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Aspects of disability in rheumatoid arthritis - a five-year follow-up in the Swedish TIRA project

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To my grandmother Eivor

PREFACE

The arthritis project 'TIRA' started in 1996, in a time of new treatment strategies that focused on rapid early interventions in patients with recent onset rheumatoid arthritis (RA). During 27 months, 320 patients were included in the project and followed regularly over eight years. A unique approach in the TIRA project was the regular involvement of a multi-disciplinary team that included occupational therapists, physiotherapists and social workers among others. The patients were assessed for genetic markers, disease markers, co-morbidity, exposure factors and lifestyle, disease activity, disability, quality of life, health economy and demography. I was enrolled in the TIRA project as an occupational therapist at the rheumatology unit in Linköping and I met with these patients in the clinical routine. As an occupational therapist, the consequences of RA have always been my focus, because the disease affects major life areas for the patients. From this point of view, my research has focused on disability in patients with early RA to facilitate their daily life activities, an interest that I maintained as a PhD student in the TIRA project.

The TIRA project is neither an incidence study nor an intervention study. The collected data has made descriptive and longitudinal analyses possible. The project has generated a database and research that describes early RA from different aspects. This thesis focuses on the course of disability in early RA. In the thesis, disability is measured by the selected disability assessments in the TIRA project, but still covering certain aspects of disability including physiological functions of the body to an individual's restricted involvement in life situations. To describe disability in a context, its relations to variables representing disease activity and contextual factors are analysed. To relate the research questions and results to a classification tool, the International Classification of Functioning, Disability and Health (ICF) has been used.

The course of disability in early RA is complex and may be seen as a parallel process to disease activity. Disability in RA was highlighted during the 1980s and since then has been incorporated in assessments and clinical work. Disability has many aspects and additional knowledge is still needed concerning the course of and relation between some of these aspects, sex differences and identification of variables of importance to decrease later disability. In the future, this added knowledge might help optimize the early interventions further.

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ABSTRACT

Rheumatoid arthritis (RA) is a progressive disease, often leading to disability. Because the disease course develops rapidly during the first years after diagnosis, more knowledge is needed about the early disease course to minimize later disability. This thesis describes the course of disability in early RA such as hand function, pain intensity, activity limitation and sick leave. In addition, this thesis compares disability between women and men and compares disability between RA patients and referents.

This thesis is primarily based on data from the 320 patients that were included in the multi-centre project in Sweden called 'Early interventions in rheumatoid arthritis' (TIRA). A wide range of outcome variables was registered between 1996 and 2006 during regular follow-ups from time for diagnosis through the eight-year follow-up. Outcome regarding disease activity and disability of RA patients still remaining in TIRA at the three and five year follow-up respectively are used in this thesis. Data concerning sick leave were obtained for the patients during six years (1993-2001) – three years before and three years after diagnosis. Referents were included in two of the studies. Data regarding disability in referents were obtained according to hand function and activity limitation using the Health Assessment Questionnaire (HAQ). Data for sick leave were obtained for six years in referents, for the same period as the RA patients.

For most variables, disability in RA was most pronounced at time of diagnosis but before intervention started. Disability was then reduced already at the 3-month follow-up and thereafter affected but stable during the following five years. The exception was participation, reflected by sick leave, a variable that was stable from inclusion to three years from diagnosis. Activity limitation, pain intensity and sick leave in RA that represents different aspects of disability were explained by other aspects of disability and contextual factors rather than by disease activity. RA affects women and men differently in some aspects. Women had more severe course of activity limitations than men according to HAQ. Men were more affected than women in range of motion, although the differences were small in a clinical perspective. However, pain intensity and frequency of sick leave did not differ between women and men. Patients with RA have pronounced disability in relation to referents although several variables improve soon after diagnosis. This discrepancy refers to hand function as well as activity limitations and sick leave. The frequency of sick leave increased during the year before diagnosis in relation to referents and was thereafter high compared to sick leave in referents.

ABBREVIATIONS

ACR	American College of Rheumatology
Anti-CCP	Anti-Cyclic Citrullinated Peptides
CRP	C- Reactive Protein
DAS-28	28-joint count Disease Activity Score
DMARD	Disease-Modifying Antirheumatic Drug
ESR	Erythrocyte Sedimentation Rate
FA	Factor Analysis
GAT	Grip Ability Test
HAQ	Health Assessment Questionnaire
ICD-10	International Classification of Diseases, Tenth Revision
ICF	International Classification of Functioning, Disability and Health
ICIDH	International Classification of Impairment, Disability and Handicap
IQR	Inter-Quartile Range
NSAID	Non-Steroidal Anti-Inflammatory Drug
MLR	Multiple Linear Regression
OMERACT	Outcome Measures in Rheumatology
PC	Principal Component
PCA	Principal Component Analysis
PGA	Physician's Global Assessment of disease activity
PLS	Partial Least Squares by means of Projection to Latent Structures
PLS-DA	Partial Least Squares Discriminant Analysis
RA	Rheumatoid arthritis
RF	Rheumatoid Factor
sd	standard deviation
SOFI	Signals of Functional Impairment
TIRA	Swedish acronym for 'early intervention in RA'
VAS	Visual Analogue Scale
VIP	Variable Influence on Projection

ORIGINAL PAPERS

This thesis is based on the following studies, which are referred to by their Roman numerals:

- I Björk, M., Thyberg, I., Haglund, L., Skogh, T. Hand function in women and men with early rheumatoid arthritis. A prospective study over three years (the Swedish TIRA project). *Scandinavian Journal of Rheumatology* 2006; 35:15-19.
- II Björk, M., Thyberg, I., Skogh, T., Gerdle, B. Hand Function and Activity Limitation According to Health Assessment Questionnaire in Patients with Rheumatoid Arthritis and Healthy Referents: 5-Year Followup of Predictors of Activity Limitation (The Swedish TIRA Project). *The Journal of Rheumatology*, 2007; 34:296-302.
- III Björk, M., Gerdle, B., Thyberg, I., Peolsson, M. Multivariate relationships between pain intensity and other aspects of health in rheumatoid arthritis – cross sectional and five year longitudinal analyses (the Swedish TIRA project). (*Disability and Rehabilitation*, in press).
- IV Björk, M., Thyberg, I., Rikner, K., Balogh, I., Gerdle, B. Sick leave before and after diagnosis of rheumatoid arthritis in relation to referents – A report from the Swedish TIRA project. (submitted)

BACKGROUND

Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory disease often leading to disability (1). In a Swedish adult population, the annual incidence of RA has been estimated to 24/100 000 (2) and the prevalence about 0.5-0.7% (3, 4); women are affected about twice as often as men (5-7).

The aetiology of RA is still unknown but complex genetic factors, as well as life style and exposure factors are of importance (8-11). For scientific purposes of classification of RA, the 1987 revised classification criteria according to the American College of Rheumatology (ACR) are still in use (12) (**Table 1**).

Table 1: The 1987 revised ACR criteria for classification of RA*.

Criterion	
1.	Morning stiffness
2.	Arthritis of three or more joint areas
3.	Arthritis of hand joints
4.	Symmetric arthritis
5.	Rheumatoid nodules
6.	Serum rheumatoid factor
7.	Radiographic changes

* Criterion 1-4 must have been present for at least 6 weeks.

These criteria are less sensitive in early RA (13) since they were developed based on patients with an average disease duration of more than seven years. Earlier in the disease course, it is more difficult to diagnose a patient based only on clinical signs. The Norfolk Arthritis Register (NOAR) (14) notes that patients with early arthritis should not be classified immediately.

It has been reported that about 10% of early RA patients enter a natural remission (15) even though the concept of remission is debatable (16). Remission can occur by itself (natural remission) or due to effective interventions.

The course of RA varies. Several factors have been identified as possible predictors for the course of the disease. The most important predictors of radiological damage are Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Rheumatoid Factor (RF) and antibodies to Cyclic Citrullinated Peptides (anti-CCP) at time for diagnosis. Health Assessment Questionnaire (HAQ) is the best predictor of disability (17). Disability is present already early in the disease process (18, 19) although early intervention improves disability and disease activity within the first months after diagnosis (20). In a longer perspective, disability deteriorates and leads to substantial economic consequences for the individual, their families and society (21). For example, 12 months after diagnosis a major part of the patients are work disabled (22), this makes RA one of the most expensive diseases due to productivity loss. The early stages of the disease are important for the outcome. A rapid management response based on knowledge of the early disease course may lower the indirect costs since failure to decrease disease activity during the first six months has been identified as a predictor of disability pension (23).

International Classification of Functioning, Disability and Health (ICF)

The ICF (24) provides a classification to express health and health-related states. An earlier version of ICF – the International Classification of Impairment, Disability and Handicap (the ICIDH) – focused on consequences of disease (25) whereas the ICF focuses on the components of health. ICF provides a language that describes functioning. A health condition in ICF refers to a disease, disorder, injury or trauma. The health condition is coded using the International Classification of Diseases, Tenth Revision (ICD-10), which provides an aetiological framework. In other words, ICD-10 provides a diagnosis such as RA, and ICF is a classification of functioning.

The structure of ICF contains several levels. It contains two parts: 'Functioning and Disability' and 'Contextual Factors'. Functioning is the positive and disability the negative aspect of the interactions between the individual and the contextual factors. The contextual factors compose the context of an individual's life. Furthermore, these parts are divided into components: functioning and disability into 'Body Functions and Structures' and 'Activities and Participation'. Body functions are physiological and psychological functions of the body system and body structures are the structural or anatomical parts of the body such as organs and limbs. Activity refers to an execution of a task or an action. Participation is a person's involvement in a life situation. 'Environmental factors' and 'Personal factors' belong to the Contextual Factors. Environmental factors include all aspects of the environment, both physical and social; these factors form the context of an individual and influence the individual's functioning. The personal factors are the contextual factors that refer to the individual such as age, sex, social status and life experiences (**Figure 1**).

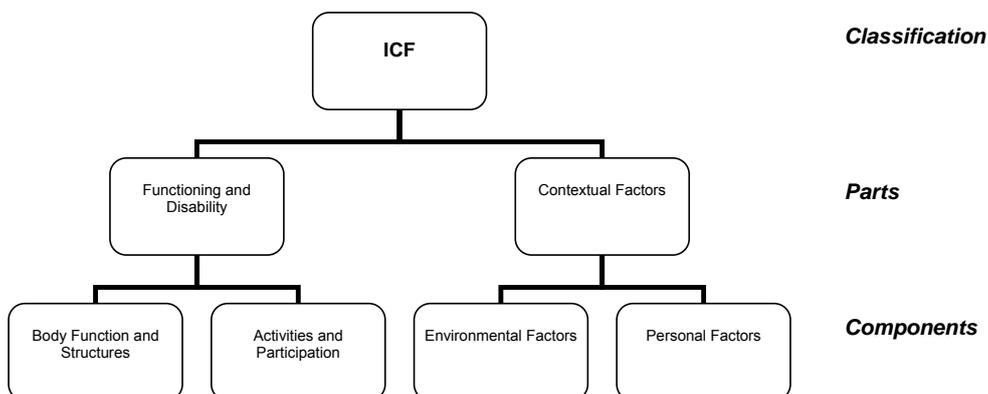


Figure 1: Structure of ICF (24).

The components in ICF interact with one another; therefore, if one component is affected, it may modify another component or the health disorder. If body functions and structures are affected, this is referred to as an impairment. The limitation of activities is called an activity limitation and in participation a participation restriction. Furthermore, in

ICF 'functioning' serves as an umbrella term including body functions, activities and participation. The negative aspect of functioning is disability and includes impairments, activity limitations and participation restrictions (Figure 2).

