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# **Disease and disability in early rheumatoid arthritis**

*A 3-year follow-up of women and men in the Swedish TIRA project*

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# ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which often leads to disability. This study is based on three years' follow-up data generated by patients included during 27 months 1996-1998 in a Swedish multi-centre project named 'early interventions in rheumatoid arthritis' (TIRA). Disease activity, disability and health-related quality of life (HRQL) were assessed by clinical and laboratory analyses, and self-reported estimations. The course during three years and relations between clinical/laboratory assessments versus HRQL were studied separately in women and men. The relation between grip force and self-reported activity limitations was analysed, and finally the use and effects of assistive devices were evaluated separately for women and men.

Clinical/laboratory assessments and self-reported HRQL were substantially affected at the time for diagnosis, but the relations between clinical/laboratory assessments and self-reported HRQL were weak. Among the studied clinical/laboratory variables used here grip force, walking speed, and possibly physician's global assessment of disease activity showed most stable relationships with the HRQL. However, the time course of clinical/laboratory and self-reported HRQL measurements followed similar patterns. Thus, most variables had improved considerably at the 3- and 6-months' follow-ups and then remained stable but still affected over three years. An exception was the SF-36 scale 'general health', which was reduced to the same extent during the whole study period. As judged by the 'Health Assessment Questionnaire' (HAQ) and 'Evaluation of Daily Activities Questionnaire' (EDAQ), activity limitations were more pronounced in women than in men. By contrast, as reflected by 'Signals of Functional Impairment' (SOFI), men had slightly more affected function of the hands and upper extremities. Women with RA had about half of the grip force compared to male patients, which is in accordance with the differences between healthy women and men. At diagnosis, the grip force was reduced to about 30% in RA patients compared to healthy referents of the same sex. Already three months later, it improved but was still reduced to about 50% of healthy referents. Further analyses revealed that HAQ and EDAQ were strongly related to grip force independently of sex. Grip force below 114 N was found to be associated with substantial activity limitation in women as well as in men. Assistive devices (ADs) were more frequently used by women (78%) than men (54%), and were found to reduce activity limitations. The subgroups of women and men using ADs were comparable regarding disease activity and disability, and were generally more affected regarding activity limitations, compared to the subgroups that did not use ADs. Within the subgroups of patients using ADs, women and men had equivalent HAQ status and ADs were reported to reduce activity limitations in both women and men with recent-onset RA.

The weak relation between clinical/laboratory assessments and self-reported HRQL supports the results by others. By means of HAQ, more pronounced activity limitations have been reported previously in women with RA, compared to male patients. In the present study, similar differences were recorded by EDAQ. Further analyses showed that reduced grip force was closely related to activity limitations independently of sex. This offers a new explanation to poor female outcome recorded by HAQ.



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**Papers I-IV.**



# LIST OF PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

## I.

Thyberg I, Hass UA, Gerdle B, Skogh T.

Recent-onset rheumatoid arthritis: a 1-year observational study of correlations between health-related quality of life and clinical/laboratory data.

*J Rehabil Med* 2005;37 (in press; E-pub 21 January 2005)

## II.

Thyberg I, Hass UA, Nordenskiöld U, Skogh T.

A survey of the use and effect of assistive devices in patients with early rheumatoid arthritis: a two-year follow-up of women and men.

*Arthritis Rheumatism (Arthritis Care Res)* 2004;51:413-421

## III.

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).

*Scand J Rheumatol* 2005 (in press)

## IV.

Thyberg I, Hass UA, Nordenskiöld U, Gerdle B, Skogh T.

Activity limitation in rheumatoid arthritis correlates with reduced grip force regardless of sex (the Swedish TIRA project).

*Submitted*

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# ABBREVIATIONS

ACR	American College of Rheumatology
AD	assistive device
CRP	C-reactive protein
DAS-28	28-joint count disease activity score
DMARD	disease-modifying anti-rheumatic drug
EDAQ	Evaluation of Daily Activities Questionnaire.
ESR	erythrocyte sedimentation rate
GAT	Grip Ability Test
HAQ	Health Assessment Questionnaire
HRQL	health-related quality of life
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability and Health
ILAR	International League Against Rheumatism
IQR	inter-quartile range
NSAID	non-steroidal anti-inflammatory drug
OMERACT	Outcome Measures for Arthritis Clinical Trials
PCA	principal component analysis
PGA	physician's global assessment of disease activity
PLS	partial least squares or projection to latent structures
RA	rheumatoid arthritis
RF	rheumatoid factor
SD	standard deviation
SF-36	Short Form 36
SIMCA	soft independent modelling of class analogy
SOFI	Signals of Functional Impairment
SPSS	statistical packages for the social sciences
TIRA	Swedish acronym for 'early intervention in RA' (Tidig Intervention vid RA)
VAS	visual analogue scale
WHO	World Health Organization

# INTRODUCTION

## *Disease and disability*

Identification of signs and symptoms associated to defined disease states is the basis for establishing medical diagnoses and for deciding upon interventional strategies. The categorization of diseases proposed by the World Health Organisation (WHO) is published in 'International Classification of Diseases' (ICD) (WHO, 1997). As a consequence of the interplay between disease and environmental factors, many patients within a number of medical specialities are also afflicted by disability (Haglund, 1912; Thyberg, 2004), and in 2001 WHO presented a taxonomy of disability 'The International Classification of Functioning Disability and Health' (ICF) (WHO, 2001). The ICF aims at providing a basis to understand and to study health-related states, outcomes and determinants. A further aim was to establish a common terminology, to permit comparisons across countries and to provide a systematic coding for health information systems. ICF includes the components; body functions and structures, activity limitation and participation restriction, environmental factors, and personal factors. 'Disability' is the umbrella term for the negative aspects of 'body functions and structures', as well as for 'activity limitation and participation restriction'. Barriers/hindrances is the negative aspect of 'environmental factors', whereas the component 'personal factors' is not specified in the classification and therefore not applicable. In medical care, physicians mainly concentrate on the disease process and on interventions modifying the disease process and/or giving symptomatic relief. Occupational therapists, physiotherapists and social workers, on the other hand, highlight disabilities and barriers/hindrances as well as interventions directed to reduce the disabilities and to eliminate the barriers as a part of a rehabilitation programme. In clinical investigational practice, as well as in clinical research, a number of uniform generic as well as disease-specific assessments are employed to identify the type and extent of disease and disability respectively.

## *Rheumatoid arthritis (RA)*

RA is a chronic inflammatory disease often leading to disability (Scott et al, 2005). The classification of RA is presently based on the seven 1987 revised American College of Rheumatology (ACR) criteria, where at least four should be fulfilled in order to merit for a diagnosis of RA (Arnett et al, 1988). These criteria were originally validated for established disease, and also require symptom duration of at least 6 weeks, limiting the utility of the present ACR criteria in recent-onset disease (Visser, 2005). These shortcomings, together with the introduction of new sensitive and highly RA-specific diagnostic tests for antibodies against citrullinated proteins (Zendman et al, 2004) make it conceivable that new classification/diagnostic criteria will soon be suggested. The constitutive factors and events initiating RA are not fully understood, but it is known that complex hereditary factors as well as life style and exposure factors are of aetiological importance (Reckner Olsson, 2004; Klare-skog et al, 2004). Autoimmune reactions and impaired inflammation control are important for the pathogenesis and outcome of the disease (Sweeney & Firestein, 2004).

The yearly incidence of RA in Sweden is about 25/100.000 (Söderlin et al, 2002) and the prevalence in the adult Swedish population is 0.5-0.7% (Simonsson et al, 1999; Larsson et al, 1991). Overall, RA is about twice as prevalent in women as in men – the sex difference being most pronounced at young age (Masi, 1994). The peak incidence of RA occurs at about 40-60 years of age (somewhat lower average age in women than in men). Already early on in the disease, the inflammatory process leads to a multitude of functional limitations (Pincus et al, 1984; Sherrer et al 1986; Lindquist et al 2002; Young et al, 2000; Paper I; Paper II). Previous studies have described the course in early RA regarding the disease process and different aspects of health (Kroot et al, 2000; Jansen et al, 2001, Welsing et al, 2001; Lindqvist et al, 2002). Disability in RA diminishes within the first year after diagnosis and therapy, and then either remains stable but still affected (Welsing et al, 2001), or slowly worsens over time (Chea et al, 1996; Lindqvist et al, 2002). RA is also associated with a shortened life span, mainly due to coronary vascular disease

(Goodson et al, 2002; Watson et al, 2003). The course and outcome of RA is difficult to predict in the individual patient, but several factors have been identified as prognostic markers early in the disease, e.g. age (Glennås et al, 2000; Peltoma et al, 2000), pain score, serum levels of C-reactive protein (CRP) (Jansen et al, 2000), the presence of rheumatoid factor (Lindqvist et al, 2004), antibodies to citrullinated peptides (Kastbom et al, 2004), and activity limitations reported by the HAQ (Glennås et al, 2000; Jansen et al, 2000; Deighton et al, 1992). HAQ has been claimed to be the best predictor of life expectancy, compared to laboratory, radiographic and physical examination data (Wolfe et al, 2003).

