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PAIN PATTERNS IN EARLY RHEUMATOID ARTHRITIS

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Cover illustration: Magnolias, 1945, by Frida Kahlo. Frida Kahlo (1907-1954) was a Mexican painter who was injured in a traffic accident at the age of 18, which caused lifelong severe pain. Her experience of pain was a motive in several of her paintings.

Pain patterns in early rheumatoid arthritis

THESIS FOR DOCTORAL DEGREE (Ph.D)

By

Joakim Lindqvist

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POPULAR SCIENCE SUMMARY OF THE THESIS

Rheumatoid arthritis (RA) is a chronic autoimmune disease that is characterized by joint inflammation. The inflammation may lead to swelling, tenderness, and pain in the affected joints, and if the inflammation is not suppressed, it may lead to irreversible damage of joint structures and subsequent loss of normal joint function. The introduction of new antirheumatic treatments during recent decades has considerably advanced the management of RA and it is now possible to successfully suppress the inflammation in a large part of the patients, thereby preventing, or significantly delaying, the development of structural joint damage.

In the wake of this therapeutical development, however, it has become evident that some patients with RA continue to experience significant levels of pain, despite that the inflammation is under control. It seems, therefore, as if the pain may become uncoupled from the underlying rheumatic condition and persist as a disease entity in itself. This pain may manifest as continuous pain in the joints after the inflammation has resolved, and it may also become widespread and affect other parts of the body, such as muscles and tendons.

Chronic pain may lead to significant impairment of physical and mental health-related quality of life and may also interfere with the ability to participate in social activities and occupational work. Chronic pain is therefore an important feature of ill-health that needs to be addressed and adequately managed to support patients to regain a satisfactory health status and an ability to engage in social and working life.

In this thesis, we have studied patterns of pain expression in patients with RA during the first years of the disease. In study I, we assessed the prevalence of widespread non-joint pain (WNP), which was defined as pain outside the joints in all four body quadrants, and we found that 8% of the patients met the criteria for WNP 3 years after diagnosis. The patients with WNP displayed a significantly impaired physical and mental health status compared with the patients without WNP. We further found that patients who had developed WNP 3 years after diagnosis of RA displayed significantly higher levels of pain and functional disabilities already at the time of diagnosis, without displaying higher levels of inflammation.

In study II, we used a statistical method called cluster analysis to identify subgroups of patients 3 years after diagnosis, based on features of pain, fatigue, anxiety, depression, and overall physical and mental health status. Three clusters were identified, where cluster 1 (46%) constituted a group of patients who were doing very well, with a health status comparable to the general Swedish population, where cluster 2 (39%) constituted an intermediate group, and where cluster 3 (15%) constituted a group of patients with high levels of pain, fatigue, and impaired physical and mental health status. When comparing cluster 3 with cluster 1 in terms of clinical characteristics at the time of diagnosis, we found that the patients in cluster 3 displayed higher levels of pain and functional disabilities, and to a larger extent had pain problems already before the onset of RA. The patients in cluster 3 were also to a larger extent women and had a higher body mass index. The patients in cluster 1

displayed higher levels of inflammation, as assessed by the number of swollen joints, at the time of diagnosis.

In study III, we assessed the impact of high pain levels on measures of disease activity and the ability to reach formal treatment targets. We also assessed if patients who do not reach formal treatment targets because of high levels of pain, even though there are no signs of inflammatory activity, were more likely to have their antirheumatic treatment adjusted. We defined 'inflammatory remission' as the absence of swollen joints together with normal erythrocyte sedimentation rate and C-reactive protein level below 10 mg/L. We found that 19-22% of the patients who were in inflammatory remission still failed to reach the formal treatment target of remission in the Disease Activity Score of 28 joints (DAS28). Conversely, we found that of all patients who failed to reach DAS28 remission, 12-19% were in inflammatory remission. We further found that patients who failed to reach DAS28 remission despite being in inflammatory remission were more likely to have their antirheumatic treatment adjusted compared with patients in inflammatory remission who reached DAS28 remission, at consecutive follow-up visits 6, 12, and 24 months after RA diagnosis.

In conclusion, we found that pronounced pain problems were present in a substantial proportion of the patients 3 years after diagnosis of RA. The patients with pain problems at 3 years displayed characteristic features already at the time of diagnosis, with higher levels of pain, functional disabilities, and previous pain problems, but did not display an increase in inflammatory disease activity. The characteristic features displayed at this early stage of RA should enable early identification of patients at risk of developing a chronic pain condition and promote the adoption of directed pain management interventions.

We further found evidence that high levels of pain may impact some of the variables that constitute the commonly used measures of disease activity so that formal treatment targets, based on these measures, may fail to be reached even in the absence of signs of inflammatory disease activity. We also found that patients who fail to reach formal treatment targets, despite being in inflammatory remission, are more likely to have their treatment adjusted. The findings of this study support the notion that chronic pain should be acknowledged as a separate disease entity that might obscure the evaluation of the rheumatic disease activity. Interventions for the management of chronic pain may be conducted in parallel with the management of the rheumatic disease and the two management strategies may benefit from one another by addressing the condition from different perspectives.

ABSTRACT

Study I

Widespread non-joint pain in early rheumatoid arthritis

Objective: The aim of the study was to assess the development of widespread non-joint pain (WNP) in a cohort of patients with early rheumatoid arthritis (RA), the associated health-related quality of life (HRQoL), and clinical and demographical risk factors for WNP.

Methods: Incident cases with RA, from the Swedish population-based study Epidemiological Investigation of Rheumatoid Arthritis (EIRA), with a follow-up of at least 3 years, constituted the study population. WNP was defined as pain outside the joints in all four body quadrants and was assessed at the 3-year follow-up. Patients who reported WNP were compared to patients without WNP regarding HRQoL, measured by the Short Form-36, at 3 years, and clinical and demographical characteristics at the time of RA diagnosis.

Results: A total of 749 patients constituted the study sample, of whom 25 were excluded after reporting having severe pain already before RA diagnosis. At the 3-year follow-up, 8% of the patients reported having WNP as well as statistically significant worse HRQoL. At the time of RA diagnosis, the patients with WNP had worse pain and pain-related features, while no difference was seen in the inflammatory parameters.

Conclusion: WNP occurs in a substantial subset of patients with RA, also early in the course of the disease, and the HRQoL for these patients is significantly reduced. Patients who develop WNP at 3 years are distinguishable already at the time of diagnosis by displaying more pronounced pain ratings together with an average level of inflammatory disease activity.

Study II

Unmet needs in rheumatoid arthritis: A subgroup of patients with high levels of pain, fatigue, and psychosocial distress 3 years after diagnosis

Objective: The study objective was to identify subgroups of patients with rheumatoid arthritis (RA) based on their health status 3 years after diagnosis and to assess potential associations to clinical presentation at diagnosis.

Methods: This observational study included patients with RA with 3-year follow-up data from the Swedish Epidemiological Investigation of RA (EIRA) study, collected from 2011 to 2018. Hierarchical agglomerative cluster analysis, based on symptoms of pain, fatigue, sleep quality, mood disturbances, and overall health-related quality of life (HRQoL), was used to identify subgroups 3 years after diagnosis. Modified Poisson regression was used to estimate risk ratios (RRs) and 95% confidence intervals (CIs) for the associations between the subgroups and patient characteristics at diagnosis.

Results: A total of 1055 individuals constituted the study population, of whom 1011 had complete data on the clustering variables and were thereby eligible for analysis (73% women, median age 58 years). The following three clusters were identified: Cluster 1 (466 patients with good health status), Cluster 2 (398 patients in an intermediate group) and Cluster 3 (147 patients with high levels of pain and fatigue together with markedly impaired HRQoL). Cluster 3 was associated to higher baseline pain (RR: 3.71 [95% CI: 2.14-6.41]), global health (RR: 6.60 [95% CI: 3.53-12.33]) and Stanford Health Assessment Questionnaire (RR:

4.40 [95% CI: 2.46-7.87]), compared with cluster 1 (highest compared to lowest quartiles). An inverse association was seen for baseline swollen joint count (RR: 0.51 [95% CI: 0.34-0.85]).

Conclusion: A subgroup of patients with RA experience high levels of pain, fatigue, and psychosocial distress 3 years after diagnosis. This subgroup displayed pronounced pain and functional disabilities already at diagnosis.

Study III

Failure to reach treatment targets despite being in inflammatory remission among patients with early rheumatoid arthritis: Associations to the use of disease-modifying antirheumatic drugs

Objective: The study objective was to assess the proportion of patients with early rheumatoid arthritis (RA) who fail to reach formal treatment targets despite being in inflammatory remission, and to assess patterns of use of disease-modifying antirheumatic drugs (DMARD's), in comparison with patients who are likewise in inflammatory remission but who reach the formal treatment targets.

Methods: Patients newly diagnosed with RA were identified in the Swedish Rheumatology Quality Register (SRQ) (n = 11,784). Disease activity score based on 28 joints (DAS28) and DMARD-treatment were assessed at RA diagnosis and at 3-, 6-, 12-, and 24 months thereafter. Inflammatory remission was defined as: swollen joint count (0-28) = 0 and C-reactive protein <10 mg/L and normal erythrocyte sedimentation rate. Primary treatment targets were DAS28 remission (<2.6) and DAS28 low disease activity (LDA) (≤3.2). The proportion of patients in inflammatory remission who failed to reach the DAS28 targets was assessed at each follow-up visit. Patients who failed to reach DAS28 targets despite being in inflammatory remission were compared with patients in inflammatory remission who reached treatment targets, in terms of new DMARD starts during follow-up. Risk ratios (RR) and 95% confidence intervals (CI) for DMARD starts were estimated with Poisson regression.

Results: Overall, 34%, 39%, 44%, and 47%, respectively, were in inflammatory remission at 3, 6, 12, and 24 months. Among these, 20%, 22%, 20%, and 19%, respectively, failed to reach DAS28 remission, and 8%, 9%, 7%, and 8%, respectively, failed to reach DAS28 LDA. Patients who failed to reach DAS28 targets despite being in inflammatory remission at the same visit were more likely to start a new DMARD treatment (RR (95% CI) at 6 months = 1.59 (1.29-1.96), 12 months = 1.52 (1.23-1.87)), and 24 months = 1.47 (1.20-1.80) when DAS28 remission was the target, and at 3 months = 1.35 (1.06-1.71), 6 months = 1.84 (1.42-2.39), 12 months = 1.71 (1.29-2.27), and 24 months = 1.78 (1.39-2.27) when DAS28 LDA was the target. The start of a new DMARD did not affect the likelihood of reaching the treatment target at the subsequent visit for these patients.

Conclusion: A substantial proportion of patients with early RA who are in inflammatory remission fail to reach formal treatment targets. These patients might be at risk of overtreatment with DMARD's.

LIST OF SCIENTIFIC PAPERS

I. **Widespread non-joint pain in early rheumatoid arthritis**
Schelin M*, Westerlind H*, Lindqvist J, Englid E, Israelsson L, Skillgate E, Klareskog L, Alfredsson L, Lampa J.
Scandinavian Journal of Rheumatology. 2021;50(4):271-9.

II. **Unmet needs in rheumatoid arthritis: A subgroup of patients with high levels of pain, fatigue, and psychosocial distress 3 years after diagnosis**
Lindqvist J, Alfredsson L, Klareskog L, Lampa J*, Westerlind H*.
ACR Open Rheumatology. 2022;4(6):492-502.

III. **Failure to reach treatment targets despite being in inflammatory remission among patients with early rheumatoid arthritis – associations to the use of disease-modifying antirheumatic drugs**
Lindqvist J, Askling J, Lampa J.
Manuscript.

* Equal contribution

Scientific papers not included in the thesis

I. **Rheumatoid arthritis patients display B-cell dysregulation already in the naïve repertoire consistent with defects in B-cell tolerance**
Wang Y, Lloyd KA, Melas I, Zhou D, Thyagarajan R, Lindqvist J, Hansson M, Svärd A, Mathsson-Alm L, Kastbom A, Lundberg K, Klareskog L, Catrina AI, Rapecki S, Malmström V, Grönwall C.
Scientific Reports. 2019;9(1):19995

II. **Active conventional treatment and three different biological treatments in early rheumatoid arthritis: phase IV investigator initiated, randomized, observer blinded clinical trial**
Hetland ML, Haavardsholm EA, Rudin A, Nordström D, Nurmohamed M, Gudbjornsson B, Lampa J, Hørslev-Petersen K, Uhlig T, Grondal G, Østergaard M, Heiberg MS, Twisk J, Lend K, Krabbe S, Hejl Hyldstrup L, Lindqvist J, Hultgård Ekwall AK, Lederballe Grøn K, Kapetanovic M, Faustini F, Tuompo R, Lorenzen T, Cagnotto G, Baecklund E, Hendricks O, Vedder D, Sokka-Isler T, Husmark T, Aga Ljoså MK, Brodin E, Ellingsen T, Söderbergh A, Rizk M, Reckner Olsson Å, Larsson P, Uhrenholt L, Just SA, Stevens DJ, Bay Laurberg T, Bakland G, Olsen IC, van Vollenhoven R, on behalf of the NORD-STAR study group.
British Medical Journal. 2020;371:m4328

CONTENTS

LIST OF ABBREVIATIONS

ACPA	Anti-citrullinated protein antibody
ACR	American college of rheumatology
BMI	Body mass index
CRP	C-reactive protein
DAS28	Disease activity score of 28 joints
DMARD	Disease-modifying antirheumatic drug
e.g.	Exempli gratia (“For example”)
EIRA	Epidemiological investigation on rheumatoid arthritis
ESR	Erythrocyte sedimentation rate
EULAR	European alliance of associations for rheumatology
et al.	Et alii (“and others”)
HADS	Hospital anxiety and depression scales
HAQ	Stanford health assessment questionnaire
IASP	International association for the study of pain
ICD	International classification of diseases
i.e.	Id est (“That is”)
LDA	Low disease activity
PGA	Patient global assessment of health
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RR	Risk ratio
SF-36	Short form health survey with 36-items
SJC	Swollen joint count
SRF	Swedish society for rheumatology
SRQ	Swedish rheumatology quality register
TJC	Tender joint count
WNP	Widespread non-joint pain

1 INTRODUCTION

1.1 RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic autoimmune disease primarily characterized by joint inflammation. The joint inflammation commonly affects synovial joints of the extremities in a symmetric manner and cause swelling, tenderness, and pain in the affected joints (1, 2). If the inflammation is not controlled, it may lead to irreversible damage of joint structures and subsequent functional impairment.

The prevalence of RA in Sweden has been estimated to 0.7% (3) and a similar prevalence is also found in other parts of the world (4, 5). The yearly incidence in Sweden is approximately 40 cases per 100 000 inhabitants, which means that approximately 4000 new cases of RA are diagnosed in Sweden every year (6). As for many autoimmune conditions, RA is more common in women, who represent two thirds of the patients.

The disease is heterogenous in its manifestations, but typically presents insidiously with arthralgia, morning stiffness and swelling of the affected joints. There are no formal diagnostic criteria for RA and the diagnosis is ultimately based on the clinical judgement of the rheumatologist, guided by the clinical presentation and laboratory findings. There are, however, classification criteria, which are formally intended for identification of homogenous populations for research purposes but may function as diagnostic support. The latest classification criteria were jointly elaborated by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) and were published in 2010 (7). The criteria are based on a scoring algorithm that assess the number and distribution of affected joints, laboratory markers of inflammation, and the presence or absence of RA-associated autoantibodies, namely rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). The criteria may be applied if (a) the patient has at least one joint with definitive clinical synovitis, and (b) the synovitis is not better explained by another disease (Table 1.1).

1.1.1 Pathogenesis

The etiology of RA is still largely unknown and the etiological process may differ between different subgroups of patients (8). In general, genetic and environmental factors are believed to interact in the loss of tolerance of immune cells towards bodily-specific structures. Genetic variants that are associated with an increased risk of RA include genes that affect the function of cells in the adaptive immune system, the most prominent of which is the HLA-DRB1 shared epitope, which affects the antigen-presenting function of T-cells (8).

The loss of tolerance may develop in relation to proteins that have undergone post-translational modifications. These modifications may in turn be induced by environmental stressors, e.g., by the effect of smoking on the lung mucosa, in relation to periodontitis in the

oral mucosa, or by effects of the gut microbiome (9). The activation of auto-reactive immune cells is believed to occur outside the joints, in secondary lymphoid tissues or in bone marrow. The mechanisms by which the autoimmune reaction transitions to joint structures is not well understood but is believed to involve an interaction of innate and adaptive immune responses (10). When synovitis is initiated, however, it is believed to be perpetuated by positive feedback loops (9).

Table 1.1. The 2010 ACR/EULAR classification criteria for rheumatoid arthritis. A total score is calculated by adding the separate scores from categories A-D. The classification criteria are met if the total score is ≥6. The criteria are applicable if (a) the patient has at least one joint with definitive clinical synovitis, and (b) the synovitis is not better explained by another disease

Criterion	**Score**
A. Joint involvment:	
- One large joint	0
- 2-10 large joints	1
- 1-3 small joints (with or without large joint involvment)	2
- 4-10 small joints (with or without large joint involvment)	3
- >10 joints (at least 1 small joint)	5
B. Serology (One test result is needed for classification):	
- Negative RF *and* negative ACPA	0
- Low-positive RF *or* low-positive ACPA	2
- High-positive RF *or* high-positive ACPA	3
C. Acute phase reactants (One test result is needed)	
- Normal CRP *and* normal ESR	0
- Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms:	
- <6 weeks	0
- ≥6 weeks	1

Large joints: Shoulders, elbows, hips, knees, and ankles. Small joints: Wrists, metacarpophalangeal-, proximal interphalangeal-, thumb interphalangeal-, and second through fifth metatarsophalangeal joints. RF = Rheumatoid factor. ACPA = Anti-citrullinated protein antibody. CRP = C-reactive protein. ESR = Erythrocyte sedimentation rate.

