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## - physical fitness, function, and mortality

Doctoral thesis

**NTNU**
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
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Department of Clinical and Molecular Medicine

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# Byrden av revmatoid artritt – kondisjon, funksjon, og dødelighet

Leddgikt (revmatoid artritt) rammer nesten 1 % av den voksne befolkningen og omtrent dobbelt så mange kvinner som menn. I tillegg til betennelse i ledd og symptomer som smerte og utmattelse innebærer leddgikt også en høyere risiko for hjerte-kar sykdom. Videre har leddgiktpasienter høyere risiko for tidlig død sammenlignet med den generelle befolkningen, samt lavere kondisjon. Kondisjon er et viktig mål på helse, og dårlig kondisjon er en risikofaktor for tidlig død. Vi ønsket å finne ut hvordan leddgikt påvirker overlevelse og om leddgikt har like stor betydning for overlevelse som diabetes. Vi ville også undersøke i hvor stor grad leddgiktpasienter har lavere beregnet kondisjon sammenlignet med friske kontroller, og vi ønsket å identifisere faktorer relatert til fysisk form i denne pasientgruppen.

Våre funn tyder på at leddgikt i seg selv i likhet med diabetes er forbundet med høyere risiko for tidlig død, men at det er bedre å ha leddgikt enn diabetes med tanke på overlevelse. Vi fant lavere beregnet kondisjon blant leddgiktpasienter sammenlignet med friske kontroller. Høyere forekomst av fysiske symptomer og negative følelser forklarte 74 % av denne forskjellen i kondisjon. Videre så vi at pasientens vurdering av sin egen sykdom og mestringstro for trening var relatert til fysisk form målt med en 6-minutters gangtest.

Denne avhandlingen viste at pasienter med leddgikt har høyere risiko for tidlig død og lavere beregnet kondisjon enn kontroller. Både fysiske symptomer og negative følelser kunne forklare noe av leddgiktpasientenes lavere beregnede kondisjon. Det er derfor svært viktig å ta tak i livsstilsfaktorer, kondisjon, og mental helse i tillegg til medikamentell behandling for å forbedre leddgiktpasienters helseutsikter. Vi fant flere pasientrapporterte utfallsmål som var relatert til fysisk form slik som mestringstro for trening og grad av negative følelser. Disse utfallsmålene kan være nyttige i klinisk praksis og i forskningssammenheng. Sammen med et mål på fysisk kondisjon eller fysisk aktivitet kan disse utfallsmålene bidra til å identifisere pasienter som kan ha nytte av ekstra oppfølging.

***Metoder:*** I overlevelsesdelen av studien brukte vi datamateriell fra Helseundersøkelsen i Trøndelag. Vi fulgte 387 leddgiktpasienter, 2,898 diabetespasienter, 33 pasienter med begge sykdommene, og 63,903 kontroller i omtrent 18 år frem til 31.12.2014. For å undersøke faktorer som påvirker fysisk form rekrutterte vi 227 leddgiktpasienter og 300 friske kontroller, og en undergruppe av pasientene utførte en 6-minutters gangtest. Kondisjon ble beregnet med kondisjonskalkulatorer. Cox-regresjon ble benyttet for overlevelsesanalysen. Strukturelle ligningsmodeller og multivariabel lineær regresjon ble benyttet for å vurdere faktorer relatert til fysisk form.

***Navn kandidat:*** Ingrid Sæther Houge
***Institutt:*** Institutt for klinisk og molekylær medisin
***Veiledere:*** Vibeke Videm og Mari Hoff
***Finansieringskilde:*** Fakultet for medisin og helsevitenskap ved NTNU

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Ingrid Sæther Houge, Trondheim 2023

# TABLE OF CONTENTS

# LIST OF ARTICLES

The present PhD thesis was conducted at the Department of Clinical and Molecular Medicine, NTNU - Norwegian University of Science and Technology. The work is a continuation of the Medical Student Research Thesis completed by the candidate in 2020 at the same department. The work consists of 3 papers which will be referred to as Study I, II, and III throughout the thesis.

**Study I:** Houge IS, Hoff M, Thomas R, Videm V. Mortality is increased in rheumatoid arthritis or diabetes compared to the general population – the Nord-Trøndelag Health Study. Scientific Reports. 2020;10(1):3593.

**Study II:** Houge IS, Hoff M, Halsan O, Videm V. Exercise Self-Efficacy and patient global assessment were associated with 6-min walk test distance in persons with rheumatoid arthritis. Clinical Rheumatology. 2022;41:3687-96.

**Study III:** Houge IS, Hoff M, Videm V. The association between rheumatoid arthritis and reduced estimated cardiorespiratory fitness is mediated by physical symptoms and negative emotions: a cross-sectional study. Clinical Rheumatology. 2023. Published online ahead of print.

## SUMMARY

Patients with rheumatoid arthritis (RA) have higher mortality rates than the general population as well as lower cardiorespiratory fitness. They also have an increased risk of myocardial infarction of similar magnitudes as patients with diabetes. Prior to this thesis, mortality in RA and diabetes had not been directly compared in a longitudinal population-based setting. Moreover, as improving or maintaining physical fitness is important for long-term health, further insight into factors associated with physical fitness in RA patients may inform clinical practice and the development of intervention programmes.

We wanted to investigate whether RA patients had higher mortality rates and lower physical fitness compared to controls, and identify factors associated with physical fitness in RA patients.

We used data from the population-based Trøndelag Health Study linked to the Norwegian Cause of Death Registry for Study I. Cox proportional hazard regression was applied to compare mortality rates in patients with RA, patients with diabetes, and controls. We also compared the distribution of deaths due to diseases of the circulatory system, neoplasms, and diseases of the respiratory system.

To investigate factors associated with physical fitness, we recruited RA patients and healthy controls. The distance walked during a 6-minute walk test and the cardiorespiratory fitness estimated from non-exercise formulas were used as physical fitness measures. Study II applied multivariable linear regression to explore factors associated with the distance walked during the 6-minute walk test. We used Pearson's correlation coefficient and a scatterplot to assess the relationship between walk test distance and estimated cardiorespiratory fitness. Study III applied structural equation modelling to evaluate whether more physical symptoms and negative emotions could explain the association between RA status and reduced estimated cardiorespiratory fitness.

Study I included 387 RA patients, 2,898 diabetes patients, 33 patients with both diseases, and 63,903 controls. Median follow-up time was 18 years. When taking age, sex, smoking, body mass index, hypertension, creatinine, total cholesterol, and previous cardiovascular disease into account, RA patients and diabetes patients had higher mortality rates than controls. Compared to the controls, RA patients had 24 % higher mortality rates in the adjusted models. The corresponding estimates for diabetes patients ≤75 years and >75 years were 83 % and 49 % higher mortality rates than controls, respectively. The distribution of death causes in the

RA patients was not statistically significantly different from the distribution in diabetes patients or controls.

Study II included 79 RA patients. Age, body mass index, smoking habits, patient global assessment, and self-efficacy for exercise were associated with how far the participants walked during the 6-minute walk test. Moreover, the fitness measures distance walked during the 6-minute walk test and estimated cardiorespiratory fitness were significantly correlated ($r=0.61$, $p<0.0001$). Study III included 227 RA patients and 300 controls. RA patients had on average 1.7 mL/kg/min lower estimated cardiorespiratory fitness than controls when taking age and sex into account ($p=0.002$). Higher prevalence of physical symptoms and negative emotions explained 74 % of the relationship between RA status and lower estimated cardiorespiratory fitness.

This thesis demonstrated that RA patients had higher mortality rates and lower estimated cardiorespiratory fitness than controls. Higher prevalence of physical symptoms and negative emotions could explain a large proportion of the difference in estimated physical fitness between RA patients and healthy controls. It is therefore extremely important to address lifestyle, physical fitness, and mental health in addition to pharmacological treatment to improve long-term health among RA patients. We also identified several patient-reported measures associated with physical fitness. These measures are tools that can be useful in clinical practice and in exercise interventions. Together with some measure of physical fitness or physical activity, these tools may help to identify patients who would benefit from extra follow-up.

## ABBREVIATONS

ACPA - anti-citrullinated protein antibody

ACR - American College of Rheumatology

ACSM - American College of Sport Medicine

AHA - American Heart Association

CI - confidence interval

CRF - cardiorespiratory fitness

CRP - C-reactive protein

CVD - cardiovascular disease

CV - cardiovascular

DAS28-CRP - disease activity score in 28 joints - C- reactive protein

DMARD - disease-modifying anti-rheumatic drugs

eCRF - estimated cardiorespiratory fitness

ESR - erythrocyte sedimentation rate

EULAR - European Alliance of Associations for Rheumatology

FysKond2 - Study about factors influencing physical activity and cardiorespiratory fitness in patients with inflammatory arthritis

HADS-D - the depression subscale of the Hospital Anxiety and Depression Scale

HR - hazard ratio

HuLARS - HUNT Longitudinal Ankylosing Spondylitis and Rheumatoid Arthritis Study

HUNT - the Trøndelag Health Study

ICD - International Classification of Diseases

PROMs - patient-reported outcome measures

RA - rheumatoid arthritis

RF - rheumatoid factor

SEM - structural equation modelling

$VO_{2max}$ - maximal oxygen uptake

$VO_{2peak}$ - peak oxygen uptake

6MWT - 6-minute walk test

6MWD - 6-minute walk test distance

# 1 INTRODUCTION

## 1.1 Rheumatoid arthritis

### 1.1.1 Epidemiology and symptoms

Rheumatoid arthritis (RA) is a type of inflammatory arthritis and in Norway the prevalence of RA is estimated to 0.78 % of the adult population (1, 2). The incidence rates are approximately 2 times higher in women compared to men, and highest in the 65 to 75-year age group (3). However, the disease can debut both in early and late adulthood. RA is characterized by inflammation in synovial joints that may lead to destruction of the joints if not treated (1). Common symptoms of RA are painful and swollen joints, morning stiffness, and fatigue. RA typically involves the joints of the hands and feet symmetrically, though may also affect larger joints (4). RA is a systemic disease with extra-articular manifestations involving several organ systems, including the skin, the eyes, the lungs, and the heart (1, 5).

Another feature of RA is altered body composition, called “rheumatoid cachexia”. Rheumatoid cachexia involves reduction in muscle mass and maintained or increased fat mass (6). This is observed in approximately 19 % of RA patients, however, due to different definitions the prevalence estimates in individual studies vary from 1 to 54 % (7).

RA can be divided into seropositive or seronegative disease (1). Seropositive RA usually means that the patient has a positive test for either rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA). Nevertheless, with more sensitive detection methods and newly discovered autoantibodies several seronegative patients may be reclassified as seropositive (8). Seropositive RA is sometimes considered a separate disease, with higher risk of joint destruction and a more aggressive disease course (8, 9).

### 1.1.2 Risk factors

Genetics play an important role in RA development (1, 10). Having a first degree relative with RA is associated with a 2-to-4-fold increased risk of developing RA and the hereditability of RA is estimated to be around 40 % (11). Genome-wide association studies have found more than 100 risk loci associated with RA, and the region that has been most studied is HLA-DRB1 (4). Genetic factors interact with environmental factors, such as smoking cigarettes (10, 12). Smoking is the environmental risk factor with the strongest association with RA development and approximately 20 % of all RA cases and 35 % of ACPA positive RA cases can be attributed to smoking (4, 12). Moreover, smoking has a dose-response relationship with the risk of RA (10, 12). Other risk factors for developing RA

are female sex, older age, periodontitis, low socioeconomic status, exposure to air pollution, exposure to silica dust, and a history of depression (1, 4, 13-15). Obesity and low levels of physical activity are also associated with increased risk of developing RA, at least in women (16, 17).

### 1.1.3 Classification criteria

The RA classification criteria are used to identify an entity of relatively homogenous individuals who can be included in research, as well as a tool in the diagnostic process (18). However, a rheumatologist can set an RA diagnosis in patients not fulfilling the classification criteria or decide to not set an RA diagnosis in patients fulfilling the classification criteria if the clinical data suggest that another diagnosis is more likely.

**Table 1: American College of Rheumatology/European Alliance of Associations for Rheumatology 2010 classification criteria for rheumatoid arthritis.**

| Domain | | Points |
|---|---|---|
| A. Joint involvement [a] | 1 large joint | 0 |
| | 2-10 large joints | 1 |
| | 1-3 small joints | 2 |
| | 4-10 small joints | 3 |
| | >10 joints including at least 1 small joint | 5 |
| B. Serology | Negative RF and negative ACPA | 0 |
| | Low positive RF and/or ACPA | 2 |
| | High positive RF and/or ACPA | 3 |
| C. Acute phase reactants | Normal CRP and normal ESR | 0 |
| | Abnormal CRP/ ESR | 1 |
| D. Patient-reported symptom duration | <6 weeks | 0 |
| | ≥6 weeks | 1 |

[a] Joint involvement: swollen/tender joints upon examination.
Abbreviations: ACPA - anti-citrullinated protein antibody, CRP - C-reactive protein, ESR - erythrocyte sedimentation rate, RF - rheumatoid factor.

The American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) 2010 classification criteria include the domains joint involvement, serology, acute-phase reactants, and duration of symptoms, see Table 1 (18). The classification criteria should only be applied if the patient currently has active clinical synovitis in at least 1 joint that is not better explained by another disease. The ACR/EULAR

2010 classification criteria give a total score which ranges from 0 to 10, and a total score of ≥6 is required to classify a patient as definite RA. Patients with joint erosions typical of RA can also be classified as having RA even if the patient does not score ≥6 points for the ACR/EULAR 2010 criteria. Patients who have fulfilled the criteria in the past would also be classified as definite RA. The revised ACR 1987 criteria that were formerly used placed more emphasis on later manifestations of the disease (19). Compared to the 1987 criteria, the 2010 criteria identify RA patients earlier in their disease course, have higher sensitivity, though lower specificity (20). Moreover, patients fulfilling the 2010 criteria have a milder disease course in terms of joint damage compared to those fulfilling the 1987 criteria (21). This might be because the 2010 criteria can be fulfilled by individuals with a less severe disease and by individuals who actually have with other types of inflammatory arthritis with milder disease course.

### 1.1.4 Remission and disease activity

Remission is the absence of signs of significant disease activity (22). When evaluating disease activity, physical examination of joints, patient-reported outcome measures (PROMs), and blood tests measuring inflammation are relevant information. PROMs are measures of the impact of disease which are patient-reported. PROMs can be based on a single question, or on a questionnaire with several items, and can capture aspects like pain, fatigue, psychological distress, function, social support, and quality of life (23). A PROM that is common in the follow-up of RA patients is the patient global assessment. The patient global assessment is the patient's rating of overall disease activity either on a 100 mm visual analogue scale or on a 0 to 10 numerical rating scale (24). When scoring, the patient may consider symptoms of RA, functional impairment, psychological distress, or other factors. Several different phrases are used for the patient global assessment, and these are not interchangeable.

Disease activity is often assessed with a composite measure with a cut-off value for remission. An example is the disease activity score in 28 joints - C-reactive protein (DAS28-CRP). DAS28-CRP is based on swollen and tender joint counts of 28 specified joints, the patient global assessment, and CRP, and each item is multiplied by a coefficient and added together. DAS28 can be calculated with CRP or erythrocyte sedimentation rate (ESR), without an acute phase reactant, and without the patient global assessment. It is an ongoing debate whether the patient global assessment should be removed from the remission criteria, as patients may have ongoing pain and fatigue despite being in clinical remission (24-26).

### 1.1.5 Treatment of rheumatoid arthritis

The pharmacological treatment of RA includes conventional synthetic disease-modifying antirheumatic drugs (DMARDs), targeted synthetic DMARDs, and biological DMARDs as well as glucocorticoids (1). The EULAR recommendation for treatment in newly diagnosed patients is to start with a combination of conventional synthetic DMARDs, preferably methotrexate, and low-dose glucocorticoids. Until the treatment target has been reached, the disease activity should be monitored at least every 3 months (27). The treat-to-target approach has been very successful in improving disease activity and long-term outcomes in RA patients (22, 27, 28). The goal is sustained remission, or low disease activity if remission cannot be achieved for example in long-standing disease.

### 1.1.6 Costs of rheumatoid arthritis

RA is associated with substantial financial cost for the society, both direct costs like medications and healthcare services and indirect costs such as loss of work productivity and decreased societal participation (1). Results from Sweden indicate that the mean annual cost per person in terms of healthcare cost and productivity loss was 2 to 3 times higher among RA patients compared the matched comparators from the general population in 2010 (29). Further, more than half of the total costs of RA were the indirect costs (29, 30). In Sweden, there was a 90 % reduction in hospital days due to RA from 1990 to 2010, accompanied with approximately 50 % reduction in sick leave days due to RA and 30 % reduction in individuals on disability pension due to RA (30). These numbers imply tremendous improvements in outcomes and ability to work. However, the costs of RA medications increased substantially in the same time period resulting in a net increase of total costs of RA by 32 %. Since then, the costs of biological and targeted synthetic DMARDs have decreased by approximately 50 % per user according to Norwegian data, which is related to the development and production of biosimilars (31). Interestingly, PROMs have a stronger association with subsequent sick days than objective measures of disease activity (32).

## 1.2 Mental health comorbidities

Certain mental disorders are common in individuals with RA (33). RA patients do have higher risk of developing depression, anxiety, and bipolar disorder than matched individuals without RA (34). This has clinical implications as poor mental health can affect cognitive and behavioural responses, quality of life, disease outcomes, and long-term health (33). The present thesis will focus on 2 aspects of mental health, namely depression and stress.

