Clinically suspect arthralgia and early rheumatoid arthritis: advances in imaging and impact on daily life

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General introduction and outline

1 Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a chronic disabling disease, due to recurrent joint inflammation. It is an auto-immune disease that is characterised by erosive polyarthritis with inflammation of mainly the small joints of hands and feet, but it can also affect large joints. The prevalence of RA is estimated as 0.5-1% in the population of adults in western countries.[1] In the Netherlands, approximately 12.400 patients were newly diagnosed with RA in 2017.[2] The disease can occur at any age but predominantly affects middle-aged persons, is more often present in woman than in men.[3] The aetiology of RA is still largely unknown and even though the disease often presents with joint inflammation, it is likely that it consists of a heterogeneous disease with several different risk factors. In general, joint inflammation in RA is caused by the activation of the immune system,[3] and although the disease primarily manifests the joints, it should be considered a syndrome that includes extra-articular phenomena like vasculitis, pulmonary involvement and other systemic complications.[4] Even though the exact causes of RA have not been elucidated yet, several risk factors have been identified. These may involve a combination of genetic, environmental and stochastic factors. Increased risks have been found for smoking, familiar predisposition and female gender.[5] Classically, RA lead to deformity of joints, consequently to destruction as a results of erosions in cartilage and bone. This had a major impact on daily life and physical functioning.[4] During the last decades treatment strategies have improved which resulted in a decreased prevalence of structural damage. However, irrespective of these improved therapeutic options, RA continuous to affect individuals tremendously. Chronic inflammation of the joints can still cause joint destruction with severe pain, loss of function, stiffness and fatigue as result.[6, 7] This significantly affects their contribution to society, through work loss and reduced daily functioning and it continuous to majorly impact a patients' quality of life.[8, 9]

Developmental stages of RA

The developmental course of RA is incompletely understood, it is however recognized that it consists of several phases.[10] The phase preceding that of clinically detectable (chronic) arthritis is already symptomatic, this stage is called Clinically Suspect Arthralgia (CSA). Patients with CSA can be recognized by rheumatologists via a combination of clinical characteristics. These 'CSA patients' are at increased risk to develop RA.[11] Their clinical characteristics were also described by a EULAR taskforce.[12] CSA patients have, based on their clinical characteristics, approximately 18-20% chance on RA development within the next 2 years,[11] which can increase in case of presence of certain laboratory of imaging findings. Also other pre-RA phases can be acknowledged. For example, it was established that systemic auto-immunity can be recognized by the presence of specific auto-antibodies (e.g. ACPA, RF), even years before symptoms have developed. Also genetic and environmental risk factors pose a certain risk on individuals.[13] However, these other 'pre-RA phases' can be challenging to identify and are not studied in this thesis. After the development of arthritis, a substantial part of these CSA patients can be diagnosed with RA. However, in certain patients with early inflammatory arthritis (IA), a specific diagnosis cannot yet be

established, at the onset of arthritis. These patients are called undifferentiated arthritis (UA), which is defined as IA not fulfilling the criteria for RA and also not caused by any other specific cause of arthritis. Part of the patients with UA develop RA during follow-up. A flowchart of these developmental stages of RA are illustrated by Figure 1.1.