The inflamed synovium has been observed to contain accumulations of T-cells, which suggest a T-cell dependent inflammatory phase. However, a potential antigen for the activated T-cells has been identified (10). The inflamed synovium will eventually come to contain a large number of activated immune cells, including macrophages and neutrophiles, as well as T- and B-cells. The activated immune cells release large amounts of

proinflammatory cytokines and other mediators. Important proinflammatory cytokines include IL-6 and TNF-α (10). Invasion of macrophages and proliferation of resident fibroblasts lead to synovial hypertrophy and the formation of an inflammatory pannus that may affect surrounding tissues. The release of degrading enzymes from the inflammatory pannus, together with the action of osteoclasts, may cause irreversible destruction of cartilage and bone surfaces in the joint.

1.1.2 Measures of disease activity

Recommendations for the use of disease activity measures for RA were formulated by a working group for ACR in 2012 (11). The working group identified 63 different previously proposed measures of disease activity in RA, of which 6 were recommended. These included 3 measures based solely on patient-reported outcomes and 3 measures based on a combination of patient-reported and clinically derived outcomes. The three combinatory disease activity measures were the Disease Activity Score with 28 joint counts (DAS28), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) (11).

1.1.2.1 Disease activity score with 28 joint counts (DAS28)

A first version of the disease activity score (DAS) was proposed in 1990 (12). It was elaborated through a statistical procedure that identified variables important for distinguishing between high and low disease activity states. The resulting variables were (a) an assessment of tender joints called the Ritchie Index, (b) a swollen joint count of 44 joints, (c) the erythrocyte sedimentation rate (ESR), and (d) the patient's global assessment of health (PGA). A computational formula was proposed to provide a continuous overall score of disease activity (12). In 1995, a modified version of DAS, based on 28 joint counts of tender and swollen joints (DAS28), was proposed and demonstrated to have similar performance and validity as the original DAS (13). Later, cutoff values for DAS28 remission and low disease activity (LDA) were proposed (14, 15). The DAS28 is one of the most widely used measures of disease activity in RA (11).

1.1.2.2 Simplified disease activity index (SDAI)

The SDAI was proposed in 2003, as a simplified and more intuitive assessment of disease activity intended for use in clinical practice, which did not require a complex mathematical calculation, as for DAS28 (16). The SDAI was elaborated as a modification of a previously proposed index for disease activity in reactive arthritis and is calculated as the arithmetic sum of the included variables. The variables were chosen from previously defined core set outcome measures in RA (17), and consisted of tender and swollen joint counts based on 28 joints, PGA on visual analog scale (VAS) (0-10 cm), physician's global assessment of disease activity on VAS (0-10 cm), and C-reactive protein (CRP) in mg/dl (16). Cutoff scores for disease activity states were subsequently defined (18).

1.1.2.3 Clinical disease activity index (CDAI)

The CDAI was proposed in 2005, as a reduced version of SDAI, where CRP was omitted (19). The purpose of the elaboration of CDAI was to provide a method for a quantifiable assessment of disease activity in clinical practice, which was applicable also in the absence of laboratory tests. The authors showed, by statistical argument, that CDAI had similar performance as SDAI. The CDAI is computed in the same way as SDAI, except for the omission of CRP. Cutoff points for remission and other disease activity states were elaborated in relation to the previously defined cutoffs for DAS28 and SDAI (20).

1.1.2.4 Definition of remission

In 2011, a joint working group from ACR and EULAR published recommendations for the definition of remission in RA for clinical trials (21). The working group evaluated previous definitions of remission based on existing indices and elaborated a new definition, based on a Boolean approach. The Boolean definition of remission included a 28 joint count of tender and swollen joints, PGA measured on a 0-10 cm scale, and CRP measured in mg/dl and required that each of the included variables had a value of ≤1. This definition, together with the definition of remission based on SDAI (≤3.3), was found to be most stringent and consistent with good functional and radiographic outcomes and were thereby recommended.

The definition of remission based on CDAI (≤2.8) showed similar results as SDAI and the Boolean definition of remission in predicting long term good outcome but was not formally recommended. The DAS28 definition of remission (<2.6) was, to a larger extent, associated with significant residual disease activity and to future development of radiographic changes compared to the other measures. A significant number of swollen joints were frequently present among patients classified as being in DAS28 remission in the evaluated data, where the maximum number of swollen joints found in a patient in DAS28 remission was 21 out of 28 (21).

1.1.3 Management of rheumatoid arthritis

The inflammatory disease activity in RA may lead to irreversible destruction of joint structures and subsequent loss of joint function (8). The primary goal in the management of RA is therefore to suppress the inflammatory activity and thereby prevent, or at least delay, the development of structural damage. The approach of aiming to treat the disease to inflammatory remission is formally described in the “treat-to-target” recommendations, formulated by an international task force of rheumatology health professionals and patient representatives, which was first published in 2010 (22), and updated in 2014 (published in 2016) (23).

The recommendations state that clinical remission, defined as the absence of signs and symptoms of significant inflammatory disease activity, should be the primary target for the treatment of RA, while low disease activity may be an acceptable therapeutic target in some

circumstances. The recommendations further state that disease activity should be assessed regularly using validated composite measures, and that drug therapy should be adjusted at least every three months, until the desired target is reached.

Recommendations for the pharmacological management of RA have recently been updated by the Swedish Society for Rheumatology (SRF) (24), and are also available from EULAR (25) and ACR (26). These three guidelines may differ in some minor respects, such as in the choice of specific disease-modifying antirheumatic drugs (DMARDs) for specific subpopulations and in some aspects of the stepwise escalation of therapy, but the broad approach is similar. Briefly, the guidelines recommend initial monotherapy with a conventional synthetic DMARD (csDMARD), preferentially methotrexate but hydroxychloroquine or sulfasalazine may be considered for patients with low disease activity. The initial csDMARD monotherapy may be combined with short-term oral glucocorticoids for patients with high disease activity.

If there is an inadequate response to the first line of treatment, the treatment may be escalated by switching to another csDMARD, by adding additional csDMARDs to the initial monotherapy, or by adding a biological DMARD (bDMARD) or a targeted synthetic DMARD (tsDMARD) to the initial monotherapy. The strategy for treatment escalation should be guided by the level of disease activity and the presence or absence of negative prognostic markers, such as high titers of ACPA or RF, or the presence of erosions. A b- or tsDMARD should preferentially be used in combination with a csDMARD but may be used as monotherapy in case of intolerance to available csDMARDs. If there is an inadequate response to the first line of b- or tsDMARDS, one may switch to other b- or tsDMARDs, either of the same class, or of other classes. Oral glucocorticoids may be used as bridging therapy until initiated DMARD therapies have reached their effect. Glucocorticoids should preferentially only be used over limited periods and be tapered as soon as clinically feasible.

For patients in sustained remission over a period of at least 3-12 months, tapering and/or discontinuation of DMARDs may be considered. Tapering of b- or tsDMARDs may be performed by lowering the dose or increasing the time interval between drug administrations, and discontinuation may be considered for patients in sustained remission, especially if csDMARD monotherapy is continued. Complete discontinuation of DMARD treatment may be considered in rare cases but the risk of new flares is high and the reinstitution of the same DMARD may not be sufficient to avert the new flare (25).

Treatment advances during recent decades have greatly improved the outlook for patients diagnosed with RA. These advances include the introduction of new and effective therapeutical targets, such as b- and tsDMARD’s, and strategies for earlier identification and diagnosis of patients together with prompt initiation of therapy. Advances of treatment strategies also include the approach of keeping tight control of the disease and aiming for a target of remission or low disease activity throughout the course of the disease. Although the management of RA continues to pose a challenge, these paradigm shifts have made it possible to suppress the inflammatory disease activity and thereby prevent or significantly

delay the development of joint damage and improve quality of life for a large part of the patients with RA (27).

1.2 UNMET NEEDS IN RHEUMATOID ARTHRITIS

The therapeutical advances during recent decades have undoubtedly improved the management of patients with RA. Clinical remission is now a feasible goal for many patients and severe joint damage has become less common. In the wake of this development, however, other features than inflammatory disease activity have gained increased importance for many patients with RA. These features include persistent pain, fatigue, and other aspects of physical and mental well-being. These symptoms often persist despite adequate antirheumatic treatment and are sometimes collectively referred to as "unmet needs" in RA (28). Two of the most prominent persistent symptoms of high concern for patients with RA are pain and fatigue (29, 30).

Fatigue is described by patients with RA as an exhausting and overwhelming tiredness that may have severe impact on daily activities and emotional well-being (31). Fatigue may be a symptom of ongoing arthritis but may also persist after the inflammation has resolved (32). Severe fatigue has been reported in 41% of patients with RA (33) and fatigue is associated with severe implications for physical functioning, emotional wellbeing, and for the ability to engage in social activities (34). Evidence for effective treatments for fatigue is limited (32). Patients have reported that pacing, regular rest, and careful planning of activities may be appropriate management strategies (31). Limited evidence further suggest that physical activity and cognitive behavioral therapy may be beneficial for the management of fatigue (32).

1.3 PAIN IN RHEUMATOID ARTHRITIS

Pain is one of the most prominent concerns for patients with RA. When asked about their top priority in terms of treatment outcome, patients with RA frequently rate pain as their primary concern (29, 30). Pain is one of the cardinal signs of inflammation and is a prominent feature of ongoing arthritis. For a large part of the patients, the pain subsides when the inflammatory process resolves (35, 36). However, for some patients the pain persists after the inflammation has resolved and appear to become uncoupled from the underlying inflammatory disease (37, 38). This persistent pain may manifest as continuous arthralgia despite no apparent signs of inflammatory disease activity and may also develop into widespread pain that also involves non-joint structures, such as muscles and tendons (39, 40).

1.3.1 Epidemiology of pain in RA

1.3.1.1 Prevalence of fibromyalgia among patients with RA

Early work in the field of persistent pain in RA have been done by Frederick Wolfe and his colleagues who described the prevalence and health status of RA-patients with ”fibrositis” in the mid 1980’s (41, 42). Fibrositis was an early term used to describe a condition of widespread pain and decreased pain thresholds, which was later replaced by the term fibromyalgia. Wolfe et al. described that 12.2% of 1473 consecutive new patients with RA in an outpatient rheumatology clinic met the criteria for secondary fibrositis (41). Later, Wolfe et al. investigated predictors for the development of secondary fibromyalgia in previously fibromyalgia negative patients with long established RA (40). They found that fibromyalgia developed at a rate of 5.3 cases per 100 patient years and that important predictors of secondary fibromyalgia were socio-demographic disadvantages, psychosocial distress, comorbidities, more severe RA, and fibromyalgia-associated symptoms at baseline.

The incidence and predictors of secondary fibromyalgia have also been studied in patients with newly diagnosed arthritis, by Lee et al. (43). The authors found that the cumulative incidence of secondary fibromyalgia was 5.9% at 12 months and 9.2% at 36 months. The development of secondary fibromyalgia was associated with higher baseline pain ratings and poorer mental health, while an inverse association was seen for ACPA-positivity. No associations were found in relation to markers of inflammation.

The prevalence of fibromyalgia in patients with established RA vary between different studies. A systematic review of the prevalence of fibromyalgia in RA found a reported prevalence between 5-52% and a pooled prevalence of 21% (44). This is considerably higher than in the general population, where the estimated prevalence of fibromyalgia is around 2% (45).

1.3.1.2 Prevalence of widespread pain among patients with RA

Another way of assessing pain problems in patients with RA is to assess the prevalence of chronic widespread pain. Definitions of widespread pain form integral parts of the 1990 and 2016 ACR classification criteria for fibromyalgia (46, 47), and in 2019, a definition of widespread pain intended as a standalone measure, was proposed (48). The 1990 definition of widespread pain is still the most widely used (49) and is defined as “pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present” (46). For a diagnosis of fibromyalgia, the pain must have been present for at least 3 months, thereby classifying the pain as chronic.

The prevalence of chronic widespread pain in the general Swedish population has been reported to be around 10% (50). The incidence rate for the development of widespread pain in patients with RA has been reported to be 3-folded increased compared to the general

population (51) and the prevalence of widespread pain in patients with established RA has been reported to be 34% (52).

In early RA, chronic widespread pain has been reported in 36% of female patients 2 years after diagnosis (53). The prevalence of widespread pain has also been assessed and compared between two Swedish cohorts, 6 years after diagnosis of RA (54). The study assessed the 1990 widespread pain criteria and a modified version of the standalone measure from 2019 in one tight control cohort and one conventional cohort, and found that the prevalence of the 1990 definition of widespread pain was similar between the two cohorts (27% and 31% respectively), while the more conservative 2019 criteria was present in 10% in tight control cohort and 23% in the conventional cohort, suggesting that tight disease control early in the course of the disease may be protective for future development of chronic pain (54).

1.3.2 Chronic pain – Burden of disease

The *Global Burden of Disease Study* from 2019 reports that the leading cause of years lived with disability in Sweden is musculoskeletal disorders, including chronic pain (55, 56). Almost 25% of the total functional disabilities in the Stockholm County is estimated to be caused by chronic pain (57). Chronic pain is thereby a health issue with considerable impact on both the individual and the society. For the individual, chronic pain has considerable negative impact on physical and emotional functioning (58), as well as on the ability to engage in social and working life (59, 60). For society, the direct and indirect costs of chronic pain conditions, including costs for sick-leave, early retirement, rehabilitative measures, and loss of production, have been estimated to amount to 25% of total health care expenditures in Sweden and 7-8% of the Swedish state budget (61).

1.3.2.1 Challenges of clinical management

The management of chronic pain may pose a challenge for both patients and health care professionals. Patients with chronic pain often report having their symptoms neglected or questioned when seeking care, and frequently experience unsatisfactory treatment results (62, 63). Health care professionals, on the other hand, may experience guilt and feel ineffective and unsuccessful in their ability to treat patients with chronic pain (64). Quick and simple solutions for the management of chronic pain are rare and the resources for thorough pain interventions are often limited to a few clinical settings. In a 2016 report on behalf of the Swedish Association of Local Authorities and Regions, a group of experts concluded that there is a lack of competence in pain medicine within the health care system, that resources for chronic pain management is insufficient, and that multidisciplinary pain rehabilitation clinics are absent in many parts of Sweden (65).

A contributing factor to the challenges experienced by both patients and health professionals in the management of chronic pain may be that the mechanisms underlying the perpetuation of chronic pain, in the absence of objectively verifiable findings, for a long time has not been

well understood. Pain that is experienced in the absence of an identifiable organic cause has been questioned as to its actual existence and relevance, also by health care professionals. In later years, however, the knowledge about potential underlying mechanisms in chronic pain has increased and in 2016, the International Association for the Study of Pain (IASP), defined a new mechanism of pain, termed nociplastic pain, which is further discussed below.

1.3.3 Mechanisms of pain in RA

The IASP defines pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". Until 2016, two main mechanisms of pain were formally defined: nociceptive pain and neuropathic pain.

1.3.3.1 Nociceptive and neuropathic pain

Nociceptive pain refers to pain induced by noxious stimulation of pain receptors and is defined as: "Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors". Neuropathic pain had previously been quite broadly defined as "Pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation of the peripheral or central nervous system" (66). This broad formulation, which included the term "dysfunction", made the definition of neuropathic pain applicable to a broad range of pain conditions, including generalized pain syndromes such as fibromyalgia, where the mechanisms of pain were not fully understood but believed to involve dysfunctional neural pain processing.

1.3.3.2 Nociplastic pain

The definition of neuropathic pain was, however, reformulated in 2011, to a more restrictive definition which reserved the term neuropathic pain for "Pain caused by a lesion or disease of the somatosensory nervous system" (66). The new definition of neuropathic pain resulted in that a large group of patients with chronic pain syndromes could neither be classified as having nociceptive nor neuropathic pain. This led to the proposal of the novel term "nociplastic pain", which was defined as "Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" (67).

Nociplastic pain is thus defined as pain that is neither nociceptive nor neuropathic. The scientific evidence for nociplastic pain mechanisms may still be debated (68), but nociplastic pain is believed to arise as a consequence of altered neural processing of pain signals (67). For patients with RA, both nociceptive and nociplastic mechanisms may contribute to the overall pain experience, sometimes in a complex interplay. The role of these two aspects of pain in the context of RA is further discussed below.

1.3.3.3 Acute inflammatory pain

Pain that arises as a consequence of a known organic cause and that resolves when the noxious stimuli has ceased, may be referred to as acute pain. Acute pain may be elicited by mechanical or chemical stimulation of nociceptive nerve endings or by insults to the somatosensory nervous system. One prominent cause of acute pain is inflammation, which may occur in association with other painful stimuli, such as mechanical injury, or by itself as in the case of arthritis.

Inflammation causes pain through stimulation of peripheral nociceptors by neuropeptides, proinflammatory cytokines, chemokines and other inflammatory mediators (69), which together with the recruited and activated immune cells constitute the inflammatory milieu in the inflamed joint. These mediators activate surface receptors on the nociceptive neurons and contribute to the upregulation of additional receptors, which leads to hypersensitivity of the activated neurons. This sensitization of peripheral nociceptive neurons leads to hyperalgesia (increased pain in response to a painful stimulation) and allodynia (pain in response to a normally non-painful stimulus) in the affected area.

Repeated nociceptive input from the primary afferent neurons may also lead to increased excitability of second order neurons, located in dorsal horn of the spinal cord. These neurons convey the nociceptive signals to higher brain regions, after modulatory input from locally residing interneurons and immune cells, and from descending pathways in the spinal cord. Sensitization of these second order neurons leads to further enhancement of nociceptive signals in the central nervous system. These dorsal horn neurons receive input from a wider perceptive field of primary afferent neurons which leads to enhancement of signals from areas outside the primarily affected area. This gives rise to secondary hyperalgesia and allodynia (hyperalgesia and allodynia in areas surrounding the primarily affected area).

Both peripheral and central sensitization are involved in acute inflammatory pain and the augmented pain signals constitute important warning signals of potential tissue damage. This sensitization process normally subsides when the nociceptive stimulation cease. In some cases, however, the sensitization persists despite that the noxious stimuli have subsided, and acute pain may thereby develop into chronic pain.

