UMEÅ UNIVERSITY

Aspects of physical activity in Rheumatoid Arthritis

Associations with inflammation and cardiovascular risk factors

Kristina Hörnberg

Department of Public Health and Clinical Medicine, Rheumatology

Umeå 2018

Responsible publisher under Swedish law: the Dean of the Medical Faculty

ISBN: 978-91-7601-850-7
ISSN: 0346-6612
New Series No: 1949
Electronic version available at: http://umu.diva-portal.org/
Printed by: UmU Print Service, Umeå University
Umeå, Sweden 2018

To my family

Table of Contents

Abstract

Background Rheumatoid Arthritis (RA) is associated with an increased risk for cardiovascular disease (CVD), partially attributable to systemic inflammation and traditional risk factors for CVD. Since physical activity (PA) is strongly related to CVD in the general population, the aim of this thesis was to describe aspects of PA in patients with RA, and further to analyse associations with disease activity, traditional risk factors for CVD and subclinical atherosclerosis.
Methods In papers I and II, newly diagnosed RA patients were followed for two (n=66) and mean (SD) 16 (2) (n=25) years respectively. Disease activity and aerobic capacity were measured in both groups. In paper II, the 25 patients were also examined for traditional risk factors for CVD, body composition, with pulse wave analysis and carotid ultrasound. Self-efficacy was assessed using a questionnaire. In paper III, a combined heart rate and movement monitor was used to measure PA in 84 patients with early (< 2 years) and 37 patients with long-standing (mean [SD] 16 [2] years) RA. Data were analysed for associations with disease activity, traditional risk factors for CVD and subclinical atherosclerosis, as above. Finally, in paper IV, a pilot study including 13 patients, median (Q1-Q3) age 57 (44-64) years, was conducted to analyse the feasibility as well as the effects of ten weeks of spinning exercise, on aerobic capacity, traditional risk factors for CVD and inflammation.
Results In papers I and II, aerobic capacity was maintained at follow-up. In paper I, median (Q1-Q3) aerobic capacity was 31 (27-39) ml/kg/min at baseline and 33 (25-38) ml/kg/min after two years. In paper II, median (Q1-Q3) aerobic capacity was 32 (28-42) ml/kg/min at baseline and 33 (28-39) ml/kg/min after 16 years. In multiple linear regression analysis, adjusted for baseline aerobic capacity, disease activity during the first two years after diagnosis explained 53 % of the aerobic capacity level after 16 years [β=-0.14, p=0.004]. Higher aerobic capacity was associated with more favourable measures of risk factors for CVD and self-efficacy over time and at follow-up. In paper III, 37 % of the patients with early and 43 % of the patients with long-standing RA, did not reach the national recommendations of PA. Total PA as well as more time spent in moderate to vigorous PA were associated with more favourable risk factors for CVD. Patients with higher disease activity and functional disability were less physically active. In paper IV, intensive spinning exercise proved to be a feasible method, that significantly improved aerobic capacity, systolic blood pressure and the number of tender joints.
Conclusions Aerobic capacity, which could be maintained despite several years of disease, was related to risk factors for CVD and to self-efficacy. Higher disease activity in early disease predicted lower aerobic capacity after 16 years. Higher PA level was associated with a more beneficial cardiovascular profile; however, an insufficient level of PA was found in a substantial proportion of patients. Furthermore, we found, that intensive spinning exercise was a feasible method for the group included, to improve aerobic capacity and blood pressure without detrimental effects on disease activity. Physical activity and aerobic capacity have roles to play in the cardio protective management and are, as other modifiable risk factors, suggested to be estimated regularly. Higher disease activity is known to increase the risk of CVD in RA, and as disease activity also seems to negatively impact future aerobic capacity, interventions and support for health enhancing PA should have high priority in these patients.

Abbreviations

ACPA	anti-citrullinated protein antibody
ACR	American College of Rheumatology
AIx	augmentation index
ASES	Arthritis Self-Efficacy Scale
AUC	area under the curve
BMI	body mass index
BMR	basal metabolic rate
BP	blood pressure
BPao	aortic blood pressure
CCA	common carotid artery
CDAI	Clinical Disease Activity Index
CHF	congestive heart failure
cIMT	carotid intima media thickness
CRP	C-reactive protein
CV	cardiovascular
CVD	cardiovascular disease
DAS	Disease Activity Score
DIT	diet-induced thermogenesis
DLW	doubly-labelled water
DMARD	disease modifying anti-rheumatic drug
DXA	dual energy X-ray absorbtiometry
ECG	electrocardiogram
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FM	Fibromyalgia
HAQ	Health Assessment Questionnaire
HR	heart rate
IL	interleukin
Kcal	kilocalories
LDL	low-density lipoprotein
MET	metabolic equivalent
MI	myocardial infarction
MTP	metatarsophalangeal
MVPA	moderate to vigorous physical activity
NSAID	non-steroidal anti-inflammatory drug
PAEE	physical activity energy expenditure
PAL	physical activity level

PP	pulse pressure
PWA	pulse wave analysis
PWV	pulse wave velocity
RA	Rheumatoid Arthritis
REE	resting energy expenditure
RER	respiratory exchange ratio
RF	rheumatoid factor
RPE	rating of perceived exertion
RPM	revolutions per minute
RQ	respiratory quotient
SOFI	Signals of Functional Impairment
SRQ	Swedish Rheumatology Quality Register
TEE	total energy expenditure
TNF	tumor necrosis factor
TRAM	Tidig Reumatoid Artrit Mottagning
VAS	visual analogue scale
WHO	World Health Organization
VO_2max	maximal oxygen uptake

Sammanfattning på svenska

Bakgrund

Reumatoid artrit (RA) är en systemisk, inflammatorisk sjukdom som kännetecknas av kronisk inflammation i leder och omgivande mjukdelar, men även andra organ kan drabbas. Inflammationen har en nedbrytande effekt på ledernas brosk och intilliggande ben, som kan leda till felställningar, nedsatt rörlighet och muskelstyrka. Vanliga symtom är smärta, svullnad, och stelhetskänsla, men även allmän sjukdomskänsla och trötthet, som ofta medför att förmågan att vara fysiskt aktiv försämras. Vid RA finns också en ökad risk att insjukna i eller avlida till följd av kardiovaskulär sjukdom (KVS). Förutom de traditionella riskfaktorerna, anses den systemiska inflammationen vid RA bidra till en ökad aterosklerosutveckling. Bland allmänbefolkningen är fysisk aktivitetsnivå och syreupptagningsförmåga starkt relaterade till lägre risk för KVS, medan dessa samband är mindre beforskade vid RA.

Syfte

Syftet med denna avhandling var därför att beskriva olika aspekter av fysisk aktivitet hos patienter med RA samt att analysera sambanden med sjukdomsaktivitet, traditionella riskfaktorer för KVS samt subklinisk ateroskleros.

Metod

I studie I och II undersöktes 66 respektive 25 individer vid tidpunkten för RA diagnos. I studie I genomfördes uppföljande mätningar under två år samt i studie II efter i genomsnitt 16 år. Sjukdomsaktivitet och syreupptagningsförmåga undersöktes. I studie II undersöktes också traditionella riskfaktorer för KVS, kroppskonstitution, subklinisk ateroskleros och tilltro till den egna förmågan. I studie III användes en kombinerad hjärtfrekvens- och rörelsemonitor för att mäta fysisk aktivitetsnivå hos 84 individer med tidig och 37 individer med långvarig RA. Data analyserades beträffande samband med sjukdomsaktivitet, traditionella riskfaktorer för KVS och subklinisk ateroskleros. Slutligen inkluderades 13 personer med RA i en träningsstudie, där effekterna av spinningträning tre gånger i veckan under tio veckor undersöktes gällande genomförbarhet och effekter på traditionella riskfaktorer för KVS, syreupptagningsförmåga och inflammation.

Resultat

Studie I visade, att syreupptagningsförmågan bibehölls över tid, men den grupp som svarat på behandling hade högre syreupptagningsförmåga än de som inte svarat på behandling. I studie II var syreupptagningsförmågan medelgod och oförändrad efter 16 års sjukdom. Högre sjukdomsaktivitet under de första två åren efter diagnos var associerad till lägre syreupptagningsförmåga efter 16 år. Högre syreupptagningsförmåga var relaterad till mera fördelaktiga värden för flera traditionella riskfaktorer för KVS vid uppföljningen, men också över tid. Flera samband fanns också mellan högre tilltro till egen förmåga och högre syreupptagningsförmåga. I studie III var den fysiska aktivitetsnivån densamma i grupperna med tidig och långvarig RA, men 37 % av patienterna med tidig och 43 % av de med långvarig RA uppnådde inte nationella rekommendationer för fysisk aktivitet. Högre total fysisk aktivitet och högre andel medel- till högintensiv fysisk aktivitet var associerade till bättre värden för flera KV riskfaktorer. Patienter med högre sjukdomsaktivitet och högre grad av aktivitetsbegränsningar var mindre fysiskt aktiva. I studie IV resulterade spinningträning tre gånger/vecka under tio veckor i ökad syreupptagningsförmåga, minskat systoliskt blodtryck och färre ömma leder. Vid studiens start var högre sjukdomsaktivitet och större aktivitetsbegränsningar relaterade till lägre syreupptagningsförmåga. Kompletterande analyser visade, att högre syreupptagningsförmåga relaterade till mera fördelaktiga värden för traditionella KV riskfaktorer och subklinisk ateroskleros vid studiens start, efter träningsperioden och även vid den uppföljande mätningen efter 25 veckor.

Konklusioner

Syreupptagningsförmågan, som kunde bibehållas trots lång tids sjukdom, var relaterad till riskfaktorer för KVS och till tilltron till den egna förmågan. Högre sjukdomsaktivitet vid tidig sjukdom medförde en lägre syreupptagningsförmåga efter 16 år. Högre fysisk aktivitetsnivå var relaterad till bättre kardiovaskulär riskprofil, dock uppnådde en betydande andel patienter inte de nationella rekommendationerna för fysisk aktivitet. Spinningträning visade sig vara en lämplig träningsmetod för deltagarna, som resulterade i ökad syreupptagningsförmåga och lägre systoliskt blodtryck, utan negativ påverkan på sjukdomsaktiviteten. Tvärtom noterades ett minskat antal ömma leder efter träningsperioden. Fysisk aktivitet och syreupptagningsförmåga har betydelse för preventionen av KVS vid RA, och bör, liksom andra modifierbara riskfaktorer, mätas regelbundet. Tidigare studier har visat, att högre sjukdomsaktivitet ökar risken för KVS vid RA. Eftersom sjukdomsaktiviteten också verkar ha en negativ påverkan på framtida

syreupptagningsförmåga, bör interventioner och stöd för hälsofrämjande fysisk aktivitet prioriteras hos dessa patienter.

Original papers

This thesis is based on the following papers, referred to in the text by their Roman numerals I-IV:

I. Hörnberg, K., Lindström, B., Rantapää-Dahlqvist, S. Body function in patients with early rheumatoid arthritis. A 2-year prospective study. Advances in Physiotherapy 2007;9:144-50.

II. Hörnberg, K., Sundström B., Innala, L., Rantapää-Dahlqvist, S., Wållberg-Jonsson S. Aerobic capacity over 16 years in patients with rheumatoid arthritis: relationship to disease activity and risk factors for cardiovascular disease. PLoS ONE 2017;12(12):e0190211. https://doi.org/10.1371/journal.pone.0190211.

III. Hörnberg, K., Pomeroy, J., Sandberg, C., Sundström, B., Södergren, A., Ångström, L., Wållberg-Jonsson, S. Physical activity in early and long-standing RA - relations to disease activity, cardiovascular risk factors and subclinical atherosclerosis. Manuscript.

IV. Hörnberg, K., Ångström, L., Wållberg-Jonsson, S. Benefits of spinning exercise on cardiovascular risk factors in rheumatoid arthritis: a pilot study. Cardiopulmonary Physical Therapy Journal 2014;25(3):68-74.

Authors KH and LÅ contributed equally to this work.

Reprints were made with kind permission of the respective publisher.
In addition to the above papers, the thesis includes results that have not previously been published.

Background

Rheumatoid arthritis

Epidemiology, pathogenesis and aetiology

Rheumatoid arthritis (RA) is the most common chronic inflammatory disease, prevalent in 0.5-1 % of the adult population worldwide (1). The incidence rate is approximately 5-50 new cases per 100.000 residents each year (1). The incidence is about 3 times as high in women as in men (1), the difference being less obvious after menopause (2). The debut of disease occurs at all ages, but the peak age of incidence is 55-64 years in women and 65-75 in men (2). The disease involves autoimmune reactions and autoantibodies commonly present are rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). The release of pro-inflammatory cytokines, such as tumor necrosis factor (TNF) and Interleukin-1 (IL-1) stimulate the production of acute phase reactants, *e.g.,* C-reactive protein (CRP), in the liver. The risk of developing RA is to ~60% attributable to genetic factors and if one member of a pair of identical twins has RA, then the other member has a 15% risk of developing the disease (2). Further, hormonal factors, environmental factors as obesity, infections and airway exposures like cigarette smoking, contribute to the risk of developing RA (2). Recent reports present inverse associations between physical activity and risk of disease development (3) as well as physical activity before the debut of RA symptoms and the severity of RA (4).

Clinical features

Rheumatoid arthritis is characterized by systemic and local inflammation, symmetric polyarticular synovitis with subsequent damage to articular cartilage and underlying bone. Common early features include swollen and tender joints in fingers, wrists and forefeet, but any joint can be affected (5). There is also a range of associated extra-articular manifestations affecting internal organs, skin and blood vessels (1). Periods with acute flares alternate with calmer periods and remission. Major symptoms are morning stiffness, pain and fatigue, often with consequent activity limitations in

performing daily tasks and reduced physical activity. Disease progression varies, but impaired range of motion, muscle strength (6, 7) and aerobic capacity (8, 9) are common consequences of the disease. Impairments and activity limitations may lead to a vicious circle with reduced physical activity consequently causing further impairments and activity limitations.

Advances in treatment strategies over the past decades with early diagnosis and more potent pharmacological treatments, have resulted in decreased disease activity and improved health status for patients with RA (10), demonstrated by improved functional and working ability (11) as well as decreased rates of joint surgery (12). Nevertheless, even though disease activity improves, longitudinal studies have presented a progress of joint and muscle impairments and activity limitations over the years, with a worse outcome for women (6). In a Finnish population of RA patients with a mean disease duration of 11 years, RA was associated with a more than 7-fold risk of disability compared to that of the general population (13). Patients with higher disease activity in early disease often experience higher levels of disability over time (14). Further, the disease has a substantial impact on health-related quality of life (15) and perceived general health (11), leaving RA as a condition with great impact on many aspects of life.

There are many manifestations of additional health conditions associated with RA and the prevalence of comorbidity is increasing over time (11, 16). Life expectancy is decreased among patients with RA, mainly attributable to cardiovascular disease (CVD) (17, 18). Other potential comorbidities include certain forms of cancer, interstitial lung fibrosis, infections, depression, osteoporosis and diabetes (19).

Diagnosis

Diagnosis of RA is based upon classification criteria established by the American College of Rheumatology (ACR) in 1987 (20) (Table 1). The criteria were revised by the ACR and the European League against Rheumatism (EULAR) in 2010 in order to increase sensitivity to patients with recent-onset RA (5) (Table 2).

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

Classification of RA requires the presence of at least four of the following criteria and criteria 1-4 must have been present for at least six weeks:
1. Morning stiffness in and around joints lasting at least 1 hour before maximal improvement;
2. Soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician;
3. Swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints;
4. Symmetric swelling (arthritis);
5. Rheumatoid nodules;
6. Presence of rheumatoid factor;
7. Radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints

Table 2. The 2010 ACR/EULAR criteria for the classification of RA.

Definite clinical synovitis in at least one joint; Absence of alternative diagnosis better explaining the synovitis; A total score of at least 6 (of a possible 10) added in the following four categories;	
Criteria	**Score**
Joint involvement;	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least one small joint)	5
Serology (at least one test result is needed for classification);	
Negative RF and negative anti-CCP antibodies	0
Low-positive RF or low positive anti-CCP antibodies	2
High-positive RF or high-positive anti-CCP antibodies	3
Acute phase reactants;	
Normal CRP level and normal ESR	0
Abnormal CRP level or abnormal ESR	1
Duration of symptoms;	
< 6 weeks	0
≥ 6 weeks	1

Pharmacological and non-pharmacological treatment

Since RA is a chronic, progressive disease, affecting several perspectives of health, treatment involves a team embracing different healthcare professionals. The EULAR (21) recommends early initiation of pharmacological treatment, including systemic corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs). Biological DMARDs, created by a biological process, in contrary to the synthetic DMARDs, were introduced in the late 90´s and are considered highly effective (1, 12). In parallel, EULAR recommends non-pharmacological interventions including patient information, educational programmes, dynamic exercise and occupational therapy. They promote the use of physical activity and exercise for the management of RA (21).

According to Swedish recommendations, preventive and rehabilitative measures should be offered early to all patients with RA. Coaching and self-management programs are considered important components in order to achieve patient participation, positive health outcomes and a healthy lifestyle (22). Physiotherapy measures often include individually tailored dynamic exercise for range of motion, muscular strength and aerobic capacity (23-25). The efficacy of exercise on muscle strength, aerobic capacity, and functional ability, without adverse effects on disease activity, is well documented (26-30).

Physical activity

Definitions and key concepts

Physical activity, exercise and maximal aerobic capacity are crucial terms in this thesis and need to be clarified to avoid being confused with one another. According to Caspersen *et al* (31), *physical activity* is defined as “any bodily movement produced by skeletal muscles that results in energy expenditure”, including the four domains occupational, domestic, transportation and leisure time activities (32). *Exercise* is a subcategory of physical activity that is planned, structured, and repetitive, aiming at improving or maintaining one or more components of physical fitness (31).

Physical activity can be quantified by its *duration, frequency and intensity*. Duration describes the time spent in different intensities and frequency the number of sessions

over a period of time (32, 33). The intensity of physical activity can be characterized as *relative* or *absolute*, the former determined as the per cent of an individual´s maximal aerobic capacity (maximal oxygen uptake, VO_2max) or maximal heart rate (HR). The absolute intensity is based on the energy required to perform the activity, *e.g.,* kilocalories (kcal, 1 litre of O_2 consumption ≈ 5 kcal of energy) or multiples of *metabolic equivalents* (METs). One MET is roughly equivalent to the resting energy expenditure (REE≈ 3.5 ml VO_2/kg/min). Commonly used cut-off points when describing absolute intensity of physical activity are 1-1.5 METs for sedentary activity, 1.6-2.9 METs for low intensity, 3-5.9 METs for moderate intensity, and 6 METs and more for vigorous intensity (32). Moderate to vigorous activity can also be defined by the relative intensity of ≥ 50 % of maximal HR or ≥ 45 % of VO_2max (32) or can be subjectively rated as ≥ 12-14 (somewhat hard) on the Borg Rating of Perceived Exertion Scale (RPE, Table 3) (34).

Table 3. The Borg RPE Scale

Scale	Level of exertion
6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	

The three factors that impact on daily *total energy expenditure* (TEE) are; *basal metabolic rate* (BMR), *diet-induced thermogenesis* (DIT) and *physical activity energy expenditure* (PAEE). The BMR accounts for 60-75%, DIT for about 10% and PAEE for the remaining 15-30% of the TEE (33). The BMR can be measured by indirect calorimetry or calculated by using the parameters sex, age and body weight (35). However, BMR is

known to be elevated in patients with RA due to inflammation (36, 37), and new equations have been provided to more accurately predict BMR in patients with RA (37).

A common presentation of daily physical activity is the *physical activity level* (PAL), which is calculated as PAL = TEE/BMR. Physical activity level can be categorized into low (<1.45), moderate (1.45-1.6) and high (>1.6) (38).

Maximal aerobic capacity is a measure of cardiovascular fitness and exercise capacity representing some aspects of the physical activity level. It describes the maximal amount of oxygen (VO_2 max) a person can consume from inspired air each minute, while performing dynamic near-maximal exercise involving a large part of total muscle mass (33). It is dependent on the ability of the cardiovascular system to deliver oxygenated blood to the muscles and also on the ability of the muscles to take up and utilize the oxygen in energy production. It can be expressed in METs, in VO_2 l/min, or in VO_2 ml/kg/min. Individual values can vary from about VO_2 10 ml/kg/min in patients with congestive heart failure (CHF) up to VO_2 80-90 ml/kg/min in athletes (33).

Recommendations for physical activity

The public health recommendations for physical activity in adults are as follows (39-42):

- Long-lasting periods of inactivity should be avoided
- Substantial health benefits are obtained from accumulating, in bouts of ≥ 10 minutes, 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity aerobic activity, or an equivalent of both
- Additional and more extensive health benefits are obtained by increasing aerobic physical activity
- Moderate to high intensity muscle-strengthening activities involving major muscle groups should be performed ≥ 2 days per week
- Older adults with poor mobility should perform exercises that maintain or improve flexibility and balance ≥ 2 days per week

- Individuals, who cannot reach recommended amounts of physical activity due to health conditions, should be as physically active as their abilities and condition allow

Specific recommendations regarding sedentary time are not available.

Recommendations for RA patients are similar. However, physical activity should be individually designed and adjusted to accommodate changes of disease activity and symptoms; exercises for flexibility should be included (23).

Evaluation of physical activity: objective and subjective methods

Given the importance of regular physical activity to decrease the risk of CVD and in maintaining overall health, it is important to register physical activity by valid and reliable methods, sensible to change. According to current recommendations, assessment in 10-minute bouts of activity rather than minute by minute, using objective measurement tools, are advocated (43).