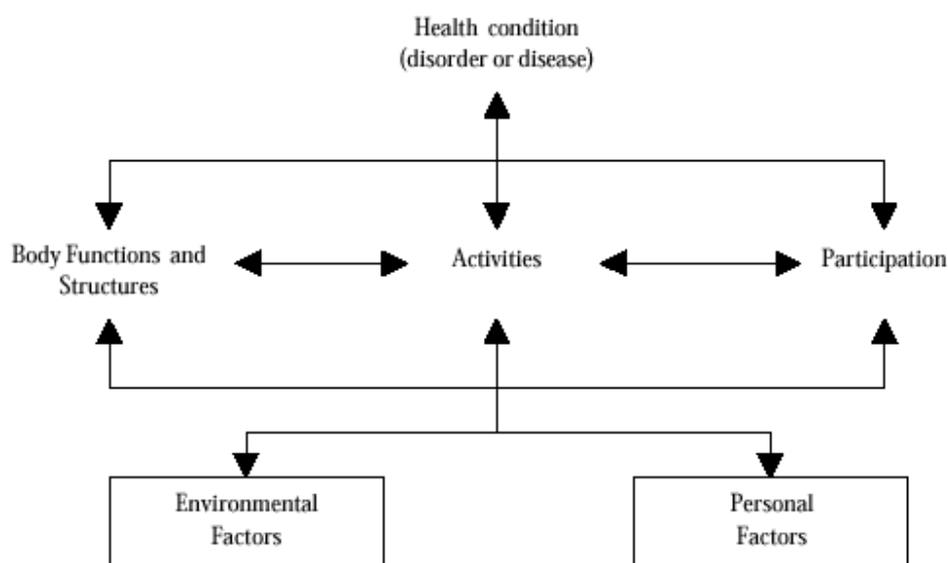


Figure 2: Interactions between the components of ICF (24).

Disability in RA

Body Function and Structures

The inflammatory process in RA often starts with a slowly altering feeling of tiredness, muscle pain and stiffness in joints especially in the morning. The pain and stiffness are probably caused by the inflammatory process in the synovium. All joints can be affected but the disease often starts in the wrists and the small joints of the hands or feet (26). Joint damage assessed with X-ray appears early in the disease course and were seen in 70% of the patients after three years according to van der Heijde et al.(27)

The inflammatory process affects body functions and structures: with subsequent increased pain, decreased range of motion, and decreased muscle strength (18, 28). Pain is a major concern in RA and despite medical treatment the patients continue to suffer from pain (29). Pain is expressed by the patients as one of the most important symptoms to reduce because of its consequences (30). For example, pain in the wrist, which is common at onset of RA, reduces grip force and endurance in the hand (26).

The inflammatory process in joints can cause an imbalance in muscles and tendons causing joint deformities that further increases stiffness and pain and decreases strength (26). Early interventions and knowledge of early impairments are of importance to reduce manifest deformities.

Activities and Participation

Hand function is usually described solely as grip force or grip ability, but additional aspects must be considered. Hand function is of great importance for activity performance and has been defined as the ability to use hands to perform daily activities (31). Hand function is affected early in RA and deteriorates during the disease course (32).

Activity limitations increase during the disease course (33) even though there is a different pattern in early RA with an improvement shortly after diagnosis (20). However, despite the early improvements, activity limitations are reported and rather stable one year after diagnosis. Most limitations concern activities in eating and drinking and in outdoor mobility (34). Later in the disease course, outdoor mobility as well as strenuous activities – such as washing clothes and cleaning – are restricted (35). Two years after diagnosis, 78% of women and 54% of men in the TIRA cohort used assistive devices that reduced their activity limitations significantly with respect to eating and drinking (34).

A review focusing on participation restrictions in RA (36) found that patients with RA had an increased risk for work disability already early in the course of the disease. Burton et al. (22) found that 22-76% of patients with RA were on sick leave six months after diagnosis and 36-84% after 12 months. Sick leave increased most rapidly during the following six months after diagnosis (37, 38). The improvements in activity limitations and impairments during the first months after diagnosis are well known (20), but knowledge about work disability early in the disease course is limited.

Recreation and leisure, foremost socializing, were affected with patients experiencing participation restrictions in social activities (36, 39). Eight years after time for diagnosis, 75% of the patients had altered leisure time activities and half of them were not satisfied with their recreation, a dissatisfaction that resulted in emotional distress (40).

Contextual factors

Not only does RA affect the individual but also the social environment (e.g., friends and family) and society. The societal costs for RA are high because of both direct costs (health care costs) and indirect costs (productivity loss) (41). A study from the UK showed that arthritis is expensive for the patients and their family and friends. For example, house chores were an area for special need; often family and friends helped these patients (42). In addition, family and friends often provided help with transport (43).

The social network and the social support from relatives and friends are important for the long-term course of RA (44) because of the increasing dependence on others as a consequence of disability and increasing participation restrictions (37, 40).

Personal factors, defined as the personal qualities not referred to the health condition, in ICF (24), can significantly influence the disability due to RA. For example, patients who are distressed in the early stages of RA are at risk for developing chronic distress. During the course of disease, the correlation between distress and disease activity decreases and

the level of distress is affected by support from the social environment (45). In addition, the patient's coping strategies are important. Coping with pain in early RA can affect disability later in the course of RA (46).

Outcome

Outcome assessments in RA were previously limited to disease activity, or when focusing on consequences, the physiological ones. The interest in obtaining information regarding the impact of the disease on functioning is relatively new (47). In 1980, HAQ (48) was introduced to assess disability in RA. Since then, many other assessments have been developed. The Outcome Measures in Rheumatology (OMERACT) is an international initiative to improve outcome assessments in rheumatology. This work started in 1992 and has generated an approach for 'what' we should assess and 'how' we should assess it. 'What' should we assess includes the patients' and their caregivers' opinions about relevant outcomes. These outcomes are often stable over time. 'How' to assess is constantly evolving since new instruments and techniques are developed continuously (49). The five domains proposed by OMERACT cover a wide range of aspects: Health Status, Disease Process, Damage, Mortality, and Toxicity/Adverse Reactions. These should be covered by every longitudinal observational study. Two additional domains, Work Disability and Costs, were recognized as important, but need not be used in all longitudinal observational studies (50). Disability is a focus of outcome assessment in the disease specifically OMERACT as well as in the universal ICF.

To facilitate the use of the ICF components in relation to a specific health condition, such as RA, the categories most important for the health disorder have been identified in 'core sets'. In RA, the first core sets were published in 2004 by Stucki et al. (51). The preliminary core sets were developed through a formal decision-making and consensus process by 17 experts (clinicians representing members of a multi-disciplinary team) from 12 countries. Their work identified a set of ICF categories of importance for functioning in RA. The largest number of categories was selected from the component Body Function (26%). The component Body Structures were included to 19%, the component Activities and Participation in 33%, and the component Environmental factors in 22%.

These core sets for RA have been evaluated and discussed in relation to their usefulness and in relation to core sets created for other health conditions. One discussion of core sets in general is that it facilitates the documentation (both in research and in practical work) of disability as an interaction between the health condition, the individual, and the environment. Still, there is a danger associated with reducing the framework of ICF to specific core sets related to a particular health condition since it may change the focus from the bio-psycho-social impact on functioning to the disease (52), a change that could result in a loss of the broad perspective of functioning.

Both the validation process with the ICF core sets for RA and the OMERACT have highlighted the patients' perspectives and resulted in recommendations of using the perspectives of those who experience the disease in outcome assessments. In validation of the ICF core sets, patients confirmed the included core sets but also raised some additional aspects not covered by the core sets, such as social support, side effects of

medication and fatigue (53). Fatigue has also been raised in OMERACT as an important outcome after including the patient's perspective (54). The difference between the patient's view and the care giver's views on what to assess is growing (55, 56). This may be because patients are 'taking charge' of their disease, which emphasizes that the prioritized outcomes should include the overall situation of the patient (57).

Differences between women and men in RA

Söderlin et al. (2) reported that, the annual incidence of RA in Sweden is 29/100 000 for women and 18/100 000 for men. The prevalence increases with age and the peak age for onset is lower in women than in men (5). Although RA is more common in women than in men in all age groups, the sex difference is more obvious at a younger age (5). Women with RA tend to have more involvement of small joints in hands and feet, whereas men have more involvement in knees and hips (58). Women have a lower grip force than men (34), a finding also seen in the general population (28). Women report more pain than men (59) and more activity limitations. At one and two years after diagnosis, women more frequently report activity limitations and a higher frequency of using assistive devices (34). RA negatively affects psychological factors such as depression, anxiety, coping and helplessness with a higher prevalence in women (60).

According to participation restrictions, the disease also affects the possibility to maintain leisure activities to a greater extent in women compared to men (39). According to work functioning, it is unclear whether it is affected differently in women and men with RA. Some studies (43, 61) identified women as having a higher risk for work disability, but no differences between the sexes has also been found (38). However, women with RA tended to be employed part time to a higher extent than men, worked with more administrative work (38) and had more adaptations at work compared to men with RA (62). This may indicate that the differences in work functioning between women and men are complex and related to the work situation – the nature of the job, the level of physical demands and the degree of autonomy (63) – rather than sex per se.

Interventions

The goals with the interventions in RA are to keep disease activity low, to prevent joint damage, decrease pain, maintain functioning in activities of daily life and work and increase quality of life (64).

Pharmacological interventions

During the last decade, management of patients with RA has made remarkable progress in terms of early accurate diagnosis, early aggressive medication with traditional disease-modifying antirheumatic drugs (DMARDs), introduction of new potent biological anti-rheumatic pharmacotherapy, and structured clinical follow-up of outcome measures (65). Pharmacological interventions for rheumatoid arthritis with both conventional DMARDs and new biological agents have become more effective and have changed treatment strategies (66). The treatment goal in early RA should be to achieve clinical remission in order to prevent structural damage and long-term disability. Early aggressive treatment of

rheumatoid arthritis – such as combination of DMARDs and oral corticosteroids or biological therapies – is associated with decreased disease activity, slower radiological progression and less disability (65, 67, 68). Inflammation in patients with rheumatoid arthritis should be suppressed as early as possible (69). DMARDs are effective against symptoms of rheumatoid arthritis, but biological agents (e.g., anti-TNF) in combination with methotrexate offer greater suppression of progression of structural damage (69).

There is no universal consensus concerning the choice of initial drug or whether single DMARDs or combinations should be given as initial treatments (67, 70). Combining DMARDs is a widely used therapeutic strategy (67). Currently, anti-TNF therapy is normally reserved for patients who have failed traditional DMARDs. The question still remaining is whether TNF-blocking drugs are better used if given early in terms of less indirect costs even if the direct costs increase (66). The TNF-blocking therapy is effective, but there also remains concerns about long-term risks (67). Even if current treatment approaches can lead to important benefits in patients with early arthritis, future research is needed to target pharmacological interventions more selectively and to determine which patients respond best to various agents or combinations (71).

Rehabilitation

Rehabilitation is a complex process with the patient's need in focus. Rehabilitation is characterized by collaboration between professionals from different disciplines creating a comprehensive view based on an integration of a range of knowledge. A fundamental aspect of rehabilitation is the patient's influence and participation (72). Rehabilitation in RA often includes several health care professionals collaborating in a multi-disciplinary team; this approach has been identified as an effective treatment approach (73, 74). The team often includes rheumatologists, occupational therapists, physiotherapists, social workers and nurses (75). Patient education, aiming at teaching patients about RA, is an intervention often provided by the whole team. Patient education is often provided early in the disease course in groups or individually in structured educational programmes (76).

The team members also have their distinct goals. The occupational therapist concentrates on restoring and maintaining the patient's functioning to facilitate activities in daily living and participation in society. Common interventions are joint protection, splints and assistive devices (i.e., dressing or eating devices) and adaptations at home, at work or in the car. In a review (77) focusing on evidence of interventions, six major areas for occupational therapy were identified: comprehensive occupational therapy training of motor functions, instruction on joint protection and energy conservation, assistive devices, splints and training of skills. The evidence for these interventions is limited because of sparse literature. However, splints can reduce pain both immediately (78) and after a longer period (79). There is also limited evidence that comprehensive occupational therapy (all interventions combined) (77, 80) and instruction on joint protection (81) reduce disability.

The main scope for the physiotherapist in rehabilitation of patients with RA is to restore, maintain or improve body functions and structures (82). Exercise therapy, such as aerobic and strengthening exercises and hydrotherapy (83), has been identified as an important

treatment since it improves muscle strength and physical fitness (84, 85). A wide range of physical modalities are provided such as thermotherapy (cold packs and hot packs) (86, 87), ultrasound (88) and transcutaneous electrical nerve stimulation, aiming at relieving pain and restoring function. In addition, specific manual techniques are used to facilitate and restore function in joints and muscles.

The social worker plays a role in restoring and maintaining functioning from the social perspective in preventing, soothing or solving personal problems or problems in the social environment in or outside the family (89). The patient with RA also meets other team members and professionals outside the team. Since a major part of the patients are work disabled ten years after diagnosis (90), vocational rehabilitation are needed (91). About 20% of the rheumatic patients also use complementary medicine outside the medical services (92).

Early intervention in RA

Early RA used to be defined as less than five years with the disease, but is nowadays decreased to 24 months or less (69). The management of early RA has become more focused on rapid referral with early assessment and early treatment (69). To diagnose and start intervention in patients later in the disease process increases the risk of persisting disability and inflammation (68).

