.44) (n=8)	0.13 (0-0.13) (n=13)
Medication use, n (%)	52 (50%)	22 (51.2)	23 (48.9)
Paracetamol, n (%)	43 (82.7)	19 (86.4)	20 (87.0)
NSAIDs, n (%)	14 (26.9)	6 (27.3)	4 (17.4)
Morphinomimetics, n (%)	11 (21.2)	7 (31.8)	2 (8.7)
Lower Back Complaints			
No of Patients, n (%)	203 (60.1)	99 (64.3)	85 (55.9)
Duration of complaints, median (IQR) years	10 (4-20)	8 (3-15)	10 (4-20)
Positive ASAS-IBP, n (%)	75 (36.9)	30 (30.3)	37 (43.5)
Pain in preceding week, mean (SD)	39.0 (27.1)	39.9 (25.9)	36.4 (28.6)
RMDQ score, median (IQR)	4 (1-10)	5 (2-10)	3 (1-9)
Medication use, n (%)	86 (42.4)	41 (41.4)	36 (42.4)
Paracetamol, n (%)	66 (76.7)	36 (87.8)	24 (66.7)
NSAIDs, n (%)	21 (24.4)	8 (19.5)	9 (25.0)
Morphinomimetics, n (%)	25 (29.1)	15 (36.6)	9 (25.0)

If patients reported joint complaints, the median symptom duration was about 7 years with a mean VAS pain score of 43.4 over the prior week. About 50% indicated to use medication for their joint complaints. Patients suffering from tendon complaints reported a lower median symptom duration with 4 years. The mean VAS pain score over the prior week is similar at 42.8 even as medication use (50.9%). Tendon complaints are more often reported by patients with UC (30.9%) compared with CD (27.9%). The HAQ was completed by 228 patients suffering from either joint or tendon complaints. Disability was higher if patients indicated to suffer from both joint and tendon complaints (n=80) with a median score of 0.63 (IQR 0.25-1.25), compared with suffering only from joint complaints (n=127; median score 0.38) or tendon complaints (n=21; median score 0.13). If looking into the type of IBD, patients with CD had a higher median score (0.5; IQR 0.13-1) than patients with UC (0.25; IQR 0.13-0.63) (Table 2).

Of the 203 patients who indicated to have complaints of the lower back, 75 patients had a positive ASAS-IBP questionnaire (36.9%), meaning their lower back complaints had an inflammatory component. The RMDQ median score was 4 (IQR 1-10), with higher scores for CD patients (5; IQR 2-10) compared to UC patients (3; IQR 1-9). Median duration of complaints was 10 years with mean VAS pain score of 39.0. Medication was used by 58.8% of the patients (Table 2).

Influence of Musculoskeletal Complaints on Health Related Quality of Life

The total score for the IBDQ was significantly lower in for patients with MSC (165.4±27.8) compared to patients without MSC (182.8±26.3), where lower scores represent worse HRQoL (Table 3). When looking into the four different subscores, these were all significantly lower for patients with MSC compared with patients without MSC, except bowel symptoms in UC patients which were lower but not significantly (p=0.06). Overall, the scores for UC were slightly higher than the scores for CD.

SF-36 was completed by all 338 patients. Compared with the Dutch reference population, patients with IBD had lower scores on all dimensions, with lower scores for CD compared to UC (Figure 3). If the distinction is made between IBD patients with and without MSC, it can be demonstrated that IBD patients without MSC showed similar scores on almost all domains as the Dutch reference population, while patients with MSC scored significantly lower on all domains (Figure 4). When dividing the MSC into joint, tendon or back complaints, all three domains of MSC showed comparable decrease in subscores compared with the Dutch reference population. As in the IBDQ, the scores for UC were slightly higher than the scores for CD. Looking into non-inflammatory and inflammatory (positive ASAS-IBP or rheumatological diagnosis) MSC, the scores on both IBDQ and SF-36 were lower for patients with inflammatory MSC than for patients with non-inflammatory MSC.

Table 3 Mean scores of the IBDQ questionnaire in IBD patients with and without MSC

	IBD		CD		UC	
	No MSC	MSC	No MSC	MSC	No MSC	MSC
Number of Patients, n	64	274	21	133	38	114
Total score (range 0-224)	183.6 (26.7)	165.4 (27.8)	180.1 (30.5)	158.2 (26.9)	187.0 (24.7)	174 (26.2)
Bowel Symptoms (range 0-70)	58.0 (8.6)	52.9 (8.9)	58.6 (9.2)	51.1 (8.7)	58.3 (8.5)#	55.4 (8.6)#
Systemic Symptoms (range 0-35)	25.5 (6.2)	21.2 (5.9)	25.4 (6.0)	19.8 (5.7)	26.1 (6.4)	22.7 (5.5)
Social Function (range 0-35)	31.9 (4.9)	29.3 (5.9)	30.2 (5.8)	27.4 (6.4)	32.9 (4.1)	31.3 (4.5)
Emotional Function (range 0-84)	68.2 (10.1)	62.1 (11.6)	66.0 (11.6)	59.9 (11.4)	69.7 (9.4)	64.6 (11.5)

For all differences between No MSC and MSC p-value is lower than 0.05, except for #

Figure 3. Mean scores for the SF-36 in CD and UC patients, compared with the Dutch reference population

	PF	RF	BP	V	SF	RE	MH	GH
Dutch Reference Population	82,5	77,7	80,2	65,9	84,2	87,2	77,3	69,4
UC	82,5	70,8	67,2	55,8	78,9	80,0	73,5	52,3
CD	70,7	51,7	56,9	44,1	70,0	69,2	67,7	42,9

Figure 4. Mean scores for the SF-36 in IBD patients with and without MSC, compared with the Dutch reference population

	PF	RF	BP	V	SF	RE	MH	GH
Dutch Reference Population	82,5	77,7	80,2	65,9	84,2	87,2	77,3	69,4
No MSC	89,7	76,5	82,5	62,2	86,3	85,2	76,7	59,4
MSC	73,0	57,4	56,5	47,0	71,5	72,2	69,1	44,4

Influence of Musculoskeletal Complaints on Work Status & Productivity

Of the participating IBD patients, 73.8% was currently employed, which is lower than the employment status in the general Dutch population (93.2%). Of the patients who were currently unemployed, 45.6% (n=41) reported to be work-disabled, of whom 82.9% were 80-100% work-disabled. If comparing IBD patients with and without MSC differences can be shown. Table 4 shows the percentages of absenteeism and presenteism and the mean work productivity loss and activity impairment subdivided by the cause (IBD, joint complaints, tendon complaints or lower back complaints). The level of unemployment was higher in IBD patients suffering from any kind of MSC compared with IBD patients not suffering from IBD. If patients were unemployed; work-disability was an important cause in patients with MSC. The percentage of absenteeism (=absence) caused by MSC was comparable to the percentage of absenteeism caused by IBD. The percentage of presenteism (=reduced effectiveness while at work) caused by IBD was 36.4% compared to 53.1% caused by lower back complaints, 61.2% for joint complaints and 63.4% for tendon complaints. Both work productivity loss (=overall work impairment) and activity impairment were higher if caused by any kind of MSC compared to if caused by IBD.

Table 4 Work status and productivity in IBD patients with or without joint, tendon or lower back complaints

	Without MSC	With MSC		
	IBD(n=69)	Joint (n=214)	Tendon (n=104)	Back (n=203)
Activity Impairment, mean (SD)	0.17 (0.24)	0.36 (0.27)	0.33 (0.27)	0.29 (0.28)
Not Working	14 (20.3)	67 (31.3)	33 (31.7)	56 (27.6)
Work-disabled, n (%)	1 (1.4)	38 (17.8)	19 (18.3)	33 (16.3)
80-100%, n (%)	Unknown	27 (71.1)	17 (89.5)	28 (84.8)
Working	55 (79.7)	147 (68.7)	71 (68.3)	147 (72.4)
Absenteism, n/N (%)	5/51 (9.8)	14/131 (10.7)	6/61 (9.8)	8/129 (6.2)
Presenteism, n (%)	20 (36.4)	90 (61.2)	45 (63.4)	78 (53.1)
Work productivity loss, mean (SD) N	0.14 (0.25) N=51	0.23 (0.28) N=131	0.27 (0.32) N=61	0.20 (0.27) N=129

Discussion

This study demonstrates that MSC are frequent in patients with IBD and have great impact on the burden of disease. The impact of these MSC is demonstrated by significantly lower scores in quality of life, in both physical and mental health domains. With regard to work status and productivity, IBD patients with MSC are less often employed and if they are employed, they experience more presenteism and work productivity loss.

The prevalence of MSC was fairly high (80%) in our study, compared to the general population in the Netherlands (53.9%).[24] A lot of studies have been performed concerning the prevalence of rheumatic manifestations in IBD patients, but most focus on inflammatory rheumatic manifestations as SpA with arthritis and sacroiliitis. One population based study from Norway reported on the prevalence of non-inflammatory joint pain and this was estimated at 16%.[25] However, they only studied joint complaints and our sample consists of all forms of MSC pain. A recent study from the Netherlands looked into the prevalence of arthropathy in IBD patients, defined as chronic back pain for at least 3 months and/or peripheral joint swelling at presentation or in the past year and they report a prevalence of 60.1%.[26] The percentage of patients in our study with joint or back pain (excluding tendon complaints) is slightly higher at 72.5%. This difference could be explained by the fact that we used self-reported joint or back complaints without specific criteria like they used.

The impact of MSC in IBD patients on quality of life is considerable. This was also demonstrated in the non-inflammatory joint pain study from Norway and the study from the Netherlands with more or less comparable scores on the SF-36 and IBDQ.[25,26] Several other studies have been performed on the quality of life in patients with IBD. Most show decreased quality of life[1,3,27,28], while some studies show no difference between IBD patients and the reference population[2,29]. However, most studies do not

make the distinction between IBD with and without MSC. A recent study from the Netherlands did show decreased quality of life as measured with the SF-36 and short-IBDQ in patients with joint complaints compared to IBD patients without joint complaints.[26] In our study, the quality of life of patients with IBD was lower than the quality of life of the reference Dutch population. However, if making the distinction between IBD patients with and without MSC, the SF-36 scores for IBD patients without MSC are comparable with the Dutch reference population. Since the quality of life for IBD patients with MSC was significantly lower on all domains, it could certainly be possible that a large part of the quality of life in IBD patients is determined by EIMs like MSC.

With regard to work productivity and activity impairment, the study from van der Have et al also showed higher work and activity impairment for IBD patients with joint/back pain compared to IBD patients without joint/back pain.[26] More data is available on the influence of IBD in general on work productivity, but not specifically for the additional burden of MSC in these patients. A large systematic review showed that IBD patients experience a high burden in work-related outcomes, but the factors causing this are not investigated.[30]

This study has several limitations. First, only 25% of participating patients was male, so there seems to be an overrepresentation of women in our sample. However, in the initial unselected selection out of the GP databases, the percentage of women was already slightly higher (62.1%). Second, we did not do a clinical evaluation of the patients, so certain information like IBD classification or IBD activity was not available. Third, it is possible that a selection bias towards patients with MSC occurred and that the prevalence of MSC in this study is overestimated. Although we asked patients to participate irrespective of their complaints, we cannot rule out that patients with MSC were more prone to participate. If these limitations are taken into account, we think that this study provides valuable data on the impact of MSC in patients with IBD. We have a fairly large sample of IBD patients with complete data. In addition, this study is one of the first to describe the various components of the burden of unselected MSC in IBD patients from HRQoL to impact on work status and productivity. In this study we selected the IBD patients from primary care. Although the vast majority of patients will be treated by a gastroenterologist for their IBD, patients could also visit their GP if experiencing MSC. Most likely, if patients are not aware of the fact that MSC could be an extra-intestinal manifestation of IBD, they will visit the GP with MSC. This primary care setting is therefore also important in detecting these MSC in IBD patients. Another advantage of selecting IBD patients from various GP databases, is that it gives a good unselected representation of the general IBD population in the Netherlands. We recruited GPs from various regions of the Netherlands, thereby also representing a large variety in hospitals where the IBD patients will be treated.

In conclusion, EIMS like MSC have significant impact on the quality of life and work productivity in patients with IBD. The reduced quality of life found in IBD seems to be explicitly influenced by MSC. Gastroenterologists and general practitioners should be aware of this frequent extra-intestinal manifestation of IBD to aid early recognition as it could possibly be a symptom of SpA, which is well treatable in early stages.

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Part II.

Awareness and Early Recognition of Spondyloarthritis in Patients at Risk

Chapter 6.

Awareness of Spondyloarthritis in General Practitioners and their Patients: A Cross-sectional Survey in Primary Care

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Submitted

Abstract

Objective. To assess (1) the current skills of general practitioners (GPs) with regard to their ability to identify symptoms of spondyloarthritis (SpA) and (2) the level of awareness of SpA symptoms among patients at risk.

Methods. A cross-sectional study was set up in (1) Dutch GPs and (2) in patients having psoriasis (PSO) or inflammatory bowel disease (IBD). A survey was developed and sent out to GPs and patients in various regions of the Netherlands and included questions about recognition of inflammatory symptoms and SpA specific features. The patient survey focused on the presence of musculoskeletal complaints and the awareness of developing SpA.

Results. 312 of the 949 GPs returned the survey (response rate 32.9%), with 185 GPs having completed the survey. With regard to the recognition of signs of inflammatory pain, especially classic symptoms like morning stiffness and pain relieve by NSAIDs were recognized, whereas other symptoms like pain improvement with exercise were poorly recognized. Of all patient at risk 42.6% were aware of the possibility of developing SpA, this was 43.1% in PSO and 41.9% in IBD patients.

Conclusions. Overall, recognition of inflammatory disease by GPs is suboptimal, with about 50% recognizing less than half of the features known to be indicative of inflammatory joint or back pain. In addition, less than half of the patients with PSO or IBD are aware of the possibility of developing SpA. The recognition of SpA in primary care both by patients and GPs needs improvement in order to facilitate the necessary referrals to rheumatologists.