Objective methods

The "gold standard" for the assessment of physical activity is considered to be the doubly-labelled water (DLW) assessment of TEE (44). Patients drink water labelled with the two stable isotopes deuterium (^{2}H) and oxygen-18 (^{18}O) and energy expenditure is calculated based on the elimination rate of the two isotopes in urine and by knowing the respiratory quotient (RQ) of the food ingested during the observation period (44). The DLW assessment is a valid, but quite expensive method providing an average measure of total energy expenditure over a period of time.

Other objective methods are direct observation and registration using different kinds of activity monitors/motion sensors. Simple pedometers count the number of steps taken, while the more complex accelerometers can measure all of the above-mentioned dimensions, *i.e.* intensity, duration and frequency, and provide more

detailed information about the physical activity behaviour (32). Accelerometers register acceleration/deceleration due to gravity, some of them in combination with measurement of HR or skin temperature and transform the data into counts. Using monitors validated against DLW (45) with a minimum measurement period of four consecutive days are recommended in individuals with RA, in order to achieve a good representation of the physical activity pattern (46).

Subjective methods

Physical activity can be measured by self-report; through the completion of questionnaires or diaries/activity logs or by interviews. The advantages are the relatively low cost, that it is convenient and applicable to large numbers of patients. However, self-reported physical activity measures show only low or moderate correlation with objectively measures, being dependent on accuracy in recall, interpretation and motivation of the subject (43). In a study comparing objectively and subjectively measured physical activity and evaluating their associations to maximal aerobic capacity, RA patients reported that they were less sedentary and were more engaged in higher intensity activities than what was objectively assessed by an accelerometer (47).

Evaluation of aerobic capacity: maximal and sub-maximal tests

The level of aerobic capacity is partly dependent on the level and intensity of physical activity. It is strongly related to CVD risk and regular estimations of aerobic capacity are recommended in the clinical management of patients with RA (25). It can be measured by maximal or sub-maximal tests and also by algorithms using no exercise data (33). The result can serve as a basis for exercise prescription and guidance.

Maximal tests

The “gold standard” method to measure aerobic capacity is testing with a progressive increase of intensity until exhaustion, while collecting and analysing respiratory gases (33). The test is usually performed on a treadmill or an ergometer bicycle in a laboratory setting. The criteria to ensure that the person has reached maximal aerobic metabolism may vary between different studies, but common criteria are: a plateau in VO_2 consumption with increasing exercise intensity, a respiratory exchange ratio (RER) of at least 1.10-1.15, a blood lactate level of at least 8-10 mmol/L, and attaining HR exceeding 90 % or within at least 10 beats/min of the estimated predicted maximal HR (220-age). Rating of at least 18 units on the Borg RPE scale (Table 3) (34) may also indicate that maximal effort is reached.

However, a maximal effort is hardly possible to achieve since the performance is strongly influenced by subjective factors such as perceived exhaustion and level of motivation. Thus, the value measured is usually the *peak aerobic capacity* (VO_2 peak), *i.e.,* the highest value of oxygen consumption measured during a graded exercise test (33). Older people or patients with chronic disease, such as RA, may be unable to satisfactorily achieve the effort required, due to muscle fatigue and pain, as well as the clinician´s inability to push the participant towards exhaustion. Therefore, a sub-maximal test is an option to estimate the aerobic capacity.

Submaximal tests

Aerobic capacity can also be predicted by submaximal tests whilst walking, running, stepping or using an ergometer bicycle (33). One of the most frequently used is the Åstrand submaximal ergometer test (48). It is based on the linear relationship between HR and oxygen consumption and estimates aerobic capacity using the steady-state HR. Besides correcting for work load, sex and body weight, an age-correcting factor is included in the test to account for the decrease in maximal HR with age (49). However, there is a margin of error in the predicted test value, partly because the individual variation in maximal HR not accounted for and the individual difference in exercise economy. One standard deviation from the average maximum HR for individuals of the same age is considered to be ±10 beats/min (33, 50). Thus, submaximal testing tends to underestimate or overestimate aerobic capacity in 15 % of healthy subjects, mainly due to the individual variation in maximal HR (50).

Physical activity and cardiovascular health in the general population

Extensive data in the medical literature demonstrate the beneficial effects of physical activity on CV mortality (51) and risk of CVD in the general population, partly by the favourable effects on blood pressure, blood lipids, blood glucose and obesity (52). Physical activity also has the ability to influence inflammatory marker levels and thus potentially lower the risk for CVD (53). In a meta-analysis, Sattelmair, *et al.,* found the inverse association between physical activity level and risk of a myocardial infarction (MI) to be stronger in women than in men (54). Possible explanations presented were biological differences or methodological considerations, like sex differences in physical activity reporting or the lower rate of MI in women, affecting the analyses.

There seems to be a dose-response relationship between physical activity and health, with additional benefits with increasing physical activity (54). According to guidelines, moderate to vigorous physical activity (MVPA) should be performed in bouts of ≥10 minutes, but physical activity shorter than 10 minutes, are also related to CV health, independent of the number of bouts ≥ 10 minutes (55). Accordingly, sedentary behaviour is a risk factor for disease, regardless of the level of physical activity (56) and aerobic capacity (57). Current recommendations provide most of the achievable longevity benefits, but additional health effects have been found up to approximately 3 to 5 times the recommended levels, and in the general population (median age 62 years at inclusion), there does not appear to be an elevated mortality risk with physical activity levels up to 10 times the recommended minimum. (51).

Aerobic capacity and cardiovascular health in the general population

Aerobic capacity is inversely, and strongly, related to CVD and all-cause mortality (58, 59) possibly even more closely related to CVD than physical inactivity (52). Aerobic capacity has also been described as a more powerful predictor for CVD than traditional risk factors (60). In a meta-analysis including healthy men and women, Kodama et al found that 1 MET (≈3.5 ml O_2/kg/min) higher aerobic capacity was associated with a 13% reduction in mortality risk and 15% decrease in CVD risk (59). Individuals with aerobic capacity ≥7.9 METs (≈28 ml O_2/kg/min) had substantially lower rates of all-cause mortality and CVD events compared with those with lower aerobic capacity (59). In a study including more than 5 700 women, the strength of the prediction was even

higher. In this investigation, the risk of death was reduced by 17% for every increase in aerobic capacity by 1 MET (61). Aligned with previous research, men who were able to maintain or increase their aerobic capacity over time, also had beneficial effects for both all-cause and CVD mortality compared with those who deteriorated in aerobic capacity (62). The prognostic power of aerobic capacity on mortality is similar among men who are taking beta blocking agents and those who are not, and in apparently healthy as well as in patients with CV conditions (60).

Cardiovascular disease in rheumatoid arthritis

Atherosclerotic CVD is the most common cause of death globally. It is a group of disorders of the heart and blood vessels, including MI, stroke, and peripheral arterial disease (63).

Epidemiology of cardiovascular disease in rheumatoid arthritis

A major complication in patients with RA is the development of accelerated atherosclerosis, increasing the risk for CVD mortality (17) and morbidity (64). In a study of a cohort of patients with RA from the county of Västerbotten, Sweden, Wållberg Jonsson and colleagues found the CVD mortality in RA patients to be increased by 46 % compared with the general population (17). A meta-analysis including 111 000 patients indicated similar mortality ratios (18).

A meta-analysis comprising more than 14 000 patients, found the overall risk of incident CVD to be increased by 48 % compared with the general population with an increased risk of 68 %, 41 % and 87 % for MI, stroke and congestive heart failure (CHF) respectively (65). The increased risk seems to be evident early in the course of RA. A Swedish research team, studying a large nationwide cohort, presented a 40% increased risk for MI in RA patients during the first years of disease (66). In accordance with the general population, the incidence had decreased over the years studied, however, the relative risk remained the same (66). Furthermore, the added risk for an MI seems to be highest among women <50 years of age (67), to be similar to the risk of individuals 10 years older without RA or comparable to that of patients with diabetes mellitus (67). The risk of stroke seems to evolve more slowly than the risk of MI (68), but to a greater extent lead to death following the CV event (69).

Surrogate measures of atherosclerosis

Vascular dysfunction reflects the very early and reversible signs of atherosclerosis and can work as surrogate marker for CVD (70). This can be measured by *e.g.* pulse wave analysis (PWA) (71) or by carotid intima-media thickness (cIMT) using ultrasound (72). Several studies have confirmed vascular dysfunction in patients with RA, measured by PWA (73, 74) and by cIMT (75, 76) and the vascular dysfunction seems to be present in very early RA (77, 78). Pulse wave analysis measures arterial stiffness and endothelial function by pulse wave velocity (PWV) and augmentation index (AIx). The PWV (m/sec), which is the "gold standard" for estimating global arterial stiffness (79), is measured through the aorta and a higher velocity is reflecting stiffness of the artery. Additionally, reflected pressure waves are generated when forward pressure waves, created by ventricular contraction, meet peripheral arterial branch points and peripheral resistance. In elastic vessels, reflected waves tend to arrive back at the aortic root during diastole. In stiffer arteries, the reflected waves will return earlier, adding to the forward wave and augmenting the systolic pressure. The AIx represents the change in the central aortic pulse pressure between the second and the first wave divided by the pulse pressure (79) (Figure 1) (80).

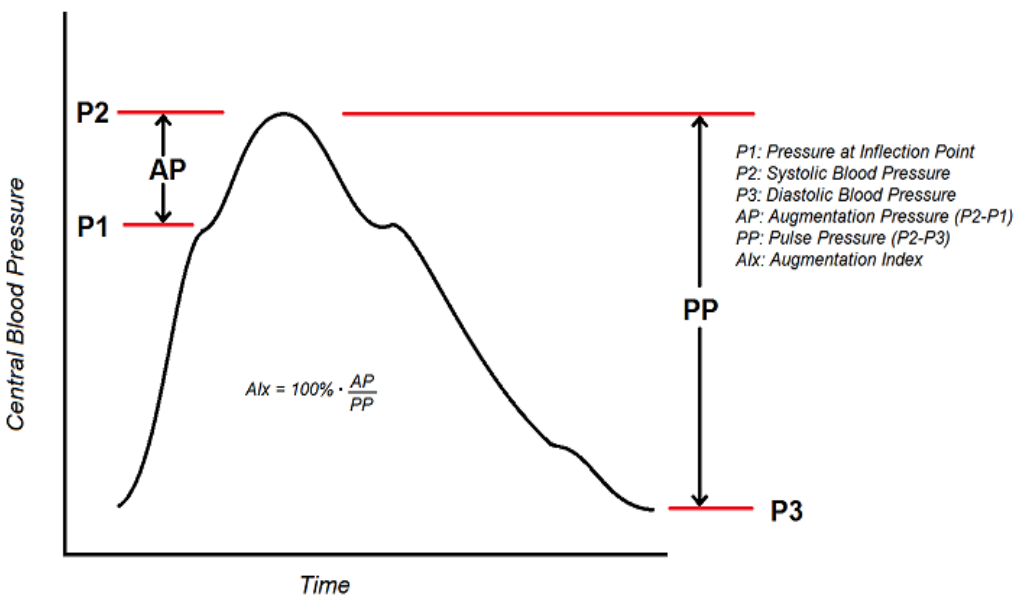

Figure 1. Determination of the augmentation index from the central pressure wave form. (Icternol). CC BY-SA 4.0.

Factors associated with cardiovascular disease in rheumatoid arthritis

Several factors are behind the increased risk of CVD in RA patients, the most frequently discussed in the literature are the impact of traditional CVD risk factors, inflammation, pharmacotherapy and insufficient PA. In a recent report on a cohort of RA patients collected in ten countries, about 50% of CVD events was attributed to traditional CVD risk factors and about 30% to RA related factors (81).

Traditional cardiovascular disease risk factors

Traditional modifiable CVD risk factors include smoking, obesity, hypertension, diabetes and dyslipidaemia. The increased CV morbidity and mortality is partly attributable to an increased prevalence of traditional CVD risk factors (16, 82) and the negative effect on CV health seems to be potentiated by higher disease activity (16, 83). Compared with control subjects, several CVD risk factors have been shown to be more prevalent in individuals already prior to the onset of RA, being more obvious in younger individuals (84).

Current and ex-smokers have been described to be more prevalent among RA patients (82), which is not unexpected, since smoking is a risk factor for developing RA (84). The prevalence of hypertension has been increased in several reports (16). On the other hand, a meta-analysis showed no significant difference in the prevalence of hypertension between RA patients and controls (82). Diabetes mellitus and dyslipidaemia are more common than in the general population (82). Somewhat paradoxically, high disease activity is associated with lower levels of total cholesterol and low-density lipoprotein (LDL) cholesterol whilst their CVD risk is elevated. This dyslipidaemia is purported to be partly explained by an increased consumption of and reduced synthesis of lipoproteins caused by inflammation (85).

A major part of individuals with RA suffer from rheumatoid cachexia, with loss of fat free mass and progressively increased fat mass in the presence of stable or even slightly decreased body weight (36). In a Swedish study, including patients, median age 65 years, with moderate and high disease activity, 38% of the included patients were categorized as having rheumatoid cachexia (86). The distribution of body fat also seems to be altered, since central obesity is more prevalent in RA patients than in healthy controls (78). This alteration in body composition is an effect of chronic

systemic inflammation and occurs already in the early years of the disease. The cachexia interferes with the interpretation of Body Mass Index (BMI) as a surrogate marker for body fat and thereby for CVD risk. Stavropoulos-Kalinoglou and associates suggested new RA-specific BMI thresholds of 23 kg/m^2 for overweight and 28 kg/ m^2 for obesity, thresholds where the relationship between body fat and BMI was comparable to that of healthy controls (87). Furthermore, body mass has a paradoxical effect in RA compared with the general population, since a low BMI has been associated with higher CVD mortality (88).

The traditional CVD risk factors contribute, including genetic factors, older age and male sex, to the excess incidence of CVD in RA. However, traditional CVD risk factors do not explain all of the excess risk of CVD in RA. After adjusting for traditional risk factors for CVD, there is still unexplained CV mortality and morbidity associated with having RA alone, suggesting that RA is an independent risk factor for CVD (81).

Inflammation

Several studies have confirmed the independent contribution of chronic inflammation to the CV mortality and morbidity (16, 81, 89). Rheumatoid arthritis and atherosclerosis are both regarded as inflammatory-driven diseases and C-reactive protein (CRP), being a marker of inflammation, predicts CVD in healthy (90) as well as in patients with inflammatory arthritis (91). There are similarities between the chronic inflammatory process present in chronic rheumatoid synovitis and the inflammatory process in the atherosclerotic blood vessels, with elevated concentrations of CRP, IL-6 and TNF-α and similar cellular recruitment and activation (92).

Several manifestations of RA inflammation, such as the cumulative inflammatory burden, the number and duration of flares over time (93), functional disability, extra-articular manifestations, disease duration as well as RF (89), contribute to the risk of CVD.

Pharmacotherapy

The use of NSAIDs has been associated with increased CVD risk in the general population, however, the effect on RA patients remains controversial. Results presented from a Danish nationwide cohort study indicated a 22 % increased risk for CVD associated with NSAIDs, however, the risk was lower compared to non-RA individuals (94). Glucocorticoids are generally considered to have a dose dependent adverse effect on CVD risk, and current EULAR recommendations and guidelines advice cautiousness as it comes to doses and treatment periods (95). On the contrary, the use of DMARDs (16, 89) and biological agents (96) have been suggested to decrease CVD risk, mainly by their beneficial effect on disease activity.

Insufficient level of physical activity

The well-known detrimental effects of physical inactivity on CVD risk in the general population, seem to be evident also in individuals with RA. Less physically active patients with RA have a significantly worse CVD risk profile compared with more physically active patients (97, 98), also after adjustment for duration, activity and severity of RA (99). Sedentary behaviour is associated with increased long-term CVD risk independently the amount of MVPA (100). A study by Khoja and associates highlights that even low intensity physical activity is better than none, as light intensity physical activity was associated with lower CVD risk in RA (101).

Physical activity in rheumatoid arthritis

An overview of studies regarding levels of physical activity, measured by objective methods, are presented in Table 4. Studies on physical activity among individuals with RA mainly report insufficient physical activity levels, when compared with public health recommendations outlined to maintain health (101-105) and also compared with healthy controls (8, 43, 106, 107). This seems to be evident already in early disease (108, 109). In addition, they seem to have difficulties in maintaining health-enhancing physical activity levels over time (110). A large Swedish survey including healthy adults and individuals with different chronic diseases, reported that 74% of the individuals

with RA and 60% of the healthy subjects did not reach recommended levels of PA (111). The proportion being physically inactive and time spent sedentary seems to be higher compared with the general population, but similar to patients with other chronic conditions (112).

Studies using objective assessments of physical activity as DLW or different kinds of accelerometers, generally show higher proportions being physically inactive compared with data generated from self-report (112). Roubenoff and associates used DLW, but also a monitor and a questionnaire to measure physical activity in women with RA and controls (113). Participants who exercised more than once per week were excluded. They found that daily physical activity energy expenditure was mean (SD) 681 (257) kcal/day, about 247 kcal less for patients with RA in comparison to matched controls. The results correlated significantly with the data from the activity monitor, but not with the questionnaire. Almeida, *et al.,* found somewhat higher physical activity levels (841 kcal/d) measured by a multisensory activity monitor (46).

Patients with RA seem to spend more time sedentary and in light activities and to be less active in moderate and vigorous activities compared with their healthy counterparts (106, 114). Furthermore, the daily patterns of physical activity have been shown to differ from healthy controls, with lower physical activity levels in RA patients compared with controls in the morning and in the late afternoon (106), a difference evident also in early disease (115). Conversely, levels of physical activity comparable to that of the general population (7) or to controls (116), have also been presented. Additionally, a number of studies have presented self-assessed PA levels well over the recommended levels of health-enhancing PA (117, 118).

The association between physical activity levels and CVD risk has been evaluated in a number of studies, showing a beneficial relationship between higher level of physical activity and a more beneficial CVD risk factor profile (98-101, 114, 119-121) as well as a lower level of arterial dysfunction (122).

Aerobic capacity in rheumatoid arthritis

An overview of studies regarding aerobic capacity levels in patients with RA are presented in Table 5. Patients with RA have been shown to have reduced aerobic capacity in comparison with healthy controls (123-125), and compared with norm data (126, 127). A study published recently, including 144 RA patients with disease lasting six years and low disease activity, concluded that the aerobic capacity was alarmingly

low [mean (SD) 21 (6) ml/kg/min] (9). Aerobic capacity ≤ 28 ml O_2/kg/min is associated with a substantially increased risk for CVD events and all-cause mortality (59). On the contrary, other studies have presented test results similar to healthy controls (128-131), and to reference data from the general population (7), although in two of the studies, sedentary people were chosen as control subjects (129, 130).

Studies describing the associations between aerobic capacity and cardiovascular health in patients with RA are sparse, but higher levels of aerobic capacity have been associated with a better cardiovascular profile (9) and lower levels of CRP (131).

Table 4. Studies presenting levels of physical activity in patients with RA as measured by objective methods.

Author, year country (ref)	N (%women) RA/Controls	Age, years, RA	Disease duration, years	Disease activity	BMI	Activity monitor (days worn)	Physical activity	p
Roubenoff, 2002 USA (113)	20(100)/ 20(100)	47(14)	7.7(6.5)	ESR:30(20) Swollen joints: 5(5) Tender joints: 5(7)	25.3(4.5)	DLW (14)	**PAEE**: RA: 2849(1075) kJ/day Controls: 3883(1732) kJ/day **PAL:** RA: 1.70(0.24) Controls: 1.89(0.35)	<0.04 <0.07
Hagfors, 2005 Sweden (132)	9/0	Not reported	Not reported	Not reported	Not reported	DLW (14)	**PAL:** 1.68(0.15)	
Prioreschi, 2013 South Africa (106)	50(100)/ 22(100)	48(13)	8.2(6.4)	CRP: 20(31) Tender joints: 4(5) Swollen joints: 3(3)	32(9)	Actical (14)	**Sedentary:** RA: 71(11) % per day Controls: 62(11) % per day **95th percentile of counts:** RA: 22612(12255) Controls: 37091(17650)	 0.002 <0.001
Prioreschi, 2015 South Africa (133)	RA, normal bone mass: 21(100)/ RA, low bone mass: 9(100)	Normal: 51(10) Low: 57(12)	Normal: 9.6(8.5) Low: 16.5(10.6)	CDAI: Normal: 7.7(6.1) Low: 13.8(10.9)	Normal: 35.3(7.6) Low: 28.2(7.8)	Actical (7)	**Sedentary, % per day:** Normal: 65(11), Low: 74(10) **Light, % per day:** Normal: 23(16), Low: 18(8) **Moderate, % per day:** Normal: 12(6), Low: 8(3) **Vigorous, % per day:** Normal: 0.02(0.04), Low: 0.00(0.01) **Meeting guidelines n/total:** Normal: 10/21, Low: 3/8	0.05 0.10 0.06 0.40 0.73
Semanik, 2011 USA IMPAACT study (134)	171(82)/0	55(14)	13.5(10)	Not reported	28(6)	ActiGraph, GT1M (7)	**Activity counts/day:** 220506(106022) **Light:** 477(103) min/day **MVPA:** 19(19) min/day **Bouted MVPA ≥10 min:** 9(13)	

Lee, 2012 USA IMPAACT study (104)	176(83)/0	55(range 23-86)	13.5(10.2)	Not reported	Not reported	ActiGraph, GT1M (7)	42% of the patients had zero 10 min bouts of MVPA/week **Light:** 478(103) min/day **MVPA:** 19(19) min/day	
Gilbert, 2016 USA IMPAACT study (135)	172(83)/0	55(14)	13.4(10.2)	Self-assessed (range 1-9): 6.44(7.97)	28.0(6.7)	ActiGraph, GT1M (7)	**Sedentary:** 9.9(1.4) hours/day	
Fenton, 2017 UK PARA study (100)	61(67)/0	55(12)	7.0(9.0)	ESR: 14(14) CRP: 7(9)	Height: 1.66 (0.09) Weight: 77.2 (16.9)	ActiGraph, GT3X (7)	**Sedentary:** 498(68) min/day **Light:** 269(69) min/day **MVPA:** 18(17) min/day **Sedentary breaks:** 84(14)/day **Sedentary bouts ≥20 min:** 5.8(2.1)/day **Time/sedentary bouts ≥20 min:** 31(2)	
Yu, 2015 UK PARA study (47)	68(62)/0	55(13)	7.2(8.7)	Not reported	27.8(5.4)	ActiGraph, GT3X (7)	**Sedentary:** 569(124-765) min/day **Light:** 267(144-390) min/day **Moderate:** 14(0-34) min/day **Vigorous:** 0(0-0) min/day **MVPA:** 14(0-34) min/day	
Hashimoto, 2015 Japan (136)	20(80)/ 20(80)	69(5)	<1y: 25% 1-5y: 10% ≥5y:65%	DAS28: 3.59(1.22)	21.4(3.6)	ActiGraph Mini-Motionlogger (6-7)	**Activity counts/min:** RA: 199(27) Controls: 223(29) **Low activity ratio <40 counts/total minute counts:** RA: 11(6) % Controls: 5(3) %	<0.01 <0.01
Rongen-van-Dartel, 2014 Netherlands (137)	RA, low activity level=below group average ≥90% of time: 42(79) RA, high activity level: 125(54)	Low: 57(11) High: 55(11)	Low: 9.5 (6.0-17.2) High: 10.0 (5.0-16.0)	DAS28: Low: 3.28(1.18) High: 3.07(1.23)	Low: 26.7(24.3 -29.0) High: 24.5(22.7 -26.7)	Actilog (12)	**PA counts/day:** Whole group: 73(27) Low: 43(9) High: 83(23)	

Table 4. Continued.