### 1.2.1 Depression

The overlap of symptoms in RA and depression, like fatigue, poor sleep, and changed appetite, can be a diagnostic challenge. This could lead to overestimation or underestimation of the prevalence of depression in RA patients. In a meta-analysis, 17 % of the RA patients had a major depressive disorder when this was assessed in psychiatric interviews according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (35). However, different definitions or methods gave different estimates of the prevalence of depression, ranging from less than 1 % to 66 % in the individual studies. In a sample of 4,187 British RA patients, 30 % had a depressive episode within the first 5 years after diagnosis (36). A Canadian study reported that RA patients had higher risk of developing depression than matched controls with an adjusted incidence rate ratio of 1.46 (95% confidence interval (CI) 1.35, 1.58) (37). Moreover, depression also increases the risk of developing RA (15, 38, 39). Data from the United Kingdom indicate that individuals with major depressive disorder had 38 % higher risk of developing RA than to controls (15).

There are several theories as to why RA and depression show a bidirectional relationship (38, 40, 41). RA and depression have some common risk factors like female sex, low socioeconomic status, and smoking (12, 13, 42). Further, being diagnosed with a chronic disease and experiencing pain, fatigue and disability can affect the mood. However, the current view is that RA and depression likely also share some pathophysiological mechanisms (41). Some of the discussed mechanisms involve increased concentration of pro-inflammatory cytokines, alterations of neurotransmitter systems in the brain, dysregulation of the hypothalamic-pituitary-adrenal axis, and negative effect on synaptic plasticity (38, 40, 41).

### 1.2.2 Psychological stress

Stress is a broad concept that can be used about physiological stress, major or minor life-events, reaction to life events, effort-reward imbalance, interpersonal stress, or feeling of not being able to cope with the challenges in one's life. The presence of a chronic disease can also be considered a stressor (33). There has been a discussion whether RA and psychological stress also exhibit a bidirectional relationship, however, the findings have been less consistent than for depression. RA patients appear to experience more work stress and interpersonal stress than healthy controls (43). Moreover, recently diagnosed RA patients reported more recent stressful life events compared to matched controls, and individuals with symptoms of post-traumatic stress disorder after traumatic events were more likely to develop RA (44-47).

Psychological distress was also associated with increased risk of developing inflammatory arthritis in an at-risk cohort of 448 individuals (48). However, a study of 241 individuals with clinically suspect arthralgia did not find an association between psychological stress and the progression to inflammatory arthritis (49).

### 1.2.3 Relationship between depression, stress, and disease outcomes

Depression and stress are associated with each other and with worse outcomes among RA patients (33). Depression is associated with more severe disease, more pain, more fatigue, and increased cost (40, 50-53). Depression may also affect disease activity, remission, response to treatment, and adherence to treatment (33, 54-56). A large British study of RA patients initiating biological treatment found that depression was associated with reduced improvement in tender and swollen joint count, ESR, and the patient global assessment (54). Similarly, stress may influence disease activity, pain, and fatigue (33, 57, 58). As depression and stress impact disease outcomes, these are important targets in the care of RA patients. Better mental health can improve the course of disease through better self-management and better adherence to treatment. EULAR therefore recommends regular assessment of mental health in patients with inflammatory arthritis (59).

## 1.3 Extra-articular manifestations and comorbidities

Several extra-articular manifestations and diseases are associated with RA, see Figure 1. These include Secondary Sjögren's Syndrome, pericarditis, vasculitis, scleritis, fibromyalgia, rheumatoid nodules, osteoporosis, hypertension, certain types of malignancies, pulmonary disease, and cardiovascular disease (CVD) (5, 60-66). The association between RA and several of these diseases such as osteoporosis, certain types of malignancies, pulmonary disease, and CVD are probably related to a combination of inflammation, lifestyle factors, and side effects of medications (62, 65, 67-69). RA patients have a modest increased risk of malignancies compared to the general population, in particular increased risk of lung cancer and malignant lymphoma (62-64). However, they have reduced risk of colorectal cancer and a non-significant trend towards reduced risk of breast cancer and cervical cancer (64). In terms of pulmonary diseases, RA patients have increased risk of chronic obstructive pulmonary disease, asthma, interstitial lung disease, and pleuritis (65, 70, 71).

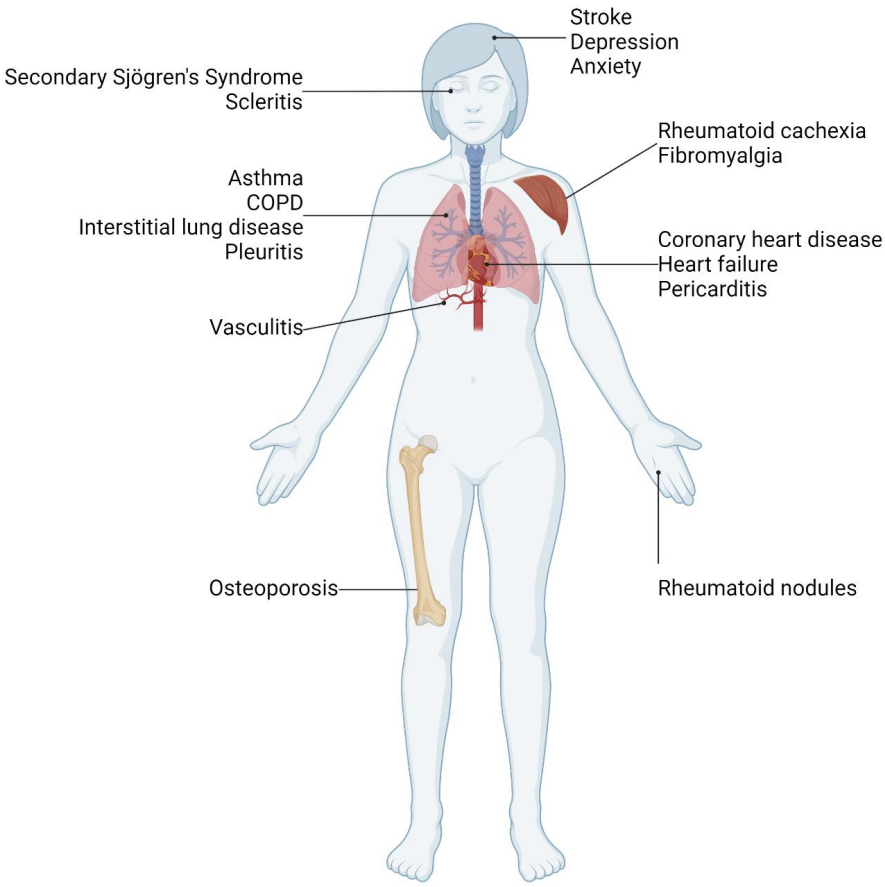


**Figure 1: Selected extra-articular manifestations and comorbidities associated with rheumatoid arthritis.**
Abbreviations: COPD - chronic obstructive pulmonary disease. Created with BioRender.com.

Similarly, individuals with RA have an increased risk of CVD (66, 67). A meta-analysis of 41,490 RA patients concluded that they had 48 % higher risk of an incident cardiovascular (CV) events (95 % CI 36 %, 62 %) compared to the general population (66). More specifically, they had 68 % higher risk of myocardial infarction, 41 % higher risk of cerebrovascular accidents, and 87 % higher risk of congestive heart failure. Another study found that the risk of myocardial infarction in RA patients is approximately equal to persons without RA who are 10 years older (72). Furthermore, RA is associated with worse prognosis following an acute CV event, increased risk of in-hospital mortality, recurrent CV event, and long-term mortality (73-76). Because of the increased risk of CVD, EULAR recommends multiplying CVD risk prediction models by a factor of 1.5 if the patient has RA, unless RA is

already part of the prediction model (77). EULAR also recommends CVD assessment at least every 5 years, optimal disease control, a healthy diet, regular exercise, and smoking cessation for all patients with inflammatory joint disorders.

The excess risk of CVD in RA patients has been compared to the excess risk in diabetes patients (78-81). Diabetes is a well-known risk factor for CVD and premature mortality, which has resulted in extensive guidelines on how to manage the elevated CVD risk in diabetics (82, 83). These recommendations focus on glycaemic control, optimizing lifestyle habits, reducing obesity, screening for CVD and kidney disease, lipid lowering therapy, antithrombotic therapy, and antihypertensive therapy. Diabetes is also characterized by subclinical chronic inflammation (84).

Dutch researchers reported that RA patients and diabetes patients had increased risk of prevalent and incident CVD, and their excess risk was of similar magnitude (78, 79). In a cross-sectional study, RA patients and diabetes patients matched for age, sex, and disease duration had similar severity and frequency of preclinical atherosclerosis, and significantly worse compared to healthy controls (85). Furthermore, a nationwide Danish study applying data from 1997 to 2006 found that both RA patients and diabetes patients had increased risk of incident myocardial infarction compared to the general population, with an adjusted incidence rate ratio of 1.7 in both groups (72). However, a large study from the United States by using data from 2006 to 2010 concluded that RA was not a CVD risk-equivalent to diabetes (86). They reported that although RA patients had significantly higher risk of myocardial infarction and stroke than the general population, the incidence rates in the RA group was considerably lower than in the diabetes group. The age-and sex-standardized incidence rates of myocardial infarction were 10.7 in the diabetes group, 5.7 in the RA group, and 4.2 in the control group. Further, the age- and sex-adjusted incidence rate ratio for myocardial infarction was 1.4 (95 % CI 1.3, 1.5) in the RA group and 2.5 (95 % CI 2.5, 2.6) in the diabetes group compared to the general population. The different estimates for the relative risk in RA patients might be explained by calendar year, improvements in medical treatment, and regional differences. In summary, the literature suggests that RA and diabetes are both associated with excess risk of CVD (72, 78-80, 85, 86). The risk appears to be higher in diabetes patients than in RA patients, though there might be regional differences given the finding of comparable risk of myocardial infarction in the Danish study (72).

## 1.4 Mortality

RA has been associated with approximately 40 to 50 % higher mortality rates compared to that in the general population (87, 88). However, others have reported no excess mortality in RA patients in recent years (89, 90). Lacaille et al. found that the 5-year mortality in Canadian RA patients diagnosed in 1996 to 2000 was higher than in the general population (adjusted hazard ratio (HR) 1.40, 95 % CI 1.30, 1.51), whereas the 5-year mortality among those diagnosed in 2001-2006 was not increased (adjusted HR 0.97, 95 % CI 0.89, 1.05) (89). Contrary, Gonzalez et al. reported a widening mortality gap between RA patients and the general population in the United States (91). In a large inception cohort form the United Kingdom, Abhishek et al. found that the absolute mortality rates in RA patients decreased with time but was still higher than the general population (92). This is in line with most of the published results; lower absolute mortality rates compared to some decades ago, but still higher rates than in the general population (87, 88, 92).

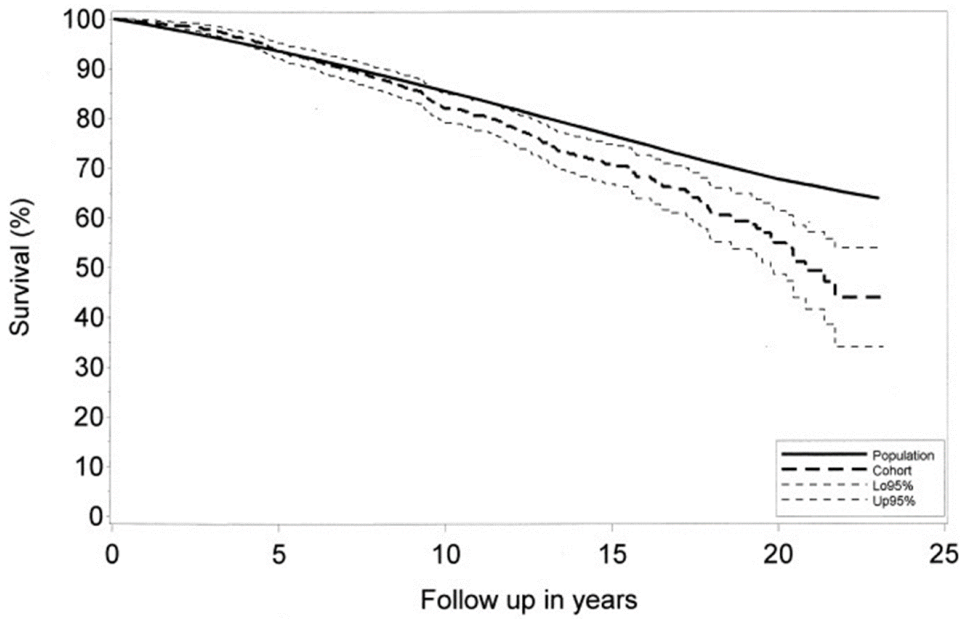


**Figure 2: Excess mortality in rheumatoid arthritis emerges after 10 years.**
Originally published by Radovits et al. (93). Radovits et al. followed 1,049 patients with recent onset rheumatoid arthritis for up to 23 years. The figure shows the survival curve for the patients with rheumatoid arthritis with the 95 % confidence intervals, and the expected survival curve for the general population matched for age, sex, and calendar year. Reprinted with permission from John Wiley and Sons.

Several researchers have described that the excess mortality emerges 10 years or more after onset of RA, see Figure 2 (93, 94). This highlights the importance of long follow-up time. The main cause of death among persons with RA is diseases of the circulatory system (95, 96). Moreover, RA patients also have increased mortality rates due to diseases of the respiratory system and malignancies (64, 96).

To our knowledge, the impact of RA and diabetes on all-cause mortality had not been directly compared in a population-based setting prior to the start of the present thesis. A large study from the United States that studied individuals undergoing elective non-cardiac surgery between 1998 and 2002 compared individuals with RA and/or diabetes to individuals without either of these diseases (97). The RA patients had lower risk of CV events or mortality during hospitalization compared to patients with diabetes, and no increased risk compared to individuals without RA or diabetes. This study only addressed the incidence of adverse events short-term (during hospitalization), and the decisions to perform surgery are influenced by a variety of clinical factors and the risk evaluation of the clinicians. Thus, perioperative mortality does not give any information about mortality rates in the population in general. A population-based study could provide more insight into whether mortality rates in RA patients and diabetes patients are increased to a similar extent compared to the mortality rates in the general population.

## 1.5 Physical activity and exercise

### 1.5.1 Definitions

Physical activity can be defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" (98). Activities of daily living like cooking, cleaning, personal care, as well as exercise are types of physical activities. Exercise is "planned, structured, repetitive, and purposive in the sense that improvement or maintenance of 1 or more components of physical fitness is an objective" (98). Important dimensions of physical activity are frequency, duration, intensity, and modality. Light, moderate, and vigorous intensity corresponds to modalities such as slow walking, brisk walking, and running, respectively. Other physical activity modalities are cycling, swimming, gardening, playing tennis etc.

### 1.5.2 Benefits and risks

The importance of physical activity and exercise is well established. Studies in the general population have shown that physical activity has positive effects on strength,

cardiorespiratory fitness (CRF), mental health, and survival (99-103). Physical activity reduces the risk of numerous somatic diseases such as diabetes, hypertension, CVD, cancer, and gallstone disease (101, 102). Regular physical activity might also reduce the risk of developing RA in women (17). A meta-analysis of randomized controlled trials found that exercise interventions reduced the risk of falling by 21 % in community-dwelling older adults (104). Furthermore, physical activity has beneficial effects on plasma lipid profile, atherosclerotic plaque stability, endothelial function, myocardial function, insulin sensitivity, blood pressure, and bone mineral density (105-107).

A lot of the benefits from physical activity observed in the general population are probably also applicable to RA patients (108, 109). Exercise interventions in RA patients have demonstrated that physical activity can improve strength, CRF, endothelial function, and CV risk profile (109-112). Moreover, exercise has positive effects on body composition, possibly reversing rheumatoid cachexia (6, 113, 114). Other benefits demonstrated in exercise trials include reduced pain, improved function, improved quality of sleep, and a small beneficial effect on fatigue (115-117). Furthermore, exercise might reduce disease activity and the level of acute phase reactants among RA patients, though this might vary by baseline disease activity, exercise modality, exercise intensity, and duration of the intervention (115, 118). RA patients participating in regular physical activity are less often hospitalized (119). They also tend to have better lipid profiles, less fatigue, less pain, less functional disability, less comorbidities, and report better mental well-being (108, 120, 121).

Given the wide variety of physical activity modalities, it is not surprising that modality of physical activity influences the expected benefits. If the primary goal is to reduce the risk of falling, exercises that challenges balance are more efficient compared to simply walking (104). Similarly, to improve, maintain, or attenuate loss of bone mineral density, weight bearing exercises and strength training are preferred (106).

There are some risks associated with physical activity and exercise, nonetheless, there is consensus that the benefits far outweigh the risks in most adults (101). The most common exercise-related adverse events are soreness and musculoskeletal injuries (101, 122). Strenuous physical activity in untrained individuals, particularly eccentric exercises or downhill running, can lead to rhabdomyolysis. Rhabdomyolysis is characterized by pain out of proportion, muscle swelling, myoglobinuria, and elevated serum creatinine phosphokinase, and can in rare instances be complicated by acute renal failure (123). Acute CV events and

sudden cardiac events may occur during physical activity (101, 124). The risk of acute CV events is transiently increased during vigorous physical activity, though regular physical activity is associated with lower overall incidence of CVD (124).

In the past, RA patients were told to avoid hard exercise. Practices such as bed rest were recommended because clinicians and patients feared that exercise could increase disease activity and harm the joints (125). This theory has been refuted. It has been repeatedly demonstrated that physical activity and exercise do not cause flares and are safe and beneficial for RA patients (110, 114, 126). The precautions regarding physical activity are the same for RA patients as for the general populations (126).