Introduction

Musculoskeletal complaints (MSC) are very common in the general population and account for about 20% of consultations in primary care.[1,2] A part of these MSC could be caused by inflammatory rheumatic diseases (IRD) like rheumatoid arthritis (RA) and spondyloarthritis (SpA), which are the most common IRD with prevalences of 0.4-1.3% and 0.2-1.6% respectively.[3,4] As in RA, effective treatment for SpA is available as is the evidence that treatment should be initiated as early as possible.[5,6] Short disease duration before starting treatment leads to better treatment response with its consequences for daily life.[7,8]

Initiating treatment early requires early diagnosing of SpA. To aid early diagnosing, both physicians and patients at risk (psoriasis (PSO) or inflammatory bowel disease (IBD)) play an important role. For rheumatologists, a lot of effort has been put into reducing the diagnostic delay by developing internationally accepted diagnostic algorithms for SpA that will help the rheumatologist to diagnose these diseases in an early phase of the disease.[9-11] Moreover in several countries early arthritis clinics were set up, providing early access to specialized rheumatology care for patients with arthritis.[12,13] However, to optimize early referral to these clinics, recognition of IRD by the physicians who refer is a must. In countries with a primary care healthcare system, like the Netherlands, GPs will refer to secondary care. Since a single test for screening on rheumatic diseases does not exist, GPs have to distinguish inflammatory from non-inflammatory musculoskeletal disease based on their own skills. In addition, another factor to decrease diagnostic delay are the patients themselves. Several studies have been performed concerning patient delay in RA, which show that symptom interpretation was a key factor in seeking help at the onset of RA.[14-16] By educating patients at risk, patients could be informed to consult a GP when they experience MSC. Where internationally campaigns for rheumatoid arthritis increased the awareness in both GPs and patients, the focus of SpA lags behind.[17,18]

The aim of this survey was (1) to assess the current practice of GPs with regard to their ability to identify inflammatory signs and symptoms suggestive of SpA and (2) to assess whether patients at risk for SpA (i.e. patients with PSO or IBD) are aware of the risk of developing SpA.

Materials & Methods

General Practitioners

A survey was sent out to GPs from various regions in the Netherlands (city and surroundings of The Hague, Gouda, Dordrecht, Breda, Tilburg and Den Bosch) in the Netherlands, selected out of a central database containing approximately 10 000 GPS.

GPs received the survey by mail, including an accompanying letter asking the GPs for ten minutes of their time to complete the survey. In addition, the survey was handed out during several plenary training sessions for GPs organized by different hospitals. Approximately two weeks after receiving the survey either during a training or by mail, GP practices were called by medical students to remind them of the survey. Besides these reminders, the survey was sent again to all GPs who had not responded to the survey within a month.

Patients

GPs were recruited (either via the GP-survey of directly by personal letter) to invite their patients with PSO or IBD to participate in this study. Subsequently these patients were selected out of GP databases based on ICPC coding (S91 for PSO and D94 for IBD). In the Netherlands, the ICPC is the standard for coding and classification of signs and symptoms in general practice.[19] Patients between 18 and 55 years of age were invited to participate by an invitation letter including a reply slip. The maximum age was set at 55 years in an attempt to prevent including a lot of osteoarthritis patients.

Patients willing to participate returned their reply slip and received the set of questionnaires to complete either via a specially developed electronic system or on paper if preferred.

Besides the recruitment via GPs, we also contact patient organizations. The "Crohn en Colitis Ulcerosa Vereniging Nederland (CCUVN)" included information about our study with an invitation to participate in their newsletter which was sent out to 5400 patients with IBD via e-mail. The "Psoriasis Vereniging Nederland (PVN)", placed an advertisement on their website and sent out our invitation letter as an attachment to their two-monthly magazine (target population 4500 psoriasis patients).

This study was exempted from medical ethical approval by the medical ethical committee of the Erasmus University Medical Centre as patients only had to complete a set of questionnaires (MEC-2014-269). All patients signed the reply slip when they agreed to participate.

GP Survey

We developed a survey partly based on a study by Jois et al that assessed the current practice of GPs.[20] This study focused on the recognition of inflammatory back pain as a symptom of ankylosing spondylitis. Since we were interested in the ability of GPs to recognize signs and symptoms of the total group of axial and peripheral SpA, we added some extra questions. After setting up the survey, it was discussed in a group of rheumatologists and researchers from the rheumatology department to make sure that the included questions were clearly stated.

The final survey included questions about the recognition of signs and symptoms that indicate inflammatory peripheral as well as axial manifestations. We also included questions about the

importance and assessment of certain diagnostic tests like HLA-B27, rheumatoid factor (RF) and anti-citrullinated protein antibody(ACPA). The importance was measured on a scale from 0 to 10 where 0 meant "not important at all" and 10 meant "very important". For the assessment, GPs were asked when they would decide to use these diagnostic tests. We asked about knowledge of associated SpA features (like PSO, IBD, uveitis, enthesitis and dactylitis), familiarity with the term SpA if GPs educate their patients at risk for SpA (e.g. patients with PSO, IBD and uveitis).

Patient Questionnaires

The set of questionnaires included questions about demographics, characteristics of their disease (PSO or IBD) and the presence of MSC (joint, tendon or back). Patients were asked if they were aware of the possibility of developing a rheumatic condition and if so, how they became aware.

Statistical Analysis

Descriptive statistics were used to describe participant characteristics and survey outcomes in STATA 14. Statistically significant differences for baseline characteristics and patients' awareness between patients recruited via the GP or via the patient organization were tested with the t-test or Chi square test, where appropriate. A p-value below 0.05 was considered as statistically signicant.

Results

General Practitioners

After sending out the survey to 1019 GPs, it turned out that 70 GPs were no longer working in the practice, either because they were GPs in training and had moved on or because the GP retired. In total, 312 of the 949 GPs responded (32.9%). Of these, 127 GPs indicated that they did not want to participate in the survey, mostly because they found it too time consuming. The remaining 185 GPs (19.5%) completed the survey.

The responding GPs had a mean age of 47.2 years (SD 10.3 years) and 48.1% were male. Mean time working as a GP was 16.0 years (SD 10.6 years). Forty percent of the GPs indicated to be working fulltime and 40% indicated to supervise GPs in training in their practice.

Knowledge of Spondyloarthritis

Almost all GPs (97.2%) indicated to be familiar with the term spondyloarthritis. However, the majority associated SpA with ankylosing spondylitis (90.9%) and sacroiliitis (53.1%). More than half of the GPs (55.4%) associated SpA solely with these axial manifestations. Up to one third of the GPs associated the term SpA with psoriatic arthritis (24.0%) and Inflammatory Bowel Disease (34.3%). GPs associated

SpA less with SpA features such as uveitis (13.1%), dactylitis (4.0%) and enthesitis (5.1%). Interestingly, 14.9% of GPs thought SpA is associated with rheumatoid arthritis.

Signs, symptoms and blood tests

With regard to the signs and symptoms GPs associate with inflammatory joint pain, morning stiffness lasting for longer than 30 minutes and pain relieve by NSAIDs were recognized by the majority of GPs (Table 1). This was similar for inflammatory back pain.

If we look at the knowledge of specific criteria of inflammatory joint pain, 57.3% of GPs knew less than half of all 6 criteria. For inflammatory back pain this was 39.4%. For both inflammatory joint and back pain, only 4 GPs (2.2%) were able to indicate all six respectively eight features.

Table 1 Proportion of GPs who identified correct signs of inflammatory joint and back pain (n=185)

Signs of inflammatory pain	Joint	Back
Insidious onset of complaints, n (%)	53 (28.7)	90 (48.7)
Symptom duration>3 months, n (%)	57 (30.8)	93 (50.3)
Pain improved with exercise, n (%)	25 (13.5)	39 (21.1)
Pain not relieved by rest, n (%)	30 (16.2)	40 (21.6)
Pain relieved by NSAIDs, n (%)	162 (87.6)	152 (82.2)
Morning Stiffness>30min, n (%)	142 (76.8)	139 (75.1)
Nocturnal Pain, n (%)	Not Applicable	145 (78.4)
Alternating Buttock Pain, n (%)	Not Applicable	38 (20.5)

With regard to importance of determining rheumatoid factor, GPs valued this with a mean score of 5.2 (SD2.2), for ACPA the mean score was 5.7 (SD 2.0) and for HLA-B27 it was 6.5 (SD 2.2). Reasons to check rheumatoid factor status, ACPA status or HLA-B27 status are summarized in table 2. Rheumatoid factor is most often checked in patients who often return with complaints, while ACPA is most often checked in patients with inflammatory complaints. About one third of GPs indicated to check HLA-B27 in patients with inflammatory complaints, while 44.3% indicated to never check HLA-B27 status in their patients (Table 2).

Table 2 Reasons to check rheumatoid factor, ACPA and HLA-B27 status

	Rheumatoid Factor	ACPA	HLA-B27
Every patient with complaints, n (%)	1 (0.54)	0	1 (0.54)
Patients who often return with complaints, n (%)	103 (55.7)	94 (50.8)	20 (10.8)
Patients with inflammatory complaints, n (%)	90 (48.7)	104 (56.2)	64 (34.6)
Patients with a positive family history, n (%)	51 (27.6)	48 (26.0)	20 (10.8)
Never, n (%)	28 (15.1)	22 (11.9)	82 (44.3)
I don't know what it is, n (%)	0	4 (2.2)	5 (2.7)

Associated SpA Features

When a patient presents with inflammatory joint or back pain, most GPs indicated to ask for the SpA features psoriasis, inflammatory bowel disease and uveitis, whereas enthesitis and dactylitis are not often asked for (Table 3).

Table 3 Proportion of GPs who ask about associated SpA features when a patient presents with inflammatory joint or back pain (n=185)

Associated SpA Features	
Psoriasis, n (%)	155 (83.8)
Inflammatory Bowel Disease, n (%)	134 (72.4)
Enthesitis, n (%)	35 (18.9)
Dactylitis, n (%)	35 (18.9)
Uveitis, n (%)	116 (62.7)
Urinary tract or gut infection in preceding month, n (%)	72 (38.9)

Education of patients at risk for SpA

With regard to educating patients with psoriasis or inflammatory bowel disease about their increased risk of developing SpA, only 3.3% of GPs indicated to always educate these patients. Twenty-nine GPs (15.9%) indicated to never educate their patients about this increased risk and 37.4% educate less than half of their patients at risk.

Patient Survey

Psoriasis

In total, 1220 PSO patients between 18-55 years of age were selected out of 81 GP databases, of which 606 patients responded. Of the responders, 461 were willing to participate. Reasons not to participate were mainly not having PSO (n=79) or lack of interest (n=51). Via the patient organization, 203 patients responded, of which 177 agreed to participate.

Of the in total 638 patients who agreed to participate, 552 (86.5%) completed the questionnaires. The mean age of the participating PSO patients was 45.2 (SD 8.5) years with 46.7% being male. Mean time suffering from PSO was 19.0 (SD 12.0) years with 71.4% currently treated by their GP. Patients from

the patient organization were significantly older (46.5 vs 44.7 years), suffering significantly longer from PSO (16.5 vs 24.4 years) and significantly more often treated by a dermatologist.

With regard to awareness, 238 patients (43.1%) indicated to be aware of the possibility of developing a rheumatic condition already before the study-invitation, with more than one third having gained this knowledge themselves (Table 4). Patients participating via the patient organisation were significantly more aware than patients selected via the GP ($p<0.01$).

Inflammatory Bowel Disease

For IBD, 535 patients aged 18-55 years were selected out of 81 GP databases, of which 316 responded. Of the responders 273 were willing to participate. Reasons not to participate were mainly not having IBD (n=22) and not interested (n=15). Via the patient organization 116 patients agreed to participate, leading to a total of 432 patients willing to participle. Of these patients, 344 (79.6%) completed the questionnaires. The mean age of these 344 patients was 42.2 (SD 9.4) years with 25.4% being male. Forty-five per cent suffered from ulcerative colitis (UC), 45.6% from Crohn's disease (CD) and in 9.4% the type of IBD was unspecified. Mean time suffering from IBD was 12.3 (SD 9.3) years. The distribution between CD and UC was statistically significantly different for patients recruited via the GP versus the patient organization, with CD patients being more often recruited via the patient organization.

With regard to awareness, 41.9% was aware of the possibility of developing a rheumatic condition before the invitation for the study, with the majority being informed by their medical specialist (Table 4). As with the PSO patients, IBD patients selected via the patient organization were significantly more aware than patients selected via the GPs ($p<0.01$).

Table 4 Level of Awareness in Patients with Psoriasis or IBD

	Psoriasis (n=552)	IBD (n=344)
% Awareness	43.1	41.9
% Informed by GP	13.5	1.4
% Informed by medical specialist	24.4	40.3
% Via family and friends	18.5	9.7
% By information gathering	34.0	39.6
% Patient organization	8.4	2.8
% Other	1.3	6.3

Discussion

This survey among GPs and patients at risk for SpA in the Netherlands demonstrates that the knowledge and awareness of patients for axial and peripheral SpA could be improved. Almost 60% of GPs did not recognize half of the features indicative of inflammatory peripheral joint disease, for

inflammatory axial disease this percentage is slightly lower but still 40%. More than half of the GPs associated SpA this solely with the axial manifestations and especially dactylitis and enthesitis were poorly recognized. These SpA features were also not often asked for in patients presenting with inflammatory musculoskeletal symptoms. Besides, the majority of GPs indicated to never or seldom educate their patients at risk for SpA (e.g. patients with psoriasis or IBD). From the patient perspective, less than half of the patients with PSO or IBD are aware of the possibility of developing a rheumatic condition. If patients are aware, the majority of them gained this knowledge by themselves and were not informed by a medical professional.

IRD is difficult to diagnose for GPs. Although the estimated prevalence of RA and SPA is around 2%, for the individual GP this prevalence is fairly low and therefore most GPs have little experience in clinically evaluating IRD. A recent study from Newsum et al used electronical medical records from GPs to assess how they identify peripheral arthritis.[21] They showed that GPs often evaluate the classical symptoms of arthritis; pain, swelling, warmth, redness and loss of function, while rheumatologists work with the inflammatory features as mentioned in this paper. In about 20% morning stiffness and family history were reported, while about 75% of GPs from this survey said they ask for morning stiffness

Regarding the inflammatory back pain, we show low knowledge of the criteria for inflammatory axial disease. This is in line with Van Onna et al who showed insufficient knowledge about axial SpA in a qualitative study in primary care in the Netherlands by interviewing GPs.[22] The results of our study are slightly different from the results of the survey in the United Kingdom, where 17% of GPs was unable to recognize more than half of the features.[20] This difference could be explained by the fact that the study from the UK is eight years old and awareness might have improved over the last couple of years. With regard to symptoms indicative of inflammatory axial disease, morning stiffness lasting longer than 30 minutes and pain relieve by NSAIDs were among the most frequent recognized features in their survey as well. Recently, a similar survey about inflammatory back pain and axial SpA was performed among secondary care specialists in the UK. The recognition of IBP seems slightly better with 28% recognizing all 8 features and only 7% recognizing less than 4 features.[23]

When interpreting the results of this study, certain strengths and limitations should be taken into account. We received a completed survey from a fairly large number of GPs representing different regions in het Netherlands. We also aimed to make the survey as complete as possible by including questions about both peripheral and axial joint manifestations. We think a survey is an adequate way to assess the current practice of GPs as it is possible to reach a large amount of GPs. Unfortunately our response rate was quite low at 32.9%. Ideally we would have liked to achieve a higher response

rate, but we were not able to achieve this despite the fact that we used several evidence-based recommendations to increase response, like personal letters, postal reminders and called all GPs to remind them of the survey.[24,25] However, despite the fact that the response rate was quite low, the participating GPs are an accurate reflection of the total GP population in the Netherlands.[26] For the patient part, we achieved a large sample of patients with PSO and IBD and to the best of our knowledge not much is known about awareness in patients at risk for SpA. A possible limitation is that a lot of patients who participated were suffering from MSC. One could say that these patients would be more aware since they have complaints and might already have been looking for possible causes.