Several longitudinal projects (93-97), including patients with early RA, have been established during the last decades. One of the early RA projects starting in Sweden was the "TIRA" project (Swedish acronym for "early intervention in rheumatoid arthritis"). TIRA started in 1996 in cooperation between ten rheumatology units in South-east of Sweden: Eskilstuna, Jönköping, Kalmar, Linköping, Lindesberg, Motala, Norrköping, Oskarshamn, Västervik, and Örebro. The aims with the TIRA project were to establish clinical routines for early diagnosis and multi-disciplinary interventions, to launch a network for cooperation and to generate a database for research. During eight years, a cohort of patients with early RA was regularly followed-up and data concerning epidemiology, genetics, disease activity, disability and health economics were collected.

The intention with the TIRA project was to include all patients diagnosed with RA during 1996-1998. Although the TIRA project is not an incidence study, the incidence rate based on the number of patients included in TIRA at the rheumatology unit in Linköping in relation to people living in the municipality is estimated to 22/100 000, a rate that is comparable to rates from published incidence studies using the same inclusion criteria with rates of 24/100 000 (2), 29/100 000 (98). That is, the higher proportion of women and the mean age at onset in the TIRA project agree with other cohorts (93-97).

AIMS

The specific aims of each study were as follows:

The aims of **Study I** were to evaluate the course of hand function over 3 years, to investigate sex differences in hand function, and also to study correlations between and within different hand function assessments, focusing on grip ability, grip force, and range of motion.

The aims of **Study II** were to compare hand function and HAQ between healthy referents and patients with RA in women and men, to analyze the relationship between hand function and HAQ and to determine whether patient characteristics at diagnosis can predict the patient's HAQ score 5 years after the diagnosis of RA.

The aims of **Study III** were to analyse the relationships between pain intensity and other aspects of health used to assess disease activity and disability in patients with early RA and to examine if such relationships were different between women and men.

The aims of **Study IV** were to describe sick leave during three years before and three years after diagnosis of RA in relation to sick leave in Swedish referents during the corresponding period and to identify predictors of sick leave during the third year after diagnosis of RA.

Four overall aims were seen throughout the studies forming the structure of this framework:

- To describe the course of disability in RA, especially with hand function, pain intensity, activity limitation and sick leave in focus (Study I-IV)
- To identify and describe relations between different aspects of disability in RA (Study I-IV)
- To compare disability in men and women with RA (Study I-IV)
- To compare disability in RA and referents (Study II and IV)

METHODS

Subjects

In all four studies in this thesis, patients from the TIRA project were included. In Study II and IV, referents were also included.

Patients

During 27 months in 1996 to 1998, 320 patients (67% women) with early RA (onset of joint swelling ≤ 12 months but ≥ 6 weeks) were recruited to the TIRA project (34). All primary health care units in the area were asked to promptly refer all patients reporting swollen joints since at least six weeks but no longer than 1 year to the rheumatology unit at their connecting hospital. The enrolled patients fulfilled $\geq 4/7$ RA classification criteria (12) or at least exhibited morning stiffness ≥ 60 minutes, symmetrical arthritis, and arthritis of small joints. The mean age of the patients at inclusion was 56 years ((standard deviation (sd) 15). On average the women were younger, (55 years, sd 15) than the men (59 years, sd 15).

The cohort was followed from diagnosis (M0) with regular follow-ups after 3, 6, 12, 18, 24, 36, 48 and 60 months (M3-M60). At all follow-ups, the patients met with a physician, an occupational therapist and a physiotherapist, and the patients were given individual treatment based on their needs. At the 5-year follow-up (M60), 8 of the 10 rheumatology units still participated in the TIRA project with a total study population of 251 patients (Figure 3).

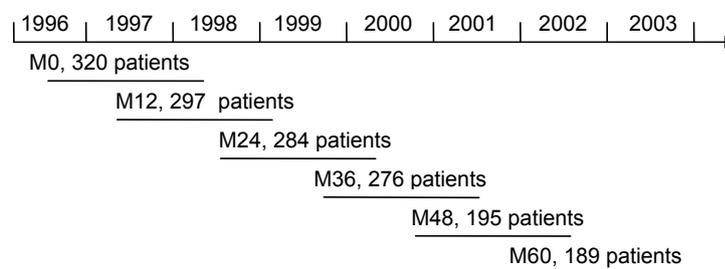


Figure 3: Number of patients in the TIRA cohort from inclusion (M0) to the fifth year follow-up (M60)

Study I included the 276 patients still remaining in the TIRA project at the third year follow-up. Study II and III included the 189 patients that remained in the TIRA project at the fifth year follow-up. In Study IV, patients younger than 62 years at inclusion were selected from the 276 patients still remaining in the TIRA project at the third year follow-up (Table 2).

Referents

In Study II and IV, referents were included. In Study II, the referents were recruited from staff at the hospitals in Linköping and Norrköping and through pensioners' associations. Sixty-two women (mean age 59 years, sd 15) and 61 men (mean age 60 years, sd 15) with self-perceived normal hand function were included. The referents were recruited so as to have the same age distribution as the patients in the TIRA cohort at M36.

In Study IV, a referent was randomly matched to each of the 120 patients for age, sex, and hometown. The matching process was made by the Swedish social insurance agency and based on the Swedish population.

Drop outs

In the TIRA cohort, patients dropped out during the study period for different reasons such as moving from the area, they did not wish to participate, or they had died. The dropouts in Study I, II and III were significantly older than the patients in the study group. In Study II and III, the proportion of men was higher among the dropouts and the dropouts also had significantly lower ESR than the included patients. In Study IV, the dropouts did not differ from the included patients with respect to age, sex, disease activity and disability. No dropouts were identified among the referents in Study II or IV.

Study design

The studies included in this thesis are based on quantitative data. All studies are longitudinal, but Study II and III also contain cross-sectional analyses (**Table 2**).

Table 2: Study designs including subjects and period of used data.

Study	Design	Subjects	Data collection
Study I	Quantitative and longitudinal	276 patients (69%women)	M0, M3, M6, M12, M18, M24 and M36
Study II	Quantitative, longitudinal and cross-sectional	189 patients (69% women) and 123 referents (50%women)	M0, M3, M6, M12, M18, M24, M36, M48 and M60
Study III	Quantitative, longitudinal and cross-sectional	189 patients (69% women)	M0, M3, M6, M12, M18, M24, M36, M48 and M60
Study IV	Quantitative and longitudinal	120 patients (76% women) and 120 referents (76% women)	M0-M36 and three years before diagnosis

The four studies in this thesis are based on data from the TIRA project from different periods. All studies are longitudinal and include data from inclusion to the fifth year follow-up. In Study IV, retrospective data was also used concerning sick leave for the three years before diagnosis (**Figure 4**).

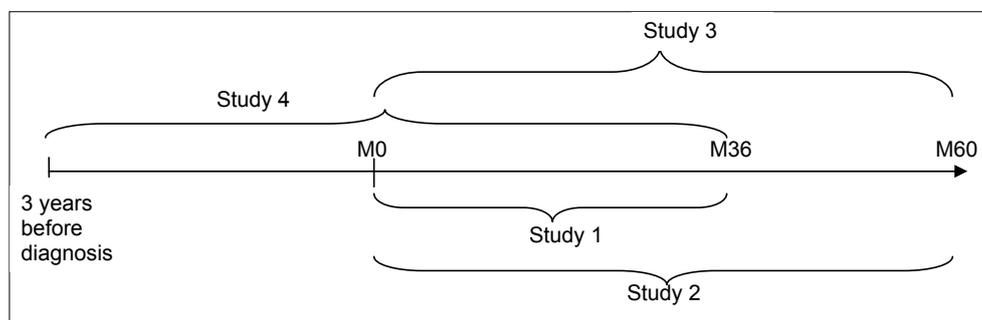


Figure 4: Study periods in the studies in relation to diagnosis (M0) and follow-ups.

Outcome variables

A wide range of outcome variables concerning disease activity and disability, listed in **Table 3**, were considered in this thesis.

Disease activity

Anti-cyclic citrullinated peptide (anti-CCP) antibody was analyzed in serum samples taken at inclusion (cut off value for positive anti-CCP reaction: 25 units/ml.) (99). The erythrocyte sedimentation rate (ESR) and serum level of C-reactive protein (CRP) were analysed at all planned visits. Both ESR and CRP are markers of inflammation, but in RA, CRP is a better reflection of ongoing systematic inflammation, whereas ESR may be a better marker of disease severity over time (100).

Disability

At all follow-ups, a 28-joint count of tender and swollen joints (101) was registered and the physician's global assessment of disease activity (PGA) was estimated on a 5-degree scale (0-4), where 0 corresponds to no activity and 4 represents high activity (102). Disease activity was also assessed by calculating the 28-joint count disease activity score (DAS-28) (103). DAS-28 is a validated index including the 28-joint count of tender and swollen joints; ESR and general health were assessed using a Visual Analogue Scale (VAS). Number of fulfilled ACR criteria (12) was registered at time of diagnosis and after three years.

Grip force in Newton (N) was measured using the electronic instrument Grippit™ (AB Detektor, Göteborg, Sweden). Peak and average values were achieved during a 10 second period for both hands. The test-retest score in women with RA (the right hand) has previously been shown to be high regarding peak ($r=0.89$) as well as average values ($r=0.92$). Referent values for men and women has been identified to be 432 N and 229 N for average value in their right hand (28).

Grip ability was assessed using the 'Grip Ability Test' (GAT) developed by Dellhag and Bjelle (31). GAT consists of three items: "put a flexigrip stocking over the non-dominant

hand”, “put a study clip on an envelope” and “pour water from a jug”. The score (10-276) is based on how long each activity takes to perform. A high score corresponds to decreased hand function and a score of 20 or less was considered as normal hand function. The reliability according to intraobserver test was calculated as $r=0.99$ and interobserver test as $r=0.95$ (31).

Range of motion was measured using the instrument ‘signals of functional impairment’ (SOFI). The test is divided into three parts: upper limb function (SOFI-upper limb), lower limb function (SOFI-lower limb), and hand function (SOFI-hand). The scoring is an ordinal rating scale 0-2, where 0 indicates “full function” and 2 “cannot perform”. The possible range in score is 0-12 in SOFI-upper limb function and 0-16 in SOFI-lower limb function and a score of 0 was assumed as normal. In the SOFI-hand, the possible range in score is 0-16 where a low score indicates a full function. The index has been evaluated regarding reliability, validity and sensitivity and was found to be acceptable (104). Walking time was defined as the time it took to walk (with or without assistive devices) 20 meters. This assessment has not been tested regarding validity or reliability.

The HAQ (48) measures activity limitations and was self-reported by the TIRA patients at the time of inclusion and at the follow-ups. It consists of 20 questions in eight subcategories: dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. The response alternatives for each of the 20 questions are ‘without any difficulty’ (score=0), ‘with some difficulty’ (score=1), ‘with much difficulty’ or ‘with use of an assistive device’ (score=2), and ‘unable to do’ (score =3). The highest score obtained for any question of a given subcategory determines the score for the subcategory. A total score (0-3) is calculated based on the sum of the scores for the various subcategories divided by the number of subcategories that were answered. The Swedish version of HAQ, used in the present study, is valid and reliable (105).

The patients were also asked to report their pain intensity on average during the last week. This was estimated on a 100-mm VAS ranging from 0 (no pain at all) to 100 (worst possible pain). Wellbeing was estimated in the same manner, 0 representing ‘best possible wellbeing’ and 100 ‘worst possible wellbeing’.

Data concerning sick leave was obtained from the Swedish social insurance agency for the patients for three years before inclusion in TIRA through three years after inclusion. Since the employer is responsible for the economical compensation during the first 14 days (1 January 1997 to 31 March 1998 the first 28 days), these days are not included in the Swedish social insurance agency’s data and consequently not obtained for the patients. Data were grouped for each quarter during the six-year period. Sick leave was divided into number of days with sickness benefit, rehabilitation benefit, and disability pension. The number of days was recalculated to equal full-time days.

At the time of diagnosis, the patients completed a questionnaire about highest educational level (compulsory school, folk high school, upper secondary school or university or other significant education), marital status (unmarried, married, divorced or widow/widower), number of children living at home, and annual income. An epidemiological study provided type of work data at time of RA diagnosis (106). The sample in the

epidemiological study and Study IV agreed to 56%. Using a standard categorization system, one physician specialized in occupational medicine and one industrial hygiene engineer independently categorised the patients' type of work at time of diagnosis. The categories of work type were 'heavy material handling', 'heavy repetitive', 'medium heavy variable', 'light repetitive', and 'administration/computer work' (107).