Author, year country (ref)	N (%women) RA/Controls	Age, years, RA	Disease duration, years	Disease activity	BMI	Activity monitor (days worn)	Physical activity	p
Paul, 2014 UK (138)	19(84)/19(84)	52(12)	13.6(9.3)	ESR: 13(7) CRP: 12(15)	24.9(4.9)	ActivPAL (5)	**Steps/day:** RA: 6052(1955) Controls: 11045(4329) **Sedentary:** RA: 1130(103) min/day Controls: 1063(97) min/day **MVPA:** RA: 25(11) min/day Controls: 55(27) min/day	<0.001 0.029 <0.001
Piva, 2010 USA (139)	47(100)/0	56(7)	14.3(8.4)	DAS28: 3.0(0.8)	27.9(6.5)	SenseWear Armband (10)	**≥3METs:** 199(103-317) kcal/day **Steps/day:** 7151(2637)	
Almeida, 2011 USA, (46)	53(100)/0 (47 measured PA)	56(7)	14.3(8.4)	DAS28: 3.0(0.8)	27.9(6.5)	SenseWear Armband (7)	**≥1MET:** 1050(331) kcal/day **≥2METs:** 642(309) kcal/day **≥3METs:** 239(178) kcal/day **Daily no of steps:** 7260(2710)	
Khoja, 2016 USA (101)	98(85)/0	58(9)	14(6-22)	DAS28: 3.44 (2.65-4.31)	28.4(24.4 -33.8)	SenseWear Armband (8)	**≤1 MET:** median 589 min/day **1.1-1.9 METs:** median 208 min/day **2-2.9 METs:** median 128 min/day **≥3 METs:** median 36 min/day **Steps/day:** median 6324 Weekly 150 min ≥3 METs in 10 min bouts were achieved by 17%	

Huffman, 2014 USA (116)	27(63)/27(63)	55 (48-67)	6.7 (1.8-18.1)	DAS28: 2.6(1.2-3.8)	31.1(23.2 -34.5)	StayHealthy RT3 (7)	**Sedentary:** RA: 837(760-887) min/day, 91(87-94) % Controls: 829(766-887) min/day, 91(86-94) % **Low PA:** RA: 72(56-94) min/day, 8(6-11) % Controls: 84(48-105) min/day, 8(5-12) % **Moderate PA:** RA: 5(1-13) min/day, 0(0-1) % Controls: 8(4-16) min/day, 1(0-2) % **High PA:** RA: 0(0-1) min/day, 0(0-0) % Controls: 1(0-3) min/day, 0(0-0) % **Very high PA:** RA: 0(0-0) min/day, 0(0-0) % Controls: 0(0-0) min/day, 0(0-0) %	 N.S. N.S. N.S. N.S. N.S.
Hernández-Hernández, 2014 Spain, (114)	50(88)/ 50(92)	54(7)	6.3(4.7)	DAS28: 3.7(1.4)	29.2(5.8)	StayHealthy RT3 (5)	**Light activity:** RA:56(33) min/day Controls: 51(29) min/day **Moderate activity:** RA: 22(15) min/day Controls: 29(21) **Vigorous activity:** RA: 0.6(0.2-1.6) min/day Controls: 2.2(0.6-6) min/day **MVPA:** RA: 23(16) min/day Controls: 33(27) min/day **PAEE:** RA: 539(214) kcal/day Controls: 515(258) kcal/day	 N.S. N.S. 0.00 0.02 N.S.

Table 4. Continued.

Author, year country (ref)	N (%women) RA/Controls	Age, years, RA	Disease duration, years	Disease activity	BMI	Activity monitor (days worn)	Physical activity	p
AbouAssi, 2017 USA, (121)	50(70) (41 measured PA)/ 39(69)	55(13)	Not reported	DAS28: 3.0(1.4)	30.5(7.5)	StayHealthy RT3 (7)	**<1MET:** RA: 91(6) % /week controls: 89(6) %/week **≥3 METs:** RA: 1(2) %/week controls: 2(1) %/week	N.S. N.S.
Munneke, 2001 Netherlands (140)	41(68)/0	55(range 35-69)	6 (range 1-26)	DAS4: 3.9 (range 1.2-6.8)	Not reported	Dynaport ADL monitor (1)	**Locomotion:** 5.9(2.5) % / 24 h **Standing:** 19.3(6.8) % / 24 h **Sitting:** 32.5(9.5) % / 24 h **Lying:** 42.1(8.8) % / 24 h	
Raftery, 2009 UK, (141)	RA: 12(100)/ FM: 12(100)	Not reported	Not reported	Not reported	Not reported	Numact (1)	**Steps/day:** RA: 9916 FM: 11397 **Seconds standing:** RA: 15949 FM:15549	N.S. N.S.
Hegarty, 2015 New Zealand, (142)	RA: 70(73)/ OA: 70(62)	RA: 62(12) OA: 69(8)	17(12.2)	DAS28: 3.6(1.2)	Not reported	Pedometer, Braintek (7)	**Steps/day:** RA: 4512±2641 OA: 4270±2547	N.S.

Data is presented as mean(SD) or median(Q1-Q3) when not stated otherwise. P refers to analyses of differences between groups.
BMI=body mass index, ESR= erythrocyte sedimentation rate, DLW=doubly labelled water, PAEE=physical activity energy expenditure, PAL=physical activity level (total energy expenditure/resting energy expenditure), CRP= C-reactive proteins, CDAI=Clinical Disease Activity Index, MVPA=moderate to vigorous physical activity, DAS= Disease Activity Score, DAS28=Disease Activity Score based on assessment of 28 joints, DAS4= Disease Activity Score based on four variables, N.S.=not significant, MET= metabolic equivalent, FM= fibromyalgia, OA= osteoarthritis.

Table 5. Studies presenting levels of aerobic capacity (ml/kg/min) in patients with RA.

Author, year country (ref)	N (%women) RA/Controls	Age, years RA/controls	Disease duration, years	Disease activity	Body composition	Test method	Aerobic capacity (ml/kg/min)	p
Ekblom, 1974 Sweden (143)	31(100)/0	Mean 56	Mean 11.6 (range 2-30)	Not presented	Not presented	Max bicycle test	1.17(0.04) L/min, 29.5% lower than reference data	
Beals, 1985 USA (144)	8(75)/6(67) sedentary controls	50(9)	4.4(3.0)	ESR: 38(10) Tender or swollen joints: 37.0(8.5)	Weight: 65.5(12.0) kg	Max bicycle test	**RA:** 15.9(2.2) **Controls:** 20.5(2.0)	N.S.
Minor, 1988 USA (126)*	40(85)/0	54(14)	10.8(7.9)	Tender joints: 17.3(12.2) Swollen joints: 14.4(9.8)	Not presented	Max treadmill test	**Female:** 17.8(4.9) 62% of predicted value **Male:** 19.4(7.0) 81% of predicted value	
Ekdahl, 1992 Sweden (123)	67(64)/ 77(61)	53(10)/ 51(10)	10.6(7.8)	ESR: 25(19) CRP: 24(28) Ritchie Index: 11.5(8.2)	Height, weight: Female: 164.1(5.6) cm 66.1(11.6) kg Male: 177.9(6.8) cm 75.6(10.7) kg	Submax bicycle test	**Female:** **< 54 years, RA:** 22.3(6.8) **Controls:** 31.7(12.1) **> 54 years, RA:** 18.7(3.5) **Controls:** 21.9(5.3) **Male:** **< 54 years, RA:** 24.0(4.3) **Controls:** 27.6(7.4) **> 54 years, RA:** 18.7(4.1) **Controls:** 25.1(6.1)	<0.001 <0.001 <0.001 <0.001
Minor, 1995 USA (145)*	42(100)/0	50.3(11.9)	8.0(8.0)	Morning stiffness: 1.3(1.1) hours Joint count: 10.4(9.7)	%body fat: 31.9(7)	Max treadmill test	22.0(8.4)	

Table 5. Continued.

Author, year country (ref)	N (%women) RA/Controls	Age, years RA/controls	Disease duration, years	Disease activity	Body composition	Test method	Aerobic capacity (ml/kg/min)	p
Rall, 1996 USA (125)*	RA: 8(62)/ young controls: 8(62), old controls: 8(62)	RA: 42(13)/ young controls: 26(2) old controls: 70(5)	14.6(12.5)	ESR: 37(15)	BMI:25.0(4.3)	Max bicycle test	**RA:** 22.9(4.2) **Young controls:** 40.2(10.3) **Old controls:** 20.7(5.0) RA vs young controls: RA vs old controls:	 <0.001 N.S.
Cimen, 2001 Turkey (124)	25(68)/ 21(76)	48(14)/ 46(13)	9.9(6.6)	Ritchie index: 9.2(6.2)	BMI: 26.1(5.0)	Max bicycle test	**RA:** 65.6(16.9) **Controls:** 77.4(11.7)	< 0.01
Häkkinen, 2002 Finland (128)	ERA: 12(100) LRA: 11(100) Controls: 12(100)	ERA:41(9) LRA:49(7)	ERA: 2.9(0.6) LRA: 14.5(4.5)	ESR: ERA: 7.4(6.0) LRA:12.9(7.7) Joint Index: ERA: 1.8(2.5) LRA: 4.8(3.7)	%body fat: ERA: 30.4(6.6) LRA:34.3(7.3)	Max bicycle test	**ERA:** 26.7(6.8) **LRA:** 23.1(6.1) **Controls:** 24.8(2.3)	N.S. between groups
de Carvalho, 2003 Brazil (130)	35(89)/ Sedentary controls: 35(89)	48(8)	8	ESR: 36 Ritchie Index: 4.0	BMI: 24.9(3.4)	Max treadmill test	**FCI:** 24.9 (n=7) **FCII:** 21.9 (n=6) **Controls:** 24.5 (n=22)	N.S. between groups
Eurenius, 2005 Sweden (7)	298(76)/0	57 (range 19-90)	< 6.5	DAS28: 3.51 (range 0-7.37)	Not presented	Submax bicycle or treadmill test	Similar to norm data	

Kurtais, 2006 Turkey (129)	19(100)/ 15(100)	48(8)	10.8(7.2) months	ESR: 26(16) DAS28: 3.9(1.5)	Not presented	Max treadmill test	**RA:** 23.7(4.9) **Controls:** 26.6(6.0)	N.S.
Bilberg, 2005 Sweden (146)*	43 with RA, 20 in execise and 23 in control group	Exercise: 49 (range 32-62) Controls: 46 (range 21-65)	Exercise: 31(15.8) Controls: 35(17.1) months	DAS28: Exercise: 4.1(1.5) Controls: 4.0(1.3)	Not presented	Submax bicycle test	**RA exercise group:** 34.0(10.9) **RA control group:** 34.2(6.7)	
Haglund, 2009 Sweden (147)	52(62)/0	53 (range 23-66)	≤6	Tender joints: 4 (range 0-26) Swollen joints: 3 (0-24)	BMI:26 (range 19-37) Female: 25 (20-34) Male:28 (19-37)	Submax treadmill test and submax bicycle test	**Treadmill:** **Female:** 27 (range 23-39) **Male:** 36 (range 31-46) **Bicycle:** **Female:** 28 (range 19-52) **Male:** 26 (range 17-44)	
Chang, 2009 Taiwan (127)	66(85)/0	Men: 54(17) Women: 51(11)	Not presented	Not presented	BMI: Women: 21.8(4.5) Men: 23.5(4.0)	Max treadmill test	**Women:** 22.6 (5.5), 78% of predicted value **Men:** 27.4 (8.1), 92% of predicted value	
Cooney, 2013 UK (148)	30(80)/0	53(10)	Women: 13.0(1.9) Men: 12.8(1.8)	DAS28: Women: 2.9(0.3) Men: 2.0(0.3)	BMI: Women: 25.8(5.1) Men: 28.3(5.1)	Max bicycle test	**Women:** 19.2(4.1) **Men:** 22.3(4.0)	
Munsterman, 2013 Netherlands (149)	60(73)/0	52(10)	10(0-41)	DAS28: 3.4(1.4)	Not presented	Submax treadmill test	27.8(3.8), **Female:** 26.4(3.0) **Male:** 31.7(2.6)	
Stavropoulos- Kalinoglou, 2013 UK (150)*	36(78)/0	54(10)	6(4-10)	DAS28: 3.2(1.1)	BMI:28.8(5.1)	Max treadmill test	23.7(6.8)	

Table 5. Continued.

Author, year country (ref)	N (%women) RA/Controls	Age, years RA/controls	Disease duration, years	Disease activity	Body composition	Test method	Aerobic capacity (ml/kg/min)	p
Nordgren, 2015 Sweden (151)**	220(81)/0	59(9)	12(9.6)	Not presented	BMI:26.7(4.9)	Submax bicycle test	28.6(8.6)	
Metsios, 2015 UK (9)	144(70)/0	54(12)	6.0(3-10)	DAS28: 3.2(2.3-4.5)	Height: 1.66 (1.59-1.71) Weight: 76.8 (65.5-90.0)	Max treadmill test	20.9(5.7)	
Osailan, 2016 UK (152)*	96(68)/0	54(13)	7.9(9.1)	ESR: 10(5-22) CRP:5(2-9)	BMI: 27.8 (23.9-31.0)	Max treadmill test	20.6(5.1)	
Zoli, 2017 Italy (131)	20(75)/ 10(80)	52(12)	0.5(0.2)	DAS44: 3.9(1.2)	BMI: 25.5(2.9)	Max treadmill test	**RA:** 25.2(5.4) **Controls:** 23.2(3.2)	N.S.

*Baseline values in an exercise intervention study, **During physical activity trial. Data are presented as mean(SD) or median(Q1-Q3) when not presented otherwise. P refers to analyses of differences between groups. ESR= erythrocyte sedimentation rate, N.S.=not significant, CRP= C-reactive proteins, BMI=body mass index, ERA=early RA, LRA=long-term RA, FC=functional class, DAS28=Disease Activity Score based on the assessment of 28 joints, DAS44= Disease Activity Score based on the assessment of 44 joints.

Management of cardiovascular disease risk

Recommendations and guidelines

The EULAR recommendations for CVD risk management (95), include optimal disease activity control with regular CVD risk assessment and treatment of hypertension and hypercholesterolemia. Glucocorticoids and NSAIDs should be prescribed with caution. As CVD risk prediction models tend to underestimate the risk for individuals with RA (153), they advocate a use of a 1.5 multiplicator factor in all patients with RA. In line with the European guidelines on CVD prevention (154), healthy lifestyle recommendations, including a healthy diet, regular exercise and smoking cessation, are emphasized for all patients irrespective of CVD risk. High-intensity exercise is recommended for those accustomed to activity. Swedish guidelines regarding CVD risk prevention in RA (155) are in line with the European recommendations.

Effect of exercise interventions on cardiovascular risk factors

Exercise has been shown to positively affect the cardiovascular profile (119), as measured by CRP (150), body composition (150, 156), endothelial function (157) and cardiac autonomic function (158), as well as aerobic capacity (150, 151, 159-161) and 10-year CVD event probability (150).

Factors related to physical activity

Numerous studies have been exploring possible factors related to physical activity in patients with RA. The somewhat disparate evidence has been reviewed by Larkin *et al,* who concluded that positive correlations were found between physical activity and motivation for physical activity, self-efficacy, perceived health and previous physical activity levels, while physical activity was negatively correlated with fatigue (162). A review of patients' perceived barriers, facilitators and benefits of physical activity and exercise, concluded that fatigue and pain were perceived both as barriers to physical activity, but reductions in the same variables were also perceived as benefits of physical activity (163).

Most studies reporting on factors related to physical activity have a cross-sectional design, thus, the findings do not provide evidence for a causal relationship between the variables studied. However, in a longitudinal study of a large cohort of RA patients, Demmelmaier *et al* found, that having a stable high physical activity level over two years, was mainly predicted by male sex and already established physical activity at baseline (117). Compared with having a stable low physical activity level, the group with stable high physical activity presented higher self-efficacy for exercise and less activity limitation (117). Baseline physical activity levels have proven to be a strong predictor also in other longitudinal studies (164, 165). Furthermore, changes in disease activity have been shown to correlate inversely with variations in physical activity as assessed by accelerometer (114) and by self-report (166).

Variables found to be associated with lower levels of physical activity are morning stiffness (115), longer disease duration, worse functional ability (106), radiographic joint damage (167), obesity (102), depression (168), as well as higher age, (167), lower formal education (108) and being white (103). Psychosocial variables have been shown to be more strongly correlated with physical activity behaviour than disease-related and sociodemographic ones (110, 116).

Rationale for this thesis

People living with RA experience a number of consequences of the disease, many of them beneficially affected by physical activity and exercise. Without adverse effects on disease activity, physical activity and exercise can positively affect joint and muscle function, aerobic capacity, balance, bone mass, functional ability, depression and perceived general health. The risk for CVD is substantially increased in RA. Studies of the general population as well as of patients with RA, show beneficial effects of physical activity on systemic inflammation as well as endothelial function and several traditional risk factors for CVD including body composition. The potential of physical activity as a treatment of RA is, therefore, substantial.

Although the effect of physical activity on CVD risk is well known and widely explored in the general population, it is a relatively new field of research in rheumatology. Many factors need to be further investigated. Since the habits of physical activity vary between countries in the general population and probably do so also among RA patients, we need more information on the physical activity levels of Swedish RA

patients. As yet, we know very little about the change of aerobic capacity from disease onset and over the years with RA, since knowledge is mainly based on cross-sectional studies. Furthermore, we need to better understand the effects of physical activity and exercise interventions on CVD risk factors, as well as factors associated with physical activity or aerobic capacity, in order to better guide our patients into a healthier lifestyle. Clearly, there are many areas that need further attention and this thesis addresses some of the aspects.

Aims

The overall aim for this thesis was to describe aspects of physical activity in patients with RA, with a prospective, cross-sectional as well as an interventional approach, and also to analyse associations with disease activity, cardiovascular risk factors and subclinical atherosclerosis.

The specific aims of the different papers included were:

I. To analyse joint and muscle function and aerobic capacity over 24 months in a group of patients with early RA in relation to age at disease onset and to measurement of pain and disease activity

II. To analyse aerobic capacity at disease onset and after 16 years and the change over time in patients with RA, and to describe factors associated with aerobic capacity at follow-up. We also aimed to identify possible associations between baseline aerobic capacity and future measures of CVD risk factors and atherosclerosis. Finally, we wished to identify baseline factors that predict aerobic capacity after 16 years

III. To objectively measure and compare the level of physical activity in patients with early and long-standing RA, and to investigate its associations with disease activity, risk factors for CVD and measures of subclinical atherosclerosis.

IV. To examine the effects of 10 weeks of spinning exercise on traditional risk factors for CVD, aerobic capacity and inflammation in patients with RA

Materials and Methods

Settings

Early rheumatoid arthritis clinic (TRAM, acronyme for Tidig Reumatoid Artrit Mottagning)

Since 1995, individuals with early RA (*i.e.*, symptomatic for <12 months) at the Department of Rheumatology, county of Västerbotten, have been included in the early rheumatoid arthritis clinic (TRAM), and followed prospectively. Those included are ≥18 years of age and all fulfil the criteria for RA according to the ACR (20). The department of Rheumatology is the only reference centre for rheumatological patients in the county. Thus, the TRAM cohort is very close to the actual adult RA population in Västerbotten. During regular visits over the years, patients are being evaluated regularly and offered pharmacological treatment following the standard care, aiming at remission. In addition, those included have regular contact with a multidisciplinary team including occupational therapist, physiotherapist, social worker and nurse during the first two years following diagnosis. Thereafter treatment is based on individual needs. The objective of rehabilitation is to minimize impairment and disability by providing information about how to manage different consequences of the disease. The importance of physical activity and exercise is emphasized, and patients are given advice about ways to overcome obstacles by finding more appropriate activities *etc*. Individual treatment is provided as and when needed. Participants in paper I-III were recruited from the TRAM cohort.