Over the last years it has been tried to increase awareness for diseases in general but especially for rheumatic diseases via guidelines and education of GPs. The Dutch College of General Practitioners (NHG) has set up a guideline for arthritis, supporting GPs in the workup of patients with inflammatory joint complaints.[27] With regard to education, despite the fact that only a small selected group of GPs can be reached this way, education does seem to improve referral of patients suspected of having SpA.[28-30] However, guidelines and education alone does not seem to be sufficient. Two reviews, of which one was specifically aimed at inflammatory arthritis, showed that referral from primary to secondary care could also be improved via the use of self-administered questionnaires, referral sheets or triage by a specialist in a primary care setting.[29,30]

With regard to patient awareness, we show that this should also be improved since less than half of the patients at risk are aware and the majority of GPs indicated to never or seldom educate their patients. To increase this awareness in patients at risk and thereby reducing patient delay, several options have been studied, for example community case finding strategies, public awareness programs and internet and website information.[30,31] As the Netherlands has a very extensive primary health care system, GPs themselves should also be involved in patient education.

In conclusion, the knowledge and awareness of GPs with regard to distinguishing non-inflammatory symptoms from inflammatory rheumatic disease should be improved in order to facilitate early diagnosis and treatment. More research is necessary to analyse the impact of adequate referral strategies like referral sheets or triage by a rheumatologist in a primary care setting. Educating patients at risk could also be an important factor in enhancing early recognition, as at the moment less than half of the patients at risk is aware of the possibility of developing SpA. Furthermore, the result of this survey can be used by rheumatologists for optimizing their education programs in for both colleagues and patients at risk on SpA.

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Chapter 7.

Performance of Screeningtools for Psoriatic Arthritis: A Cross-sectional study in Primary Care

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Abstract

Objective. To compare the screening performance of the PEST, PASE & EARP questionnaires for detecting psoriatic arthritis (PsA) among psoriasis patients in a primary care setting.

Methods. In a cross-sectional study, 473 primary care psoriasis patients at risk for PsA completed the PEST, PASE & EARP questionnaires and were clinically evaluated by a trained research nurse. A PsA case was defined by a rheumatologist according to the CASPAR criteria. Sensitivity and specificity were determined for the PEST and EARP cut-offs (≥3) and the PASE cut-offs (≥44 and ≥47).

Results. PsA was diagnosed in 53 patients. The PEST had a sensitivity of 0.68 and a specificity of 0.71. The PASE was validated for two different cut-offs. The cut-off of 47 led to a sensitivity of 0.59 and a specificity of 0.66, whereas the lower cut-off of 44 led to a sensitivity of 0.66 and a specificity of 0.57. For the EARP and we found a sensitivity of 0.87 with a specificity of 0.34.

Conclusions. The PEST questionnaire has the most favourable trade-off between sensitivity and specificity to screen for PsA. However, as the prevalence of psoriasis and PsA is fairly low in primary care, screening only psoriasis patients with musculoskeletal complaints may be a better allocation of resources.

Introduction

Psoriatic arthritis (PsA) is an inflammatory joint disease, associated with psoriasis.[1] Increasing evidence suggests that diagnosing PsA early and subsequently provide early treatment, improves patients' outcomes substantially.[2-5] Since in the majority of cases the symptoms of the skin precede the musculoskeletal symptoms, an opportunity for screening arises.[6] Physicians who treat patients with psoriasis, like general practitioners (GPs) and dermatologists, should pay attention to these musculoskeletal symptoms, as timely referral to a rheumatologist can assure early diagnosis and adequate treatment.

To enhance early recognition by dermatologists and GPs several screening questionnaires were developed, like the PEST, PASE and EARP.[7-9] These were mostly developed in secondary care and until now four different validation studies have been published, also mostly in secondary care.[10-13] However, in many western countries including the Netherlands the majority of patients remain under care of their GP. Screening in a primary care setting may therefore be very useful.

The primary objective of this study was to compare the screening performance of the validated PEST, PASE & EARP questionnaires in detecting PsA among primary care psoriasis patients.

Methods

Patients

Between June 2013 and March 2014 a large cross-sectional study in primary care was performed. Ninety-seven GPs from the greater Rotterdam area were willing to participate, with an average patient population of 1600 patients aged 18 years and over per GP. Participating GPs selected their psoriasis patients aged 18 years and over using ICPC code S91 (International Classification of Primary Care code for psoriasis).[14] The ICPC is widely used for coding signs and symptoms in primary care in the Netherlands. All identified psoriasis patients received an invitation from their GP asking them to participate in our study. If patients were willing to participate they were called by a trained interviewer to verify the ever presence of musculoskeletal complaints (either joints, tendons or lower back). The interviewer also verified whether they had a diagnosis of psoriasis and sufficient knowledge of the Dutch language to complete the questionnaires. For the purpose of screening we only included patients who were at risk for the target disorder (PsA), so patients with an established diagnosis of PsA were excluded. All patients fulfilling the inclusion criteria during the telephone interview were invited for clinical evaluation. Ethics approval from the Dutch Medical Ethical Committee (M12-1275) was obtained as well as written informed consent from all participating patients. Detailed information on methodology and inclusion is written in our recently published paper.[15]

Data collection

Screeningtools

Patients were asked to complete a set of questionnaires just before clinical evaluation. Three screening questionnaires were completed; PEST (Psoriasis Epidemiology Screening Tool), PASE (Psoriatic Arthritis Screening & Evaluation) & EARP (Early Arthritis for Psoriatic Patients Questionnaire).[7-9] In brief, PEST consists of five yes/no questions and was developed in the UK in a primary care setting. It is considered positive if three or more questions are answered positively. In addition, a manikin is included on which patients can tick off stiff, swollen or painful joints.[8] It has been validated multiple times in secondary care and its sensitivity ranges from 0.28 to 0.77 while its specificity ranges from 0.37 to 0.98.[10-13]

PASE was developed in the USA and consists of 15 questions with a 5-point answer scale (from strongly disagree to strongly agree). The cut-off was set at 47 in the development, but in the first validation by the same group a cut-off value of 44 provided better sensitivity and specificity.[7,16] This questionnaire has been validated in different studies and for its developmental cut-off of 47 the sensitivity ranges from 0.24 to 0.75 and the specificity from 0.39 to 0.94.[3,10,13] Looking at the cut-off of 44, the sensitivity increases towards 0.76-0.91, whereas the specificity remains in the same range with 0.41-0.67.[9,13]

EARP is one of the more recently developed screening tools and was developed in Italy in 2012. It consists of 10 yes/no questions with a cut-off value of 3 or higher to be considered positive.[9] This questionnaire has not been validated yet.

The PEST and PASE questionnaire were available in Dutch translation, while the EARP was translated by the research team before the start of the study.

Clinical Evaluation

All patients who reported MSC during the telephone interview were clinically evaluated by a trained research assistant, blinded for the outcomes of the questionnaires. A detailed history was completed, focusing on psoriasis, musculoskeletal complaints and other factors like family history and comorbidities. Physical examination focused on the skin, nails, joints and entheses. Psoriasis severity was assessed by the PASI score. The nails were visually inspected and in case of abnormalities a photograph was taken which later on was evaluated for the presence of nail psoriasis by a dermatologist. The joints were evaluated for tenderness and swelling using the 66/68 joint count. For the evaluation of the entheses, the LEI and MASES scores were used. These scores are based on tenderness upon manual palpation. If clinical evaluation resulted in at least one tender enthesis,

patients were referred for an ultrasonographic examination by an independent trained examiner using Esaote Mylab60 (probe LA 435). US enthesitis was defined as the presence of power Doppler (PD) signal (<2mm of the bony cortex) or in case of the plantar fascia an increased thickness of the enthesis (>4.4mm) as PD signal could not be obtained at the plantar fascia

Case definition

The diagnosis of PsA was based on the CASPAR criteria[17], where patients must have inflammatory articular disease in the joints, spine or entheses. On top of this, at least 3 out of the following 6 points are required: the presence of psoriasis (current (2 points) or history), presence of psoriatic nail dystrophy, absence of rheumatoid factor, dactylitis (diagnosed by rheumatologist) and radiographic evidence of juxtaarticular new bone formation. The presence of peripheral arthritis and axial disease were confirmed by a rheumatologist. Since there is no commonly accepted clinical definition for enthesitis, we decided to use a combination of clinical characteristics and positive Power Doppler signal at the enthesis (<2mm of the bony cortex).

Statistical Analysis

Descriptive statistics were used to describe the patient characteristics. Sensitivity and specificity were calculated using the diagti command in STATA 14.

Results

Study participants

For this analysis we had 473 psoriasis patients with MSC at risk for PsA available. The mean age of the 473 evaluated patients was 55.7 years (SD 13.9) and 51.0% were male (Table 1). Mean psoriasis duration was 20.7±16.2 years, with 73.2% of the psoriasis diagnoses confirmed by a dermatologist. The remaining 26.9% of psoriasis cases were confirmed by the GP. At clinical evaluation 71 patients (15.0%) had nail abnormalities consistent with psoriatic nail dystrophy. Median PASI score in the study population was 2.3 (IQR 1-4).

Table 1 Characteristics of 473 psoriasis patients with musculoskeletal complaints screened for PsA

	Psoriasis without PsA (n=420)	Axial manifestations or Peripheral Arthritis* (n=17)	Enthesitis** (n=36)
Mean Age, years (±SD)	**55.9 (14.0)**	**47.4 (10.7)**	**58 (12.3)**
Male sex, n (%)	216 (51.4)	8 (47.1)	17 (47.2)
Body Mass Index, mean (±SD)	27.8 (4.8)	27.9 (6.2)	30.0 (4.1)
Median Psoriasis Symptom Duration, years (IQR)	15 (8-30)	15 (4-30)	20 (11-37)
Psoriasis Diagnosis by Dermatologist, n (%)	302 (71.9)	13 (76.5)	31 (86.1)
Nail psoriasis, n (%)	64 (15.2)	5 (29.4)	2 (5.6)
PASI, median (IQR)	2.2 (1-4)	3 (1.3-4)	3.1 (1.7-4.4)
Median MSC Symptom Duration, years (IQR)			
Joints	8 (4-14)	12.5 (2-23)	10 (5-25)
Lower Back	12 (5-25)	18 (9-25)	33 (14-41)
LEI, median (IQR)	0 (0-0)	0 (0-1)	1 (1-2)
MASES, median (IQR)	0 (0-0)	0 (0-3)	2 (0-3)

PsA=Psoriatic Arthritis, PASI=Psoriasis Area&Severity Index, MSC=musculoskeletal complaints, LEI=Leeds Enthesitis Index, MASES= Maastricht Ankylosing Spondylitis Enthesitis Score
*Axial manifestations & arthritis are the patients who were diagnosed as having PsA by the rheumatologist.
**Enthesitis, confirmed by ultrasound, are the patients who would have a diagnosis of PsA based on the CASPAR criteria

Performance of screeningtools

53 out of 473 patients fulfilled our case definition of inflammatory joint disease for which we evaluated the three screeningtools. The PEST questionnaire was completed by all 473 patients. The sensitivity was 0.68 (95% CI 0.54-0.80) and the specificity was 0.71 (95% CI 0.67-0.76). The PASE questionnaire was completed by 461 patients, 12 patients did not complete this questionnaire. For the original cut-off value of 47 the sensitivity was 0.59 (95% CI 0.44-0.72) and the specificity 0.66 (95% CI 0.61-0.71). When using the cut-off value of 44 the sensitivity increased towards 0.66 (95% CI 0.52-0.79) whereas the specificity dropped to 0.57 (95% CI 0.52-0.62). The EARP questionnaire was complete by 465 patients, 8 patients did not complete this questionnaire. The sensitivity was 0.87 (95% CI 0.75-0.95) and the specificity 0.34 (95% CI 0.30-0.39) (Table 2).

Table 2 Sensitivity and specificity of PEST, PASE & EARP

	AUC	Cut-off	True Positive	False positive	True negative	False negative	Sensitivity	Specificity
PEST	0.71	≥ 3	36	120	300	17	0.68 0.54-0.80	0.71 0.67-0.76
PASE	0.64	≥47	31	139	269	22	0.59 0.44-0.72	0.66 0.61-0.71
		≥44	35	176	232	18	0.66 0.52-0.79	0.57 0.52-0.62
EARP	0.68	≥ 3	46	273	139	7	0.87 0.75-0.95	0.34 0.30-0.39

The sensitivity and specificity were calculated separately for enthesitis and axial or peripheral manifestations of PsA. These results were very similar and can be found in supplemental file S1. When only selecting patients without systemic therapy for their psoriasis (5 methotrexate, 4 ciclosporin, 4 etanercept & 5 adalumimab), the sensitivity increased slightly with approximately 0.02 while the specificity remained more or less the same (see supplemental file S1).

With regard to false negatives, i.e. the patients with PsA who are missed when using these screeningtools, 60% of axial manifestations were missed by the PEST (Table 3). For peripheral arthritis only 16.7% was missed by the PEST, while for enthesitis 33.3% of the cases were missed. For the PASE one third of the peripheral arthritis was missed, independent of the cut-off value, while 36.1% and 44.4% of enthesitis was missed when using the cut-off values of respectively 44 and 47. Axial manifestations were missed in 20% when using the cut-off value of 44 and in 40% then using the cut-off value of 47. EARP missed 16.7% of the peripheral arthritis, 11.1% of the enthesitis and 20% of axial manifestations.

Table 3 Number of Missed Cases per Questionnaire per Manifestation of PsA

	PEST n (%)	PASE44 n (%)	PASE47 n (%)	EARP n (%)
Peripheral Arthritis (n=12)	2 (16.7)	4 (33.3)	4 (33.3)	2 (16.7)
Enthesitis (n=36)	12 (33.3)	13 (36.1)	16 (44.4)	4 (11.1)
Axial Manifestations (n=5)	3 (60)	1 (20)	2 (40)	1 (20)

Influence of prevalence

Improving early recognition of PsA in primary and secondary care is challenging. Given the different performance of the screeningtools, the question what would be best to do in clinical practice

is often asked. To answer this question one has to consider the performance of the tools but also the harm and benefit of the decision after screening and the prior probability of having the disease. Interpreting these factors together creates relevant information to make an informed decision whether or not to implement a certain screeningtool in primary care or dermatological care. The ideal scenario for the performance would be to have perfect sensitivity and specificity so both patients and non-patients receive optimal care. Unfortunately, perfect tests are often not available in practice, so one has to trade off sensitivity against specificity or vice versa. The choice in this trade-off directly relates to the subsequent clinical decision, in our case referral to the rheumatologist. One could argue that the EARP would be the best screeningtool to use, because of its high sensitivity (0.87), where only a few patients would be missed. However, when choosing for the EARP, this would also result in about 70% false positive patients because of the low specificity. This becomes especially relevant if the prior probability, here the prevalence of psoriasis and the prevalence of psoriatic arthritis, is low. If the prevalence of PsA is low, say 3 per 100 patients as found in our primary care sample[15], 70% of the 97 non-PsA patients will be identified as potential PsA and referred to the rheumatologist. This means that the rheumatologist will have to see 26 psoriasis patients in order to find one patient with PsA, maybe not the best way to use scarce outpatient clinic time. We believe the PEST fits the trade-off between sensitivity and specificity best, although this still means that a rheumatologist has to see 15 patients to find one true PsA as the prevalence we found was 3.2% (increasing towards 7.0%, depending on how we dealt with the non-responders).[15] If the prevalence of PsA is moderate, say 30 per 100 patients in dermatological care, the same test will lead to 20 detected PsA cases and 20 false positive cases. In this case one in every two referred patients actually has PsA. A graph of the influence of various prevalences on the posterior probability of having PsA, when using different tests can be found in supplemental file S2.

