# The burden of early axial spondyloarthritis

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# Chapter 8

## Summary and General Discussion

In this final chapter, the most important findings of the studies presented in this thesis are summarized, placed in a broader perspective, and possibilities for future research are discussed grouped by three themes. The three themes are: the value of a positive family history of spondyloarthritis (SpA), the impact of axial SpA (axSpA) on health outcomes in the early phase of axSpA, and illness perceptions and coping strategies of patients with axSpA.

The studies presented in this thesis were performed using data from three cohorts of patients suspected of axSpA with (inflammatory) back pain ≥ 3 months: the worldwide Assessment in SpondyloArthritis international Society (ASAS) cohort[1-3] which included patients with a back pain onset < 45 years, the French DEvenir des Spondyloarthropathies Indifférenciées Récentes (DESIR) cohort[4] which included patients aged between 18-50 years with inflammatory back pain persisting < 3 years, and the European SPondyloArthritis Caught Early (SPACE) cohort[5] which included patients aged ≥ 16 years with back pain persisting ≤ 2 years and an onset of back pain < 45 years.

The ASAS defined a positive family history of SpA as a documented history of radiographic axSpA, but also of uveitis, psoriasis, inflammatory bowel disease (IBD), or reactive arthritis in first- or second-degree relatives.[3] In the early 1990s a positive family history was introduced as a feature in classification criteria for axSpA patients in the Amor and ESSG criteria and nowadays it is part of the widely used ASAS classification criteria. Although these classification criteria for axSpA were extensively tested and validated, it is quite striking that the definition of a positive family history was never tested nor validated before it was being used in any of the classification criteria. This definition is simply based on consensus of experts. However, it is apparently regarded as useful for identifying patients with axSpA as experts support this definition and the definition has remained essentially unchanged in the last 30 years.

In **Chapter 2** we studied the value of various aspects of this definition in identifying patients who are human leukocyte antigen-B27 (HLA-B27) positive and therefore have an increased risk of axSpA. In the ASAS cohort, a worldwide cohort of patients suspected of axSpA, only a positive family history of axSpA could be used to identify patients who are HLA-B27 positive, while a positive family history of uveitis, reactive arthritis, IBD, and psoriasis were not useful in this regard. Similar results were found irrespective of ethnicity or in the presence of a positive family history in first- or second-degree family members.

These findings were also confirmed in the DESIR and SPACE cohorts investigated by Ez-Zaitouni et al (2018)[6], but in addition to a positive family history of axSpA in this study they reported that a positive family history of uveitis was also associated with HLA-B27

positivity. However, if a choice can be made testing the HLA-B27 status is preferred as HLA-B27 positivity has a higher positive predictive value than a positive family history as referral tool to secondary care for patients suspected of axSpA.[7, 8]

The potentially added value of a positive family history in diagnosing axSpA when the HLA-B27 status is already known was assessed in **Chapter 3**. Three definitions of a positive family history were tested; the current ASAS definition of a positive family history for SpA (including all five diseases), a positive family history for radiographic axSpA, and a positive family history for uveitis. A positive family history is common among patients suspected of axSpA as one-third of the patients had a positive family history in all three cohorts in **Chapter 3**. We showed that when HLA-B27 status was known none of the three definitions of a positive family history was associated with a diagnosis of axSpA anymore in patients with different ethnical backgrounds. We found that HLA-B27 negative familial axSpA exists but is relatively rare and that even in absence of HLA-B27 positivity a positive family history did not contribute to an axSpA diagnosis. Thus, a positive family history of SpA has a limited value in diagnosing axSpA when HLA-B27 status is known.

The results of **Chapters 2** and **3** have implications for the use of the criterion 'positive family history'. When broad HLA-B27 testing is not useful (e.g. in general practice because of too low prevalence of SpA), the presence of a positive family history of axSpA and a positive family history of uveitis in first- and second-degree family members can to some extent be used to predict HLA-B27 positivity in patients suspected of axSpA as demonstrated in **Chapter 2** and the study by Ez-Zaitouni et al (2018). However, it is important to realize that a positive family history is usually reported by patients themselves and the validity of such a report is often at stake for obvious reasons. Moreover, a substantial number of patients with HLA-B27 positive axSpA do not have a positive family history. When diagnosing patients suspected of axSpA, **Chapter 3** suggests that rheumatologists should rather not give extra weight to a positive family history when a patient's HLA-B27 status is already known.