### 1.5.3 Physical activity recommendations

Regular physical activity and exercise are strongly recommended for the general population and are a core part in the management of many chronic diseases. As physical activity and exercise are safe for patients with inflammatory arthritis, the physical activity recommendations for the general population published by the American College of Sport Medicine (ACSM) and the American Heart Association (AHA) are considered applicable to this patient group as well (101, 126, 127). They recommend performing ≥30 minutes of aerobic exercise at moderate intensity ≥5 days per week (≥150 minutes per week), or ≥20 minutes of aerobic exercise at vigorous intensity ≥3 days per week (≥75 minutes per week), or a combination of these. Furthermore, they recommend performing exercises to maintain or increase muscular strength and endurance ≥2 days per week, incorporate flexibility and neuromotor exercise training, and reducing time spent sedentary. For inactive individuals, substantial health benefits may be achieved even by small increases in physical activity level (102).

### 1.5.4 Physical activity in persons with rheumatoid arthritis

Although physical activity is safe, beneficial, and highly recommended for patients with RA, a large proportion of persons with RA does not fulfil the ACSM/AHA recommendations for physical activity. RA patients engage in less physical activity at vigorous intensity, have lower energy expenditure, and are more sedentary compared to controls and/or the general population (108, 128, 129). An international study published in 2008 involving 5,235 RA patients from 21 countries estimated that only 14 % of these patients exercised at moderate intensity at least 3 times per week and 71 % did not engage in regular exercise (130). There was large variation between the different countries, and the percentage that reported to

exercise at moderate intensity ≥3 per week ranged from 6 % in Argentina to 32 % in Finland. In a large Swedish study, only 21 %, 14 %, and 11 % of the RA patients reported to have met the ACSM/AHA recommendations for aerobic physical activity, muscle training, or both domains, respectively, for more than 6 months (121). The uptake of the ACSM/AHA physical activity recommendations may have improved since then, and a Dutch study reported that the percentage of RA patients engaging in ≥150 minutes of exercise per week had increased between 2013 and 2016, from 25 % to 57 % (131). The different methods and questionnaires used to evaluate physical activity habits, as well as regional variations, make it challenging to compare estimates across studies. Furthermore, self-reported physical activity has only low to moderate correlation with objective measures of physical activity (132).

Why are so many RA patients not participating in regular physical activity? There are many factors that influence human behaviour, for example previous habits, social setting, and knowledge. Some barriers to physical activity reported by RA patients are time constraints, cost, pain, fatigue, lack of information, and lack of knowledge (133). Furthermore, some patients still fear that exercise can cause joint damage or flares (134). Pain has been negatively associated physical activity in several studies of RA patients, however, the systematic reviews by Ingram et al. and by Larkin et al. reported that pain was not significantly associated with physical activity (120, 130, 135). In a study of 345 RA patients, the level of pain was similar among physically active and inactive participants, yet the active group had higher confidence that they could be active despite pain (136). This illustrates that the psychological dimension is very important to maintain or change behaviour.

An important psychological aspect is motivation for a specific behaviour. Motivation for exercise has been associated with exercise behaviour in RA patients (108, 120). Self-Determination Theory describes several distinct types of motivation, which lie on the self-determination continuum (137). This continuum ranges from amotivation through extrinsic motivation to intrinsic motivation, with increasing degree of self-determination. Amotivation is a state where one lacks intention to act. Extrinsic motivation can be divided into 4 regulatory styles, from external regulation to integrated regulation. In external regulation one performs the task due to external factors for example to avoid punishment or to receive a reward, whereas in integrated regulation the task is accepted as important to the individual for example as a mean to achieve a personal goal. Intrinsic motivation is the most self-determined and autonomous type of motivation where the individual performs the behaviour because he or she enjoys and values the behaviour, and not due to external factors. According

to Self-Determination Theory, there are 3 innate psychological needs, namely the needs for competence, relatedness, and autonomy (137). Intervention can be designed to address these, with patient education targeting competence, a good patient-physician relationship contributing to relatedness, and choice of for example modality and self-determined goal ensuring some autonomy.

Another relevant psychological concept is self-efficacy, which is the belief in one's ability to manage certain challenges. Self-efficacy is closely related to actual behaviour and is task-specific. Self-efficacy for exercise is the belief that one can perform regular exercise under different circumstances and has been positively associated with current and maintained physical activity in RA patients (121, 136). According to Self-Efficacy Theory, there are 4 sources of self-efficacy; namely mastery of experience, vicarious experience, verbal persuasion, and physiological feedback (138). Thus, self-efficacy can by influenced by intervening on these 4 aspects. Intervention involving learning by doing, motivational interviews, self-regulation sessions, cognitive behavioural therapy, goal setting, positive feedback, role modelling, and patient education can increase autonomous motivation and self-efficacy for exercise (139-141).

## 1.6 Physical fitness

### 1.6.1 Definitions

Whereas physical activity and exercise are types of human behaviours, physical fitness has been defined as "a set of attributes that people have or achieve that relates to the ability to perform physical activity" (98). Caspersen et al. divide the components of physical fitness into 2 groups: health-related fitness and skill-related fitness (98). CRF, muscular strength, and muscular endurance are examples of health-related components of fitness, whereas balance, coordination, and speed are examples of skill-related components of fitness. CRF can be considered the overall ability to transport and utilize oxygen to perform physical work, and depends on the CV, respiratory, and muscular system (142).

### 1.6.2 Measuring physical fitness

There are many physical tests that measure different components of physical fitness. The focus in this thesis was on CRF assessed with a cardiopulmonary exercise test or estimated with non-exercise formulas, and functional capacity captured with the submaximal 6-minute walk test (6MWT).

*1.6.2.1 Cardiopulmonary exercise test*

The gold standard to measure CRF is a cardiopulmonary exercise test that is usually performed either on a treadmill or a cycle ergometer. During a cardiopulmonary exercise test the workload gradually increases until maximal oxygen uptake ($VO_{2max}$) is reached, or until exhaustion (143). $VO_{2max}$ is measured as mL/min, mL/kg/min, or in metabolic equivalents. At $VO_{2max}$, the oxygen uptake levels off despite increasing workload, reaching a plateau in $VO_2$ (144). If this is not achieved, other measures are sometimes used to assess the likelihood of having reached $VO_{2max}$, such as percentage reached of predicted maximal heart rate, blood concentration of lactate, rating of perceived exertion, the respiratory exchange ratio, or a verification phase (143-147). If the $VO_{2max}$ criteria are not met, the results are referred to as the peak oxygen uptake ($VO_{2peak}$).

Although a cardiopulmonary exercise test gives the most accurate measure of CRF, there is a small risk of adverse events such as incident CVD and even death. The incidence of serious adverse events is around 1 per 10,000 tests (147). To minimize the risk, it is important to screen for contraindications, terminate the test early if needed, and ascertain that the benefit of the test outweighs the potential risk for the individual (144, 148). Cardiopulmonary exercise tests are becoming more available in some countries (144). However, these tests are relatively expensive, require equipment and trained personnel, and are not yet feasible in most clinical settings.

*1.6.2.2 Submaximal exercise tests*

There are multiple tests of physical fitness that do not rely on maximal exertion. A submaximal exercise test that has been widely used is the 6MWT (149, 150). In the 6MWT, the individual is instructed to either walk as far as possible or as fast as possible for 6 minutes and to walk back and forth on a flat surface. To make the test results more reliable the guidelines from the American Thoracic Society should be followed closely (149). They recommend using standardized instructions and to perform the test on a 30 m indoor walking course. The 6MWT is a more practical test in clinical practice compared to a cardiopulmonary exercise test as it requires less time, equipment, and resources. This is a test of functional capacity and is relevant for the function in daily living. Previous studies have demonstrated an inverse association between the 6MWT and the New York Heart Association Functional Classification, and a moderate to strong correlation between 6MWT and CRF (150-152). Another example of a submaximal test is the Timed Up and Go Test, in

which the individual rises from a chair, walks 3 m forward, before returning and sitting down in the chair again (153).

*1.6.2.3 Estimated cardiorespiratory fitness*

It is possible to estimate CRF (eCRF) from sub-maximal tests, for example from the 6MWT (152, 154). There are also several non-exercise formulas that estimate CRF based on measures such as age, sex, body composition, smoking habits, and exercise habits (142, 155, 156). The benefit of calculating eCRF is that it does not require any physical test and is relatively simple. A drawback is that eCRF formulas tend to overestimate the fitness of unfit individuals and underestimate the fitness of the most fit individuals (156).

### 1.6.3 Importance of physical fitness

Physical fitness is an important marker of overall health. Low CRF is associated with increased risk of diabetes, CVD, dementia, disability, depression, and higher mortality rates (142, 157-161). CRF might be a stronger predictor of CV events than measures of physical activity and AHA argues that CRF should be considered a vital sign (142, 162). Moreover, physical fitness as captured by the 6MWT and eCRF calculated with non-exercise formulas has also been associated with long-term outcomes like cardiac events, dementia, and mortality (163-168). In fact, a Norwegian study found that 3.5 mL/kg/min higher eCRF was associated with 21 % lower CV mortality rates, and 15 % and 8 % lower all-cause mortality rates among men and women, respectively (168).

CRF is modifiable and can be improved by exercise (169). However, there are several other factors than exercise that affect CRF (170). Men generally have higher CRF than women, and CRF declines with increasing age (171). It has been estimated that up to 50 % of the variance by $VO_{2max}$ may be explained by hereditary factors (170, 172). Genetics are also important for the response to exercise (170, 173). There are genetic variations that are associated with both low CRF and worse CVD risk profile (174). Furthermore, some genes are associated with both low CRF and with several noncommunicable diseases such as CVD, type II diabetes, and Alzheimer's disease (175, 176). Body composition is associated with CRF and given that $VO_{2max}$ often is given as mL/kg/min, weight changes will inevitably affect this measure. Moreover, CRF is associated with resting heart rate, which is an important marker of health by itself, associated with inflammation, several somatic diseases, and mortality (171, 177). Other factors that have been associated with CRF include socioeconomic status, education, smoking habits, alcohol consumption, and CRP (171).

### 1.6.4 Physical fitness in persons with rheumatoid arthritis

Physical fitness is obviously an important indicator of overall health in individuals with RA as well. Poor CRF or eCRF is associated with less favorable body composition, higher blood pressure, insulin resistance, and overall worse CV risk profile in RA patients (178-180). Several measures of physical fitness have been associated with all-cause mortality in this patient group, including self-reported function, grip strength, and modified 25-foot walk time (93, 181-184).

Persons with RA tend to have lower CRF compared to the general population (179, 185, 186). Metsios et al. found alarmingly low CRF levels in a sample of 144 RA patients from the United Kingdom with mean CRF of 21 mL/kg/min (178). This study only included patients free from CVD, cancer, diabetes, obstructive or restrictive pulmonary disease, pregnancy, current infection, recent joint surgery, and amputation, and only patients capable of performing a cardiopulmonary exercise test on a treadmill. Therefore, these RA patients might have been fitter than the overall British RA patient population.

A Norwegian study found substantially higher fitness levels in their sample of 93 patients; mean CRF was 28 mL/kg/min in women and 38 mL/kg/min in men (179). Even though these Norwegian RA patients were fitter than the British patients, they had lower CRF compared to healthy Norwegian adults. The Norwegian study had fewer exclusion criteria compared to the British study; namely unstable heart conditions, chronic obstructive or restrictive pulmonary disease requiring oxygen therapy, and inability to perform the cardiopulmonary exercise test on a treadmill. The British patients were somewhat younger, had shorter disease duration, higher disease activity, and fewer comorbidities compared to the Norwegian patients (178, 179). Some of the differences in fitness between these populations might be explained by regional and cultural difference in physical activity habits. For example, Norwegians are relatively active compared to inhabitants in many other European countries (187).

Another Norwegian study that used non-exercise formulas to calculate eCRF reported faster age-related decline in eCRF among RA patients compared to controls (185). This analysis involved 189 persons with RA and 27,594 controls from the general population. In contrast, a Swedish study of 25 RA patients found similar fitness level assessed with a submaximal exercise test on a static cycle ergometer around disease onset and at follow-up approximately 16 years later (188). Noteworthy differences between these studies are a much smaller sample size in the Swedish study and different methods of estimating CRF. There was also

considerably loss to follow-up in the Swedish study, as 57 RA patients within the specified age group were tested at baseline, and only 25 of these were tested after 16 years. This loss to follow-up was due to factors like patients moving out of county, physical impairment, use of beta-blockers, some had deceased, and some declined the invitation. A study involving fitness testing is also prone to selection bias whereby fit individuals are probably more likely to agree to participate. Selection bias might have been a greater issue for the Swedish study which involved a submaximal exercise physical test than for the Norwegian study which used non-exercise formulas to estimate eCRF (185, 188).

The same Swedish study also observed a trend that patients responding poorly to treatment after 2 years had a decline in eCRF at follow-up (median eCRF 41 mL/kg/min at baseline and 33.2 mL/kg/min at follow-up) and that patients responding well to treatment increased in eCRF (median eCRF 30 mL/kg/min at baseline and 33 mL/kg/min at follow-up) (188). However, this trend was not statistically significant.

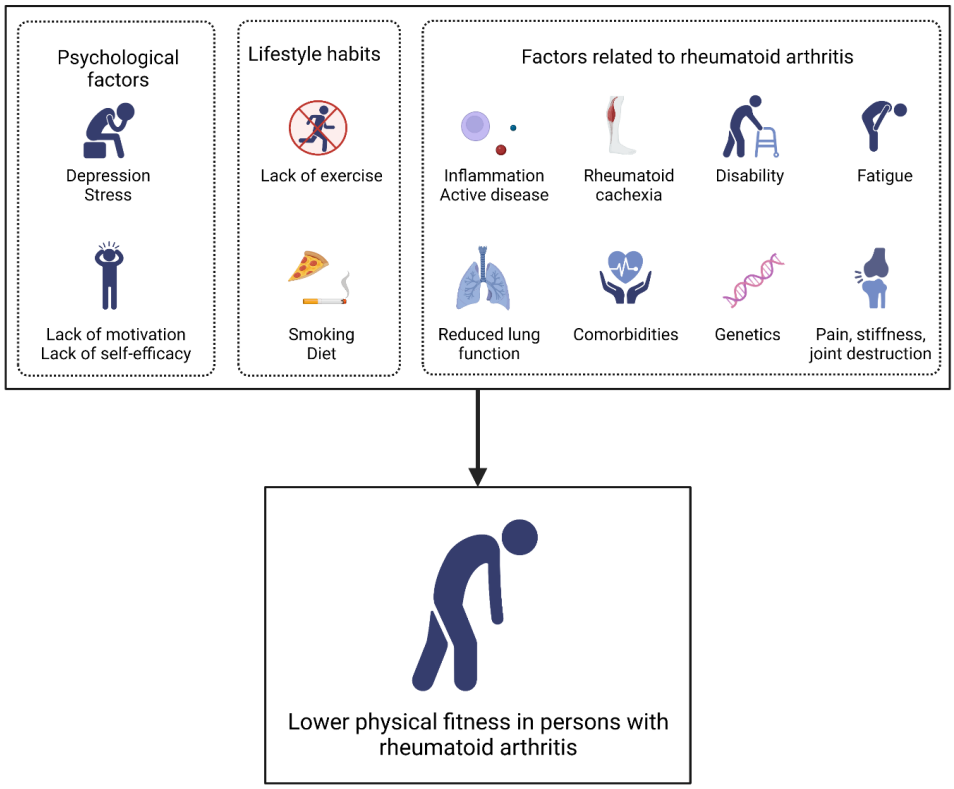


**Figure 3: Factors possibly contributing to lower physical fitness in persons with rheumatoid arthritis.**
Created with BioRender.com.

There are likely many reasons why RA patients appear to have lower fitness levels than healthy adults. In broad terms these can be grouped into 3 major categories; psychological factors, lifestyle habits, and RA-related factors, see Figure 3. Many of the factors in the figure interact with each other, some are speculative, and several might not have a causal relationship with CRF. Persons with unhealthy lifestyle habits such as smoking and low physical activity have a higher risk of developing RA, and perhaps low physical fitness predates the onset of RA (12, 17). Inflammation in RA can lead to joint destruction and muscle wasting, which may result in disability and poor functional capacity (1, 6). Moreover, RA patients have a more pro-inflammatory muscle phenotype compared to matched controls, and the muscle concentrations of inflammatory markers in RA patients are associated with disease activity, disability, pain, and physical inactivity (189). Symptoms of RA together with psychological distress may also affect exercise habits, which directly impact physical fitness (130, 133, 190, 191). However, exercise might reverse some of the negative effects of inflammation on body composition and has positive effects on several RA-related symptoms (109, 115, 117). In summary, the explanation for lower fitness levels in RA patients is multifactorial and complex.

## 1.7 Psychological distress, physical activity, physical fitness, and mortality

Psychological distress, lifestyle habits, and physical fitness interact with each other and influence mortality rates. Depression is associated with a reduction in physical activity and an increased risk of developing a sedentary lifestyle (191). Similarly, stress has an inverse association with physical activity (190, 192). In a review of 168 studies investigating the effect of stress on physical activity, 73 % of the included studies found an inverse relationship between stress and physical activity, whereas 17 % of the studies found a positive relationship (190). As discussed by the authors of the review, an explanation of these opposite findings could be that some individuals use physical activity as a way of coping with stress. In addition to influencing physical activity habits, stress has been associated with lower improvements in strength and CRF after exercise interventions and poorer recovery after exercise (193-195).

On the other hand, exercise can improve depressive symptoms both in the general population and in clinically depressed patients (196). Similarly, high physical fitness reduces the risk of developing depression, and physical fitness has an inverse association with both depressive symptoms and perceived stress (160, 197, 198). All these factors, namely depression, stress,

low physical activity, and/or low fitness, are associated with higher mortality rates (103, 161, 199, 200). The association between depression and higher mortality rates has also been reported among RA patients (34, 201). Overall, RA patients have lower physical fitness levels as well as worse mental health compared to the general population (37, 179, 185). This underpins that in addition to treating the rheumatic disease, addressing lifestyle, physical fitness, and mental health is important to optimize long-term outcomes in RA patients.