Discussion

In this large primary care based study among psoriasis patients we validated three of the existing screening questionnaires for PsA. The PEST had the best performance with a sensitivity of 0.68 (i.e. 68% of the PsA cases were identified) and a specificity of 0.71 (i.e. 29% was falsely identified as PsA). The PASE performed slightly worse with a sensitivity of 0.59 for the cut-off of 47 and 0.66 for the cut-off of 44. The specificity for the PASE cut-off of 47 was 0.66 and 0.57 for the cut-off of 44. The EARP has not been validated before and while the sensitivity we found (0.87) is comparable to the sensitivity in the development study (0.85), the specificity was considerably lower with 0.34 (vs 0.92 in development study).[9]

As we did one of the first validations in primary care, it is interesting to put this in perspective with studies that have validated the tools in secondary care. Three out of four studies showed sensitivity of 0.63-0.91[10,12,13], while one study among psoriasis patients with and without musculoskeletal pain resulted in sensitivity of 0.24-0.28[11]. Specificity varied from 0.37-0.80 in the same three studies while 0.94-0.98 was found in the other study. Why these strong differences occurred is unclear, but it may have to do with patient selection and/or case definition. Recently, the CONTEST group developed a new screeningtool based on the best performing items of several individual screeningtools for PsA using data from secondary care.[18] Recently it was validated and compared with the PEST in a primary care setting. Compared to our study, they found slightly lower sensitivity and specificity for the PEST in their cohort.

With a prevalence of PsA in the range of 3-7% implementing a screeningtool for all psoriasis patients seems a big effort to identify approximately one PsA patient per GP at a given moment. Another option could be to screen patients only if they suffer from musculoskeletal complaints. The prevalence of PsA increased in our study than towards 9.8%, which would lead to approximately three PsA patients per practice. Adding the PEST in this situation, would increase the probability of having PsA after a positive PEST screening tool towards 20% (see supplemental file S2).

Besides implementing a screening tool, raising awareness among both patients with psoriasis and GPs could also aid early recognition. On the one hand, one could think about making patients themselves more aware of their risk at developing PsA, this could be achieved by setting up campaigns involving for example psoriasis patients organisations. One could also think about educating GPs by local rheumatologists, this seems to be an effective way to enhance adequate referral from primary to secondary care for early referral of any inflammatory arthritis including PsA.[19]

Certain strengths and limitations should be taken into account when interpreting the results of this study. One of the strengths of our study is that it is one of the first validations of the screening tools in primary care. Most developments (except PEST) and validations have been performed in secondary care. Secondly, our study is the first validation of the EARP questionnaire and we have a fairly large and complete database of psoriasis patients at risk for PsA. With regard to limitations, we only included patients with musculoskeletal complaints in this study. This implicates that the specificity figures we found are probably an underestimation if interpreted for a cross section of the psoriasis patient spectrum.

In conclusion, in our primary care based study the PEST questionnaire has the most favourable trade-off between sensitivity and specificity to screen for PsA. However, as the prevalence of both psoriasis and PsA is fairly low in our primary care setting, screening only patients suffering from

musculoskeletal complaints instead of all patients with psoriasis is likely to be a better allocation of resources.

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Supplemental File S1 Sensitivity and specificity of PEST, PASE & EARP according to type of psoriatic arthritis (Axial, Peripheral Arthritis or Enthesitis)

Table S2.1S Performance of Screeningtools in non-DMARD-users

	Cut off	True Positive	False positive	True negative	False negative	Sensitivity	Specificity
PEST	≥ 3	35	116	288	15	0.70	0.713
						0.554-0.821	0.666-0.757
PASE	≥47	30	135	255	20	0.600	0.654
						0.452-0.736	0.604-0.701
	≥44	34	168	222	16	0.680	0.569
						0.533-0.805	0.518-0.619
EARP	3	44	258	134	5	0.898	0.342
						0.778-0.966	0.295-0.391

Table S2.2 Performance of Screeningtools in patients with articular or axial disease

	Cut off	True Positive	False positive	True negative	False negative	Sensitivity	Specificity
PEST	≥ 3	12	144	312	5	0.71	0.68
						0.44-0.90	0.64-0.73
PASE	≥47	11	159	285	6	0.65	0.64
						0.38-0.86	0.60-0.69
	≥44	12	199	245	12	0.71	0.55
						0.44-0.90	0.50-0.60
EARP	3	14	305	143	3	0.82	0.32
						0.57-0.96	0.28-0.37

Table S2. Performance of Screeningtools in patients with Entheseal Disease

	Cut off	True Positive	False positive	True negative	False negative	Sensitivity	Specificity
PEST	≥ 3	24	132	305	12	0.67	0.70
						0.49-0.81	0.65-0.74
PASE	≥47	20	150	275	16	0.56	0.65
						0.38-0.72	0.60-0.69
	≥44	35	174	231	18	0.64	0.56
						0.46-0.79	0.51-0.61
EARP	3	32	287	142	4	0.89	0.33
						0.74-0.97	0.29-0.38

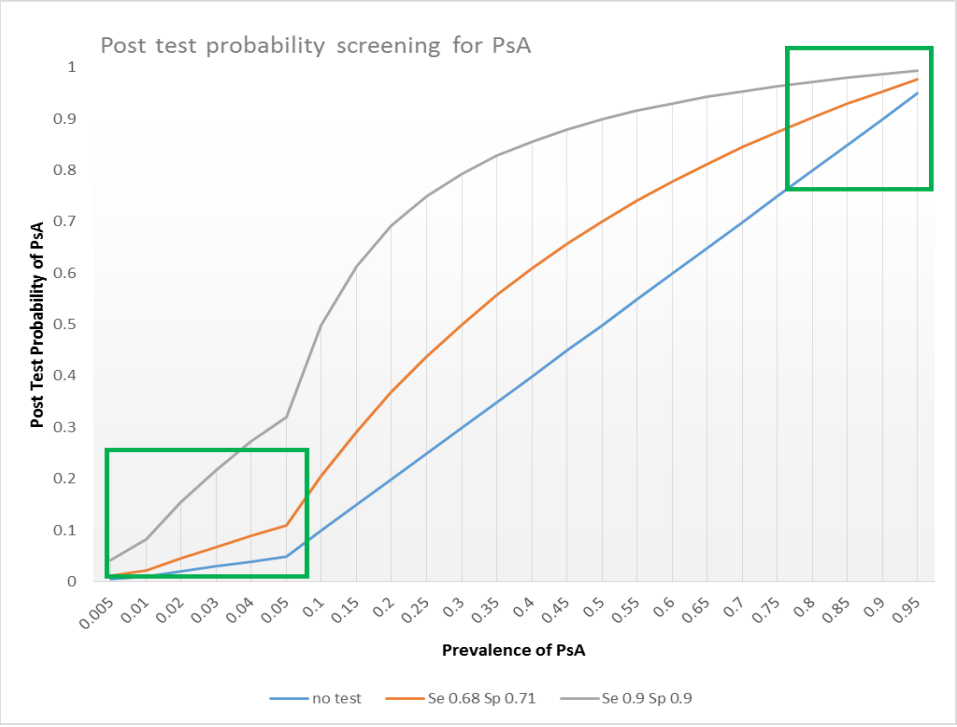
Table S3 Parameter estimates used in the sensitivity analysis for the non-responders (n=891)

	Scenario 1	Scenario 2	Scenario 3
First step:	MSC prevalence among responders (n=1673; 49.2%)	MSC prevalence among those returning the reply slip but did not want to participate (n=704; 23.3%)	MSC prevalence among those returning the reply slip but did not want to participate (n=704; 23.3%)
Second step:	PsA prevalence among MSC (n=823; 9.8%)	PsA prevalence among MSC (n=823; 9.8%)	PsA among those with MSC and clinically evaluated (n=524;13.0%)

Supplemental File S2 Which tool to use, influence of prevalence

Figure 1 illustrates the influence of the PsA prevalence of the population screened on the added value of screening for PsA with the PEST questionnaire.

Fig 1. Influence of Prevalence on the additional value of the PEST



On the X-axis the prevalence of PsA is varied between 0.5 per 100 and 95 per 100 psoriasis patients. On the Y-axis the post-test-probability (i.e. positive predictive value), calculated as odds, is presented combining the prevalence with the sensitivity and specificity (i.e. the positive Likelihood ratio) of a screeningtool. This is in other words the prevalence of PsA after you have a PEST questionnaire with a score of 3 or higher (positive PEST). The blue line indicates the situation in which we would not use any screeningtool. The orange line indicates the situation with the performance of the PEST questionnaire as found in this study. The difference between the blue line and the orange line shows the information gain you have by using the PEST questionnaire. As is shown, the information gain is lower in the low and high prevalent disease than in the prevalence range in between. This suggests that adding a screeningtool in these middle part of the prevalence

distribution does not help very much, unless there are serious consequences from missing a case (i.e. death). The grey line indicates the situation of an almost ‘perfect test’ with a sensitivity and specificity of 0.9. Compared to the difference between blue and orange line, the information gain is substantially higher, as one would expect.

Chapter 8.

Which Tool to use when Screening for Psoriatic Arthritis in Psoriasis Patients in a Primary Care Setting?

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Abstract

Background. Early treatment of PsA can prevent joint damage, but requires early recognition. To aid this, several screening tools have been developed with suboptimal performance. Recently, a new screening tool was developed based on the best performing items of previous screeningtools. The objective of this study was to assess the additional value of this CONTEST questionnaire in psoriasis patient in a primary care setting compared to existing tools.

Methods. Data from the SENSOR study was used, a cross-sectional study in adult primary care psoriasis patients. Sensitivity, specificity and area under the curve (AUC) were calculated for the CONTEST with a cutoff of 4, as well as the CONTEST-w (weighted version, cutoff of 8) and the CONTEST-jt (including the PEST manikin, cutoff of 5). Its performance was compared to the PEST, PASE and EARP.

Results. For this analysis 473 psoriasis patients at risk for PsA were available. The AUC of the CONTEST questionnaires ranged between 0.67-0.69 and sensitivities between 0.30-0.51 in our primary care population, whereas the specificities were between 0.74-0.86. On sensitivity the PEST (0.68), PASE(0.66) and EARP(0.87) performed better than the CONTEST questionnaires, whereas the specificities of the CONTEST were slightly higher than those of the PEST (0.71), PASE (0.57) and EARP (0.34).

Conclusion. The performance of the CONTEST questionnaires in PsA screening did not seem to exceed the performance of the PEST, PASE or EARP in a primary care setting unless you are interested in patients not having the disease

Background

Psoriatic Arthritis (PsA) is a chronic inflammatory rheumatic disease, usually preceded by psoriasis. Adequate treatment is available for PsA and since increasing evidence suggests patients benefit from timely treatment, it is important to recognize these patients early.[1,2] Over the last couple of years several screeningtools were developed in order to enhance this early recognition of patients with PsA. Most of these screeningtools have been validated in several settings.[3-6] Unfortunately, the discriminative properties of these tools are slightly disappointing.

One of the validation studies was the CONTEST study, which was set up in order to perform a head-to-head comparison of three popular screening questionnaires (PEST, PASE & TOPAS) in a secondary care setting.[3] They found lower sensitivities and specificities than previously reported and AUCs around 0.6. However, the prevalence of PsA increased according to the number of positively answered questionnaires. This led them to develop a new screening questionnaire (CONTEST questionnaire), based on the best performing items of the individual questionnaires.[7] Since this is yet another screening tool, the question raises which tool could best be used to screen psoriasis patients for the presence of PsA. Various validations have been performed, but mostly in secondary care settings. However, primary care could also play an important role in screening. The objective of this study was therefore to compare the performance of the newly developed CONTEST questionnaires with the existing ones in a primary care setting.

Methods

Patients

Between June 2013 and March 2014 a cross-sectional study in primary care was performed, the SENSOR study. Ninety-seven GPs from the greater Rotterdam area participated and selected their adult psoriasis patients using ICPC code S91 (International Classification of Primary Care code for psoriasis).[8] All identified psoriasis patients received an invitation from their GP asking them to participate in the study. If patients were willing to participate they were contacted by telephone by a trained interviewer to verify the presence of musculoskeletal complaints (either joints, tendons or lower back). The interviewer also verified whether they were diagnosed with psoriasis and sufficient knowledge of the Dutch language to complete the questionnaires. Ethics approval from the Dutch Medical Ethical Committee (M12-1275) was obtained as well as written informed consent from all participating patients. Extensive information about the patient selection in the SENSOR study is available in our previously published paper.[9]

Clinical Evaluation

All patients with any type of musculoskeletal complaints (MSC) were invited for clinical evaluation by a trained research nurse. Beforehand, all patients completed a set of questionnaires including the screening questionnaires PEST, PASE & EARP. During clinical evaluation a detailed history was taken as well as a physical examination of skin, nails, joints, entheses and spine. The nails were visually inspected and in cases of abnormalities a photograph was taken for further evaluation of nail psoriasis by a trained dermatologist. Entheses were assessed with the LEI and MASES scores, which are based on tenderness upon manual palpation. If one or more entheses were tender during clinical evaluation, the patient was referred for ultrasonographic evaluation by an independent trained examiner using Esaote Mylab60 (probe LA 435).