Our findings from **Chapter 3** could have also implications for classifying axSpA patients. Since the introduction of the ASAS classification criteria there have been concerns about the criteria for various reasons. For example, there have been concerns that the clinical arm might not have sufficient sensitivity and specificity. At this moment, a positive family history is one of the SpA features in the ASAS classification criteria for axSpA and in these criteria a positive family history has an independent contribution on top of HLA-B27 positivity. **Chapter 3** raises questions about the relative weight of a positive family history in the ASAS classification criteria for axSpA. The performance of the ASAS classification criteria for axSpA is currently re-evaluated in a worldwide prospective cohort, named the

CLassification of Axial Spondyloarthritis Inception Cohort (CLASSIC) study. Refinements of the criteria may be proposed and tested if the current ASAS classification criteria for axSpA do not meet a sufficiently high level of specificity (≥90%) while preserving sensitivity of ≥75%. This setting is appropriate to test if the criterion 'positive family history' is redundant and should be removed from these classification criteria, reweighted, or combined with the criterion HLA-B27 positivity. These options could be considered while preserving a similar level of specificity and sensitivity as set out in the analysis plan of the CLASSIC study and obtained with the original ASAS classification criteria for axSpA when using the rheumatologist's diagnosis as external standard.

The definition of a positive family history for SpA according to ASAS might be questioned as only a positive family history of axSpA and a positive family history of uveitis were associated with HLA-B27 carriership. This indicates that the associations between a positive family history (of all five diseases) and HLA-B27 carriership are mostly driven by a positive family history of axSpA and a positive family history of uveitis. Therefore, limiting the ASAS definition of a positive family history for SpA into a positive family history of axSpA and/or uveitis may be considered.

In our study, the majority of the analysed patients had a white or Asian ethnicity, the two largest axSpA populations worldwide.[9] However, there was an under-representation of patients with for example an African or Arabic ethnicity. Moreover, other ethnicities than a white or Asian ethnicity are also hardy addressed in existing literature. Therefore, it would be recommended to address also other ethnicities in future studies. It might be difficult to replicate our findings in populations in which the prevalence of HLA-B27 is low or virtually absent, such as in Arabic and African black populations.[10, 11]

The studies in **Chapters 2** and **3** investigated patients with predominantly axial symptoms and not patients with predominantly peripheral symptoms. Future research could further investigate the value of a positive family history among patients with or at risk of peripheral disease, as currently the same definition of a positive family history is used for both axial and peripheral SpA. Different definitions of a positive family history for axial and peripheral SpA might be necessary as for example psoriasis might be more relevant for patients with peripheral disease.[12]

The previous part discussed how the identification of patients at risk of axSpA could be improved. This is important as patients could be treated earlier if we are able to better identify patients. The earlier patients with axSpA are treated, the earlier the burden of disease could be reduced. Moreover, the course of the disease could possibly be influenced by a timelier treatment. However, the disease burden in an early phase of

axSpA is not well investigated. We studied the disease burden of early axSpA by measuring the impact of axSpA on quality of life, work productivity, and participation in daily activities. In **Chapters 4** and **5** we assessed and quantified the impact of disease activity on Health-Related Quality of Life (HRQoL) and work productivity over time in patients with early axSpA. We also assessed if the impact is similar in prognostically relevant subgroups. The impact of axSpA on work productivity was assessed by four variables; absenteeism, presenteeism, work productivity loss, and activity impairment. Absenteeism represents the working hours lost due to axSpA (i.e. sick leave), presenteeism represents the decreased performance at work due to the axSpA (i.e. inefficiency at work), work productivity loss is a summary measure representing the total work impairment due to axSpA, and activity impairment represents the impairment in daily activities outside work due to axSpA.

**Chapters 4** and **5** demonstrate that physical HRQoL, work productivity, and daily activities are seriously impacted even in the earliest phase of the axSpA and are as substantially impacted as longstanding axSpA. Disease activity decreased over time, which was associated with improvements in physical HRQoL, work productivity, and daily activities. Nevertheless, the burden of early axSpA remained substantial over time despite these improvements. The mental HRQoL was comparable to the general population and remained stable over time. These chapters show that there is still a lot of room of improvement to decrease the burden of early disease further.