### *Interventions*

Disease interventions can be divided into those that prevent, cure, reduce symptoms and/or rehabilitate. To date we know of only few possibilities of primary prevention regarding RA, although several exposure and occupational factors have been suggested (Reckner Olsson et al, 2004). Cigarette smoking has repeatedly been shown to be a risk factor for developing rheumatoid-factor- (RF-) positive RA, and recently it was reported that this risk is strongly related to the presence of ‘shared epitope’, i.e. a genetically determined structure in the antigen-presenting pocket of HLA-DR4/DR1 molecules (Padyukov et al, 2004). Estrogen is a factor, which may be protective against RA (Reckner Olsson et al, 2001; Doran et al, 2004) and which is known to ameliorate established disease (d’Elia-Forsblad et al, 2004). The most important pharmacological intervention strategy today is to institute disease-modifying anti-rheumatic drugs (DMARDs) as early as possible in the disease, which is known to improve the outcome (Scott et al, 2004). The ultimate goal of anti-rheumatic therapy in RA is to achieve complete remission. Although this is achieved in some patients, and others experience partial remission, the disease process still leads to tissue destruction and disability in many patients. Scott and co-workers also emphasised the importance of reducing disability and improving quality of life in RA, regarding the limited possibilities to achieve complete remission/cure in RA (Scott et al, 2005). Rehabilitation programmes for patients with RA aim at making it possible for them to perform activities at their optimal level. Describing this aspect of health in terms of ICF, this relates to ‘body functions and

structures' and 'activities and participation' (Vliet Vlieland, 2004). Based on the ICF definition, Cieza & Stucki propose that functioning, in a rehabilitation perspective, should not merely be regarded as an outcome, but also the starting point for the clinical assessments, interventions and evaluations (Cieza & Stucki, 2005).

When measuring outcome, many variables can be considered, and there is a growing interest to identify core sets, which can be used in clinical settings as well as in research. In 1999 the 'Outcome Measures for Arthritis Clinical Trials' (OMERACT) proposed that outcome assessments in arthritis should include a variety of aspects associated to the disease process. Hence, 5 core domains were recommended for longitudinal observational studies, i.e. 'health status', 'disease process', 'damage', 'mortality', and 'toxicity/adverse reactions' (Wolfe et al, 1999). Work disability and costs were also recognised as important. Furthermore, OMERACT gave examples of how to record the disease process, for instance by assessing the number of swollen and tender joints, global assessment of disease severity, and analysis of acute phase reactants. The health status domain was proposed to include questionnaires representing disease-specific and generic quality of life instruments as well as instruments regarding pain, fatigue, physical function, and psychosocial function. The domains that OMERACT constituted for outcome measuring are specific for arthritis.

Based on the ICF classification system, two core sets for measuring RA were proposed by 17 rheumatologists from 12 countries, one brief and one comprehensive (Stucki et al, 2004; Stucki et al, 2004). These core sets represent a selection of ICF categories that can serve as minimal standards for reporting of functioning and health in multi-professional assessments in RA. The ICF core set defines which aspects of health, that might be measured, but does not state how it should be performed (Stucki & Grimby, 2004). This is in contrast to OMERACT, ACR, and WHO/'International League Against Rheumatism' (ILAR), who all define both *what* to measure and *how* to measure by recommending instruments. ICF can thereby be used as a subset of the dimensions proposed to be included in the OMERACT, ACR, or WHO/ILAR.

Another way of classifying outcome measuring is to define aspects of health as judged by professionals, based upon laboratory tests and clinical assessments in contrast to aspects of health estimated by the patient. The patient's self-reported impression of health may be addressed as 'health-related quality of life' (HRQL), including suffering from pain, fatigue, and disability, and also broader aspects of emotional and social well-being (Garratt et al, 2002). The HRQL questionnaires quantify the impact of RA from a patient's perspective and direct the physician's attention to items that are important to the patient (Russak et al, 2003). The outcome variables, as exemplified by OMERACT to be used in observational studies, include professionals' judgements of laboratory tests and clinical assessments as well as HRQL questionnaires. The ICF core set identifies aspects to be measured and may include professional judgements as well as the patient's self-reported experience of health. By using ICF as a reference framework, it is possible to analyse which components that are covered and important outcome variables included in a study (Stucki et al, 2004).

### *Differences between women and men*

There is a growing interest concerning differences in outcome between women and men, and differences between sexes regarding the outcome of RA have been reported in a number of studies. In a recently published review Harrison and co-workers reported a higher risk of joint destruction, fewer extra-articular manifestations, and higher rates of depression in women than in men. Women were also seen to suffer more from pain and scored higher in HAQ than did men (Harrison, 2003). More pronounced disability in women compared to men has been reported using HAQ, both in early RA (Weyand et al, 1998; Tengstrand et al 2004) and in long-standing disease (Glennås et al, 2000), as well as regarding the course even when adjusting for severity of the disease and observed physical function (Affleck et al, 1999). Apart from sex, factors such as age, disease activity, and joint destruction correlate to HAQ (Young et al, 2000; Deighton et al, 1992; Katz & Criswell, 1996; Kuiper et al, 2001; Thompson & Pegley, 1991). Just as the case in a normative population (Frazer et al, 1999; Nordenskiöld & Grimby, 1993) women with RA have lower grip force than men with RA (Desrosiers et al, 1995; Sollerman, 1980;

Napier, 1956). There is a need for further studies that focus on sex differences, in order to optimise intervention strategies in women and men respectively (Harrison, 2003).

### *'Early intervention in rheumatoid arthritis'*

#### *(the Swedish TIRA project)*

As implied by the need for early diagnosis and early intervention in RA, the multi-centre project 'TIRA' started 1996 (Hallert et al, 2003) in co-operation between 10 rheumatology units in southeast Sweden. The main purpose was to establish clinical routines for early diagnosis and early multi-professional interventions, and to establish a research cohort for longitudinal observation. Clinical examinations were performed by physicians, occupational therapists, and physiotherapists and a database was created. In the TIRA study a wide range of different aspects are covered. This offers the possibility to combine analyses reflecting genetic markers, exposure and lifestyle factors, disease-specific markers, disease activity markers, tissue markers, disease-specific disability assessments, generic HRQL assessments, and costs. After inclusion in the study, regular follow-ups were performed after 3, 6, 12, 18 months, and then once a year. A number of studies based on the TIRA cohort have recently been published regarding for instance exposures and lifestyle (Reckner-Olsson et al, 2004; Reckner-Olsson et al, 2001), disease and disease activity markers (Rydén et al, 2002; Skogh et al, 2003; Kastbom et al, 2004), disease activity and disability (Hallert et al, 2003; Paper I; Paper II; Paper III), and health economy (Hallert et al, 2004).

The studies included in this thesis are all based on the TIRA cohort and the scientific rationales are related to disability and sex differences regarding outcome. In early RA, the knowledge is limited concerning aspects of health assessed by allied health professionals in relation to the patients' self-reported assessments. There is also a need to analyse the impact of hand function and grip force in women and men separately, and the relation between grip force and activity limitations. Further, the knowledge about the use and effect of assistive devices in women and men with early RA is restricted.

# AIMS

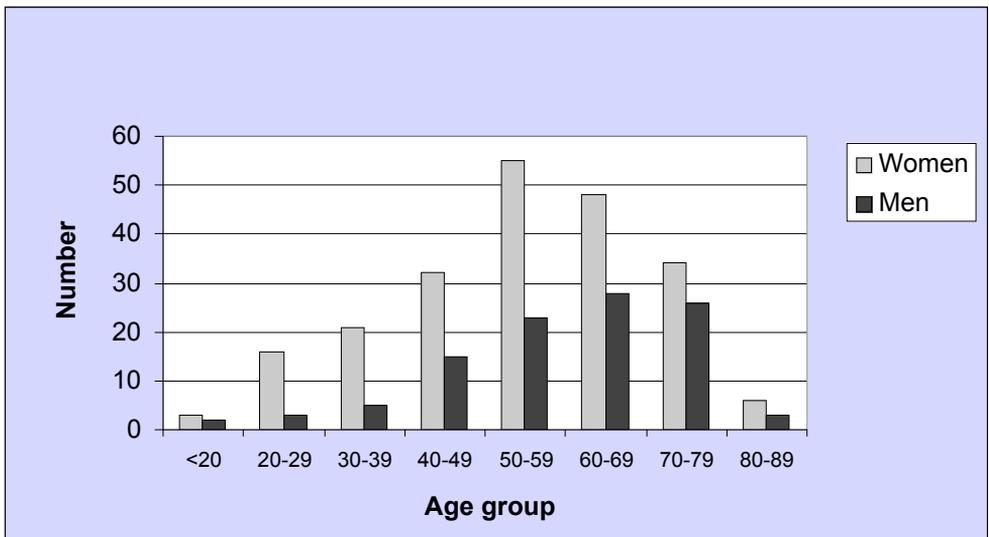
The aims of this project were:

- To describe early RA in terms of clinical/laboratory assessments and HRQL regarding
  - clinical and laboratory assessments of disease and disability as judged by professionals during one year from diagnosis.
  - self-reported HRQL during one year from diagnosis.
  - correlations between clinical/laboratory assessments and self-reported HRQL.
  