Case Definition

The diagnosis of PsA was made based on the CASPAR criteria.[10] To fulfill these criteria a patient must have inflammatory articular disease in the joints, spine or entheses. In addition, at least 3 out of the following 6 points are required: the presence of psoriasis (current (2 points) or history), presence of psoriatic nail dystrophy, absence of rheumatoid factor, dactylitis (diagnosed by rheumatologist) or radiographic evidence of juxtaarticular new bone formation. The presence of peripheral arthritis and axial disease were confirmed by a rheumatologist. Since no commonly accepted clinical definition for enthesitis is available, we decided to use a combination of clinical characteristics and positive Power Doppler signal (<2mm of the bony cortex) at the same enthesis to diagnose enthesitis.[11]

CONTEST questionnaires

In the initial study, a new questionnaire was developed via three different methods, namely the CONTEST (addition of questions), the CONTEST-w (weighted version using logistic regression) and the CONTEST-jt (adding a manikin).[7] The questionnaires consisted of the best performing items of the individual screeningtools PEST, PASE and ToPAS. The CONTEST consists of eight questions and the total score is the sum of all individual positively answered questions (range 0-8), the cut off for a positive questionnaire was set at four in the development cohort. The CONTEST-w consists of the same eight items, but item PEST4 ('have you had pain in your heel?') weighted as two and item TOPAS2A (in our dataset PEST3; 'do your fingernails or toenails have holes or pits?') as five. The total score of this weighted version sums up to 13 and the cutoff was set at eight. The third variation was the CONTEST-jt, this version includes the PEST manikin. If a patients has ticked of 6 or more locations on the PEST manikin, one point is added to the total sum. This questionnaire thus has a score range from 0 to 9 and the cutoff was set at five. Table 1 provides an overview of the different versions of the CONTEST questionnaires.

In our dataset the answers to the individual questions of the PEST (Psoriasis Epidemiology Screening Tool)[12] and PASE (Psoriatic Arthritis Screening and Evaluation)[13] were available, but the ToPAS (Toronto Psoriatic Arthritis Screen)[14] was not included in our study. Since three questions from the CONTEST questionnaire originated from the TOPAS, we replaced these items with data we did have available (Table 1). The two items regarding the nail abnormalities were replaced with the question about nails from the PEST and an assessment of nail photographs, the question about neck pain was replaced by data from the PEST manikin. Performance of the individual PEST and PASE screeningtools can be found in our previously published paper.[15]

Table 1 Overview of the different versions of the CONTEST questionnaire, including substitutes used in the SENSOR study

	CONTEST (0-8)	CONTEST-w (0-13)	CONTEST-jt (0-9)	Substitutes in the SENSOR
PEST 4	Have you had pain in your heel?	Weight 2		
PEST 5	Have you had a finger or toe that was completely swollen and painful for no apparent reason?			
PASE 3	My back hurts			
PASE 4	My joints become swollen			
PASE 5	My joints feel "hot"			
TOPAS 2A	Have you ever noticed any of these changes in your fingernails: pits in the nails as shown in Figure 1	Weight 5		PEST 3. Do your fingernails or toenails have holes or pits?
TOPAS 2B	Have you ever noticed any of these changes in your fingernails: lifting of the nail from the nailbed as shown in Figure 2			Assessment of the nail photographs by a dermatologist
TOPAS 7	Have you ever had neck pain lasting at least 3 months that was not injury related?			PEST mannikin: Positive when the neck is checked.
PEST Mannikin ≥6 joint ticked			1 point	

Statistical Analysis

Sensitivity, specificity and area under the curve (AUC) were calculated for all three versions of the CONTEST and the PEST, PASE & EARP using STATA 14. Additionally, we did a subgroup analysis in which we approximated the patient selection of the CONTEST study, meaning only patients with at least one positive screeningtool were invited for clinical evaluation. As we did not include the TOPAS, we selected only patients with a positive PEST or PASE questionnaire in this subgroup analysis.

Results

Patients

For this analysis 473 psoriasis patients with MSC were available (Figure 1). The mean age of these patients was 55.7 years (SD 13.9) and 51.0% were male. Mean psoriasis duration was 20.7±16.2 years,

with 73.2% of the psoriasis diagnoses made by a dermatologist. The remaining 26.9% of psoriasis cases were made by the GP. Median PASI score in the study population was 2.3 (IQR 1-4). During clinical evaluation 71 patients (15.0%) had nail abnormalities consistent with psoriatic nail dystrophy. Table 2 provides the clinical details for psoriasis patients with and without PsA. PsA was newly diagnosed by a rheumatologist in 17 cases. Within the PsA cases 11 patients (64.7%) presented solely with peripheral arthritis. Five cases (29.4%) of axial PsA were diagnosed and one patient (5.9%) presented with a combination of axial PsA and peripheral arthritis. Moreover, we also identified 36 cases of enthesitis, in which the inflammatory component was confirmed by US, resulting in a total of 53 PsA cases. More information about the prevalence of PsA in our population can be found in our previously published paper.[9]

Figure 1. Flowchart of recruitment of psoriasis patients

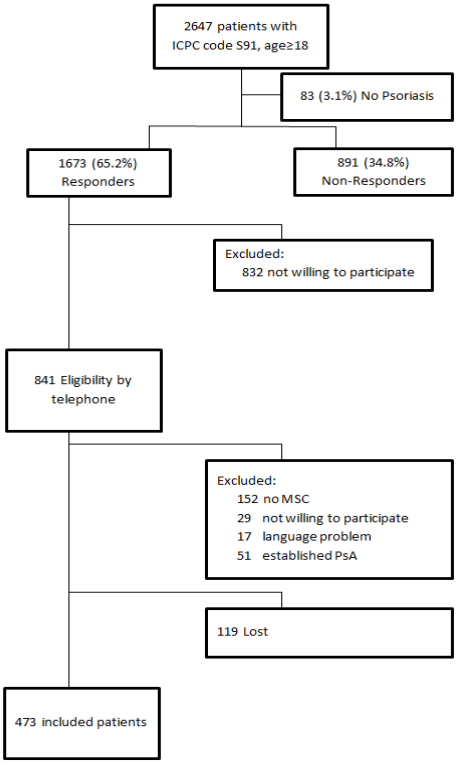

Table 2 Characteristics of the 473 participating psoriasis patients

	Psoriasis patients* (n=420)	Axial manifestations & Peripheral Arthritis* (n=17)	Enthesitis* (n=36)
Mean Age, years (±SD)	55.9 (14.0)	47.4 (10.7)	58.0 (12.3)
Male sex, n (%)	216 (51.4)	8 (47.1)	17 (47.2)
Body Mass Index, mean (±SD)	27.8 (4.8)	27.9 (6.2)	30.0 (4.1)
Median Psoriasis Symptom Duration, years (IQR)	15 (8-30)	15 (4-30)	20 (11-37)
Psoriasis Diagnosis by Dermatologist, n (%)	302 (71.9)	13 (76.5)	31 (86.1)
Nail psoriasis, n (%)	64 (15.2)	5 (29.4)	2 (5.6)
PASI, median (IQR)	2.2 (1-4)	3 (1.3-4)	3.1 (1.7-4.4)
Median MSC Symptom Duration, years (IQR)			
Joints	8 (4-14)	12.5 (2-23)	10 (5-25)
Lower Back	12 (5-25)	18 (9-25)	33 (14-41)
LEI, median (IQR)	0 (0-0)	0 (0-1)	1 (1-2)
MASES, median (IQR)	0 (0-0)	0 (0-3)	2 (0-3)

*Axial manifestations & arthritis are the patients who were diagnosed as having PsA by the rheumatologist. Enthesitis are the patients who would have a diagnosis of PsA based on the CASPAR criteria. Established PsA are the patients already diagnosed with PsA at the beginning of the study and psoriasis patients are the patients with MSC but without PsA.

Performance of the CONTEST

The AUCs for the three different versions of the CONTEST were all around 0.7 in our primary care population (Table 3). Sensitivities ranged from 0.30 for the CONTEST-w to 0.51 for the CONTEST-jt and 0.53 for the CONTEST. Specificity was highest for the CONTEST-w at 0.86, while de specificities for the CONTEST-jt and CONTEST were lower at 0.77 and 0.74 respectively.

When comparing the performance of the CONTEST with the already existing screeningtools, differences can be shown. First of all, where the AUC of the CONTEST questionnaires are lower than the AUC of the other three screeningtools in the development studies, this difference is not as obvious in our SENSOR population. The sensitivities of the CONTEST questionnaires are lower than the sensitivities of the other questionnaires in our population, whereas the specificities for the CONTEST are slightly higher.

Subgroup Analysis

For the subgroup analysis, where patients were selected in approximately the same way as in the initial development study, 227 patients were available as they had a positive PEST (value ≥3) and/or PASE (value≥47). AUC was the same for all three versions of the contest at 0.60. Sensitivity was comparable between the CONTEST and the CONTEST-jt versions, with 0.64 and 0.62 respectively, whereas the CONTEST-w had a lower sensitivity at 0.36. Specificities of the CONTEST and the CONTEST-jt were also in the same range with 0.49 and 0.54 respectively, while de specificity of the CONTEST-w was 0.71 (Table 3).

Discussion

In this study we compared the recently developed CONTEST questionnaires with three other existing screeningtools in a primary care setting. Although the AUCs for the CONTEST are comparable between the development and this validation, the discriminative properties differed. In our primary care setting, sensitivity was considerably lower whereas specificity was higher for all three versions. When we approximated the patient selection of the development (i.e. those with a positive PEST and/or PASE), these differences became smaller, but were still present. Comparing the CONTEST with the already existing screeningtools PEST, PASE and EARP in our primary care setting, showed no additional value of the CONTEST. Lowering the cutoffs of the CONTEST questionnaires (CONTEST to 2, CONTEST-w &-jt to 3) could increase its value by increasing the sensitivity (0.89, 0.81, 0.81 respectively), but as this is at the expense of the specificity (0.33, 0.37, 0.43 respectively) it would result in a lot of unnecessary referrals.

The developers of the CONTEST aimed to develop a questionnaire with considerably improved performance than the previously developed individual screening questionnaires. Although the performance in the initial development study seemed to be better than the performance of the individual questionnaires (PEST, PASE, ToPAS), this could not be fully replicated in their validation cohorts from Utah and Dublin.[6,7,12] The Dublin study [4] included consecutive patients from dermatology clinics and showed low sensitivity and high specificity for all three CONTEST questionnaires. The Utah study[6] included patients from a psoriasis registry as well as dermatology clinics and the performance of the CONTEST questionnaires was slightly worse than in its development cohort.

The results of this study should be interpreted in the light of the setup of the study. The TOPAS was not included in our study and we therefore had to substitute the questions from the TOPAS that were included in the CONTEST with data we did have available. We replaced the items with very similar questions and were therefore able to give a good estimation of its performance in a primary care setting. The considerably different results for CONTEST-w might, however, be explained by these replacements, as an item from the TOPAS is weighted as five in this version and we had to substitute this item with an item from the PEST. As the mean age of our included population is 55 years of age, it is to be expected that some other diagnoses like osteoarthritis may be causing the musculoskeletal complaints in our population. We chose to only include patients with musculoskeletal complaints and although this may have resulted in a slight underestimation of the specificity, we think it is a representative population to test such a screeningtool. Since the prevalence of both psoriasis and PsA is fairly low in primary care, it may be a better use of resources to screen only those patients suffering from musculoskeletal complaints instead of all patients with psoriasis.

In conclusion, in this study we assessed the additional value of the CONTEST questionnaires over the already existing screeningtools in a primary care setting. We showed that the newly developed CONTEST questionnaires did not exceed the performance of the already existing screeningtools PEST, PASE and EARP.

Table 3 Performance of the Different Screeningquestionnaires in the development study and SENSOR dataset

	AUC			Sensitivity			Specificity		
	Development	SENSOR	SENSOR selection*	Development	SENSOR	SENSOR selection*	Development	SENSOR	SENSOR selection*
CONTEST (cutoff 4)	0.69 (0.57-0.81)	0.69 (0.61-0.76)	0.60 (0.50-0.70)	0.86	0.53 (0.39-0.67)	0.64 (0.48-0.78)	0.35	0.74 (0.70-0.78)	0.49 (0.41-0.56)
CONTEST-w (cutoff 9)	0.74 (0.63-0.85)	0.67 (0.59-0.74)	0.60 (0.50-0.69)	0.86	0.30 (0.18-0.44)	0.36 (0.22-0.52)	0.48	0.86 (0.82-0.89)	0.71 (0.64-0.78)
CONTEST-jt (cutoff 5)	0.70 (0.58-0.82)	0.69 (0.61-0.76)	0.60 (0.49-0.70)	0.86	0.51 (0.37-0.65)	0.62 (0.46-0.76)	0.37	0.77 (0.73-0.81)	0.54 (0.46-0.61)
PEST (cutoff 3)	0.91 (0.86-0.97)	0.71 (0.64-0.79)	NA	0.92	0.68 (0.54-0.80)	NA	0.78	0.71 (0.67-0.76)	NA
PASE (cutoff 47)	0.84	0.64 (0.56-0.71)	NA	0.82	0.59 (0.44-0.72)	NA	0.73	0.66 (0.61-0.71)	NA
PASE (cutoff 44)	0.84	0.64 (0.56-0.71)	NA	0.76	0.66 (0.52-0.79)	NA	0.76	0.57 (0.52-0.62)	NA
EARP (cutoff 3)	0.90 (0.85-0.95)	0.68 (0.61-0.75)	NA	0.85	0.87 (0.75-0.95)	NA	0.92	0.34 (0.30-0.39)	NA

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Part III.

General Discussion, Summary & Addendum

Chapter 9.

General Discussion

Over the years it has become more and more apparent that early recognition of SpA is important. However, early signs of inflammatory SpA resembles those of aspecific low back pain or joint pain. Therefore it is not easy to disentangle those with benign symptoms from those with inflammatory symptoms. To prevent screening all patients with aspecific joint or back pain it is necessary to increase the prior probability by selecting subpopulations. Patients with psoriasis or IBD have an increased risk of developing SpA and are thus good examples of groups to focus on in the early recognition of SpA. In the Netherlands, we have an extensive primary healthcare system. It is therefore most likely that patients with psoriasis or IBD who suffer from musculoskeletal complaints, will visit their general practitioner for these complaints. To get more insight in the early recognition of SpA in primary care, this thesis focused on the following aims:

- To get insight in the prevalence of PsA and ultrasound findings in enthesitis in psoriasis patients in a primary care setting
- To give an overview of the prevalence of axial and peripheral SpA in IBD patients
- To describe the burden of musculoskeletal complaints in patients with IBD
- To evaluate the awareness of SpA in both GPs and patients with IBD or PSO
- To assess the optimal screening-strategy for PsA in a primary care setting

To answer these questions, the cross sectional SENSOR and AppSpA study were set up. The SENSOR study was a study in primary care in which we included patients with psoriasis who had musculoskeletal complaints. The AppSpA study consisted of two parts; first the GP-part in which we invited GPs to complete a survey on knowledge of inflammatory symptoms and SpA-specific features. The patients-part included patients at risk for SpA, i.e. patients with psoriasis or IBD between 18 and 55 years of age. These patients were selected out of GP databases and completed questionnaires on awareness, presence of musculoskeletal complaints, quality of life and work participation.