Table 3: Outcome variables used in the studies and their main focus related to ICF.

Variables	ICF-component	Follow-up	Study			
			I	II	III	IV
Disease activity						
ESR (mm/h)	NA	All	X	X	X	X
CRP (mg/L)	NA	All	X	X	X	X
Anti-CCP	NA	All				X
ACR criteria (n)	NA	M0 and M36	X			
Disability						
Swollen joints (0-28)	Body function & structure	All	X	X	X	X
Tender joints (0-28)	Body function & structure	All	X	X	X	X
DAS-28 (score)	Body function & structure	All	X			
PGA (0-4)	Body function & structure	All		X	X	X
SOFI-hand (0-16)	Body function & structure	All	X	X	X	X
SOFI-upper (0-12)	Body function & structure	All	X	X	X	X
SOFI-lower (0-16)	Body function & structure	All		X	X	X
Grip force (N)	Body function & structure	All	X	X	X	X
Pain (0-100 mm)	Body function & structure	All	X	X	X	X
GAT (10-276)	Activities and participation	All	X	X	X	X
Walking time (sec)	Activities and participation	All		X		
HAQ (0-3)	Activities and participation	Yearly	X	X	X	X
Wellbeing (0-100 mm)	NA	All		X		X
Sick leave (days)	Activities and participation					X
Marital status (cat)	Personal factors					X
Children (n)	Personal factors					X
Education (cat)	Personal factors					X
Annual income (SEK)	Personal factors					X
Type of work (cat)	Environmental factors					X

TIRA=the Swedish acronym for the project 'early interventions in rheumatoid arthritis'; ICF=International Classification of Functioning, Disability and Health; ESR=Erythrocyte Sedimentation Rate; CRP=serum C-Reactive Protein; Anti-CCP=Anti-Cyclic Citrullinated Peptide; ACR= American College of Rheumatology; DAS-28=28-joint count Disease Activity Score; PGA=Physician's Global Assessment of disease activity; GAT=Grip Ability Test; SOFI-hand=Signals Of Functional Impairment in hand; SOFI-lower=Signals Of Functional Impairment in lower limb; SOFI=Signals Of Functional Impairment in upper limb; HAQ=Health Assessment Questionnaire; Pain=pain intensity assessed with a visual analogue scale; cat=category; n=number; SEK=Swedish crowns; NA=Not applicable.

Statistical analyses

A variety of methods were used (Table 4). All statistics were performed using SPSS or SIMCA P+. Median and inter-quartile range (IQR) were presented in relation to non-parametric statistics and mean and standard deviation in relation to parametric statistics. A p-value of 0.05 or less was considered statistically significant. In Study II a correction for multiple tests was applied using Tukey's method.

Table 4: Statistical analyses used in Study I-IV.

Methods	Study			
	I	II	III	IV
Wilcoxon signed-rank-test	X			
Mann-Whitney U-test	X			
Spearman's rho-rank-correlation	X			
ANOVA		X	X	X
Student's t-test		X	X	X
Pearson Chi-Square		X		
PLS		X	X	X
PLS-DA		X		
PCA			X	
Hierarchical PLS			X	

ANOVA=Analysis Of Variance; PLS=Partial Least Squares or Projection to Latent Structures; PLS-DA=Partial Least Squares Discriminant Analysis, PCA=Principal Component Analysis.

Univariate analyses

To analyse the overall differences during the study period, ANOVA was used (Study II-IV). Differences between or within groups were calculated using the non-parametric Wilcoxon signed-rank-test and the Mann–Whitney U-test (Study I) and the parametric Student's t-test (Study I-IV). In Study I, the correlations between different aspects of hand function were calculated using the Spearman's rho-rank-correlation.

The descriptive data were presented as median and inter quartile range (Study I) or mean and standard deviation (Study II-IV). In Study III, pain intensity (0-100 mm, VAS) was divided into the categories mild pain (0-40 mm), moderate pain (41-70 mm) and severe pain (71-100 mm) based on earlier identified cut-off limits (108-110).

Multivariate analyses

In Study II, III and IV, multivariate projection methods were used using the software SIMCA P+. The basic methods used were Principal Component Analysis (PCA) and Partial Least Squares by means of Projection to Latent Structures (PLS) (111). These methods were developed for industrial sectors. The three basic analytical questions to which these projection methods can be applied are (a) overview of data, (b) classification and/or discrimination among groups of observations and (c) regression modelling between two blocks of data (X and Y). These basic analytical questions are also familiar in health related research even though traditionally multivariate methods like multiple linear regression and factor analysis are used more often. The basic assumption in projection methods like PCA and PLS is that data can be reduced to a few latent variables that summarize the original variables.

The process of a PCA analysis can be viewed in the following example: Assume we have eight variables (in the example named A-H) that measure different aspects of disability in 20 patients. It is reasonable to assume that these eight variables are related to each other and therefore not independent. In a PCA, the overall pattern of correlations between these variables may be visualized and at the same summarised by latent variables.

In the PCA, each variable (A-H) defines a co-ordinate axis. Since we have eight variables in our example, we have to assume an eight-dimensional co-ordinate system. Since an

eight-dimensional space is rather hard to imagine, the example will be illustrated by the first three variables (A-C). Each subject is defined by a point in the co-ordinate system (**Figure 5**).

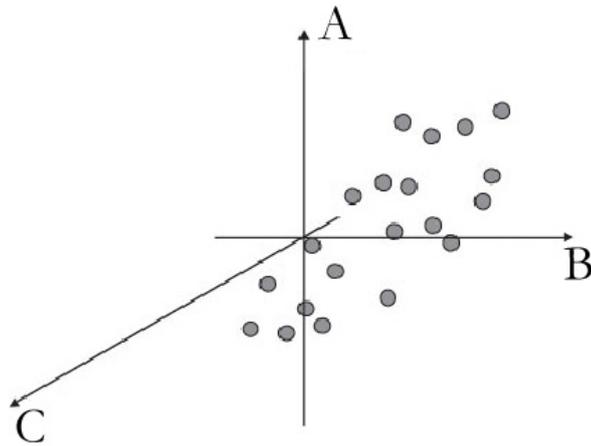


Figure 5: A co-ordinate system with three axis representing variables A, B and C. Each subject is defined by a point in the three-dimensional space. Modified with permission from Eriksson et al. (111).

The first Principal Component (PC) is placed in the direction of the largest variation. The second PC indicates the second largest variation orthogonally oriented to the first PC. The cross point between the PC's is locally placed at origin in the three dimensional space. The number of PC's calculated depends on the validity of the model. In our example, the data set with the eight original variables reflected two latent variables, PC1 and PC2 (**Figure 6**).

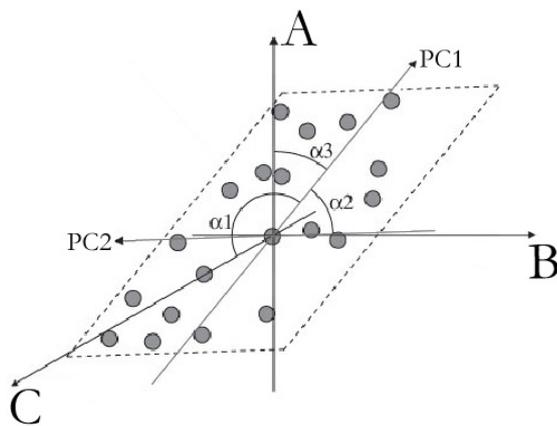


Figure 6: PC1 and PC2 in relation to the original variables. Modified with permission from Eriksson et al. (111).

A component consists of a vector of numerical values between -1 and 1, referred to as loading. The loading refers to the angel between the variable and the PC and expresses the degree of correlation between the variable and the component. Variables with high

loading (+ or -) on the same PC are intercorrelated. The result of projection of each original variable is a t-score, the coordinate value in the space related to the PC (**Figure 6**).

Two types of plots can be used to interpret the components in the model. The score plot (based on the t-scores) shows the relation between the different subjects. Subjects close to each other in the score plot have similar variable characteristics. The corresponding plot, the loading plot, shows how the variables are related to each other and how they influence the different components in the model.

To interpret the total model, a value of how much variation the PCs explain (R^2) is given together with a value of the predictive power of the model (Q^2). The Q^2 value is calculated using a cross-validation technique by SIMCA-P+. The basic idea of the cross validation is to keep a portion of the data out of the model, develop a number of parallel models from the reduced data and predict the omitted data by the different model. Finally, the predicted values are compared to the actual ones. In conclusion, by using the PCA, we have transformed an original set of correlated manifest variables into a new set of uncorrelated latent variables (the principal components). When projecting the original variables to the components, we were able to understand the relation and pattern between the eight original variables.

PCA reflects the relation between X-variables in contrast to PLS, which calculates the covariance between a set of X-variables and set of Y-variables. PLS is useful if we want to predict an outcome such as activity limitation (Study II) or sick leave (Study IV). In PLS, PCs are projected based on the same techniques as in PCA and the R^2 (one value in relation to X and one value in relation to Y) and Q^2 values are given. PLS provides variable-related parameters to facilitate the interpretation of the model. The variable influence on projection (VIP) identifies the most prominent variables for the model. X-variables with a $VIP \geq 0.8$ are considered as the most influential variables in the model (111).

PCA and PLS have some important advantages. The methods do not require interval-scaled data and it is not sensitive to violations of multivariate normality. Because they have no assumptions about independence of observations, they are only slightly influenced by collinearity among the original variables. They may be used with small samples and even with more original variables than subjects. A disadvantage of the methods comes when there is a very explicit model to test and the latent variables are not of interest (112). In health-related research, these methods can visualize a complex pattern of variables that a human observer would be unable to detect and therefore this may develop clinical knowledge and help us evaluate it (113).

Two extensions of PLS were used in the studies. In Study II, to regress HAQ after five years with patient characteristics at diagnosis as X variables, a PLS-based technique (partial least squares discriminant analysis (PLS-DA)) was used. The aim with the PLS-DA was to discriminate two groups from each other and identify the most important variables for the discrimination (111). In a PLS-DA, the X-variables consist of the original

variables and the Y-variable is a dummy-variable that describes a class membership, which in Study II was identified as affected or not affected HAQ.

In Study III, hierarchical modelling, based on both PCA and PLS, was used. The advantage of this projection is that data are formed into ‘meaningful blocks’ before analysing to facilitate the interpretation (111). These blocks may be chosen in different ways. In Study III, blocks were generated using the loading plot from a PCA with the included variables. The variables were divided into four blocks primarily according to the correlation structure of the PCA and secondarily to their conceptual meaningfulness in terms of their theoretical relation to each other (**Figure 7**).

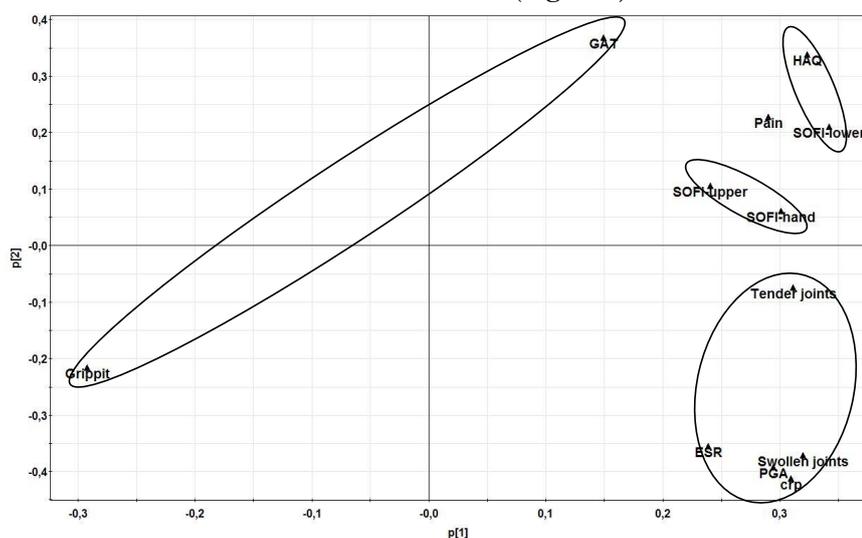


Figure 7: Principal component analysis model of the variables (the variable loading plot) at M60 for all subjects. The different blocks are marked with a circle. PGA=Physician’s Global Assessment of disease activity; CRP=C-Reactive Protein; ESR=Erythrocyte Sedimentation Rate; HAQ=Health Assessment Questionnaire; SOFI=Signals of Functional Impairment.