## 1.8 Knowledge gaps

Before the start of the present work, it was not clear whether RA could impact long-term mortality to the same degree as diabetes. It had been suggested that RA could be a CV risk equivalent to diabetes, and several studies had demonstrated excess CV and all-cause mortality in RA patients (66, 72, 78-80, 87, 92, 95). A study with RA patients, diabetes patients, and controls recruited from the same population with long follow-up had not previously been performed and was warranted. Information on whether RA and diabetes have similar impact on mortality could be of interest for patients, healthcare professionals, and health authorities.

Previous research had shown that RA patients have lower CRF compared to the general population (179, 185, 186). However, few studies had investigated the association between PROMs and physical fitness in RA patients, and whether PROMs could explain some of this observed difference in physical fitness between RA patients and the general population. PROMs associated with physical fitness in individuals with RA could represent potential targets for interventions to improve physical fitness and long-term health in this patient population. Such PROMs could also be useful to identify patients who may benefit from additional support, follow-up, referral to physiotherapy etc.

# 2 HYPOTHESES AND AIMS

## 2.1 Hypotheses

The overall hypothesis for the present thesis was that RA is a risk factor for increased mortality rates and reduced eCRF, and that PROMs explain a significant portion of the variation in physical fitness among RA patients. This overall hypothesis was detailed in the following 5 specific hypotheses:

**Hypothesis 1:** RA represents a risk factor for increased mortality rates of similar magnitude as diabetes

**Hypothesis 2:** The percentage of deaths due to diseases of the circulatory system among persons with RA is similar to the percentage among persons with diabetes and higher than the percentage in the general population

**Hypothesis 3:** PROMs and RA-specific disease measures are associated with functional capacity in persons with RA as measured with the 6MWT

**Hypothesis 4:** eCRF calculated with a non-exercise formula is significantly associated with functional capacity measured with the 6MWT in persons with RA

**Hypothesis 5:** Persons with RA have lower eCRF calculated with non-exercise formulas than healthy individuals, partly explained by more physical symptoms and more negative emotions

## 2.2 Aims

The overall aim of the present thesis was to evaluate RA as a risk factor for excess mortality and reduced eCRF, and to explore the relationship between PROMs and physical fitness. The following 5 aims correspond to the 5 specific hypotheses:

**Aim 1:** To compare all-cause mortality rates in persons with RA, persons with diabetes, and the general population

**Aim 2:** To compare causes of death in persons with RA to that in persons with diabetes and the general population

**Aim 3:** To assess the associations of different PROMs and RA-specific disease measures with functional capacity as measured with the 6MWT in persons with RA

**Aim 4:** To assess the relationship between eCRF calculated with a non-exercise formula and functional capacity measured with the 6MWT in persons with RA

**Aim 5:** To compare eCRF calculated with non-exercise formulas in RA patients and in healthy controls, and to assess the role of physical symptoms and negative emotions as mediators between the presence of RA and eCRF

# 3 PARTICIPANTS AND METHODS

## 3.1 Study populations

All participants were recruited in Trøndelag county in Norway. Inclusions and exclusions for Study I, II, and III are presented in Figure 4. An overview of the aims with corresponding study population, and statistical method is presented in Table 2.

**Table 2: Overview aims, study populations, and statistical methods.**

| Aim | Study | Population | Statistical method |
|---|---|---|---|
| 1) Compare mortality rates in RA patients, diabetes patients, and controls | I | HUNT2 and HUNT3 | Kaplan Meier survival curve<br>Cox regression analysis |
| 2) Compare causes of death in RA patients, diabetes patients, and controls | I | HUNT2 and HUNT3 | Comparing confidence intervals |
| 3) Assess associations between PROMS and disease-specific variables with 6MWD in RA patients | II | Subgroup of FysKond2 | Multivariable regression analysis |
| 4) Assess relationship between eCRF and 6MWD in RA patients | II | Subgroup of FysKond2 | Pearson correlation coefficient<br>Scatterplot |
| 5) Compare eCRF in RA patients and healthy controls, evaluate potential mediators between RA status and eCRF | III | FysKond2 | Structural equation modelling |

Abbreviations: eCRF - estimated cardiorespiratory fitness. FysKond2 - Study about factors influencing physical activity and cardiorespiratory fitness in patients with inflammatory arthritis. HUNT2 - 2nd survey of the Trøndelag Health Study. HUNT3 - 3rd survey of the Trøndelag Health Study. PROMS - patient-reported outcome measures. RA - rheumatoid arthritis. 6MWD - distance walked during 6-minute walk test.

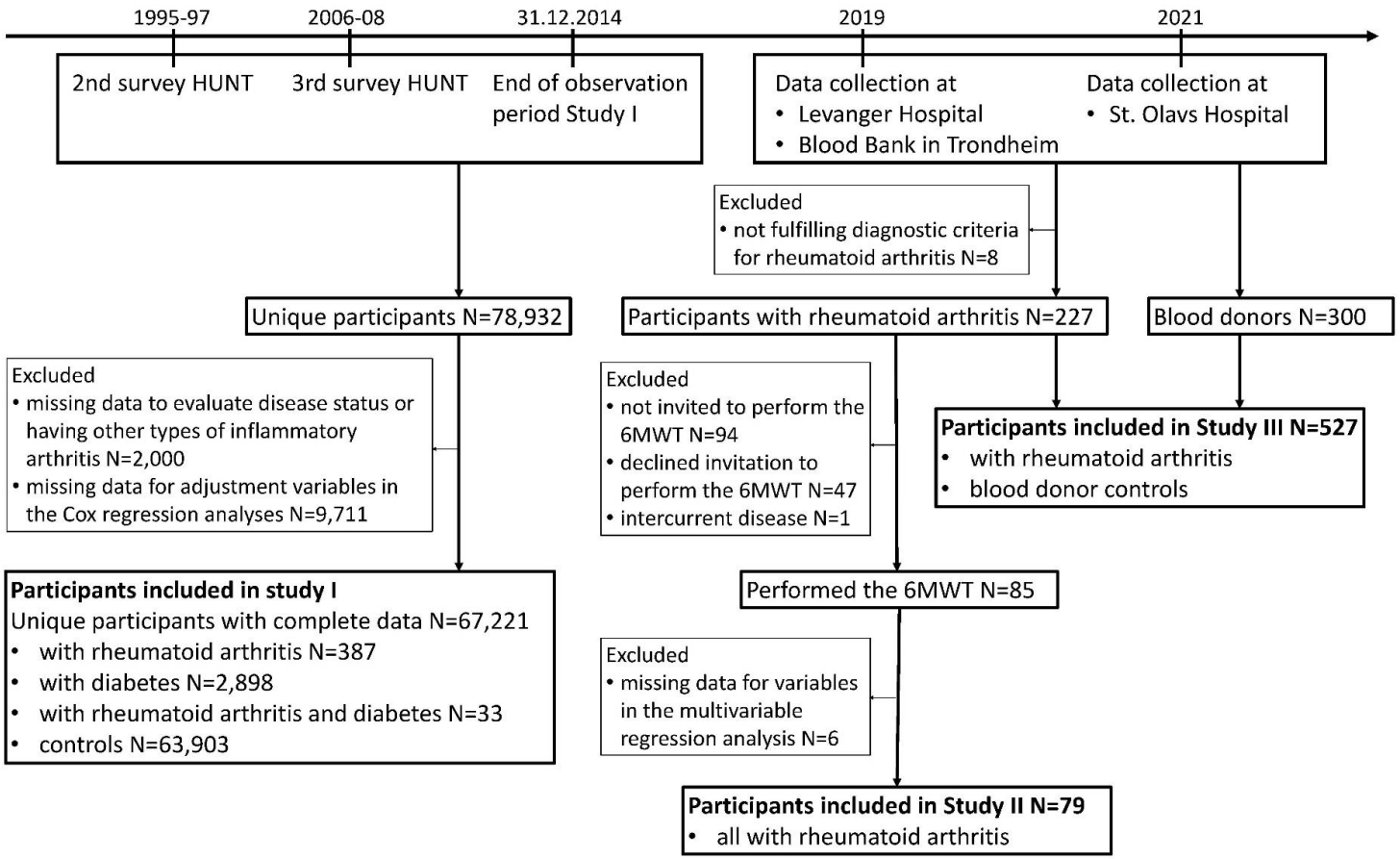


**Figure 4: Flowchart of participants in Study I, II, and III.**
Abbreviations: HUNT - the Trøndelag Health Study. 6MWT - 6-minute walk test. N - number.

### 3.1.1 Trøndelag Health Study

Study I used data from the Trøndelag Health Study (HUNT), which is a large population-based longitudinal study (202, 203). Study I was part of a sub-study of HUNT, the HUNT Longitudinal Ankylosing spondylitis and RA Study (HuLARS). HuLARS applies data from HUNT to investigate associations between different risk factors, RA, ankylosing spondylitis, CVD, and mortality. All inhabitants ≥20 years in the northern region of Trøndelag county in central Norway have been invited to participate in each of the 4 HUNT surveys that have been conducted. The population in the region is predominantly Caucasian and has been relatively stable over the past decades with low in- and out-migration.

Data for the first HUNT survey (HUNT1) were collected in 1984 to 1986, and further HUNT surveys have since then been performed with 11-year intervals. Data from the second (HUNT2, 1995 to 1997) and the third (HUNT3, 2006 to 2008) surveys were used for Study I (202, 203). Close to 94,000 individuals were invited to each of these 2 surveys. Invitations to participate were sent by mail to all inhabitants in the region, and the envelope also contained information about the study and the first part of the questionnaire (203). Those willing to participate came for a visit at a health examination site set up in their municipality. Some questionnaires were given to all participants, whereas others were given to subgroups, for example participants reporting to have specific diseases or symptoms. Several sub-studies of HUNT invited specific groups to further testing or follow-up, for example the testing of CRF in 4,631 healthy individuals in HUNT3 (203, 204).

### 3.1.2 Study of factors influencing physical activity and cardiorespiratory fitness in patients with inflammatory arthritis

Study II and Study III used data from a larger study named “Factors influencing physical activity and CRF in patients with inflammatory arthritis” (FysKond2). FysKond2 is a study of the relationship between PROMs and physical activity or physical fitness in patients with inflammatory arthritis. So far, a group of RA patients and a group of healthy controls have been recruited, and other patient groups will be recruited in the future. Study II used data from a subgroup of the RA patients, whereas Study III used data from all the RA patients and the controls in FysKond2. The RA patients were recruited from the rheumatology outpatient clinics at Levanger Hospital from May to December in 2019 and at St. Olavs Hospital, Trondheim University Hospital, from October to December in 2021. At St. Olavs Hospital, patients with stable disease can be transferred to a patient-centred follow-up programme. These patients are followed by their general practitioner and can contact the rheumatology

department when there is a change in disease activity. Both patients with scheduled appointments at the outpatient clinics and a random selection of patients in the patient-centred follow-up programme were contacted about the project. An information letter was mailed to patients with a physical appointment before these patients were approached during their visit to the hospital. If they agreed to participate, they did so before or after their appointment, or brought the questionnaire home and mailed it back in a return envelope. RA patients in the patient-centred follow-up programme or those who had a digital appointment at St. Olavs Hospital were first sent an information letter by mail, then contacted by telephone, and if they agreed to participate the questionnaire was sent by mail with a return envelope.

Blood donors were recruited as controls and approached during a visit to the Blood Bank at St. Olavs Hospital from May to August in 2019. They participated after they had donated blood. The controls therefore all fulfilled the requirements for being allowed to donate blood, and could for example not have history of cancer or serious CVD, current infections, anaemia, or be pregnant (205). First, we invited all blood donors. However, as there were many blood donors in their 20s, we later only invited those over the age of 35 years and then those over the age of 40 years to recruit a control group more comparable to patients with inflammatory arthritis.

## 3.2 Classification of participants

All RA diagnoses were verified in hospital records. The ACR/EULAR 2010 criteria were used to assess RA status (18). If there was missing information to evaluate the ACR/EULAR 2010 criteria, an RA diagnosis according to the revised ACR 1987 criteria was also accepted (19). For participants in HUNT2 and HUNT3 (Study I), a review of hospital records was previously performed for those with self-reported RA (206). For participants in FysKond2 (Study II and Study III), the hospital records were reviewed for all RA participants.

Persons self-reporting to have diabetes and/or use anti-diabetic medications and/or with non-fasting blood glucose >11.1 mmol/L were classified as diabetics in HUNT2 and/or HUNT3 (Study I). Participants who fulfilled the criteria for diabetes in HUNT2 and not HUNT3 were classified as diabetes patients in HUNT3 as well (N=6).

Participants in HUNT without enough information to evaluate RA or diabetes status, and participants with other types of inflammatory arthritis were excluded from Study I, see Figure 4. Participants in HUNT who did not fulfil the criteria for RA or diabetes as described above

were classified as controls in Study I. As mentioned earlier, blood donors were the control group for Study III.

## 3.3 Data sources

An overview of the data sources for Study I to III is presented in Table 3. All participants filled in questionnaires. Participants in Study I, II, and III reported their smoking habits. The participants in HUNT answered questions regarding medical history. They also answered questionnaires about pain, physical activity habits, psychological distress, and quality of life, though we did not have access to those data for Study I. The participants in FysKond2 filled in questionnaires about physical activity, physical symptoms, function, stress, and depressive symptoms as further described below.

**Table 3: Data sources for Study I, II, and III.**

| Information collected by | Study I (HUNT2 and 3) | Study II and III (FysKond2) |
|---|---|---|
| Questionnaire | Smoking status, comorbidities | Smoking status, height, weight, physical symptoms, depressive symptoms, perceived stress, self-efficacy for exercise, patient global assessments, function, physical activity habits, and estimated cardiorespiratory fitness |
| Physical examination | Height, weight, resting heart rate, blood pressure | Resting heart rate, 6-minute walk test (subgroup) |
| Hospital records | RA diagnosis, seropositivity, and RA duration available from previously conducted validation study | RA status, seropositivity, RA duration, disease activity score, comorbidities, and medications |
| Blood sample | Creatinine, total cholesterol, and glucose | - |
| Norwegian Cause of Death Registry | Vital status and causes of death until 31.12.2014 | - |

Abbreviations: FysKond2 - Study about factors influencing physical activity and cardiorespiratory fitness in patients with inflammatory arthritis. HUNT2 - 2nd survey of the Trøndelag Health Study. HUNT3 - 3rd survey of the Trøndelag Health Study. RA - rheumatoid arthritis.

For all RA patients (Study I to III), data regarding RA diagnosis, seropositivity, and duration of RA were available from the hospital records. Information about anti-rheumatic medications, comorbidities, and the last documented value for DAS28-CRP were also

collected for the patients in FysKond2. Seropositivity was defined as a positive test for RF and/or ACPA.

Data from the Norwegian Cause of Death Registry until 31.12.2014 were linked to data from HUNT for Study I using the 11-digit Norwegian personal identification number (207). This registry has information about all deaths in Norway, as well as about the deaths of Norwegian citizens abroad, and information about the causes of death. The underlying cause of death was considered the cause of death and coded according to the International Classification of Diseases 10$^{th}$ revision (ICD-10), or according to ICD 9$^{th}$ revision (208, 209).

In HUNT, non-fasting blood samples were collected, and physical examinations were performed involving measurement of resting heart rate, blood pressure, weight, and height. The participants wore light clothing and no shoes for the weight and height measurements. Resting heart rate was recorded for participants in FysKond2, measured by the research team for those with a physical visit and by the patients themselves among those who sent their questionnaire in the post. Weight and height were self-reported in FysKond2. Body mass index was calculated by dividing weight in kg by the squared value of height in m.

The RA patients in FysKond2 who were recruited during a physical visit at the outpatient rheumatology clinics were invited to perform a 6MWT. They could participate in FysKond2 with or without performing the 6MWT.

## 3.4 Patient-reported outcome measures

The questionnaires in FysKond2 measured several PROMs further described in this section.

### 3.4.1 Physical symptoms

Level of joint pain, morning stiffness, and pain in neck, back or hips were evaluated with the 3 questions; “How intense has your joint pain been in the past 6 months?”, “How much joint stiffness do you have when you wake up in the morning?”, and “How much pain do you have in your neck, back or hips?”. Each question was answered on a Likert scale from 0 to 10, with higher scores indicating more intense symptoms.

### 3.4.2 Disease-related patient-reported outcome measures

Self-reported function in the past week was measured with the modified Health Assessment Questionnaire in the RA group (210). The score is based on 8 items concerning the ability to perform different tasks. Each item is rated on a 0 to 3 Likert scale, from “able to do with no difficulties” to “unable to do”. Examples of tasks included in this questionnaire are getting

out of bed, bending down and picking up something from the ground, and getting in and out of a car. The overall score is the mean score of the 8 items, with lower overall scores indicating better function.

The patients rated their disease activity level with the patient global assessment that used the following phrasing: “Please consider the activity of your rheumatic disease in the past week. When considering all the symptoms, how do you think your state is?”. The patients answered on a visual analogue scale with the range of 0 to 100 mm, with higher scores indicating more symptoms.

### 3.4.3 Psychological variables

The Norwegian version for the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) was used to evaluate level of depressive symptoms in the past week (211, 212). HADS-D consists of 7 items where the participant indicates how well different statements apply to them, for example “I still enjoy the things I used to enjoy” with the options “definitely as much”, “not quite as much”, “only a little” and “hardly at all”. Each item gives a sub-score of 0 to 3, and the sub-scores for the 7 items are added. The possible overall range is from 0 to 21, with higher scores indicating more depressive symptoms. HADS-D has been extensively used and are validated in several patient populations including in RA patients (213, 214). HADS-D focuses on psychological aspects of depression rather than somatic symptoms. This was considered preferable over other scales as some somatic symptoms are common both in RA and depression and may result in falsely high depression scores in RA patients. A score ≥8 may indicate a possible case of clinical depression. However, HADS-D was not designed to diagnose depression in individuals (213). This threshold of ≥8 had a sensitivity of 0.59 and a specificity of 0.83 to detect clinical depression in a sample of 150 RA patients (214).