- To study disease and activity limitations considering
  - the extents of activity limitation in women and men with early RA.
  - the effect of ADs.
  - identification of signals indicating a need for early AD intervention.
  
- To study hand function with respect to
  - disease impact on hand function during the first three years after diagnosis of RA.
  - differences in hand function between women and men.
  - correlations between and within different hand function measures.
  
- To study activity limitations concerning
  - differences between women and men in the extent of activity limitations and grip force at the 36-months' follow-up.
  - the relation between activity limitations and grip force.

# PATIENTS AND METHODS

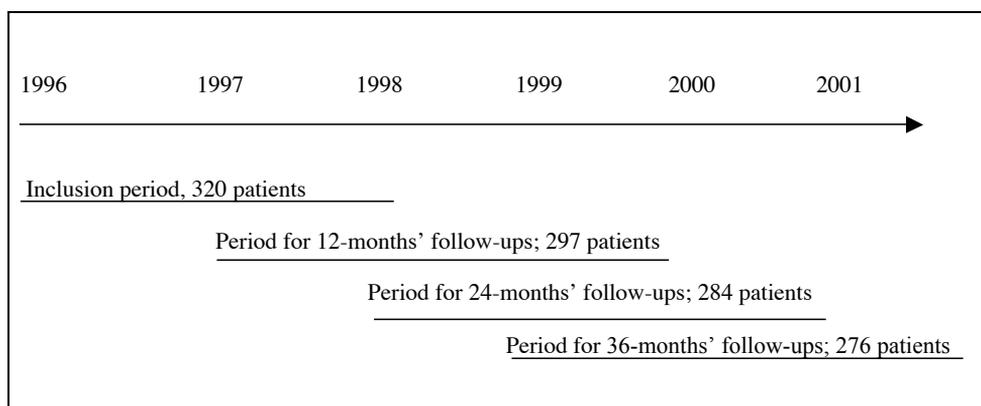
## *The TIRA cohort*

Totally, 320 patients with recent-onset ( $\leq 1$  year) RA were included in the Swedish TIRA project between January 1996 and March 1998, 215 women and 105 men (Figure 1). The first signs of arthritis (joint swelling) were observed by the patient at least six weeks, but not more than one year, before diagnosis. All patients fulfilled at least 4 of 7 criteria for RA as defined by the 1987 revised ACR classification criteria (Arnett et al, 1988) *or* suffered from morning stiffness (60 minutes or more as judged by the patients), and symmetrical arthritis, and arthritis in small joints of the hands and/or feet (metacarpo-/metatarso-phalangeal and/proximal interphalangeal joints or wrists). Particle-agglutinating rheumatoid factor (RF) was present in 60% of the sera at diagnosis.



**Figure 1.** Sex and age distribution of the 320 TIRA patients.

The four papers in this thesis are based on data from the time for diagnosis to the 36-months' follow-up in the TIRA cohort (Figure 2). The first paper is based on the 297 patients remaining in the study at the 12-months' follow-up, the second paper is based on the 284 patients remaining in the study at the 24-months' follow-up, and the third and fourth papers are both based on the 276 patients remaining in the study at the 36-months' follow-up (Figure 2). The 44 patients who dropped out during the period from diagnosis and inclusion to the 36-months' follow-up (24 women and 20 men) were significantly older than the study group, but there were no significant differences regarding the 28-joint count disease activity score (DAS-28) (Preevo et al, 1995) or HAQ (Ek Dahl et al, 1988). All patients gave written informed consent to participate and the local ethics committees of the participating units approved the study protocol.



**Figure 2.** Number of patients included during the years 1996 – 1998 and number of patients remaining at the follow-ups during the first three years.

### *Outcome variables*

In total, 25 outcome variables are considered in this thesis. One of the variables, DAS-28 (Prevo et al, 1995), is a composite index based upon four of the other variables. In the HRQL questionnaire 'Short Form-36' (SF-36) 8 of the 25 variables are subscales (Ware & Sherbourne, 1992). The variables are categorized as 'laboratory' or 'clinical' assessments or 'self-reported' HRQL. Table 1 lists all assessments, and states their category and how often the measurements were performed.

**Table 1.** Outcome assessments at the visits.

<b>Variable</b>	<b>Category</b>	<b>Visits</b>
ESR (mm/1st h)	Laboratory	All
CRP (mg/L)	Laboratory	All
Swollen joints (0-28)	Clinical	All
Tender joints (0-28)	Clinical	All
DAS-28 (score)	Composite index	All
PGA (0-4)	Clinical	All
Pain (VAS 0-100 mm)	Self-reported	All
Grip force (N)	Clinical	All
Morning stiffness (min)	Self-reported	All
GAT (0-276)	Clinical	All
SOFI-hand (0-16)	Clinical	All
SOFI-upper limb (0-12)	Clinical	All
SOFI-lower limb (0-16)	Clinical	All
Walking speed (sec)	Clinical	All
HAQ (0-3)	Self-reported	All
EDAQ (0-3)	Self-reported	12, 24, 36 months
Well-being (VAS mm)	Self-reported	All
SF-36 (8 scales):		
Physical function (0-100)	Self-reported	Diagn.,6 ,12,18, 24, 36 months
Role physical (0-100)	Self-reported	Diagn.,6 ,12,18, 24, 36 months
Bodily pain (0-100)	Self-reported	Diagn.,6 ,12,18, 24, 36 months
General health (0-100)	Self-reported	Diagn.,6 ,12,18, 24, 36 months
Vitality (0-100)	Self-reported	Diagn.,6 ,12,18, 24, 36 months
Social function (0-100)	Self-reported	Diagn.,6 ,12,18, 24, 36 months
Role emotional (0-100)	Self-reported	Diagn.,6 ,12,18, 24, 36 months
Mental health (0-100)	Self-reported	Diagn.,6 ,12,18, 24, 36 months

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DAS-28 = 28-joint count disease activity score (based upon the number of swollen and tender joints respectively, ESR and the patient's self-estimated general health on a visual analogue scale = VAS); PGA = physician's global assessment of disease activity; GAT = Grip Ability Test; SOFI = Signals of Functional Impairment; HAQ = Health Assessment Questionnaire; EDAQ = Evaluation of Daily Activities Questionnaire; SF-36 = Short Form 36.

### *Clinical and laboratory assessments*

Erythrocyte sedimentation rate (ESR) and CRP were used as laboratory markers of inflammation. A 28-joint count of swollen and tender joints was employed (Fuchs

& Pincus, 1994) and the physician's global assessment of disease activity (PGA) was reported (Scott, 1993). Grip force in the right hand was tested using a digital electronic device ('Grippit', Detektor AB, Göteborg, Sweden) (Nordenskiöld & Grimby, 1993). The average grip force value (N) during 10 seconds was recorded. The 'Grip Ability Test' (GAT) was performed as described by Dellhag & Bjelle (Dellhag & Bjelle, 1995). Functional impairment in hand (0-16), upper limb (0-12) and lower limb (0-16) were assessed by 'Signals of Functional Impairment' (SOFI) (Eberhardt et al, 1988) and 'Walking speed' was defined as the time it took to walk 20 m as fast as possible indoors, if necessary the patients used their own assistive devices.

### *Self-reported HRQL*

The patients estimated the duration of morning stiffness, and graded the average pain and well-being during the last week on a visual analogue scale (VAS). Disability, as evaluated by HAQ (Ekdahl et al, 1988) and by 'Evaluation of Daily Activities Questionnaire' (EDAQ) (Nordenskiöld et al, 1998) respectively, was reported at the time for diagnosis and at the 12-months' follow-up. Generic HRQL were reported by SF-36 (Ware & Sherbourne, 1992). The 8 scales in SF-36 consist of 4 physical scales ('physical function', 'role physical', 'bodily pain' and 'vitality') and 4 mental scales ('general health', 'social function', 'role emotional' and 'mental health') (Sullivan et al, 1994, manual Swedish).

### *Data collection*

The majority of data were collected at the visits except EDAQ, which was completed by the patient in her/his home and sent back by mail to the rheumatology unit.

