

Extra-articular manifestations and comorbidities in spondyloarthritis : epidemiological and clinical aspects

Citation for published version (APA):

Stolwijk, C. (2015). *Extra-articular manifestations and comorbidities in spondyloarthritis : epidemiological and clinical aspects*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20150424cs>

Document status and date:

Published: 01/01/2015

DOI:

[10.26481/dis.20150424cs](https://doi.org/10.26481/dis.20150424cs)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

CHAPTER 10

Summary



SUMMARY

Spondyloarthritis (SpA) is a group of interrelated chronic rheumatic diseases characterized by inflammation of the axial skeleton, inflammation of the peripheral joints, and extra-articular manifestations (EAMs) comprising acute anterior uveitis (AAU), psoriasis, and inflammatory bowel disease (IBD). The EAMs are considered to belong to the SpA concept. In addition to the articular and extra-articular SpA manifestations, patients may suffer from conditions which do not belong to the concept of SpA, such as cardiovascular disease. These conditions are not part of the SpA concept and are therefore referred to as comorbidities. Comorbidity is the general term for such conditions that occur in addition to an index disease.

This thesis focuses on the prevalence of SpA and aspects of conditions outside the joints in patients with SpA. Key questions addressed in this thesis include the epidemiology of SpA, the epidemiology of EAMs in patients with ankylosing spondylitis (AS), the risk of specific comorbidities, and the measurement of comorbidity for research purposes.

Part I: Prevalence of Spondyloarthritis

Chapter 2 describes a systematic literature review on the prevalence of SpA and its subtypes. In total, 84 studies were identified that estimated the prevalence of SpA, AS, psoriatic arthritis (PsA), reactive arthritis (ReA), SpA associated with IBD, and undifferentiated SpA (uSpA). For SpA, AS, and PsA, a sufficient number of studies was available to perform a meta-analysis. This meta-analysis showed a pooled population prevalence for SpA of 0.55% (95% CI 0.37-0.77); for AS of 0.18% (95% CI 0.15-0.23); and for PsA of 0.15% (95% CI 0.12-0.18), with very high heterogeneity (>99%) among the studies. Subgroup-analyses and meta-regression analyses were performed to identify demographical and methodological variables that could explain part of this heterogeneity. Geographic region was an important determinant of the prevalence of SpA and AS. Generally, it can be stated that prevalence estimates were higher in studies from Europe and North America, compared with Asia, the Middle East, and Africa. This may be particularly explained by differences in the prevalence of HLA-B27, which is associated with the prevalence of SpA. Further, the prevalence of SpA, and AS in particular, was higher in male compared with female subjects. The prevalence of PsA, on the other hand, was significantly higher in studies with a higher mean age of the population studied. With respect to methodological variables, the prevalences of SpA and PsA were positively related to the year of data collection (i.e. higher prevalences in more recent studies), whereas the prevalence of AS was not. Further, the case definition used was significantly related to the prevalence estimates. In general, prevalence estimates were higher in population studies in which a screening method followed by a confirmation phase was used compared with hospital or register based studies in which diagnosis was based on medical records or

international classification of disease (ICD) codes. With respect the final confirmation of the case definition, prevalence estimates were higher when patients were classified according to the European Spondyloarthritis Study Group (ESSG) criteria for SpA or the (modified) New York criteria for AS compared with other case definitions, such as medical records diagnoses.

Part II: Epidemiology of extra-articular manifestations

Chapter 3 and **chapter 4** describe the epidemiology of EAMs in patients with AS, including the prevalence, the incidence, and the risks of developing an EAM in patients with AS compared with the general population. Chapter 3 comprises a systematic literature review on the prevalence of EAMs in patients with AS, and chapter 4 assesses the prevalence, incidence and risks of EAMs in patients with AS in the Clinical Practice Research Database (CPRD) from the United Kingdom. In the CPRD study, 4,101 patients with AS were matched with up to seven control subjects without AS by year of birth, sex, and practice (n=28,591).

First, the epidemiology of acute anterior uveitis (AAU) in AS was studied. In the systematic review, a pooled prevalence of 25.8% (95% CI 21.1 to 27.6) was found in 143 studies in which patients had a mean disease duration of AS of 15.9 (SD 5.9) years (chapter 3). In CPRD, a prevalence of AAU of 11.9% at diagnosis of AS and of 24.5% after 20 years of disease was found (chapter 4). In both studies, it was shown that the prevalence of AAU was significantly associated with disease duration of AS. In other words, patients with AS may develop a first episode of AAU many years after the diagnosis of AS. Further, it was shown in the review that the prevalence of AAU differs between geographic areas. The highest prevalence estimates of AAU in patients with AS were reported in studies from Europe and North America. Similarly to the prevalence of SpA itself, this could be explained first of all by differences in HLA-B27 in different geographic areas. With respect to the methodological factors, the prevalence of AAU was associated with selection of patients. The prevalence of AAU was on average lower in studies with a low risk of bias concerning random selection of patients. In CPRD, the incidence of AAU was 8.9 per 1000 person years in patients with AS, and 0.4 per 1000 person years in controls. After adjustment for possible confounders, the risk of developing a first episode of AAU after diagnosis of AS was 15.5-fold increased in patients compared with controls. This risk was highest in younger patients (16-39 years), in male patients and in patients with shorter disease duration. Nevertheless, 10 years after the index date, the risk of developing a first episode of AAU was still 9-fold increased.