1.3.3.4 Chronic non-inflammatory pain

Chronic pain may be defined as pain that persists beyond normal healing time. However, the notion of normal healing time is not always easily defined, and for practical reasons, chronic pain is often defined as pain that lasts or recurs for longer than 3 months (70). In contrast to acute pain, the pain signals induced by chronic pain does not necessarily imply potential tissue damage and does thereby no longer function as physiologically meaningful warning signals.

The transition from acute to chronic pain involves a transition of pain mechanisms, from the noxious stimulation of nociceptive nerve endings in acute pain, to factors that are intrinsic to

the pain pathways in chronic pain. This altered nociception, for which the term nociplastic pain has been coined, is believed to play an important role in the perpetuation of many chronic pain conditions. The notion of nociplastic pain is so far primarily based on the absence, rather than on the presence, of specific findings. While the specific mechanisms may not yet be fully understood, research in the field is continuously advancing.

1.3.3.5 Putative nociplastic pain mechanisms

Nociplastic pain is believed to involve self-perpetuating sensitization of nociceptive neurons. Peripheral sensitization may play a role in nociplastic pain conditions, however, central sensitization is believed to be the dominating mechanism (71). Central sensitization may be regarded as a collective term for functional changes in nociceptive neurons in the central nervous system that lead to augmented pain signals. These functional changes include hypersensitivity of second order nociceptive neurons in the dorsal horn of the spinal cord and impaired function of the endogenous pain control systems.

The dorsal horn neurons may become sensitized through a complex interplay of contributing factors, which involve persistent nociceptive input, release of activating neurotransmitters, upregulation of senescent receptors, and properties inherent to neurons such as temporal summation and long-term potentiation (61, 69). It further involves the modulatory actions of the descending spinal pathways of the endogenous pain control systems which originate in the brain and brainstem and influence the activity of the dorsal horn neurons (72). Furthermore, local neuroinflammation resulting from interactions between nociceptive neurons and resident immune cells, primarily glial cells, has been proposed as a mechanism by which nociplastic pain is perpetuated (69).

The endogenous pain modulatory system consists of pathways that originate in the cerebral regions and through descending spinal pathways project to the dorsal horn, where the processing of pain is modulated. The pain modulation was originally seen as primarily inhibitory, but later evidence have suggested that it provides a balance of facilitatory and inhibitory influences that overall determines the output of the nociceptive transmission (72).

The descending pathways consist of several parallel systems of neurotransmitters and receptors that exert their effects at several levels in the dorsal horn, including synaptic terminals of nociceptive afferents, excitatory and inhibitory interneurons, the secondary projection neurons, as well as synaptic terminals of other descending pathways. The neurotransmitters, and corresponding receptors, that are involved in these pathways include e.g. noradrenaline, serotonin, dopamine, histamine, acetylcholine, as well as endogenous opioids and cannabinoids (72).

Impaired function of the descending pain modulatory pathways is believed to be an important factor behind the symptomatology in chronic pain conditions such as fibromyalgia (73). The impaired modulatory function shifts the equilibrium of excitatory and inhibitory modulation of a pain free state to a state with enhanced excitation and reduced inhibition of pain signals

(73). The impaired pain inhibition acts on all segmental levels of the spinal cord and may lead to generalized hyperalgesia and allodynia.

When the pain is generated and maintained by mechanisms of altered pain processing it may no longer be regarded as a symptom of another underlying pathology, but rather as a disease entity itself (37, 70, 71).

1.3.4 Nociceptive and nociplastic pain in patients with RA

The term nociplastic pain was intended for both clinical and research contexts (71). While investigative methods such as quantitative sensory testing and functional neuroimaging may provide signs suggestive of altered pain processing, there are no clinically useful and reliable diagnostic tests to verify the presence of nociplastic pain in individual patients in the clinical context. In the clinical context therefore, the notion of nociplastic pain may be regarded as a conceptual framework rather than an objectively verifiable pathology.

It is acknowledged that nociplastic and nociceptive pain frequently co-occur in patients with RA (71, 74). In the individual patient, it may be difficult to discern to what extent the pain is caused by nociceptive or nociplastic mechanisms. The etiology of the pain may, however, have important implications for clinical decision making. The presence of nociceptive pain may imply that there is inflammatory disease activity that could be managed by adjusted DMARD therapy. The presence of nociplastic pain, however, suggests that there is a chronic pain condition over and above the rheumatic disease and that pain management interventions may be called for. Moreover, if the notion of nociplastic pain is not acknowledged and the pain of a patient with RA is incorrectly interpreted as inflammatory disease activity, it may lead to escalated DMARD treatment even in the absence of inflammatory activity.

Support for discerning the presence of nociplastic pain in musculoskeletal conditions is provided by the clinical criteria and grading system for nociplastic pain, elaborated by an IASP working group (71). These criteria classify the presence of nociplastic pain as either possible or probable, based on pain characteristics that are assessed in four different categories. The criteria are displayed in Table 1.2.3. In short, the criteria assess pain duration and distribution, evidence of nociceptive and neuropathic pain, history of pain hypersensitivity, comorbid symptoms, and an examination of evoked hypersensitivity phenomena. Depending on the number of categories that are fulfilled, nociplastic pain is classified as either possible or probable.

If there are signs of nociplastic pain, these symptoms should preferentially be addressed in parallel with the management of the rheumatic disease. The overarching principles of the EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis state that the health professional should have a basic understanding of the bio-psycho-social nature of pain and that the management of pain should be guided by the individual needs of the patient (75). The role of the rheumatologist in the parallel

management of the rheumatic disease and the chronic pain condition may include the initial identification of a nociplastic pain condition, to provide adequate and understandable information about the nature of the pain condition, and by guiding the patient to further pain management interventions based on the individual needs of the patient.

Table 1.2.3. Clinical criteria for the assessment of nociplastic pain, elaborated by an IASP working group. Each section, 1 to 4, is assessed separately. Possible nociplastic pain may be classified if sections 1 and 4 are fulfilled. Probable nociplastic pain may be classified if all four sections are fulfilled.

Clinical criteria and grading for nociplastic pain affecting the musculoskeletal system
1. All of the following is true for the pain: - The pain is chronic (>3 months duration) - The pain is regional or widespread, rather than discrete - There is no evidence that nociceptive pain (a) is present or (b) if present, is entirely responsible for the pain - There is no evidence that neuropathic pain (a) is present or (b) if present, is entirely responsible for the pain
2. There is a history of pain hypersensitivity in the region of pain (any of the following): - Sensitivity to touch - Sensitivity to pressure - Sensitivity to movement - Sensitivity to heat or cold
3. Any of the following symptoms are present: - Increased sensitivity to sound, light, or odors - Sleep disturbance with frequent nocturnal awakenings - Fatigue - Cognitive symptoms such as impaired memory and difficulties with concentration, etc.
4. Evoked pain hypersensitivity phenomena can be elicited in the region of pain (any of the following): - Static mechanical allodynia - Dynamic mechanical allodynia - Heat or cold allodynia - Painful after-sensation after the assessment of any of the above
The pain may be classified as: (a) *Possible* nociplastic, if sections 1 and 4 are fulfilled (b) *Probable* nociplastic, if all of the sections, 1 to 4, are fulfilled

1.4 A BRIEF DESCRIPTION OF FIBROMYALGIA

Fibromyalgia is a prototypical chronic widespread pain syndrome, believed to be driven by nociplastic pain mechanisms. It is characterized by widespread pain and tenderness and commonly also include features such as fatigue, sleep disturbances and cognitive symptoms such as impaired memory and difficulties to concentrate attention. Fibromyalgia is estimated to affect around 2% of the general population (45, 76), while significantly higher prevalence is found among patients with other chronic pain conditions (77). The majority of patients with fibromyalgia, up to 80%, are women (78).

The most prominent risk factor for the development of fibromyalgia is the presence of persistent localized pain, which is reported by more than 80% of the patients (78). The preceding localized pain may involve neck- and back pain, trauma, and other chronic diseases such as rheumatic diseases. Twin-studies have further suggested that there is a significant hereditary component (79). Other known risk factors for fibromyalgia include mental health symptoms such as anxiety and depression, sleep disturbances, overweight, and physical inactivity (80).

Beside the mechanisms of nociplastic pain, other pathophysiological aberrations have also been implicated in fibromyalgia. These include a dysfunction of the autonomic nervous system, with elevated basal activity of the sympathetic nervous system in combination with a decreased sympathetic activation in relation to physical activity and stress (81). Decreased blood perfusion of muscular tissue and muscular ischemia have also been demonstrated (82, 83), which could be a consequence of dysfunctional autonomic regulation of blood flow. Studies of cerebrospinal fluid in patients with fibromyalgia have shown decreased levels of pain-regulating neurotransmitters such as serotonin, norepinephrine, and dopamine (84), as well as signs of neuroinflammation by detection of increased levels of inflammatory markers (85, 86).

1.4.1 A short history of terminology

The first medical descriptions of "rheumatism" were provided by Guillame de Baillou in the 16th century. Two centuries later, the term "muscular rheumatism" had come to be used to describe painful musculoskeletal disorders without articular deformities (87). In 1904, the term fibrositis was coined by WR Gowers, under the viewpoint that the condition referred to as muscular rheumatism was caused by inflammation of the fibrous tissue of the muscles (88). The term fibrositis was later used by HA Smythe when he provided one of the first modern descriptions of fibromyalgia in 1972 (87, 89). Smythe also provided an early set of diagnostic criteria based on the presence of chronic pain, tender points, fatigue, sleep disturbances and morning stiffness (90, 91).

Although the term fibrositis was recognized as a misnomer during this period, since the condition was no longer believed to be caused by inflammation of fibrous tissue, the use of

the term continued during the 1970's and 80's (92, 93). The term fibromyalgia was first proposed in 1976, in an editorial of the 22nd Rheumatism Review of the American Rheumatism Association (87, 91), and during the 1980's both terms coexisted before consensus for the use of the term fibromyalgia was reached during the development of the first ACR criteria in 1990 (91).

1.4.2 The development of classification criteria

The symptoms that are associated with fibromyalgia may vary in both severity and expression, and different features may be more or less prominent in different individuals (94). To define the features that most accurately delineates the target population is therefore a challenging task, and several sets of criteria have been proposed and revised over the years.

Early criteria emphasized the presence of tender points, which was believed to reflect a peripheral pathology of muscles and tendons. It was later understood, however, that the tender points constituted structures that were more sensitive to pressure in everyone and that the increased tenderness of patients with fibromyalgia reflected a generalized pain sensitivity (78). Later criteria abandoned the assessment of tender points and instead focused on pain distribution and other somatic symptoms. The differences between the criteria have resulted in that they encircle partly different populations. For example, there is a larger proportion of men and an increase in overall prevalence when comparing the 2016 criteria to the 1990 criteria (78).

1.4.2.1 Early criteria and the 1990 ACR classification criteria

One of the earliest criteria, proposed by Smythe in 1979, defined fibrositis as (1) the presence of widespread aching for longer than three months, (2) local tenderness at 12 of 14 specified sites, (3) skin-roll tenderness over the upper scapular region, (4) disturbed sleep with morning fatigue and stiffness, and (5) no abnormalities of ESR, aspartate aminotransferase (ASAT), RF, antinuclear factor (ANA) or muscle enzymes, nor on sacroiliac x-rays (93). Subsequent to the initial work by Smythe, a set of pioneering fibromyalgia investigators each proposed their own set of criteria during the 1980's, which agreed on the presence of tender points as a crucial component, but disagreed on the number and distribution of them, as well as on the significance of other somatic features (95). These investigators eventually came together in a joint effort to elaborate the 1990 ACR classification criteria for fibromyalgia, which by then had been reduced to the combination of widespread pain and at least 11 of 18 tender points (46).

1.4.2.2 The 2010 ACR criteria

The 2010 criteria for fibromyalgia were developed to provide an alternative method of diagnosis that did not include a tender point assessment, and to provide a scale of symptom severity. The criteria were not intended to replace the 1990 criteria but rather to function as an alternative since it had been acknowledged that the tender point assessment was perceived

as impractical and rarely performed in clinical practice (96). Further motives for the new criteria were that other symptoms, not part of the 1990 criteria, had become acknowledged as key features of fibromyalgia, and that a symptom severity scale would enable comparisons between patients and over time.

The criteria were based on two components, a widespread pain index (WPI), ranging from 0-19 painful body sites, and a symptom severity scale (SSS), which assessed fatigue, waking unrefreshed, cognitive symptoms, and other somatic symptoms on a total scale of 0-12. The criteria could be satisfied by a combination of WPI and SSS scores, provided that the symptoms had been present for at least 3 months and were not better explained by another disorder (96). As an overall score of symptom severity, WPI and SSS were combined to an overall score, ranging from 0-31.

A feature of the new criteria that is of significance for the assessment of fibromyalgia and widespread pain in patients with RA, is that the WPI excludes peripheral joints. The index of body sites that constitute the WPI was developed specifically to distinguish patients with fibromyalgia from patients with RA and osteoarthritis, and among a large number of variables, the non-articular pain index proved to be the best discriminator (97).

1.4.2.3 The 2011 ACR criteria

The 2010 criteria had eliminated the clinical examination of tender points, but the evaluation of the somatic symptoms still required an assessment by clinical personnel. To enable complete self-administration and thereby make the criteria assessable by questionnaires, a modified version of the criteria was proposed in 2011 (98). In the modified version, the somatic symptoms were assessed by the patients, preserving a total SSS-score of 0-12.

In conjunction with the development of the 2010/2011 criteria, the term “fibromyalgianess” had been proposed to describe fibromyalgia-related symptoms as a continuum of symptom severity rather than a dichotomous condition (94). The authors of the 2010/2011 criteria discussed the overall symptom severity scale that added the WPI and SSS to an overall score of 0-31 as a continuous assessment of fibromyalgia symptom severity and proposed that a cutoff of ≥13 best separated patients who would be classified as fibromyalgia according to the 2010 criteria (98).

1.4.2.4 The 2016 ACR criteria

The 2010/2011 ACR criteria were again revised in 2016 (47). The 2016 revision harmonized the differences between the 2010 clinician-based, and the 2011 patient-based assessment of somatic symptoms to provide a set of criteria to be used both in the clinical setting and in survey formats. The 2016 revision also added a criterion for widespread pain, which had not been part of the 2010/2011 criteria, where a count of painful body sites had been used regardless of its distribution. The new widespread pain criterion required the presence of pain in at least 4 of 5 body regions, where the body regions consisted of the four body quadrants

and the axial skeleton. Each region consisted of three body sites, based on the 2010/2011 WPI (with the exclusion of the jaws, the chest, and the abdomen).

A further revision was made in reference to concurrent disease conditions. The 2010/2011 criteria included the reservation that a diagnosis of fibromyalgia was valid if the symptoms were not sufficiently explained by another disorder. The 2016 revision, however, stated that "A diagnosis of fibromyalgia is valid irrespective of other diagnoses", which was also the position of the 1990 criteria (46, 47).

1.4.2.5 The 2019 standalone measure of widespread pain

In 2019, a group of authors involved in the elaboration of the ACR criteria for fibromyalgia proposed a new definition of widespread pain, intended as a standalone measure (48). The authors acknowledged that the still widely used 1990 definition of widespread pain was never intended to be used as a standalone measure and that its somewhat ambiguous formulation had led to a variety of interpretations (49). The 2019 criteria were a further development of the 2016 criteria for widespread pain. In addition to the presence of pain in at least 4 of 5 regions, the new criteria also required pain in at least 7 of the 15 specified body sites.

1.4.2.6 The ICD-11 definition of widespread pain

A description of chronic widespread pain as a standalone entity is also provided in the elaboration of the 11th revision of the International Classification of Diseases (ICD-11) (70). The ICD-11 defines chronic primary pain syndromes as "Pain in one or more anatomical regions that persists or recurs for longer than 3 months and is associated with significant emotional distress or functional disability and that cannot be better accounted for by another chronic pain condition" (70). Chronic widespread pain is regarded as a subcategory of chronic primary pain syndromes and is defined as pain in at least 3 body quadrants plus the axial skeleton (99). The pain should not be directly attributable to a nociceptive process in the painful regions and there should be features consistent with nociplastic pain, such as spontaneously evoked pain, allodynia, hyperalgesia, and identified psychological or social contributors. It is further stated that chronic primary pain syndromes should be regarded as disease entities in themself, in contrast to chronic secondary pain syndromes which are linked to other underlying diseases.

1.4.2.7 Other criteria for fibromyalgia

In addition to the criteria endorsed by ACR, several other sets of criteria for fibromyalgia have been proposed. These include, for example, the AAPT core diagnostic criteria from 2018, which are defined as the presence of pain in at least 6 of 9 body sites that have been present for at least 3 months, together with moderate to severe sleep problems or fatigue *(100)*. For further diagnostic support, a list of common symptoms is also provided, including tenderness to pressure, cognitive symptoms, musculoskeletal stiffness, and hypersensitivity to environmental stimuli such as bright lights, loud noises, perfumes and cold.

Further criteria have been proposed by Arnold et al. in 2012, based on a combination of pain distribution, other psychosomatic symptoms, and an assessment of tender points, joints, and blood tests (101), as well as by Bennett et al. in 2014, based on pain distribution and a set of cognitive and somatic symptoms (102).

1.5 PAIN MANAGEMENT

1.5.1 Overarching principles

The EULAR guidelines for the health professional´s approach to pain management in patients with inflammatory arthritis include a set of overarching principles that state that (a) the management of pain should be guided by a patient-centered framework where the patient's preferences, needs, and values are considered, (b) the health professional should acknowledge the bio-psycho-social underpinnings of chronic pain states and recognize the specific interactive and mutually influencing factors that are important for the individual patient, (c) optimal management of the underlying rheumatic condition is crucial for pain control, and (d) the health professional should be able to differentiate between localized nociceptive pain and generalized pain due to dysfunctional pain regulation to help direct the optimal pain management strategy (75).