Autoantibodies in RA

Factors that have been associated with RA development were different within certain subpopulations of RA patients. Therefore it has been recognized that RA is a heterogeneous disease that can be divided into (at least) two different subsets. Roughly, these groups are considered to consist of patients with auto-antibodies against anti-citrullinated protein antibodies (ACPA) or rheumatoid factor (RF) and patients without these auto-antibodies.[14] RF is detected in up to 60-80% of patients with RA, but can also occur in patients with other auto-immune diseases like systemic lupus erythematosus, mixed connective tissue disease, primary Sjögren and non-autoimmune diseases like chronic infections and even in patients with old age.[15] RF has long been used for the detection of RA. It is prevalent in 60-80% of RA-patients and has a sensitivity of approximately 54% and a specificity of 91%.[16, 17] More recently, ACPA has been recognized. These antibodies are prevalent in approximately 50-90% of RA populations.[16, 18–20] ACPA are considered equally sensitive as RF, but more specific for RA. Its specificity ranges up to 98%.[16] Next to the most commonly used antibodies, namely ACPA and RF, also other less prevalent antibodies can be recognized. Unfortunately, not all RA patients can be detected via laboratory testing of auto-antibodies, because in up to half of the patients with established RA they cannot be detected. Today, the major subsets of RA are divided as ACPA-positive and ACPA-negative RA. They are considered as two different disease entities with differences in etiopathology, as both subsets have differences in genetic and environmental risk factors.[5] ACPA-positive RA has always been considered as the more severe subset of RA, as the presence of ACPA is associated with more severe joint destruction and a higher mortality rate.[21–23]

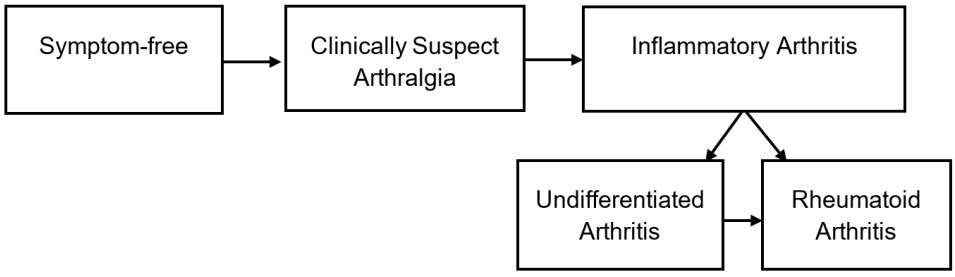

Figure 1.1: Clinically identifiable developmental stages of RA that were studied in this thesis.
A symptom-free control group; patients with arthralgia and without clinical arthritis with the clinically suspect arthralgia (CSA); patients were followed on the development of clinical inflammatory arthritis; part of these patients developed undifferentiated or rheumatoid arthritis.

Classification criteria

In RA, classification criteria have been developed with the aim to provide a more homogeneous subset of patients, particularly for research purposes. In this thesis, the 1987- and the 2010-classification criteria have been applied.[24, 25] The 2010 ACR/EULAR classification criteria have been developed with the aim to identify patients earlier in the disease course.[24] Thereby, it has been established that the 2010-criteria have indeed caused earlier classification of RA-patients, which enabled these patients to be enrolled in trials shorter after disease onset.[26] The criteria are more sensitive and slightly less specific than the 1987-criteria.[27] Both different sets of classification criteria and their differences are illustrated by Table 1.1. While in order to prevent damage and in light of research that has shown that earlier treatment leads to better disease outcomes, the 2010-criteria have been developed, these criteria also have certain drawbacks. Main differences between the 1987- and 2010-criteria are amongst others a stronger weight of autoantibodies in the 2010-criteria. Thus, a potential disadvantage of the 2010-criteria is that patients without auto-antibodies are recognized relatively later on in the disease course compared to patients with auto-antibodies. Moreover, autoantibody-negative patients require the presence of >10 involved joints to fulfil the criteria for RA.[10, 28] Currently, it is still challenging to appoint patients with joint complaints more precisely that will progress to imminent RA.