Prevalence

The first part of this thesis focused on the prevalence and burden of SpA in patients at risk. The prevalence of PsA in patients with psoriasis was investigated within the SENSOR study. In this study, 524 patients with psoriasis were clinically evaluated and we found a prevalence of PsA in psoriasis patients of 3.2%. This number increased towards 4.6% if patients with solely enthesitis were also taken into account. Enthesitis was defined as active inflammation on ultrasound in combination with a tender enthesis at the same site. According to this definition, 40 patients (36%) had clinically relevant enthesitis.

The prevalence of SpA in patients with IBD was established with a systematic review and meta-analysis. We found a pooled prevalence of 11% for sacroiliitis and 3% for its subtype ankylosing spondylitis. The pooled prevalence for peripheral arthritis was found to be 14%.
Once the prevalence was established, we looked at the impact of musculoskeletal complaints for patients with IBD and showed that the musculoskeletal complaints had significant impact on quality of life.

Awareness

To aid early recognition, physicians and patients should be aware of the concept of SpA. In the first part of the AppSpA study we therefore invited general practitioners to complete a questionnaire regarding inflammatory symptoms and features of SpA. We showed that almost 60% of GPs did not recognize half of the symptoms indicative for inflammatory peripheral joint disease, for inflammatory axial disease this was 40%. The second part of the AppSpA study focused on patients at risk, i.e. patients with psoriasis or IBD. We found that only 42.6% of patients with psoriasis or IBD was aware of the fact that they could develop SpA.
Besides increasing awareness, the use of screeningtools could also aid early recognition. We therefore evaluated the performance of the PEST, PASE and EARP screeningtools for PsA in our study population. The PEST screeningtool was found to have the best trade-off between sensitivity (0.68) and specificity (0.71). We also investigated the added value of a newly developed screeningtool (CONTEST). The difference between the CONTEST and the PEST, PASE, EARP was so small that we concluded that the CONTEST does not exceed the performance of these older tools.

Generalizability

As the most important findings of this thesis are summarized above, it is important to look into the generalizability of our results. The following part of the discussion will focus on several aspects of generalizability, namely population definition (including recruitment of subjects and eligibility criteria), patient characteristics and definition of outcome.

The first thing to look at is the study population, including recruitment and in- & exclusion criteria of participants. In the estimation of disease prevalence the recruitment of all patients at risk is of utmost importance. In case of PsA among psoriasis patient in primary care that meant that we needed to reach out to every possible patient that was diagnosed with psoriasis. In the set-up of the study this was extensively accounted for by selecting patients based on ICPC code. To ensure whether this code

was applied correctly to the participating patients, we also verified the diagnosis of psoriasis or IBD with the patients themselves.

The results of the SENSOR study apply to those adult patients that reported regular spells of MSC. Patient that initially consult the GP with a single spell still may be at risk, but due to our requirement of regular spells, current results do not apply to those with a single spell of MSC. Given the high frequency of GP consultations for MSC the prevalence of PsA is likely to be lower than in those with regular spells, but it is unclear how much lower.

In the AppSpA study we included patients aged 18 to 55 years of age. The upper limit of 55 years was chosen as we saw in the SENSOR study, where no age limit was applied, that the mean age of the participating patients was fairly high. The incidence of SpA above the age of 55 years is very low, while in this age group other problems like osteoarthritis play a more important role.

In both studies self-selection of patients may be an issue. Patients who have a lot of musculoskeletal complaints could have been more interested in participating in a study than patients who do not suffer that much from their musculoskeletal complaints. In the AppSpA study the invitation stated that the study was about musculoskeletal complaints. Although we explicitly asked patients to participate irrespective of the presence of musculoskeletal complaints, it is possible that the prevalence of musculoskeletal complaints in this study is an overestimation.

The second subject to look at in the context of generalizability are the patient characteristics. In the SENSOR study about half of the patients was male, comparable with a general psoriasis population.[1] The mean age of our population was 55.8 years, which is older than the peak incidence of psoriasis which is between 30 and 50 years of age. It is therefore possible that we missed some cases of PsA among the younger population. Our study population consisted for 98% of Caucasian people, although the prevalence of psoriasis is highest in Caucasian people, it also occurs in people from other parts of the world. In the AppSpA study there seemed to be an overrepresentation of females as only 25% of the participants was male. Most studies show an equal distribution between males and females, although some studies tend to show a trend towards female predominance in Europe and North-America.[2] Nonetheless, it should be taken into account that the results described in chapter 5 of these thesis may not be a completely adequate representation with regard to gender.

The definition of the outcome is also an important factor for the generalizability of the results. The outcome in the SENSOR study was a diagnosis of PsA, which was made by a rheumatologist. As enthesitis is still very difficult to diagnose, we used the CASPAR criteria to diagnose PsA based on enthesitis. In the CASPAR critera enthesitis is stated as an entry criteria, so patients with solely

enthesitis (without arthritis or axial involvement) could classify as PsA. However, when a patients would classify as having enthesitis is not defined. This is why we chose to combine clinical evaluation (LEI/MASES) with ultrasound findings. In this way we tried to diagnose enthesitis as objective as possible. In addition, the CASPAR criteria are classification criteria and not diagnostic criteria, so one could say they are not to be used to diagnose a disease. This is why we mentioned the prevalence of enthesitis separately in our prevalence study. During our study we found that many participating rheumatologists found it difficult to diagnose PsA solely based on enthesitis, as it seems quite unspecific and there is still so much unknown.

In the AppSpA study, the main outcome in the patient-part was the presence of musculoskeletal complaints. As the AppSpA study consisted only of questionnaires, the prevalence of musculoskeletal complaints is self-reported. However, this seems to be an adequate way to describe the prevalence of musculoskeletal complaints, as there is no objective measure available and it is always self-reported by the patients. The questionnaires we used to describe quality of life and work participation were all validated self-reported questionnaires. The same goes for the GP-part, were we also used a self-developed survey to get insight in their knowledge of SpA. We think the results of this study give good insight in the gaps in the knowledge of SpA and would not have differed much if we would have used interviews for example.

Overall, we think the results of our studies are representative of the Dutch situation. In the Netherlands we have an extensive primary care system, which we used in our studies. We used ICPC codes to include every patient with psoriasis to get a fair estimate of the prevalence of PsA in the end. By combining ultrasound and clinical examination we were also able to give an adequate estimate of the prevalence of enthesitis, as a clear definition is still lacking. In the AppSpA studies the prevalence of musculoskeletal complaints may be overestimated and there is an overrepresentation of females, which should be taken into account. However, the use of questionnaires is an adequate way to get an overview of the knowledge gaps of GPs and complaints of the patients.

Implications for clinical practice

In this thesis we showed that musculoskeletal complaints and SpA occur frequently in patients at risk, i.e. patients with psoriasis or IBD. However, these complaints are often not recognized as being SpA, as medical professionals and patients themselves often are not aware of the link between psoriasis or IBD and SpA. Increasing this awareness is important as it could aid early recognition. In the following part of the discussion ways to increase this awareness are described.

Increasing Awareness

Multiple target groups can be distinguished to increase awareness; general practitioners, medical specialists and patients themselves.

General Practitioners

Over the last years it has been tried to increase awareness for rheumatic disease via guidelines and education of GPs. However, guidelines and education alone does not seem to be sufficient. Two reviews, of which one was specifically aimed at inflammatory arthritis, showed that referral from primary to secondary care could also be improved via the use of self-administered questionnaires, referral sheets or triage by a specialist in a primary care setting.[3,4]

Looking into self-administered questionnaires or referral sheets, the screeningtools for PsA as described in this thesis might be useful in this matter. They could play an important role to aid necessary referrals and avoid the unnecessary ones. Unfortunately the sensitivity and specificity of these tools remains moderate, also in primary care as described in chapter 7.[5-8] The PEST screeningtool seems to perform relatively well and is very short and easy to complete. However, axial manifestations are not represented in the PEST. It might therefore be useful to use another tool if patients present themselves with axial manifestations. Multiple referral tools have been developed for axial SpA, among which the Berlin, MASTER, RADAR, ASAS and CaFaSpA.[9-13] For the Dutch situation with an extensive primary care system, the CaFaSpA seems to be most feasible, as you don't need any invasive or costly investigations like laboratory tests or imaging.

To increase awareness another quite simple thing that might aid recognition is linking of ICPC codes. If a patient has psoriasis or IBD this will be registered by ICPC code in the electronic patients file of the GP. If a patient presents later on with musculoskeletal complaints, the GP will add a new ICPC code for this complaint. It might be rather useful if some sort of pop-up will occur to draw attention to the fact that the patient also has a diagnosis of psoriasis or IBD.

Triage by a specialist in a primary care setting could also be useful. The GP could select patients with possible inflammatory symptoms, who could be evaluated by a specialist in an easily accessible, low-cost setting. If the rheumatologist confirms the presence of inflammatory symptoms, the patient would be referred to secondary care for specialized care.

Medical Specialists

Besides the GPs, medical specialists should also be involved when improving awareness. All IBD patients will be treated by a gastroenterologist, while a certain part of the psoriasis patients (e.g. the more severe psoriasis or psoriasis with a lot of comorbidity) will be treated by a dermatologist. A

recent study showed that the knowledge about in this case axial SpA was insufficient in medical specialists, leading to diagnostic delay.[14] To increase awareness in this group, certain strategies for GPs could also be used, like education and the use of screeningtools. As in a primary care setting, the PEST could also be used in dermatology practice. Another way to improve care for psoriasis and IBD patients in secondary care is setting up standardised referral pathways, or as called in Dutch 'zorgpaden'. The purpose of such a standardised referral pathway is to standardize care with regard to, in this case, screening for MSC in patients with psoriasis or IBD. The other way around could also be useful; patients from the rheumatologist with abdominal or skin problems can be easily referred to the right specialist. Another advantage in the secondary care setting is the presence of specialized nurses or physician assistants who could be very helpful in these matters.

Patients

It is to be expected that the highest increase in awareness could be achieved in the patient group. GPs and medical specialists have very little time during their consultations and see many patients per day. If patients themselves are aware of the link between MSC and their IBD/psoriasis, they can actively ask their GP or medical specialist about their complaints. To increase this awareness in patients at risk and thereby reducing patient delay, several options have been studied, for example community case finding strategies, public awareness programs and internet and website information.[4,15]

For patients with psoriasis or IBD, public awareness campaigns or posters in the waiting room of the GP may not be the right way to go. SpA in these patients is relatively rare compared to the general prevalence of musculoskeletal complaints. It may be more efficient to add information about musculoskeletal complaints and SpA to the information folders of psoriasis and IBD. In that way, when patients are diagnosed with psoriasis or IBD, they will receive an information folder about their disease and directly have information about their risk of developing SpA. For psoriasis this could be implemented in general practice as well as in outpatient clinics dermatology. For IBD patients, as they will all visit a gastroenterologist to be diagnosed with IBD, it is more efficient to implement this at the gastroenterology outpatient clinic. Some of the larger hospital have physician assistants especially for IBD patients, which would be an excellent opportunity to inform these patients about SpA. In addition to medical professionals, the patient organizations for psoriasis and IBD could also play an important role. The patient organizations have a broad reach among patients and could inform their patients via their website, newsletters, social media etcetera.

Recommendations for further research

Over the years a lot of different classification criteria for SpA have been developed.[16-20] The most recent set of criteria are the ASAS criteria developed around 2010.[19,20] When using these criteria a distinction is made between axial and peripheral SpA, based on the most predominant symptoms. A lot of studies can be found on spondyloarthritis, but these studies mostly only cover axial spondyloarthritis. Data about prevalence, quality of life, and work participation of peripheral SpA are scarce. Our recommendation would therefore be to conduct more research on peripheral SpA.

Our second recommendation for further research would be to develop screeningtools and screening strategies voor SpA in patients with IBD. For PsA multiple screeningtools and strategies have been developed and although SpA in IBD occurs as frequently, no screeningtools are available. As all patients with IBD will be attending an outpatient gastroenterology clinic, this can be a good opportunity for screening. Some of the larger hospitals even work with IBD specialized nurses, who could be trained in screening these patients. If you look for example at the existing screeningtools for PsA, most of these questions are fairly general and could be applied to SpA in IBD patients as well. It would be interesting to set up a study in a gastroenterology outpatient clinic, using parts of the screeningtools developed for PsA to see which items are most indicative of a diagnosis of SpA.

Awareness for SpA should be improved, however the best way to achieve this is still unclear. It would be very interesting to set up a trial to compare standard care as used nowadays with the use of screeningtools and with triage of a rheumatologist/rheumatology nurse. The screeningtools could be implemented fairly easily as most GP practices work with practice assistants. They have proven to be very useful in chronic care for for example patients with diabetes or chronic obstructive pulmonary disease. Patients with psoriasis or IBD could be selected by ICPC code and complete the screeningtool, the practice assistant could aid in checking the completed tools and arrange a referral to secondary care if necessary. In a head-to-head comparison, practices should be randomized to either use standard care, screeningtools or triage by a rheumatologist.

In the secondary care setting, the added value of using screeningtools should be investigated. These tools are not used in daily practice nowadays but could lead to more adequate and early referrals to the rheumatologist.

For both the screeningtools for PsA as the referral tools for axial SpA, multiple tools have been developed over the years. Most of these tools have also been validated in different cohorts. However, studies looking at the impact of implementing such tools is lacking. Literature shows that early

diagnosis of rheumatic disease leads to better outcomes in the longterm. However, focusing on early recognition, also leads to more patients referred to secondary care which is rather costly. On top of that, care nowadays becomes much more patient-centered with shared-decision making becoming more and more important. So the question raises, what is the actual benefit for the patient? With the severe destructing forms of SpA, it seems rather clear that preventing this as much as possible by starting treatment early on is beneficial. But patients who present with mild forms of SpA, what is the additional value of diagnosing and treating as early as possible for them? Does it increase their quality of life? I think patients who might suffer from inflammatory joint disease should always be seen by a rheumatologist, for example in a less costly construction like consultation in a primary care setting. However, it should be investigated what the value is of diagnosing and treating patients with mild forms early on, for both the patients and the costs associated with this.

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Chapter 10.

Summary
Samenvatting

Summary

Chapter 1 provides a general introduction to this thesis. Spondyloarthritis (SpA) is an umbrella term for a group of inflammatory rheumatic diseases. It can manifest with axial symptoms (low back pain, sacroiliitis) or peripheral symptoms (arthritis, enthesitis, dactylitis). Patients with psoriasis or inflammatory bowel disease (IBD) have an increased risk of developing SpA, as there are many overlapping mechanisms in the pathogenesis of these diseases leading to subtypes of SpA as psoriatic arthritis (PsA) and SpA in IBD patients (IBD-SpA). Early recognition of SpA is important, as early and adequate treatment lead to better outcomes in the longterm. This thesis is divided in two parts. The first part described the prevalence and impact of SpA in patients at risk, while the second part focused on early recognition by means of increasing awareness and using screeningtools.