### *Statistical analyses*

All statistics were performed using the statistical packages for the social sciences (SPSS) for Windows (version 10.0 or 11.5) or soft independent modelling of class

analogy (SIMCA-P) (version 10.0). For variables under investigation, median (Md) and inter-quartile range (IQR) or mean values and one standard deviation (1 SD) are reported. In all statistical analyses,  $p < 0.05$  was regarded as significant. Percentage distribution was calculated for ongoing medication and reported difficulties in EDAQ. Wilcoxon's signed ranks tests were used to test differences between related samples and Mann-Whitney U-test was used to test differences between independent samples. Test of differences between several samples was performed by Kruskal-Wallis test. Differences between the study group and a reference population was tested by the normal test. Principal component analysis (PCA) was performed to analyse the relationships between variables and Partial least squares or projection to latent structures (PLS) (Eriksson et al, 1999), was used to investigate the relationships between groups of variables. Subgroups of patients were identified by K-means cluster analysis.

### *Interventions*

After clinical examination, the patient was offered medication and multi-professional intervention (physicians, occupational therapists, physiotherapists, social workers) when considered adequate. Ongoing medication was registered at all visits. All patients were offered patient education programme carried out by the multi-professional teams in the period between the 12- and 24-months' follow-up.

# RESULTS

## Paper I

### *Patients and interventions*

The 297 patients remaining in the TIRA study at the 12-months' follow-up (Figure 2), 202 women and 95 men, were included in this study. The period from diagnosis to the 12-months' follow-up was studied. At the time for diagnosis 72% of the patients had ongoing non-steroidal anti-inflammatory drugs (NSAIDs), 20% had oral corticosteroids, and 2% had ongoing disease-modifying anti-rheumatic drugs (DMARDs). 47% were prescribed DMARDs at diagnosis. At the 12-months' follow-up 59% of the patients had ongoing NSAIDs, 35% oral corticosteroids and 70% DMARDs.

### *Clinical/laboratory assessments and self-reported HRQL*

Both clinical/laboratory assessments and self-reported HRQL revealed moderate disease activity and disability, at the time for diagnosis. The majority of the variables had improved significantly at the 6-months' follow-up and remained stable but still affected to the 12-months' follow-up. The exception was the general health scale in SF-36, which was constantly affected throughout the study period.

### *Correlation between self-reported HRQL and clinical/laboratory variables at diagnosis*

No, or only weak, correlation existed between the clinical/laboratory and HRQL variables at the time for diagnosis, and the variation between patients was more prominent regarding the self-reported variables due to the fact that they loaded markedly upon the first and only significant component. Among the self-reported variables, HAQ, SF-36 (all scales), and pain (VAS) were found to be the most important. Of all clinical/laboratory assessments, the three SOFI variables, grip force, GAT and walking speed were associated with the greatest variations between patients. As expected from these results, only weak correlations existed between the

self-reported and clinical/laboratory variables according to the PLS analysis. Only 18% of the variation in the HRQL was explained by the clinical/laboratory variables, of which grip force, walking speed, SOFI-lower and PGA proved to be significant regressors.

### *Correlation between HRQL and clinical/laboratory variables at the 12-months' follow-up*

Also at the 12-months' follow-up the correlation was weak between the two sets of variables. Only 20% of the variation in the self-reported variables were explained by the clinical/laboratory variables. PGA, grip force, walking speed, tender and swollen joint counts were significant regressors.

### *Relationships between assessments at diagnosis and at the 12-months' follow-up*

A small part of the variation (7%) in the self-reported HRQL at the 12-months' follow-up was explained by the clinical/laboratory variables at diagnosis, walking speed, grip force, GAT, and SOFI-lower were significant regressors. HRQL variables at diagnosis regressed 15% of the variation in the HRQL variables at the 12-months' follow-up and the clinical/laboratory variables at diagnosis regressed 17% of the variation in the clinical/laboratory variables at the 12-months' follow-up.

## Paper II

### *Patients and intervention*

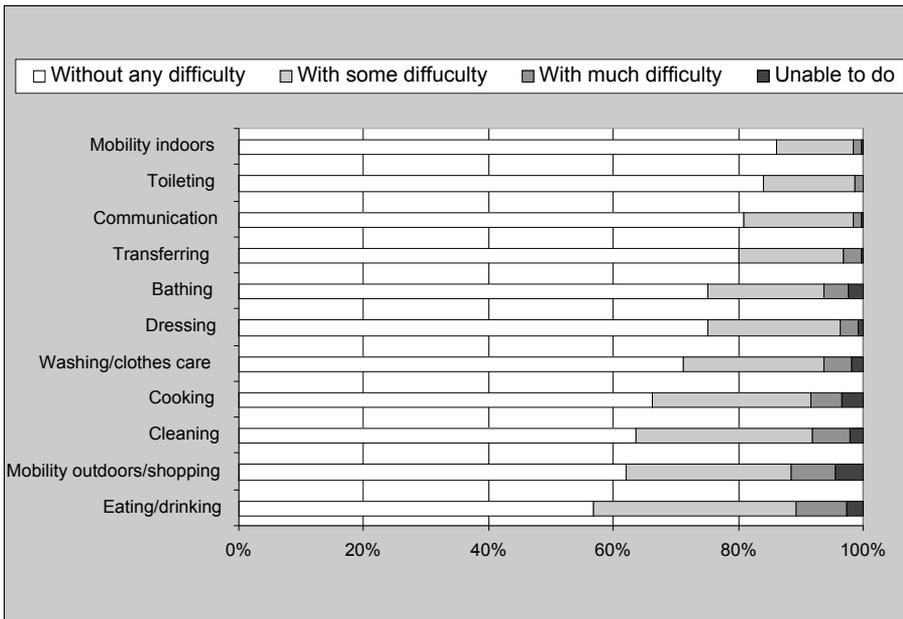
Of the 284 patients remaining in the TIRA project at the 24-months' follow-up (Figure 2), the 215 patients (Md 55 years and 56 men Md 63) who completed EDAQ at both the 12- and 24-months' follow-ups were included. The 69 patients who dropped out (37 women and 32 men) did not differ from the study group regarding age, ESR, PGA, DAS-28, grip force, pain or HAQ at the time for diagnosis or at the 12-months' follow-up. No differences were found between the 215 women and men in the study group regarding the proportion at the 12- and 24-months' follow-up. Neither did the use of DMARDs differ significantly at the 12-months' follow-up, whereas significantly more women (72%) were treated with DMARDs compared to men (59%) at the 24-months' follow-up. 80% of the patients participated in the patient education.

### *Disease course*

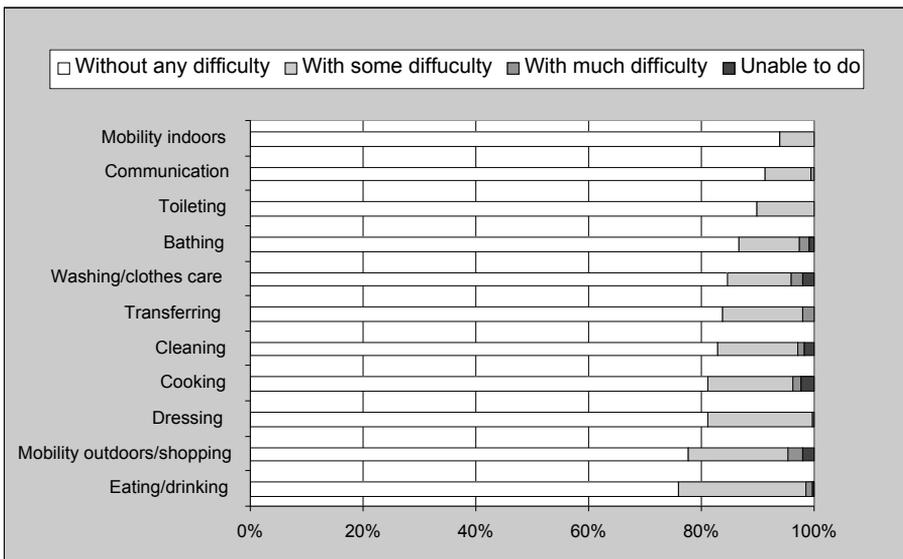
None of the variables representing the disease course, apart from reduced pain in women, changed significantly between the 12- and 24-months' follow-ups. Compared to men, women had a significantly higher HAQ score at both visits and women also had significantly lower grip force than men at both visits.

### *Activity limitations at the 12- and 24-months' follow-ups*

Women, more frequently than men, reported difficulties to perform activities (Figures 3 and 4) at both the 12 and 24-months' follow-ups as assessed by EDAQ. The most frequently reported difficulty for both women (Figure 3) and men (Figure 4) concerned activities in the dimensions eating/drinking and mobility outdoors/shopping.



**Figure 3.** Percentage distribution of difficulties to perform activities in each dimension in 'Evaluation of Activity Questionnaire' among women.



**Figure 4.** Percentage distribution of difficulties to perform activities in each dimension of 'Evaluation of Activity Questionnaire' among men.

### *Use and effect of ADs at the 24-months' follow-up*

124 women (78%) used AD. Totally, 802 ADs were used by these 124 women, with an average of 6 ADs per user. In comparison, 30 men (54%) used 181 AD, giving an average of 6 ADs per user. For the whole groups of 159 women and 56 men, the average number of ADs used was 5 and 3 respectively. ADs reduced difficulties significantly and the most frequently reported beneficial effect was reported, by women as well as by men, regarding ADs used for the dimension eating/drinking.