Subjects and study designs

An overview of the study designs and descriptive data for the participants included in paper I-IV is presented in Table 6.

Table 6. Overview of the study designs and descriptive data in paper I-IV. Data are presented as mean(SD), as median(Q1-Q3) or as number, as appropriate.

	Paper I		Paper II	Paper III		Paper IV
Study design	Prospective study		Prospective study	Cross-sectional study		Intervention study
Recruited from	TRAM (baseline values)		TRAM (follow-up values)	TRAM		Waiting list (baseline values)
Subgroups	Whole group	Tested for aerobic capacity		Early RA	Long-standing RA	
Sex, female/male, n	46/20	32/11	20/5	59/25	31/6	12/1
Age, years	50.9 (15.2)	43.6 (13.1)	58.0 (52.0-63.5)	56.1 (14.3)	58.4 (9.7)	57.0 (44.0-63.5)
Disease duration, years	0	0	16.2 (2.4)	1.4 (0.38)	16.3 (2.3)	12.0 (6.0-22.0)
DAS 28	4.6 (4.1-5.6)	4.5 (3.9-5.6)	2.93 (1.35)	2.79 (1.39)	2.79 (1.28)	3.2 (2.6-4.3)
Rheumatoid factor			24 (96)	64 (76)	33 (89)	
ACPA			19 (76)	58 (69)	24 (65)	
Pain, VAS, 0-100 mm	49 (25-72)	46 (23-63)	18 (7-60)	28 (25)	26 (26)	26 (18-40)
HAQ, 0-3			0.13 (0.0-0.32)	0.38 (0.0-0.75)	0.13 (0.0-0.5)	0.63 (0.19-0.88)

Disease duration=time since diagnosis. DAS28= Disease Activity Score, ACPA=Anti-citrullinated protein antibodies, VAS= Visual Analogue Scale, HAQ= Health Assessment Questionnaire.

Paper I

Sixty-eight patients, included in TRAM between 1995- 1999, were consecutively invited to participate in this prospective study. Sixty-six of them (44 women and 20 men) accepted and were followed for 24 months. Patients > 60 years of age or prescribed beta blocking medication, were excluded from the test of aerobic capacity.

Paper II

Patients eligible to participate in this prospective study were those incorporated in TRAM between 1995 and 2002. Additional inclusion criteria were: having performed test for aerobic capacity at the time of diagnosis, aged ≤75 years at follow-up and still living in Västerbotten county. Exclusion criteria were prescription of beta blocking medication and functional impairment hindering test of aerobic capacity. In total, 33 patients (26 women and 7 men) were invited to participate in the study, of these 25 (20 women and 5 men) accepted.

Paper III

Paper III is a cross-sectional study, including participants with early as well as long-standing RA, included in TRAM and aged ≤75 years. The early RA patients were diagnosed during the years 2013-2016, 12-24 months prior to consecutively being invited to participate in the study. Additionally, all patients included in TRAM in 1995-2002, still living in the county of Västerbotten, were invited as a group with long-standing disease. Exclusion criteria were serious lung, heart or neurological diseases and functional limitations, hindering physical activity to a higher extent than limitations caused by RA. Out of the 122 invited with early RA and 57 invited with long-standing RA, 84 with early and 37 with long-standing RA participated.

Paper IV

Sixty out-patients on a waiting list to the Department of Rheumatology, University Hospital, Umeå, were consecutively invited to participate in this intervention study. Inclusion criteria were: either sex, aged 18-69 years, a diagnosis of RA according to the

established 1987 criteria (20) and with a stable disease throughout the 3 months prior to entry into the study. Exclusion criteria were: inability to tolerate group cycling due to functional impairment including the presence of serious cardiac, lung or neurological disease(s). Patients prescribed beta-blockers were also excluded. Finally, 13 were included into the study group.

Assessments

An overview of assessments used in paper I-IV is presented in Table 7.

Table 7. Overview of assessments used in paper I, II, III and IV.

Paper	I	II	III	IV
Disease activity and severity				
DAS 28	X	X	X	X
CRP		X	X	X
Pain VAS	X	X	X	X
Rheumatoid factor		X	X	
ACPA		X	X	
Functional ability				
HAQ		X	X	X
Joint- and muscle function				
SOFI	X		X	
Cardiovascular risk factors				
Blood pressure		X	X	X
Blood lipids		X	X	X
Blood glucose		X	X	
Waist circumference		X	X	
Smoking habits		X	X	X
Atherosclerosis				
cIMT		X	X	
Pulse Wave Analysis		X	X	X
Body composition				
DXA		X	X	
BMI		X	X	X
Physical activity				
Actiheart monitor			X	
Aerobic capacity				
Sub-maximal ergometer test	X	X*		X
Self-efficacy				
ASES		X		

* age correction according to Tanaka et al (169). DAS28= Disease Activity Score, CRP= C-reactive protein, VAS= Visual Analogue Scale, ACPA= Anti-citrullinated protein antibodies, HAQ= Stanford Health Assessment Questionnaire, SOFI= Signals of Functional Impairment, cIMT= carotid intima-media thickness, DXA= Dual energy X-ray absorbtiometry, BMI= body mass index, ASES= Arthritis Self-Efficacy Scale.

Demographic and disease related data

Age, sex and disease duration were presented, as well as current medication. Erythrocyte sedimentation rate (Westergren method, mm/hour), CRP, RF and ACPA, were analysed according to routine methods. Disease activity was assessed by DAS28 (170), comprising the composite of the number of tender and swollen joints (171), the ESR and patient self-assessed general health on a Visual Analogue Scale (VAS, 0-100, higher scores represent a worse global health). In paper IV, the number of tender and swollen joints were self-assessed by the patient (172) and in paper I-III by a rheumatologist. The range of the DAS28 is 0-9.4 and a score of < 3.2 represent low, 3.2-5.1 moderate, and > 5.1 high disease activity (170). Response to therapy, based on DAS28, was defined according to the EULAR response criteria for RA (173). The area under the curve (AUC) (174) for DAS 28 was calculated from the values recorded at the time of diagnosis and during the following 24 months. Pain during the week preceding the assessment was self-assessed using VAS.

Traditional risk factors for cardiovascular disease

In papers II-IV, traditional CV risk factors were measured. Blood pressure (mm Hg) was measured during the pulse wave analysis, described below. Blood lipids (cholesterol, triglycerides and HDL) and blood glucose (mmol/L) were analysed according to routine pathology methods. Body mass index was calculated based on body weight and body height (kg/m^2) and waist circumference (cm) was measured midway between the lower costal margin and the iliac crest with the patient standing and the arms hanging freely. The measurement was made to the nearest 5 mm and performed at the end of a normal expiration. Any history of CVD and reported tobacco use were recorded.

Atherosclerosis

Pulse Wave Analysis (PWA) and carotid ultrasonography were used for measures of subclinical atherosclerosis.

Pulse wave analysis

Pulse wave analysis (PWA) was undertaken using an Arteriograph Type TL2 v.1.10.1.11 and v. 3.0.0.3 (TensioMed Ltd, Budapest, Hungary). The patients rested supine in a quiet room for 10 minutes before three measurements were made in the right arm with a simple upper arm cuff used as a sensor. The average values of brachial systolic and diastolic blood pressure (BP), aortic systolic BP (BPao), pulse pressure (PP), PWV, AIx and resting HR were noted (79). Reference values for PWV are available, based on participants living in eight European countries (175).

Carotis ultrasonography

A Seqoia 512 ultrasound system (Siemens [Acuson] Corp, Upplands-Väsby, Sweden) with a linear 9L transducer was used to measure the combined thickness of intimal and medial arterial wall, which constitutes the intima media thickness (cIMT). The artery wall was examined to identify areas of increased thickness, which represent early stages of atherosclerosis. During the examination, the patient was lying supine with the head slightly extended and directed away from the side being examined. The cIMT of the right and left common carotid artery (CCA) were measured on three end diastolic images (defined by R wave on attached tree lead electrocardiogram [ECG]) along one-centimeter long longitudinal segments of CCA just proximal to the carotic bulb. Based on the three measurements, mean values for cIMT was calculated for both sides (72). According to European guidelines on CVD prevention in clinical practice, a value > 0.9 mm is considered abnormal (154) and a value ≥ 75th percentile of the reference value for a person´s age, sex and race indicates increased CVD risk (72). According to the Carotid Atherosclerosis Progression Study (CAPS), the 75th percentile for 55 years old women and men are 0.78 mm and 0.84 mm respectively (72, 176).

Body composition

Dual energy X-ray absorptiometry (DXA) was used to measure body composition on a Lunar Prodigy X-ray Tube Housing Assembly, Brand BX-1L, Model 8743; GE Medical Systems, Madison, WI, USA). In paper III, about 20% of the patients were measured on

a Lunar iDXA Forma; GE Medical Systems, Madison, WI, USA, due to change of equipment at the laboratory. In DXA, small amounts of X-ray produce a total body image. The X-ray is composed of two energy levels that are absorbed differently by bone, lean and fat tissues. Using different algorithms, the computer software application assists in determining the amount of bone, lean and fat tissues based on these differences in absorption (177). During the test, the patients lie on their back and remain in their normal clothing, except for metal or thick plastic details, which need to be removed.

The components of body composition presented in this thesis are total body weight (kg), body mass index (BMI, kg/m^2), lean body mass (kg), fat free mass (kg), body fat per cent (%), android fat (g) and gynoid fat (g). The World Health Organization (WHO) defines overweight as BMI ≥ 25 kg/m^2 and obesity as BMI ≥ 30 kg/m^2. Lean body mass includes the combined weight of the internal organs, bones, muscles, water, ligaments and tendons. Included in this mass is the weight of the essential fat in the organs, central nervous system and bone marrow. To obtain the fat-free mass, the weight of the essential fat is subtracted from lean body mass. Body fat per cent is the total mass of fat divided by total body mass. Android fat is the distribution of fat mainly around the trunk and upper body, while the gynoid fat is distributed around the hips, thighs and bottom. In Swedish reference data including women and men aged 20-75 years, the average fat per cent was 33.7±7.8 % in women and 23.9± 6.6 % in men, with increasing values by age (178).

Functional ability

Functional ability was measured by the Health Assessment Questionnaire (HAQ), a questionnaire developed to measure functional ability in RA (179). It includes 20 questions in eight categories of functional activities – dressing, rising, eating, walking, hygiene, reach, grip, and usual activities, with the response on a scale from zero (no disability) to three (completely disabled). In every category, the highest scores are added, and finally divided by eight. The minimal clinically important difference has been set to 0.20 (180).

Joint and muscle function

In papers I and III, joint and muscle function was evaluated using a performance index, Signals of Functional Impairment (SOFI) (181). The index comprises four items for hand

function, four items for upper limb function and four items for lower limb function, using a rating scale with three alternatives (0 normal, 1 partly impaired, 2 unable to perform) for each. The resulting range of the SOFI score is 0-48. A score of less than 12 reflects mild impairment. The index is developed to measure functional impairment in RA and is sensitive to long-term changes of joint and muscle function. The validity and reliability are considered satisfactory (181).

Physical activity

In paper III, physical activity was measured using Actiheart (CamNtech Ltd., Cambridge, UK), a waterproof combined heart rate and movement monitor (Figure 2) (182). During the recordings, the data was stored in 30 second intervals. At the end of each interval, the mean of the last 16 R-R waves was converted to beats-per-minute and written to the memory. Uniaxial acceleration was measured as counts and summed up over the interval by a piezoelectric element contained in the monitor, generating an electric charge in response to time-varying acceleration.

Figure 2. The Actiheart monitor. Image source: CamNtech Ltd., Cambridge, UK (183).

The monitor was attached to the left side of the chest using two standard ECG electrodes (Red Dot 2560, 3M, St Paul, MN, USA). Prior to initializing the long-term recording, a signal test was performed in accordance with the manufacturer´s instructions (183), to ensure the correct placement of the device. The patients were thereby instructed to wear the monitor around the clock for seven consecutive days and to continue with their habitual activities. They were only to take the monitor off

for changing the ECG electrodes, which they were advised to do at least once during the week.

Data were then downloaded to a computer and cleaned from potential measurement noise. A valid day was defined as a day with at least 600 minutes of valid HR data. Adjustments were made for wear time and data was analysed regarding

- mean accelerometer counts per minute, as a measure of total volume of physical activity,
- time spent in MVPA, as per cent of wear time and as minutes per day,
- the proportion meeting the public health recommendations of daily MVPA ≥21.4 minutes (150 min/week),
- sedentary time, as percentage of wear time.

A cut-off for MVPA (3 METs), was estimated by 1.75 x resting HR, with resting HR defined as the median value of the 30 lowest HRs registered for each day of valid HR data (184). Sedentary time was calculated using intervals of valid HR data and zero accelerometer counts per minute. The results of the Actiheart measurements were compared with reference material based on Swedish and European population (185).

Aerobic capacity

In papers I, II and IV, aerobic capacity was estimated by a submaximal ergometer bicycle test described by Åstrand (paper I and IV; Monark Ergomedic 818E, paper II, Monark Ergomedic 818E in the baseline tests and Monark 928 G3 in the follow-up tests [Vansbro, Sweden]) (50) while wearing a chest worn heart rate monitor. The participants cycled at a constant pace for about six minutes until they reached steady state at about 50 % of maximal aerobic capacity. The patients rated their perceived exertion every minute during the test, which was terminated with a value of ≥17 (very hard) according to the Borg RPE Scale (Table 3) (34). The test value was estimated based on age, sex, body weight, work load and HR at steady state (48, 49). In paper II, an alternative correction for age was made by using the Tanaka equation (169). In paper II and IV, the patients were instructed to avoid heavy meals, exercise and the use of tobacco for at least two hours preceding the test. The test values were compared with Swedish reference data based on surveys from 1990/1991 (186) and 2000/2001 (187, 188) including men and women aged 20-65 years of age.

Self-Efficacy

Self-efficacy is explained as the confidence in one´s ability to perform a given behaviour, and regulates aspects of behaviour, as initiation and cessation of a behaviour and how much effort and time people spend on a task when facing obstacles (189). Exercise has been shown to promote self-efficacy, and programs designed to increase self-efficacy also increase exercise behaviour (190). Self-efficacy is an important predictor for sustained physical activity and exercise in patients with RA (163). In paper II, self-efficacy was determined using the questionnaire Arthritis Self-Efficacy Scale (ASES) (191, 192). The ASES comprises a total of 20 items, divided into three parts, concerning pain, function and other symptoms related to RA such as fatigue and depression. The scores are expressed as a value between 10 and 100 where a score of 10 represents the lowest possible self-efficacy level. The average score is calculated for each of the three parts. The instrument has been tested in patients with RA, showing sufficient validity and reliability (192, 193).

Exercise intervention

Figure 3. The spinning class. Photo Lars Ångström.

Paper IV was an evaluation of a 10-week aerobic exercise intervention. The exercise protocol was designed as a spinning class, *i.e*, interval group exercise, focusing on endurance and strength, using a stationary exercise bicycle. The sessions lasted for 45 minutes and were conducted 3 times each week for 10 weeks. The protocol, which is presented in Table 8, comprised warming up for 5 min followed by 30 min of pedalling at varying revolutions per minute (RPM) and work load corresponding to an exertion level of 13-17 (somewhat hard to very hard) according to the Borg RPE scale (34). The patients were able to choose a seated position during the whole class. The programme ended by gradually reducing the resistance, and finally, with stretching exercises for approximately 5 min. Two alternating physiotherapists gave instructions regarding variation in RPM, work load and technique. To ensure that the work load was within the desired interval, each subject rated their perceived exertion several times during every session. The participants were instructed to continue their everyday physical activities during the intervention period.

Table 8. Description of the spinning exercise protocol: technique, revolutions per minute (RPM) and rating of perceived exertion (RPE)

Minutes	**Technique**	**RPM**	**RPE (6-20)**
0-4	Warm up, technique instructions	65	11-12
4-8	Gradually increased resistance	65	13-15
8-12	Stand up or sit down with increased resistance, 20 secs x 3	50	15-17
12-15	Continuous pace and exercise load, technique instructions	65	15-16
15-19	Recovery	70	12-13
19-22	Gradually increased resistance x 3	70	14-16
22-25	Stand up or sit down with increased resistance, 20 secs x 3	55	16-17
25-29	Increased resistance in 3 steps	60	16-17
29-33	Alternating left/right leg, continuous pace and exercise load	66	15
33-36	3 high frequency intervals, “all-in”	maximum	17
36-39	Cooling down	70-30	15-11
39-45	Stretching of leg, neck and shoulder muscles	--	6-7

Ethical aspects

All studies in the thesis were performed in accordance with the Helsinki Declaration and were approved by the Regional Ethical Review Board of the University in Umeå, Sweden (paper I: Fek 99-097, § 141/99, paper II, III: Dnr 2014/356-31 and paper IV: Dnr 2011-63-31M). The participants left their consent after receiving oral and written information. In papers II-IV, the written information was constructed in collaboration with a representative from the patient organisation. The participants were informed that they could withdraw their participation whenever they wanted to during the study. Patients with serious disease and old age were excluded and a medical risk assessment was made before inclusion, in order to minimize the risk for adverse events during the tests. During the strenuous tests, the participants assessed their perceived exertion using the Borg RPE scale (34), and the test was interrupted with an assessment of 17 (very hard exertion level). Furthermore, medical staff, emergency alarm and defibrillator were available, however never used.

Statistical methods

Statistical analyses were performed using the Statistical Package of Social Sciences (SPSS), versions 10, 18 and 24 (IBM, Armonk, NY, US). In paper II and III, the value of skewness (SD) was considered for decision regarding normal distribution. Data was considered normally distributed when the value of skewness was <1 and within twice the standard error of skewness. Clinical data were presented as median with inter-quartile range (Q1-Q3), as mean ±1 standard deviation (SD) or as number with percentage (%), as appropriate.

Differences between groups were tested by the Mann-Whitney U-test, independent samples t-test or Chi^2 test. Changes for the same group over three time points were tested in papers I and IV, using the non-parametric Friedman two-way analysis of variance by ranks and further with the paired Wilcoxon rank sum test. In paper II, differences between two time points were analysed with the paired Wilcoxon rank sum test or paired t-test depending on whether the data was normally distributed or not.

Further, correlations between variables were analysed with Spearman´s rank correlation test and presented as r_s with a corresponding p-value. In paper II, univariate linear regression analyses were performed to evaluate the effect of baseline variables on aerobic capacity at follow-up. Variables with a p-value ≤ 0.2 were further analysed in multiple linear regression analysis to establish the best fitting models, depicting predictors for aerobic capacity at follow up. In paper III, univariate regression analysis was performed to evaluate the associations between variables of physical activity (dependent variables) and independent variables reflecting disease activity, CV risk factors and subclinical atherosclerosis. In the next step, multiple regression analysis was applied, where every independent variable was analysed in a separate model, adjusted for age, sex, disease duration and Actiheart wear time. In the third step, multiple linear regression modelling was performed in order to determine the presence of significant and independent factors associated with total volume of physical activity, using variables with a p-value ≤0.2 and adjusting for age, sex, disease duration and Actiheart wear time. Due to skewed distribution, the dependent variables were log-transformed in the regression analyses of paper III. Results of the linear regression analyses were presented using β, which denotes the effect of the independent variable on the dependent variable, the R^2, which presents the extent to which the model explains the variance of the dependent variable, with a corresponding 95% confidence interval (CI) and p-value. The value for statistical significance was set at a p-value of <0.05.

In paper I, imputation using the last observation carried forward method was used for missing values. Furthermore, in 18 patients, the first self-assessments of SOFI and in six patients, the first tests of aerobic capacity, were performed six months after diagnosis. According to routine in TRAM, patients were assessed every six months during the first two years of disease. Since analyses performed at inclusion and after six months did not differ in the rest of the group, results of SOFI and aerobic capacity from the six months assessments were used as inclusion measures in 18 and six patients respectively.

In paper I, the patients were dichotomized according to sex, age (medium age), SOFI scores (a score of 0 vs a score of 1 or 2 in the separate items) and response to therapy, defined according to the European League Against Rheumatism (EULAR) response criteria for RA (173) (no response vs moderate or good response). The p-value was corrected for the number of comparisons (P_c), when appropriate.

In paper II, patients were divided into groups according to sex, age and level of aerobic capacity (at the median values for age and aerobic capacity for the whole group). Analyses were also made based on response to therapy (no or moderate response vs

good response). Some data were missing at baseline, and thereby, the number of values included in the separate analyses were presented in the paper. Two patients were tested for aerobic capacity six months after diagnosis, however, those two were included in the analyses as the baseline values.

In paper III, patients were dichotomized and comparisons were made between patients with early and long-standing RA. There were no differences between the groups in the presented variables of physical activity as well as age, sex, and DAS28, and subsequently, the two groups were combined in the analyses of associations.

Results

Paper I

Joint- and muscle function

Joint- and muscle function was impaired in 61 out of 66 patients at the time of diagnosis and after 24 months 59 out of 66 patients still had impairments. At baseline, impairment was most commonly found in hands and feet. The metatarsophalangeal (MTP) joint function was impaired in 64% of the patients, finger flexion in 43%, pincer grip in 29% and thumb opposition in 21%. Further, elbow extension was impaired in 23% and hip function in 22% of the patients. The summed SOFI score decreased significantly for the whole group at 12 months (p_c= 0.042) but increased again significantly at 24 months (p_c= 0.048) to a score not significantly different from the baseline values. With few exceptions the younger patients were significantly less impaired than the older patients over the 24 months.