Earlier recognition and improved treatment strategies

Diagnostic delay is a major problem in many (chronic) diseases. In RA it has been shown that earlier treatment leads to better outcomes, and therefore general practitioners (GPs) are encouraged to refer patients with a (suspicion on) clinical synovitis within 6 weeks.[29] For the early detection and recognition, also laboratory findings of auto-antibodies have played an important role, as these aid earlier disease recognition. However, in a vast amount of patients these auto antibodies cannot be detected. Thus, when these patients present at disease onset, with an incompletely developed disease phenotype, it can be challenging to identify patients that will develop disease chronicity correctly. After diagnosis, modern advances in the medical treatment of RA, with earlier recognition and prompt initiation of treatment with disease-modifying antirheumatic drugs (DMARDs), preferably methotrexate, drastically improved disease outcomes in western countries. In combination with to treat-to-target approaches (disease activity (DAS)-steered treatment), this resulted in better disease outcomes.[21] Due to these improved treatment strategies, clinically relevant joint destruction has become infrequent.[30–34] In addition, patients' symptoms have been alleviated drastically in current rheumatology practice.[35–37] Therefore it is generally accepted that the disease has changed from a chronic disabling disease with severe malformations to a less severe disease. Nonetheless, patients do still experience symptoms like stiffness, pain and fatigue which lead to reduced performance at home and at work (Figure 1.2). Thus, although patients suffer less from severe chronic destruction and the disease has become less invalidating at first sight, the disease still severely affects the daily life of patients with RA.

Role of imaging in the early phases of rheumatoid arthritis

In some patients with early inflammatory arthritis (IA), it is not possible to establish a specific diagnosis during the first several weeks to months following symptom onset. However, it is desirable to set a diagnosis as early as possible and determine which patients will develop imminent (chronic) RA and which patients will have a self-limiting disease course without the need of a prompt therapeutic intervention. Imaging methods are considered as a more sensitive manner to detect joint inflammation than regular clinical examination.[38] MRI can depict synovitis, tenosynovitis, bone marrow oedema (BME or osteitis). Imaging techniques have shown to be useful to detect patients at risk to develop RA, both in patients with CSA and for patients with UA and therefore ultrasound (US) and MRI are both recommended in the diagnostic process of RA.[39] For these target populations validated scoring methods have been developed to provide valid and reproducible results. Even though RA is characterized by an influx of inflammatory cells and is frequently is accompanied by joint damage, MRI findings in early RA are found predictive on a group level, but yet have little predictive value in individual patients. Also in the pre-RA phase of CSA, imaging has been shown to be of value.[11] The risk to develop RA within the next two years increased in case of a positive MRI to about 30%. To improve this risk, it is currently being investigated how to optimize the MRI scanning protocol and also in which patients, MRI has the most added value.

The practicality of MRI

The MRI scans performed in this thesis, were scored according to semi-quantitative validated scoring methods and by two independent trained readers. Scoring was performed in line with the Outcome Measures in Rheumatology (OMERACT) RA MRI scoring (RAMRIS)-method.[40] RAMRIS was not developed to score MTP-joints, however others have previously adapted the RAMRIS to score MTP-joints as well.[41] Tenosynovitis was scored according to the method described by Havaardsholm et al, which was also applied at the flexor and extensor tendons at 2-5 MCP-joints. For practical reasons, like time efficiency and consequential additional costs, we scored BME on a post-contrast T1 fatsat sequence. We are aware of the fact according to RAMRIS BME is scored on a T2fatsat instead of a post-contrast, T1fatsat sequence.[42–45] But as several previous studies have shown that scoring BME on post-contrast T1, yields similar results for the detection of BME in several settings among which early arthritis and RA we deviated here from the RAMRIS BME protocol to provide more MRI scanning time.[43–46] As MRI can be costly and time-consuming for regular daily practice, we aimed to optimize the MRI scanning protocol even further. The RAMRIS-method is applied to the small joints of the hand and wrist, and also the feet are being scored. This requires repositioning of the hands and feet and thus considerable additional time. Therefore, we seek to define the additional value of MRI of the MTP-joints in addition to the hand-joints (MCP and wrist) in chapter 4. Next to MRI, ultrasound (US) is often performed in daily rheumatological practise in order to detect subclinical inflammation. Both imaging techniques are recommended in the diagnostic process of RA and no distinguishes are made between the two. By both imaging modalities, tenosynovitis and synovitis have been shown predictive for RA development.[11, 47–53]