The perceived stress scale was used to assess level of perceived stress in the past month (215). The original version of the perceived stress scale had 14 items, but we used the version with 10 items which also is widely used and has good psychometric properties (216). The items ask how often the participants have experienced different feelings of stress in the past month, for example “How often have you felt unable to control important things in your life?”, with the options “never”, “almost never”, “sometimes”, “fairly often”, and “very often”. This gives a sub-score for each item of 0 to 4. The scale of positively worded items is

reversed, and the sub-scores are added together giving a possible overall range of 0 to 40. Higher scores indicate higher levels of perceived stress.

Self-efficacy for exercise was evaluated with the Exercise Self-Efficacy Scale. This scale consists of 5 items related to the confidence in one's ability to participate in regular physical activity under different circumstances (217). The circumstances that are included in the questionnaire are when one feels tired, in a bad mood, pressed for time, when on vacation, and when it rains or snows. The participants rated their level of confidence on a Likert scale from 1 (totally disagree) to 7 (totally agree). The scores from the 5 items are added, resulting in a total possible range of 5 to 35, with higher scores implying higher self-efficacy for exercise.

## 3.5 Measures of physical activity and physical fitness

In FysKond2, 3 questions were used to evaluate physical activity habits, covering the domains of frequency, intensity, and duration. This physical activity questionnaire was first introduced in HUNT, and is short, reproducible, and has previously been associated with CRF and objectively measured physical activity (218). These 3 questions were used to evaluate fulfilment of the aerobic physical activity recommendations from ACSM/AHA, and to calculate a physical activity index (127, 156). The physical activity index was calculated by multiplying the weight from each response for the 3 questions, see Table 4.

The physical activity index was used as part of non-exercise formulas to calculate eCRF. The HUNT fitness formula developed from 4,631 healthy adults (a subgroup of HUNT3) was used to calculate eCRF for the controls (156, 168). A previous study found that HUNT fitness formula overestimated the fitness level of the least fit RA patients (219). Therefore, the RA fitness formula developed from 93 Norwegian individuals with RA was applied to calculate eCRF in the RA group (219). Both these formulas were developed from individuals who performed a cardiopulmonary exercise test on a treadmill and were recruited from the same region of Norway as the participants in FysKond2. Several variations of these 2 fitness formulas have been published, consisting of slightly different variables. We chose the formulas with body mass index as the body composition measure. The non-exercise formulas are presented in Table 5.

**Table 4: Physical activity index [a].**

| Physical activity domains | Possible answers | Weight |
|---|---|---|
| Frequency – how frequently do you exercise? | Never | 0 |
| | Less than once per week | 0 |
| | Once per week | 1 |
| | 2-3 times per week | 2 |
| | Almost daily | 3 |
| Intensity – how hard do you push yourself? | Take it easy | 0 |
| | Heavy breathing/sweat | 5 |
| | Near exhaustion | 10 |
| Duration – how long does each session last? | Less than 15 minutes | 1 |
| | 15-29 minutes | 1 |
| | 30-60 minutes | 1.5 |
| | More than 60 minutes | 1.5 |

[a]The physical activity index is calculated by multiplying the score from each question. The weighting was first published by Nes et al. in 2011 (156).

**Table 5: Non-exercise formulas to estimate cardiorespiratory fitness [a,b].**

| | Non-exercise formulas to estimate cardiorespiratory fitness |
|---|---|
| Healthy women | 70.77 - (age x 0.244) - (body mass index x 0.749) - (resting heart rate x 0.107) + (physical activity index x 0.213) |
| Healthy men | 92.05 - (age x 0.327) - (body mass index x 0.933) - (resting heart rate x 0.167) + (physical activity index x 0.257) |
| Persons with rheumatoid arthritis | 77.961 - (age x 0.358) + (sex x 28.791) - (age-sex interaction x 0.326) - (body mass index x 0.700) - (resting heart rate x 0.125) - (smoking x 1.854) + (physical activity index x 0.211) - (patient global assessment x 0.071) |

[a]Formula applied in healthy controls published by Nes et al. in 2014 (168). Formula applied in persons with rheumatoid arthritis published by Liff et al. in 2020 (219).
[b]Specifications: Coding categorical variables: sex (female=0, male=1), smoking (never smoker=0, ever smoker=1). Units continuous variables: Age (years), body mass index (kg/m²), resting heart rate (beats per minute), patient global assessment (mm). Physical activity index calculated from a physical activity questionnaire.

The RA participants in FysKond2 who were recruited during a physical visit were invited to perform a 6MWT. The participants were instructed to walk as far as possible for 6 minutes and walked back and forth along a 25 m stretch. Standardized instructions from the American Thoracic Society were followed, except for using a 25 m rather than a 30 m stretch for

practical reasons (149). The participants were asked to rate level of perceived exertion on a Borg scale from 6 (none) to 20 (maximum) before and after the 6MWT (146).

## 3.6 Statistical analyses

### 3.6.1 Descriptive statistics

Normality was assessed with visual assessment of histograms in Study I to III and with the Shapiro-Wilks test in Study II and Study III. As most of the data were not normally distributed, continuous data in this thesis are presented as median with $25^{th}$ and $75^{th}$ percentile. Categorical data are presented as number with percentage. Participants and non-participants in Study II and Study III were compared with Mann-Whitney U-test for continuous data and the Chi-square test for categorical data. All statistical analyses were performed in Stata (v15.1 for Study I, and v16 for Study II and Study III, StataCorp, TX, USA). P-values $<0.05$ were considered statistically significant.

### 3.6.2 Missing data management

In Study I and Study II, persons with missing data for variables used in the analyses were excluded. Multiple imputation of missing data for adjustment variables using chained equations assuming missing at random was performed before a sensitivity analysis in Study I (50 datasets). In Study III, maximum likelihood estimation with missing data was applied. This allowed us to include all participants in the analyses in Study III with their available data.

### 3.6.3 Analyses of mortality

The participants in Study I were followed from their baseline observation in HUNT until death or 31.12.2014. The baseline observation was defined as the first participation in HUNT with complete data for disease status and for all adjustment variables included in the mortality analysis. Crude mortality rates were calculated by dividing number of deaths by total observation time.

#### *3.6.3.1 Evaluation of causes of death*

The death causes were assessed by the chapters in ICD-10, see Table 6 (208). Mortality rates per 1,000 person year were calculated for deaths from diseases of the circulatory system, neoplasms, and diseases of the respiratory system. Further, the 95 % CI for the percentages of deaths due to these 3 chapters among RA patients, the diabetes patients, and the controls were compared. The 95 % CIs were estimated using Poisson distributions. Non-overlapping CIs were used as the criterion for a statistically significant difference. The group with both RA

and diabetes was too small to be included in this analysis. Number of events in the RA group was too low to perform Cox proportional hazard regression analysis for each death cause.

**Table 6: Chapters in the International Classification of Diseases 10th revision.**

| Chapter | Diagnostic codes |
|---|---|
| I: Certain infectious and parasitic diseases | A00-B99 |
| II: Neoplasms | C00-D48 |
| III: Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism | D50-D89 |
| IV: Endocrine, nutritional and metabolic diseases | E00-E90 |
| V: Mental and behavioural disorders | F00-F99 |
| VI: Diseases of the nervous system | G00-G99 |
| VII: Diseases of the eye and adnexa | H00-H59 |
| VIII: Diseases of the ear and mastoid process | H60-H95 |
| IX: Diseases of the circulatory system | I00-I99 |
| X: Diseases of the respiratory system | J00-J99 |
| XI: Diseases of the digestive system | K00-K93 |
| XII: Diseases of the skin and subcutaneous tissue | L00-L99 |
| XIII: Diseases of the musculoskeletal system and connective tissue | M00-M99 |
| XIV: Diseases of the genitourinary system | N00-N99 |
| XV: Pregnancy, childbirth and the puerperium | O00-O99 |
| XVI: Certain conditions originating in the perinatal period | P00-P96 |
| XVII: Congenital malformations, deformations and chromosomal abnormalities | Q00-Q99 |
| XVIII: Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified | R00-R99 |
| XIX: Injury, poisoning and certain other consequences of external causes | S00-T98 |
| XX: External causes of morbidity and mortality | V01-Y98 |
| XXI: Factors influencing health status and contact with health services | Z00-Z99 |
| XXII: Codes for special purposes | U00-U85 |

Published by the World Health Organization (208).

*3.6.3.2 Kaplan-Meier survival curve*

The Kaplan-Meier survival curve was plotted to visualize the differences in mortality in the RA group, the diabetes group, and the controls. The participants with both RA and diabetes were not included in the plot.

*3.6.3.3 Cox proportional hazard regression*

Cox regression analysis was used to compare the associations between disease status with mortality. The 95 % CIs of the HR estimates for RA and diabetes were compared whereby non-overlapping CIs was the criterion for a statistically significant difference. RA and diabetes were coded as yes/no variables. Participants with RA and diabetes contributed to the HR for both RA and diabetes. For subjects who participated in both HUNT2 and HUNT3, data were updated in HUNT3. Age was included as the time axis, and date of baseline participation was the entry time. This design ensured that all Cox regression models were adjusted for age and participants of similar age were compared.

First, Cox regression Model 1 was performed to assess the crude associations between RA and diabetes and all-cause mortality with adjustment for sex, taking age into account by including it as the time scale. Second, Cox regression Model 2 further adjusted for smoking habits (current, previous, or former smoker), body mass index (<18.5, 18–24.9, 25–29.9, 30–34.9 and ≥35 kg/m²), hypertension, creatinine, and total cholesterol. Third, Cox regression Model 3 further adjusted for previous CVD. Hypertension was defined as systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or reporting to use antihypertensive medications. Previous CVD was defined as a self-reported history of angina, myocardial infarction, and/or stroke.

To fulfil the proportional hazard assumption, an interaction term with an age group variable (>75 year: yes=1, no=0) was added for diabetes, smoking, and previous CVD. A participant who turned 75 years of age during the observation period would first contribute to the age group ≤75 years and then to the age group >75 years of age. Therefore, 2 HRs were estimated for diabetes, 1 for diabetes patients ≤75 years and 1 for diabetes patients >75 years. The interaction term with the age group variable was not added for RA in the main Cox regression Models as the proportional hazard assumption was not violated for RA and because there were few deaths among RA patients ≤75 years (N=33).

Several sensitivity analyses were performed to assess the robustness of these results. We excluded those with both RA and diabetes before repeating the Cox regression analysis. We also performed multiple imputation for adjustment variables and repeated the analysis without excluding the participants with missing adjustment variables. Further, we included an interaction term with the age group variable for RA as well. Finally, we ran the Cox regression analysis separately in each 10-year age stratum for the participants with diabetes and the controls.

### 3.6.4 Physical fitness

*3.6.4.1 Multivariable linear regression analysis*

Multivariable linear regression analysis was applied in Study II to assess the associations between different independent variables and the dependent variable, i.e. functional capacity as measured with the 6MWT. Age was categorized into tertiles to achieve acceptable model fit (<59, 59-69, ≥70 years). The following independent variables were included in Multivariable linear regression Model 1: age (in tertiles), sex, and body mass index (as a continuous variable). Multivariable linear regression Model 2 focused on relevant PROMS, and included the following independent variables; age, sex, body mass index, smoking habits (0=never smoker, 1=ever smoker), perceived stress, depressive symptoms, Exercise Self-Efficacy, and the patient global assessment. Multivariable linear regression Model 3 investigated disease-related factors and included the independent variables age, sex, body mass index, smoking habits, RA duration, DAS28-CRP, seropositivity, present use of corticosteroids, and a comorbidity variable (yes=1, no=0). The comorbidity variable was coded yes if the patient had a history of hypertension, angina, myocardial infarction, arrythmia, stroke, chronic obstructive pulmonary disease, chronic restrictive pulmonary disease, asthma, cancer, and/or diabetes according to the hospital case notes, and no if not.

Both unstandardized and standardized regression coefficients were calculated. Unstandardized regression coefficients reflect the change in the dependent variable per 1 unit increase in the independent variable, for example the expected change in the distance walked during the 6MWT (6MWD) in m per 1 kg/m² increase in body mass index. Standardized regression coefficients denote the number of standard deviations that the dependent variable changes when the independent variable increases with 1 standard deviation.

The RA patients were recruited in 2 data collection periods, in 2019 at Levanger Hospital and in 2021 at St. Olavs Hospital. Time trends may affect physical activity habits and physical

fitness, especially as the COVID-19 pandemic and the related restrictions started in the spring of 2020. A Sensitivity analysis was performed to check whether this impacted the results from the 6MWT, by adding the independent variable recruitment year (2019 or 2021) to the Multivariable linear regression Model 1.

*3.6.4.2 Relationship between measures of physical fitness*

In Study II, the relationship between eCRF and 6MWD was assessed visually with a scatterplot and with the Pearson correlation coefficient. Multivariable linear regression analysis was not considered an appropriate method to assess this relationship because the eCRF formulas consist of several important adjustment variables like sex and age which would lead to multicollinearity (see Table 5).

The modified Health Assessment Questionnaire has been referred to as a measure of physical function, functional capacity, or disability, and is routinely assessed in clinical practice. As additional analyses, Pearson correlation coefficients were calculated to assess how the modified Health Assessment Questionnaire correlated with eCRF and 6MWD.

*3.6.4.3 Structural equation modelling*

Structural equation modelling (SEM) was applied in Study III to evaluate the potential role of physical symptoms and negative emotions as mediators between RA status and eCRF. SEM is a powerful statistical framework that can handle complex models (220). The hypothesized model is drawn, and SEM is used to test how well the model fits with the observed data. SEM allows the inclusion of latent variables, multiple dependent variable, correlation between different independent variables, and is a suitable method for mediation analysis. A latent variable is a variable that is not observed or measured directly but is derived based on several observed variables that together measure a common concept. Mediation analysis tests whether a variable, known as a mediator, mediates or explains some of the association between the independent variable and the dependent variable. The mediator lies on the causal pathway between the independent variable and the dependent variable, whereby the independent variable influences the mediator, and the mediator influences the dependent variable. SEM can also include participants in the analysis that have missing data for some of the variables. A method to do this is maximum likelihood estimation with missing data, in which all available data are utilized in the analysis (220, 221). This method of handling missing data is recognized and leads to less bias than complete case analysis (221). Model fit

indices were applied to evaluate model fit, as further explained below. Both unstandardized and standardized path coefficients were calculated for all SEM models.

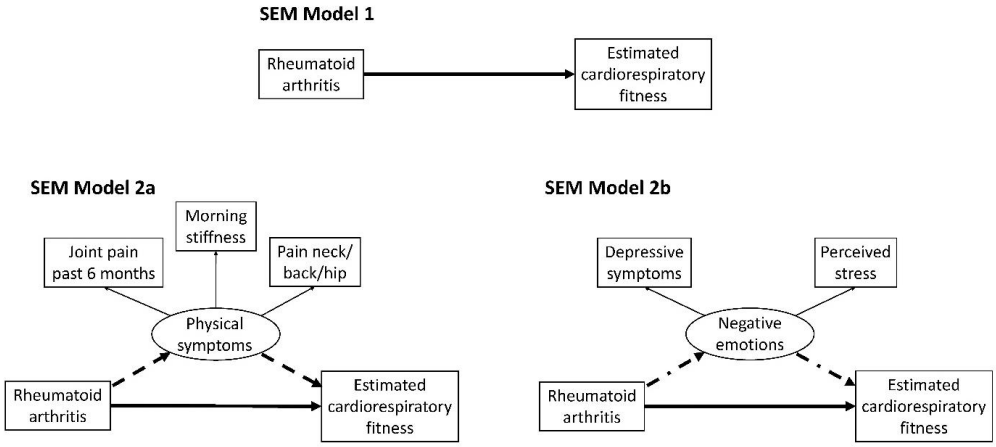


**Figure 5: Flowchart of Structural Equation Modelling Model 1, 2a and 2b.**
Structural Equation Modelling Model 1 investigated the association between the presence of rheumatoid arthritis and estimated cardiorespiratory fitness. Structural Equation Modelling Model 2a and 2b investigated the association between rheumatoid arthritis and estimated cardiorespiratory fitness when adding an indirect pathway through either physical symptoms or through negative emotions, respectively. The direct pathway is represented by a solid line (──), the indirect pathway through physical symptoms is represented by a dashed line (----), and the indirect pathway through negative emotions is represented by a dash-dotted line (─ · ─). Squares represent observed variables; circles represent latent variables. The models are adjusted for age and sex.

All following SEM Models were adjusted for age and sex and visualized in Figures 5 and 6. SEM Model 1 tested the association between RA status and eCRF. SEM Model 2a added the latent variable "physical symptoms" as a possible mediator between RA status and eCRF. Physical symptoms were based on the 3 observed variables joint pain past 6 months, morning stiffness, and pain in neck, back or hips. SEM Model 2b added the latent variable "negative emotions" to SEM Model 1. Negative emotions were derived from the observed variables depressive symptoms and perceived stress. Finally, the latent variables physical symptoms and negative emotions were both included as possible mediators between RA status and eCRF in SEM Model 3.