Disease activity (DAS 28) decreased significantly (p= 0.0001) during the period of 24 months; from a median (Q1-Q3) at inclusion of 4.6 (4.1-5.6) to 3.5 (2.8-4.5). The median value (Q1-Q3) of VAS pain for the whole group was 49 (25-72) at inclusion with a significant decrease to a stable level of 30 (15-46) after 12 months (p< 0.001). The SOFI and the DAS28 scores correlated with the strongest relationship at inclusion, while SOFI and pain correlated at inclusion but not at the follow-up at 12 and 24 months (Table 9).

Aerobic capacity

The aerobic capacity remained unchanged during the 24 months, for the whole group and when stratified for sex and age. When comparing responders with non-responders at 24 months, the responders had a higher aerobic capacity compared with non-responders both at 12 and 24 months (p= 0.024 and p= 0.005, respectively) (Table 10).

Table 9. The calculated correlation coefficients (r_s) between the four scores of Signals of Functional Impairment (SOFI) index and Disease Activity Score (DAS 28) and pain (VAS) at inclusion and at 12 and 24 months.

	DAS 28	**Pain VAS**
SOFI inclusion		
Hand	.125	.144
Upper extremities	**.343****	**.369****
Lower extremities	**.311***	.226
Summed	**.382****	**.343****
SOFI 12 months		
Hand	.201	.023
Upper extremities	.128	.088
Lower extremities	**.282***	.147
Summed	.236	.083
SOFI 24 months		
Hand	.208	.207
Upper extremities	**.248***	.181
Lower extremities	.188	.133
Summed	**.295***	.235

*p< 0.05, **p< 0.01

Table 10. Aerobic capacity (ml O_2/kg/min) for the whole group and sub groups at each time point. Data are presented as median and inter-quartile range (Q1-Q3) and the p-value refers to Mann-Whitney U-test.

Aerobic capacity	Whole group (n=43)	Responders[1] (n= 28)	Non-responders[1] (n= 15)	p[2]
Inclusion	31 (27-39)	32 (28-43)	28 (22-35)	n.s.
12 months	32 (26-38)	33 (28-39)	29 (25-33)	**0.024**
24 months	33 (25-38)	36 (26-40)	26 (23-33)	**0.005**

[1]response and no response to therapy at 24 months according to EULAR response criteria (173).
[2] responders compared with non-responders at 24 months.
n.s.= not significant.

Paper II

Aerobic capacity at disease onset and at follow-up

Aerobic capacity was maintained over the 16.2 years of follow-up for the whole group and was, compared with Swedish reference values (187), slightly below average at baseline and above average at follow-up for both men and women. Women had higher values than men at both time points (Table 11), but the median age for men was higher compared with women (48.0 vs 37.5 years at baseline). Dichotomizing into a younger and an older group at the median age (40 years) showed a numerical deterioration in the younger but improvement in the older patients, with a statistically significant difference between younger and older patients at baseline, but not at the time of follow-up (p=0.002 and p=0.103 respectively).

When dichotomizing the patients according to response (n= 12) and no response (n=13) to therapy at 24 months, no statistically significant changes over time or differences between the groups were found.

Measures related to aerobic capacity at follow-up

The correlation analyses between variables at follow-up and aerobic capacity at the same time point showed that higher aerobic capacity associated with lower levels of blood glucose (r_s=-0.508, p=0.016), BMI (r_s=-0.434, p=0.030), body fat (r_s=-0.419, p=0.037), aortic PP (r_s=-0.405, p=0.044) and resting HR (r_s=-0.424, p=0.034) as well as higher self-efficacy for performing different tasks (r_s=0.464, p=0.020).

Table 11. Aerobic capacity and self-efficacy in 25 patients with RA at baseline and at follow-up. Data are presented as median with inter-quartile range (Q1-Q3) and the p-value refers to Wilcoxon signed ranks test.

	Baseline	Follow-up	p
Aerobic capacity, ml O_2/kg/min*	32.3 (27.9-42.1)	33.2 (28.4-38.9)	.443
Women, n=20*	32.7 (29.4-42.7)	34.1 (27.6-41.2)	
Men, n=5*	27.7 (19.6-35.6)	31.6 (29.0-34.0)	
Younger*	41.7 (32.4-47.9)	36.4 (27.9-44.2)	
Older*	28.0 (26.4-32.0)	31.6 (28.4-34.1)	
Responders at 24 months*	29.7 (27.3-35.4)	32.8 (27.4-34.6)	
No responders at 24 months*	41.7 (29.1-45.9)	33.2 (29.7-41.4)	
Aerobic capacity, L O_2/min*	2.17 (1.91-2.48)	2.34 (2.13-2.59)	.253
Women, n=20*	2.17 (1.90-2.49)	2.29 (1.93-2.54)	
Men, n=5*	1.96 (1.87-2.75)	2.52 (2.39-3.44)	
Aerobic capacity, ml O_2/kg/min#	32.0 (28.0-43.5)	31.0(27.0-37.3)	.089
Women, n=20#	34.0 (30.0-44.7)	32.0 (26.9-37.8)	
Men, n=5#	27.0 (23.0-35.0)	31.0 (28.0-37.5)	
ASES			
Pain, (10-100) n=15	64.0 (36.0-74.0)	66.0 (48.0-84.0)	.443
Function, (10-100) n=16	99.0 (70.0-100.0)	95.6 (88.4-98.9)	.308
Other symptoms, (10-100) n=15	78.3 (51.6-88.3)	78.3 (67.5-90.0)	.198
Total, (10-100) n=14	77.9 (56.8-85.3)	80.9 (67.6-88.1)	.433

* age correction according to Tanaka et al. # age correction according to Åstrand et al. ASES= Arthritis Self-Efficacy Scale.

Associations between baseline aerobic capacity and follow-up measures

Patients with higher aerobic capacity at baseline were younger and presented more favourable values at follow-up in terms of aerobic capacity, BMI, body weight, waist circumference, brachial PP and self-efficacy for performing different tasks (Table 12).

Baseline measures predicting aerobic capacity after 16 years

The simple regression analyses between baseline variables and aerobic capacity at follow-up, revealed that DAS28 at inclusion (β=-3.01, p=0.019), DAS28 at 24 months (β=-2.09, p=0.036), AUC DAS28 0-24 months (β=-0.15, p=0.014) and aerobic capacity at baseline (β=0.45, p=0.004) predicted the level of aerobic capacity at follow-up. DAS28 at inclusion (p=0.017), DAS28 at 24 months (p=0.005) and AUC DAS28 0-24 months (p=0.039) showed the same associations with aerobic capacity at follow-up when measured as L/min.

Table 12. Correlation coefficients (r_s) for aerobic capacity (ml O_2/kg/min) at baseline in relation to other variables at follow-up. The correlations were calculated using the Spearman rank correlation coefficient method.

Variables at follow-up	**Aerobic capacity at baseline**	
	r_s	**p**
Age, years	-.469	**.018**
CRP, mg/L	-.373	.072
Glucose, mmol/L	-.392	.071
Aerobic capacity, ml O_2/kg/min	.557	**.004**
DXA		
BMI, kg/cm^2	-.401	**.047**
Body weight, kg	-.409	**.043**
Body fat, %	-.140	.506
Android fat, %	-.222	.287
Waist circumference, cm	-.498	**.011**
Pulse Wave Analysis		
Systolic BP, mm Hg	-.385	.057
Diastolic BP, mm Hg	-.295	.153
PP bra, mm Hg	-.415	**.039**
PP ao, mm Hg	-.286	.166
Systolic BP ao, mm Hg	-.352	.084
Resting HR, beats/min	-.379	.062
PWV, m/s	-.370	.069
ASES function	.420	**.037**

CRP=C-reactive protein, DXA= dual energy X-ray absorbtiometry, BMI=body mass index, BP=blood pressure, PP bra=brachial pulse pressure, PP ao=aortic pulse pressure, BP ao= aortic blood pressure, HR= heart rate, PWV=pulse wave velocity, ASES function= Arthritis Self-Efficacy Scale subscale for performing different tasks.

Subsequently, multiple linear regression analysis was performed to find the model best explaining the variation in aerobic capacity at follow-up. Disease activity during the first 24 months after diagnosis (AUC DAS28) explained 53 % of the aerobic capacity level at follow-up, after adjusting for baseline aerobic capacity (Table 13, model 3). Furthermore, the impact of self-efficacy was evaluated in addition to baseline aerobic capacity and AUC DAS28. This model included only 14 patients but explained 71 % of the variation in aerobic capacity levels at follow-up.

Table 13. Three multiple linear regression models. Variables in early disease associated with aerobic capacity (ml O_2/kg/min) at follow-up.

	Model 1			**Model 2**			**Model 3**		
	β (CI 95%)	**R^2**	**p**	**β (CI 95%)**	**R^2**	**p**	**β (CI 95%)**	**R^2**	**p**
Aerobic capacity baseline	0.37(0.07- 0.66)	.40	.018	0.44(0.17- 0.70)	.46	.003	0.44(0.20- 0.69)	.53	.001
DAS28 baseline	-2.09(-4.43- 0.25)	.40	.077	-	-	-	-	-	-
DAS28 24 months	-	-	-	-1.96(-3.58- -0.35)	.46	.020	-	-	-
AUC DAS28 0-24 months	-	-	-	-	-	-	-0.14(-0.23- -0.05)	.53	.004

DAS=Disease Activity Score, AUC DAS28= Area under the curve for Disease Activity Score.

Paper III

There were no differences in total physical activity or in the proportion of MVPA and sedentary time between patients with early and long-standing RA (Table 14). However, 31 (37%) of the patients with early and 16 (43%) of the patients with long-standing RA, did not reach national recommendations of 21.4 minutes of MVPA per day (150 minutes per week).

Table 14. Comparisons of physical activity variables in patients with early and long-standing RA. Data are presented as median with inter-quartile range (Q1-Q3) and the p-value refers to Mann-Whitney U-test.

	Early RA (n=84)	**Long-standing RA** (n=37)	**p**
Total physical activity			
mean accelerometry counts per minute	35.7 (24.7-54.6)	38.1 (26.4-50.7)	.915
MVPA			
% of wear time	3.2 (0.9-7.5)	2.5 (1.1-6.6)	.884
minutes per day	34.3 (8.8-75.2)	26.5 (10.8-74.2)	.933
Sedentary time			
% of wear time	53.8 (48.6-59.6)	52.0 (45.8-59.1)	.328

MVPA= moderate to vigorous physical activity. Corresponds to time ≥ 1.75 x resting HR. Sedentary time corresponds to time with valid HR data and simultaneous zero accelerometer counts per minute.

Variables associated with total volume of physical activity

In univariate linear regression analyses, lower level of physical activity was associated with older age and higher levels of ESR and HAQ. In addition, physical activity was inversely associated with a number of CV risk factors, *i.e.,* triglycerides, blood glucose, BMI, body fat, waist circumference, sleeping HR, brachial systolic and diastolic BP, aortic systolic BP and PP as well as subclinical atherosclerosis*, i.e.,* PWV, AIx and cIMT (Table 15, A). Subsequently, when the separate variables were adjusted for age, sex, disease duration and Actiheart wear time, significant associations remained for all variables, except for triglycerides, aortic PP, PWV, AIx and cIMT (Table 15, B).

Table 16 presents the result of the multiple linear regression modelling with the same adjustments (age, sex, disease duration and Actiheart wear time). The final model explained 39% of the variation of total physical activity. Lower body fat was still strongly associated with higher total physical activity. The associations with disease activity was no longer evident, however, patients with lower functional ability were less physically active.

Table 15. Linear regression analyses for variables in relation to (Log) total physical activity (mean accelerometer counts per minute).

	Mean accelerometer counts per minute			
	A		**B**	
	β (95% CI)	**p**	**β (95% CI)**	**p**
Age, years	-.015 (-0.022- -0.008)	**.000**		
Sex (male=0, female=1)	.152 (-0.069- 0.373)	.177		
Disease duration, years	.000 (-0.001- 0.001)	.783		
DAS28	-.035 (-0.107- 0.038)	.343	-.013 (-0.083- 0.057)	.716
ESR, mm/h	-.011 (-0.020- -0.002)	**.013**	-.009 (-0.018- 0.000)	**.042**
HAQ	-.330 (-0.542- -0.117)	**.003**	-.357 (-0.556- -0.158)	**.001**
Cholesterol, mmol/L	-.044 (-0.141- 0.053)	.370	.023 (-0.071- 0.117)	.627
Triglycerides, mmol/L	-.181 (-0.329- -0.033)	**.017**	-.091 (-0.234- 0.052)	.210
HDL, mmol/L	.156 (-0.045- 0.358)	.127	.109 (-0.082- 0.300)	.260
LDL, mmol/L	-.063 (-0.176- 0.050)	.269	.017 (-0.091- 0.126)	.751
Glucose, mmol/L, n=88	-.161 (-0.238- -0.085)	**.000**	-.121 (-0.199- -0.042)	**.003**
Smoker, yes=1	-.205 (-0.528- 0.119)	.213	-.163 (-0.465- 0.138)	.285
BMI, kg/m^2	-.037 (-0.055- -0.018)	**.000**	-.034 (-0.051- -0.017)	**.000**
Body fat, %	-.018 (-0.028- -0.008)	**.000**	-.023 (-0.033- -0.012)	**.000**
Waist circumference, cm	-.014 (-0.020- -0.008)	**.000**	-.011 (-0.017- -0.005)	**.001**
Sleeping HR, beats/min	-.014 (-0.027- -0.002)	**.026**	-.013 (-0.025- -0.001)	**.037**
Systolic BP, mm Hg	-.011 (-0.016- -0.005)	**.000**	-.008 (-0.013- -0.002)	**.006**
Diastolic BP, mm Hg	-.015 (-0.024- -0.006)	**.001**	-.010 (-0.019- -0.001)	**.025**
Systolic BP ao, mm Hg	-.009 (-0.014- -0.005)	**.000**	-.006 (-0.011- -0.001)	**.025**
PP ao, mm Hg	-.013 (-0.021- -0.006)	**.001**	-.007 (-0.017- 0.002)	.116
PWV, m/s	-.079 (-0.119- -.0038)	**.000**	-.038 (-0.086- 0.009)	.115
AIx bra, %	-.004 (-0.007- 0.000)	**.031**	.000 (-0.004- 0.003)	.851
AIx ao, %	-.007 (-0.014- -0.001)	**.023**	-.001 (-0.008- 0.007)	.843
cIMT, mm	-.615 (-1.151- -0.079)	**.025**	.056 (-0.544- 0.656)	.853

A: unadjusted univariate regression analyses. B: univariate regression analyses, adjusted for age, sex, disease duration and Actiheart wear time.

DAS28= disease activity score, ESR= erythrocyte sedimentation rate, HAQ= Health Assessment Questionnaire, HDL= high density lipids, LDL= low density lipids, BMI= body mass index, HR= heart rate, BP=blood pressure, BP ao= aortic blood pressure, PP ao= aortic pulse pressure, PWV= pulse wave velocity, AIx bra= brachial augmentation index, AIx ao= aortic augmentation index, cIMT= carotid intima media thickness.

Table 16. Multiple linear regression model presenting variables associated with total physical activity (mean accelerometer counts per minute).

	β	CI 95%	p
Body fat, %	-.022	-0.032- -0.011	**.000**
HAQ	-.204	-0.403- -0.006	**.044**
ESR, mm/h	-.003	-0.011- 0.006	.513

Adjusted for age, sex, disease duration and Actiheart wear time.
HAQ= Health Assessment Questionnaire, ESR= erythrocyte sedimentation rate.

Variables associated with MVPA

Younger patients spent more time in MVPA, and higher proportion of MVPA was associated with more favourable values of HDL, LDL, blood glucose, waist circumference, sleeping HR and PWV (Table 17, A). After adjustments for age, sex, disease duration and Actiheart wear time, more time spent in MVPA was associated with lower levels of HAQ, and significant associations remained with HDL, blood glucose and sleeping HR (Table 17, B).

Table 17. Linear regression analyses for variables in relation to (Log) MVPA (% of wear time).

	MVPA %			
	A		B	
	β (95% CI)	p	β (95% CI)	p
Age, years	-.037 (-0.059- -0.015)	**.001**		
Sex (male=0, female=1)	.189 (-0.494- 0.872)	.584		
Disease duration, years	.000 (-0.004- 0.003)	.930		
ESR, mm/h	-.013 (-0.041- 0.016)	.375	.002 (-0.028- 0.031)	.914
HAQ	-.585 (-1.252- 0.082)	.085	-.718 (-1.394- -0.042)	**.038**
HDL, mmol/L	.805 (0.199- 1.410)	**.010**	.800 (0.188- 1.412)	**.011**
LDL, mmol/L	-.411 (-0.751- -0.071)	**.018**	-.336 (-0.688- 0.016)	.061
Glucose, mmol/L, n=88	-.456 (-0.699- -0.214)	**.000**	-.401 (-0.658- -0.144)	**.003**
Waist circumference, cm	-.025 (-0.045- -0.005)	**.013**	-.020 (-0.041- 0.002)	.074
Sleeping HR, beats/min	-.064 (-0.102- -0.026)	**.001**	-.053 (-0.092- -0.015)	**.007**
PWV, m/s	-.165 (-0.293- -0.037)	**.012**	-.069 (-0.226- 0.089)	.390

A: unadjusted univariate regression analyses. B: univariate regression analyses, adjusted for age, sex, disease duration and Actiheart wear time.
ESR= erythrocyte sedimentation rate, HAQ= Health Assessment Questionnaire, HDL= high density lipids, LDL= low density lipids, HR= heart rate, PWV= pulse wave velocity.

Paper IV

At baseline, the median aerobic capacity of the 13 participants was 26 ml O_2/kg/min and the median systolic and diastolic BP was 138/84 mm Hg (Table 18). Overall, the subjects participated in 76% of the exercise sessions offered.

Changes over time

Shown in Table 18 are the recorded parameters at baseline, and at 10 and 25 weeks respectively. After the exercise period of ten weeks, there were significant improvements in terms of aerobic capacity, systolic BP, and the number of tender joints compared with baseline. Diastolic BP and systolic BP in aorta improved at 10 weeks, though not to a significant level. At 25 weeks, there were still significant improvements in systolic BP and at 25 weeks, BMI was also significantly improved compared with baseline. Other variables reflecting disease activity, as well as functional ability, were stable throughout the study.

Correlations

Table 19 presents the correlations between inflammatory markers and disability in relation to baseline aerobic capacity and changes in BP at 10 weeks. At baseline, participants with higher disease activity (as measured by ESR, CRP) and worse functional ability (higher ratings in HAQ) showed lower aerobic capacity. Levels of inflammation (tender joint count, pain, CRP, DAS 28) at 10 weeks showed a negative correlation with changes in BP, *i.e.,* participants with higher disease activity at ten weeks improved less after completing the exercise programme. Functional ability (HAQ) at baseline and at 10 weeks correlated inversely with changes in systolic BP after 10 weeks.

Table 18. Measures within the exercise group (n=13) at 10 and 25 weeks compared with baseline. Data are presented as median and inter-quartile range (25-75%).

	Baseline	**10 weeks**	**25 weeks**
Aerobic capacity, ml O_2/kg/min	26.0 (19.0-36.0)	33.0 (23.5-37.5)*****	31.0 (22.5-36.5)**†**
Systolic BP, mm Hg	137.8 (120.4-152.5)	126.0 (113.8-137.7)******	126.0 (117.8-139.2)**# †**
Diastolic BP, mm Hg	83.8 (72.8-92.4)	73.0 (70.0-88.4)	80.0 (74.8-88.6)
Systolic BP ao, mm Hg	137.7 (114.0-150.6)	118.0 (107.4-141.6)	122.0 (115.4-136.7)
Cholesterol, mmol/L	5.1 (4.8-6.2)	5.8 (4.7-6.0)	6.0 (5.1-6.4)
Triglyceride, mmol/L	1.15 (0.74-1.34)	1.12 (0.98-1.58)	1.00 (0.76-1.42)
BMI, kg/m^2	25.4 (22.5-31.3)	24.7 (22.4-30.1)	24.4 (21.6-29.2)**# †**
ESR, mm/h	8.0 (8.0-15.5)	10.5 (7.2-11.8)	11.0 (9.0-16.5)
CRP, mg/L	5.0 (5.0-12.0)	6.0 (3.5-10.2)	5.0 (1.4-10.0)
DAS 28	3.2 (2.6-4.3)	2.6 (2.4-3.7)	2.3 (2.1-3.4)
Tender joint count, n	2.0 (2.0-9.0)	2.0 (1.5-4.0)*****	1.0 (0.0-4.5)**†**
Swollen joint count, n	1.0 (0.0-6.0)	0.0 (0.0-4.0)	0.0 (0.0-1.0)
Global health, VAS, cm	1.9 (1.2-4.2)	1.8 (0.9-3.7)	1.5 (0.2-4.0)
Pain, VAS, cm	2.6 (1.8-4.0)	1.8 (0.8-5.0)	1.8 (0.2-4.0)
HAQ	0.63 (0.19-0.88)	0.38 (0.12-0.88)	0.50 (0.12-0.94)

† $p < 0.05$ (Friedman´s test). * $p < 0.05$ ** $p < 0.01$, 10 weeks vs. baseline, # $p < 0.05$, 25 weeks vs. baseline (Wilcoxon signed rank sum test). BP= blood pressure, ao= aorta, BMI= body mass index, ESR= erythrocyte sedimentation rate, CRP= C-reactive protein, DAS28= Disease Activity Score, VAS= Visual Analogue Scale, HAQ= Health Assessment Questionnaire.