Gender and job-type defined important prognostically relevant subgroups when considering HRQoL as outcome in **Chapter 4**; the same level of disease activity had less impact on physical HRQoL in women and white-collar workers. When considering work productivity as outcome in **Chapter 5**, the duration of chronic back pain and start of medication use defined important prognostically relevant subgroups; an improvement in disease activity was associated with less absenteeism over one year only in patients with the shortest duration of chronic back pain and in patients who started treatment. The impact of disease activity on other work outcomes (work productivity loss, presenteeism, and activity impairment) remained similar between patients with the shortest vs. the longest duration of chronic back pain or with no change vs. started any treatment.-

**Chapters 4** and **5** demonstrate that the burden of axSpA remains substantial over time even in an early disease phase. It is therefore important to further decrease this burden, as axSpA does not only affect patients with axSpA, but also their friends, family and society. About one-fifth of the patients with radiographic axSpA (r-axSpA) needed help from friends and family.[13] Partners of patients with r-axSpA also experienced impairments in their HRQoL compared to healthy controls and partners experienced difficulties with managing axSpA from limitations in leisure time activities to altered relational roles.[14, 15] Moreover,

the financial burden is also substantial in axSpA. Patients and society are affected by significant costs associated with medication, expenses by the health care provider for medical services, and non-health care costs (e.g. help in household) but also by indirect costs such as loss of work productivity and work disability.[16-18] In a large European study nearly half of the axSpA patients took their disease into account in their career choices, nearly three-fourth of the patients had difficulties with finding a job due to axSpA and more than 40% of the patients required adaptations of their work place.[19] It has even been suggested that the costs related to the impairment in work productivity are the largest financial burden.[17] As axSpA affects patients in their early adult and working life, patients but also society will experience the impact of axSpA for many years which could lead to an excessive burden of axSpA on long-term. For example, leaving the work force was predicted by prior absenteeism and absenteeism was predicted by prior presenteeism among patients with early axSpA.[20] This suggests that it is important to treat axSpA early, to strive for less impairment in work and daily life by axSpA, and possibly by providing support to partners of patients with axSpA. The European League Against Rheumatism (EULAR) indeed already recommends that in disease management individual, medical and societal costs including work productivity should be taken into account.[21]

A promising way for further decreasing the burden of (early) axSpA might be treat-to-target (T2T). Treatment of for example rheumatoid arthritis (RA) has been improved by both the development of biologics but also by aggressive T2T strategies. However, axSpA is a more heterogeneous disease and the natural disease course of axSpA may be more variable than RA. Recently, an international task force of experts published recommendations for T2T in axSpA but this task force also acknowledged that evidence is limited and more knowledge of the association between disease activity and health outcomes is necessary.[22] Our findings in **Chapter 4** and **5** support the hypothesis of T2T that T2T should aim for lower disease activity in patients with axSpA in order to maximize HRQoL and social participation over time and support the recommendation that the preferred treatment target of T2T should be clinical remission or low disease activity. Our findings demonstrate also that it is important to intervene already in an early disease phase. At this moment, one clinical trial among axSpA patients is conducted aiming at improving health outcomes by using T2T strategies in order to achieve clinical remission or low disease activity (e.g. TICOSPA NCT03043846). The trial results will provide more insight in the feasibility and cost-effectiveness in treating axSpA by a T2T strategy compared to usual care.

Moreover, the focus should not only be on T2T strategies. To date, pharmacological treatment does not completely resolve impairments in work and quality of life and a substantial unmet need for additional treatment options remains. Other factors such as

illness perceptions and coping strategies which might also impact these health outcomes are investigated in **Chapters 6** and **7**, discussed in the third part.

In clinical practice, it would be useful to be able to identify patients at a high risk of serious impairments in HRQoL or work productivity. However, it difficult to identify these patients as knowledge is limited regarding the association between disease activity and work productivity and HRQoL. In **Chapters 4** and **5** several factors have been found for defining clinically important subgroups based on gender, job type, duration of chronic back pain, start of medication use. However, it might be better to consider several factors together in defining these subgroups to better identify patients at a high risk of impairments in work and daily life. This is often not possible due to relatively small sample sizes of a subgroups considering only one of these factors, such as in **Chapters 4** and **5**. Disease trajectories describe patterns of disease activity over time and help to identify subgroups of patients which could be used for a more individualised treatment.[23] Future research could use disease trajectories in exploring which factors form clinically relevant subgroups in the association between disease activity and health outcomes and taking several of these factors into account at the same time.