The hierarchical technique is based on the procedure that each block is refined according to the most explained variation. In Study III, this was done by a PCA for each block. The t-scores from the PCAs of each block are used as new variables in a top model upon which a new projection technique may be applied (PCA or PLS). By excluding the non-explained variation in the top model, the relationship between the variables will be more precise. The method also incorporates the possibility to examine the internal relationship between the original variables in each block (111).

ETHICAL CONSIDERATIONS

All patients in the TIRA project gave written informed consent to participate. The study protocol for the TIRA project was approved by the local ethics committees associated with the participating units (Dnr 96035). All patients and referents in Study II gave written informed consent to participate. In connection to the data collection in Study IV, all patients agreed to participate.

RESULTS

Interventions

At time of inclusion, about 4% of the patients were taking DMARDs (Study I-IV), which increased to about 65% (M36) and 62% (M60). The number of patients with ongoing Non-Steroidal Anti-Inflammatory Drug (NSAID) treatment was highest at inclusion and decreased thereafter. Oral corticosteroids were used by 15% at inclusion (Study I-IV) and by about 35% at M36 and M60 (Table 5). The patients were offered multi-disciplinary interventions at the follow-ups when considered appropriate. Almost 100% of the patients had attended patient education at the clinic during their first years in the TIRA project. At M36, 5% of the patients had started anti-TNF treatment and at M60 16%.

Table 5: Percentage of the patients (women/men) with ongoing pharmacological interventions at the different follow-ups in Study I-IV.

	Study I		Study II and III			Study IV	
	M0	M36	M0	M36	M60	M0	M36
DMARD (%)	3/2	64/66	4/3	65/75	59/64	2/7	70/64
NSAID (%)	61/66	37/40	55/63	35/48	25/31	61/68	41/46
Corticost. (%)	16/15	33/33	17/14	37/39	33/32	12/18	34/29

DMARD=Disease-Modifying Anti-Rheumatic Drug; NSAID=Non-Steroidal Anti-Inflammatory Drug; Corticost=oral corticosteroids.

Course of disability in RA

Almost all variables representing disease activity and disability improved during the disease course when compared to time for diagnosis (Table 6).

Table 6: Disease activity and disability at diagnosis (M0) and after 5 years (M60) in the patients included in Study II and III. NS denotes non-significant difference between M0 and M60.

	Patients n=189		
	Diagnosis (M0)	After 5 years (M60)	M0 vs. M60
	n=189 Mean (sd)	n=189 Mean (sd)	p-value
Disease activity			
ESR (mm/1st h)	36(24)	22 (20)	p<0.001
CRP (mg/L)	29 (29)	16 (22)	p<0.001
Disability			
Swollen joints (0-28)	9 (6)	3 (4)	p<0.001
Tender joints (0-28)	9 (7)	3 (5)	p<0.001
PGA (0-4)	2 (0.8)	1 (0.8)	p<0.001
Pain (VAS 0-100 mm)	49 (25)	39 (26)	p<0.001
Wellbeing (VAS 0-100 mm)	44 (26)	37 (24)	p=0.005
Walking time (sec)	14 (7)	14 (6)	NS
SOFI-upper limb (0-12)	1 (2)	1 (2)	NS
SOFI-lower limb (0-16)	2 (2)	2 (2)	NS
Grip force (N)	122 (95)	152 (97)	p<0.001
SOFI-hand (0-16)	3 (3)	2 (2)	p=0.042
GAT (10-276)	27 (18)	22 (12)	p<0.001
HAQ (0-3)	0.86 (0.57)	0.70 (0.57)	p=0.001

sd=standard deviation; ESR=Erythrocyte Sedimentation Rate; CRP=serum C-Reactive Protein; PGA=Physician's Global Assessment of disease activity; VAS=Visual Analogue Scale; SOFI=Signals Of Functional Impairment; GAT=Grip Ability Test; HAQ=Health Assessment Questionnaire.

Hand function and activity limitation (Study I and III)

Hand function was affected at diagnosis, i.e., at inclusion in the TIRA cohort. This counts for different aspects of hand function such as range of motion (measured by SOFI), grip ability measured by GAT and grip force (measured by Grippit). Hand function improved markedly until M3. Thereafter, only SOFI-hand improved significantly in men between M12 and M18. Activity limitation, according to HAQ, improved from time of diagnosis to the fifth year follow-up (M60) (Figure 8).

Pain intensity (Study III)

Almost 60% of the TIRA patients had moderate (41-70 mm; VAS) or severe (71-100 mm; VAS) pain intensity at time for diagnosis (M0). Between M0 and M3, there was a significant improvement in pain intensity. At M60, the part of patients reporting pain intensity higher than 40 mm was nearly 50%. Of the 20% of the patients reporting a moderate or severe at M0-M6, 67% still reported this at the fifth year follow-up (Figure 9).

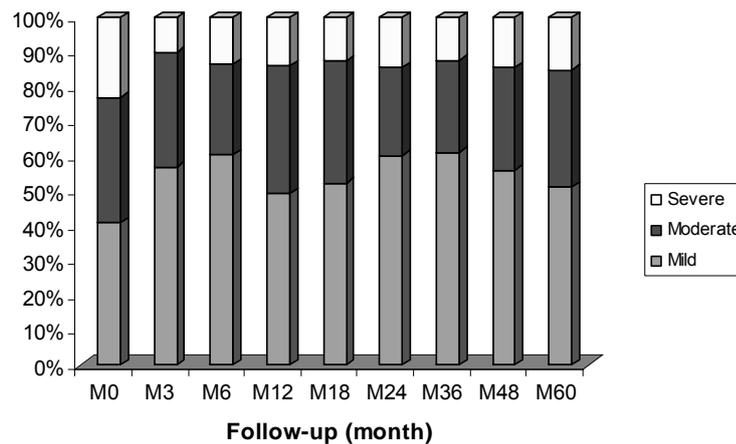


Figure 9: Percentage of patients reporting mild pain (0-40 mm), moderate pain (41-70 mm), and severe pain (71-100 mm) at the follow-ups during 5 years after diagnosis of rheumatoid arthritis (M0).

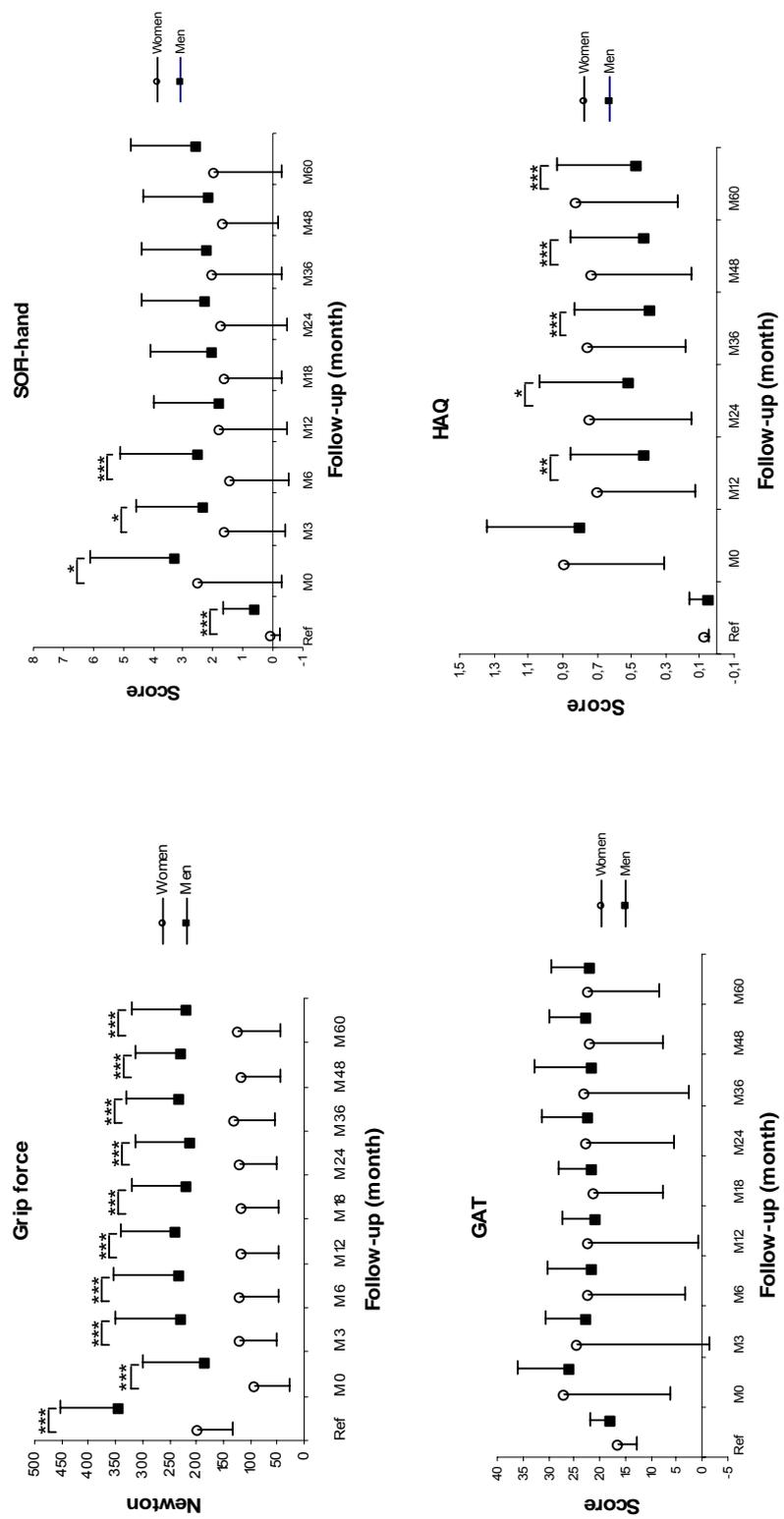


Figure 8: Mean value of grip force (right hand average value), SOFI-hand, GAT and HAQ at the different follow ups in TIRA (M0-M60) and at one occasion for healthy referents. In GAT, SOFI-hand and HAQ a high score indicates an increased disability. Bars represent +/-1sd. ■=men and ○=women. * p<0.05, ** p<0.01, *** p<0.001.

Sick leave (Study IV)

Six months before diagnosis, 31% of the future RA patients were already on sick leave. Until the first quarter after diagnosis, this part had increased to 53%, including 43% with sickness benefit, 2% with rehabilitation benefit, and 8% with disability pension. During the first quarter of the second year after diagnosis, 33% received sickness benefit, 5% rehabilitation benefit and 19% disability pension. During the study period's last quarter, 25% received sickness benefit, 3% rehabilitation benefit, and 28% disability pension (Figure 10).

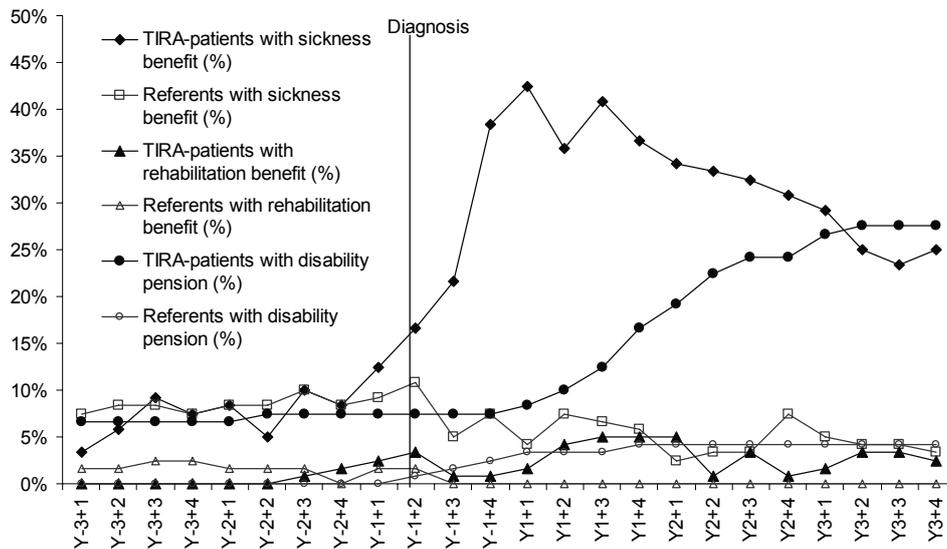


Figure 10: The rate of sickness benefit, rehabilitation benefit and disability pension during three years before and three years after diagnosis in the TIRA-cohort and in the corresponding period for the referents. The Y at the X-axis indicates the year in relation to diagnosis + quarter that year. For example, Y-3+1 = third year before diagnosis, month 1-3.