Additional analyses

The results found in paper II, regarding relationships between aerobic capacity and CV risk factors, subclinical atherosclerosis and inflammation, have led to complementary analyses (unpublished, Table 20): At baseline, aerobic capacity was inversely related to BMI and PWV. Aerobic capacity after the exercise period at 10 weeks, was inversely related to resting HR and PWV. Further, at the follow-up at 25 weeks, higher aerobic capacity correlated with lower values for systolic BP, resting HR and PWV. The inverse

relation between disease activity and aerobic capacity at baseline, was no longer prevalent at ten or 25 weeks.

Table 19. Correlation coefficients (r_s) between inflammatory markers and functional ability at baseline and at 10 weeks in relation to baseline aerobic capacity (ml O_2/kg/min) and changes (delta values) of blood pressure (BP) at 10 weeks. The correlations were calculated using the Spearman rank correlation coefficient method.

	Baseline	**Changes (delta values) at 10 weeks**		
	Aerobic capacity	**Diastolic BP**	**Systolic BP**	**Systolic BPao**
Baseline				
ESR, mm/h	-.687**	-.122	.142	.076
CRP, mg/L	-.727**	-.366	-.487	-.454
HAQ	-.572*	-.028	-.576*	-.526
10 weeks				
Tender joint count	-.038	-.173	-.556*	-.513
Pain	-.348	-.011	-.620*	-.468
CRP, mg/L	-.390	-.661*	-.765**	-.629*
DAS 28	.000	-.580*	-.495	-.545
HAQ	-.656*	-.153	-.601*	-.535

* $p < 0.05$ ** $p < 0.01$. ESR= erythrocyte sedimentation rate, CRP= C-reactive protein, HAQ= Health Assessment Questionnaire.

Table 20. Correlation coefficients (r_s) between aerobic capacity (ml O_2/kg/min) and risk factors for CVD at baseline, at ten and 25 weeks. The correlations were calculated using the Spearman rank correlation coefficient method.

		Aerobic capacity	
	Baseline	**10 weeks**	**25 weeks**
BMI, kg/m^2	-.584*	-.551	-.469
Systolic BP, mm Hg	-.424	-.388	-.574*
Resting HR	-.501	-.601*	-.575*
PWV ao, m/s	-.623*	-.782**	-.745**

* $p < 0.05$ ** $p < 0.01$. BMI= Body Mass Index, BP= blood pressure, HR= heart rate, PWV ao, aortic pulse wave velocity.

General discussion

Main findings

The present work describes aspects of physical activity, with a prospective, cross-sectional as well as interventional approach, and further, analyses associations with disease activity, traditional cardiovascular risk factors and subclinical atherosclerosis in patients with RA. In conclusion, the level of aerobic capacity was maintained from disease onset and over the follow-up periods of two and 16 years, respectively. In paper I, patients with response to therapy two years after diagnosis had higher aerobic capacity compared with patients without response. In paper II, higher disease activity during the first two years after diagnosis predicted lower aerobic capacity after 16 years. Higher aerobic capacity at the time for diagnosis implicated more favourable CVD risk profile after 16 years and the association between aerobic capacity and CVD risk factors was found also at the time of follow-up after 16 years. Paper III, presented similar levels of physical activity and sedentary time in patients with early and long-standing RA. Physical activity was associated with more favourable values for CVD risk factors and markers for subclinical atherosclerosis. Higher disease activity related to less time spent on physical activity. The pilot study showed, that the intervention with spinning exercise was feasible for the group of RA patients included, and that ten weeks of spinning exercise positively affected aerobic capacity and CV risk factors.

Aerobic capacity

In a review by Munsterman, people with RA were considered to have low aerobic capacity compared to normal values (8). In paper I and II, aerobic capacity was higher among our subjects than in several other studies published (Table 5) and the participants also had been able to maintain their aerobic capacity during the two years and 16 years of follow-up. This is a promising finding, since the importance of physical activity and exercise is highly emphasized to the patients participating in the TRAM clinic. Aligned with our results, Häkkinen et al, compared three groups of physically active women with early RA, long-standing RA and healthy controls. No difference in aerobic capacity was found between the three groups, which, suggested by the

authors, indicated that it was possible for physically active women to maintain their aerobic capacity despite several years of RA (128).

In paper I, the median (Q1-Q3) aerobic capacity of the patients included was 31 (27-39) ml/kg/min at the time of diagnosis and 33 (25-38) ml/kg/min after 24 months. The corresponding baseline values in paper II were 32 (28-44) ml/kg/min at baseline and 31 (27-37) ml/kg/min after 16 years, (32 [28-42] ml/kg/min and 33 [28-39] ml/kg/min when using the Tanaka equation (169) for age correction). The values of aerobic capacity can be evaluated in light of the cut-off value of 28 ml/kg/min, for increased CV risk and all-cause mortality in the general population, published by Kodama *et al*. (59). However, test values below 35 ml/kg/min for women and 44 ml/kg/min for men, have shown to increase the risk for having a cluster of CV risk factors (194), showing the need for improvements of aerobic capacity in patients with RA. Our results are in contrast with a recent study from UK, presenting mean (SD) 21 (5) ml/kg/min in 96 RA patients with a disease duration of 8 years (152), but closer to the test result of mean (SD) 29 (9) ml/kg/min, presented in a Swedish study of 220 patients with 12 years of disease (151), and also in concordance with Eurenius et al, who presented values similar to norm data for Swedish RA patients after 6.5 years of disease duration (9).

Nonetheless, in comparisons with norm data, we must bear in mind, that a great part of the general population is too physically inactive with regard to current recommendations, and thereby may have lower levels of aerobic capacity than desired. Furthermore, findings from older studies, performed when patients were more physically impaired due to less efficient medical and rehabilitative care, complicates comparisons with recently published studies.

Physical activity

Total volume of physical activity as well as the proportion of MVPA and sedentary time, were measured and compared between patients with early and longstanding RA. Interestingly, no significant differences were found between the groups, and disease duration was not associated with the three aspects of physical activity measured. No difference in age, DAS28 and HAQ was found between the groups, which may contribute to the similar physical activity behaviour. Both groups met the public health recommendations of physical activity (39). However, MVPA was not measured in bouts of at least ten minutes, which is specified in the recommendations. Furthermore, the

variation was large, and 37% of the patients with early and 43% of the patients with long-standing RA, failed to reach the recommended levels of physical activity.

Studies presenting objectively measured MVPA in patients with early RA are sparse, but when self-assessed in a Swedish randomized controlled study including 228 patients, close to 50% achieved the recommended level of physical activity (109), and in patients with a symptom duration of 16 weeks, 69% reached the recommended levels. One year later, after the initiation of medical treatment, the proportion had increased to 89% (166).

Findings from studies analysing objectively measured physical activity in patients with several years of disease present daily MVPA varying from median (IQR) 14 (0-34) min/day (47), mean (SD) 19 (19) min/day (134) up to median 36 min/day (101) (Table 4). The corresponding daily MVPA in our study was median (Q1-Q3) 34 (9-75) min/day in early and 26 (11-74) min/day in long-standing RA, respectively. When compared with objectively measured MVPA in healthy people living in ten European countries, RA patients can be considered less physically active. In that study, the Swedish women and men, aged mean (SD) 52(8) years, spent median (Q1-Q3) 86 (55-120) and 112 (74-166) min/day respectively, in MVPA (185).

Disease activity

Disease activity seems to be related to aerobic capacity as well as physical activity behaviour. In paper I, II and IV, we found associations between disease activity and aerobic capacity. In paper I, we found that patients who responded to therapy (173), measured at 24 months after diagnosis, had significantly higher aerobic capacity compared with non-responders both after 12 and 24 months of disease. Multiple regression modelling in paper II, showed, that disease activity in early disease predicted the level of aerobic capacity after 16 years after adjusting for baseline values of aerobic capacity. In paper IV, the relationships between markers of inflammation (measured as ESR and CRP) and aerobic capacity were strong at baseline, but no longer prevalent after the exercise period. A recent paper by Zoli *et al.* presented a significant association between disease activity, measured by CRP, and aerobic capacity in a small group of RA patients with a disease duration of ≤1 year (131). However, we have not been able to find previous studies verifying the prognostic value of disease activity on future aerobic capacity.

The opposite association, with an impact of aerobic capacity on disease activity, was found by Stavropoulos-Kalinoglou *et al.* (150). They found, that aerobic capacity was a strong predictor for improvements in DAS28 after a six months exercise period.

In paper III, higher disease activity was associated with lower level of total physical activity. No associations were found with time spent in MVPA. Our findings are in line with those of Khoja et al, who found higher disease activity to be associated with more time spent sedentary and in lower intensities, but no association was found for time spent in MVPA (101). In contrast to this, only one of the studies included in a review from 2014, found a correlation between disease activity and physical activity (162). However, this review only included six studies investigating this correlation, most of them based on self-assessed physical activity.

Traditional cardiovascular risk factors and atherosclerosis

The established beneficial associations of aerobic capacity (59) and physical activity (195) on CVD risk factors, seen in the general population, appears to also be evident in RA patients. Higher levels of aerobic capacity and physical activity were related to a more beneficial CVD risk profile. In paper II, we found significant associations between aerobic capacity and several risk factors for CVD. At the time of follow-up, aerobic capacity was related to more favourable measures of blood glucose, BMI, body fat, resting HR and PP. Baseline aerobic capacity also predicted BMI, waist circumference and PP over time. Paper IV presented significant inverse correlations at baseline between aerobic capacity and BMI as well as PWV. Aerobic capacity after the exercise period at 10 weeks, was inversely related with resting HR and PWV. Furthermore, at the follow-up at 25 weeks, higher aerobic capacity correlated with lower values for systolic BP, resting HR and PWV.

In line with our results, Metsios et al found aerobic capacity to be significantly associated with body fat and insulin resistance, but also with HDL and 10-year CVD risk after adjusting for DAS28, HAQ and physical activity (9). Furthermore, aerobic capacity was a strong predictor for improvements of the endothelial function after a six-month exercise period (157).
In paper III, higher total volume of physical activity and also higher proportion of MVPA implicated more favourable risk factors for CVD and measures of subclinical atherosclerosis. We adjusted for age, sex, disease duration and Actiheart wear time,

and found total amount of physical activity to be associated with lower values of blood glucose, BMI, body fat, waist circumference, sleeping HR, systolic and diastolic BP, and aortic systolic BP. More time spent in MVPA indicated higher HDL, lower blood glucose and lower sleeping HR. Interestingly, total amount of physical activity, *i.e.,* despite intensity, was more strongly associated with CVD risk factors than time spent in higher intensities. This is in accordance with Khoja et al, who presented equivalent or stronger associations between physical activity and CVD risk factors at lower intensities compared with moderate intensity (101). The beneficial relationship between low intensity physical activity and CVD risk was confirmed by Fenton *et al.* (100).

Self-efficacy

Self-efficacy has been shown to associate with physical activity (162) and impact on physical activity maintenance (117). Aerobic capacity can be considered as one of several measures of physical activity. In paper II, we found several associations between self-efficacy and aerobic capacity, *i.e.,* follow-up values of self-efficacy and aerobic capacity were related ($r_{s=}$.464, p=.020) and baseline aerobic capacity was related to self-efficacy at follow-up ($r_{s=}$.420, p=.037). Enhancing self-efficacy seems to be an important target for rehabilitation interventions.

Intervention

Aerobic exercise is recommended for improving aerobic capacity in patients with RA (23-25). In paper IV, we evaluated the effects of ten weeks of spinning exercise on aerobic capacity, disease activity and CV risk factors. The study was designed as a pilot study, with a small number of participants. Nevertheless, the spinning exercise induced effects, regarded to be clinically significant for the risk of CV mortality (59, 196). Aerobic capacity increased by median 7 ml/kg/min and systolic BP decreased by 11 mm Hg. A 15% risk reduction for CVD for every 1 MET (3.5 ml/kg/min) increase of aerobic capacity has been presented (59) and a 10 mm Hg reduction in systolic BP has been associated with a reduction in risk of stroke by 40% and of IHD by 30% in normotensive subjects (196). Importantly, the intensive spinning exercise did not cause any detrimental effects on disease activity. On the contrary, the number of

tender joints decreased significantly, and based on the objective measures as well as the diary notes, we could conclude, that the spinning exercise was a feasible method to improve aerobic capacity and systolic blood pressure for the patients included.

Methodological considerations, strengths and limitations

The large majority of patients in the county of Västerbotten with suspected early RA, are referred to the Department of Rheumatology, Umeå University hospital, which is the only department in the county. If diagnosed with RA, they are offered inclusion in the Early Rheumatoid Arthritis Clinic (TRAM). Thus, we consider these patients to be representative of individuals with RA in this geographical area. External validity was affected by the exclusion of patients at higher age, with serious comorbidity or functional limitations (paper I-IV) and those medicating with beta blocking agents (paper I, II and IV), indicating the present work to be valid for a slightly younger, less impaired RA population. In addition, 60 patients were invited to participate in the intervention study, whereof 13 finally participated. It was presumably the highly motivated patients who chose to participate, which may be mirrored by the high attendance to the sessions (76%).

In paper III, physical activity was estimated using the Actiheart monitor over seven days, worn continuously to avoid exclusion of water-based activities such as hydrotherapy, a popular type of exercise for patients with RA. Compared with self-assessment, this measurement is made in real time and not dependent on recall or interpretation of questions. Data was adjusted for Actiheart wear time in order to present as accurate results as possible. The Actiheart is considered a reliable and valid tool, when tested against ECG, chest-worn HR monitoring and sinusoid accelerations (182). Estimates of energy expenditure have been validated against DLW (197), but unfortunately, the monitor has not been validated in RA patients. Comparisons between studies using different activity monitors are hampered by their different proprietary formulas to clean the data from noisy signals and translate the accelerometer counts into physical activity measures (198, 199). The output styles vary and cut-off points for defining MVPA differ between monitors. Another difficulty when using accelerometers, is to distinguish non-wear time from sedentary time, since both these periods present zero counts. However, the combined accelerometer and heart rate monitor used in this study, can differentiate between non-wear time and sedentary time based on the heart rate measurements.

The “gold standard” method to measure aerobic capacity is by collecting and analysing respiratory gases during maximal effort. However, functional impairment due to RA or old age, as well as fear of aggravating symptoms or poor motivation, may be obstacles to satisfactory completion of a maximal test. In paper I, II and IV, aerobic capacity was estimated by the Åstrand submaximal ergometer test (48), recommended in patients with RA (23, 25). When tested in RA patients, the Åstrand test was considered to be highly valid and feasible but using the Tanaka age correction (169) instead of the age correction in the Åstrand test, increased validity when compared with a maximal test (200). Consequently, in paper II, we chose to correct the estimated aerobic capacity for age according to Tanaka *et al.* (169) in order to increase the validity of the test, but we also presented the test values using the original age correction factor included in the Åstrand test to facilitate comparison with other studies.

Pulse wave analysis and carotid ultrasonography were used as markers for subclinical atherosclerosis. Pulse wave velocity (201) as well as AIx and aortic systolic BP (202) improves prediction of CVD in the general population. Publications by Vlachopoulos *et al.* have presented an increased risk for CV events by about 14% with every 1 m/sec increase in aortic PWV (201) and by about 32% with each 10% increase in AIx (202). Pulse wave velocity and AIx is predictive for future CV events also in patients with RA, when using the cut-off values >9.9 m/s for PWV and $\geq$ 31 % for AIx (70). The reproducibility of PWV, measured by Arteriograph, is high (203) and there are strong correlations between measures by Arteriograph and invasively measured aortic AIx, aortic systolic BP and PWV values (71).

Increased cIMT is associated with higher prevalence of CVD (204) and predicts future CV events independently from traditional risk factors, in the general population (205) as well as in patients with RA (70). Reliability of the measurements is highly dependent on the skills of the sonographer. Hence, the major part of the measurements was made by the same sonographer and in total, only three sonographers were involved in the measurements.

Strengths of the included papers are the well-defined populations in paper I, II and III, the use of reliable and valid measurements and the long follow-up time of aerobic capacity, which, as far as known, have not been presented earlier. Limitations to consider are the small sample sizes in paper II and IV, which may have affected the results and diminished the generalizability. Nonetheless, we were able to show significant changes over time and correlations with several measures of both clinical and scientific interest. Our results also cohere with results from other studies, on RA patients as well as on the general population. We also have missing values in paper I, which, although compensated for, may have affected the results.

Clinical implications

The present findings are aligned with previous research on the beneficial associations between physical activity (98) and aerobic capacity (9) with risk factors for CVD in RA. The maintained aerobic capacity over the long follow-up time, and the predictive value of aerobic capacity on future risk factors for CVD, presented in paper II, add to previous knowledge in the field. Physical activity and exercise are cornerstones for prevention and treatment of the consequences of RA (119). The results presented herein further stress the importance of an active lifestyle in this group of patients. Spinning exercise seems to be a feasible method in order to increase aerobic capacity and lower blood pressure without adverse effects on disease activity. As a result of the pilot study, spinning exercise has become a regular activity at our department, further showing the feasibility of the method. Numerous studies have presented the importance of self-efficacy for being physically active (117). The present relations found between self-efficacy and aerobic capacity, which is one manifestation of physical activity participation, indicate that interventions aiming at increasing self-efficacy may facilitate behavioural change. Since disease activity seems to negatively impact on future aerobic capacity, patients with higher disease activity should be prioritised for interventions and support for health enhancing PA.

Measures of physical activity and aerobic capacity are encouraged to be incorporated in the clinical management, as a part of the CVD risk assessment in RA. The importance of physical activity also in the preventive work has been increasingly recognized and emphasized in the recent update of Swedish recommendations (155) as well as on European level (95). Since RA patients have been shown to underestimate their risk for CVD (206) and also interpret physical activity intensity differently than health professionals (207), test of aerobic capacity and objective measures of physical activity are recommended to clarify the picture and to serve as a basis when guiding the patients in achieving and maintaining a healthy lifestyle.

Future research

Several questions remain to be investigated further. We used traditional CV risk factors and early signs of atherosclerosis as proxies for CVD. Whether higher levels of physical activity or aerobic capacity have the potential of decreasing the number of CV events in RA still remains to be determined scientifically, which could be possible in a longitudinal study with CV events as the outcome measure. This would require a large sample size, though, as well as time and resources. Registration of aerobic capacity and measures of physical activity in the Swedish Rheumatology Quality Register (SRQ) may facilitate and serve as a basis for further studies.

Studies presenting levels of aerobic capacity in patients with RA are few and inconclusive. Some of them were conducted decades ago, when medical treatment was less efficient and patients were recommended to avoid strenuous exercise in fear of aggravating symptoms and increasing disease activity. There is a need for further research, also including analyses of associations with disease related variables and CV risk factors.

Physical activity has been shown to decrease inflammation, which also the present results from spinning exercise indicated. In a Swedish cohort (n=617), patients self-assessed their level of physical activity five years prior to RA diagnosis. Adjusted for possible confounding variables, a higher physical activity level was related to a milder disease, as measured by disease activity, pain and functional ability (4). Physical activity has also been shown to impact on the risk of developing RA (3). These results are interesting and raise questions about the impact of physical activity on RA disease.

Finally, monitoring of physical activity can be a good motivator for increasing or maintaining health-enhancing physical activity. A device for objective measurement, to be used by patients as well as an assessment tool for health professionals, need to be developed further and validated for the RA population.

Conclusions

The main conclusions of the present work are as follows:

- The majority of the patients with early RA had impairments of the joint- and muscle function over 24 months even though disease activity decreased significantly, indicating a need for regular evaluations of physical functions besides disease activity to prevent continuous development of functional losses (Paper I).

- Aerobic capacity was stable from diagnosis and over the following 24 months and patients with response to therapy had a higher aerobic capacity compared with non-responders (Paper I).

- The aerobic capacity was maintained over 16 years and higher disease activity in early stages of RA predicted lower aerobic capacity after 16 years (Paper II).

- Higher aerobic capacity was associated with more favourable measures of CV risk factors. Furthermore, high baseline aerobic capacity associated with favourable measures of cardiovascular risk factors after 16 years, indicating that aerobic capacity has a role to play in the management of CV risk in RA. Regular testing of aerobic capacity with a priority of patients with higher disease activity is advocated (Paper II).

- Total amount of physical activity as well as time spent in MVPA and sedentary was similar in patients with early and long-standing RA. However, a substantial proportion of participants did not meet national recommendations for MVPA (Paper III).

- Measures of disease activity and severity associated with lower levels of physical activity. Furthermore, higher total volume of physical activity and also higher proportion of MVPA implicated more favourable values of CV risk factors and measures of atherosclerosis (Paper III).

- In the RA patients included, intensive spinning exercise sessions three times per week for 10 weeks, was a feasible method to improve aerobic capacity

and BP to levels that are considered to be clinically relevant in decreasing the risk of CVD (Paper IV).

- The spinning exercise at the designed intensity did not induce any detrimental effects on disease activity. On the contrary, the number of tender joints decreased significantly (Paper IV).

Acknowledgements

First of all, I want to thank all participating patients for taking the time and making the efforts required to provide the data. Without you, none of this would have been possible.

I also want to express my deepest gratitude to all of you, who have given me support, encouragement and assistance during the past years. In particular, I want to thank:

My supervisor Solveig Wållberg Jonsson, for sharing your experience and knowledge and for always being available for questions. Thank you for trusting me and giving me self-confidence and inspiration to reach the goal. You are a true optimist!

My co-supervisor Björn Sundström, thank you for your encouragement and support in so many ways, for all your inspiring reflections and for comments on my texts. Your computer skills and technical knowledge have also been a blessing.

My supervisors in the early paper I, Solbritt Rantapää Dahlqvist and Britta Lindström. You introduced me to the challenges of research. I learned a lot, that inspired me for future projects. I also want to thank you, Solbritt, for your contributions as a co-writer in paper II.