Of note, work productivity loss is a patient reported outcome, consisting of absenteeism and presenteeism. It might be better to measure absenteeism by using records for employers as patients might underestimate the amount of sick leave. However, work productivity loss is mostly driven by presenteeism and the best way to measure this is by asking patients about their presenteeism as this is difficult to objectively measure. In **Chapter 4** a generic questionnaire was used to measure the HRQoL. One could argue that a disease-specific questionnaire would be more suited to measure HRQoL as generic questionnaires might underestimate the HRQoL by having no questions that are disease-specific or being adapted to the disease. However, with a generic questionnaire it is possible to make a comparison between the patients with the disease and the general population showing how large the burden of disease is.



As discussed as above, health outcomes are not only affected by biomedical factors but also by contextual factors such as illness perceptions and coping strategies.[24] The process of a patient becoming aware of his/her illness, developing perceptions about this illness, establishing coping strategies to manage this illness, and the impact of these actions on health outcomes is described by a theoretical model, the Leventhal's Common Sense Model of self-regulation (CSM).[25] In the CSM patients respond to their illness by generating illness perceptions. Illness perceptions are beliefs formulated by the patient about his/her illness, which may help them in better understanding their illness but it also represents the emotional state of a patient. As a response to these illness perceptions, coping strategies

are developed. Coping strategies are cognitive and behavioural strategies and help patients to manage stress associated with having to live with their illness.[25, 26]

In **Chapter 6** we investigated if illness perceptions and coping strategies influenced the association between back pain and health outcomes in patients with axSpA (or a suspicion thereof). **Chapter 6** demonstrates that the association between increasing self-reported back pain intensity and worsening of HRQoL and work productivity loss is substantially impacted by negative illness perceptions. A similar level of back pain intensity was associated with more impairment in physical HRQoL when patients had negative illness perceptions such as belief in severe consequences due to the illness ('*consequences*') and beliefs in chance as a cause for their illness ('*chance*'). When patients attributed more symptoms to their illness ('*identity*'), had strong negative emotions towards their illness ('*emotional representation*'), and had strong beliefs in psychological attributions as a cause such as thinking about life negatively ('*psychological attributions'*) a similar level of back pain was associated with more impairment in mental HRQoL. A similar level of back pain was related to more work productivity loss when patients had strong beliefs in severe '*consequences*'. We did not find such an impact by coping strategies.

Health outcomes might be improved by influencing illness perceptions in a positive manner and possibly by interfering with coping strategy choices. As a first step in investigating this hypothesis we investigated in **Chapter 7** if illness perceptions and usage of particular coping strategies are susceptible to changes in disease status or remain stable over time. **Chapter 7** showed that whilst back pain, disease activity, and health outcomes clearly improved over 2 years in patients recently diagnosed with axSpA, illness perceptions and coping strategies remained remarkably stable.

**Chapter 6** suggests that illness perceptions might be considered in the treatment of patients with axSpA in addition to existing treatment options when aiming to (further) improve health outcomes. Although we did not find that coping strategies impacted the association between back pain and health outcomes in **Chapter 6**, coping strategies should not be excluded. According to the CSM illness perceptions influence the usage of coping strategies and illness perceptions could be adapted based on if health outcomes improve or diminish by the impact of coping strategies due to feedback loops.[25, 26] Therefore, it is important to consider illness perceptions and related coping strategies jointly and not separately in both research and treatment.[26] Unfortunately, studies have often investigated illness perceptions and coping strategies separately and at one point in time. More steps need to be taken before the hypothesis could be confirmed that influencing illness perceptions and interfering with related coping strategies in a positive manner could be used to improve health outcomes in axSpA.