Second, the epidemiology of psoriasis in AS was assessed. In the systematic review, a pooled prevalence of 9.3% (95% CI 8.1 to 10.6%) was found, after a mean disease duration of AS of 16.7 (SD 6.2) years (chapter 3). No significant association with disease duration could be shown in the review. In CPRD, 4.1% of the patients were known with

psoriasis at diagnosis of AS, and this proportion increased to 10.1% after 20 years (chapter 4). In the meta-regression analysis, the prevalence of psoriasis was significantly associated with geographic region. The highest prevalences were found in studies from Europe and Latin America. The incidence of psoriasis was 3.4 per 1000 person-years in patients with AS, and 1.8 per 1000 person-years in controls (chapter 4). Compared with population-based controls, the risk of psoriasis was 1.5-fold (95% CI 1.1-1.9) increased. The risk was only significantly increased in the first five years after diagnosis. Thereafter the risk was comparable with population based controls.

Third, the prevalence of IBD in AS was assessed. In the systematic review, the pooled prevalence of IBD was 6.8% (95% CI 6.1 to 7.7%) after a mean disease duration of 16.7 (SD 6.3) years (**chapter 3**). The prevalence of IBD found in the meta-analysis is in line with the CPRD-study, which found a prevalence of 4.0% at the index date of AS, and a prevalence of 7.5% of IBD after 20 years of AS (**chapter 4**). The prevalence of IBD in patients with AS was also associated with geographic region, with lower prevalences in studies from Asia compared with Europe. The incidence of IBD was 2.4 per 1000 person-years in patients with AS, and 0.4 per 1000 person-years in controls. Compared with the general population, the risk of developing IBD was 3-fold (95% CI 2.3-4.8) increased during follow-up, but was only significantly increased in the first ten years of follow-up. In **chapter 5** the frequency of SpA features in patients with IBD was assessed. Three hundred and fifty consecutive patients with IBD who visited the outpatient clinic were questioned about the presence or history of possible SpA features including inflammatory back, peripheral arthritis, enthesitis, dactylitis, psoriasis and AAU. Medical records of all patients were checked to assess whether patients had ever visited a rheumatologist and whether they were diagnosed with any rheumatic diagnosis. Of all 350 patients, 129 (36.9%) patients reported at least one musculoskeletal SpA feature: 79 (22.6%) patients reported inflammatory back pain, 33 (9.4%) reported peripheral arthritis, 47 (12.0%) reported enthesitis, and 29 (8.3%) patients reported dactylitis. Medical record review showed that 66 (51.2%) patients had ever visited a rheumatologist. Axial SpA was diagnosed in 18 (27.3%) of these patients, peripheral SpA in 20 (30.3%) patients and another rheumatic disorder in 14 (21.2%) patients. Strikingly, 49.8% of the patients with musculoskeletal complaints belonging to the SpA spectrum were never referred to a rheumatologist.

Part III: Comorbidity in Ankylosing Spondylitis

In **chapter 6** we investigated the criterion and construct validity of the self-administered comorbidity questionnaire (SCQ) in patients with AS. The SCQ is a comorbidity questionnaire including 13 common medical conditions, developed to adjust for the impact of comorbidity on functional status. Ninety-eight patients who participated in the Outcome in AS International Study (OASIS) completed the SCQ. In total, 64 (65.3%) patients reported

at least one non-rheumatic comorbidity. Criterion validity was assessed by the degree to which the self-reported comorbidities in the SCQ correlated with comorbidity data from the medical records. It was shown that patients can accurately report most comorbidities, except for stomach disease and depression, which were reported more frequently by patients than retrieved from the medical records. The agreement for rheumatic conditions included in the SCQ was also low. Construct validity was assessed by correlating the SCQ with other comorbidity scores: the Charlson index and the Michaud-Wolfe index (now called Rheumatic Disease Comorbidity Index, RDCl); and by correlating the SCQ with demographics, physical function, health related quality of life (HRQoL) and AS-related disease activity. These analyses were performed both for the 'original' SCQ as well as for a modified version of the SCQ (mSCQ), in which rheumatic conditions were removed, because these conditions are difficult to distinguish by patients from the index disease (i.e. AS). The correlations between the SCQ and the Charlson index and Michaud-Wolfe index were low, but stronger for the mSCQ. We further showed that the SCQ correlated with age, HRQoL and physical function, which adds to the construct validity of the SCQ. In a multivariable regression analysis, the SCQ and mSCQ were significantly associated with HRQoL, physical function and work disability, the latter only in patients with low disease activity.