### *Patient characteristics in AD user subgroups at the 24-months' follow-up*

The subgroup of 124 women who used ADs had significantly more severe disease and more pronounced disability than the subgroup of 35 women who were not AD users. Also the subgroup of 30 men who used AD had significantly more severe disease and more pronounced disability compared to the subgroup of 26 men not using AD. Compared to healthy referents, the subgroups of women and men who used ADs had a 53% and 61% grip force reduction respectively at the 24-months' follow-up.

## Paper III

### *Patients and interventions*

The 276 patients (191 women and 85 men) still remaining in the project at the 36-months' follow-up were included in this study (Figure 2). The use of DMARDs, oral corticosteroids, NSAIDs, or analgesics did not differ significantly between women and men at diagnosis or at the 36-months' follow-up.

### *Patient characteristics*

At diagnosis men were older ( $p = 0.001$ ) and had a higher number of swollen joints ( $p = 0.02$ ) than women, but no other sex differences were found. There were no statistically significant differences between women and men at diagnosis with respect to ESR, CRP, DAS-28 or HAQ scores. However, at the 36-months' follow-up men had a significantly lower HAQ score ( $p < 0.001$ ), but still a higher swollen-joint-count ( $p = 0.04$ ). Two percent of the patients were left-handed with no significant differences in hand function in left or right hand compared to the right-handed.

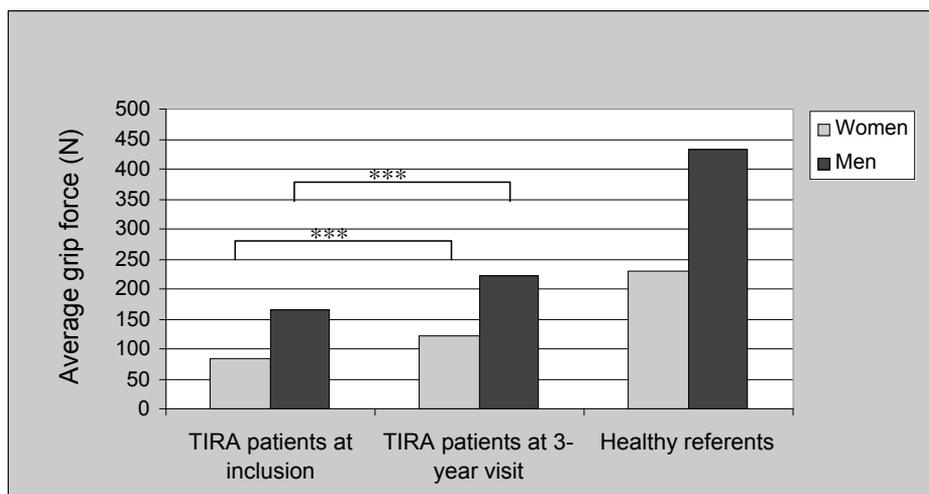
### *Course of hand function*

The hand function, as assessed by GAT, grip force, and SOFI-hand, was reduced at diagnosis in both women and men. Highly significant improvements were seen after 3 months. Thereafter no further improvements occurred, apart from SOFI-hand, which had improved significantly in men between month 12 and 18. The SOFI-upper limb scores did not change during the whole study period. Compared to 169 healthy Swedish referents (105 women and 64 men) (Nordenskiöld & Grimby, 1993), grip force reduction was seen in the patients at diagnosis. From the 3-months' follow-up and onwards, the grip force had improved to about 50% of the grip force recorded in healthy referents (Figure 5).

### *Comparison of hand function between women and men*

The grip ability, measured with GAT, did not differ significantly between women and men, except at the 18-months' follow-up where men had significantly better

hand function. In all follow-ups men also had a higher grip force. By contrast, measured by SOFI-hand, women had significantly better hand function than men as measured by SOFI-hand at all occasions, except at the 12- and 36- months' follow-ups where no significant differences were seen. SOFI-upper limb showed significantly better results for the women.



**Figure 5.** Grip force in women and men in the TIRA cohort and in healthy Swedish referents.

### *Correlations between the different hand function assessments*

GAT, grip force and SOFI-hand correlated weakly in both women and men, whereas SOFI-upper limb did not correlate with any of the hand function assessments.

### *Comparison of subgroups treated versus not treated with DMARDs*

At diagnosis 50% of the women and 50% of the men were prescribed DMARDs. At the time for diagnosis, the subgroup of women and men prescribed DMARDs scored a significantly higher median DAS-28 compared to those who were not prescribed DMARDs. The subgroup of men prescribed DMARDs at diagnosis also had higher ESR and significantly more swollen joints than those who were not pre-

scribed DMARDs. At the 36-months' follow-up, 69% of the women and 74% of the men were prescribed DMARDs. The subgroup of women prescribed DMARDs had a significantly higher median HAQ score compared to those without DMARDs and the subgroup of men prescribed DMARDs had significantly more tender joints.

A subgroup of 25 patients (19 women, 6 men) had no DMARDs prescribed at any time during the study. The subgroup of 251 patients receiving DMARDs were significantly more affected as judged by ESR, DAS-28, CRP, and the number of swollen joints. No differences were recorded regarding hand function at any time by means of GAT, SOFI or grip force comparing the subgroup of 25 patients not prescribed DMARDs with the 251 patients who used DMARDs. Both these subgroups of patients improved significantly between diagnosis and the 3-months' follow-up concerning hand function as well as ESR, DAS-28, VAS pain, CRP and number of swollen or tender joints.

## **Paper IV**

### *Patients and intervention*

Of the 276 patients remaining in the TIRA study at the 36-months' follow-up the 217 patients (Figure 2), 153 women and 64 men, who completed the EDAQ, were included. The 59 patients who had not completed the EDAQ dropped out. Age, ESR, CRP, DAS-28, grip force and HAQ did not differ between the study group and the 59 drop-outs, whereas the drop-outs reported significantly more general pain and more tender-joints. Among the 217 included patients, no differences were found between women and men regarding the proportion of patients prescribed DMARDs, NSAIDs, analgesics, or oral corticosteroids at the 36-months' follow-up.

### *Patient characteristics*

The majority of the variables did not differ significantly between women and men, but men had more functional impairment than women as judged by SOFI-upper limb.

### *Grip force and activity limitations*

The mean average grip force in men (222 N) was significantly higher than in women (126 N) and on average women had a significantly worse HAQ and EDAQ scores than men.

### *Regression analysis of activity limitations*

Activity limitations measured by HAQ and EDAQ were regressed by using 16 variables as regressors (ESR, CRP, swollen joints, tender joints, PGA, pain, grip force, morning stiffness, GAT, walking speed, SOFI-hand, SOFI-upper, SOFI-lower, well-being, age and sex). Of the 16 variables the following 6 were significant and entered the model; Grip force, walking speed, SOFI-lower, pain, well-being, and PGA. Together these 6 variables explained 55% of the variation in HAQ and EDAQ.

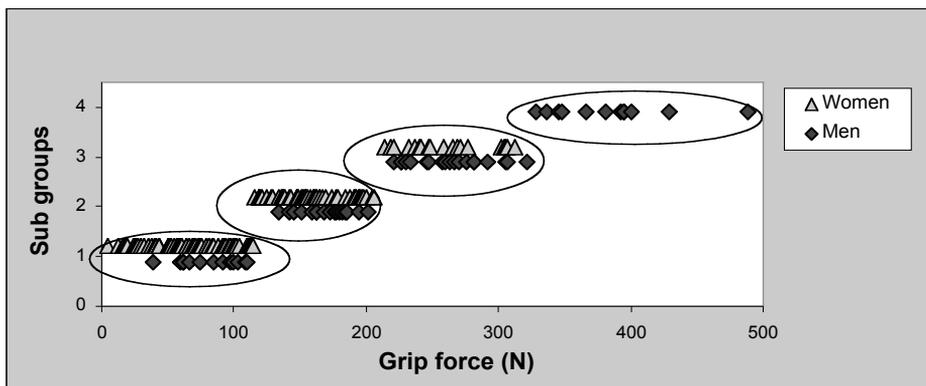
When the HAQ score alone was regressed, the same 6 significant variables entered the model and the explained variation was 61%. When only the EDAQ score was

regressed the same 6 significant variables entered the model, although grip force changed place with walking speed followed by SOFI lower, pain, well-being, and PGA. The explained variation for these 6 variables was 50%.

The average grip force in the study group showed strong negative correlation with HAQ (-0.632) as well as EDAQ scores (- 0.635).

### *Subgrouping of patients based on grip force*

Patients were divided into four subgroups based on average grip force (Figure 6). Subgroup 1 encompassed the 88 patients with the lowest grip force, where women were in majority. Also in subgroup 2, encompassing 71 patients, women were in majority. Subgroup 3 consisted of 19 men and the 19 women with the highest grip force. Finally, subgroup 4 included the 12 men with the highest grip force.