The EULAR recommendations for the management of fibromyalgia also propose a set of overarching principles (103). These principles state that (a) fibromyalgia should be recognized as a complex and heterogenous condition characterized by abnormal pain processing and other secondary features, that a full understanding of fibromyalgia requires a comprehensive assessment of pain, function, and psychosocial context, and that optimal management requires prompt diagnosis, and (b) the management of fibromyalgia should aim at improving health-related quality of life and that treatment modalities should be tailored according to individual needs, where initial focus should be on non-pharmacological therapies and where a multidisciplinary approach often is required.

Both guidelines propose a stepped-care approach where educational information is recommended for all patients, where additional unimodal interventions are recommended based on the specific needs of the patient, and where multimodal rehabilitation constitute the highest level of care intended for patients with significant disabilities.

1.5.2 Components of the pain management procedure

In pain rehabilitation, the clinical management of patients with chronic pain involves a thorough pain analysis, the formulation of a management plan, the adoption of suitable interventions, and follow-up evaluation (61).

1.5.2.1 Pain analysis

The pain analysis adopts a bio-psycho-social perspective on the pain condition and includes a thorough assessment of the symptomatology, including medical history and a clinical examination, and may include further investigations if there are signs of unmanaged underlying pathologies. The pain analysis should result in (a) an ICD-diagnosis, (b) a classification of involved pain mechanisms, and (c) a survey and analysis of important psychological and social factors.

1.5.2.2 Management plan

Based on the pain analysis, a management plan should be formulated. The management plan should consist of a written document that describes the result of the pain analysis and the planned rehabilitation procedures. The management plan should be elaborated by the health professional together with the patient and function as a common platform for the planned procedures and for their evaluation.

1.5.2.3 Interventions

The planned interventions may include one or more unimodal interventions or a multimodal rehabilitation program, based on the individual needs of the patient. A basic principle is that if less resource demanding interventions may be expected to provide lasting results, these should be tried and systematically evaluated firstly. An algorithm for the selection of patients for multimodal rehabilitation has been elaborated by the Swedish Society of Medicine in collaboration with several Swedish authorities (104). The algorithm considers the impact of the pain condition on everyday life, whether potentially treatable underlying causes have been investigated and properly managed, if the patient's pharmacological treatment is optimized, if the patient has been considered for unimodal treatment options, if there are aggravating psychosocial factors, and if the patient is willing to actively engage in the program and willing to make behavioral changes. If the criteria are met, the patient may be suggested for multimodal rehabilitation, which may be provided on primary care level or on specialist care level depending on the severity and complexity of the situation.

1.5.2.4 Evaluation

An integral part of the pain management procedure is a systematic evaluation of the applied interventions. In the context of specialist care, the outcomes of multimodal rehabilitation programs are compiled in the Swedish National Register for Pain Rehabilitation, which are subjected to continuous scientific evaluations (105-107).

1.5.2.5 Level of care

In 2016, a group of Swedish experts presented an overview of pain care in Sweden, on behalf of the Swedish Association of Local Authorities and Regions (65). The report suggested a structure of care for patients with chronic pain organized in four levels:

1. The primary care constitute the first level of care, where the majority of patients are handled. The authors suggest that the primary care develop an organisation for the management of patients with chronic pain, with designated personnel to coordinate care with other care levels and involved authorities.
2. The second line of care should include multiprofessional teams at a fewer number of units within the primary care system, to manage patients in need of coordinated interventions.
3. The third line of care should involve multidisciplinary pain units on specialist care level for patients that cannot be managed on primary care level.
4. The fourth level of care should be multidisciplinary pain centres for patients with complex pain conditions. These centres should offer inpatient care and also constitue centers for education and research.

1.5.3 Non-pharmacological interventions

Non-pharmacological interventions are the cornerstones of chronic pain management (61, 78). These may include educational activities, physical exercise, psychological interventions, occupational therapy, and other interventions such as sleep management and weight management.

1.5.3.1 Educational activities

Adequate information about the underlying pain physiology is an important factor in chronic pain management, which is recommended as a first step in the pain management procedure in the EULAR guidelines for the health professional's approach to pain management in inflammatory arthritis (75). The patients should be informed that chronic nociplastic pain is caused by a dysfunction of the pain regulatory system, which leads to augmented pain signals, such that painful stimuli may be experienced as very painful and normally painless stimulation may be experienced as painful. It is important to inform the patient that this dysfunctional pain should not be interpreted as a warning signal and does not imply threatening tissue damage, and that even though the patient may experience increased pain in relation to physical activity, it may be necessary to cope with a certain level of pain to maintain or increase functional abilities and decrease pain levels over time through maintained physical activity. It is, however, important to find a pace in relation to physical activity that is long-term tolerable (78). Educational information may be provided to the patient in written form, through online resources, or face-to-face interaction with care givers (75).

1.5.3.2 Physical exercise

Physical exercise has a prominent role in the management of chronic nociplastic pain and it is the treatment modality that has been most extensively studied, with demonstrated effects on pain alleviation and maintenance of physical function (61, 103). Physical exercise may

include a wide range of activities with varying levels of intensity and the available evidence does not clearly support one exercise modality over others (78, 103). Patients with chronic nociplastic pain often experience an increase in pain intensity after physical exercise, which typically lasts for 24-48 hours (78). A benchmark for the choice of activity, and its level of intensity, may be that the increased pain should resolve between the exercise occasions (78). If the increased pain persists over time, the exercise modality may need to be adjusted, however it should be encouraged that a suitable level of exercise is continued.

1.5.3.3 Psychological interventions

Psychological interventions are another important form of treatment modality, which form integral parts of pain rehabilitation programs. Psychological interventions aim at supporting the adoption of constructive coping strategies and may contribute to increased self-efficacy, reduced stress and anxiety, and increased health-related quality of life (78). Psychological interventions have also been shown to contribute to a reduction in pain levels (108). The most common psychological interventions in pain rehabilitation in Sweden include cognitive behavioral therapy, e.g. acceptance commitment therapy, and mindfulness-based therapies (105).

1.5.3.4 Occupational therapy

Occupational interventions may involve the use of orthotics, daily living aids, and ergonomic adaptions (75), and in the context of multimodal rehabilitation, adaptive measures in relation to the workplace may be an important component of the rehabilitation process (61). Workplace interventions may include a strategy for gradual return to work from a period of sick-leave, adjustment of working assignments, as well as ergonomic and organizational adaptations at the work environment. Another important component of multimodal rehabilitation may be to provide support for the coordination of contacts between health care providers, employer, and the Social Insurance Agency (61).

1.5.3.5 Sleep and weight management

Sleep disturbances are common among patients with chronic pain, and sleep disturbances have both been associated with the aggravation of manifested pain conditions and implicated as a risk factor for developing chronic pain (61). Advise on sleep hygiene may therefore be generally advisable in the management of chronic pain, and for patients with manifested sleep disturbances, directed interventions, such as cognitive behavioral therapy, may be considered (105).

Obesity may negatively impact on physical activity and physical function. Physical activity is an important component of pain management strategies and assessments from the Swedish National Register for Pain Rehabilitation have shown that obese patients with chronic pain display worse results from their rehabilitation than non-obese patients (109). Specific interventions for weight management and increased physical activity for obese patients may therefore be motivated.

1.5.4 Pharmacological interventions

Pharmacological therapies often form an integral part of the management of chronic pain and should be seen as one part of a multimodal management strategy. In the management of chronic nociplastic pain, analgesic drugs seldom provide more than partial pain relief and non-pharmacological therapies are often of more central importance for successful management of chronic pain. The partial pain relief that analgesics provide may, however, have important implications for the individual's capacity to manage everyday life and to engage in other pain management interventions.

The Swedish Medical Products Agency have provided guidelines for the pharmacological management of chronic pain in children and adults (110). In this thesis, the management of chronic pain in children has not been further addressed. The main messages of the guidelines are briefly summarized below.

1.5.4.1 General principles for pharmacological management of chronic pain

The guidelines state that the pain management should be guided by a bio-psycho-social perspective and employ a multimodal management, where interventions should aim at strengthening the healthy aspects of the patient, encourage constructive physical and social activities, support daily activities, and reduce the negative impact of pain. It is further stated that pain medications do not necessarily need to be part of the pain management strategy, and when they are, they should be seen as one part of a multimodal management.

A set of general principles to acknowledge before the initiation of pharmacological treatment for chronic pain are formulated in following statements (110):

- As far as possible, the underlying pain mechanisms and pain generating structures should be determined.
- The patient's expectations of the planned treatment should be assessed and realistic treatment goals should be formulated and agreed upon.
- The patient's previous experiences of pain medications should be assessed.
- Comorbidities and psychosocial factors shold be assessed.
- The risk of substance abuse should be evaluated.

1.5.4.2 Initiation and follow-up of pain medications

The guidelines recommend the following principles for the initiation and follow-up of pain medications (110):

- A thorough assessment of previous medications should be performed. Previous pain medications should be assessed in terms of effects, doses, side-effects, and reasons for discontinuation. All other concurrent medications should be assessed and interactions should be considered.

- A management plan for the follow-up and evaluation of the medication should be formulated.
- Not more than one change of medication should be made at a time and the effect should be assessed before making additional changes.
- Medications should start at the lowest recommended dose and gradually be increased if needed.
- The patient should be informed of when a treatment effect can be expected, and of common side-effects. Commonly, treatment effects may be evaluated after 2-4 weeks.
- When a treatment effect has been reached, the duration of the treatment period and its follow-up should be planned according to the management plan. A reevaluation should be performed at least every year.

1.5.4.3 Treatment recommendations based on pain mechanisms

Before starting a pain medication, it is important to inform the patient that pain medications seldom provide more than partial pain alleviation. Often a combination of drugs is necessary for optimal effects. The choice of pain medication should preferentially be based on knowledge about the underlying pain mechanisms and analgetic mode of action. However, in reality it is often not possible do predict which patients will respond to a specific treatment and trial-and-error scenarios cannot always be avoided.

For nociceptive pain, the recommendations propose a stepwise approach depending on the severity of the symptoms (110):

- Mild pain:
    - Paracetamol
    - Non-steroidal anti-inflammatory drugs (NSAIDs).
- Moderate pain:
    - Codeine
    - Tramadol
    - Buprenorphine skin patch
- Severe pain:
    - Morphine and other opioids

The recommendations for neuropathic pain are based on recommendations from an IASP special interest group for neuropathic pain (111), and are formulated based on three lines of treatment recommendations and on the strength of the available evidence (110):

- First line of treatment, strong recommendations:
    - Gabapentinoids
    - Tricyclic antidepressants
    - Selective norepinephrine reuptake inhibitors (SNRI).
- Second line of treatment, weak recommendations:

    - Tramadol
    - Capsaicin and lidocain skin patches (for local peripheral neuropathic pain)
- Third line of treatment, weak recommandations:
    - Morphine
    - Oxycodone

The recommendations for nociplastic pain are similar to the first line of treatment recommendations for neuropathic pain, i.e., gabapentinoids, tricyclic antidepressant, and SNRI, and may further include tramadol, while stronger opioids should be avoided (110).

1.5.4.4 EULAR recommendations for the management of fibromyalgia

The EULAR revised recommendations for the management of fibromyalgia recommends five pharmacological treatment options (103). In similarity with the recommendations of the Swedish Medical Products Agency, the tricyclic antidepressant Amitriptyline, the weak opioid Tramadol, and the gabapentinoid Pregabalin are recommended. In addition, two selective serotonin-norepinephrine reuptake inhibitors, Duloxetine and Milnacipran, and the muscle relaxant Cyclobenzaprine, are recommended, while no recommendations are made for SNRI-drugs. The level of evidence was weak for all the recommended drugs.

1.5.4.5 Opioids in chronic pain management

Opioids are generally not recommended as the first line of treatment in the management of chronic nociplastic pain but may provide beneficial effects in some patients (110, 112). The long-term use of opioids is associated with a risk of significant adverse effects, including tolerance and substance abuse, and should thereby be used with outermost precaution. The recommendations from the Swedish Medical Products Agency provide guiding principles for the use of opioids for chronic pain, which include an evaluation of the risk of substance abuse, a careful management plan with regular evaluations, and an emphasis on the responsibility of the prescriber to continuously follow-up the treatment until the responsibility has formally been transferred to and accepted by another prescriber (110).

1.5.5 Multimodal rehabilitation

Multimodal rehabilitation consists of coordinated interventions which involve a multi-professional team. The team of professionals should, at minimum, include a physician, a physiotherapist, and a psychologist, but may also include nurses, therapeutic counselors, and occupational therapists (78). A multimodal rehabilitation program is often the final step of organized pain management in the health care system.

As described above, the components of the pain rehabilitation procedure include a thorough pain analysis, the formulation of a management plan, adoption of suitable interventions, and a structured follow-up evaluation. The management plan should harmonize the patient's own goals with the conclusions of the pain analysis, and it should seek to establish the active role of the patient in the rehabilitation process. Common goals for the rehabilitation process may include decreased pain and psychological load, increased participation in work and social life, and improved health and quality of life (61).

An important feature of the multimodal rehabilitation is that the interventions are coordinated between the involved health professionals and that it is guided by a common understanding and by common objectives, which are evaluated during the rehabilitation process. The rehabilitation process may consist of daily activities and home assignments for a period of 4-8 weeks and may be seen as stepping board for the patient to make long-term behavioral and lifestyle changes.

1.5.5.1 Common components of multimodal rehabilitation

Common components of multimodal rehabilitation in Sweden include (a) educational activities to provide a basic understanding of underlying pain mechanisms, (b) psychological interventions, most commonly cognitive behavioral therapy including acceptance and commitment therapy, as well as mindfulness-based therapies (c) physical exercise, either in groups or individually, (d) training of daily activities that are relevant for the individual, which may include activities in everyday life and work-related activities, (e) interventions for working place adjustments, including contact with employers, visits to the work place, and adaptations of the work environment, and (f) support for the coordination of contacts with health care, workplace, insurance agencies, and other involved authorities (61).

2 RESEARCH AIMS

2.1 OVERALL OBJECTIVE

The overall objective of this thesis was to characterize the occurrence of pain problems during early stages of RA and to identify associated risk factors, concurrent clinical features, and associations between pain, measures of disease activity, and the use of antirheumatic medications.

2.2 SPECIFIC AIMS

Study 1)

In the first study, we aimed to investigate the prevalence of widespread pain outside the joint regions in patients with newly diagnosed RA, 3 years after diagnosis. We further aimed to assess the general health status of these patients at 3 years, and the association between clinical characteristics at the time of diagnosis and widespread non-joint pain at 3 years.

Study 2)

In the second study, the objective was to use cluster analysis to identify subgroups of patients, 3 years after diagnosis of RA, based on the prevalence of so-called “unmet needs” in RA, including pain, fatigue, sleep problems, and general health-related quality of life. We further aimed to assess the association between the identified subgroups and clinical characteristics at the time of diagnosis.

Study 3)

In the third study, our aim was to assess the prevalence of patients who failed to reach formal treatment targets despite being in inflammatory remission, during the first two years of RA disease. We further aimed to assess the association between the failure of reaching treatment targets despite being in inflammatory remission and likelihood of starting new antirheumatic medications.

3 MATERIAL AND METHODS

Medical research can be broadly categorized into basic, clinical, and epidemiological research (113), of which the studies of the present thesis belong to the latter category. The word epidemiology is derived from the Greek words *epi* (= upon or among), *demos* (= people or district), and *logos* (= study), which may be literarily translated into "the study of what is upon the people". A more comprehensive definition is provided in "A dictionary of epidemiology" (114), which defines epidemiology as "The study of occurrence and distribution of health-related events, states, and processes in specified populations, including the study of determinants influencing such processes, and the application of this knowledge to control relevant health problems".

In this thesis, we have studied the occurrence and distribution of pain and pain-related features among patients with early RA. For this endeavor, two major data sources have been used, the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) and the Swedish Rheumatology Quality Register (SRQ). These data sources are further described below.

3.1 DATA SOURCES

3.1.1 Epidemiological Investigation of Rheumatoid Arthritis (EIRA)

The EIRA study is a case-control study that was initiated at Karolinska Institutet in 1996 with the aim of investigating risk factors for the development of RA. The study enrolls newly diagnosed patients with RA from the south and middle parts of Sweden and recruit controls matched on age, sex, and residential area from the general population. The cases and controls provide blood samples and complete a comprehensive questionnaire which includes topics such as occupation and occupational exposures, previous diseases and vaccinations, physical activity, personal relations, and dietary habits.

Starting from 2010, a 1-year follow-up questionnaire was added to the EIRA study, and from 2011 and onwards, a 3-year follow-up questionnaire was also added. These follow-up questionnaires included more clinically oriented questions and were distributed only to the cases. The 3-year follow-up questionnaire in EIRA was used in study I to assess the occurrence of widespread pain outside the joints and the associated general health status, and in study II to identify subgroups of patients based on health-related factors sometimes collectively referred to as "unmet needs" in RA (28), i.e. pain, sleep quality, functional disabilities, general health-related quality of life, and traits of anxiety and depression.

3.1.2 Swedish Rheumatology Quality Register (SRQ)

The SRQ was initiated by the Swedish Society for Rheumatology in 1995. The register is used for monitoring of patients in clinical practice, for providing statistics of rheumatological

health care in Sweden, and for medical research. The registered data include measures of disease activity, antirheumatic treatment regimens, and patient reported outcomes, which are provided by health care professionals and patients at diagnosis and follow-up visits. More than 50 rheumatological clinics throughout Sweden contribute with data to SRQ, and approximately 85% av all cases of RA in Sweden are registered in SRQ (115).

In studies I and II, the data from SRQ and EIRA were linked together by the personal identity number assigned to all Swedish residents. We used clinical data from SRQ to assess clinical characteristics at the time of diagnosis and assessed the association to the respective 3-year outcomes based on follow-up data from EIRA. In study III, SRQ was the only data source. In this study, we used clinical data from follow-up visits during the first 2 years of RA disease to assess the prevalence of patients that fail to reach formal treatment targets despite being in inflammatory remission, and the associated likelihood of starting new DMARD-treatments.