Part I. Prevalence and Burden of Spondyloarthritis in Patients at Risk

In **chapter 2** we evaluated the prevalence of PsA and musculoskeletal complaints among psoriasis patients in a primary care setting. GPs who were willing to participate, selected psoriasis patients out of their databases and invited them to participate. Patients were eligible to participate if they were 18 years and over, had a diagnosis of psoriasis and experienced any kind of musculoskeletal complaints. Out of the total of 97 GPs who participated, 2564 psoriasis patients were selected of whom 841 were eligible and willing to participate. Participating patients completed a set of questionnaires before clinical evaluation by a trained research nurse. Clinical evaluation included assessment of the skin, joints, tendon and back. If there were indications for underlying inflammatory disease, patients were advised to consult a rheumatologist.

PsA was diagnosed by a rheumatologist in 17 cases and 64 were diagnosed with psoriasis before the study, leading to a prevalence of 3.2%. Besides these cases, 36 patients were found to have enthesitis, confirmed by ultrasound, and could classify als PsA according to the CASPAR criteria. Classifying these patients as PsA, would increase the prevalence to 4.6%. The prevalence of musculoskeletal complaints was with 32.1% comparable with the prevalence in the Dutch population.

Chapter 3 describes the ultrasound findings in the patients who were found to clinically have enthesitis. In the CASPAR criteria enthesitis is stated as an entry criteria, leading to the fact that patients with enthesitis could classify as PsA. The problem is that the definition of enthesitis is not entirely clear. We therefore performed ultrasound of the entheses on patients with clinically suspected enthesitis as defined by the LEI or MASES scores. In total, we found 111 patients with tender entheses who underwent ultrasound examination of seven entheses according to the MASEI score.

We defined clinically relevant inflammation as active inflammation on ultrasound (positive power Doppler signal or in case of the plantar fascia increased thickness) in combination with a tender enthesis at the same site during clinical examination. Forty patients (36%) of the patients had clinically relevant inflammation. The most common sites were the knee and the plantar aponeurosis. Structural changes were found in 95% of the screened psoriasis patients independent of their clinical manifestation.

Besides patients with psoriasis, patients with IBD are also at risk for developing SpA. To assess the size of this problem, we performed a systematic review and meta-analysis on the prevalence and incidence of axial and peripheral manifestations of SpA in patients with IBD as described in **chapter 4**. An extensive search strategy was set up in collaboration with the medical library, leading to 4845 potentially relevant articles. After screening the titles and abstracts and subsequently the full text of these papers, 60 were relevant and were included. Quality assessment of the included articles showed moderate overall quality. With regard to axial manifestations (i.e. sacroiliitis and ankylosing spondylitis), 53 papers reported on the prevalence in IBD patients. The pooled prevalence was 11% for sacroiliitis and 3% for its subtype ankylosing spondylitis. Forty-four studies reported on the prevalence of peripheral arthritis, leading to a pooled estimate of 14%.For the prevalence of the other peripheral manifestations few estimates were available, leading to a prevalence range from 1-54% for enthesitis and 0-5% for dactylitis. Only three studies reported on the incidence of SpA in IBD, reporting cumulative incidences from 0.48 at 10 years to 0.22 at 30 years.

We now know that SpA occurs frequently in patients with IBD. Most of these patients will suffer from musculoskeletal complaints before they are diagnosed with SpA. In **chapter 5** we looked into the burden of these musculoskeletal complaints in patients with IBD. We set up a cross-sectional survey among patients diagnosed with IBD between 18 and 55 years of age. They completed different questionnaires regarding their MSC, but also on quality of life, disability and work participation and productivity. In total, 338 patients completed the questionnaires, of whom 45.6% suffered from Crohn's disease and 45.0% suffered from ulcerative colitis. The mean age of the participants was 42.3±9.3 years and 25.4% were male. MSC were very common with a prevalence of 81.1%, with more frequent occurrence in patients with CD compared to UC. Overall, patients with IBD and MSC reported significantly lower quality of life on both the IBDQ and the SF-36. Differences could also be shown in work participation and productivity, where patients with MSC were more often unemployed, work-disabled and reported lower work productivity. With this study we showed that MSC are a very

common extra-intestinal manifestation with significant impact on quality of life and work participation and productivity. Interestingly, reduced quality of life seemed to be influenced explicitly by MSC.

Part II. Awareness and Early Recognition of Spondyloarthritis in Patients at Risk

In the first part of this thesis we established the prevalence of spondyloarthritis in patients at risk and its impact. We know that early recognition of SpA in these patients leads to earlier treatment and thereby better outcomes in the longterm. To enhance this early recognition, there should be awareness for SpA. In **chapter 6** we describe the results of the AppSpA study, which was set up to assess the current awareness for SpA in both general practitioners and patients themselves. We developed a survey for GPs to complete, focussing on recognition of inflammatory symptoms and SpA-specific features. Patients' awareness was also assessed with a survey. We invited 949 GPs to participate, of whom 312 returned the survey (response rate 32.9%) of whom 185 GPs completed the survey. With regard to the recognition of signs of inflammatory pain, especially classic symptoms like morning stiffness and pain relieve by NSAIDs were recognized, whereas other symptoms like pain improvement with exercise were poorly recognized. Almost 60% of GPs did not recognize half of the features indicative of inflammatory peripheral joint disease, for inflammatory axial disease this was 40%. The majority of GPs also associated SpA solely with axial disease. In the patient-part of this study, we saw that less than half of the patients with psoriasis or IBD was aware of the possibility of developing SpA, namely 42.6%. If they were aware of this possibility, most of them gained this knowledge themselves and were not informed by a medical professional. The results of this study indicate that there is room for improvement of the awareness for SpA in both GPs and patients at risk.

One thing that could aid early recognition and awareness is the use of screeningtools. For PsA several screeningtools have been developed. Most of these tools were developed and tested in secondary care settings. However, in the Netherlands, where we have an extensive primary care system these tools could best be used in primary care. In **chapter 7** we investigated the performance of the existing screeningtools in primary care. For this part we used data from the SENSOR study. We included 473 psoriasis patients without a diagnosis of PsA. They completed the PEST, PASE and EARP screeningtools before they were clinically evaluated by a trained research nurse. In 53 patients a diagnosis of PsA was made by a rheumatologist according to the CASPAR criteria. The PEST had a sensitivity of 0.68 and a specificity of 0.71. The PASE was validated for two different cut-offs. The cut-off of 47 led to a sensitivity of 0.59 and a specificity of 0.66, whereas the lower cut-off of 44 led to a sensitivity of 0.66 and a specificity of 0.57. For the EARP and we found a sensitivity of 0.87 with a specificity of 0.34. In this study the PEST seems to have the most favourable trade-off between sensitivity and specificity to

screen for PsA. It might however be more useful to only screen patients with musculoskeletal complaints, due to the fairly low prevalence of PsA in primary care.

As shown in chapter 7 and various other validation studies, the existing screeningtools perform moderately. This is why the CONTEST group developed a new screeningtool based on the best performing items of the previous screeningtools. In **chapter 8** we assessed the additional value of this CONTEST questionnaire in a primary care setting. Data from the SENSOR study was used and we calculated sensitivity, specificity and area under the curve for the various versions of the CONTEST. For this analysis, 473 psoriasis patients without PsA were available. The AUC of the CONTEST questionnaires ranged between 0.67-0.69 and sensitivities between 0.30-0.51 in our primary care population, whereas the specificities were between 0.74-0.86. On sensitivity the PEST (0.68), PASE(0.66) and EARP(0.87) performed better than the CONTEST questionnaires, whereas with regard to specificity the CONTEST performed slightly better than the PEST (0.71), PASE (0.57) and EARP (0.34). In our primary care setting we therefore conclude that the performance of the CONTEST does not exceed the performance of the PEST, PASE or EARP.

Chapter 9 provides a general discussion about our results. The discussion focuses on generalizability of our results and recommendations for future research. In this chapter we also describe possibilities to improve awareness for SpA and ideas for research to investigate the best way to improve this awareness.

Samenvatting

Hoofdstuk 1 vormt de algemene introductie van dit proefschrift. Spondylarthopathie (SpA) is een overkoepelende term voor een groep van inflamamtoire reumatische aandoeningen. Het kan zich presenteren met axiale symptomen (lage rugpijn, sacroiliitis) of perifere symptomen (artritis, enthesitis, dactylitis). Patienten met psoriasis of inflammatoire darmziekten (IBD) hebben een verhoogd risico op het ontwikkelen van SpA, vanwege de grote overlap in de pathogenese van deze ziekten, wat kan leiden tot de subtypes artritis psoriatica (PsA) of IBD gerelateerde SpA. Vroegherkenning van SpA is belangrijk, aangezien vroege en adequate behandeling leidt tot betere uitkomsten op de lange termijn.

Dit proefschrift bestaat uit twee delen. Het eerste deel richt zich op de prevalentie en impact van SpA in patienten met een verhoogd risico. Het tweede gedeelte richt zich op vroegherkenning en hoe dit verbeterd kan worden met het vergroten van de awareness en het inzetten van screeningtools.

In **hoofdstuk 2** wordt de prevalentie van PsA en musculoskeletale klachten bij patienten met psoriasis in de eerste lijn beschreven. Huisartsen die bereid waren deel te nemen, selecteerden de psoriasis patienten uit hun praktijk op basis van ICPC code en nodigden hen uit om mee te doen. Patienten konden deelenemen als ze 18 jaar of ouder waren, een diagnose psoriasis hadden en musculoskeletale klachten hadden. Er deden 97 huisartsen mee, die samen 2564 patienten met psoriasis in hun praktijk hadden, van wie 841 geschikt waren en mee wilden doen. Deelnemende patienten vulden een set vragenlijsten in voordat ze klinisch geevalueerd warden. De klinische evaluatie bestond uit een uitgebreide anamnese en lichamelijk onderzoek van de huid, gewrichten, pezen en rug. Als er aanwijzingen waren voor een onderliggende reumatische ziekte werden patienten geadviseerd zich naar een reumatoloog te laten verwijzen. PsA werd gediagnosticeerd door een reumatoloog bij 17 patienten en 64 patienten hadden al een diagnose PsA voordat de studie begon. Tezamen leidt dit tot een prevalentie van 3,2%. Naast deze gediagnosticeerde patienten, bleken er 36 patienten te zijn die enthesitis hadden, bevestigd met echo, die op basis van de CASPAR criteria zouden kunnen classificeren als PsA. Als je deze patienten mee zou nemen in je prevalentie, zou je op een prevalentie van 4.6% uitkomen. De prevalentie van musculoskeletale klachten was met 32.6% vergelijkbaar met de prevalentie van de algemene Nederlandse bevolking.

Zoals hierboven beschreven waren er patienten met enkel enthesitis klachten. In **hoofdstuk 3** worden de echo bevindingen bij deze patienten besproken. In de CASPAR criteria is enthesitis opgenomen als

een ingangscriteria, wat er toe leidt dat patienten met enthesitis geclassificeerd zouden kunnen worden als PsA. Het problem is echter dat er geen duidelijke definitie is van enthesitis. In deze studie hebben we daarom een echo gemaakt van de entheses van patienten die klinisch verdacht werden van enthesitis, zoals gedefineerd met de LEI en MASES scores. In total waren er 111 patienten met een pijnlijke enthesis die een echo kregen van 7 entheses zoals omschreven in de MASEI score. Onze definitie van klinisch relevante enthesitis was een combinatie van actieve inflammatie op de echo (positief power Doppler signaal of in het geval van de fascia plantaris verdikking) in combinatie met een pijnlijke enthesis op dezelfde plek. Volgens deze definitie hadden 40 patienten (36%) een klinisch relevante ontsteking van de enthesis. De meest voorkomende plekken waren de knie en de aponeurosis plantaris. Structurele afwijkingen werden gevonden bij 95% van de psoriasis patienten, onafhankelijk van hun klinische presentatie.

Naast patienten met psoriasis hebben patienten met IBD ook een verhoogd risico op het ontwikkelen van SpA. Om de grootte van dit problem in kaart te brengen, hebben we een systematic review en meta-analyse opgezet naar de prevalentie en incidentie van axiale en perifere manifestaties van SpA in patienten met IBD, zoals beschreven in **hoofdstuk 4**. In samenwerking met de medische bibliotheek werd een uitgebreide zoekstrategie opgezet, die leidde tot een total aantal van 4845 potentieel relevante artikelen. Na het screenen van de titels en abstracts en daaropvolgende de complete artikelen, bleven er 60 relevante artikelen over die werden geincludeerd. Beoordeling van de kwaliteit van de geincludeerde artikelen middels een standaard score system liet matige algehele kwaliteit zien. De prevalentie van axiale manifestaties van SpA bij patienten met IBD werd genoemd in 53 artikelen. De gepoolde prevalentie was 11% voor sacroiliitis en 3% voor het subtype ankylosing spondylitis. De prevalentie van perifere artritis werd beschreven in 44 studies, wat leidde tot een gepoolde prevalentie van 14%. De prevalentie van de andere perifere manifestaties enthesitis en dactylitis werd in maar weinig artikelen beschreven, met een prevalentie varierend van 1-54% voor enthesitis en 0-5% voor dactylitis. Er waren slechts drie studies die de incidentie van SpA bij IBD patienten beschreven, met cumulatieve incidenties van 0.48 in 10 jaar tot 0.22 in 30 jaar.

We weten nu dat SpA relatief vaak voorkomt bij patienten met IBD. Het meerendeel van deze patienten zal eerst last krijgen van musculoskeletale klachten voor ze gediagnosticeerd worden met SpA. In **hoofdstuk 5** kijken we naar de last van deze musculoskeletale klachten bij patienten met IBD. We hebben een cross-sectionele studie opgezet gebaseerd op vragenlijsten bij patienten met IBD tussen de 18 en 55 jaar. De vragenlijsten gingen over het al dan niet aanwezig zijn van musculoskeletale klachten, maar ook over kwaliteit van leven en het werkend leven. In total hebben

338 de vragenlijsten ingevuld, van wie 45.6% de ziekte van Crohn (CD) had en 45% colitis ulcerosa (UC). De gemiddelde leeftijd van de deelnemers was 42.3±9 jaar en 25.4% waren man. Musculoskeletale klachten kwamen erg veel voor met een prevalentie van 81.1%, met een hogere prevalentie bij CD dan bij UC. In het algemeen gaven patienten met IBD and musculoskeletal klachten een significant lagere kwaliteit van leven aan op zowel de IBDW als de SF36 vragenlijsten. Er werden ook verschullen gezien in werken en werkproductiviteit, waar bleek dat IBD patienten met ook msuculoskeletale klachten vaker werkeloos of arbeidsongeschikt waren en een lagere productiviteit tijdens het werk hadden. Met deze studie hebben we aangetoond dat musculoskeletale klachten een veel voorkomende extraintestinale manifestatie zijn met significante invloed op kwaliteit van leven en het werkend leven. Interessant was dat bleek da teen verminderde kwaliteit van leven bijna geheel werd beinvloed door musculoskeletale klachten.