**Figure 6.** Subgrouping patients based upon average grip force, regardless of sex.

### *Differences between subgroups*

Grip force revealed significant differences in all comparisons between subgroups. Both HAQ and EDAQ revealed significant differences in all comparisons between subgroups, except between subgroups 3 versus 4.

Differences between the subgroups regarding patient characteristics were seen preferably between subgroups 1 versus 2 and between 1 versus 3. Apart from walking

speed, no differences were seen when comparing subgroups 2 and 4, or 3 versus 4. Thus, the women and men within subgroup 1, having a mean grip force <114 N, had higher disease activity and more pronounced disability compared to the women and men within subgroup 2, with a grip force between 116-206 N. At the same time, women and men in subgroup 2, with a grip force between 116-206 N, did not differ significantly regarding patient characteristics compared the men in subgroup 4 with a grip force >328 N, although the men in subgroup 4 with high grip force, had no activity limitations as reported by HAQ. The women and men in subgroup 3, with a grip force of 214-321 N, did not differ significantly from sub group 4 regarding any variables (except the grouping variable grip force).

### *Differences within subgroups*

Within subgroups 1, 2 and 3, where men and women were grouped together according to the absolute grip force, there were no significant differences regarding difficulties to perform activities when comparing women regarding HAQ and EDAQ (Table 2). Of the 122 activities/items in EDAQ and HAQ together, the majority (116 activities/items) did not differ between women and men within the three subgroups including both women and men.

Within subgroups 2 and 3, patient characteristics showed that men were generally more affected than women concerning other functional tests and disease activity measures (Table 2). In contrast, there were essentially no differences between women and men in subgroup 1.

**Table 2.** Median (Md) and inter-quartile range (IQR) within subgroups based on grip force, and test of differences between women and men. NS denotes not significant, and P-values under 0.05 are considered as significant.

Subgroups	1		2		3		4		
	5-114		116-206		214-321		328-488		
Grip force, range	Women (n = 75) 36%	Men (n = 13) 6%	Women (n = 54) 26%	Men (n = 17) 8%	Women (n = 19) 9%	Men (n = 19) 9%	Women (n = 19) 9%	Men (n = 12) 6%	
Variables	Md (range)	Md (range)	P	Md (range)	Md (range)	P	Md (range)	Md (range)	P
ESR (mm)	17 (3-90)	36 (8-96)	<b>0.03</b>	14 (3-72)	20 (4-74)	NS	10 (2-40)	13 (2-48)	NS
Swollen joints (0-28)	3 (0-23)	2 (0-17)	NS	1 (0-15)	4 (0-17)	<b>0.015</b>	0 (0-6)	3 (0-13)	NS
Tender joints (0-28)	2 (0-22)	2 (0-14)	NS	2 (0-16)	2 (0-28)	NS	0 (0-6)	3 (0-17)	NS
DAS-28	3.79 (1.11-6.90)	4.78 (1.54-6.52)	NS	3.4 (0.85-5.65)	4.0 (2.56-5.73)	NS	2.12 (1.13-2.84)	2.78 (1.37-6.21)	<b>0.025</b>
Morning stiffn. (min)	60 (0-360)	23 (0-240)	NS	20 (0-180)	45 (0-100)	NS	0 (0-360)	20 (0-300)	NS
PGA (0-4)	1 (0-3)	2 (1-3)	NS	1 (0-3)	1 (0-3)	<b>0.010</b>	0 (0-1)	1 (0-2)	NS
Pain (VAS 100 mm)	43 (5-92)	62 (0-84)	NS	22 (0-83)	37 (8-65)	<b>0.034</b>	7 (0-80)	11 (0-72)	NS
GAT (0-276)	21 (12-119)	23 (19-86)	NS	16 (10-203)	23 (9-44)	<b>0.004</b>	15 (10-23)	17 (13-31)	<b>0.004</b>
SOFI-hand (0-16)	2 (0-8)	2 (0-12)	NS	0 (0-8)	4 (0-8)	<b>0.001</b>	0 (0-2)	1 (0-8)	<b>0.009</b>
SOFI-upper (0-12)	0 (0-7)	2 (0-7)	NS	0 (0-4)	2 (0-6)	<b>&lt;0.001</b>	0 (0-2)	0 (0-8)	NS
SOFI-lower (0-16)	2 (0-10)	2 (0-10)	NS	1 (0-10)	2 (0-6)	NS	0 (0-4)	0 (0-6)	NS
Walking speed (sec)	14 (6-48)	15 (11-27)	NS	12 (7-54)	12 (8-20)	NS	10 (0-4)	12 (8-15)	<b>0.029</b>
HAQ (0-3)	1.0 (0-2.25)	0.75 (0-1.5)	NS	0.38 (0-2.25)	0.5 (0-1.38)	NS	0.13 (7-15)	0.13 (0-1.25)	NS
EDAQ (0-3)	0.91 (0-2.36)	1.0 (0-1.75)	NS	0.50 (0-2.41)	0.58 (0.08-1.1)	NS	0.16 (0-1.38)	0.16 (0-1.25)	NS

ESR = erythrocyte sedimentation rate; DAS-28 = disease activity score (28 joint count); PGA = physicians global assessment of disease activity; VAS = visual analogue scale; GAT = Grip Ability Test; SOFI = Signals of Functional Impairment; HAQ = Health Assessment Questionnaire; EDAQ = Evaluation of Daily Activities Questionnaire; n = number.

# DISCUSSION

The outcome variables used in this study were aimed to describe aspects of health in a wide perspective representing disease activity, disease specific disability (impairments, activity limitations and participation restriction) and generic HRQL (Table 3). The intention was to combine assessments and questionnaires that were relevant for clinical problem solving as well as for research. At the same time the number of assessments and questionnaires were seen in relation to the time consumption for the patient and for the professionals, and combined to represent disease-specific and generic aspects of health. The intention was also to choose instruments that were tested regarding reliability and validity. According to the ICF classification, the variables used in this study represent impairments in body structure and body functions, activity limitations and participation restrictions (Table 3). The variables that were used to assess the disease activity mainly, represents impairments as described by ICF. The majority of the disease-specific disability variables represent activity limitation/participation restriction, but also impairments in body function. The laboratory measures ESR, CRP and general health are not applicable in ICF. The generic HRQL measured by SF-36 (8 subscales) were linked to ICF by Cieza et al, who identified 51 concepts in SF-36 and pointed out that 11 of these 51 concepts were not definable in ICF, due to the fact that they refer to health in general (Table 3). All scales in SF-36, except 'general health', include concepts that are defined in ICF. The concepts in the scales 'bodily pain', 'vitality' and 'role emotional' were definable as disability, and the concepts in the scales 'physical function' and 'mental health' were mainly also identified as disability in ICF. Concepts in 'social function' and 'role physical' were identified in ICF, but defined as a result of physical health, which is not included in ICF. The scale 'general health' includes concepts that not are definable in ICF (Cieza et al, 2002).

In the first study we classified the totally 24 outcome variables used in this study as HRQL versus laboratory/clinical assessment and analysed the relation between what patients reported in contrast to what professionals judge in clinical and laboratory tests (Table 3). According to ICF the self-reported HRQL as well as the clini-

cal/laboratory assessments represent impairments and activity limitations and participation restrictions.

The outcome variables used by physicians to assess disease activity are in accordance with international practice and constitutes a part of the physicians' judgement regarding the patients' need for intervention. Traditionally, these variables are used in research as indicators of the inflammatory process, as done in TIRA (Table 3). Together with the HAQ score, these variables are exported to the national Swedish RA register. The disease specific disability constituted a part of the multi-professional assessment (Table 3). Measuring grip force by Grippit is quickly done at the rheumatology unit and is valuable in clinical problem solving as well as in research. Grippit has been tested and found to be reliable and sensitivity to changes (Nordenskiöld & Grimby, 1993). The instruments GAT and SOFI are aimed to detect activity limitation. Although the values obtained in individual patients varied, the average values in our study group were low and close to healthy referents. Both GAT and SOFI have been tested and found to be valid instruments (Dellhag & Bjelle 1995; Eberhardt et al, 1988). The time used to walk 20 metres (walking speed) is not established and has not been validated. The HAQ instrument is internationally widely used and the HAQ score is an indicator of activity limitation for the individual patient as well as on a group level. The utility is unquestionable in clinic work as well as in research. The Swedish version of HAQ has been tested and found to be valid and reliable (Ekdahl et al, 1988). By the EDAQ instrument, patients report on a large number of activity limitations, which is helpful for problem solving and decisions on intervention in the individual patient. Besides, EDAQ also offer the possibility to assess the effect of ADs to reduce activity limitations. EDAQ has been tested and found to be valid (Nordenskiöld et al, 1988). The use of the generic SF-36 allows comparison of general HRQL in RA patients with a healthy reference population as well as with different disease states (Strömbeck et al, 2000). Besides this, SF-36 was the only instrument that represented mental aspects of health. Due to our results these mental/psychological aspects of health might be addressed more often at the visits. The Swedish version of SF-36 is valid and reliable

(Sullivan et al, 1995). Instruments assessing other mental/psychological aspects as depression, anxiety or coping would be valuable.