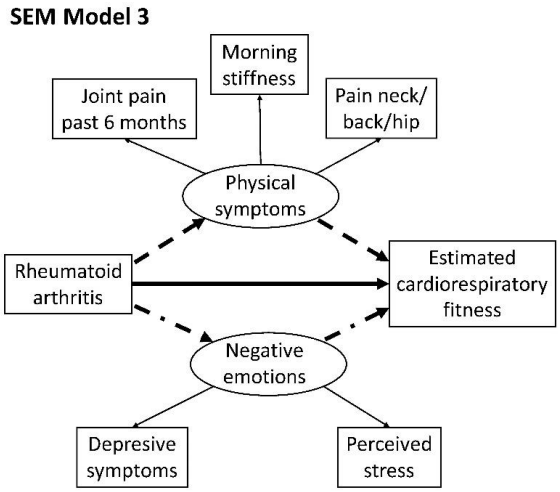


**Figure 6: Flowchart of Structural Equation Modelling Model 3.** Structural Equation Modelling Model 3 investigated the association between the presence of rheumatoid arthritis and estimated cardiorespiratory fitness, including both the direct effect and the indirect effects through physical symptoms and negative emotions. The direct pathway is represented by a solid line (──), the indirect pathway through physical symptoms is represented by a dashed line (----), and the indirect pathway through negative emotions is represented by a dash-dotted line (─ · ─). Squares represent observed variables; circles represent latent variables. The model is adjusted for age and sex.

### 3.6.5 Test of assumptions and model fit

*3.6.5.1 Assumptions*

In Study I, the proportional hazard assumption in Cox regression analysis was evaluated with Cox-Snell residuals, Schoenfeld residuals, and log-minus-log plots.

In Study II, linearity between continuous independent variables and the dependent variable 6MWD was assessed with scatterplots. Visual evaluation of residual plots was used to evaluate the assumptions of normally distributed residuals in the multivariable linear regression analysis. Collinearity between the independent variables was assessed with the variance inflation factor.

In Study III, the multivariate normality assumption in SEM was evaluated by visual evaluation of histograms and with the Shapiro-Wilks test of the continuous variables in the model. The most important variable to assess is the dependent variable in SEM, so for the SEM Models this was eCRF.

*3.6.5.2 Model fit*

The Cox regression Models in Study I were compared with the Akaike information criterion, the Bayesian information criterion, and log likelihood. Models with lower values of these measures were preferred.

The Multivariable linear regression Models in Study II were also compared with Akaike information criterion and Bayesian information criterion, as well as with $R^2$. Higher values for $R^2$ indicate that the model explains more of the variation in the observed data.

Fit of the SEM Models in Study III was evaluated the chi-square test, the root mean squared error of approximation, the Tucker-Lewis index, and the comparative fit index (220). A model with a good fit should ideally have a non-significant chi-square test, root mean squared error of approximation <0.10, Tucker-Lewis Index ≥0.90, and comparative fit index ≥0.90.

## 3.7 Ethics

All participants in Study I, II, and III provided informed consent. Study I, II, and III were approved by the Regional Committee for Medical and Health Research Ethics (project numbers 2009/661, 2018/1936 and 23420). The HUNT study was approved by the Norwegian Data Safety Authorities and the Norwegian Department of Health. Study I, II, and III followed the principles of the Helsinki declaration.

# 4 SUMMARY OF RESULTS

## 4.1 Participants

Inclusions and exclusions to Study I, II, and III are presented in Figure 4.

HUNT2 and HUNT3 had participation rates of 70 % and 54 % of those invited, respectively. After excluding those with missing data for disease status or adjustment variables and those with other types of inflammatory arthritis, 387 RA patients, 2,898 diabetes patients, 33 patients who had both RA and diabetes, and 63,903 controls were included in Study I.

The acceptance rate to participate in FysKond2 among the RA patients invited was 61 %. The patients who agreed to participate were somewhat younger (median age 64 years versus 66 years, p=0.004) and less often female (67 % versus 78 %, p=0.03) compared to those who either declined or did not respond to the invitation to participate. The acceptance rate to perform the 6MWT was 43 %, and 40 % (79 participants) of those invited to perform the 6MWT were included in Study II. The RA patients who agreed to perform the 6MWT had similar age and sex distribution as those who declined (median age 65 years versus 63 years, p=0.87; female percentage 77 % versus 73 %, p=0.53). When comparing the patients included in Study II to those who participated in FysKond2 but either declined to perform the 6MWT or were excluded from Study II due to missing data, they were not significantly different in terms of age, sex, smoking habits, physical activity habits, self-reported function, or disease activity. Still, those included in Study II had longer median disease duration (10 years versus 6 years, p=0.03). Data on non-participants were not collected for the controls in Study III. All participants in FysKond2, 227 RA patients and 300 controls, were included in Study III.

The participant characteristics for the participants in Study I to III are presented in Table 7, 8, and 9. The RA patients in Study I and Study III were older, more often female, and more often ever smokers compared to the controls. In Study I, the patients with RA and/or diabetes had higher prevalence of previous CVD than the controls. In Study III, the RA patients reported more joint symptoms and more negative emotions than the controls. The RA patients in Study II and Study III had relatively well-controlled disease and high self-reported function. A higher percentage of the RA patients FysKond2 were seropositive as compared to the RA patients in HUNT.

**Table 7: Participant characteristics at baseline in Study I [a,b].**

| | RA N=387 | Diabetes N=2,898 | RA + Diabetes N=33 | Controls N=63,903 |
|---|---|---|---|---|
| Age (years) | 58 (49, 68) | 63 (51, 73) | 66 (59, 73) | 46 (34, 60) |
| Female sex | 261 (67) | 1,369 (47) | 20 (61) | 33,781 (53) |
| Smoking status | | | | |
| Current smoker | 126 (33) | 953 (33) | 12 (36) | 15,467 (24) |
| Former smoker | 129 (33) | 682 (23) | 4 (12) | 19,010 (30) |
| Never smoker | 132 (34) | 1,263 (44) | 17 (52) | 29,426 (46) |
| Body mass index (kg/m²) | 26.0 (23.7, 29.1) | 28.7 (25.9, 32.0) | 27.8 (24.4, 30.9) | 25.7 (23.4, 28.4) |
| Comorbidities | | | | |
| Previous CVD [c] | 41 (11) | 594 (20) | 7 (21) | 4,094 (6) |
| Hypertension [d] | 199 (51) | 2,098 (72) | 26 (79) | 25,333 (40) |
| Creatinine (µmol/L) | 84 (77, 92) | 89 (80, 99) | 89 (80, 98) | 85 (77, 94) |
| Total cholesterol (mmol/L) | 6.0 (5.3, 6.8) | 6.0 (5.1, 6.9) | 5.8 (5.0, 6.8) | 5.7 (4.9, 6.5) |
| **Diabetes-specific variables** | | | | |
| Age when diagnosed (years) | | 59 (49, 68) | 61 (50, 69) | |
| Diabetes duration before first HUNT participation with diabetes (years) | | 5 (2, 11) | 6 (3, 12) | |

[a]Number with percentage or median with 25th and 75th percentile.
[b]Missing data: <4% missing for all variables.
[c]Previous cardiovascular disease defined as a self-reported history of angina, stroke, or myocardial infarction.
[d]Hypertension defined as systolic blood pressure ≥140, diastolic blood pressure ≥90, or being on blood pressure-lowering medication.
Abbreviations: RA - rheumatoid arthritis. CVD - cardiovascular disease. HUNT - the Trøndelag Health Study.

**Table 8: Participant characteristics Study II and III [a].**

| | RA participants in Study II N=79 | RA participants in Study III N=227 | Controls in Study III N=300 |
|---|---|---|---|
| Age (years) | 65 (55, 71) | 64 (53, 71) | 46 (35, 55) |
| Female sex | 60 (76) | 153 (67) | 161 (54) |
| Smoking status | | | |
| Current | 7 (9) | 21 (9) | 19 (6) |
| Former | 42 (53) | 129 (57) | 86 (29) |
| Never | 30 (38) | 77 (34) | 193 (65) |
| Body mass index (kg/m²) | 26.3 (23.6, 28.9) | 26.0 (23.3, 28.9) | 25.8 (23.4, 19.7) |
| Resting heart rate (beats per minute) | 68 (63, 76) | 68 (62, 76) | 68 (63, 73) |
| Comorbidities | | | - |
| Hypertension | 32 (41) | 68 (30) | |
| Osteoporosis | 23 (29) | 55 (24) | |
| Pulmonary diseases [b] | 20 (25) | 44 (19) | |
| Cardiovascular diseases [c] | 13 (16) | 42 (19) | |
| Malignancies | 5 (6) | 22 (10) | |
| Diabetes | 7 (9) | 14 (6) | |
| HADS-D (scale 0-21) | 3 (1, 4) | 3 (1, 5) | 1 (0, 3) |
| HADS-D ≥8 | 8 (10) | 24 (11) | 12 (4) |
| Perceived stress scale (scale 0-40) | 15 (9, 19) | 14 (9, 18) | 10 (7, 14) |
| Morning stiffness (scale 0-10) | 3 (2, 6) | 4 (1, 6) | 1 (0, 2) |
| Joint pain past 6 months (scale 0-10) | 4 (2, 5) | 4 (2, 6) | 0 (0, 2) |
| Pain in neck, back or hips (scale 0-10) | 3 (2, 7) | 4 (1, 7) | 2 (0, 4) |
| Exercise Self-Efficacy (scale 5-35) | 25 (17, 30) | 24 (17, 29) | 26 (21, 31) |
| Exercise Self-Efficacy items | | | |
| When tired (scale 1-7) | 4 (4, 6) | 4 (3, 6) | 5 (4, 6) |
| When in a bad mood (scale 1-7) | 6 (3, 7) | 6 (4, 7) | 6 (5, 7) |
| When pressed for time (scale 1-7) | 4 (3, 6) | 4 (3, 6) | 4 (3, 6) |
| When on holiday (scale 1-7) | 6 (4, 7) | 6 (4, 7) | 6 (4, 7) |
| When it rains/snows (scale 1-7) | 6 (3, 7) | 6 (4,7) | 6 (5, 7) |

[a]Number (%) or median (25th and 75th percentile).
[b]Pulmonary diseases: history of chronic obstructive pulmonary disease, chronic restrictive pulmonary disease, or asthma.
[c]Cardiovascular disease: history of myocardial infarction, angina, arrhythmia, or stroke.
Abbreviations: HADS-D - the depression subscale of the Hospital Anxiety and Depression Scale. RA - rheumatoid arthritis.

**Table 9: Rheumatoid arthritis-specific characteristics in Study I, II, and III [a].**

| | Study I | | Study II | Study III |
|---|---|---|---|---|
| | **RA (N=387)** | **RA + Diabetes (N=33)** | **RA (N=79)** | **RA (N=227)** |
| Age at RA diagnosis (years) | 55 (45, 64) | 60 (53, 70) | 48 (35, 58) | 48 (37, 58) |
| RA duration (years) | 6 (3, 9) | 7 (5, 10) | 10 (5, 23) | 11 (5, 20) |
| Seropositive (RF and/or ACPA) | 277 (72) | 24 (73) | 68 (86) | 187 (82) |
| DAS28-CRP score [b] (scale 0.0-9.4) | - | - | 2.3 (1.7, 2.9) | 2.5 (1.8, 3.1) |
| DAS28-CRP category [b] | - | - | | |
| Remission | | | 52 (66) | 125 (56) |
| Low disease activity | | | 14 (18) | 46 (20) |
| Moderate disease activity | | | 12 (15) | 47 (21) |
| High disease activity | | | 1 (1) | 6 (3) |
| mHAQ (scale 0.00-3.00) | - | - | 0.38 (0.13, 0.63) | 0.25 (0.00, 0.63) |
| Patient global assessment (mm, scale 0-100) | - | - | 27 (12, 40) | 29 (14, 48) |
| RA medication | - | - | | |
| cDMARDs | | | 34 (43) | 98 (43) |
| bDMARDs | | | 9 (11) | 28 (12) |
| cDMARDs+bDMARDs | | | 33 (42) | 88 (39) |
| no DMARDs | | | 3 (4) | 13 (6) |
| Corticosteroids | | | 21 (27) | 51 (22) |

[a]Number (%) or median (25th and 75th percentile).
[b]Last documented value from hospital record. This score was recorded ≥1 year before participation for 19 % and 43 % of the patients in Study II and III, respectively.
Abbreviations: ACPA - anti-citrullinated protein antibody. bDMARD - biological disease-modifying anti-rheumatic drugs. cDMARD - conventional disease-modifying anti-rheumatic drugs. DAS28-CRP - disease activity score in 28 joints - C-reactive protein. mHAQ - modified Health Assessment Questionnaire. RA - rheumatoid arthritis. RF - rheumatoid factor.

## 4.2 Missing data

In Study I, 2,000 (3 %) of the HUNT participants in HUNT were excluded due to missing data to evaluate disease status or because they had other types of inflammatory arthritis, and 9,711 (12 %) were excluded due to missing data for adjustment variables (Figure 4). In Study

II, 6 (7 %) participants were excluded due to missing data for variables in the multiple regression analyses (Figure 4).

In general, the percentage of missing data for each variable included in the analyses was ≤4 % in Study I to III. The exceptions in Study I were missing data for smoking habits (7 %) and blood pressure (5 %) at the baseline observation. The exception in Study III was eCRF (27 %), which was mostly due to missing data for resting heart rate which were needed to calculate eCRF. The ICD-10 codes for underlying cause of death lacked for 110 individuals (0.9 %) of those who died during in the follow-up period: nine diabetes patients and 101 controls.

## 4.3 Mortality

### 4.3.1 Number and causes of death

The number of deaths and causes of deaths in Study I are presented in Table 10. By the end of the observation period, 123 (32 %) of the participants with RA, 1,280 (44 %) of the participants with diabetes, 17 (52 %) of the participants with both RA and diabetes, and 11,641 (18 %) of the controls had died.

The most common causes of death were diseases of the circulatory system, neoplasms, and diseases of the respiratory system, in that order, see Table 10 and Figure 7. This was the order both for the participants with RA and the controls. In the diabetes group, the third most common cause of mortality was related to diabetes. The 95 % CIs for the percentage estimates among the RA patients were overlapping with the 95 % CIs for the diabetes patients and the general population for the 3 major causes of death. Therefore, the distribution of deaths among the RA patients from the 3 main deaths causes was not significantly different from the distribution among diabetes patients and controls.

The Kaplan-Meier survival curves are presented in Figure 8.

**Table 10: Number and causes of deaths in Study I [a,b,c].**

| | RA N=387 | Diabetes N=2,898 | RA + Diabetes N=33 | Controls N=63,903 |
|---|---|---|---|---|
| Number of deaths | 123 (32) | 1280 (44) | 17 (52) | 11, 641 (18) |
| Total observation time (person years) | 5,999 | 38,760 | 445 | 989,392 |
| Individual observation time (years) | 18 (13, 19) | 17 (8, 19) | 17 (9, 18) | 18 (13, 19) |
| Causes of deaths [d] | | | | |
| Infectious and parasitic diseases | 2 (2) | 26 (2) | 0 (0) | 204 (2) |
| Neoplasms | **30 (24)** | **251 (20)** | **5 (29)** | **3,558 (31)** |
| Diseases of the blood and blood-forming organs | 2 (2) | 3 (<1) | 0 (0) | 36 (<1) |
| Endocrine, nutritional and metabolic diseases | 4 (3) | **152 (12)** | **2 (12)** | 124 (1) |
| Diseases of the nervous system | 2 (2) | 20 (2) | 0 (0) | 385 (3) |
| Diseases if the circulatory system | **44 (36)** | **550 (43)** | **7 (41)** | **4444 (38)** |
| Diseases of the respiratory system | **12 (10)** | 86 (7) | 1 (6) | **871 (7)** |
| Diseases of the digestive system | 6 (5) | 41 (3) | 1 (6) | 289 (2) |
| Diseases of the musculoskeletal system and connective tissue | 9 (7) | 3 (<1) | 1 (6) | 61 (1) |
| Diseases of the genitourinary system | 3 (2) | 34 (3) | 0 (0) | 225 (2) |
| Symptoms, signs and abnormal findings | 6 (5) | 26 (2) | 0 (0) | 404 (3) |
| External causes of morbidity and mortality | 3 (2) | 47 (4) | 0 (0) | 517 (4) |
| Mortality rate per 1,000-person year | | | | |
| Overall | 21 | 33 | 38 | 12 |
| Due to diseases of the circulatory system | 7 | 14 | 16 | 4 |
| Due to neoplasms | 5 | 6 | 11 | 4 |
| Due to diseases of the respiratory system | 2 | 2 | 2 | 1 |

[a] Number (percent) or median (25th and 75th) percentile.
[b] Presented for causes of death reported in at least 2 persons with rheumatoid arthritis.
[c] The numbers for the 3 most common cause of death in each group are presented in bold.
[d] After the chapters from the International Classification of Diseases 10th revision.
Abbreviation: RA - rheumatoid arthritis.

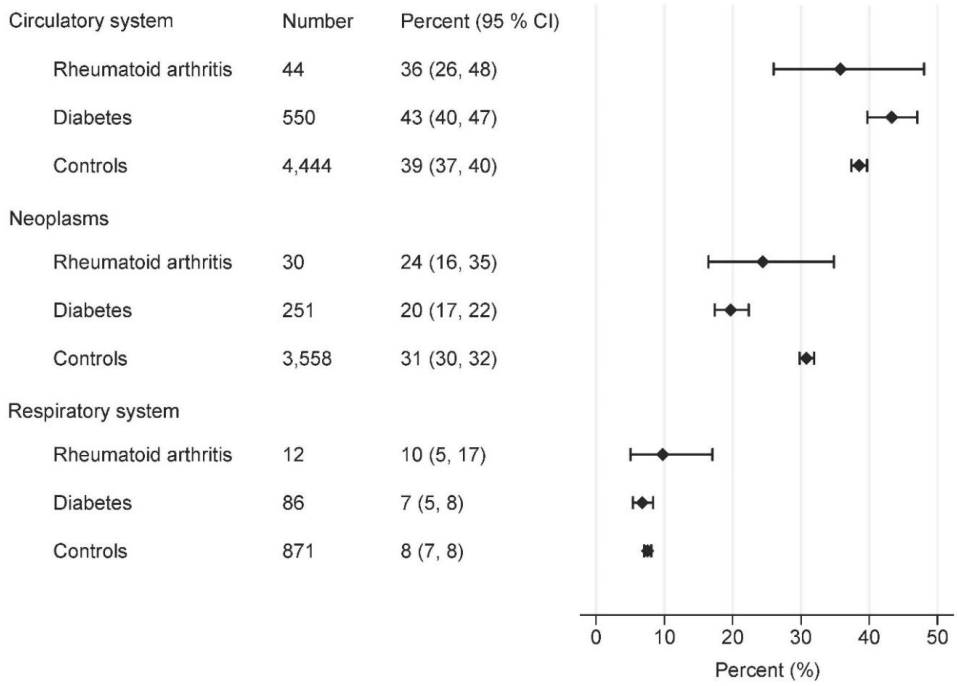


**Figure 7: Distribution of main causes of deaths by disease group.**
Presents deaths due to diseases of the circulatory system, neoplasms, and diseases of the respiratory system. Participants with both rheumatoid arthritis and diabetes are not included in the plot. The 95 % confidence intervals were calculated with Poisson distribution.
Abbreviation: CI - confidence interval.