Relations between different aspects of disability in RA

Aspects of hand function (Study I and II)

GAT, grip force and SOFI-hand correlated weakly at M36. In grip force, the average grip force value for ten seconds correlated strongly with the peak value. Comparing right and left hand values, both average grip force and peak force correlated strongly.

HAQ related to hand function (Study I and II)

HAQ correlated weakly to hand function in Study I. The strongest correlation was found between HAQ and grip force in women. In the multivariate cross-sectional correlations analyses in Study II, hand function variables (GAT, Grippit and SOFI-hand) were important predictors of HAQ at M0 and only GAT and grip force at M60 (Table 7).

Table 7: Partial least square regression (PLS) of health assessment questionnaire (HAQ) as the dependent variable (Y) and hand function variables, sex and age as predictors (X variables) in RA patients at diagnosis (M0) and 60 months after diagnosis (M60). For each variable, a variable influence of projection (VIP) is given and a variable with a VIP value >0.8 is considered to be an important predictor.

Variables	Patients M0	Patients M60
	VIP	VIP
Grip force (N)	1.43	1.68
SOFI-hand (0-12)	1.14	0.71
GAT (10-276)	1.09	1.03
Sex	0.62	0.65
Age	0.29	0.41
R ² / Q ²	0.38/0.34	0.35/0.34

GAT=Grip Ability Test; SOFI=Signals of Functional Impairment

HAQ related to disease activity and disability (Study II)

In Study II, only 8% of HAQ were explained by baseline health variables. The strongest predictor of HAQ at M60 was HAQ at M0 and thereafter grip force, SOFI-lower, sex, walking time and GAT. The disease activity variables at M0 had no significant relation to HAQ at M60 (Table 8).

Table 8: Prediction of HAQ at M60. The bottom line gives R² and Q². The variables with VIP>0.8 (above the dotted line) are most important.

Type of variable	Variables	Patients
Y (M60)	HAQ (group 0 or 1) at M60	VIP
X (M0)	HAQ (group 0 or 1)	1.97
X (M0)	Grippit	1.75
X (M0)	SOFI-lower limb	1.41
X (M0)	Sex	1.39
X (M0)	Walking time	1.27
X (M0)	GAT	1.20
X (M0)	Wellbeing	0.78
X (M0)	CRP	0.63
X (M0)	SOFI-hand	0.63
X (M0)	ESR	0.49
X (M0)	Tender joints	0.42
X (M0)	PGA	0.37
X (M0)	Pain intensity	0.30
X (M0)	Age	0.22
X (M0)	SOFI-upper limb	0.15
X (M0)	Swollen joints	0.09
R ² /Q ²		0.080/0.014

HAQ=Health Assessment Questionnaire; SOFI=Signals of Functional Impairment; GAT=Grip Ability Test; CRP=C-Reactive Protein; ESR=Erythrocyte Sedimentation Rate; PGA=Physician's Global Assessment of disease activity. HAQ group 0 indicates an unaffected HAQ score and group 1 an affected HAQ score.

Pain intensity related to disease activity and disability (Study III)

Pain intensity did not correlate with hand function in Study I (**Table 6**). In Study III, pain intensity at M0 and M60 in cross-sectional analyses was related strongest to HAQ and SOFI-lower (**Table 9**). The weakest relation was found between pain intensity and disease activity variables. In a longitudinal perspective, disease activity variables at M0 were important predictors of pain intensity at M60 in men and HAQ and SOFI-lower in women.

Table 9: VIP values in the different hierarchical PLS-models of pain intensity. Block 1 consists of PGA, swollen and tender joints, CRP, and ESR. Block 2 of HAQ and SOFI-lower limb, Block 3 of GAT and Gripit and Block 4 of SOFI-hand and SOFI-upper limb. The number in the parenthesis after VIP states the order of precedence of variable importance in the model. A VIP-value >0.8 was considered a variable with a strong relation to Y (pain intensity).

	M0			M60		
	All	Women	Men	All	Women	Men
VIP block 1	0.69 (4)	0.71 (4)	0.66 (4)	0.65 (4)	0.63 (4)	0.63 (4)
VIP block 2	1.41 (1)	1.29 (1)	1.48 (1)	1.50 (1)	1.42 (1)	1.42 (1)
VIP block 3	0.88 (2)	1.10 (2)	0.80 (3)	0.86 (2)	0.84 (3)	0.84 (3)
VIP block 4	0.86 (3)	0.77 (3)	0.85 (2)	0.78 (3)	0.94 (2)	0.94 (2)
R ² X	67.2%	54.9%	73.5%	64.7%	65.5%	68.7%
R ² Y	22%	18.2%	32.6%	33.5%	42.7%	20.5%

R²X= the explained variation in the X-block, R²Y= the explained variance in the Y-block.

Sick leave related to disease activity and disability (Study IV)

When predicting sick leave during the third year after diagnosis, the model identified a high number of days with sick leave during the first year before diagnosis as an important predictor. Other important predictors were impairment in the lower extremities (due to SOFI-lower), activity limitation according to HAQ and high pain intensity at M12. The number of days with sick leave during the second and third year before diagnosis was also an important predictor for later sick leave (**Table 10**).

Furthermore, wellbeing at M12, GAT at M0 and M12, SOFI-lower and HAQ at M0 and ESR at M12 were predictive variables. Type of work at diagnosis was also important for sick leave; working with administration or computers, i.e., low physical workload, was negatively correlated to high sick leave. A medium heavy type of work was an important regressor of sick leave during the third year after diagnosis. As also seen from Table 10, education was important for sick leave; upper secondary school was negatively correlated to high sick leave and compulsory school positively correlated.

Variables indicating disease activity (i.e., PGA, ESR, CRP, Anti-CCP and swollen or tender joints) were not identified as important in the prediction of sick leave (with the exception of ESR at M12) (**Table 10**).

Table 10: The variables important to sick leave during the third year after diagnosis. Variables with VIP-value >0.8 were defined as significant predictors. The sign “+” indicates a positive correlation to high sick leave and “-“ a negative correlation to high sick leave.

Variable	Pos (+) or neg (-) correlation	VIP-value
Sick leave during the first year before diagnosis	+	2.8
SOFI-lower M12	+	2.1
HAQ M12	+	2.0
Pain intensity M12	+	1.9
Sick leave during the second year before diagnosis	+	1.9
Sick leave during the third year before diagnosis	+	1.7
Administration/computer work	-	1.4
Wellbeing M12	+	1.4
GAT M0	+	1.4
Age	+	1.3
GAT M12	+	1.2
Medium heavy variable type of work	+	1.0
Upper secondary school as highest education	-	1.0
SOFI-lower M0	+	1.0
ESR M12	+	0.9
HAQ M0	+	0.9
Compulsory school as highest education	+	0.8
R²/Q²		0.44/0.33

SOFI =Signals of Functional Impairment; HAQ=Health Assessment Questionnaire; GAT=Grip Ability Test; ESR= erythrocyte sedimentation rate; M0= time for diagnosis; M12= 12 months follow-up.

Disability in RA in women compared to men (Study I-IV)

Hand function, assessed by SOFI, was worse in men than in women and women had significantly lower grip force than men (Study I and II). The course of HAQ differed significantly between women and men, indicating more profound activity limitations in women compared to men (Study II).

In women, the HAQ score improved significantly from M0 to M12 and then remained stable until M60 when it deteriorated significantly. In men, the HAQ score also improved significantly during the first year, but thereafter was stable without any significant changes. In Study II, the multivariate cross-sectional correlation analyses indicated that when predicting HAQ with different aspects of hand function, sex does not change the relationship between the variables. Pain intensity improved in both women and men during the first three months after diagnosis. The course of pain intensity during the five years after diagnosis did not differ significantly between women and men.

The total sick leave did not differ between men and women for the three years before diagnosis through the three years after diagnosis. In the multivariate analyses, the predictors for sick leave differed between women and men. The important predictors (VIP>0.8) for sick leave in women were almost identical to the model comprising the total study group, but the analysis identified some additional predictors; grip force at M12 and type of work were important predictors. In men, type of work was important. Working with administration or computer work was negatively correlated to sick leave after three years and identified as an important predictor. In men, more variables concerning disease activity were identified as significant predictors (ESR at M12, PGA at M12 and swollen joints at M0) (**Table 11**).

Table 11: Order of the variables important when regressing sick leave during the third year after diagnosis in men and women. Variables with VIP-value >0.8 were defined as significant predictors. The sign “+” indicates a positive correlation to high sick leave and “-” a negative correlation to high sick leave. M0 indicates diagnosis/inclusion in TIRA and M12, the 12-month follow-up.

Order of predictors	Women			Men		
	Variable	Pos (+) or neg (-) corr.	VIP	Variable	Pos (+) or neg (-) corr.	VIP
1	Sick leave during the first year before diagnosis	+	2.8	Sick leave during the first year before diagnosis	+	2.2
2	SOFI-lower M12	+	2.2	Administration/computer work	-	2.1
3	HAQ M12	+	2.2	Pain intensity M12	+	2.1
4	Pain intensity M12	+	1.8	ESR M12	+	1.9
5	Sick leave during the second year before diagnosis	+	1.7	Sick leave during the second year before diagnosis	+	1.9
6	GAT M0	+	1.6	HAQ M12	+	1.9
7	Sick leave during the third year before diagnosis	+	1.4	Wellbeing M12	+	1.8
8	HAQ M0	+	1.3	Sick leave during the third year before diagnosis	+	1.7
9	Age	+	1.2	SOFI-lower M12	+	1.5
10	Medium heavy variable type of work	+	1.2	Grippit M12	+	1.4
11	Grippit M12	+	1.2	GAT M12	+	1.3
12	Wellbeing M12	+	1.1	Heavy material handling as type of work	+	1.3
13	GAT M12	+	1.1	Light repetitive type of work	+	1.2
14	Upper secondary school as highest education	+	1.1	SOFI-hand M0	+	1.0
15	SOFI-lower M0	+	1.0	Grippit M0	+	0.9
16	Administration/computer work	-	1.0	PGA M12	+	0.9
17	Compulsory school as highest education	-	0.9	Age	+	0.9
18	SOFI-upper M0	+	0.8	Other significant education	+	0.9
19				Number of swollen joints M0	+	0.8
20				CRP M12	+	0.8
			0.43/			0.56/
			0.31			0.36

SOFI=Signals of Functional Impairment; HAQ=Health Assessment questionnaire; GAT=Grip Ability Test; ESR=Erythrocyte Sedimentation Rate; PGA=Physician's Global Assessment of disease activity; CRP=C-Reactive Protein

Disability in RA compared to referents (Study II and IV)

Study II demonstrated that hand function in patients was significantly decreased in comparison to referents (**Figure 8**). When considering the relation between activity limitation (measured by HAQ) and hand function, the HAQ score was explained by different variables in referents than in the patients. In the referents, HAQ was mainly related to age and GAT; in the patients, HAQ was most obviously linked to grip force.

Looking at sick leave, there were no significant differences between the RA patients and the matched referents the first two years before diagnosis. Six months before diagnosis was when the patients' sick leave started to increase. Thereafter, significantly more patients had sick leave compared to referents during the following study period (**Figure 10**).

DISCUSSION

The intention in this thesis was to describe disability in RA including body functions and structures as well as activities and participation. The variables used in the thesis cover all components in the ICF even though the body functions and structures together with activity and participation were in focus (**Table 3**).

Methodological considerations

External validity

The TIRA project is neither an incidence study nor an experimental study. The design of the project is a prospective longitudinal observation study that attempts to identify patterns of correlations and describe various characteristics (114). Studies with a quantitative design can be assessed in terms of validity. The external validity refers to what extent the results can be generalized to other settings. The external validity, for example, can be threatened by sample characteristics (114). The TIRA cohort is comparable to other early RA cohorts (93-97) concerning incidence rate, age and female-to-male ratio, similarities that can increase the possibility to generalize the results. However, there are some identified risk factors for RA such as smoking and educational level (8-11), which we have not considered in the present studies. Although nothing points at it, this may hypothetically affect the generalisation of the findings to other samples with RA.