Lars Ångström, co-author and colleague at the Department of Rheumatology, for hard, but interesting and enjoyable work in the spinning study and in collection of data for paper III, and also for enthusiastically reading and giving me feed-back on my own work. But most of all, thank you for all the inspiring discussions!

Co-authors Camilla Sandberg and Jeremy Pomeroy, thank you for sharing your knowledge on measurements of physical activity and analyses of the Actiheart data. Camilla, your work inspired me to broaden my perspective and include objective measurements of physical activity in my work.

Co-authors Lena Innala and Anna Södergren, for encouragement and for fruitful collaboration.

Tommy Olsson and Bo Carlberg at the Department of Public Health and Clinical Medicine, for lending us the Actiheart monitors and the Arteriograph.

Viktoria von Zweigbergk and Sonja Odeblom for administrative assistance whenever needed.

Camilla Ring, Maria Backlund and Lena Uddståhl at the Kliniskt Forskningscentrum and Emma Nyman and Elisabeth Lundström at the Department of Clinical Physiology, for skilful work. It has been a pleasure working with you all.

Simon Vallin and Marie Eriksson for your advice in statistical matters as well as Per Ivarsson and Göran Lönnberg for valuable IT support.

Brian Ellis, for skilful linguistic review.

The members of the research group in Rheumatology, for inspiring presentations and discussions.

Thanks to all my co-workers at the Department of Rheumatology for all your support along the way. I especially want to thank Gerd-Marie Alenius, head of the Department, for being supportive and providing the time for my studies, and Åsa Rådström, my nearest boss, for encouragement and for all your efforts in finding someone to replace me during my leave. My wonderful colleagues; Jörgen Sandström, Lina Vikner, Emma Larsson, Sebastian Wahl and the physiotherapy assistant Efwa Johansson, for always cheering me up and for taking care of clinical work. I am looking forward to regular Friday "fika" again! Berit Karlsson, Elisabeth Åström, Viktoria Lundfeldt, Marie Svensson, Gerd Olofsson and Martina Jonsson; thank you for always making me feel welcome at the morning coffee meetings. It means a lot to me.

Senior researchers and PhD students at the Department of Community Medicine and Rehabilitation/Physiotherapy, for sharing experiences, giving me feed-back from a physiotherapy view and for always welcoming me into your circle.

My mother Vivi, my brother and sister-in-law Thommy and Maria, their children Alexander and Linnea and of course our friends Per and Lena, for always being supportive and caring.

Thank you, my wonderful family, for being there and for reminding me that there are other, more important things in life. Niklas, my husband, my sons Anton and Emil and their girlfriends Amanda and Emma. You are the best!

References

1. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010;376(9746):1094-108.
2. Symmons DPM. Epidemiology of rheumatoid arthritis: determinants of onset, persistence and outcome. Best Pract Res Clin Rheumatol. 2002;16:707-22.
3. Di Giuseppe D, Bottai M, Askling J, Wolk A. Physical activity and risk of rheumatoid arthritis in women: a population-based prospective study. Arthritis Res Ther. 2015;17:40.
4. Sandberg ME, Wedren S, Klareskog L, Lundberg IE, Opava CH, Alfredsson L, et al. Patients with regular physical activity before onset of rheumatoid arthritis present with milder disease. Ann Rheum Dis. 2014;73(8):1541-4.
5. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American college of rheumatology/European league against rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81.
6. Kapetanovic MC, Lindqvist E, Nilsson JA, Geborek P, Saxne T, Eberhardt K. Development of functional impairment and disability in rheumatoid arthritis patients followed for 20 years: relation to disease activity, joint damage, and comorbidity. Arthritis Care Res (Hoboken). 2015;67(3):340-8.
7. Eurenius E, Stenstrom CH. Physical activity, physical fitness, and general health perception among individuals with rheumatoid arthritis. Arthritis Rheum. 2005;53(1):48-55.
8. Munsterman T, Takken T, Wittink H. Are persons with rheumatoid arthritis deconditioned? A review of physical activity and aerobic capacity. BMC Musculoskel Disord. 2012;13:202.
9. Metsios GS, Koutedakis Y, Veldhuijzen van Zanten JJ, Stavropoulos-Kalinoglou A, Vitalis P, Duda JL, et al. Cardiorespiratory fitness levels and their association with cardiovascular profile in patients with rheumatoid arthritis: a cross-sectional study. Rheumatology (Oxford). 2015;54(12):2215-20.
10. Ahlstrand I, Thyberg I, Falkmer T, Dahlstrom O, Bjork M. Pain and activity limitations in women and men with contemporary treated early RA compared to 10 years ago: the Swedish TIRA project. Scand J Rheumatol. 2015:1-6.
11. Uutela T, Kautiainen H, Jarvenpaa S, Salomaa S, Hakala M, Hakkinen A. Patients with rheumatoid arthritis have better functional and working ability but poorer general health and higher comorbidity rates today than in the late 1990s. Scand J Rheumatol. 2015;44(3):173-81.
12. Pedersen AB, Mor A, Mehnert F, Thomsen RW, Johnsen SP, Norgaard M. Rheumatoid arthritis: Trends in antirheumatic drug use, C-reactive protein levels, and surgical burden. J Rheumatol. 2015;42(12):2247-54.
13. Sokka T, Krishnan E, Hakkinen A, Hannonen P. Functional disability in rheumatoid arthritis patients compared with a community population in Finland. Arthritis Rheum. 2003;48(1):59-63.
14. Combe B, Logeart I, Belkacemi MC, Dadoun S, Schaeverbeke T, Daures JP, et al. Comparison of the long-term outcome for patients with rheumatoid arthritis with

persistent moderate disease activity or disease remission during the first year after diagnosis: data from the ESPOIR cohort. Ann Rheum Dis. 2015;74(4):724-9.
15. West E, Jonsson SW. Health-related quality of life in rheumatoid arthritis in Northern Sweden: a comparison between patients with early RA, patients with medium-term disease and controls, using SF-36. Clin Rheumatol. 2005;24(2):117-22.
16. Innala L, Moller B, Ljung L, Magnusson S, Smedby T, Sodergren A, et al. Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: a five year prospective study. Arthritis Res Ther. 2011;13(4):R131.
17. Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. J Rheumatol. 1997;24(3):445-51.
18. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum. 2008;59(12):1690-7.
19. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2007;21(5):885-906.
20. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315-24.
21. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European standing committee for international clinical studies including therapeutics (ESCISIT). Ann Rheum Dis. 2007;66(1):34-45.
22. Svensk Reumatologisk förening. Modern Reumarehabilitering [Internet]: Svensk Reumatologisk förening; 2017 [Available from: http://www.svenskreumatologi.se.
23. Professional associations for physical activity/Swedish national institute of public health. FYSS. Physical activity in the prevention and treatment of disease [Internet] Sweden 2010 [Available from: http://www.FYSS.se.
24. Forestier R, Andre-Vert J, Guillez P, Coudeyre E, Lefevre-Colau MM, Combe B, et al. Non-drug treatment (excluding surgery) in rheumatoid arthritis: clinical practice guidelines. Joint, bone, spine: revue du rhumatisme. 2009;76(6):691-8.
25. Hurkmans EJ, van der Giesen FJ, Bloo H, Boonman DC, van der Esch M, Fluit M, et al. Physiotherapy in rheumatoid arthritis: development of a practice guideline. Acta Reumatol Port. 2011;36(2):146-58.
26. Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, Schoones J, Van den Ende EC. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. Cochrane Database Syst Rev. 2009(4):CD006853.
27. Lemmey A. Efficacy of progressive resistance training for patients with rheumatoid arthritis and recommendations regarding its prescription. Int J Clin Rheumatol. 2011;6(2):189-205.
28. Stenstrom CH, Minor MA. Evidence for the benefit of aerobic and strengthening exercise in rheumatoid arthritis. Arthritis Rheum. 2003;49(3):428-34.
29. Van Den Ende CH, Vliet Vlieland TP, Munneke M, Hazes JM. Dynamic exercise therapy for rheumatoid arthritis. Cochrane Database Syst Rev. 2000(2):CD000322.

30. de Jong Z, Munneke M, Kroon HM, van Schaardenburg D, Dijkmans BA, Hazes JM, et al. Long-term follow-up of a high-intensity exercise program in patients with rheumatoid arthritis. Clin Rheumatol. 2009;28(6):663-71.
31. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126-31.
32. Strath SJ, Kaminsky LA, Ainsworth BE, Ekelund U, Freedson PS, Gary RA, et al. Guide to the assessment of physical activity: Clinical and research applications: a scientific statement from the American heart association. Circulation. 2013;128(20):2259-79.
33. McArdle W, Katch FI, Katch V. Exercise physiology: nutrition, energy, and human performance. Eighth Edition. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014 [2015].
34. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-81.
35. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr. 1985;39 Suppl 1:5-41.
36. Roubenoff R, Roubenoff RA, Cannon JG, Kehayias JJ, Zhuang H, Dawson-Hughes B, et al. Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. J Clin Invest. 1994;93(6):2379-86.
37. Metsios GS, Stavropoulos-Kalinoglou A, Panoulas VF, Koutedakis Y, Nevill AM, Douglas KM, et al. New resting energy expenditure prediction equations for patients with rheumatoid arthritis. Rheumatology (Oxford). 2008;47(4):500-6.
38. Di Pietro L, Dziura J, Blair SN. Estimated change in physical activity level (PAL) and prediction of 5-year weight change in men: the Aerobics center longitudinal study. Int J Obes Relat Metab Disord. 2004;28(12):1541-7.
39. World Health Organization. Global recommendations on physical activity for health [Internet]. Geneva: WHO; 2010 [Available from: http://www.who.int/dietphysicalactivity/factsheetadults/en/.
40. World Health Organization. Physical activity and older adults. Recommended levels of physical activity for adults aged 65 and above [Internet] [Available from: http://www.who.int/dietphysicalactivity/factsheet_olderadults/en/.
41. American heart association. American heart association recommendations for physical activity in adults [Internet] 2014 [updated Dec 14, 2017]. Available from: http://www.heart.org/HEARTORG/HealthyLiving/PhysicalActivity/FitnessBasics/American-Heart-Association-Recommendations-for-Physical-Activity-in-Adults_UCM_307976_Article.jsp#.WkN2XCNiTOQ.
42. The Public health agency of Sweden. Physical activity 2016 [updated 17-02-2016]. Available from: https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/living-conditions-and-lifestyle/physical-activity/.
43. Tierney M, Fraser A, Kennedy N. Physical activity in rheumatoid arthritis: a systematic review. J Phys Act Health. 2012;9(7):1036-48.
44. Schoeller DA, van Santen E. Measurement of energy expenditure in humans by doubly labeled water method. J Appl Physiol Respir Environ Exerc Physiol. 1982;53(4):955-9.

45. Plasqui G, Bonomi AG, Westerterp KR. Daily physical activity assessment with accelerometers: new insights and validation studies. Obesity reviews: an official journal of the International association for the study of obesity. 2013;14(6):451-62.
46. Almeida GJ, Wasko MC, Jeong K, Moore CG, Piva SR. Physical activity measured by the SenseWear Armband in women with rheumatoid arthritis. Phys Ther. 2011;91(9):1367-76.
47. Yu CA, Rouse PC, Veldhuijzen Van Zanten JJ, Ntoumanis N, Kitas GD, Duda JL, et al. Subjective and objective levels of physical activity and their association with cardiorespiratory fitness in rheumatoid arthritis patients. Arthritis Res Ther. 2015;17:59.
48. Astrand PO, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. J Appl Physiol. 1954;7(2):218-21.
49. Astrand I. Aerobic work capacity in men and women with special reference to age. Acta Physiol Scand Suppl. 1960;49(169):1-92.
50. Åstrand O, Rodahl K. Textbook of work physiology. New York: McGraw-Hill. 1970.
51. Arem H, Moore SC, Patel A, Hartge P, Berrington de Gonzalez A, Visvanathan K, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. JAMA Intern Med. 2015;175(6):959-67.
52. Bouchard C, Blair SN, Katzmarzyk PT. Less sitting, more physical activity, or higher fitness? Mayo Clinic Proc. 2015;90(11):1533-40.
53. Ertek S, Cicero A. Impact of physical activity on inflammation: effects on cardiovascular disease risk and other inflammatory conditions. Arch Med Sci. 2012;8(5):794-804.
54. Sattelmair J, Pertman J, Ding EL, Kohl HW, 3rd, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation. 2011;124(7):789-95.
55. Glazer NL, Lyass A, Esliger DW, Blease SJ, Freedson PS, Massaro JM, et al. Sustained and shorter bouts of physical activity are related to cardiovascular health. Med Sci Sports Exerc. 2013;45(1):109-15.
56. Healy GN, Wijndaele K, Dunstan DW, Shaw JE, Salmon J, Zimmet PZ, et al. Objectively measured sedentary time, physical activity, and metabolic risk: the Australian diabetes, obesity and lifestyle study (AusDiab). Diabetes Care. 2008;31(2):369-71.
57. Ekelund U, Brage S, Franks PW, Hennings S, Emms S, Wareham NJ. Physical activity energy expenditure predicts progression toward the metabolic syndrome independently of aerobic fitness in middle-aged healthy Caucasians: the Medical research council ely study. Diabetes Care. 2005;28(5):1195-200.
58. Blair SN, Kohl HW, 3rd, Paffenbarger RS, Jr., Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. Jama. 1989;262(17):2395-401.
59. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. Jama. 2009;301(19):2024-35.

60. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002;346(11):793-801.
61. Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH, et al. Exercise capacity and the risk of death in women: the St James women take heart project. Circulation. 2003;108(13):1554-9.
62. Lee DC, Sui X, Artero EG, Lee IM, Church TS, McAuley PA, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics center longitudinal study. Circulation. 2011;124(23):2483-90.
63. World Health Organization. The global burden of disease 2010. Geneva, Switzerland, World Health Organization; 2010.
64. del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum. 2001;44(12):2737-45.
65. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2012;71(9):1524-9.
66. Holmqvist M, Ljung L, Askling J. Acute coronary syndrome in new-onset rheumatoid arthritis: a population-based nationwide cohort study of time trends in risks and excess risks. Ann Rheum Dis. 2017.
67. Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Torp-Pedersen C, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. Ann Rheum Dis. 2011;70(6):929-34.
68. Holmqvist M, Gransmark E, Mantel A, Alfredsson L, Jacobsson LT, Wallberg-Jonsson S, et al. Occurrence and relative risk of stroke in incident and prevalent contemporary rheumatoid arthritis. Ann Rheum Dis. 2013;72(4):541-6.
69. Sodergren A, Stegmayr B, Ohman ML, Wallberg-Jonsson S. Increased incidence of stroke and impaired prognosis after stroke among patients with seropositive rheumatoid arthritis. Clin Exp Rheumatol. 2009;27(4):641-4.
70. Ikdahl E, Rollefstad S, Wibetoe G, Olsen IC, Berg IJ, Hisdal J, et al. Predictive value of arterial stiffness and subclinical carotid atherosclerosis for cardiovascular disease in patients with rheumatoid arthritis. J Rheumatol. 2016.
71. Horvath IG, Nemeth A, Lenkey Z, Alessandri N, Tufano F, Kis P, et al. Invasive validation of a new oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity. J Hypertens. 2010;28(10):2068-75.
72. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American society of echocardiography carotid intima-media thickness task force. Endorsed by the Society for vascular medicine. J Am Soc Echocardiogr. 2008;21(2):93-111; quiz 89-90.
73. Ambrosino P, Tasso M, Lupoli R, Di Minno A, Baldassarre D, Tremoli E, et al. Non-invasive assessment of arterial stiffness in patients with rheumatoid arthritis: a

systematic review and meta-analysis of literature studies. Ann Med. 2015;47(6):457-67.
74. Wallberg-Jonsson S, Caidahl K, Klintland N, Nyberg G, Rantapaa-Dahlqvist S. Increased arterial stiffness and indication of endothelial dysfunction in long-standing rheumatoid arthritis. Scand J Rheumatol. 2008;37(1):1-5.
75. Ambrosino P, Lupoli R, Di Minno A, Tasso M, Peluso R, Di Minno MN. Subclinical atherosclerosis in patients with rheumatoid arthritis. A meta-analysis of literature studies. Thromb Haemost. 2015;113(5):916-30.
76. Jonsson S, Backman C, O J, al e. Increased prevalence of atherosclerosis in patients with medium term rheumatoid arthritis. J Rheumatol. 2001;28:2597-602.
77. Sodergren A, Karp K, Boman K, Eriksson C, Lundstrom E, Smedby T, et al. Atherosclerosis in early rheumatoid arthritis: very early endothelial activation and rapid progression of intima media thickness. Arthritis Res Ther. 2010;12(4):R158.
78. Inaba M, Tanaka K, Goto H, Sakai S, Yamada S, Naka H, et al. Independent association of increased trunk fat with increased arterial stiffening in postmenopausal patients with rheumatoid arthritis. J Rheumatol. 2007;34(2):290-5.
79. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006;27(21):2588-605.
80. Icternol. Determination of the augmentation index from the central pressure wave form. 2015. p. Graf.
81. Crowson CS, Rollefstad S, Ikdahl E, Kitas GD, van Riel P, Gabriel SE, et al. Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. Ann Rheum Dis. 2018;77(1):48-54.
82. Boyer JF, Gourraud PA, Cantagrel A, Davignon JL, Constantin A. Traditional cardiovascular risk factors in rheumatoid arthritis: a meta-analysis. Joint, bone, spine: revue du rhumatisme. 2011;78(2):179-83.
83. del Rincón I, Freeman G, Haas R, O´Leary D, Escalante A. Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestations to atherosclerosis. Arthritis Rheum. 2005;52(11):3413-23.
84. Kokkonen H, Stenlund H, Rantapaa-Dahlqvist S. Cardiovascular risk factors predate the onset of symptoms of rheumatoid arthritis: a nested case-control study. Arthritis Res Ther. 2017;19(1):148.
85. Dessein PH, Joffe BI, Stanwix AE. Inflammation, insulin resistance, and aberrant lipid metabolism as cardiovascular risk factors in rheumatoid arthritis. J Rheumatol. 2003;30(7):1403-5.
86. Engvall IL, Elkan AC, Tengstrand B, Cederholm T, Brismar K, Hafstrom I. Cachexia in rheumatoid arthritis is associated with inflammatory activity, physical disability, and low bioavailable insulin-like growth factor. Scand J Rheumatol. 2008;37(5):321-8.
87. Stavropoulos-Kalinoglou A, Metsios GS, Koutedakis Y, Nevill AM, Douglas KM, Jamurtas A, et al. Redefining overweight and obesity in rheumatoid arthritis patients. Ann Rheum Dis. 2007;66(10):1316-21.
88. Kremers HM, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. Arthritis Rheum. 2004;50(11):3450-7.

89. Wallberg-Jonsson S, Johansson H, Ohman ML, Rantapaa-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. J Rheumatol. 1999;26(12):2562-71.
90. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. Circulation. 2004;109(21 Suppl 1):II2-10.
91. Goodson NJ, Symmons DP, Scott DG, Bunn D, Lunt M, Silman AJ. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year followup study of a primary care-based inception cohort. Arthritis Rheum. 2005;52(8):2293-9.
92. Kitas GD, Gabriel SE. Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. Ann Rheum Dis. 2011;70(1):8-14.
93. Myasoedova E, Chandran A, Ilhan B, Major BT, Michet CJ, Matteson EL, et al. The role of rheumatoid arthritis (RA) flare and cumulative burden of RA severity in the risk of cardiovascular disease. Ann Rheum Dis. 2016;75(3):560-5.
94. Lindhardsen J, Gislason GH, Jacobsen S, Ahlehoff O, Olsen AM, Madsen OR, et al. Non-steroidal anti-inflammatory drugs and risk of cardiovascular disease in patients with rheumatoid arthritis: a nationwide cohort study. Ann Rheum Dis. 2014;73(8):1515-21.
95. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis. 2017;76(1):17-28.
96. Ljung L, Rantapaa-Dahlqvist S, Jacobsson LT, Askling J. Response to biological treatment and subsequent risk of coronary events in rheumatoid arthritis. Ann Rheum Dis. 2016;75(12):2087-94.
97. Metsios GS, Stavropoulos-Kalinoglou A, Sandoo A, van Zanten JJ, Toms TE, John H, et al. Vascular function and inflammation in rheumatoid arthritis: the role of physical activity. Open Cardiovasc Med J. 2010;4:89-96.
98. Elkan AC, Hakansson N, Frostegard J, Hafstrom I. Low level of physical activity in women with rheumatoid arthritis is associated with cardiovascular risk factors but not with body fat mass--a cross sectional study. BMC Musculoskelet Disord. 2011;12:13.
99. Metsios GS, Stavropoulos-Kalinoglou A, Panoulas VF, Wilson M, Nevill AM, Koutedakis Y, et al. Association of physical inactivity with increased cardiovascular risk in patients with rheumatoid arthritis. Eur J Cardiovasc Prev Rehabil. 2009;16(2):188-94.
100. Fenton SAM, Veldhuijzen van Zanten J, Kitas GD, Duda JL, Rouse PC, Yu CA, et al. Sedentary behaviour is associated with increased long-term cardiovascular risk in patients with rheumatoid arthritis independently of moderate-to-vigorous physical activity. BMC Musculoskelet Disord. 2017;18(1):131.
101. Khoja SS, Almeida GJ, Wasko MC, Terhorst L, Piva SR. Light intensity physical activity is associated with lower cardiovascular risk factor burden in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2015.
102. Sokka T, Hakkinen A, Kautiainen H, Maillefert JF, Toloza S, Mork Hansen T, et al. Physical inactivity in patients with rheumatoid arthritis: data from twenty-one countries in a cross-sectional, international study. Arthritis Rheum. 2008;59(1):42-50.