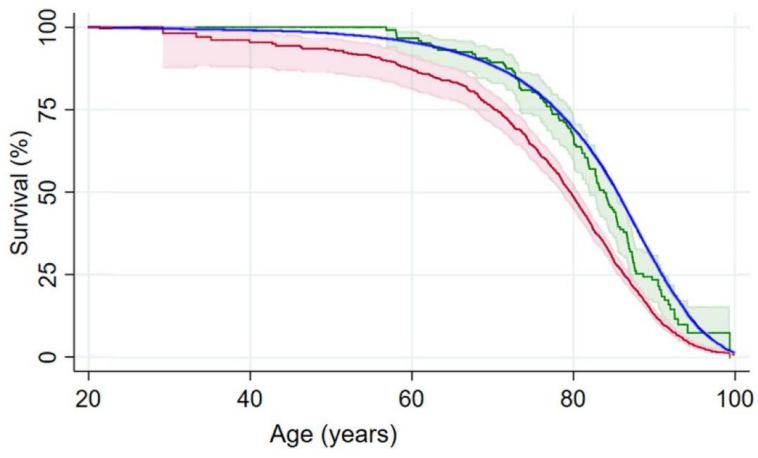


**Figure 8: Kaplan-Meier survival plot.**
Green line represents participants with rheumatoid arthritis, red line represents the participants with diabetes, and blue line represents controls. The coloured areas around each line are the 95 % confidence intervals. Participants with both diseases were not included in the plot.

### 4.3.2 Results from the Cox regression analysis

The results from the Cox regression analyses are presented in Figure 9. Both RA patients and diabetes patients had significantly higher mortality rates compared to the general population in Cox regression Models 1, 2, and 3, and the estimates only changed slightly after adjusting for important variables. The 95 % CI for RA patients was overlapping with that of diabetes patients >75 years and not with that of diabetes patients ≤75 years. Thus, the mortality rates among RA patients were statistically significantly lower than in diabetes patients ≤75 years, and not statistically significantly different from the mortality rates for diabetes patients >75 years.

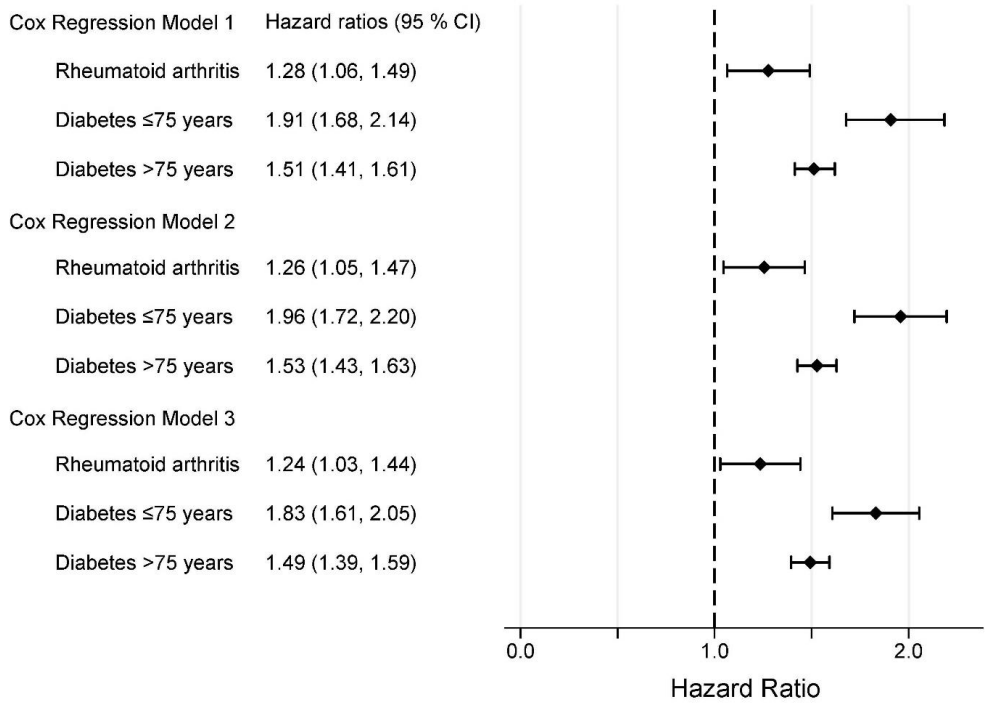


**Figure 9: Results from the Cox Regression Model 1, 2 and 3.**
Cox Regression Model 1 took age and sex into account. Cox Regression Model 2 further adjusted for smoking habits, body mass index, hypertension, creatinine, and total cholesterol. Cox Regression Model 3 further adjusted for previous cardiovascular disease.
Abbreviations: CI - confidence interval.

The sensitivity analyses demonstrated that the results were robust. Repeated analysis after excluding the participants with RA and diabetes and after multiple imputation of adjustment variables resulted in only slightly changed HR estimates. Adding an interaction term with the age group variable for RA resulted in an essentially unchanged HR estimate, but the CIs became wider, and the association was not statistically significant for RA patients ≤75 years of age. This was likely related to the few deaths in this group (N=33). The HR estimates for mortality among diabetes patients were lower in the older age groups than in the youngest age group. There was a trend with gradually lower HR estimates among diabetes patients in the older age groups.

## 4.4 Physical fitness

### 4.4.1 Physical fitness in Study II and III

The results from the 6MWT and for eCRF are presented in Table 11. The shortest and longest 6MWD were 248 m and 738 m, respectively. There were 3 participants who used a crutch when performing the 6MWT. The median perceived exertion on the Borg scale before the 6MWT was 9 ($25^{th}$ percentile to $75^{th}$ percentile 6 to 11), which increased to 11 ($25^{th}$ percentile to $75^{th}$ percentile 9 to 12) immediately after the test. The lowest and highest eCRF estimates in Study III were 10.7 mL/kg/min and 64.8 mL/kg/min. The RA patients had lower mean values for eCRF compared to controls: 8.5 mL/kg/min lower in women and 6.8 mL/kg/min lower in men.

### 4.4.2 Determinants of functional capacity

Table 12 presents the results from the Multivariable linear regression analyses. In Multivariable linear regression Model 1, higher age tertile and higher body mass index were significantly associated with lower functional capacity measured with the 6MWT. Lower Exercise Self-Efficacy and higher patient global assessment were also significantly associated with shorter 6MWD when these were added in Multivariable linear regression Model 2. None of the additional variables added in Multivariable linear regression Model 3 had a significant association with 6MWD. Multivariable linear regression Model 2 and Model 3 explained 12 % and 7 % more of the variation in the observed data for 6MWD than Multivariable linear regression Model 1.

The Sensitivity analysis showed that year of recruitment (2019 or 2021) was not statistically significantly associated with the 6MWD (p=0.39).

**Table 11: Physical activity and physical fitness in Study II and III [a].**

| | RA participants in Study II N=79 | RA participants in Study III N=227 | Controls in Study III N=300 |
|---|---|---|---|
| Physical activity frequency | | | |
| <Once/week | 9 (11) | 24 (11) | 19 (6) |
| Once/week | 12 (15) | 36 (16) | 28 (9) |
| 2-3 times/week | 37 (47) | 98 (43) | 130 (44) |
| Almost daily | 21 (27) | 68 (30) | 122 (41) |
| Physical activity intensity [b] | | | |
| Take it easy | 28 (35) | 76 (33) | 58 (19) |
| Heavy breathing/sweat | 39 (49) | 117 (52) | 211 (70) |
| Near exhaustion | 3 (4) | 7 (3) | 11 (4) |
| Physical activity duration [b] | | | |
| <15 minutes | 2 (3) | 5 (2) | 3 (1) |
| 15-29 minutes | 7 (9) | 33 (15) | 56 (19) |
| 30-60 minutes | 44 (56) | 115 (51) | 168 (56) |
| >60 minutes | 17 (22) | 48 (21) | 53 (18) |
| Fulfilling the ACSM/AHA aerobic physical activity recommendations | 23 (32) | 63 (28) | 104 (35) |
| Physical activity index (scale 0-45) | 7.5 (0.0, 15) | 7.5 (0.0, 15) | 15 (0.0, 22.5) |
| Estimated CRF (ml/kg/min) | | | |
| total | 29.0 (22.3, 35.5) | 29.1 (23.0, 36.1) | 40.0 (34.6, 44.1) |
| women | 27.2 (21.3, 34.1) | 26.6 (21.8, 34.1) | 36.2 (31.9, 40.9) |
| men | 31.1 (28.6, 44.4) | 34.9 (29.0, 44.8) | 43.1 (39.5, 48.5) |
| 6-minute walk test distance (m) | | - | - |
| total | 493 (447, 576) | | |
| women | 505 (444, 575) | | |
| men | 480 (459, 579) | | |

[a]Number (%) or median (25th and 75th percentile).

[b]Only participants asked reporting to engage in physical activity at least weekly were asked to report intensity and duration of physical activity.

Abbreviations: ACSM - American College of Sport Medicine. AHA - American Heart Association. CRF - cardiorespiratory fitness. RA - rheumatoid arthritis.

**Table 12: Results from Multivariable linear regression analyses in Study II [a].**

| | Multivariable Linear Regression Model 1 | | Multivariable Linear Regression Model 2 | | Multivariable Linear Regression Model 3 | |
|---|---|---|---|---|---|---|
| | Unstandardized coefficient (95% CI) | Standardized coefficient | Unstandardized coefficient (95% CI) | Standardized coefficient | Unstandardized coefficient (95% CI) | Standardized coefficient |
| $R^2$ of model | 0.42 | | 0.54 | | 0.49 | |
| Male sex | 27 (-9, 64) | 0.13 | 15 (-22 53) | 0.08 | 28 (-9, 66) | 0.14 |
| Age | | | | | | |
| Middle versus youngest tertile | -35 (-72, 1) | -0.20 | -39 (-74, -3)* | -0.22* | -26 (-64, 12) | -0.15 |
| Oldest versus youngest tertile | -115(-155, -76)*** | -0.59*** | -117 (-155, -79)*** | -0.60*** | -97 (-142, -53)*** | -0.50*** |
| Body mass index | -8 (-12, -5)*** | -0.39*** | -6 (-10, -2)** | -0.28** | -7 (-11, -3)** | -0.32** |
| Exercise Self-efficacy | | | 3 (1, 4)** | 0.26** | | |
| Patient global assessment | | | -1 (-2, 0)* | -0.21* | | |
| Perceived stress scale | | | -2 (-5, 1) | -0.15 | | |
| HADS-D | | | 3 (-4, 9) | 0.11 | | |
| Ever smoker (yes/no) | | | -6 (-39, 26) | -0.03 | -27 (-60, 7) | -0.15 |
| Comorbidity (yes/no) [b] | | | | | -23 (-60, 15) | -0.13 |
| DAS28-CRP | | | | | -12 (-29, 5) | -0.13 |
| Present use of corticosteroids | | | | | -24 (-61, 12) | -0.12 |
| Seropositive (positive RF and/or ACPA) | | | | | 8 (-38, 55) | 0.03 |
| Duration of rheumatoid arthritis | | | | | 0 (-1, 1) | -0.01 |

[a] *P-value <0.05, **P-value<0.01, *** P-value <0.001.

[b] Comorbidity defined as having hypertension, angina, myocardial infarction, arrythmia, stroke, chronic obstructive pulmonary disease, chronic restrictive pulmonary disease, asthma, diabetes, or cancer.

Abbreviations: ACPA - anti-citrullinated protein antibody. CI - confidence interval. DAS28-CRP - disease activity score in 28 joints - C reactive protein. HADS-D - the depression subscale of the Hospital Anxiety and Depression Scale. RF - rheumatoid factor.

### 4.4.3 Relationship between the physical fitness variables

The 2 variables measuring physical fitness, eCRF and 6MWD, were significantly associated ($r=0.61$, $p<0.0001$) in the 76 patients in Study II with data for both measures. Figure 10 shows the scatterplot with eCRF on the y-axis and 6MWD on the x-axis.

In the additional analyses, the modified Health Assessment Questionnaire score was significantly associated with both eCRF ($r=-0.34$, $p=0.003$) and 6MWD ($r=-0.29$, $p=0.01$). There were 76 and 79 patients included in these 2 correlation analyses, respectively.

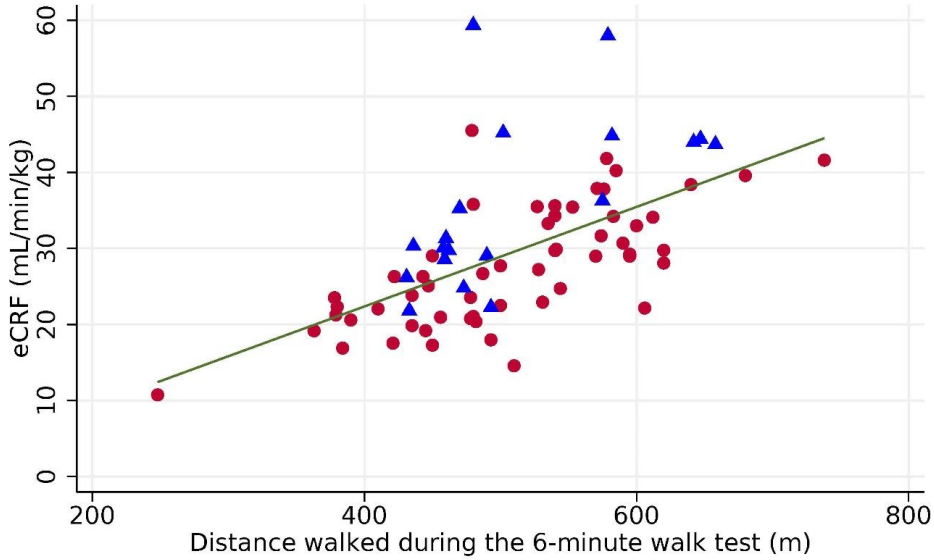


**Figure 10: Scatterplot of 6-minute walk distance versus estimated cardiorespiratory fitness.** Abbreviations: eCRF - estimated cardiorespiratory fitness. Linear regression line presented. Blue triangles represent male participants, red circles represent female participants.

### 4.4.4 Mediators of estimated cardiorespiratory fitness

The SEM Models are presented in Figures 5 and 6, and the results are presented in Table 13. In SEM Model 1, the presence of RA was associated with significantly lower eCRF when adjusting for age and sex. The unstandardized coefficient was -1.7 ($p=0.002$), indicating that the age- and sex-adjusted mean eCRF was 1.7 mL/kg/min lower in RA patients compared to controls. Both physical symptoms and negative emotions acted as mediators between RA status and eCRF in SEM Model 2a and 2b.

**Table 13: Results from structural equation modelling in Study III.**

| | Effects of rheumatoid arthritis status on estimated cardiorespiratory fitness | Unstandardized coefficient (95 % CI) | Standardized coefficient | P-value | Percent of total effect (%) |
|---|---|---|---|---|---|
| SEM Model 1 | Direct effect | -1.7 (-2.8, -0.6) | -0.089 | 0.002 | - |
| SEM Model 2a | Direct effect | -0.9 (-2.0, 0.3) | -0.045 | 0.14 | 51 |
| | Indirect effect via physical symptoms | -0.8 (-1.3, -0.3) | -0.042 | 0.002 | 48 |
| | Total effect | -1.7 (-2.8, -0.6) | -0.087 | 0.003 | - |
| SEM Model 2b | Direct effect | -0.8 (-2.0, 0.4) | -0.041 | 0.20 | 46 |
| | Indirect effect through negative emotions | -0.9 (-1.5, -0.4) | -0.048 | 0.002 | 54 |
| | Total effect | -1.7 (-2.8, -0.6) | -0.089 | 0.002 | - |
| SEM Model 3 | Direct pathway | -0.5 (-1.7, 0.8) | -0.024 | 0.46 | 26 |
| | Indirect effect through physical symptoms | -0.7 (-1.3, 0.0) | -0.034 | 0.051 | 37 |
| | Indirect effect through negative emotions | -0.6 (-1.3, 0.0) | -0.034 | 0.039 | 37 |
| | Total effect | -1.8 (-2.8, -0.7) | -0.092 | 0.001 | - |

Abbreviations: CI - confidence interval. SEM - structural equation modelling.

In the combined model, SEM Model 3, the total unstandardized coefficient was -1.8 (95 % CI -2.8, -0.7). Of the total association between RA and eCRF, 26 % was explained by RA alone (p=0.46), 37 % was explained by physical symptoms (p=0.051), and 37 % was explained by negative emotions (p=0.039). This means that 74 % of the association between RA and eCRF was mediated by physical symptoms and negative emotions.