3.2 STUDY DESIGN

Three main types of study designs in epidemiological research are cohort studies, case-control studies, and cross-sectional studies. In simple terms, a cohort study identifies subjects who are, as well as subjects who are not, exposed to a factor that is hypothesized to affect a given outcome. The subjects are observed over time, and the incidence of the outcome is compared between exposed and non-exposed subjects. A cohort study can provide evidence for a causal relationship between an exposure and an outcome. A case-control study starts by identifying cases with a given outcome and (matched) controls without the outcome, and retrospectively collects data on previous exposures. Case-control studies are often more practical to perform than cohort studies, especially when the outcome is rare. A cross-sectional study assesses the relationship between a given outcome and other variables of interest in a given population and at a given time. The prevalence of both the outcome and the other variables of interest are collected and assessed at the same time point. Since the temporal relationship between “exposure” and outcome is not deducible in a cross-sectional study design, it does not provide evidence for the direction of causal relationships between the assessed variables.

The three studies included in this thesis does not clearly match any of the three above mentioned study designs. Studies I and II use similar study designs. In similarity with a cohort study design, the data in these studies have been prospectively collected, meaning that the data on exposures (the clinical characteristics at diagnosis) have been collected prior to the data on the outcomes (widespread non-joint pain or cluster identity). In contrast to a cohort study, however, the outcomes of these studies were not predefined before the data collection was initiated. In similarity with case-control and cross-sectional designs, the starting point of these studies were the identification of patients with the outcome of interest, which was followed by a subsequent assessment of exposures and other variables of interest. In contrast to a case-control study, however, the data on exposures were not retrospectively

collected, and the controls were not selected based on matching of the cases. In contrast to a cross-sectional study design, the data on exposures and other variables of interest were not collected at the same time point as the outcome. A possible denotation for these two studies may be to call them retrospective cohort studies, which denotes cohort studies that are performed post hoc on data that is already collected for other purposes (116).

Study III is perhaps even more difficult to categorize in relation to formal study design criteria. The study is based on prospectively collected data, where outcome, exposure, and other variables of interest are repeatedly assessed at different time points. One might simply denote it as a longitudinal observational study with repeated cross-sectional assessments of outcome, exposure, and other variables of interest.

3.2.1 Bias and confounding

One reason to reflect over the nature of a study's design is that different research approaches are vulnerable to different types of biases. A bias may be defined as a systematic error in the research design that leads to inaccurate results. Numerous specific types of biases that might occur in epidemiological research have been described. These may be organized in three main groups, i.e., selection bias, information bias, and confounding bias (117).

3.2.1.1 Selection bias

Selection bias refers to systematic errors in the selection of the study population. When there is a bias in the selection of study participants, the study population will not be representative of the source population (the true population in society with the outcome of interest), and inferences made on the study population will not be generalizable to the source population, i.e., the results will not reflect the true situation.

3.2.1.2 Information bias

Information bias refers to errors in the data collection procedures, which leads to unequal quality of information between the compared groups. Errors in the data collection procedure may result in misclassification of study subjects regarding exposure, outcome, and other variables of interest. A potential source of information bias, which may lead to misclassification, is recall bias. Recall bias may occur when information on study variables is based on the recollection of individual study subjects. Subjects that are afflicted by a particular outcome may be more inclined to remember, and report, previous exposures compared to subjects who are unaffected.

3.2.1.3 Confounding

Confounding is a form of bias that affects the measure of association between an exposure and an outcome. A confounding factor is a factor other than the exposure that accounts for all, or part, of an apparent association between an exposure and an outcome. The formal

definition of a confounding factor is that (a) the factor must be a risk factor for the outcome, (b) the factor must be associated with the exposure, (c) the factor should not be a mediator between exposure and outcome (117). Considering potential confounders is crucial in the planning and conduction of studies that aim at establishing a causal relationship between an exposure and an outcome.

Another type of effect on the relationship between an exposure and an outcome by a third variable is interaction, or effect modification. Interaction occurs when the association between exposure and outcome differs at different levels of a third variable. Such a variable is called an effect modifier, since it modifies the effect of the exposure on the outcome (117).

3.3 STATISTICAL ANALYSES

Medical statistics is the science of collecting, summarizing, and analyzing data, applied to the field of medicine (118). A guiding principle for both medical research and practice is the notion of evidence-based medicine, which refers to the use of current best evidence in the practical care of patients (119). The production of reliable medical evidence is highly dependent on the correct application and interpretation of statistical methods in medical research. However, medical statistics seldom provide exact answers. The answers are often approximations, which in turn are based on assumptions of an ideal data structure. The renowned 20th century statistician George Box famously expressed this as "All statistical models are wrong, but some are useful" (120). A continuous challenge for medical researchers is therefore to correctly apply and interpret statistical methods, to provide reliable and practically useful medical evidence.

3.3.1 Descriptive statistics

Descriptive statistics refers to a collection of methods for organizing, displaying, and describing a sample of data (121). This includes an assessment of the distribution, central tendency, and variation of the included variables. In all the respective data sets of the studies included in this thesis, the continuous variables were visually inspected by histograms and/or probability plots to determine their distribution. Normally distributed variables were assessed with means and standard deviations, and the Student's t-test was used for statistical comparisons. Non-normally distributed variables were assessed with median and interquartile range, displayed as the first and third quartile values, and the Wilcoxon rank sum test was used for statistical comparisons. For categorical variables, numbers and percentages were calculated, and Chi square test or Fisher's exact test (if cell counts were below 5) were used for statistical comparisons. The significance level of the statistical tests was set to 5%.

3.3.2 Regression analysis

Regression analysis is a statistical model that describes the relationship between an outcome variable (a dependent variable) and one or more explanatory variables (independent variables) (114). The term "regression" has originated from the British anthropologist Sir Francis Galton (1822-1911), who developed the technique to investigate the relationship between heights of parents and their children (122). He observed that parents who were unusually tall or short, tended to have children whose height were closer to the population mean. He called this phenomenon "regression towards mediocrity", which was later rephrased to "regression towards the mean", a term which came to represent the general tendency of extreme values to be followed by values closer to the population mean when measures are repeated (118). Today, a wide variety of regression analyses exist that each apply to certain sets of conditions. In the studies of this thesis, we have used Poisson regression and a modification of it called modified Poisson regression.

3.3.2.1 Poisson regression

Poisson regression derives its name from the French mathematician Siméon Denis Poisson (1781-1840), who described a probability distribution which was named Poisson distribution (123). In Poisson regression, the outcome variable is assumed to have a Poisson distribution. The assumptions underlying a Poisson distribution is that (a) it is a count of events that occur within a given time or space, (b) the events are independent of each other, i.e., the occurrence of one event does not influence if, or when, another event occurs, (c) the rate at which the events occur is assumed to be constant over the given time or space interval, (d) two events cannot occur at exactly the same instant. A further characteristic of a Poisson random variable is that the mean of the count is equal to its variance.

In Poisson regression, the average number of events that occur within the given time or space is depicted by the Greek small letter lambda, λ. This average number of events can be expressed as an event rate, and the Poisson regression model attempts to predict the expected rate of events based on one or more explanatory variables. In somewhat technical terms, the explanatory variables are linked, through a linear function, to the natural logarithm of the expected rate. As for all statistical models, the Poisson regression model is based on a set of assumptions, which need to be fulfilled for correct inference to be made from the model output. The assumptions include that the outcome variable is coherent with the characteristics of a Poisson variable, described above, and that the natural logarithm of the mean rate, $\log(\lambda)$, should be a linear function of the explanatory variables.

The output measure of a Poisson regression model is a rate ratio. The rate ratio is a factor by which the outcome variable is multiplied with when the explanatory variable increases with one unit.

3.3.2.2 Modified Poisson regression

Poisson regression may also be applied to prospectively collected data with a binary outcome variable. The binary outcome variable may then be regarded as a count that only assumes two levels. However, when Poisson regression is applied to binary outcomes, the standard error will be overestimated (124), which will lead to imprecise confidence intervals. To account for this, a modified Poisson regression model with robust, or "sandwich", error estimation has been proposed (124). The robust error estimator allows for correct estimations of error despite that the error term will be misspecified in the original model.

An advantage of the modified Poisson regression model is that it provides a risk ratio as output measure, in contrast to the odds ratio that is provided in logistic regression models that are otherwise commonly used for binary outcomes. The odds ratio will approximate the risk ratio if the outcome is rare, but with more common outcomes the odds ratio will significantly deviate from the risk ratio (125). It has been argued that the interpretation of odds ratios is less intuitive than risk ratios, and that potential misinterpretation of odds ratios might lead to exaggerated conclusions, especially among people outside the field of expertise (124). So, while logistic regression is the model of choice in case-control studies, where direct assessments of risk is not possible, modified Poisson regression may be preferable for prospectively collected data with binary outcomes.

3.3.3 Cluster analysis

Cluster analysis refers to a set of statistical methods used to organize data into subgroups based on characteristics that are intrinsic to the data. The purpose of cluster analysis is to find naturally occurring or otherwise useful subgroups of objects, based on how similar or dissimilar they are from one another. A variety of different cluster analysis methods are available, which differ in various aspects of their clustering techniques and applicability. Examples of clustering methods include hierarchical clustering, K-means clustering, and Density-based Spatial Clustering of Applications with Noise (DBSCAN-clustering). In the second study of this thesis, we made use of a hierarchical clustering procedure called hierarchical agglomerative cluster analysis, which is further discussed below.

3.3.3.1 Hierarchical agglomerative cluster analysis

In hierarchical agglomerative cluster analysis, the objects are stepwise joined based on how similar they are. Agglomerative refers to that the objects are joined together based on similarity, as opposed to a divisive clustering procedure, where objects are separated based on dissimilarity. Hierarchical refers to the stepwise procedure, where each step of the procedure consists of joining together the two objects that are most similar to one another. The procedure starts with each object as a separate cluster and ends with all objects joined

together in a single entity. The procedure is visualized by a tree diagram, a so-called dendrogram, with the individual objects as "leaves", the single joined entity as the "trunk", and the levels of stepwise joining as the "branches" (Figure 3.3.3).

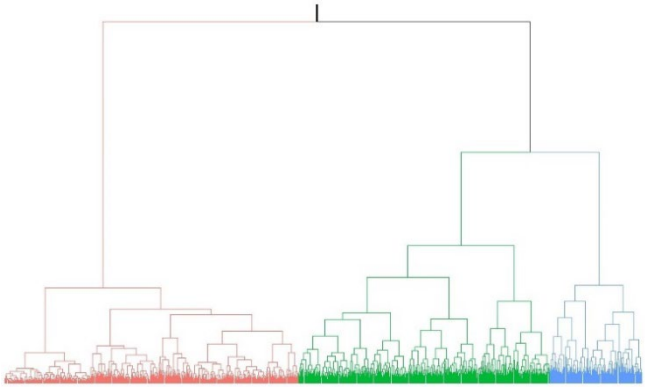


Figure 3.3.3. Dendrogram – A visualization of the hierarchical agglomerative clustering procedure.

3.3.3.2 Assessment of cluster tendency

A general feature of cluster analysis is that the algorithms will identify clusters in the data they are applied to, regardless of whether there is a natural clustering tendency in the data or not. It is therefore advisable to assess the data for clustering tendency before applying a cluster algorithm, to explore if the data is suitable for cluster analysis. A common approach to assess clustering tendency is to assess the spatial distribution of the data and observe signs of non-randomness, or non-uniformity (126). These methods may include a graphical output of the data structure such as the Visual Assessment of cluster Tendency (127), or statistical outputs such as the agglomerative coefficient (128) and the Hopkins statistic (129).

3.3.3.3 Distance measures

A fundamental component of all clustering procedures is a measurement of distance between each pair of objects. The most common method of assessing distance in cluster analysis is the Euclidean distances (130). Euclidean distances are the square root of the sum of the squared differences between each pair of clustering variables for two objects. The distances between each pair of objects form a distance matrix, which is recalculated at each step of the hierarchical clustering procedure. To avoid disproportional influence on the distance measures based on the scale of the variables, the clustering variables should be standardized.

3.3.3.4 Linkage methods

A variety of linkage methods are available for how to apply the distance measure to clusters of objects (130). The distance can, for example, be measured between the two nearest objects, or the two farthest objects in each cluster, or to a measure of central tendency in the cluster. One commonly used method is Ward's linkage method, which assesses the sum of the squared distances within each cluster. For each step of the clustering procedure, two clusters are joined such that the increase in the sum of the squared distances is minimized (130). This procedure will tend to emphasize the formation of small and compact clusters.

3.3.3.5 Deciding on the optimal number of clusters

As described above, a hierarchical agglomerative cluster analysis starts with each object as a separate cluster and stepwise joins clusters together based on similarity, until all objects are joined together. The clustering algorithm does not determine what the optimal number of clusters is, i.e., what number of clusters that produce the most well-formed clusters. This will

need to be evaluated and decided upon by the investigator. The decision may be guided by visual inspection of the dendrogram, where larger changes in distance on the vertical axis, at which new clusters are formed, represents the joining of clusters that are farther apart from each other.

Besides the visual inspection of the dendrogram, numerous statistical methods are available that apply a statistical criterion to assess the optimal number of clusters. The *NbClust (131)* extension package to the statistical software R (132) has gathered 30 such statistical indices, which can be applied simultaneously. *NbClust* provides the result of each index as well as an overall suggestion based on majority. There is, however, no gold standard method to determine the optimal number of clusters. Different methods may be more or less useful depending on the particular clustering procedure, and in the end, it is up to the investigator to make the decision based on available information and prior knowledge about the data and the statistical procedures.

3.3.3.6 Cluster validation

A final step in the clustering procedure is to validate the identified clusters. Validation may include external and internal validation approaches. External validation methods validate the identified clusters in relation to an external reference, such as a separate set of data with known properties. It may also include the application of the clustering procedure on randomly divided subsets of the data, or on a new validation data set, in which case the resulting clusters should be similar. Internal validation methods validate the clusters based on information intrinsic to the clustering data. Internal validation indices are commonly based on three main aspects of the clustering structure, namely (i) compactness, i.e., how similar the objects are within clusters, (ii) separation, i.e., how clearly separated the clusters are from each other, and (iii) connectivity, i.e., the extent to which objects are placed in the same cluster as their nearest neighbor (133). The internal validation indices are largely the same indices that are applied to assess the optimal number of clusters.

An example of an internal validation index is the Silhouette analysis, which assesses the distance between each object in one cluster to objects in neighboring clusters. The Silhouette statistic, known as the Silhouette width or Silhouette coefficient, assumes a value between -1 and +1. Higher values indicate that objects are distant from neighboring clusters and thereby clearly separated, a value of 0 indicate that the object is on the decision boundary between two clusters, and a negative value indicate that the object might be better classified to another cluster. The index provides an average Silhouette statistic for the cluster solution it is applied to, and the distribution of the statistic among the objects in each cluster are graphically displayed in a Silhouette plot (see Figure 4.2.2).

3.4 ETHICAL CONSIDERATIONS

The World Medical Association has developed a set of ethical principles for medical research involving human subjects, known as the declaration of Helsinki (134). The principles state that it is the duty of the medical researcher to safeguard the health, well-being, and rights of study participants. Two important principles for medical research involving human subjects include the informed consent of the study participant and the approval of the study protocol by an ethical review committee.

The informed consent of the study participant is a fundamental requirement in most types of medical research, regulated by The Act Concerning the Ethical Review of Research Involving Human Subjects, in the Swedish law (135). This principle can, however, be waivered under some circumstances. The law paragraph state that the principle of informed consent may be waivered if the research infers insignificant risks and discomfort for the study subject and the result of the research may be of benefit to the study subject or other persons with the same or similar disorder (135). This statement may be applied to register-based research, where it might not be feasible to obtain informed consent from each individual study subject. Whether a study protocol meets these criteria is decided upon by an ethical review committee at the Swedish Ethics Review Authority.

One important ethical aspect of register-based research is the safeguarding of sensitive personal data. The handling of personal data is regulated in the European General Data Protection Regulation (GDPR), and further specified in national Swedish regulations, such as the Patient Data Act. A fundamental requirement for handling of personal data in register-based research is the approval of the Swedish Ethics Review Authority. The data should be handled such that sensitive data cannot be coupled to specific individuals and the researchers need to make sure that the data cannot be accessed by unauthorized personnel and that the data is not disseminated outside the credited investigators.

The participants in EIRA, included in studies I and II, have all provided informed consent, and the study protocol of EIRA and its follow-up studies have been approved by the Ethical Review Authority. For the data from SRQ, informed consent is waivered. Each individual research project based on data from SRQ needs to be reviewed and approved by the Ethical Review Authority as well as by the steering committee of SRQ. The data used in all three studies included in this thesis, have been handled at the Clinical Epidemiology Division of the Department of Medicine, Solna, at Karolinska Institute. The data have been de-identified and stored on secure servers, to which only study specific researchers have had access. We believe that the results of these studies may be of benefit to the study subjects or to other patients with similar conditions, and that the risks and discomforts of the study subjects have been minimal.

4 MAIN RESULTS

4.1 STUDY I

The results of study I showed that 8% of the patients with newly diagnosed RA had developed widespread pain outside the peripheral joint regions, 3 years after diagnosis. Widespread pain was assessed on a pain mannequin that excluded the peripheral joint regions and was defined as pain outside the joints in all four body quadrants (Figure 4.1.1).

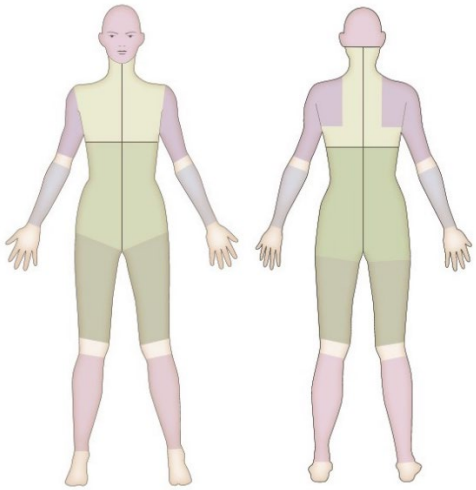


Figure 4.1.1. Pain Mannequin used to assess widespread non-joint pain, defined as pain outside the joints in all four body quadrants. The body quadrants were delineated in the midsagittal plane and at the distal end of sternum in the transversal plane. Each body quadrant is further subdivided into six smaller areas, excluding the peripheral joint regions.