103. Iversen MD, Frits M, von Heideken J, Cui J, Weinblatt M, Shadick NA. Physical activity and correlates of physical activity participation over three years in adults with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2016.
104. Lee J, Dunlop D, Ehrlich-Jones L, Semanik P, Song J, Manheim L, et al. Public health impact of risk factors for physical inactivity in adults with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012;64(4):488-93.
105. van den Berg MH, de Boer IG, le Cessie S, Breedveld FC, Vliet Vlieland TP. Are patients with rheumatoid arthritis less physically active than the general population? J Clin Rheumatol. 2007;13(4):181-6.
106. Prioreschi A, Hodkinson B, Avidon I, Tikly M, McVeigh J. The clinical utility of accelerometry in patients with rheumatoid arthritis. Rheumatology (Oxford). 2013;52:1721-7.
107. Mancuso CA, Rincon M, Sayles W, Paget SA. Comparison of energy expenditure from lifestyle physical activities between patients with rheumatoid arthritis and healthy controls. Arthritis Rheum. 2007;57(4):672-8.
108. Wikstrom I, Book C, Jacobsson LT. Difficulties in performing leisure activities among persons with newly diagnosed rheumatoid arthritis: A prospective, controlled study. Rheumatology (Oxford). 2006;45(9):1162-6.
109. Brodin N, Eurenius E, Jensen I, Nisell R, Opava CH, Group PS. Coaching patients with early rheumatoid arthritis to healthy physical activity: a multicenter, randomized, controlled study. Arthritis Rheum. 2008;59(3):325-31.
110. Demmelmaier I, Bergman P, Nordgren B, Jensen I, Opava CH. Current and maintained health-enhancing physical activity in rheumatoid arthritis: a cross-sectional study. Arthritis Care Res (Hoboken). 2013;65(7):1166-76.
111. Arne M, Janson C, Janson S, Boman G, Lindqvist U, Berne C, et al. Physical activity and quality of life in subjects with chronic disease: chronic obstructive pulmonary disease compared with rheumatoid arthritis and diabetes mellitus. Scand J Prim Health Care. 2009;27(3):141-7.
112. Pinto AJ, Roschel H, de Sa Pinto AL, Lima FR, Pereira RMR, Silva CA, et al. Physical inactivity and sedentary behavior: Overlooked risk factors in autoimmune rheumatic diseases? Autoimmun Rev. 2017.
113. Roubenoff R, Walsmith J, Lundgren N, Snydman L, Dolnikowski GJ, Roberts S. Low physical activity reduces total energy expenditure in women with rheumatoid arthritis: implications for dietary intake recommendations. Am J Clin Nutr. 2002;76(4):774-9.
114. Hernandez-Hernandez V, Ferraz-Amaro I, Diaz-Gonzalez F. Influence of disease activity on the physical activity of rheumatoid arthritis patients. Rheumatology (Oxford). 2014;53(4):722-31.
115. Prioreschi A, Hodkinson B, Tikly M, McVeigh JA. Changes in physical activity measured by accelerometry following initiation of DMARD therapy in rheumatoid arthritis. Rheumatology (Oxford). 2014;53(5):923-6.
116. Huffman K, Pieper C, Hall K, St Clair E, Kraus W. Self-efficacy for exercise, more than disease-related factors, is associated with objectively assessed exercise time and sedentary behaviour in rheumatoid arthritis. Scand J Rheumatol. 2014.

117. Demmelmaier I, Dufour AB, Nordgren B, Opava CH. Trajectories of physical activity over two years in persons with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2016;68(8):1069-77.
118. Semanik P, Wilbur J, Sinacore J, Chang RW. Physical activity behavior in older women with rheumatoid arthritis. Arthritis Rheum. 2004;51(2):246-52.
119. Verhoeven F, Tordi N, Prati C, Demougeot C, Mougin F, Wendling D. Physical activity in patients with rheumatoid arthritis. Joint, bone, spine : revue du rhumatisme. 2016;83(3):265-70.
120. Stavropoulos-Kalinoglou A, Metsios GS, Smith JP, Panoulas VF, Douglas KM, Jamurtas AZ, et al. What predicts obesity in patients with rheumatoid arthritis? An investigation of the interactions between lifestyle and inflammation. Int J Obes. 2010;34(2):295-301.
121. AbouAssi H, Connelly MA, Bateman LA, Tune KN, Huebner JL, Kraus VB, et al. Does a lack of physical activity explain the rheumatoid arthritis lipid profile? Lipids Health Dis. 2017;16(1):39.
122. Crilly MA, Wallace A. Physical inactivity and arterial dysfunction in patients with rheumatoid arthritis. Scand J Rheumatol. 2013;42(1):27-33.
123. Ekdahl C, Broman G. Muscle strength, endurance, and aerobic capacity in rheumatoid arthritis: a comparative study with healthy subjects. Ann Rheum Dis. 1992;51(1):35-40.
124. Cimen B, Deviren SD, Yorgancloglu ZR. Pulmonary function tests, aerobic capacity, respiratory muscle strength and endurance of patients with rheumatoid arthritis. Clin Rheumatol. 2001;20(3):168-73.
125. Rall LC, Meydani SN, Kehayias JJ, Dawson-Hughes B, Roubenoff R. The effect of progressive resistance training in rheumatoid arthritis. Increased strength without changes in energy balance or body composition. Arthritis Rheum. 1996;39(3):415-26.
126. Minor MA, Hewett JE, Webel RR, Dreisinger TE, Kay DR. Exercise tolerance and disease related measures in patients with rheumatoid arthritis and osteoarthritis. J Rheumatol. 1988;15(6):905-11.
127. Chang CL, Chiu CM, Hung SY, Lee SH, Lee CS, Huang CM, et al. The relationship between quality of life and aerobic fitness in patients with rheumatoid arthritis. Clin Rheumatol. 2009;28(6):685-91.
128. Hakkinen A, Haanonan P, Nyman K, Hakkinen K. Aerobic and neuromuscular performance capacity of physically active females with early or long-term rheumatoid arthritis compared to matched healthy women. Scand J Rheumatol. 2002;31(6):345-50.
129. Kurtais Y, Tur BS, Elhan AH, Erdogan MF, Yalcin P. Hypothalamic-pituitary-adrenal hormonal responses to exercise stress test in patients with rheumatoid arthritis compared to healthy controls. J Rheumatol. 2006;33(8):1530-7.
130. de Carvalho MR, Tebexreni AS, Salles CA, Barros Neto T, Natour J. Oxygen uptake during walking in patients with rheumatoid arthritis--a controlled study. J Rheumatol. 2004;31(4):655-62.
131. Zoli A, Bosello S, Comerci G, Galiano N, Forni A, Loperfido F, et al. Preserved cardiorespiratory function and NT-proBNP levels before and during exercise in patients with recent onset of rheumatoid arthritis: the clinical challenge of stratifying the patient cardiovascular risks. Rheumatol Int. 2017;37(1):13-9.

132. Hagfors L, Westerterp K, Skoldstam L, Johansson G. Validity of reported energy expenditure and reported intake of energy, protein, sodium and potassium in rheumatoid arthritis patients in a dietary intervention study. Eur J Clin Nutr. 2005;59(2):238-45.
133. Prioreschi A, Makda MA, Tikly M, McVeigh JA. Habitual physical activity, sedentary behaviour and bone health in rheumatoid arthritis. Int J Sports Med. 2015;36(12):1021-6.
134. Semanik P, Lee J, Manheim L, Dipietro L, Dunlop D, Chang RW. Relationship between accelerometer-based measures of physical activity and the Yale physical activity survey in adults with arthritis. Arthritis Care Res (Hoboken). 2011;63(12):1766-72.
135. Gilbert AL, Lee J, Ma M, Semanik PA, DiPietro L, Dunlop DD, et al. Comparison of subjective and objective measures of sedentary behavior using the Yale physical activity survey and accelerometry in patients with rheumatoid arthritis. J Phys Act Health. 2016;13(4):371-6.
136. Hashimoto T, Yoshiuchi K, Inada S, Shirakura K, Wada N, Takeuchi K, et al. Physical activity of elderly patients with rheumatoid arthritis and healthy individuals: an actigraphy study. Biopsychosoc Med. 2015;9:19.
137. Rongen-van Dartel SAA, Repping-Wuts H, van Hoogmoed D, Knoop H, Bleijenberg G, van Riel PLCM, et al. Relationship between objectively assessed physical activity and fatigue in patients with rheumatoid arthritis: Inverse correlation of activity and fatigue. Arthritis Care Res. 2014;66(6):852-60.
138. Paul L, Rafferty D, Marshall-McKenna R, Gill JM, McInnes I, Porter D, et al. Oxygen cost of walking, physical activity, and sedentary behaviours in rheumatoid arthritis. Scand J Rheumatol. 2014;43(1):28-34.
139. Piva SR, Almeida GJ, Wasko MC. Association of physical function and physical activity in women with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2010;62(8):1144-51.
140. Munneke M, de Jong Z, Zwinderman AH, Tijhuis GJ, Hazes JM, Vliet Vlieland TP. The value of a continuous ambulatory activity monitor to quantify the amount and intensity of daily activity in patients with rheumatoid arthritis. J Rheumatol. 2001;28(4):745-50.
141. Raftery G, Bridges M, Heslop P, Walker DJ. Are fibromyalgia patients as inactive as they say they are? Clin Rheumatol. 2009;28(6):711-4.
142. Hegarty RS, Conner TS, Stebbings S, Treharne GJ. Feel the fatigue and be active anyway: Physical activity on high-fatigue days protects adults with arthritis from decrements in same-day positive mood. Arthritis Care Res (Hoboken). 2015.
143. Ekblom B, Lovgren O, Alderin M, Fridstrom M, Satterstrom G. Physical performance in patients with rheumatoid arthritis. Scand J Rheumatol. 1974;3(3):121-5.
144. Beals CA, Lampman RM, Banwell BF, Braunstein EM, Albers JW, Castor CW. Measurement of exercise tolerance in patients with rheumatoid arthritis and osteoarthritis. J Rheumatol. 1985;12(3):458-61.
145. Minor MA, Hewett JE. Physical fitness and work capacity in women with rheumatoid arthritis. Arthritis Care Res. 1995;8(3):146-54.

146. Bilberg A, Ahlmen M, Mannerkorpi K. Moderately intensive exercise in a temperate pool for patients with rheumatoid arthritis: a randomized controlled study. Rheumatology (Oxford). 2005;44(4):502-8.
147. Haglund EK, Bremander AB. Aerobic capacity in patients with rheumatoid arthritis: a comparison of two submaximal test methods. Musculoskeletal Care. 2009;7(4):288-99.
148. Cooney JK, Moore JP, Ahmad YA, Jones JG, Lemmey AB, Casanova F, et al. A simple step test to estimate cardio-respiratory fitness levels of rheumatoid arthritis patients in a clinical setting. Int J Rheumatol. 2013;2013:174541.
149. Munsterman T, Takken T, Wittink H. Low aerobic capacity and physical activity not associated with fatigue in patients with rheumatoid arthritis: a cross-sectional study. J Rehabil Med. 2013;45(2):164-9.
150. Stavropoulos-Kalinoglou A, Metsios GS, Veldhuijzen van Zanten JJ, Nightingale P, Kitas GD, Koutedakis Y. Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. Ann Rheum Dis. 2013;72(11):1819-25.
151. Nordgren B, Friden C, Demmelmaier I, Bergstrom G, Lundberg IE, Dufour AB, et al. An outsourced health-enhancing physical activity programme for people with rheumatoid arthritis: exploration of adherence and response. Rheumatology (Oxford). 2015;54(6):1065-73.
152. Osailan A, Metsios GS, Rouse PC, Ntoumanis N, Duda JL, Kitas GD, et al. Factors associated with parasympathetic activation following exercise in patients with rheumatoid arthritis: a cross-sectional study. BMC Cardiovasc Disord. 2016;16:86.
153. Arts EE, Popa C, Den Broeder AA, Semb AG, Toms T, Kitas GD, et al. Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. Ann Rheum Dis. 2015;74(4):668-74.
154. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: The sixth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European association for cardiovascular prevention & rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315-81.
155. Svensk Reumatologisk Förening. Rekommendationer för kardiovaskulär primärprevention vid inflammatorisk reumatisk sjukdom [Internet]: Svensk Reumatologisk Förening; 2017 [updated 2017. Available from: http://www.svenskreumatologi.se.
156. Lemmey AB, Marcora SM, Chester K, Wilson S, Casanova F, Maddison PJ. Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. Arthritis Rheum. 2009;61(12):1726-34.
157. Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJ, Nightingale P, Sandoo A, Dimitroulas T, et al. Individualised exercise improves endothelial function in patients with rheumatoid arthritis. Ann Rheum Dis. 2014;73(4):748-51.

158. Janse van Rensburg DC, Ker JA, Grant CC, Fletcher L. Effect of exercise on cardiac autonomic function in females with rheumatoid arthritis. Clin Rheumatol. 2012;31(8):1155-62.
159. de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Jansen A, Ronday KH, et al. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. Arthritis Rheum. 2003;48(9):2415-24.
160. van den Ende CH, Hazes JM, le Cessie S, Mulder WJ, Belfor DG, Breedveld FC, et al. Comparison of high and low intensity training in well controlled rheumatoid arthritis. Results of a randomised clinical trial. Ann Rheum Dis. 1996;55(11):798-805.
161. Sandstad J, Stensvold D, Hoff M, Nes BM, Arbo I, Bye A. The effects of high intensity interval training in women with rheumatic disease: a pilot study. Eur J Appl Physiol. 2015;115(10):2081-9.
162. Larkin L, Kennedy N. Correlates of physical activity in adults with rheumatoid arthritis: a systematic review. J Phys Act Health. 2014;11(6):1248-61.
163. Veldhuijzen van Zanten JJ, Rouse PC, Hale ED, Ntoumanis N, Metsios GS, Duda JL, et al. Perceived barriers, facilitators and benefits for regular physical activity and exercise in patients with rheumatoid arthritis: A review of the literature. Sports Med. 2015;45(10):1401-12.
164. Eurenius E, Brodin N, Lindblad S, Opava CH, Group PS. Predicting physical activity and general health perception among patients with rheumatoid arthritis. J Rheumatol. 2007;34(1):10-5.
165. Iversen MD, Fossel AH, Ayers K, Palmsten A, Wang HW, Daltroy LH. Predictors of exercise behavior in patients with rheumatoid arthritis 6 months following a visit with their rheumatologist. Phys Ther. 2004;84(8):706-16.
166. Konijn NP, van Tuyl LH, Boers M, den Uyl D, Ter Wee MM, Kerstens P, et al. Effective treatment for rapid improvement of both disease activity and self-reported physical activity in early rheumatoid arthritis. Arthritis Care Res (Hoboken). 2016;68(2):280-4.
167. van der Goes MC, Hoes JN, Cramer MJ, van der Veen MJ, van der Werf JH, Bijlsma JW, et al. Identifying factors hampering physical activity in longstanding rheumatoid arthritis: what is the role of glucocorticoid therapy? Clin Exp Rheumatol. 2014;32(2):155-61.
168. Katz P, Margaretten M, Trupin L, Schmajuk G, Yazdany J, Yelin E. Role of sleep disturbance, depression, obesity, and physical inactivity in fatigue in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2016;68(1):81-90.
169. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. J Am Coll Cardiol. 2001;37(1):153-6.
170. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38(1):44-8.
171. Ritchie DM, Boyle JA, McInnes JM, Jasani MK, Dalakos TG, Grieveson P, et al. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. Q J Med. 1968;37(147):393-406.

172. Riazzoli J, Nilsson JA, Teleman A, Petersson IF, Rantapaa-Dahlqvist S, Jacobsson LT, et al. Patient-reported 28 swollen and tender joint counts accurately represent RA disease activity and can be used to assess therapy responses at the group level. Rheumatology (Oxford). 2010;49(11):2098-103.
173. van Gestel AM, Prevoo, M. L. L., van´t Hof, M. A., van Rijswijk, M. H., van de Putte, L. B., van Riel, P. L. C. M. Development and validation of the European league against rheumatism response criteria for rheumatoid arthritis. Arthritis Rheum. 1996;39:34-40.
174. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ. 1990;300(6719):230-5.
175. Reference Values for Arterial Stiffness Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. Eur Heart J. 2010;31(19):2338-50.
176. Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid atherosclerosis progression study (CAPS). Stroke. 2006;37(1):87-92.
177. Pietrobelli A, Formica C, Wang Z, Heymsfield SB. Dual-energy X-ray absorptiometry body composition model: review of physical concepts. Am J Physiol. 1996;271(6 Pt 1):E941-51.
178. Larsson I, Lissner L, Samuelson G, Fors H, Lantz H, Naslund I, et al. Body composition through adult life: Swedish reference data on body composition. Eur J Clin Nutr. 2015;69(7):837-42.
179. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23(2):137-45.
180. Pope JE, Khanna D, Norrie D, Ouimet JM. The minimally important difference for the health assessment questionnaire in rheumatoid arthritis clinical practice is smaller than in randomized controlled trials. J Rheumatol. 2009;36(2):254-9.
181. Eberhardt KB, Svensson B, Mortiz U. Functional assessment of early rheumatoid arthritis. Br J Rheumatol. 1988;27(5):364-71.
182. Brage S, Brage N, Franks PW, Ekelund U, Wareham NJ. Reliability and validity of the combined heart rate and movement sensor Actiheart. Eur J Clin Nutr. 2005;59(4):561-70.
183. Camntech. The Actiheart user manual [Internet] 2017 [updated 12/01/2017]. Available from: http://www.camntech.com.
184. Assah FK, Brage S, Ekelund U, Wareham NJ. The association of intensity and overall level of physical activity energy expenditure with a marker of insulin resistance. Diabetologia. 2008;51(8):1399-407.
185. InterAct Consortium, Peters T, Brage S, Westgate K, Franks PW, Gradmark A, et al. Validity of a short questionnaire to assess physical activity in 10 European countries. Eur J Epidemiol. 2012;27(1):15-25.
186. Engström L. LIV 90. Rapport 1, Livsstil, prestation, hälsa: Motionsvanor, fysisk prestationsförmåga och hälsotillstånd bland svenska kvinnor och män i åldrarna 20-65 år (Folksams skriftserie. B;264). Stockholm: Folksam; 1993.
187. Ekblom B, Engstrom LM, Ekblom O. Secular trends of physical fitness in Swedish adults. Scand J Med Sci Sports. 2007;17(3):267-73.

188. Ekblom-Bak E, Engström L, Ekblom Ö, B. E. LIV 2000: Motionsvanor, fysisk prestationsförmåga och levnadsvanor bland svenska kvinnor och män i åldrarna 20-65 år. Stockholm: Gymnastik- och Idrottshögskolan; 2011.
189. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev. 1977;84(2):191-215.
190. Keller C, Fleury J, Gregor-Holt N, Thompson T. Predictive ability of social cognitive theory in exercise research: an integrated literature review. Online J Knowl Synth Nurs. 1999;6:2.
191. Lorig K, Chastain RL, Ung E, Shoor S, Holman HR. Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. Arthritis Rheum. 1989;32(1):37-44.
192. Lomi C. Evaluation of a Swedish version of the Arthritis self-efficacy scale. Scand J Caring Sci. 1992;6(3):131-8.
193. Lomi C, Nordholm LA. Validation of a Swedish version of the Arthritis self-efficacy scale. Scand J Rheumatol. 1992;21(5):231-7.
194. Aspenes ST, Nilsen TI, Skaug EA, Bertheussen GF, Ellingsen O, Vatten L, et al. Peak oxygen uptake and cardiovascular risk factors in 4631 healthy women and men. Med Sci Sports Exerc. 2011;43(8):1465-73.
195. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012;380(9838):219-29.
196. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.
197. Brage S, Westgate K, Franks PW, Stegle O, Wright A, Ekelund U, et al. Estimation of free-living energy expenditure by heart rate and movement sensing: A doubly-labelled water study. PloS one. 2015;10(9):e0137206.
198. Ward DS, Evenson KR, Vaughn A, Rodgers AB, Troiano RP. Accelerometer use in physical activity: best practices and research recommendations. Med Sci Sports Exerc. 2005;37(11 Suppl):S582-8.
199. Semanik P, Song J, Chang R, Manheim L, Ainsworth B, Dunlop D. Assessing physical activity in persons with rheumatoid arthritis using accelerometry. Med Sci Sports Exerc. 2010;42:1493-501.
200. Nordgren B, Friden C, Jansson E, Osterlund T, Grooten WJ, Opava CH, et al. Criterion validation of two submaximal aerobic fitness tests, the self-monitoring Fox-walk test and the Astrand cycle test in people with rheumatoid arthritis. BMC Musculoskelet Disord. 2014;15:305.
201. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;55(13):1318-27.
202. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J. 2010;31(15):1865-71.

203. Baulmann J, Schillings U, Rickert S, Uen S, Dusing R, Illyes M, et al. A new oscillometric method for assessment of arterial stiffness: comparison with tonometric and piezo-electronic methods. J Hypertens. 2008;26(3):523-8.
204. Burke GL, Evans GW, Riley WA, Sharrett AR, Howard G, Barnes RW, et al. Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults. The Atherosclerosis risk in communities (ARIC) study. Stroke. 1995;26(3):386-91.
205. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation. 2007;115(4):459-67.
206. van Breukelen-van der Stoep DF, Zijlmans J, van Zeben D, Klop B, van de Geijn G, van der Meulen N, et al. Adherence to cardiovascular prevention strategies in patients with rheumatoid arthritis. Scand J Rheumatol. 2015;44(6):443-8.
207. Brodin N, Swardh E, Biguet G, Opava CH. Understanding how to determine the intensity of physical activity--an interview study among individuals with rheumatoid arthritis. Disabil Rehabil. 2009;31(6):458-65.