Enrolment in the TIRA project was based on either fulfilment of $\geq 4/7$ of the 1987 revised classification criteria by ACR (12) or at least: 'morning stiffness ≥ 60 minutes, symmetrical arthritis, and arthritis of small joints' (34). The inclusion criteria beyond the ACR classification could possibly introduce a threat to generalisability. However, the use of the ACR criteria in early RA is questionable since they are based on patients with longstanding RA (12). The criteria have been found to be less sensitive for detecting early RA (13), but they are useful in predicting a clinically more severe disease (115). Several patients not fulfilling the ACR criteria at onset develop the disease over time (102).

Despite the 'generous' criteria for inclusion in the TIRA project, $>95\%$ of the TIRA patients met the ACR criteria. Further, the TIRA cohort is comparable to other cohorts according to disease activity and disability. At time of diagnosis, the TIRA patients had an average value of 5.2 (sd 1.2) in DAS-28, a value that is comparable to an Austrian early RA cohort with an initial value of 5.5 (95). The corresponding values after 12 months were 3.7 in the TIRA cohort and 3.2 in the Austrian cohort, indicating a similar disease course. Using six European studies, Scott et al. (1) calculated the mean value of HAQ at time of diagnosis to be 0.92 and after three years to be 0.74, which can be compared with the TIRA cohort with the corresponding values 0.89 and 0.67.

Referents were selected in two of the studies (II and IV). The rationale for including referents in two of the studies was to control for the context and isolate the impact of RA on hand function and activity limitation (Study II) and sick leave (Study IV). Two different selection strategies were used. In Study II, the number of referents was set to

120 (50% women) and then expressed as percentage of each age group according to the distribution in age groups in the TIRA cohort. A sample size calculation (116) showed that the number of referents were sufficient to detect differences between the groups. The major part of the referents was employed at the hospitals in the County of Östergötland. To increase the generalisability, a randomised selection from the Swedish population had been desirable. Nordenskiöld et al. (28) presented reference values for grip force (229 N (sd 64) in women and 432 N (sd 96) in men), values that differ from the referent values in Study II (198 N (sd 66) in women and 343 N (sd 110) in men). Grip force is dependent on age (117), which differed between the two studies and might explain some of the differences regarding reference values.

In Study IV, the referents were randomly selected from the Swedish population and matched to a TIRA patient on individual basis with respect to sex, age, and hometown. The 1:1 ratio between referents and patients was based on a sample size calculation. Sick leave among the referents was not equal to the proportion of sick leave in the Swedish population at this time; this discrepancy partly occurred because of another age distribution among the referents (due to the matching to the TIRA patients) and the higher proportion of women. Both age and female sex are factors known to alter sick leave rate (62, 118).

Statistical conclusion validity

Statistical conclusion validity refers to considerations in connection to the data evaluation and includes topics such as statistical power, reliability of assessments, statistical analyses methods and multiple comparisons (114). In the studies including referents (Study II and IV), power has been an issue since the design of the study was developed. The number of referents was calculated to detect differences between patients and referents based on earlier reported results, and/or expected values for the different outcomes.

The assessments used in the TIRA project were selected to describe a wide range of aspects of health representing disease activity, different parts of disability and contextual factors. Since the TIRA project is accomplished in the clinical routine, the intention was also to use assessments of relevance both for clinical work and for research. The reliability and validity of the assessments were also taken into consideration. With few exceptions the assessments used have been evaluated. Because walking time, used in Study II, has not been evaluated and since it showed a skewed distribution, it was omitted from further analyses. SOFI, which has been tested for validity and reliability with satisfactory results (104), has not been widely used, but is easy to perform and has showed predictive qualities in Study II and III. The assessments in TIRA are closely related to the proposed core sets based on the ICF (51) and cover body function and structures as well as activities and participation (**Table 3**). The assessments in the TIRA project were selected during 1995, when the options to assess disability were rather limited. Today we have a broader range of assessments to choose from. This, in combination with consideration of the patient's perspective (54, 56) should probably result in more assessments related to participation and contextual factors, if a new selection was to be done today.

Different statistical methods have been used in the different studies. In Study I, we used non-parametric methods to describe the course of hand function. The non-parametric methods were used since for example SOFI is based on an ordinal scale. Furthermore, in Study II-IV, we chose parametrical tests. To use parametrical tests such as Student's t-test, data should be continuous, the standard deviation in each group compared should be comparable, and observations in each group should have a normal distribution (119). Although the originators to HAQ (48) and SOFI (104) use parametric statistics in the development, the scale can be discussed in this perspective. To scrutinize the impact of parametric statistics to describe course and differences between women and men in Study II-IV, the analyses have been remade with non-parametric statistics; the results showed no difference.

Correction of multiple tests has been recommended to improve the statistical conclusion validity (120). In this thesis, correction for multiple tests has not been used consequently since the use of these methods is debatable (121). The traditional Bonferroni method is often overly conservative and results in a loss of statistical power (120). However, there are other, less conservative methods. In Study II, we used Tukey's correction method, which has a 'weaker' control. Regardless of method, the aim with these corrections is to avoid false positives when several dependent or independent statistical tests are being performed simultaneously; in other words to avoid type I errors (to reject the null hypothesis when the null hypothesis is in fact true) (116). These corrections may also create some problems. For example, type I errors cannot decrease without increasing type II errors (122) (the probability of accepting the null hypothesis when the alternative is true) (116). Adjustments for multiple comparisons should be applied when we are interested in the universal hypothesis (121). If we are interested in a specific hypothesis, Bonferroni (or the softer method Tukey used in Study II) adjustment has restricted application (121). The recommendation, which we have used in Study I, II and IV is instead to describe, why and what tests were carried out and which level of significance was preferred (121). We also focused on trends in differences in, for example, the course of hand function between women and men rather than significant differences at a specific follow-up.

In Study II-IV, we used different multivariate methods, all based on projection methods (PCA and PLS) not widely used in health-related research. These methods are developed and foremost used in industry with application areas such as process monitoring, quality control and multivariate calibration. In some aspects the methods are adjusted for these application areas, which is a weakness to be aware of. The advantages of PCA and PLS – such as they do not require interval scale data, are not sensitive to violations of multivariate normality, have no assumptions about independence of cases, are not hampered by collinearity among the variables and may be used with small sample sizes (112) – make the methods very useful in health-related research. The data used in this kind of research – e.g., from the TIRA project – are often dependent variables for relatively small groups that often have some missing values and have different levels of scales. PCA and PLS has earlier been used in occupational therapy (123), rheumatology (124) and psychology (113) research.

Henningson et al. (113) mentioned PCA and PLS as important new methods in their research in clinical psychology and psychotherapy. They put these methods into a context of model development and revealed a hard modelling approach and a soft modelling approach. Hard modelling proceeds from predetermined assumptions and solely relies on theory or earlier research. Soft modelling, on the other hand, is less prejudiced and relies more on empirical knowledge. PCA and PLS can be seen as soft modelling approaches that focus on over viewing data and classification and/or discrimination among groups of subjects (111). Therefore, these methods give us the opportunity to connect theory with clinical knowledge. We can use our clinical experience to identify relevant variables, include a broad range of other variables and use this soft modelling approach to evaluate their multivariate relationships (113).

In terms of advantages with PLS and PCA plus hard and soft modelling approaches, alternatives to these methods can be discussed. Factor Analysis (FA) is widely used and has many similarities to PCA. Although both are data reduction techniques, there is an important difference in the aim of reduction. FA finds the factors that explain the inter-correlation among the variables, whereas PCA reduces the number of variables to a few components that form new independent variables and explain the maximum possible variation. Because there are no assumptions about common factors explaining the correlations in PCA, this refers to a soft modelling approach (113). Furthermore, Multiple Linear Regression (MLR) is an alternative to predict activity limitation (Study II), pain intensity (Study III) or sick leave (Study IV), but MLR is less stable in presence of collinearity in the independent variables and larger sample sizes are needed to achieve high power (111). MLR can be seen as a more hard modelling approach considering the separate variables rather than the multivariate correlations among them. Harrison (13) and Visser (125) highlight the use of multivariate evaluations to describe the course of RA. By using PLS and PCA as more soft modelling approaches, we obtained knowledge of the complex unprejudiced relationship between the variables.

General discussion of the results

Course of disability

Study I, II and III reported that disability improved considerably during the first months after diagnosis. This has partly been reported earlier in the Swedish TIRA cohort as several disease activity measures (ESR, CRP, DAS-28, and PGA). In addition, activity limitations assessed by HAQ improved considerably within the first three months after diagnosis and then remained essentially stable (20). One obvious explanation for the improvement is the effect of early pharmacological treatment. However, in Study I, the 25 patients who were not treated with DMARDs at any time during the study period showed similar significant improvements in hand function within the first three months after inclusion (data not presented). The patients in the TIRA project also met a multi-disciplinary team from the time for diagnosis and were offered interventions. Since the TIRA project is not an intervention study, it is not possible to evaluate the effect of distinct therapy regimens. Anyway, the improvements in disability despite medical treatment highlight the importance of interventions from the multi-disciplinary team. The role of

the multi-disciplinary team has earlier been identified as important in the life of patients with RA (82).

Early improvements during the first months were also seen in pain intensity in Study III. However, even if improvement were seen in the whole TIRA cohort, an analysis on individual basis showed that about 20% of the patients reported moderate to severe pain intensity at all three follow-ups during the initial six months (M0-M6). Sixty-seven percent of these patients reported pain intensity > 40 mm VAS at the five-year follow-up. According to Burckhardt et al. (126), one goal with interventions is to reduce the pain intensity in patients with RA below 40 mm on a VAS. This goal was not used in the clinical routine in the TIRA cohort, but can be seen as a theoretical goal. The results from Study II showed that this goal was not achieved, since a subgroup of patients reported more than 40 mm pain intensity during the whole study period. Being unable to reduce pain intensity has been reported as an issue by the patients (127). The relatively high proportion of patients with high pain intensity is alarming from the perspective that high pain intensity increases the risk of widespread pain conditions. This is known to be associated with prominent negative consequences with respect to prevalence of other symptoms including depression, reduced quality of life, and participation in the society (128).

Interestingly, the course of sick leave reported in Study IV did not follow the same early improvements as the other variables, since it did not improve to the same extent directly after diagnosis. This pattern of sick leave has also been identified in other European studies (37, 38) and may indicate the complexity of relations between the health condition (RA), body functions and structures, activities, participation and contextual factors according to ICF (24). The dynamic interaction among the parts in ICF is not a one-to-one relationship. Consequently, early interventions at time for RA diagnosis, may for example affect activity limitations and impairment without improving participation restrictions. This highlights the need for detailed knowledge about the complexity, in order to provide effective interventions specifically aimed at reducing participation restrictions.

Although sick leave has been identified as an outcome variable of health (129), it is also a variable that is affected by society due to for example economic services, systems and policies. During the study period, some major changes were made in the work-related systems, possibly affecting the rates of sick leave in the study group. For instance, the number of days compensated by the employer in the beginning of a sick leave spell was changed from 14 to 28 between 1997 and 1998. The regulations for disability pension have also changed, and from 1997 it is based on assessment strictly in relation to the medical conditions of the individual (130). Sick leave is often used as an outcome measure of social consequences of the person with a disease (131). Although, the degree of overlap between illness (the ill health the person identifies themselves with) and disease (a condition that is diagnosed by a physician) in relation to sick leave has been identified as rather low (132). This may explain the different trends over time regarding sick leave and other aspects of disability among the TIRA patients. This means that sick leave is not only an outcome of disability but also of for example the type of work (as seen in Study IV)

and work demands (132) or of other environmental factors such as the physician's role in handling the sickness certification (133).

Relations between different aspects of health

In Study I, we evaluated three aspects of hand function – grip ability, grip force and range of motion. Although statistically significant, the correlations found between the instruments were weak, suggesting that they assess different aspects of hand function. It is likely that other aspects may also be relevant to hand function. A model of the functional assessment of the hand has been developed for hand-injured clients (134) with a framework valuable also regarding patients with RA. The model identifies four main components: personal constraints (physical and psychological status), hand roles (unimanual and bimanual), hand actions (reach, grasp and manipulate objects) and task parameters (object, movement pattern and performance demands). Based on this model, Grippit assesses strength included in the 'physical status', and SOFI-hand assesses range of motion also included in the 'physical status'. GAT, however, is to be found in several parts of the model – 'hand roles', 'hand actions', and also 'task parameters'. One part of the model not measured in the TIRA project is the 'psychological status', which includes motivation and self-perception of hand function (134). A self-assessed aspect of hand function could have been an interesting complement together with self-reported pain intensity in the hands. Since the ability to perform activities with the hands also depends on will and motivation (135), it would also be interesting to study the patients' experiences of their hand function in daily activities and correlate this to the assessed hand function.