The patients who reported widespread non-joint pain (WNP) at 3 years also reported statistically significantly lower scores on all the eight domains of the 36-item Short Form Health Survey (SF-36), which assesses physical and mental aspects of a patient's health status (Figure 4.1.2).

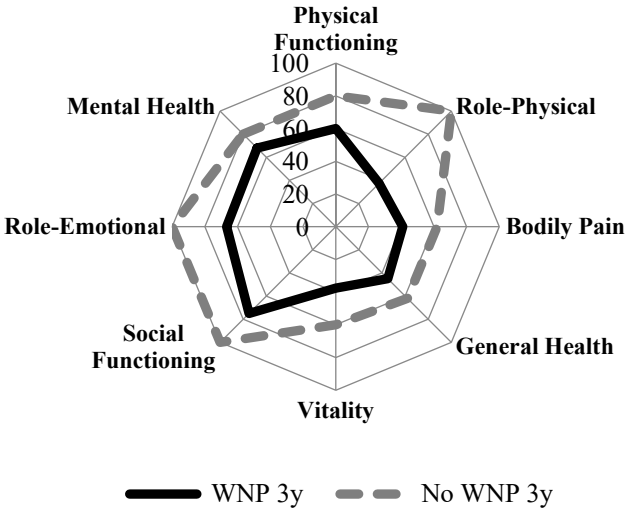


Figure 4.1.2. Spidergram displaying the health status at 3 years, as assessed by SF-36, for patients with, and without, widespread non-joint pain (WNP). The figure shows median values for each of the eight SF-36 domains, analyzed by Wilcoxon rank-sum test. All the differences were statistically significant at $p < 0.001$

Patients who developed WNP at 3 years after diagnosis displayed characteristic features already at the time of diagnosis, in terms of higher levels of pain and pain-related features, such as PGA and the functional impairment index Stanford Health Assessment Questionnaire (HAQ). Patients with WNP at 3 years also displayed higher level of overall disease activity at

diagnosis, as assessed by DAS28. This difference in DAS28 was driven by the pain-related components, i.e., PGA and tender joint count (TJC). The inflammatory components of DAS28, i.e., ESR and swollen joint count (SJC) did not differ between the groups. The development of WNP at three years also showed a significant association to age and smoking. The risk ratios (RR) for the association between a selection of the significantly associated baseline characteristics and WNP at 3 years are displayed in Table 4.1.

Table 4.1. Univariate risk ratios (RR) and 95% confidence intervals (CI) for the association between baseline clinical characteristics at diagnosis and widespread non-joint pain at 3 years.

	Quartile levels	N	RR (95% CI) for WNP at 3y	p-value	p-value for trend
DAS28	0.00 - 4.36	136	1.00 (Ref.)		**0.004**
	4.37 - 5.24	135	2.00 (0.61-6.50)	0.25	
	5.25 - 6.06	135	2.69 (0.91-7.94)	0.073	
	6.07 - 8.37	136	**4.03 (1.40-11.60)**	**0.01**	
DAS28-CRP	0.00 - 4.00	138	1.00 (Ref.)		**<0.001**
	4.01 - 4.80	139	3.31 (0.93-11.77)	0.064	
	4.81 - 5.57	138	3.00 (0.83-10.85)	0.099	
	5.58 - 8.05	136	**6.43 (1.95-21.22)**	**0.002**	
TJC	0 - 4	175	1.00 (Ref.)		**<0.001**
	5 - 7	128	1.90 (0.62-5.82)	0.26	
	8 - 11	130	**4.67 (1.80-12.07)**	**0.002**	
	12 - 28	145	**3.35 (1.23-9.12)**	**0.018**	
Pain	0 – 32	146	1.00 (Ref.)		**0.004**
	33 – 50	136	1.27 (0.43-3.69)	0.67	
	50 – 72	142	2.00 (0.79-5.06)	0.14	
	73 – 100	139	3.17 (1.29-7.79)	**0.012**	
PGA	0 - 30	143	1.00 (Ref.)		**0.006**
	31 - 51	146	1.77 (0.62-5.02)	0.29	
	52 - 69	134	2.49 (0.89-6.93)	0.081	
	70 – 100	141	**3.16 (1.18-8.43)**	**0.021**	
HAQ	0 - 0.50	154	1.00 (Ref.)		**<0.001**
	0.51 - 0.88	131	2.39 (0.92-6.19)	0.074	
	0.89 - 1.38	139	**3.31 (1.25-8.74)**	**0.016**	
	1.39 - 2.88	140	**3.93 (1.51-10.20)**	**0.005**	

The continuous variables are categorized in quartiles. Univariate risk ratios are analyzed by modified Poisson regression. DAS28 = Disease activity score of 28 joints, DAS28-CRP = DAS28 with C-reactive protein, TJC = Tender joint count, PGA = Patient global assessment of health, HAQ = Stanford health assessment questionnaire. Ref. = Reference. Pain and PGA were assessed on visual analog scales (0-100 mm), where higher scores indicate worse outcome.

4.2 STUDY II

In study II, the hierarchical agglomerative clustering procedure identified 3 clusters of patients with RA, 3 years after diagnosis. The first cluster consisted of 46% (N = 466) of the patients, who were doing very well in terms of the assessed clustering variables, which included measures of pain, fatigue, sleep status, mood disturbances, and general health status. The third cluster consisted of 15% (N = 147) of the patients with had high levels of pain and fatigue, as well as impaired sleep status, and impaired physical and mental health. The second cluster was an intermediate group consisting of 39% (N = 398) of the patients. The dendrogram of the hierarchical cluster analysis is displayed in Figure 4.2.1.

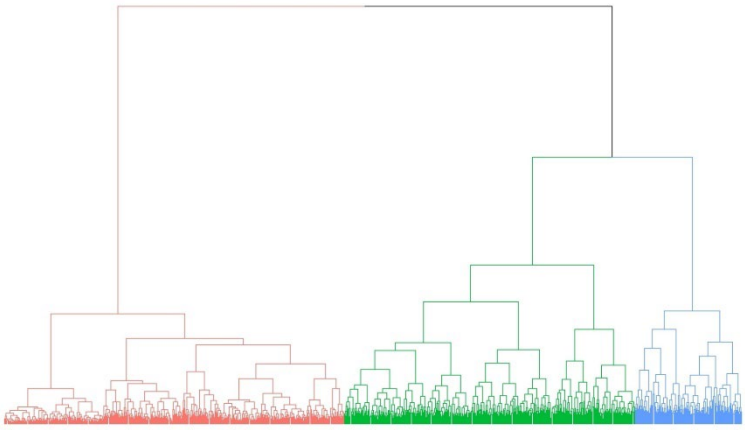


Figure 4.2.1. Dendrogram displaying the stepwise formation of the three clusters. The first cluster (in red) consisted of patients who were doing well (46%). The second cluster (green) consisted of an intermediate group (39%), and the third cluster (blue) consisted of patients with high levels of pain, fatigue, and impaired general health (15%).

The quality of the identified clusters was assessed by a Silhouette plot. The Silhouette plot showed that clusters 1 and 3 were fairly cohesive, with the majority of individual subjects assuming a positive Silhouette statistic. The second, intermediate, cluster displayed a large dispersion with half of the individual subjects assuming a negative Silhouette statistic, indicating a less well-formed cluster (Figure 4.2.2).

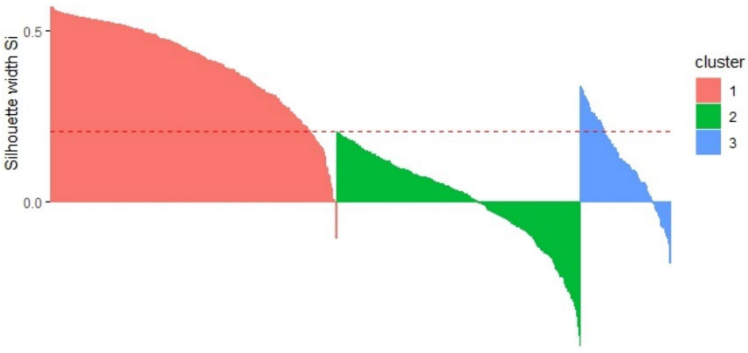
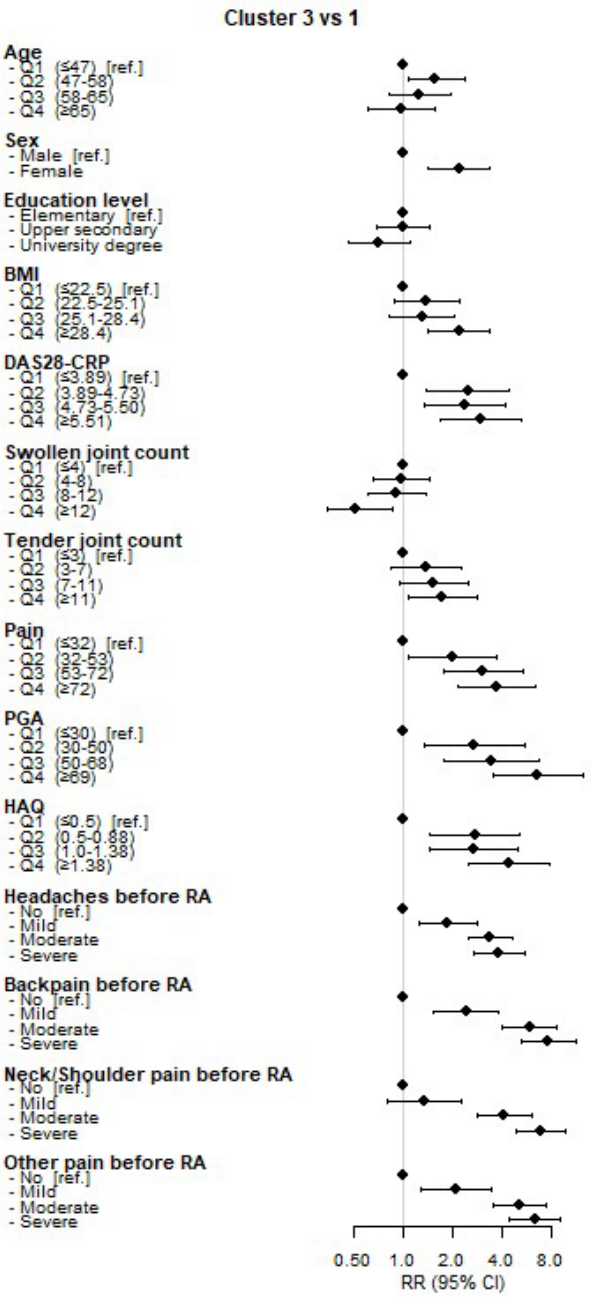


Figure 4.2.2. Silhouette plot displaying the spread of the Silhouette statistic among individual subjects in each cluster.

In similarity with study I, the association between clinical characteristics at diagnosis and the cluster outcome at 3 years was assessed. Cluster 3 was associated with female sex and higher body mass index (BMI), compared to cluster 1. Cluster 3 was further associated to higher

levels of pain and disability at diagnosis, while a higher number of swollen joints at diagnosis was associated to a decreased risk of ending up in cluster 3, compared to cluster 1.



The strongest association for ending up in cluster 3 compared with cluster 1 was seen for the highest compared to lowest quartile of PGA, and for having severe problems with back pain compared to no problems with back pain before onset of RA, which inferred a RR (95% CI) of 6.60 (3.53-12.33) and 7.65 (5.25-11-16), respectively (Figure 4.2.3). The baseline variables BMI, DAS28-CRP, HAQ, VAS pain, VAS PGA, and the level of pain problems before onset of RA displayed a strong dose-response association for ending up in cluster 3 compared with cluster 1 (p-value for trend <0.001). Similar associations were seen for ending up in cluster 2 compared with cluster 1, although with generally weaker associations (See Figure 3, in paper II).

Figure 4.2.3. Forest plot displaying risk ratios (RR) and 95% confidence intervals (CI) for the association between baseline characteristics and cluster 3, in reference to cluster 1. The continuous variables are divided into quartiles and the lowest quartile is used as reference. The associations are analyzed by modified Poisson-regression. BMI = Body mass index, DAS28-CRP = Disease activity score of 28 joints based on C-reactive protein, PGA = Patient global assessment, HAQ = Stanford health assessment questionnaire.

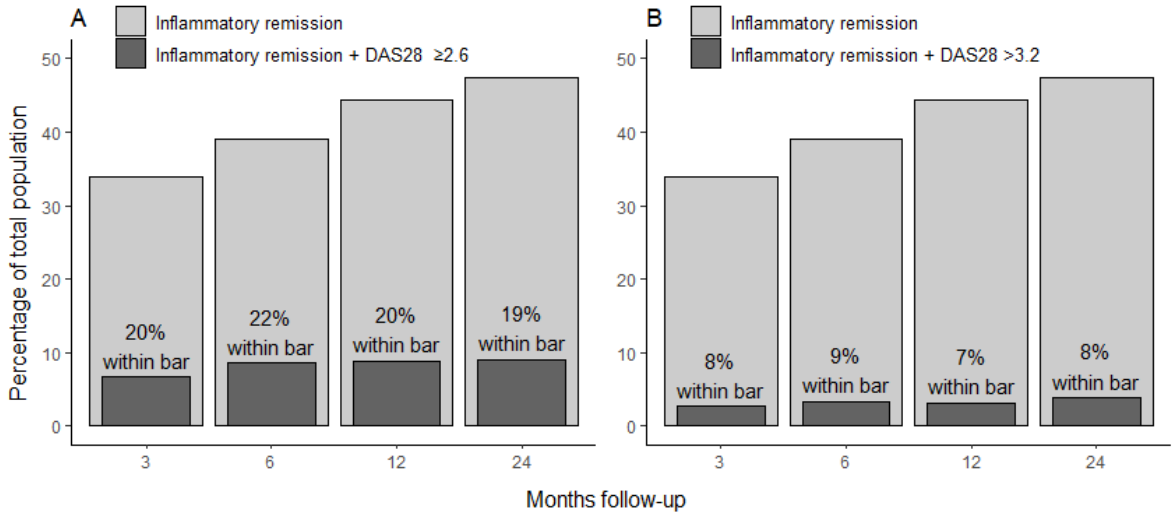
4.3 STUDY III

Study III examined the relationship between a state of inflammatory remission and formal treatment targets and investigated potential signs of escalated treatment for patients who failed to reach formal treatment targets despite being in inflammatory remission.

Inflammatory remission was defined as no swollen joints in the 28 joint count, together with normal ESR and CRP <10mg/L. Normal ESR was defined according to the reference levels of the Karolinska University Laboratory, <20 mm/h for women <60 years, <30 mm/h for women ≥60 years, <10 mm/h for men <60 years and <20 mm/h for men ≥60 years. The primary treatment targets were DAS28 remission (<2.6) and DAS28 low disease activity (LDA) (≤3.2).

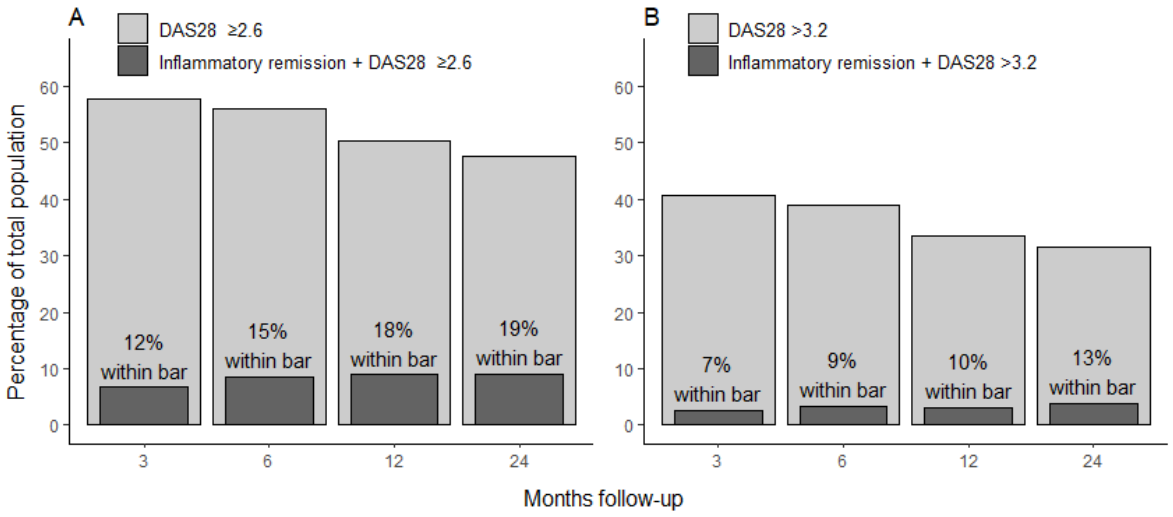
A total of 11,784 patients with newly diagnosed RA, registered in SRQ, were followed for a period of two years, with follow-up visits at 3, 6, 12, and 24 months. The proportion of patients who were in inflammatory remission at the respective follow-up visit was 34%, 39%, 44%, and 47%. Among these patients, 20%, 22%, 20%, and 19%, respectively, failed to reach DAS28 remission (Figure 4.3.1, Panel A), and 8%, 9%, 7%, and 8%, respectively, failed to reach DAS28 LDA (Figure 4.3.1, Panel B).

Figure 4.3.1. Bar charts displaying the proportion of patients who were in inflammatory remission at follow-up visits, and the proportion of the patients in inflammatory remission who failed to reach the treatment targets: (A) DAS28 remission (<2.6), and (B) DAS28 low disease activity (≤3.2).