Table 1.1: Classification criteria for Rheumatoid Arthritis

ACR 1987 criteria*	ACR/EULAR 2010 criteria**
1. Morning stiffness Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement	*1. Joint involvement* 1 large joint: 0 2-10 large joints: 1 1-3 small joints (with or without large joints): 2 4-10 small joints (with or without large joints): 3 >10 joints (at least one small joint): 5
2. Arthritis of 3 or more joint areas At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints	*2. Serology (at least one test result needed for classification)* Negative RF and negative ACPA: 0 Low-positive RF or low-positive ACPA: 2 High positive RF or high positive APA: 3
3. Arthritis of hand joints At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint	*3. Acute-phase reactants (at least one test result is needed for classification)* Normal CRP and normal ESR: 0 Abnormal CRP or normal ESR: 1
4. Symmetric arthritis Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)	*4. Duration of symptoms* <6 weeks: 0 ≥6 weeks: 1
5. Rheumatoid nodules Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician	
6. Serum rheumatoid factor Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5 of normal control subjects	
7. Radiographic changes Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)	

*Rheumatoid arthritis if he/she has satisfied at least 4 of the 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. ** Target population: patients who 1) have at least one joint with definite clinical synovitis (swelling); 2) with the synovitis not better explained by another disease. Definite score at least 6 of 10.

However, its usefulness in daily practise in individual cases has yet to be established. MRI is more expensive and time-consuming than US, nonetheless MRI also has its advantages like its high sensitivity to detect inflammation and its easily reproducibility. Another benefit of MRI is that it can depict bone marrow oedema (BMO). Advantageous for US is its easy availability in many hospitals due to lower costs, however, US scanning is machine and operator dependent and US cannot visualize BMO. Which modality of the two is superior needs to be determined in a longitudinal cohort. However, both are recommended in the early detection of RA due to their pros and cons. We analysed the comparability of US and MRI in a cross-sectional manner. By this first step that, we aimed to establish whether both modalities can be used interchangeably, or if this assumption is invalid.

Imaging in healthy symptom free individuals

The significance of findings at MRI have been put in a different perspective, when it was established that inflammatory characteristics found by MRI can also be found in the general symptom-free population.[54, 55] They largest study was performed by Mangnus et al. and they showed that these inflammatory findings increase with age. This finding had major implications, as it implies that inflammation found at MRI is not limited to inflammatory diseases only but can also occur in the healthy population, in persons that do not experience any joint symptoms, thus without arthralgia of any kind and certainly no arthritis. Based on the observation, a cut-off for positivity of an MRI is proposed in this thesis in chapter 2, which has the aim to prevent the detection of false positive MRI results.

Application of imaging methods for classification of RA

Imaging methods have shown to detect inflammation more sensitively than regular clinical examination. Thus, joints can be affected that are neither swollen nor tender at examination.[38] In light of these findings and due to the predictive value of imaging-detected inflammation, it was recommended to use imaging tools to ascertain the number of involved joints for the classification criteria for RA according to the 2010-criteria.[24] This notion suggests that next to the clinical finding of at least one swollen joint at physical examination, imaging tools are recommended to aid the detection of inflamed joints.[56] Although this addition seems logical, it was mainly based on expert opinion. Namely, its consequences have not been explored previously. Only a few (not peer-reviewed) abstracts have aimed to answer this question. We therefore examined the effects of the addition of imaging methods to determine the number of affected joints for the classification of RA patients by the 2010 ACR/EULAR classification criteria in chapter 3.