**Table 3.** Main focus of outcome variables in the TIRA-study in relation to the ICF components.

The TIRA-study		ICF components				
Outcome	Instruments	Body structures	Body functions	Activity and participation	Environmental factors	Not applicable
Disease activity	ESR (mm/1st h)	-				ESR
	CRP (mg/L)	-				CRP
	PGA (0-4)	Impairment	Impairment			
	Swollen joints (0-28)	Impairment				
	Tender joints (0-28)	Impairment				
	Pain (VAS mm) *		Impairment			
	General health (VAS mm)*					General health
	Morning stiffn. (min) *		Impairment			
Disease specific disability	Grip force (N)		Impairment			
	GAT (0-276)			Activity limitation		
	SOFI-hand (0-16)			Activity limitation		
	SOFI-upper (0-12)			Activity limitation		
	SOFI-lower (0-16)			Activity limitation		
	Walking speed (sec)			Activity limitation		
	HAQ (0-3) *			Activity limitation Participation restr		
	EDAQ (0-3) *			Activity limitation Participation restr.	Assistive devices	
Generic HRQL	SF-36 (0-100) * 8 subscales		Partly Impairment	Partly Activity limitation Participation restr		SF-36 partly not applicable

TIRA = Swedish acronym for Early Interventions in Rheumatoid Arthritis; ICF = International Classification of Functioning Disability and Health; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; PGA = physician's global assessment of disease activity; VAS = visual analogue scale; GAT = Grip Ability Test; SOFI = Signals of Functional Impairment; HAQ = Health Assessment Questionnaire; EDAQ = Evaluation of Daily Activities Questionnaire; SF-36 = Short Form 36; HRQL = Health Related Quality of Life; \* = self-reported HRQL.

The recently recommended core sets for outcome measuring in RA includes a large number of domains in the ICF classification (Stucki et al, 2004). The comprehensive core set includes 96 ICF categories, and the brief core set includes 39 ICF categories representing impairments in body structures and body function, activity limitations, participation restriction and environmental aspects. Cieza & Stucki (2005) propose that it is time to rethink and redefine what should be measured when addressing functioning and disability in patients with RA. They also conclude that

ICF is useful for understanding the interactions among outcome variables and when planning studies where disability is examined. The majority of the aspects of health that are included in this study are proposed to be included in agreement with the recommended ICF comprehensive core set (except ESR, CRP and general health). At the same time the majority of the ICF-domains are not covered in this study. This means that there is a need for further prospective research on RA to elucidate the many aspects of health defined by ICF. However, the SF-36 used in our TIRA-study represents additional aspects that are relevant in the multi professional problem solving in the rehabilitation process.

Arthritis patients with symptom duration of less than 12 months were recruited to the Swedish TIRA cohort. Multi-professional interventions and structured follow-ups were carried out in all cases, regardless of the degree of disease activity. Although, patients with slowly developing disease were excluded, due to the diagnosis criteria, it is reasonable to believe that the Swedish TIRA cohort is a fair approximation of the average Swedish recent-onset RA population and a valuable reference for future prospective cohorts.

### *Clinical/laboratory assessments and self-reported HRQL, paper I*

The bearing of the disease on health during the first year after diagnosis of RA was categorized in terms of HRQL reported by the patients as well as laboratory tests and clinical assessments by professionals, and in all respects the findings in TIRA were similar to those of others. Thus, regarding SF-36 the findings in TIRA confirmed those of Kosinski et al (2002), apart from the scale 'general health' which we found to be constantly reduced at the same level during the whole study period. Like us Kosinski found that the SF-36 rating of mental health was relatively similar comparing RA patients and healthy persons. Apart from lower values concerning 'role physical' and 'bodily pain' in an RA population with a mean disease duration of 13 years, Husted et al. (2001) found SF-36 results comparable to ours at the 12-months' follow-up. In paper I, most of the analysed variables, self-reported as well as laboratory and clinical evaluations, improved considerably within 3-6 months

after diagnosis and then remained stable over the study period in harmony with a previous report from the Swedish TIRA cohort (Hallert et al.2003).

Similar to previous studies (Deighton et al, 1992; Katz & Criswell, 1996; Thompson & Pegley, 1991; Harrison, 2003) HAQ revealed that women experienced significantly more activity limitations than men in the TIRA cohort. Unsurprisingly, high age was found to be associated with more activity limitations. Despite this, however, PLS regression analyses have not pointed at any significant influence of age or sex concerning the multivariate relations between clinical/laboratory and self reported variables (unpublished data). Our PCA analyses showed that the HRQL variables explained more of the variation in HAQ scores between subjects than did clinical/laboratory variables both at diagnosis and at the 12-months' follow-up. The correlations between clinical/laboratory and HRQL variables were weak. This suggests that HRQL estimation, in addition to traditional assessments of disease activity and functional ability, offers important information for the professional care of patients with RA. SF-36 has been put forward as a valuable tool for this purpose (Talamo et al, 1997; Birrell et al, 2000). The PLS analyses verified that the physician's global assessment of disease activity, grip force, and walking speed were stable significant regressors of the HRQL set of variables at diagnosis as well as 12 months later. Grip force and walking speed were the most important clinical/laboratory variables at diagnosis when regressing the self-reported variables at the 12 months' follow-up. In summary, these results indicate that only a few clinical variables, most importantly grip force and walking speed, and possibly to some extent PGA, show stable relationships with the HRQL set of variables. Based upon our findings, however, it is not possible to accurately predict HRQL with clinical/laboratory measures, since about 80% of the variation in the HRQL variables was unexplained at the time for diagnosis and 12-months' follow-up of early RA. The precision was still lower in a prospective perspective. Our findings that the relation between clinical/laboratory assessments and HRQL are weak and at the same time follow a similar course indicates a need for further analyses to clarify the relation between different aspects of health in order to understand more about possible effects of different interventions. Undoubtedly, HRQL is also influenced by psy-

chosocial factors, which is in accordance with a traditional medical rehabilitation theory stressing that interventions should be based on an assessment of body function as well as the social situation of an individual patient.

### *Activity limitation and assistive devices, paper II*

Already one year after diagnosis, the TIRA patients reported limitations in many daily activities. After 24 months, difficulties related to the dimension eating/drinking and mobility were the most frequent, followed by cleaning. This pattern has also been reported by patients with longstanding RA (Nordenskiöld et al, 1998; Rogers & Holm, 1992). Between the 12- and 24-months' follow-ups, the extent of activity limitations was constant for both women and men regarding most daily activities. The same pattern was seen for most other aspects of the disease course in this study group (Hallert et al, 2003).

Considering traditional female and male roles, it was not unexpected that women with RA reported significantly more activity limitations than did men, in the dimensions cleaning and washing/clothes care. Neither was it any great surprise that men had low response rates regarding activities such as 'putting hair rollers', 'picking up needles', and 'turning up hem of a skirt'. When scrutinizing the EDAQ protocol, it is obvious that the instrument has a strong female bias, indicating a need for further development in a gender perspective. At the same time, the significant differences in activities concerning the dimensions eating/drinking and mobility outdoors/shopping probably lack this bias. Differences between women and men have not been studied previously using EDAQ, but have been reported in a number of studies regarding HAQ (Deighton et al, 1992; Katz & Criswell, 1996; Thompson & Pegley, 1991; Harrison, 2003). The activity limitations in our study group were probably not caused by RA alone, but may have been influenced by co-morbidity and/or age-related disability too. In a disability perspective, however, the total pattern of difficulties in the RA population is also clinically relevant.

To the best of our knowledge, the findings that women used substantially more ADs than men have not been reported earlier. This difference is not surprising bearing in

mind the more pronounced activity limitations in women. ADs were found to significantly reduce limitations in daily activities in both women and men. Further, 78% of the women and 54% of the men reported use of ADs indicating a need for specific assessment of the early requirements for AD intervention in RA. These needs may be met by early patient education programmes that include a presentation of the possibilities offered by different types of AD (Eckloff & Thornton, 2002). Our result show that women and men who use AD had substantially higher DAS-score, lower grip force and higher HAQ score than the patients not using AD:s. The score in the Swedish version of HAQ is calculated by adding the highest score within each of the 8 dimensions, and then divided by 8. The 'use of AD' in any of the 20 items is scored as '2' as is the scale step 'with much difficulty'. This means that frequent use of ADs automatically increases the HAQ score. Because of this we compared HAQ score analysed in accordance with the instructions to an alternative HAQ score, where the score '2' due to use of AD was ignored. When comparing these two HAQ scores we found no difference whatsoever (unpublished results). Consequently, the higher HAQ score seen in the subgroups of patients using ADs was not influenced by the reported use of ADs.