In Study II, the relation between hand function and activity limitation (i.e., GAT, grip force and SOFI-hand in relation to HAQ) were evaluated. Our results support that grip force is an important predictor of HAQ both in a cross-sectional and a longitudinal perspective, with grip force being the most prominent predictor. In contrast, Dellhag and Bjelle (32) identified a stronger correlation between grip ability and HAQ than between grip force and HAQ in patients with longstanding RA (disease duration 6-10 years). The explanation for this discrepancy is not immediately obvious. HAQ was only explained to a small extent by hand function at time of diagnosis. In line with previous reports (136), baseline HAQ was the best predictor of HAQ five years later. Tightly following baseline HAQ, we showed that grip force at baseline was the most important predictor of five-year HAQ, a finding that strengthens our notion that HAQ strongly depends on grip force (124). In accordance to Häkkinen et al.(137), we found that impairment in the lower extremities (SOFI-lower limb) was an important predictor of HAQ at the five-year follow-up. Furthermore, agreeing with previous studies (124, 138), our results showed that HAQ at the five-year follow-up was not explained by disease activity.

Weak relations between disease activity and disability were also found for pain intensity (Study III) and sick leave (Study IV). In the context of ICF, this relation represents the connection between the health condition and disability. The ICF states that the presence, for example, of an existing impairment depends on a cause, the health condition. But the cause may not be sufficient enough to explain the resulting impairment (24). The impossibility to explain pain intensity by disease activity, however, was not surprising

since the complexity of pain intensity is well known. It depends on underlying pathologic processes as well as factors such as sensitizing at different levels of the pain system, the psychological status, past pain experience, cultural background, environment, and genetics (139, 140), i.e., all components in the ICF. ICF has moved away from classification of the consequences of a disease to components of functioning (24). This can be interpreted as to focus on individual and his or her functioning as a complex system, instead of the disease and its impact on the individual. The new perspective adds complexity and challenges for the professionals working with rehabilitation.

The relation between disease activity and sick leave seems to vary. In Study IV, ESR at M12 was the only predictive disease activity variable. This variable was also identified by Young et al. (38). Anti-CCP has been identified as a predictor of disease (141) and disease course (99) and was therefore of interest as a predictor in Study IV, but it was not associated with sick leave. Our results generally agreed with other results implying that disease activity is not important for sick leave (142). As in Study II and III, SOFI-lower and HAQ were important predictors of sick leave. HAQ has been identified as a predictor of work disability (38, 118, 143), indicating the close relation between activity limitation and participation restrictions in the context of ICF (24). The strongest predictor of sick leave during the third year after diagnosis was sick leave before diagnosis. History of sick leave has also been identified as a predictor in other studies (123, 144).

An important issue in research on sick leave is to distinguish between the factors leading to a disease and the factors leading to sick leave, since a disease is not an immediate cause of sick leave (130). Work functioning should be assessed in the context of the barriers or hindrances in the work situation rather than the severity of a disease or disability (130, 145). In Study IV, we identified the degree of physical demand in work to be of importance for sick leave. Manual work (146), non-professional or non-administrative work, and a physically demanding work (143) have earlier been found to be important for sick leave among RA patients. Furthermore, a physically demanding work and low educational level are closely associated (62, 147), which also was shown in Study IV. Age is a well-known factor associated with increased sick leave in the general population (148) as well as among patients with RA (118, 143), and Study IV confirmed the importance of this factor. Although it is well known that RA causes an economical burden for the patient and his or her family (42, 43), the annual income was not identified as a predictor of sick leave. The number of children living at home and marital status have earlier been identified in the general population as factors not related to sick leave (130); this agrees with our results.

The included variables in the analysis (Study IV) explained 44% of sick leave three years after diagnosis of RA. In other words, 56% is still unexplained partly due to missing important variables in the TIRA project and therefore not included in the analysis. For example, the degree of psychosocial demand and sense of control at work has in general been identified as related to sick leave (130, 149). In RA, the possibility to adjust the physical environment (40), the work tasks and working hours (38, 40) are important even if not considered in the present study.

Disability in RA in women compared to men

It is well known that women with RA have a more severe disease course than men (13, 58), a finding confirmed by HAQ (Study II). However, in the studies on pain intensity (Study III) and sick leave (Study IV), sex was not identified as an important variable or predictor in the multivariate analyses. Concerning pain intensity, our findings disagree with earlier studies where pain has been reported more frequently by women (150). There may be several reasons that sex was not seen as influential. One is that differences may not be reduced only to biological differences between the sexes. As Thyberg et al. (151) argued, the differences in activity limitations between women and men with RA can be explained by grip force rather than by sex per se or by differences in the disease activity.

Since the 1970s, Swedish women are in general more on sick leave than men (130). We did not find this difference among RA patients. One explanation may be that there were significantly more men than women ($p=0.036$, calculated with Mann-Whitney U-test) in the sample that worked in the category 'heavy material handling' (32% in men and 4% in women). It has earlier been shown that high physical demands at work is a risk factor for sick leave in patients with RA (90). Although men in general are employed in jobs with a higher physical loading than women (152), being diagnosed with RA may make the performance of the work more difficult. Also, even if a health condition like RA affects the work functioning, being on sick leave or not is also determined by contextual factors including for example the possibility of adjustments of work tasks and working time or pace. A low possibility of adjustments at work has been identified to be associated with an increased risk of sick leave (153). Possibility of adjustments varies from work place to work place, and women and men have different types of jobs implying different opportunities to adjust (154). A question that can be raised in this context is whether the possibility to make adjustments at work is higher at workplaces or sectors with lower physical workload, and also dominated by women. Among the patients with RA, significantly more women ($p=0.036$, 65% women and 36% men) were employed in jobs categorized either as 'light repetitive' or 'administration/computer work' including for example childcare, assistants, secretaries or teachers. In the perspective of this question, women with RA may have greater possibilities to adjust their workplace with the aim to continue work even after diagnosis of RA. This may be one other explanation of why women with RA in Study IV are not more on sick leave than the men in the study.

Disability in RA compared to referents

Since healthy men on average have higher grip force than healthy women (28), it was no surprise to find that also among patients with early RA men had significantly higher grip force. Nordenskiöld and Grimby (28) found that women with RA (mean age 55 years) of a disease duration of 5-32 years (mean 12) had about 80% reduced grip force compared to healthy women. In Study I, the corresponding reduction was about 70% at diagnosis and about 50% later in the course of disease in relation to the same normative data. Comparison of the two studies in this respect is difficult due to differences in the study populations, for instance regarding age and disease duration at inclusion and the different interventional strategies.

Interestingly, in the cross-sectional perspective, HAQ was explained by different hand function variables in referents compared with RA patients at baseline and after five years. Hence, GAT was the strongest predictor of HAQ in the referents, whereas grip force was the strongest predictor in RA patients.

As it comes to sick leave, there were no differences in either sickness benefit, rehabilitation benefit, or disability pension in patients with RA compared to referents until six months before diagnosis when sick leave among the patients started to increase. This indicates that the 'becoming patients' are not different from the referents due to sick leave until their symptoms of RA arise. Since the inclusion criteria in TIRA did not allow symptoms more than 12 months prior to enrolment, this may explain the increased sick leave among the TIRA patients before diagnosis.

CONCLUSIONS AND ADDED KNOWLEDGE

- Disability in RA is most pronounced at time for diagnosis. Disability is reduced during the following three months and thereafter disability remains stable until the five-year follow-up. The exception is sick leave, which is affected at diagnosis and thereafter stable during three years.
- Activity limitation, pain intensity and sick leave in RA that represent different aspects of disability are explained by other aspects of disability and contextual factors rather than by disease activity. The used multivariate methods were useful to illustrate these complex relationships.
- Women and men are affected differently by RA in some aspects of disability. Women have significantly more activity limitations than men according to HAQ. Men are more affected than women regarding range of motion in their hands. Although statistically significant, the clinical significance of these differences is debatable. No differences were seen between women and men in pain intensity and sick leave. The set of significant variables that predicted later disability included some different variables in women compared to in men.
- Patients with RA have pronounced disability in relation to referents even though several variables improve soon after diagnosis.

These results add knowledge to disability in early RA by indicating the need for early assessment of impairment, activity limitation and participation as complement to disease activity in clinical routine when planning interventions in relation to the patient's functioning. Participation, in this thesis represented by sick leave, needs to be in special focus in clinical assessments and intervention planning since it does not follow the same pattern of early improvement.

The availability of referent values for GAT and SOFI hand function and referent values for HAQ in a Swedish population is important when interpreting disability in clinical practice and in research. The extent of disability in hands and activity limitation should be interpreted in relation to expected levels in women and men when planning interventions.

FURTHER RESEARCH

Since the Swedish TIRA project started in 1996, there are new effective disease modifying therapies available. This makes the TIRA cohort a unique historic reference cohort. In 2006, a new cohort, TIRA-II, was launched and 500 patients will be included. The aims in TIRA-II are similar to those in TIRA: providing early multi-disciplinary interventions and establishing a database for research including genetic markers, contextual factors, disease activity, disability and costs. The TIRA project offers a unique possibility for comparison between treatment strategies and outcome ten years ago with today's strategies and outcomes in many aspects.

As a consequence of the findings in this thesis based on TIRA, further research regarding sick leave is ongoing. Due to experiences from TIRA, some adjustments have been done in the collecting of data in TIRA-II. In TIRA-II, a number of variables are added that are supposed to be of importance for sick leave such as personal factors including for example coping strategies and environmental factors including the work situation. This might shed more light on the relationships between aspects of health and sick leave, providing the possibility for early identification in clinical practice of patients at risk for high sick leave.

SAMMANFATTNING PÅ SVENSKA

Reumatoid artrit (RA; ledgångsreumatism) är en kronisk och progressiv sjukdom som ofta leder till funktionshinder av olika grad. Redan under de första åren utvecklas funktionshinder och det finns ett behov av ökad kunskap om den tidiga sjukdomsutvecklingen för att kunna minimera graden av funktionshinder senare under sjukdomsutvecklingen. Studierna i avhandlingen beskriver en femårsuppföljning av patienter med RA och beskriver utvecklingen av funktionshinder vid tidig RA, speciellt avseende handfunktion, smärtintensitet, aktivitetsbegränsning och sjukfrånvaro. Syftet var också att jämföra funktionshinder hos män och kvinnor med RA, att identifiera och beskriva relationer mellan olika aspekter av funktionshinder och jämföra funktionshinder vid RA med referenter.

Studierna är baserade på data från det tidiga artrit projektet TIRA (Tidiga Insatser vid Reumatoid Artrit) som startades som ett samarbetsprojekt mellan 10 reumatologenheter i Sydöstra sjukvårdsregionen. Under strukturerade uppföljningar från tidpunkten för diagnos av RA bedömdes patienternas hälsa ur ett flertal aspekter såsom sjukdomsaktivitet och funktionshinder under åtta år från 1996 till 2006. 320 patienter inkluderades i projektet och aktuella studier baseras på de patienter som fortfarande deltog i projektet efter tre respektive efter fem år. Referenter inkluderades i två av studierna för jämförelse data gällande aktivitetsbegränsning enligt Health Assessment Questionnaire (HAQ), handfunktion och sjukfrånvaro.

Studierna visade att funktionshinder vid RA är mest uttalade vid diagnostillfället. Därefter minskar funktionshindret något under de följande tre månaderna för att sedan stabiliseras. Undantaget är sjukfrånvaron som ökar precis innan diagnostillfället för att sedan stabiliseras. Aktivitetsbegränsning, smärtintensitet och sjukfrånvaro vid RA representerar olika delar av funktionshinder och förklaras av olika aspekter av funktionshinder samt kontextuella faktorer snarare än sjukdomsaktivitet. Kvinnor och män påverkas olika av sjukdomen ur vissa aspekter. Kvinnor har en sämre sjukdomsutveckling gällande aktivitetsbegränsning bedömt med HAQ och män påverkas mer vad gäller rörelseomfång. Utvecklingen av smärtintensitet och sjukfrånvaro var däremot inte olika mellan kvinnor och män med RA. I relation till referenter hade patienter med RA betydande mer funktionshinder vad gäller handfunktion, aktivitetsbegränsning och sjukfrånvaro trots förbättringen direkt efter diagnostillfället.

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