Patient reported outcomes

Due to the improved treatment strategies of the last decades there has been a shift in the importance of certain outcome measures in RA. While traditionally the severity of RA was measured by progression of joint damage and mortality. Joint damage has become increasingly infrequent,[30–34] and also increased mortality is no longer evidently present.[35–37] These traditional outcomes have become increasingly infrequent and

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a shift towards other outcomes, important for RA-patients have been investigated. In a study that aimed to determine these patient reported outcomes (PROs), it was found that according to patients, important outcomes are pain, fatigue and independence.[6] Independence is a key aspect of daily life, which can be reflected by for example physical functioning, but also activities in daily life and performance at work.[57] These outcomes are not solely important from a patients' perspective, but also for society, as decreased functioning in daily life activities can pose a substantial burden and lead to considerable costs. Next to the shift from the traditional outcomes due to an improved disease course, PROs also have become increasingly important due to shared decision making, which also places the patients central when deciding a treatment strategy.

Morning stiffness

RA patients often experience symptoms of the joints and besides pain and swelling also stiffness is often experienced. Their stiffness is characterized by its prominence during morning hours. This phenomenon is therefore called morning stiffness. It is considered as characteristic of RA and can be prevalent in 40-50% of patients.[58] In addition, the symptom has been a part of classification and remission criteria for years and it has been associated with functional disability. Morning stiffness poses a substantial burden on patients' perceived disease burden. Nonetheless, its underlying processes are still poorly understood.[58] It is presumed that both systemic and local inflammation underlie

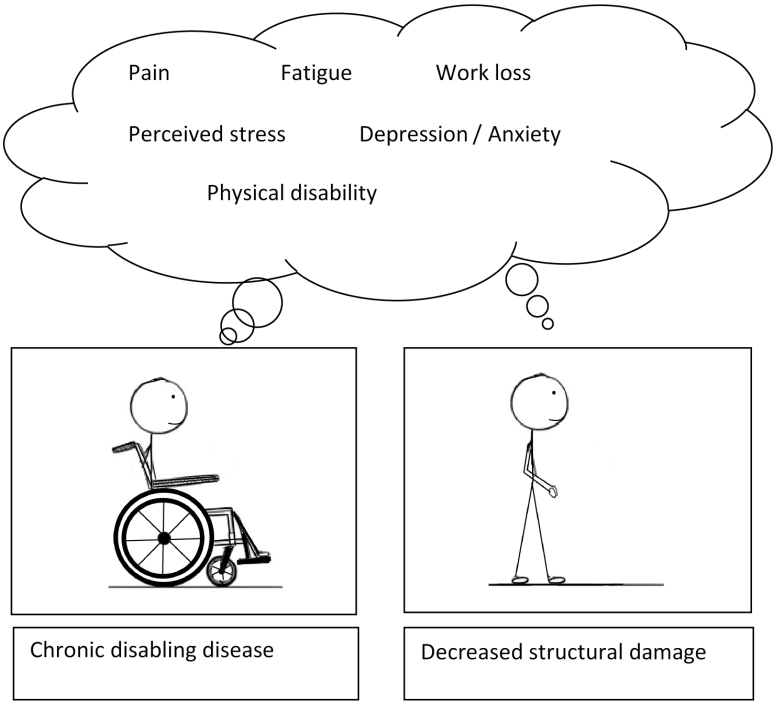

Figure 1.2: Phenotype of rheumatoid arthritis patients over the past decades.

morning stiffness.[59] Most studies focussed on systemic factors, which is intuitive as the circadian rhythm of symptoms parallels late night and early morning rises of pro-inflammatory markers. The time-relationship and observation that morning stiffness could be relieved by the application of low-dose prednisone during the night makes it likely that systemic inflammatory markers contribute to morning stiffness.[60] Morning stiffness is generally experienced as most pronounced at the hand-joints. In addition to joint stiffness being maximal in the early morning, grip strength is also lowest at this time-point.[61] Therefore it is presumable that local inflammation, besides systemic inflammation, is also important for the occurrence of morning stiffness. However, in proportion to the number of studies focussing on systemic markers, the association with local inflammation is less well studied. While morning stiffness is generally most pronounced at the hand-joints, it is presumable that local inflammation is important for the occurrence of MS. The fact that morning stiffness is a hallmark symptom of RA of which we do not fully understand the pathophysiology prompted us to perform a large cross-sectional MRI-study in which we aimed to determine if tenosynovitis, also in relation to synovitis, at small joints associated with MS in patients with UA and RA, in chapter 7.