### *Hand function and grip force, paper III*

Similar to most other variables studied in the TIRA cohort, hand function improved within three months after diagnosis in the study. Jansen et al found similar rapid changes studying other functional and disease activity variables soon after diagnosis and intervention (Jansen et al, 2000). In the present study, the 25 patients not treated with DMARDs, had the same significant improvement within the first three months as those treated with DMARDs. The explanation to this observation is not immediately obvious, but illustrates that early DMARD therapy is not the sole explanation to the rapid improvements seen soon after the diagnosis of early RA. All TIRA patients were offered a mix of pharmacological and health professional interventions according to individual judgements, and evaluation of distinct therapy regimens were not a primary issue. It is conceivable that the physicians were keener to institute early potent DMARDs in the most severe cases according to their global as-

assessments of disease activity. As shown in another TIRA-based study this was indeed the case, and despite a more aggressive DMARD regimen, a less favourable disease course was actually seen, most likely due to the more severe disease from the start (Kastbom et al, 2004).

The average grip force of female RA patients with duration of 5-32 years was reduced with about 80% compared to healthy women. In a healthy population, the average grip force of women can be expected to be about 50% that of men (Nordenskiöld & Grimby, 1993), and this relative sex difference was seen also in the TIRA study population. Fraser et al reported that grip strength in normal subjects correlated strongly to a number of anthropometric measurements, e.g. forearm circumference/length/volume, hand circumference/length/volume, and various general anthropometric variables such as weight, height and age (Fraser et al, 1999). In contrast to grip force, men were more affected than women with regard to the average value of the SOFI-hand test. A similar sex difference regarding SOFI-hand is seen also in a healthy reference population (to be published). The average SOFI scores for hand and upper extremity varied between 0-1 in women and 0-3 in men. The importance in clinical practice of these very low values is doubtful. This accounts also for the small but significant differences in SOFI score between women and men. In contrast to grip force and SOFI-hand, the grip ability test did not reveal any sex differences. It has been argued that hand function may rely on a person's ability to develop and use compensatory movements to overcome functional disabilities caused by arthritis (Mc Phee, 1987). Speculatively, men and women may use different strategies to accomplish the tasks in GAT. Hypothetically, men may take advantage of their strength, whereas women could benefit from their greater range of motion to carry out GAT.

According to Mc Phee, assessments of hand function should focus on the person's ability to perform activities in daily life (Mc Phee, 1987). Although the instruments disclose sex differences and differences over time, it is important to discuss their relation to the patients' ability to perform daily activities. For example, grip force measurement, which is a predictor of disease activity in RA, is dependent both on

pain and joint deformity (Nordenskiöld & Grimby, 1997) and also correlates to HAQ (Paper I). Further, a significant relationship has been reported between grip force and the dynamic use of hands in activity (Fowler & Nicol, 2001). The maximal voluntary contraction is the most frequently reported aspect of grip force (Desrosiers et al, 1995; Nordenskiöld & Grimby, 1993). However, it is questionable whether this is the most appropriate measure to assess the functionally relevant aspects of impairment. Lagerström & Nordgren (1998) claimed that the muscles' ability to maintain contraction might be more important to activities in daily living. The GAT instrument is strongly correlated to the 'Disability of the Arm, Shoulder and Hand' (DASH) questionnaire (Adams et al, 2004).

#### *Activity limitation and grip force, paper IV*

At all follow-ups, women had lower grip force and more activity limitations as measured by HAQ and EDAQ except at diagnosis where the HAQ scores did not differ significantly between sexes. Similar HAQ scores at diagnosis in women and men might be due to higher percentage reduction in grip force at diagnosis (70%) compared to at the follow-ups (50%) as men in the subgroups of patients with grip force <214 have substantially higher average HAQ score (>0.58) than men in subgroups of patients with grip force >214 N who have lower HAQ score <0.16. EDAQ was not evaluated at diagnosis in order to limit the number of examinations at this occasion. In both women and men, the activity limitations three years after diagnosis were of approximately the same magnitude as after one and two years (Paper II). By HAQ, several investigators have reported more pronounced activity limitations in women than in men (Sherrer et al, 1986; Young et al, 2000; Hallert et al, 2003; Deighton et al, 1992; Thompson & Pegley, 1991; Sokka et al, 2003), which has been taken as an indication of a more severe disease course in women (Katz & Criswell, 1996). The HAQ score has also been found to increase with increasing age in RA patients as well as in healthy individuals (Sokka et al, 2003). Kuiper and co-workers have argued that the postmenopausal state may be responsible for the major part of the outcome difference between women and men with RA (Kuiper et al, 2001). In contrast, it was recently reported that there were no signifi-

cant differences in HAQ scores between women and men in a general Finnish population with a mean age of 55 years (Krishnan et al, 2004).

Regression analysis showed that grip force was the strongest regressor of activity limitation represented by HAQ and EDAQ scores together, closely followed by walking speed, SOFI-lower and pain. The same regressors were significant predictors of HAQ alone, whereas walking speed was the strongest predictor of EDAQ closely followed by grip force. Sex and age were not identified as significant regressors and the degree of activity limitation, as reflected by HAQ and EDAQ, was directly associated to grip force regardless of sex. These findings offer a plausible explanation to the repeatedly reported sex difference concerning activity limitations, i.e. the functional abilities reflected by HAQ and EDAQ is to a great extent explained by the muscular strength in the hands (and probably also the lower limb). Compared to a healthy Swedish reference population (Nordenskiöld & Grimby, 1993), the grip force reduction one year after the diagnosis of RA was about 50 percent in both sexes. Men, having about double the average grip force of women, end up with a 'normal female grip force' after a 50% reduction. Thus, the 50% grip force reduction in RA, as seen in both women and men in this study, could be expected to have less impact on the HAQ and EDAQ outcomes in men. After subdividing RA patients into 4 groups with respect to grip force, the sex differences concerning HAQ and EDAQ outcomes disappeared. This, however, does not exclude that grip force/hand function and other functional abilities may also be associated to disease activity (Welsing et al, 2001). Our findings elucidate the fact that the average HAQ score in a study group is dependent on the percentage distribution of women and men. This needs to be taken in consideration when comparing HAQ scores between study groups with different distributions of women and men.

Within the subgroups of patients, based upon the grip force, women and men had the same degree of activity limitations. In subgroup 1, including the patients with lowest grip force, the degrees of activity limitation were essentially the same in women and men. In subgroups 2 and 3 there were no differences in the majority of variables, and in the few variables that differed significantly, men were more af-

affected than women. This indicates that men with low grip force are more affected than women with corresponding grip force.

Women and men within subgroup 1, having a (mean) grip force <114 N, had higher disease activity and more pronounced disability compared to the women and men within subgroup 2 with a grip force between 116-206 N. At the same time, women and men in subgroup 2, with a grip force between 116-206 N did not differ significantly regarding patient characteristics compared the men in subgroup 4 with a grip force >328 N, although the men in subgroup 4 had no activity limitations as reported by HAQ. The women and men in subgroup 3, with a grip force of 214-321 N, did not differ significantly from subgroup 4 regarding any variables (except the grouping variable grip force).

To conclude, our finding that activity limitations are dependent on grip force, regardless of sex, offers an explanation to the repeatedly reported observation that women with RA have a less favourable disease course than men. The higher disability scores in women than in men, is probably to a great extent dependent on their lower muscular strength compared to men. When comparing activity limitations reflected by HAQ and/or EDAQ, women and men with the same grip force did not differ with respect to HAQ or EDAQ outcome.

# GENERAL CONCLUSIONS

- All clinical/laboratory and self-reported HRQL variables were substantially affected at the time for diagnosis of early RA. The course of most of these variables followed similar patterns, i.e. significant improvements were seen within 3-6 months and then remained stable, but still affected during follow-up for three years.
- The relations between clinical/laboratory assessment and self-reported HRQL were weak illustrating that HRQL measurements highlight aspects distinct from the clinical/laboratory assessments as judged by professionals. This information may prove important for the decision-making concerning early interventional strategies in clinical practice.
- Women developed substantially more pronounced activity limitations than men, as judged by HAQ and EDAQ. In contrast, by means of SOFI, men had significantly more affected function of the hands and upper extremities.
- Grip force was substantially reduced at baseline. It improved rapidly after diagnosis, but remained reduced to about 50% compared to healthy women and men. As expected, men had higher grip force than women on average. When subgrouping the patients with regard to grip force, regardless of sex, it was found that activity limitations reflected by HAQ and EDAQ were strongly related to grip force and to the same extent in both sexes. A grip force below 114 N was found to be associated with substantial activity limitations in both women and men. This indicates that constitutional differences in grip force are strongly related to the level of activity limitation, since RA women have lower grip force than RA men. The same is seen in healthy individuals.
- Women used assistive devices more frequently than men, and ADs were found to reduce activity limitations in self-care and domestic life. The subgroups of women and men that used ADs were comparable regarding disease activity and disability, and the subgroups using ADs were generally more affected than the subgroups that did not.

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