Conversely, we found that the proportion of patients who failed to reach DAS28 remission at 3, 6, 12, and 24 months was 58%, 56%, 50%, and 48%, respectively. Among these patients, 12%, 15%, 18%, and 19%, respectively, were in inflammatory remission (Figure 4.3.2, Panel A). Similarly, the proportion of patients who failed to reach DAS28 LDA at 3, 6, 12, and 24 months, was 41%, 39%, 33%, and 32%, respectively. Among these patients, 7%, 9%, 10%, and 13%, respectively, were in inflammatory remission (Figure 4.3.2, Panel B).

Figure 4.3.2. Bar charts displaying the proportions of patients who failed to reach DAS28 targets at follow-up visits, and the proportion of the patients who failed to reach DAS28 targets who simultaneously were in inflammatory remission.



To assess potential signs of an increased likelihood of treatment escalation in patients who failed to reach formal treatment targets despite being in inflammatory remission, we compared the likelihood of starting a new DMARD between patients in inflammatory remission who reached treatment targets and patients in inflammatory remission who failed to reach treatment targets.

Among patients in inflammatory remission, those who failed to reach DAS28 remission were more likely to start a new DMARD at 6 months (RR (95% CI)) = 1.55 (1.25-1.91), 12 months = 1.51 (1.22-1.86), and 24 months = 1.47 (1.20-1.81), but not at 3 months = 1.14 (0.95-1.38), compared to patients who reached DAS28 remission (Table 4.3.1). Correspondingly, patients in inflammatory remission who failed to reach DAS28 LDA were more likely to start a new DMARD at 3 months = 1.33 (1.05-1.69), 6 months = 1.74 (1.34-2.26), 12 months = 1.63 (1.23-2.16), and 24 months = 1.68 (1.31-2.17) compared to the patients who reached DAS28 LDA (Table 4.3). Similar patterns were also seen for treatment targets based on SDAI and ACR/EULAR Boolean remission (Table 4.3.1).

Table 4.3.1. Table displaying the likelihood (relative risk) of starting a new DMARD at the respective follow-up visits, comparing patients in inflammatory remission who failed to reach, vs. reached, the treatment targets: (a) DAS28 remission = <2.6, (b) DAS28 low disease activity = ≤3.2, (c) SDAI remission = ≤3.3, (d) SDAI low disease activity = ≤11.0, and (e) ACR/EULAR Boolean remission.

Patients in inflammatory remission:	3 months RR (95% CI)	6 months RR (95% CI)	12 months RR (95% CI)	24 months RR (95% CI)
DAS28 ≥2.6 vs. DAS28 <2.6	1.14 (0.95-1.38)	**1.55 (1.25-1.91)**	**1.51 (1.22-1.86)**	**1.47 (1.20-1.81)**
DAS28 >3.2 vs. DAS28 ≤3.2	**1.33 (1.05-1.69)**	**1.74 (1.34-2.26)**	**1.63 (1.23-2.16)**	**1.68 (1.31-2.17)**
SDAI >3.3 vs. SDAI ≤3.3	**1.27 (1.09-1.50)**	**1.29 (1.04-1.58)**	**2.01 (1.63-2.48)**	**1.55 (1.29-1.88)**
SDAI >11.0 vs. SDAI ≤11.0	1.21 (0.93-1.58)	**2.23 (1.75-2.85)**	**2.14 (1.66-2.77)**	**1.77 (1.36-2.29)**
Boolean non-remission vs. Boolean remission	**1.28 (1.08-1.50)**	**1.42 (1.14-1.77)**	**1.77 (1.42-2.20)**	**1.50 (1.23-1.82)**

The risk ratios (RR) and 95% confidence intervals (CI) were analyzed by modified Poisson-regression, adjusted for age, sex, and year of inclusion in SRQ (2011-2015 vs. 2016-2020). The RR refers to the multiplicative effect on the "risk" of starting a new DMARD at the follow-up visit for patients in inflammatory remission who failed to reach treatment targets, in reference to patients in inflammatory remission who reached the corresponding targets.

The average rate of new DMARD starts for all patient visits during the follow-up period, 3-24 months, was 0.26 new DMARD starts per visit (8098 new DMARD starts in a total of 30,685 patient visits). For visits where patients were in inflammatory remission, the average rate of new DMARD starts was 0.18 (1893 new DMARD starts in 10,732 visits). For visits where patients failed to reach DAS28 remission despite being in inflammatory remission, the average rate of new DMARD starts was 0.22 (405 DMARD starts in 2046 visits), and for visits where patients in inflammatory remission reached DAS28 remission, the rate of new DMARD starts was 0.16. This difference was statistically significant, RR = 1.36 (95% CI = 1.22-1.51). The corresponding figures for visits where patients in inflammatory remission failed to reach, vs. reached DAS28 LDA, was a rate of 0.27 (218 DMARD starts in 815 visits) compared to a rate of 0.17 (1539 DMARD starts in 9352 visits), RR = 1.56 (95% CI = 1.35-1.80). Similar patterns were seen for treatment targets based on SDAI and ACR/EULAR Boolean remission. The rates of new DMARD starts for the accumulated patient visits during the follow-up period, where patients were in inflammatory remission and stratified by treatment targets are displayed in Table 4.3.2.

Table 4.3.2. Table displaying (i) the accumulated number of visits during the follow-up period where patients were in inflammatory remission, stratified by treatment targets, (ii) the total number of new DMARD starts during these visits, (iii) the average rate of new DMARD starts per visits, and (iv) the rate ratio, comparing visits with patients in inflammatory remission who failed to reach, vs. reached, the treatment targets.

Visits with patients in inflammatory remission, stratified by treatment targets:	Total number of visits during follow-up period, 3-24 months	Total number of DMARD starts during follow-up, 3-24 months	Rate of DMARD starts per visit, mean (SD)	RR (95% CI)
DAS28 ≥2.6 vs. DAS28 <2.6	2046 vs. 8121	405 vs. 1307	0.22 (0.45) vs. 0.16 (0.40)	**1.36 (1.22-1.51)**
DAS28 >3.2 vs. DAS28 ≤3.2	815 vs. 9352	218 vs. 1539	0.27 (0.48) vs. 0.17 (0.41)	**1.56 (1.35-1.80)**
SDAI >3.3 vs. SDAI ≤3.3	4676 vs. 4861	977 vs. 660	0.21 (0.45) vs. 0.14 (0.37)	**1.48 (1.34-1.64)**
SDAI >11.0 vs. SDAI ≤11.0	732 vs. 8805	221 vs. 1416	0.30 (0.50) vs. 0.16 (0.40)	**1.72 (1.49-1.98)**
Boolean non-remission vs. Boolean remission	6104 vs. 4063	1211 vs. 546	0.20 (0.43) vs. 0.13 (0.38)	**1.41 (1.28-1.56)**

The rate ratios (RR) are analyzed by Poisson regression, adjusted for age, sex, and year of inclusion in SRQ (2011-2015 vs. 2016-2020). SD = Standard deviation.

5 DISCUSSION

This thesis aimed to explore different perspectives of pain manifestations among patients with early RA. The prevalence of pain outcomes and early clinical characteristics associated with the pain outcomes were explored, as well as the impact of pain on measures of disease activity and its potential influence on treatment decisions. The main results of the individual studies are discussed below.

5.1 STUDY I

In the first study of the thesis, we defined the outcome "widespread non-joint pain" (WNP), defined as pain outside the peripheral joint regions in all four body quadrants. We found that 8% of the patients met the criteria for WNP 3 years after diagnosis. We further assessed the association between clinical characteristics at the time of diagnosis and WNP at 3 years and found that the development of WNP was associated with higher levels of pain and disability, but not to inflammatory disease activity, at diagnosis.

5.1.1 Assessment of widespread pain

A common way to assess the presence of a generalized pain condition among patients with other chronic diseases is to assess the presence of widespread pain. Several definitions of widespread pain have been proposed over the years, based on the location and distribution of painful body sites (46-48, 70). Among these definitions, the still most widely used is the widespread pain criterion of the 1990 ACR criteria for fibromyalgia (46, 49), which is also the definition used in most studies of widespread pain in patients with RA. The criteria define widespread pain as pain located above and below the waist, on the right and left side of the body, and along the axial skeleton. No distinction is made between joint pain and non-joint pain, and the criteria state that the presence of another clinical disorder does not exclude a diagnosis of fibromyalgia. Critique of the 1990 definition of widespread pain has been raised by the authors themselves in later publications (48), where they state that the definition was never intended as a standalone measure of widespread pain, that the formulation of the criteria are somewhat ambiguous and have led to various interpretations (48, 49), and that the definition, as it is formulated, may be fulfilled by as little as pain in one hand and one contralateral foot if there is pain along the axial skeleton (48). The authors instead proposed a definition of widespread pain which excludes peripheral joint regions and may be fulfilled by pain in 4 of 5 body regions and at least 7 of 15 individual body sites (48).

Given the variation in the definitions of widespread pain, and the differing populations they are applied to, direct comparisons between studies may be difficult. Several Swedish studies have, however, assessed widespread pain in patients with RA. One study, by Bilberg et al., assessed the prevalence of widespread pain, according to the 1990 ACR criteria, in women with early RA and found that 36% met the criteria two years after diagnosis (53). Another

study, by Aronsson et al., assessed the prevalence of widespread pain six years after diagnosis, in two separate cohorts (54). The investigators found that the 1990 definition of widespread pain was met by 27% in a tight control cohort and by 31% in a conventional cohort, and that the 2019 standalone criteria for widespread pain (48) was met by 10% and 23% respectively in the two cohorts. The prevalence of widespread pain has further been investigated in a Swedish cohort of long-established RA, where 34% met the 1990 criteria for widespread pain (52).

Several factors complicate a direct comparison between our study and the previous assessments of widespread pain in RA. Beside the definition of widespread pain, the duration of the rheumatic disease is also an important factor for the assessment of widespread pain, since previous studies have indicated that the prevalence of fibromyalgia in patients with RA increase with increasing disease duration (40, 43). Nevertheless, it would be expected that a definition of widespread pain that excludes peripheral joints will find a significantly decreased prevalence, which is also suggested by the considerably lower prevalence found in our study compared to the studies based on the 1990 criteria.

Interestingly, the prevalence of WNP in our study is similar to the cumulative incidence of secondary fibromyalgia found in a cohort of early inflammatory arthritis (43). The study by Lee et al. found that 9% of the patients had developed fibromyalgia, based on the clinical judgement of the physician, 3 years after diagnosis. These similarities suggest that a more restrictive definition of widespread pain, such as the definition of WNP in our study, may be more reflective of a pronounced pain syndrome, that has developed over and above RA.

The prevalence of secondary fibromyalgia found by Lee et al. is also similar to the prevalence of widespread pain according to the 2019 definition found by Aronsson et al. in a cohort of patients with tight disease control (54). In contrast to the proposed 2019 definition of widespread pain (48), however, it seems like Aronsson et al. have included peripheral joints in the assessment. An exclusion of peripheral joints would probably lead to additionally decreased prevalence, which further suggests that tight disease control may be beneficial to prevent the development of chronic pain.

The purpose of excluding peripheral joints from the assessment of widespread pain in our study, was to attempt to distinguish symptoms of the underlying rheumatic disease from symptoms attributable to a chronic pain condition. An assessment of widespread pain, as a condition that has developed over and above the rheumatic disease, may be overestimated among patients with a rheumatic joint disease, if the peripheral joints are included. One of the leading investigators behind the ACR criteria for fibromyalgia, Frederick Wolfe, investigated factors that distinguished patients with fibromyalgia from patients with RA and patients with osteoarthritis, and found that an assessment of pain distribution which excluded peripheral joint regions most accurately distinguished patients with fibromyalgia (97). This non-articular pain index came to form the basis for the assessment of widespread pain in the revised ACR criteria for fibromyalgia in 2010/2011 and 2016 (47, 96, 98), as well as in the 2019 standalone measure of widespread pain (48).

The revised criteria for fibromyalgia were, however, not available when the assessment of WNP was elaborated for the follow-up questionnaires in EIRA. Albeit that the assessments were elaborated independently, the exclusion of peripheral joints is a common feature, and analogously with the 2016 and 2019 criteria for widespread pain, WNP also requires pain in four body regions. In contrast to the ACR criteria for widespread pain, however, the assessment of WNP does not include a separate assessment of pain along the axial skeleton.

A chronic pain condition may be regarded as a disease entity in itself rather than as a symptom of other underlying pathologies. This notion has been propagated by the introduction of nociplastic pain as a separate pain mechanism (67, 71) and by the categorization of chronic primary pain syndromes in the ICD-11 (70). The distinction between symptoms of ongoing arthritis and symptoms of a chronic pain condition may therefore have important implications for the treatment strategy. The former suggests that the antirheumatic treatment may need to be optimized while the latter imply that targeted pain management interventions may be considered.

An assessment of widespread pain that excludes peripheral joints may not by itself be sufficient to distinguish patients with a chronic pain condition from patients with active rheumatic disease. Patients with fibromyalgia may also experience pain in the joints (136) and other features than pain distribution alone may be of importance to assess chronic pain conditions (70). Any categorical criteria may therefore lead to misclassifications and arbitrary cutoffs (94). The exclusion of joint pain may nevertheless be one important step to identify patients with RA who have developed a chronic pain condition over and above the rheumatic disease.

5.1.2 Characteristics at diagnosis

The findings of our and other studies suggest that patients with RA who will develop a pain condition over and above the rheumatic disease may display distinguishing features early in the course of the disease (40, 43). In our study, we found that the patients who had developed WNP at 3 years had higher levels of pain and disability already at the time of diagnosis. We also found an association between WNP and smoking, and that WNP was more common in the age group between 50-59 than in younger and older age groups. We did, however, not find an association between higher levels of inflammation and later development of WNP.

In similarity with our study, Lee et al. found that the development of fibromyalgia was associated with higher pain ratings and higher tender joint counts at RA diagnosis (43). In contrast to our study, however, Lee et al. found that the development of fibromyalgia was negatively associated to ACPA-positivity. Risk factors for the development of fibromyalgia have also been investigated in established RA, by Wolfe et al., who found that higher levels of pain and disability were associated with later development of fibromyalgia (40). Wolfe et al. also found an association to smoking, as well as to factors related to socioeconomic status and mood disturbances.

Taken together, these findings suggest that the development of a widespread pain syndrome may be preceded by symptoms that could make individuals at risk identifiable at an early stage of disease. These symptoms may include pain levels that are unproportionally high in relation to the inflammatory disease activity, as well as psychological and lifestyle factors such as anxiety, depression, and smoking. The possibility to identify patients at risk of developing a widespread pain syndrome provides ground for early adoption of pain management interventions. Strategies for pain management may then work in parallel with efforts to suppress the inflammatory disease activity.

5.2 STUDY II

In the second study of the thesis, we used cluster analysis to identify three subgroups of patients based on pain, fatigue, sleep problems and general physical and mental health status 3 years after diagnosis. We further assessed the association between these subgroups and clinical characteristics at diagnosis. We found that patients who had high levels of pain, fatigue and psychosocial distress at 3 years were more often women, had higher levels of pain and disability at diagnosis, and to a larger extent had pain problems already before onset of RA. Patients who were doing well at 3 years displayed a higher number of swollen joints at the time of diagnosis.

5.2.1 Identifying patients with severe symptoms

In order to make assessments of health data more easily interpretable, it is often necessary to organize the data into separate categories. In reality, however, health symptoms may often vary along a continuous spectrum rather than assume distinct categories. For example, the term “fibromyalgianess” has been coined to describe a gradient of symptoms related to fibromyalgia, which may or may not reach the threshold for diagnosis. These symptoms have been shown to occur a long a severity gradient in patients with RA and a dichotomous threshold will therefore inevitably impose an arbitrary distinction (94).

In study I, we identified a category of patients with pronounced pain symptoms based on pre-defined criteria for the distribution of pain outside the joints. In study II, on the other hand, we adopted an unbiased approach to identify patients with severe symptoms, based on intrinsic characteristics of the data. Chronic pain conditions, such as fibromyalgia, are commonly associated with symptoms of depression, fatigue, sleep disturbances, and cognitive impairments (96). These symptoms, and other aspects of physical and mental functioning, have been discussed as “unmet needs” in patients with RA, which refers to the higher prevalence of these symptoms among patients with RA compared to the general population, and that these symptoms often persist despite adequate antirheumatic treatment (28). In this study, we used the occurrence of these symptoms to identify subgroups of patients with different levels of symptom severity.

5.2.2 The identified subgroups

The clustering procedure identified three subgroups with varying levels of symptom severity 3 years after diagnosis. The largest subgroup (cluster 1) consisted of 46% of the patients, who were doing very well in terms of the included health variables. This subgroup displayed little to no symptoms of pain and fatigue and had a physical and mental health status comparable to the general Swedish population (137). The smallest subgroup (cluster 3) consisted of 15% of the patients who displayed high levels of pain and fatigue, and markedly impaired physical and mental health status. The median pain intensity level in this group exceeded the previously proposed Patient Acceptable Symptom State for pain (138), and fatigue levels were well above a previously defined cutoff for high level of fatigue in patients with RA (139). The physical and mental health status as assessed by SF-36 displayed scores well below previously reported pooled mean scores among patients with RA (140), and scores on the Hospital Anxiety and Depression Scales (HADS) showed signs of possible anxiety disorder. The second subgroup (cluster 2) was an intermediate group that consisted of 39% of the patients who displayed some signs of pain, fatigue, and impaired physical and mental health status, however of more discrete magnitude than in cluster 3.

5.2.2.1 A comparison of pain outcomes

The clustering procedure thus identified a subgroup of 15% of the patients with high levels of pain, fatigue, and generally impaired health status, that was considerably larger than the 8% with WNP in study I. A review of the SF-36 scores reported by patients with WNP in study I and corresponding scores for patients in cluster 3 shows that the scores are lower for cluster 3 in all eight physical and mental components, including bodily pain. This may suggest that the restrictive definition of WNP leaves out a significant proportion of patients with severe pain problems. The cluster analysis sorts patients together based on how similar they are, and the result of the cluster analysis suggests that a larger proportion of patients may constitute a more homogenous group of patients with severe pain and pain-related symptoms.