Depression in relation to the emergence of RA

In addition to the symptoms of fatigue, pain and stiffness reported by patients, another frequently encountered adversity in chronic diseases are mental health disorders. Particularly anxiety and depression pose a burden on patients with RA. It has been reported that RA patients have an increased prevalence of psychological stress.[62] Generally, in chronic inflammatory diseases, psychological stress is considered to negatively affect the disease course.[63] The effects of psychological stress have been thoroughly investigated within patients with established RA. It is known that patients can have a deranged stress response, particularly in patients with a high disease activity.[64–66] The mechanism by which psychological stress affects inflammation is expected to work via activation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system, which thereafter is associated with the release of neurotransmitters (i.e. norepinephrine), hormones (i.e. cortisol) and activation of immune cells.[63, 67, 68] Thus, during increased psychological stress, the normal down regulation of the inflammatory response is hindered, possibly causing pro-inflammatory effects. However alternatively, stress can also be a consequence of symptoms and physical limitations without having exacerbating effects on inflammation in the phase of CSA. Patients themselves often experience stress and question whether this could have had an effect on the occurrence or flaring of their disease. However, until now, the stress response was unresearched in pre-RA phases and therefore it is currently unknown if daily stress can trigger or, more generally, precedes RA development.

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Cohorts studied in this thesis

Clinically Suspect Arthralgia cohort

In 2015 the CSA cohort was started at the Leiden outpatient clinic. The CSA is a population-based inception cohort with patients with complaints of arthralgia of <1 year, of whom the rheumatologist think that it is suspect to progress to RA. Patients were followed for 2 years for the development of arthritis. Follow-up ended earlier when clinical arthritis had developed.[11] Patients were never treated with DMARDs in the phase of CSA. After arthritis-development, patients were mostly included in the early arthritis clinic cohort.

Leiden Early Arthritis Clinic cohort

In 1993, the Leiden Early Arthritis Clinic (EAC) cohort was started at the outpatient clinic. The EAC is a population-based inception cohort with patients that present for the first time at the outpatients clinic with recent onset IA, with a symptom duration of <2 years. They required clinical synovitis of at least 1 joint to be eligible for inclusion.[69]

Symptom-free volunteers

Symptom-free volunteers were examined by MRI and served as a reference for MRI-detected inflammation (n=193). They were recruited via advertisements in local newspapers and websites and had no history of inflammatory rheumatic diseases, no joint symptoms during the last month and no evidence of arthritis at physical examination, as described in reference.[55] The different sets of patients and the visits they had are schematically depicted in Figure 1.3. As illustrated, all patients underwent a baseline 1.5T gadolinium-enhanced MRI of unilateral MCP(2-5)-, wrist- and MTP(1-5)-joints.