The results of **Chapter 7** suggest that illness perceptions and coping strategies do not change spontaneously and are rather independent of a decrease in disease status in patients with early axSpA. Our findings are in line with other observational studies among patients with other diseases including rheumatic disease and the only other study among patients with (longstanding r-)axSpA.[27-35] Nevertheless, randomized controlled trials showed that illness perceptions changed after being specifically targeted by an intervention such as a cognitive behavioral therapy or a group education program among patients with other diseases including diabetes.[36-45] This suggest that illness perceptions and related coping strategies might be improved in patients with axSpA when they are targeted by specific therapeutic interventions.

The next step would be performing a randomized controlled trial which compares usual care with usual care plus an additional intervention targeting negative illness perceptions and related coping strategies. Based on **Chapter 6** the following illness perceptions form possible targets for this intervention; '*consequences*', '*chance*', '*emotional representation*', '*identity*', and '*psychological attributions*'. Possibly the use of the coping strategies '*decreasing activities*' and '*pacing*' could be discouraged as these coping strategies were negatively associated to physical HRQoL in **Chapter 6**. The choice for the type of intervention could be based on a comparison of the results of interventions performed in other randomized controlled trials, the feasibility of these interventions, and consulting experts in the field of psychological interventions.



Another step would be to determine when changes in illness perceptions and coping strategies are truly relevant changes. This is difficult to assess because no data are available on clinically important changes in illness perceptions and coping strategies. Future research could focus on defining minimally clinically important differences. However, a particular illness perception may have a negative, positive, or mixed impact on health outcomes depending on which coping strategies are used. This makes the interpretation of a single illness perception or coping strategy difficult as the combination of illness perceptions and coping strategies are numerous. Mediation analyses might be used to reveal the most commonly used pathways and show all direct and indirect effects of illness perceptions and coping strategies.

Furthermore, it would be interesting to investigate if patients in an early disease phase differ in illness perceptions and coping strategies from patients with longstanding disease. It is important to explore illness perceptions and coping strategies in these disease phases as different treatment strategies might be necessary or illness perceptions and coping strategies might be more susceptible to change in a certain disease phase. It has been hypothesized that over time patients gain more experience with their illness and

treatment which could lead to different illness perceptions and coping strategies.[26] It has also been hypothesized that illness perceptions mainly change in the initial period after a diagnosis and in a late phase of the disease it might be more difficult to change these illness perceptions.[46, 47] However, other theories assume that illness perceptions and coping strategies are not susceptible to change anymore once illness perceptions have been formed and coping strategies have been chosen, which may have taken place already before patients are seeking medical care for their complaints.[48]

The only study which investigated the association between illness perceptions and HRQoL among patients with longstanding axSpA, using the brief version of the questionnaire in **Chapter 6**, suggests that illness perceptions might differ between early and longstanding axSpA. This study found that having more concerns, part of the '*emotional representation*' of the illness[49], was associated with worsening of the physical HRQoL[50] while in **Chapter 6** the illness perceptions '*consequences*' and '*chance*' were associated with decreased physical HRQoL. This suggest that other illness perceptions might become more important in a later disease stage. However, coping strategies do not seem to differ between early and late phases of the disease. We found that '*decreasing activities*' and '*pacing*' were often used by patients with early axSpA and another study also showed that '*pacing*' was often used as a coping strategy among patients with longstanding axSpA.[27] Future research may address if illness perceptions and coping strategies differ between early and late phases of the disease by comparing patients with a short symptom duration to patients with longstanding disease. This is important to investigate, because different treatment strategies might be used for patients in an early vs. longstanding disease phase.

**Concluding remarks**

In summary, the studies reported in this thesis have brought us more knowledge for better identifying patients with axSpA, more insight in the impact of early axSpA on health outcomes, and more knowledge of illness perceptions and the use of coping strategies in patients with axSpA. Better knowledge and insights could help us in making a timely diagnosis, providing treatment sooner, and exploring additional treatment options, which in turn could hopefully reduce the burden of axSpA.

Based on this thesis, future axSpA research should focus on investigating the relative weight of a positive family history in classifying patients, investigating patients with other ethnicities than white or Asian ethnicity, and investigating how the burden of axSpA could be decreased. Possibly, T2T strategies could be used to improve health outcomes among patients with axSpA. Another promising way, which needs extensive research, could be influencing illness perceptions and coping strategies by targeted therapeutic interventions to decrease the impact of axSpA on health outcomes. These are both challenging and exiting times as for early axSpA only the tip of the iceberg has been revealed and underwater more is waiting to be revealed.

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