It is, however, possible that symptoms of active arthritis may have contributed to the features displayed in cluster 3, since the clustering variables may have reflected both arthritic and non-arthritic symptoms. Available clinical data at 3 years showed slightly higher levels of inflammation in cluster 3 compared to the other clusters, albeit on generally low levels. The proportion of missing data for these clinical variables were, however, high and the impact of inflammatory disease activity could not be further clarified in this material. It is therefore possible that cluster 3 may include both patients with chronic nociplastic pain and patients with severe RA.

Another reflection over the difference between the two studied outcomes is that the WNP criterion only assesses one dimension, the pain distribution. The severity of a chronic pain condition may not be appreciated only by the intensity or distribution of pain symptoms but also by the implications on emotional wellbeing and functional abilities. The classification of widespread pain according to ICD-11 requires that the pain is associated with significant

emotional distress or significant interference with daily activities (70). This emphasizes that pain is more than a physical sensation and that psychosocial aspects are important factors to consider in a chronic pain condition. In clinical practice, the implications on emotional wellbeing and functional ability may be the most important factors that guide treatment decisions for pain management. A unidimensional criterion for widespread pain may dismiss patients with severe psychosocial implications of pain, whose pain happens to not be distributed according to the specified criteria.

5.2.3 Characteristics at diagnosis

In analogy with the findings of study I, patients in cluster 3 displayed higher levels of pain and disability at diagnosis, and cluster 3 was further associated with higher BMI and with a larger proportion of women. Moreover, there was a strong association between cluster 3 and the presence of pain problems before onset of RA. Interestingly, a higher number of swollen joints at diagnosis was negatively associated with the risk of ending up in cluster 3, compared to cluster 1. In other words, a higher number of swollen joints at diagnosis was associated with a more favorable outcome at 3 years.

The findings of this study further support that patients who are at risk of developing a chronic pain condition may display characteristic features already at the time of diagnosis. The findings further suggest that at least a part of the patients who have developed chronic pain have had pain problems already before onset of RA. Persistent regional pain is an important risk factor for the development of fibromyalgia (61). The persistent regional pain may gradually develop into a generalized pain syndrome through sensitization of nociceptive neurons. Some patients with RA may develop a generalized pain syndrome as a consequence of their rheumatic disease, without any prior pain problems. Other patients, however, may already be at any stage of chronic pain development at the onset of the rheumatic disease.

Regardless of the temporal relationship between the rheumatic disease and the development of chronic pain, early identification of individuals at risk should be a feasible goal. A parallel management strategy of antirheumatic suppression of inflammatory disease activity and a stepped care approach for pain management may reciprocally benefit one another by addressing the disease management from different perspectives.

5.2.4 Limitations – the role of inflammation and treatment

A limitation to both study I and II was that we were not able to fully assess the role of inflammatory disease activity in relation to the pain outcomes. In study I, the pain outcome (WNP) was designed to assess symptoms of pain over and above potential joint symptoms. However, we could not assess if the patients with WNP also differed in their concurrent inflammatory status. In study II, we could not determine the extent to which active

inflammatory disease might have contributed to the features of cluster 3. The reason for this is the amount of missing clinical data at the 3-year follow-up in EIRA. The linkage of data between EIRA and SRQ provides the possibility to combine extensive patient-reported data from EIRA with clinical data from SRQ. At the time of diagnosis, clinical data from SRQ is available for more than 80% of the study population in EIRA. At the 3-year follow-up, however, clinical data is available for less than 50% of the study population and there may be significant time spans between the follow-up in EIRA and the closest registered visit in SRQ. Because of the missing clinical data during follow-up, we were also not able to assess the role of DMARD therapy in relation to the pain outcomes.

Treatment strategy may play a role for the development of chronic pain. Aronsson et al. have demonstrated that the prevalence of chronic widespread pain, according to the 2019 ACR definition, was significantly less frequent in a cohort of patients with tight control compared to a conventional cohort (54). It has previously been demonstrated that early intensive treatment increases the likelihood of reaching remission for patients with RA (141) and it is also known that persistent localized pain is an important risk factor for the development of fibromyalgia (78). It may therefore be speculated that shorter periods of pain caused by inflammatory disease activity may decrease the risk of sustained central sensitization and the development of a chronic nociplastic pain condition.

5.3 STUDY III

In the third study of the thesis, we defined a state of inflammatory remission and assessed the proportion of patients in inflammatory remission who nevertheless failed to reach formal treatment targets during the first two years after RA diagnosis. Among the patients who were in inflammatory remission at follow-up visits, 3, 6, 12, and 24 months after diagnosis, 19-22% failed to reach DAS28 remission, and 7-9% failed to reach DAS28 LDA. The patients in inflammatory remission who failed to reach treatment targets displayed significantly higher pain levels compared to the patients who reached the targets. Patients in inflammatory remission who failed to reach the treatment targets were also more likely to start new DMARD treatments compared to patients in inflammatory remission who reached the treatment targets.

5.3.1 Disease activity and inflammatory remission

Measures of disease activity in RA are based on a combination of inflammatory variables and pain-related variables. The variables are combined to an overall score and cutoff values are defined to depict categorical levels of disease activity. The overall scores do not distinguish between inflammatory and pain-related variables and high levels of pain-related features may prevent formal treatment targets form being reached also in the absence of inflammatory disease activity (39).

In this study, we defined a state of inflammatory remission based on the inflammatory components of the disease activity measures. To estimate the extent to which non-inflammatory features prevent formal treatment targets from being reached, we assessed the proportion of patients who failed to reach treatment targets among patients who were in inflammatory remission. For the more liberal treatment targets, DAS28 LDA and SDAI LDA, higher levels of pain-related features were necessary to prevent the targets from being reached. Hence, the proportion of patients in inflammatory remission who failed to reach these targets were around 10% at follow-up visits. Conversely, there was a higher proportion of patients in inflammatory remission who failed to reach the more restrictive treatment targets, around 50% for SDAI remission and around 60% for ACR/EULAR Boolean remission, since even discretely elevated levels of pain and tenderness were enough to prevent these targets from being reached.

A major drawback of all the commonly used measures of disease activity in RA is that they are based on the assessment of only 28 specific joints. These joints include the small joints of the hands, the wrists, elbows, shoulders, and knees. The joints of the feet, which are frequently affected in patients with RA, are not included. Because of the lack of information on the inflammatory status of the joints in the feet, we can at best make educated guesses about the reasons behind the failure to reach formal treatment targets among patients who are in inflammatory remission based on the 28 joint count. An important component of the disease activity measures, in this context, is the patient's subjective rating of overall health, PGA. When the inflammatory components of the disease activity measures are unaffected, the treatment targets may be prevented by the tender joint count and PGA. While the interpretation of the tender joint count is rather unambiguous, it is not as clear what the PGA represents.

It has previously been reported that active arthritis in the feet may occur in patients without active arthritis in the 28 joint count, and that these patients display elevated levels of PGA (21, 142, 143). It is therefore possible that active arthritis in the feet may influence PGA and thereby contribute to the failure of reaching treatment targets observed among the patients who were in inflammatory remission in our study. However, the proportion of patients without swollen joints in the 28 joint count who have swollen joints in the feet, has previously been reported to be low, around 3-6% (142, 144). Moreover, a study that evaluated the presence of sonographic signs of inflammation in patients with high PGA who were otherwise in remission found that PGA-levels did not reflect inflammatory activity (145), and previous investigations of the influence on PGA by other clinical variables have not identified swollen joints as a major contributing factor (146-148). The major contributing factors to PGA have been pain, fatigue, and functional impairment (146), with several studies identifying pain as the single most important factor (147-149). Hence, while active arthritis in the feet may contribute to the failure of reaching treatment targets in some of the patients in inflammatory remission, it does not seem to be a major contributing factor. The most important factor seems to be pain, which is also supported by the high levels of pain reported by these patients in our study.

5.3.2 Treat-to-target implications

The treat-to-target recommendations, elaborated by an international task force in 2010, formulates the current treatment paradigm in RA (22). The recommendations, updated in 2014 (23), state that the primary target for the treatment of RA should be a state of clinical remission. Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity. If clinical remission is not possible to reach, low disease activity may be an acceptable therapeutic goal. The recommendations further state that the disease activity should be monitored by the use of validated composite measures, and that drug therapy should be adjusted at least every three months, until the desired treatment target is reached.

As discussed in the previous section, the usefulness of composite disease activity measures, and treatment targets based on these measures, may be questioned for patients who display high levels of pain in the absence of significant inflammatory disease activity. In these patients, a strict adoption of the treat-to-target injunction of adjusting therapy until the target is reached may lead to ill-motivated treatment adjustments. In our study, we found that patients in inflammatory remission who failed to reach formal treatment targets were more likely to have their treatment adjusted, compared to patients in inflammatory remission who reached the treatment targets.

The actual causes for the treatment adjustments in patients who were in inflammatory remission cannot be fully elucidated in the available material. Reasons for changing the DMARD-treatment may be signs of disease activity that is not captured by the available data, intolerance to the previously initiated DMARD, and the misinterpretation of nociplastic pain as a symptom of inflammation. To clarify the actual motives for the observed changes in treatment, a survey or interview study of treating physicians may be needed. The available data does, however, suggest that other reasons than obscured inflammatory disease activity may influence the decision to change ongoing treatments. In our material, the DMARD-treatment was changed in 20-30% of the visits where patients failed to reach formal treatment targets despite being in inflammatory remission. Given that previous studies have reported the presence of swollen joints in the feet in 3-6% of patients without swollen joints in the 28 joint count, it seems unlikely that arthritis in the feet would explain the observed rate of DMARD-changes in our study. In addition to not having any swollen joints in the 28 joint count, our definition of inflammatory remission also included a normal ESR and CRP below 10 mg/L, which further suggests a limited role of active arthritis outside the 28 joint count.

The absence of swollen joints does, however, not necessarily mean that treatment changes are not justified. As mentioned above, intolerance may be a significant contributing factor to the observed changes of treatment. Patients with chronic pain often experience other somatic symptoms and signs of psychosocial distress and it may, speculatively, be possible that these patients are more likely to also experience significant treatment side effects. Another potential scenario could be that a patient with chronic pain does not have any obvious joint swellings, but it might nevertheless be suspected that low grade inflammation is significantly

contributing to the pain symptoms, in which case a period of escalated antirheumatic treatment may be tried and evaluated for its effect on the pain.

Optimized antirheumatic treatment may thus play a role in the optimization of pain management. The findings of these studies do, however, highlight that chronic nociplastic pain conditions should be acknowledged as disease entities that may need to be managed in parallel with the rheumatic disease, which means that the patient should be adequately informed about the condition, and that directed pain management interventions should be considered if need be. The findings further stress that overall scores of composite measures of disease activity should be interpreted with precaution, especially if there are signs of chronic pain.

5.4 POTENTIAL BIASES

In case-control studies, the selection of cases and controls is a major source of potential selection bias. The process for selection of cases in EIRA is therefore of importance for the study populations in study I and II. A previously performed non-participation analysis of the cases and controls in the baseline population of EIRA showed that cases of RA who did not participate in EIRA were slightly older, had lower income, lower educational level, and were to a larger extent not born in Sweden, compared to participating cases (150). The total participation rate among cases was 82%.

In conjunction with the current studies, we further assessed non-participation in the 1- and 3-year follow-up questionnaires in EIRA (unpublished work). The response rates of the 1- and 3-year follow-up questionnaires were 85% and 77% respectively. Non-participation in the 1-year follow-up was associated with lower age, lower educational level, and not being born in Sweden. It was further associated with higher levels of pain, fatigue, impaired general health, functional disabilities, and impaired mood, at the closest registered visit in SRQ. Non-participation in the 3-year follow-up was associated with lower age, lower educational level, not being born in Sweden, and not living together with another adult. At the closest registered visit in SRQ, non-participants displayed higher levels of fatigue and DAS28.

The findings of these non-participation assessments suggests that there is a selection bias in the recruitment of cases in EIRA and its follow-up questionnaires. The assessments indicate that lower socioeconomic status, and higher levels of pain and functional impairments, are overrepresented among non-participants. Given the described characteristics of the non-participating cases, and that non-participation occurs on several levels (at inclusion in baseline EIRA and again at follow-up), it is likely that this selection bias has affected the outcomes in studies I and II in such a way that the prevalence of the pain-related outcomes may be underestimated.

Recall bias is a type of information bias that may have implications for retrospectively collected data. The 3-year follow-up questionnaire in EIRA includes questions on whether

the patient experienced pain problems before the onset of RA. The likelihood of recollecting previous pain experiences may be affected by the current pain status. Patients affected by pain at the 3-year follow-up may therefore be more prone to remember, and report, previous pain experiences compared to patients who are currently unaffected by pain. The information on previous pain experiences may therefore be subjected to recall bias. In study I, the information on previous pain experiences was used to exclude patients with severe previous pain problems from the subsequent assessment of WNP at 3 years. In study II, previous pain experiences were assessed as baseline risk factors for ending up in the identified clusters at 3 years. In study I, the potential recall bias may have led to an increased a priori exclusion of patients currently affected by pain, while in study II it may have led to overestimations of previous pain problems as risk factors for subsequent pain.

Selection bias may also influence participation in SRQ. The registration of patient-reported data in SRQ requires basic computer skills and sufficient Swedish language skills, which may lead to systematically skewed participation. It is also possible that patients with severe comorbidities and short life expectancies to a lesser degree are included, which may lead to a skewed selection based on health status. In general, non-participation in epidemiological studies tend to be associated with worse health status and lower socioeconomic status, which may lead to underestimations of health outcomes (150-152). In the context of SRQ, however, the impact of this potential selection bias is probably of lesser magnitude. The registration of patient-reported outcomes in SRQ is a routine procedure at clinical visits to rheumatology clinics and clinical personnel is often available to assist the patient if needed. The large coverage of prevalent cases of RA in Sweden (115) also indicate that selection bias is not a prominent feature in SRQ.

6 CONCLUSIONS

The studies of this thesis explored patterns of pain manifestations among patients with early RA. In the first two studies, we identified subgroups of patients with signs of severe pain problems. We showed that the pain problems were associated with significantly decreased physical and mental health status, and that signs of a pain-driven phenotype were present already at diagnosis of RA. These studies indicate that pain problems are a significant cause of affliction for a part of the patients during early stages of RA disease. In the third study, we showed that the presence of pain problems also may complicate the assessment and evaluation of disease activity, and that it may influence clinical decision making. The presence of pain problems, therefore, not only affect the health status and wellbeing of the patient but also pose an additional challenge for the management of the rheumatic disease.

It may be a challenging task to discern signs of a chronic nociplastic pain condition from nociceptive signs of ongoing inflammation and effective pain interventions may not be readily available. The acknowledgement of chronic pain as a disease entity that may need a separate management approach is nevertheless an important step towards an optimal treatment strategy, which preferentially may involve parallel strategies for pain management and antirheumatic control of inflammation.

The main conclusions of the individual studies are listed below:

Study I:

- A total of 8% of the patients with early RA had developed widespread pain outside the joints (WNP) 3 years after diagnosis.
- Patients with WNP reported significantly worse physical and mental health status compared to patietns without WNP.
- Patients who developed WNP at 3 years displayed characteristic feauters alreadey at the time of diagnosis by reporting higher levels of pain and disability without an increase in the inflammatory parameters.

Study II:

- An unbiased clustering procedure identified three subgroups of patients with varying levels of health status at 3 years after RA diagnosis:
    - Subgroup 1 (46%) consisted of patients who were doing very well at 3 years, with a health status comparable to the general Swedish population.
    - Subgroup 2 (39%) consisted of an intermediate group with somewhat affected health status.
    - Subgroup 3 (15%) consisted of patients with high levels of pain, fatigue and psychosocial distress.

- The patients in subgroup 3 displayed higher levels of pain and disability at the time of diagnosis and to a larger extent experienced pain problems already before onset of RA.
- The patients in subgroup 1 displayed higher levels of inflammation at diagnosis, as assessed by the number of swollen joints.

Study III:

- At follow-up visits, 3-24 months after RA diagnosis, 34-47% of the patients were in inflammatory remission. Among these patients 19-22% failed to reach DAS28 remission and 7-9% failed to reach DAS28 low disease activity.
- Patients who failed to reach the formal treatment targets despite being in inflammatory remission were more likely to start a new DMARD-treatment compared to patients in inflammatory remission who reached the formal treatment targets.
- Chronic non-inflammatory pain may impact on measures of disease activity in RA. In the evaluation of disease activity, chronic pain should be acknowledged as a separate disease entity and chronic pain management may need to be conducted in parallel with the management of the rheumatic disease.

7 POINTS OF PERSPECTIVE

The studies of this thesis, and other studies before, have highlighted that chronic pain is common among patients with RA, and that chronic pain may significantly impact emotional wellbeing and the ability to engage in social activities and working life. An objective ahead for rheumatological clinical care may be to optimize the management of the additional needs of these patients, which may include the incorporation of the EULAR recommended stepped-care approach for pain management as part of the clinical routine.

As a first step, this may include making online educational material easily available. This may include educational material on pain mechanisms, pain management, and other self-management strategies. It may also include further guidance for where patients may turn for other specific interventions, such as sleep interventions and weight management.

A second step may include making intermediary interventions more easily available. Intermediary interventions may be offered patients who do not qualify for multimodal rehabilitation or patients who would benefit from continuous support after a rehabilitation period. A surging modality in pain management are so-called meditative movement therapies, which include yoga, tai chi and qi gong. These interventions have shown promising results in pain management trials and are included in the EULAR recommendations for the management of fibromyalgia. A pain management intervention based on a yoga-mindfulness program was part of the planned PhD-projects for this thesis, but the trial was interrupted by the Covid-19 pandemic and could not be finished in time. A personal goal ahead is to continue to develop yoga-mindfulness-based self-management programs and to continue their evaluation in clinical trials.

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