In het eerste gedeelte van dit proefschrift hebben we de prevalentie van SpA in risicogroepen vastgesteld en de impact hiervan. We weten dat vroegherkenning van deze patienten leidt tot eerdere behandeling en daarmee tot betere uitkomsten op de lange termijn. Om deze vroegherkenning te verbeteren, moet er awareness komen voor SpA. In **hoofdstuk 6** beschrijven we de resultaten van de AppSpA studie welke opgezet is om de huidige awarenesss voor SpA bij huisartsen en patienten met psoriasis of IBD in kaart te brengen. We ontwikkelden een enquete voor huisartsen, gericht op herkenning van inflammatoire symptomen en symptomen specifiek voor SpA. We hebben 949 huisartsen uitgenodigd om deel te nemen, van wie 312 de enquete teruggestuurd hebben (response 32.9%), van wie op hen beurt 181 huisartsen de enquete ingevuld hadden. ALs we kijken naar de herkenning van symptomen van inflammatoire klachten, bleek dat met name de klassieke symptomen zoals ochtendstijfheid en verbetering van de klachten door NSAIDs herkend werden. Andere symptomen zoals verbetering van de pijn bij beweging werden slecht herkend. Bijna 60% van de huisartsen herkenden minder dan de helft van de kenmerken duidend op inflammatoire perifere gewrichtsklachten. Voor inflammatoire axiale klachten lag dit percentage op 40%. De meerderheid van de huisarts associeerden SpA alleen met axiale SpA. In het patientendeel van deze studie zagen we dat minder dan de helft (42.6%) van de patienten met psoriasis of IBD op de hoogte was van hun verhoogde risico op het ontwikkelen van SpA. Als patienten hiervan wel op de hoogte waren, had het merendeel ditz elf opgezocht en was niet geinformeerd door een arts. De resultaten van deze studie laten zien dat er ruimte is voor verbetering in de awareness voor SpA bij zowle huisartsen als patienten met een verhoogd risico.

Een van de mogelijkheden om vroegherkenning in de hand te werken is het inzetten van screeningtools. Voor PsA zijn er diverse screeningtools ontwikkeld, het meerendeel in de tweede lijn. In Nederland hebben we echter een uitgebreid eerstelijnszorg system, waardoor deze hulpmiddelen het beste in de eerste lijn ingezet kunnen worden. In **hoofdstuk 7** hebben we de werking van de bestaande screeningtools onderzocht in een eerstelijns populatie. Voor dit gedeelte hebben we data van de SENSOR studie gebruikt en 473 patienten zonder diagnose van PsA geincludeerd. Deze patienten hebben de PEST, PASE en EARP vragenlijsten ingevuld voordat ze een klinische evaluatie ondergingen. Bij 53 van deze patienten is een diagnose van PsA gesteld door de reumatoloog. De PEST had in deze stduie een sensitiviteit van 0.68 en een specificiteit van 0.71. De PASE is gevalideerd voor twee verschillende afkapwaarden. De afkapwaarde van 47 leidde tot een sensitiviteit van 0.59 en een specificiteit van 0.66, waar de lagere afkapwaarde van 44 leidde tot een sensitiviteit van 0.66 en een specificiteit van 0.57. De EARP had een sensitiviteit van 0.87 met een specificiteit van 0.34. In deze studie lijkt de PEST de beste balans te hebben tussen sensitiviteit en specificiteit om te screenen op PsA. Vanwege de relatief lage prevalentie van PsA in de eerstelijn zou het zinvol kunnen zijn om alleen de patienten met musculoskeletale klachten te screenen.

Zoals uit **hoofdstuk 7** blijkt, hebben de bestaande screeningtools geen ideale sensitiviteit en specificiteit. Om deze reden heeft de CONTEST studiegroep een nieuwe screeningtool opgezet gebaseerd uit de best onderscheidende vragen van bestaande screeningtools. In **hoofdstuk 8** hebben we bekeken of deze nieuwe vragenlijst meerwaarde heeft ten opzichte van de eerder ontwikkelde vragenlijsten in de eerste lijn. Data van de SENSOR studie werd gebruikt en we berekenden sensitiviteit, specificiteit en area under the curve (AUC) voor de diverse versies van de CONTEST vragenlijst. Voor deze analyse hadden we 473 patienten zonder PsA beschikbaar. De AUC voor de CONTEST versies varieerde tussen de 0.67 en 0.69. De sensitiviteit in onze eerstelijnspopulatie lag tussen de 0.30 en 0.51, met een specificiteit tussen de 0.74 en 0.86. Als we kijken naar sensitiviteit, doen zowel de PEST (0.68) als de PASE (0.66) en de EARP (0.87) het beter dan de CONTEST, maar qua specificiteit doet de CONTEST het beter dan de PEST (0.71), PASE (0.57) en EARP (0.34). In onze eerstelijnspopulatie zijn we tot de conclusie gekomen dat de CONTEST geen meerwaarde heeft boven de al bestaande PEST, PASE of EARP.

Het laatste hoofdstuk van dit proefschrift, **hoofdstuk 9**, is een algemene discussie van de resultaten beschreven in dit proefschrift. De discussie richt zich op de generaliseerbaarheid en aanbelevlingen voor toekomstig onderzoek. In dit hoofdstuk worden ook manieren beschreven om de awareness voor SpA te vergroten en ideeen om dit in de praktijk te onderzoeken.

Addendum

About the Author

Maren Charlotte Karreman werd op 30 januari 1988 geboren in Rotterdam. Zij groeide op in Rotterdam en haalde in 2006 haar VWO+ diploma op Scholengemeenschap Schravenlant in Schiedam. Direct aansluitend is zij via decentrale selectie toegelaten tot de geneeskunde opleiding aan de Erasmus Universiteit te Rotterdam. Het keuze-onderzoek ter afsluiting van de doctoraal werd uitgevoerd op de afdeling Huisartsgeneeskunde met een onderzoek naar corticosteroïd-injecties in het schouder gewricht. Aansluitend begon zij aan haar co-schappen en werd de interesse voor de reumatologie gewekt. Het oudste co-schap werd gedaan op de afdeling reumatologie en interne geneeskunde van het Maasstad Ziekenhuis.

Gedurende dit oudste co-schap bleek er een plek als onderzoeker vrij te komen voor een jaar in het Erasmus MC om de SENSOR studie op te zetten. Onder begeleiding van dr. J.J. Luime en dr. A.E.A.M. Weel heeft zij toen gedurende een jaar de SENSOR studie opgezet en uitgevoerd. Dit project bleek een mooie opstap naar een volledig promotie traject, gebaseerd op de data uit de SENSOR studie en de nieuw op te zetten AppSpA studie. Het promotietraject werd uitgevoerd onder begeleiding van dr. J.J. Luime, dr. A.E.A.M. Weel en prof. dr. J.M.W. Hazes en was een samenwerking tussen het Erasmus MC, het Maasstadziekenhuis en The Dutch Institute of Rheumatology (TDIOR BV).

Sinds 1 november 2016 is zij begonnen aan haar opleiding tot reumatoloog (opleider dr. R.J.E.M. Dolhain), startend met de vooropleiding interne geneeskunde in het Maasstad Ziekenhuis te Rotterdam (opleider dr. M.A. van den Dorpel).

Maren is op 4 september 2015 getrouwd met Remco Hof en op 15 maart 2017 zijn zij ouders geworden van hun dochter Maeve.

PhD Portfolio

Name PhD student: Maren Charlotte Karreman
Erasmus MC Department: Rheumatology
Research School: NIHES
PhD period: February 2013- October 2016
Promotor: Prof. dr. J.M.W. Hazes
Co-promotors: dr. J.J. Luime & dr. A.E.A.M. Weel

	Year	Workload (ECTS)
General courses		
- Workshop Endnote	2013	0.3
- Workshop Systematic Literature Search in Pubmed	2013	0.3
- Workshop Systematic Literature Search in Other Databases	2013	0.3
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek'	2014	1.0
- Research Integrity	2015	0.3
- Biomedical English Writing and Communication	2015	3.0
Specific courses (e.g. Research school, Medical Training)		
- NIHES Biostatistical methods I	2014	5.7
- NIHES Quality of Life	2015	0.9
- NIHES Missing Values	2015	0.7
- NIHES Planning & Evaluation of Screening	2015	1.4
- NIHES Topics in Meta-Analysis	2015	0.7
- NIHES Clinical Epidemiology	2015	5.7
Seminars and workshops		
- Department Research Meetings	2013-2016	1.0
- CICERO Meetings	2013-2016	1.0
Presentations & Conferences		
- GRAPPA Fellows Symposium, Geneva, Switzerland [1 Oral Presentation]	2014	2.0
- Maasstad Wetenschapsdag [1 Poster Presentation]	2014	1.0
- Dutch Society for Rheumatology (NVR) Conference, Papendal, the Netherlands [1 Oral Presentation]	2014	2.0
- American College of Rheumatology (ACR) Conference, Boston, USA [2 Poster Presentations]	2014	1.0
- GRAPPA Educational Workshop, Antwerp, Belgium [Attendance]	2015	0.5
- European League Against Rheumatism (EULAR) Conference, Rome, Italy [2 Poster Presentations]	2015	1.0
- International Federation of Psoriasis Associations (IFPA) 4th World Psoriasis & Psoriatic Arthritis Conference, Stockholm, Sweden [1 oral presentation, 2 poster presentations]	2015	2.0
- Dutch Society for Rheumatology (NVR) Conference, Papendal, the Netherlands [3 Poster Presentations]	2015	1.0
- Maasstad Wetenschapsdag [2 Poster Presentations]	2015	1.0

- European League Against Rheumatism (EULAR) Conference, London, United Kingdom [4 Poster Presentations]	2016	1.0
- 10th International Congress on Spondyloarthritides, Gent, Belgium [5 Poster Presentations]	2016	1.0
- Dutch Society for Rheumatology (NVR) Conference, Papendal, the Netherlands [3 Poster Presentations]	2016	1.0
Teaching		
- Teaching course 'Kritisch Lezen' to 1st year medical students	2014	1.0
- Teaching course 'Diagnostiek' to 4th year medical students	2015	1.0
- Teaching course 'Klinisch Redeneren' to 1st year medical students	2015-2016	1.0
Other		
- Travelgrants Reumafonds, Erasmus Trustfonds & EULAR		
- Travel bursary GRAPPA Fellows Symposium		
- Study Management of SENSOR & AppSpA Studies		
- Developing standardised care pathways (zorgpaden) for co-management of dermatology-rheumalogy and gastroenterology-rheumatology Maasstad Hospital		

List of publications

This Thesis

M.C. Karreman, A.E.A.M. Weel, M. van der Ven, M. Vis, I. Tchetverikov, T. Nijsten, M. Wakkee, J.M.W. Hazes, J.J. Luime. *Prevalence of Psoriatic Arthritis in Primary Care Patients with Psoriasis*. Arthritis Rheumatol, 2016 Apr;68(4):924-31

M. van der Ven, **M.C. Karreman**, A.E.A.M. Weel, I. Tchetverikov, M. Vis, T. Nijsten, J.M.W. Hazes, J.J. Luime. *Adding Ultrasound to Clinical Examination reduced Frequency of Enthesitis in Primary Care Psoriasis Patients with Musculoskeletal Complaints.*
Clin Exp Rheumatol. 2016 Nov-Dec;34(6):1020-1025

M.C. Karreman, A.E.A.M. Weel, M. van der Ven, M. Vis, I. Tchetverikov, T. Nijsten, M. Wakkee, J.M.W. Hazes, J.J. Luime. *Performance of Screeningtools for Psoriatic Arthritis: A Cross-sectional Study in Primary Care*.
Rheumatology (Oxford). 2017 Apr 1;56(4):597-602

M.C. Karreman, J.J. Luime, J.M.W. Hazes, A.E.A.M. Weel. *The Prevalence and Incidence of Axial and Peripheral Spondyloarthritis in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis.*
J Crohns Colitis. 2017 May 1;11(5):631-642

M.C. Karreman, J.M.W. Hazes, C.J. van der Woude, A.E.A.M. Weel. *Musculoskeletal Complaints cause Significant Burden in Patients with Inflammatory Bowel Disease: A Survey among Patients.*
Submitted

M.C. Karreman, J.M.W. Hazes, A.E.A.M. Weel. *Awareness of Spondyloarthritis in General Practitioners and their Patients: A Cross-sectional Survey in Primary Care.*
Submitted

M.C. Karreman, A.E.A.M. Weel, M. van der Ven, M. Vis, I. Tchetverikov, T. Nijsten, M. Wakkee, J.M.W. Hazes, J.J. Luime. *Which Tool to use when Screening for Psoriatic Arthritis in Psoriasis Patients in a Primary Care Setting?*
Submitted

Other

N.M. Basoski, T.M. Kuijper, **M.C. Karreman**, A.E.A.M. Weel, P.L.C.M. van Riel. *Improvement in Shared Decision Making in Patients with Rheumatoid Arthritis in the Maasstad Hospital in Rotterdam*.
Submitted

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Allereerst mijn promotor, professor Hazes. Beste Mieke, bedankt voor alle begeleiding de afgelopen jaren. Ondanks de altijd drukke agenda, was er altijd tijd in te plannen voor overleg en tijd voor waardevolle feedback op de artikelen. Na elk overleg waren de grote lijnen weer duidelijk en kon ik met frisse moed weer verder.

Ik had de eer om begeleid te worden door twee co-promotoren, met een hele goede mix tussen wetenschap en kliniek.
Angelique, ik herinner me nog een gesprek tijdens mijn oudste co-schap waarin je zei het is gelukt je enthousiast te maken voor het vak als reumatoloog, nu nog voor het onderzoek. Toen zei ik dat dat waarschijnlijk niet ging lukken, maar nu ligt er toch een boekje. Iets wat begon met een project van een jaar, is uitgegroeid tot een volledig promotietraject. Bij elk overleg keek jij altijd weer naar het verband met de kliniek, wat heel waardevol geweest is voor mijn stukken. Bedankt voor dit alles.
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Klinisch onderzoek doen is niet mogelijk zonder patiënten. Ik wil daarom alle patiënten die deelgenomen hebben aan zowel de SENSOR als de AppSpA studie hartelijk bedanken. Ook de huisartsen die bereid waren hun patiënten voor ons onderzoek uit te nodigen wil ik hiervoor bedanken. Tot slot wil ik de Psoriasis Vereniging Nederland (PVN) en de Crohn en Colitis Ulcerosa Vereniging Nederland (CCUVN) bedanken voor hun medewerking aan de AppSpA studie.

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"It is more fun to talk with someone who doesn't use long, difficult words but rather short, easy words like "What about lunch?" - Winnie the Pooh

Ik denk dat er geen zin is die meer van toepassing is op de club promovendi van de reumatologie destijds. We hebben hard gewerkt, maar het was ook altijd gezellig. Gewoon even lunchen in het park, high-tea-en of sushi eten en even niet over het onderzoek praten.
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