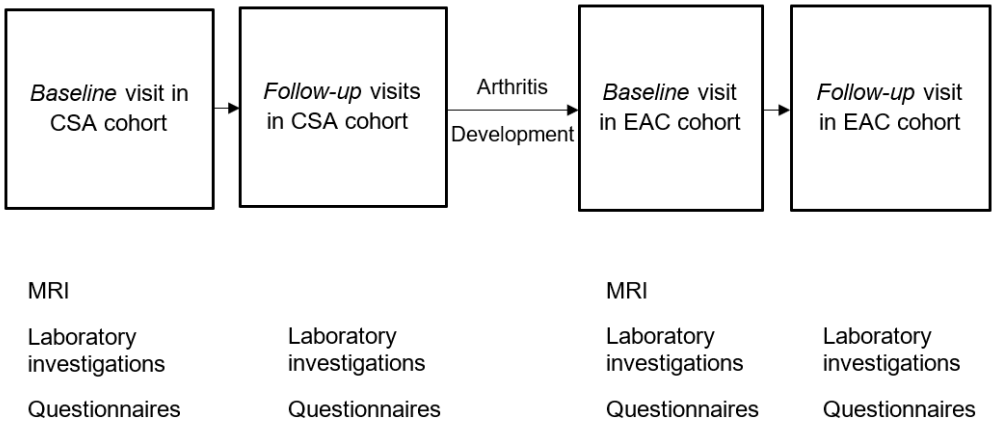

Figure 1.3: Overview of study protocol of cohorts for studies performed in this thesis.

Outline of this thesis

In **part I**, we investigated the value of imaging techniques in the early phases of RA.
In **Chapter 2** we start by examining the application of a cut-off for MRI-detected inflammation based on a reference population of healthy symptom-free controls. We propose a cut-off for 'MRI-positivity' for the early detection of RA. For this purpose, we used the previously published prevalence of low grade inflammation at MRI of healthy controls to determine the predictive accuracy of inflammation at MRI in patients with clinically suspect arthralgia for progression to inflammatory arthritis and also for patients with undifferentiated arthritis for progression to RA. Although a cut-off for positivity is common for other tests in medicine, this phenomenon is novel for MRI in the early detection of RA. In **Chapter 3** we examined the impact of joints detected by MRI for the determination of the number of involved joints for the 2010 ACR/EULAR classification criteria. Inflammation of joints at MRI were used to determine joint counts in addition to clinically affected swollen joints, as this was suggested in the original manuscript of the development of the 2010 ACR/EULAR classification criteria. Patients were followed for DMARD-initiation during follow-up as proxy for RA-development. In **Chapter 4** we examined the complementary value of MRI of the feet (MTP1-5) in addition to MRI of the hands (MCP2-5 and wrist) in patients with clinically suspect arthralgia in order to critically assess the time-efficiency of the current MRI scanning and scoring protocol. Thereafter we focussed on the comparability of two different imaging techniques in **Chapter 5**. Ultrasound is much more easy available than MRI in daily rheumatology practice, while MRI is considered more sensitive and provides more reproducible results. We compared cross-sectional data of semi-quantitative scores produced by both techniques in patients with early inflammatory arthritis and clinically suspect arthralgia.

In **part II**, we focussed on patient-reported outcomes in patients at risk of or with RA. Due to improved treatment strategies, these patient reported determinants of the disease have become more important, because due to improved treatment strategies the traditional outcomes (i.e. damage) have become infrequent.
In **Chapter 6** we explore the differences between ACPA-positive and ACPA-negative RA in terms of patient-reported outcomes including physical functioning and restrictions at work. Another commonly experienced symptom by patients with RA is morning stiffness. While this symptom is experienced by the majority of RA patients, its aetiology is still unknown. It is presumed that it reflects inflammation of the joints. Therefore, we examined in **Chapter 7** the relationship between morning stiffness and MRI-detected subclinical tenosynovitis in patients with RA. In these analyses we also took the presence of concomitant synovitis into account. Further, we investigated in **Chapter 8** the relationship between psychological stress and inflammation in the preclinical phase of RA. In general practise it is a commonly asked question whether daily stress could have caused a patients' RA. Therefore, we examined the relationship between daily psychological stress at inclusion in the cohort by two questionnaires with inflammation measured at MRI, by serology (CRP) and longitudinally on the development of clinically apparent inflammatory arthritis, in patients with CSA. After

arthritis onset, psychological stress and MRI data was examined after inclusion in the EAC cohort. In **Chapter 9** we further examined the impact of psychological stress on the disease activity of patients with early RA.

Finally, in **part III**, **Chapter 10** provides a summary and discussion of the results that are described in this thesis.

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