In **chapter 7** the incidence and risks of cardiovascular morbidity was assessed in patients with AS compared with the general population, including the role of non-steroidal-anti-inflammatory drugs (NSAIDs). All patients with newly diagnosed AS were identified from CPRD and matched with up to 7 controls. Hazard ratios (HR) for development of ischemic heart disease (IHD) and acute myocardial infarction (AMI) were calculated. Adjustments were made for age, gender, comorbidity, and drug use, including NSAIDs. The age-gender adjusted HR for developing IHD was not significantly increased (HR 1.20, 95% CI 0.97-1.48) in patients with AS. After stratification for gender, the risk of IHD was increased in female patients only (HR 1.88, 95% CI 1.22-2.90). After adjustment for potential confounders, the risk of IHD was not significantly increased in male (HR 0.94, 95% CI 0.73-1.21) nor in female patients (HR 1.31, 95% CI 0.86-2.08). Recent NSAID use explained this change for an important part, (HR IHD adjusted for age and NSAID in females 1.57, 95% CI 0.99-2.48). In patients with AS who used an NSAID in the last three months before an event, the HR of IHD was significantly increased (1.36, 95% CI 1.00-1.85) compared with controls. The risk of developing IHD was particularly increased in patients who used a COX-2 inhibitor (HR 3.03, 95% CI 1.61-5.69). The risk of developing an AMI was not significantly increased in patients with AS: the age-gender-adjusted HR was 0.91 (95% CI 0.65-1.28) and the fully-adjusted HR was 0.76 (95% CI 0.53-1.09).

Chapter 8 evaluated the effect of infliximab on symptoms of depression in patients with AS in a subgroup analysis of a randomized-controlled trial: the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT). Furthermore, this

study tried to explore whether depressive symptoms in patients with AS are secondary to disease-related functional impairment and pain, or that depressive symptoms are the result of the inflammatory immune response, for example as a result of increased levels of anti-TNF- α . Patients were randomized to receive infliximab (n=17) or placebo (n=6) until week 24 after which all patients continued with infliximab until week 54. Depressive symptoms were measured with the Center for Epidemiological Studies Depression Scale (CES-D, range 0-60) at week 0, 6, 12, 24, and 54. We showed that the mean depression score was high at baseline (15.7, SD 8.0) and that 47.8% of patients had a CES-D score ≥ 16 , which is indicative of clinical depression. After six weeks of infliximab, the CES-D score had decreased in the infliximab group and was significantly lower in the infliximab group compared with the placebo group ($p=0.03$). After 24 weeks, the mean CES-D score was still lower in the infliximab group than in the placebo group, although the difference did not reach statistical significance (CES-D score 10.8 (SD 11.4) versus 16.2 (SD 6.8), $p=0.07$). Generalized estimating equation (GEE) analyses of covariance showed a trend towards significance between the infliximab and placebo-group for CES-D scores over 24 weeks ($p=0.06$). At week 24, 20% of the patients in the infliximab group and 57% of the infliximab group had a CES-D score indicating clinical depression ($p=0.17$). In patients with depression at baseline in the infliximab group, the improvement in depression-scores was moderately related to the improvement in disease activity (BASDAI, $r=0.76$, $p=0.03$) and physical function (BASFI, $r=0.74$, $p=0.04$) at week 24. Importantly, the correlation between improvement in CES-D score and improvement in BASDAI score was lower after six weeks of treatment compared with later ascertainments, which may be explained by a faster improvement in depression scores than BASDAI scores. These findings suggest, but do not prove, that the improvement in depressive symptoms in patients with AS who were treated with infliximab were not only a result of improvement in pain and functional impairment, but also a result of a more direct effect of TNF- α inhibition.

In **chapter 9** the main findings of this thesis were discussed. First, it was discussed how co-existing diseases should be conceptualized in patients with SpA. Pathogenetically, there is a clear difference between EAMs and comorbidities, because EAMs are disease manifestations belonging to the SpA concept rather than distinct entities, in contrast to comorbidities which lack this relation. For diagnosis and treatment in clinical practice and for outcome measurement in research, however, it often seems more practical to consider EAMs also as distinct entities. Second, methodological considerations were discussed including external validity and measurement of EAMs and comorbidity. Generalizability of the prevalence of SpA and EAMs is hampered by genetic differences in HLA-B27 among populations, whereas cause-relation studies are more generalizable, although effect-modification may play a role. Because comorbidity has an important impact on different outcomes, such as HRQoL and participation, it is relevant to measure comorbidity. The approach of measuring comorbidity is dependent on the study type

and research question. Third, implications for research and research challenges were discussed. This thesis contributed to the knowledge on EAMs and comorbidity in patients with SpA, but many more questions remain to be answered, for example with respect to the role of EAMs in the concept of SpA and etiopathogenic concepts of comorbidity. Finally, recommendations for clinical practice were made with respect to EAMs and comorbidity. The high prevalence of EAMs and comorbidity asks for a reorganization of the way we deliver healthcare.