## 4.5 Assumptions and model fit

Overall, the assumptions for the statistical analyses were considered met and the model fit for the models were acceptable. The interaction term with the age group variable for diabetes, smoking, and previous CVD was added in the Cox regression analyses in Study I to achieve proportional hazards. The independent continuous variables in the Multivariable linear regression Models in Study II had sufficiently linear association with 6MWD, the residuals were normally distributed, and there was no evidence of collinearity. Moreover, age was categorized into tertiles in the multivariable linear regression analyses as this improved model fit. $R^2$ for the Multivariable linear regression Models are presented in Table 12. The dependent variable in the SEM Models in Study III was normally distributed. The only SEM model fit index not within the preferred range for the SEM Models was the p-value for the chi-square test in SEM Model 3, though it was close to non-significance (p=0.047).

# 5 DISCUSSION

## 5.1 Main findings

In Study I, we demonstrated that RA patients had higher mortality rates compared to controls from the general population. The RA patients had excess mortality of similar magnitude as diabetes patients >75 years, though lower relative excess mortality than what was observed in diabetes patients ≤75 years. There was no statistically significant difference in the percentage of deaths due to the 3 main causes of death between RA patients and controls.

In Study II, Exercise Self-Efficacy and the patient global assessment, but not objective or composite RA disease measures, were associated with the 6MWD. Moreover, the physical fitness variables eCRF and 6MWD had a statistically significant association.

In Study III, the RA patients had lower eCRF than healthy controls in analyses adjusted for age and sex. Physical symptoms and negative emotions mediated this negative association between RA and eCRF.

## 5.2 Methodological considerations

Before discussing the finding of the thesis, we will discuss the methodology and factors influencing internal and external validity. Internal validity reflects whether the results in a study are true for the study population, whereas external validity reflects whether the results from a study can be generalized to other populations or other settings (222). Internal validity is influenced by random error, systematic error, and confounding (223). Random error is incorrect results due to chance, is equally likely to misrepresent the truth in either direction, and can be reduced by increasing sample size (222, 224). Systematic error, or bias, is related to the methodology in a study and leads to misrepresentation of the truth in a specific direction (224).

### 5.2.1 Selection bias

Selection bias is a type of systematic error and arises when the association between the independent and dependent variable differs in the study sample compared to in the target population (222). If only patients with well-controlled disease and with few disabilities agreed to participate in FysKond2, the relationship between disease activity and functional capacity might not reflect the association among RA patients overall. Factors affecting study enrolment and loss to follow-up can lead to selection bias.

*5.2.1.1 Recruitment of participants*

At study enrolment, both HUNT and FysKond2 strived to reduce selection bias. All inhabitants ≥20 years of age in the region were invited for HUNT, and examination sites were set up in each municipality to reduce travel distances. In FysKond2, all RA patients with an appointment on the recruitment days and a random selection of the participants in the patient-centred follow-up programme were invited. No extra trip to the hospital was required as they were asked to participate before or after an appointment, or by filling in the questionnaire at home. Similarly, all eligible blood donors who came to the blood bank on the recruitment dates were invited to participate. There were few exclusion criteria, though understanding Norwegian was required in both HUNT and FysKond2.

The decision to participate in a study is not random, and may represents a selection bias (223). An example of this is volunteer response bias. A study about physical activity such as FysKond2 might be more appealing to individuals with a positive attitude towards physical activity and exercise, especially if the study requires one to do a physical test. Perhaps the invitation to the 6MWT for the RA patients with physical appointments resulted in a more pronounced volunteer response bias in this group. Even though they could participate in the study without performing the 6MWT, information about the 6MWT in the information letter might have led those who were least physically fit to decline to participate in the study at all. The RA patients were requested to perform the test before or after their appointment at the rheumatology departments. Several patients expressed willingness to perform the 6MWT but did not have time on the day of their appointment for example because someone was picking them up. Perhaps the acceptance rate to perform the 6MWT had been higher if the patients could have come back on a different date. Unfortunately, this was not possible due to practical reasons such as the COVID-19 restrictions. However, many patients with low physical activity levels participated in the study and the majority did not meet the aerobic physical activity recommendations from ACSM/AHA (127).

*6.2.1.2 Control groups*

The population-based design in HUNT ensured that we had controls from the same population and had the same baseline data for all participants. There was no systematic difference in the recruitment of RA patients, diabetes patients, and controls as all inhabitants in the region were invited regardless of disease status. The controls in Study I were younger than the patients, but due to the large number of controls there were many more controls in the older age groups than there were patients. Important factors that could differ between the

patients and controls, like sex, previous CVD, hypertension, and body mass index were adjusted for in the Cox regression analysis. Furthermore, as age was used as the time scale, patients were compared to controls of the same age.

Blood donors were chosen as the control group in Study III because they are relatively easy to recruit and vary in background and age. The recruitment strategies were different for the RA patients and the controls in FysKond2. The controls were for example not asked to perform a 6MWT and recruited between May and August whereas the majority of the RA patients were recruited in the fall or winter. The fact that the controls were not invited to do a 6MWT could have led to less volunteer response bias than for the RA patients, and perhaps a higher percentage of the least active individuals agreed to participate. In addition, there may be seasonal variation in physical activity, physical symptoms, depressive symptoms, stress etc. Some individuals might engage in more physical activity when it is warm outside than during the winter months, though, others may engage in less physical activity during summer holiday when their schedule differs from the rest of the year. We cannot exclude the possibility that the different recruitment strategies led to a selection bias.

Another concern regarding the blood donor is if they were too healthy and too young compared to the RA patients. Individuals with cancer, serious CVD, or infection are not allowed to donate blood and therefore the comorbidities likely differed between the patients and the controls (205). Nevertheless, there are no restrictions regarding joint and muscle symptoms for blood donors, which are common symptoms both in the general population and in patients with rheumatic diseases.

Some of the underlying differences like age and sex were adjusted for in the SEM models. An alternative approach could have been to recruit individuals coming to an outpatient clinic or to their general practitioner as controls. This might have resulted in sample more similar to the RA patients in terms of age and comorbidities. However, individuals for example attending a general practitioner's office would not be representative of the general population either. Individuals with psychiatric disorders and individuals on sick leave seek medical help from their general practitioner more often than the population overall. Moreover, acute illnesses like infections or a traumatic incidence could be the reason they seek medical help, and these circumstances could change their physical activity habits and perhaps reduce the likelihood that they would agree to participate.

*5.2.1.3 Loss-to-follow-up bias*

Loss to follow-up can also cause selection bias if the loss to follow-up is non-random and related to the exposure variables and to the outcome variable (222, 223). In Study I, this could have been an issue if for example the RA and diabetes patients had both higher mortality than the general population and were more likely to be lost to follow-up. If RA or diabetes patients who died during the follow-up period were lost to follow-up more often than controls who died, this could have resulted in an underestimation of the differences in mortality between the patient groups and the controls. However, data for vital status from the Norwegian Cause of Death Registry have very high accuracy for deaths inside Norway or among Norwegians abroad and therefore loss to follow-up was not a major issue (207). Study II and Study III were cross-sectional, and therefore loss to follow-up after participation was not relevant.

### 5.2.2 Information bias

The influence of errors from the data collection on the results of the study is called information bias and this is another type of systematic error (222). Information bias is influenced by misclassification and measurement error. Examples of misclassification could be to classify an individual with RA as a healthy control or classify a former smoker as a never smoker. Measurement error occurs when a measured variable does not reflect the true value for an individual (222). An example of measurement error could be if self-reported weight and height misrepresented the true value for participants in FysKond2. Information bias can be differential or non-differential. Differential information bias means that the level of misclassification depends on the values of other variables, for example if true hypertension in Study I was less often diagnosed in controls than in diabetes patients. Other types of information bias are recall bias and detection bias (222). Recall bias arises when exposed and unexposed individuals differ in how they recall or report information about specific variables, whereas detection bias occurs if the likelihood that a disease is detected differs by exposure status.

*5.2.2.1 Diagnoses*

Self-reported diagnoses can lead to misclassification because self-report is prone to imperfect memory and disease understanding by participants and misinterpretation of questionnaires. A previous study only found a RA diagnosis in hospital records for 19 % of those self-reporting to have RA in HUNT2 or HUNT3 and found no false-positive RA cases among a random selection of individuals reporting to not have RA (206). Thus, self-reported RA is often

inaccurate. It is therefore a strength that Study I to III applied RA diagnoses that had been confirmed against hospital records.

On the other hand, the diabetes diagnoses in Study I were based upon self-reported diabetes, measurement of glucose, and self-reported medications. In a validation study using data from HUNT1, self-reported diabetes had a sensitivity of 99 % and specificity of 98 % compared to a physician's diagnosis in medical records in a subgroup of participants reporting either to have (N=169) or not have diabetes (N=338) (225). This implies that self-reported diabetes is relatively accurate. We further increased the accuracy of our diabetes definition by also including diabetes medication and glucose measurements. We could not distinguish between type I and type II diabetes in Study I, but assume the majority were type II based on the distribution of diabetes in Norway (226).

To be classified as a RA or diabetes patient the diagnoses had to be present before the participation in HUNT or FysKond2. Thus, we studied prevalent cases, and the results are therefore not directly comparable to inception studies. An inception cohort follows patients from the time of diagnosis or early in the disease course and thereby only includes incident cases. A study of prevalent cases includes patients with short and long disease duration ranging from days to decades. This distinction matters because some disease manifestation may first be apparent after several years of disease, such as radiographic damage in RA. Furthermore, in an inception cohort the initial treatment would follow the same treatment strategies for all patients, whereas in a study of prevalent cases the initial treatment varies greatly according to the treatment guidelines at the time of diagnosis. Some of the participants in Study I may have developed RA or diabetes after they participated in HUNT and may be part of the control group. Considering the large number of controls, this would probably not affect the overall results.

*5.2.2.2 Dependent variables*

In Study I, the dependent variables were all-cause mortality and causes of death. As mentioned earlier, data for vital status had high accuracy for the participants in Study I. Therefore, misclassification of the dependent variable for the Cox regression analysis was not a major issue.

There was an ICD code for 99 % of the observed deaths. In Norway, the attending physician is required to fill in a death certificate, in which one must select the immediate and underlying cause of death. The cause of death is checked with autopsy in approximately 10 %

of all deaths (227). A study of all autopsies performed in Norway in 2005 found that the autopsy resulted in a change of ICD chapter for the underlying cause of death in 32 % of cases, and percentage of deaths due to diseases of the circulatory system increased from 37 % to 44 % in the group that underwent autopsy (228). This shows the uncertainty in death cause evaluation based on death certificates, which could lead to misclassification of causes of deaths. However, the sample selected for autopsy is not representative for all deceased as the autopsy is often initiated if the cause of death or circumstances surrounding the death is unclear. Moreover, the Norwegian Cause of Death Registry strives to improve the quality of the registry. They use an automatic coding system, follow the guidelines from the World Health Organization regarding coding of death causes, request more clinical data from the attending clinician if necessary, and incorporate data from other health registries and from autopsies (229). This work ensures that the information on death causes have as high quality as possible and is comparable to other countries applying the same diagnostic codes and the guidelines from the World Health Organization. As the controls were younger on average than the RA patients and the diabetes patients, caution is required when comparing of causes of death between the groups.

In Study II and Study III, the dependent variables were the physical fitness variables 6MWD and eCRF, respectively.

The 6MWT is a submaximal exercise test and gives a measure of functional capacity. For a physical test to be as valid as possible, the test subjects must understand and follow the instructions. Phrasing, tone, and frequency of encouragement can influence the results from the 6MWT. Therefore, the standardized test guidelines from the American Thoracic Society were followed closely with standardized instructions and encouragements given every minute, and all 6MWTs were performed with the same tester (149). The walking course was 25 m instead of the recommended 30 m for practical reasons. Shorter walking course means more turns, which can lead to shorter 6MWD (230). However, the walking course was 25 m for all participants in Study II and it is very unlikely that the shorter walking course would impact the associations between the independent variables and the 6MWD. The degree to which the patients pushed themselves during the test varied, but this was also expected.

The second fitness measure applied in the present thesis was the eCRF. The eCRF is a less accurate measure than CRF measured with a cardiopulmonary exercise test as it is based on self-reported data and calculated based on CRF results from a reference population.

Calculating eCRF was chosen over cardiopulmonary exercise testing due to available financial and human resources, the targeted sample size, and the planned timeline for recruitment. The fact that no maximal exercise test was required might have increased the acceptance rate to participation, the representativity, and the size of the sample. We aimed to include at least 200 RA patients and 200 controls for Study III, and it had not been feasible to achieve this number of participants and measure CRF for all with the available resources for the project. An adequate sample size is necessarily to perform SEM analysis and reduces the probability that random errors explain the observed associations. To assess the validity of the eCRF estimates in Study II and Study III, the quality and relevance of the studies that developed the eCRF formulas, as well as the accuracy of the variables included in the formulas should be considered.

The RA fitness formula was developed using a sample of 93 Norwegian RA patients: 68 women and 25 men (179, 219). For that study, 100 patients were recruited, 40 from the outpatient clinic at St. Olavs Hospital, 54 from the patient-centred follow-up programme, and 6 responded to a rheumatology newsletter announcement (179). Of these 100 patients, 93 were included in the formula development. More than 80 % reached $VO_{2max}$ during the cardiopulmonary exercise test and only 10 % reported lower extremity complaints above "somewhat painful" during the test (179). There were few patients in the younger age groups, especially for men: 1 male patient in the age group 20-39 years and 2 male patients in the age group 40-49 years, and these 3 men had relatively high CRF. Furthermore, the men in the study that developed the RA-specific eCRF formula had lower mean DAS28-CRP and higher function than the women, likely because a larger proportion of the men was recruited from the patient-centred follow-up programme (179). Together, this could have led to differential measurement error with overestimation of fitness level in the younger male RA patients in Study II and Study III. Apart from slightly lower median age (median age 60 years vs 64 years), the summary characteristics for the patients in the study developing eCRF and for the patients in FysKond2 were similar (219).

Despite the issues discussed above, it was better to use the RA fitness formula for the RA patients in FysKond2, as previous findings indicate that the HUNT fitness formula significantly overestimates the fitness level of RA patients (219).

The HUNT fitness formula was developed based on 4,631 healthy individuals (156). This was a sub-study of HUNT3 and performed about a decade before the cardiopulmonary

exercise test of the RA patients. This formula was chosen to calculate eCRF for the controls because it was developed in the same region as our participants were recruited from and has been associated with several important endpoints (165, 168). Further, the HUNT fitness formula is among the non-exercise formulas recommended by the AHA to calculate eCRF in healthy individuals (142).

The variables that are part of both eCRF formulas are age, sex, physical activity habits, body mass index, and resting heart rate, and the RA fitness formula also includes smoking habits and the patient global assessment (Table 5). Physical activity habits were self-reported, which is less accurate than objectively measured physical activity. Further, the physical activity questionnaire assessed habitual physical activity, but did not involve a dimension of how long the individual has performed physical activity at this level. Whether a person has been exercising regularly for 2 weeks or 2 years would likely influence physical fitness. Self-reported physical activity can be affected by recall bias. RA patients might for example report light physical activity as more strenuous than controls. Moreover, physical activity habits may be overreported because physical activity is socially desired, especially in individuals scoring high on the personality trait "social desirability" (231). Nevertheless, our patients responded to the same physical activity questionnaire used for the development of the eCRF formulas (156, 219). The fitness formulas thereby take the general tendency to overestimate physical activity levels into account. It is also more feasible to use a questionnaire to assess physical activity than objective measures such accelerometer data and easier to interpret. Moreover, to our knowledge no eCRF formula has been developed or validated in RA patients which uses accelerometer data as part of the formula.

Body mass index was calculated from self-reported weight and height, which undoubtedly is prone to uncertainty. Weight and height were measured by research personnel in the studies that developed the eCRF formulas, thus the body mass index variable in Study II and Study III is less accurate. This uncertainty could be larger for specific groups. Obese patients with low activity level might be less likely to weigh themselves and might vary more in weight than leaner individuals who perform regular physical activity. Smoking habits and the patient global assessment are self-reported by nature.

The last variable in the eCRF formulas is resting heart rate. For the RA patients who came to the hospital, this was measured by the research team after the patient had been sitting for at least 5 minutes. However, a large portion of the RA patients participated by mail. They were

instructed to sit for 10 minutes before they measured their own heart rate, but the instructions might have been misunderstood. Many of these RA patients did not measure their heart rate, which unfortunately resulted in missing data for eCRF for about a quarter of the RA patients. Resting heart rate was measured by the research team for all controls after they had been sitting for at least 5 minutes. The heart rate was systematically measured after blood donation for practical reasons. Blood donation might affect heart rate, and even minor changes in heart rate could lead to a biased eCRF results for the control group. A study reported a U-shape curve of heart rate during blood donation, with higher heart rate right before, lower heart rate during, and higher heart rate again right after blood donation (232). However, the blood donors in that study were not required to sit and rest before or after donation so light physical activity from moving around could also be the cause of this U-shaped curve. Several other studies have not found significant changes in heart rate after blood donation (233, 234).

In summary, the RA fitness formula and the HUNT fitness formula were the most appropriate available non-exercise formulas for the RA group and the control group, respectively (156, 219). A concern in terms of the variables in the formulas is that body mass index was self-reported, though this was so for all participants. The second concern was the resting heart rate. However, it was measured by research personnel for more than half of patients and all controls, and clear instructions were provided on how to measure heart for those measuring heart at home. Furthermore, several studies indicate that blood donation does not significantly change heart rate (233, 234). Thus, the accuracy of the eCRF was probably acceptable, but future studies using these non-exercise formulas should be aware of the mentioned issues.

*5.2.2.3 Independent variables*

Data for previous CVD were self-reported in HUNT and are prone to recall bias and detection bias (222). Diabetes patients are for example informed that they are at increased risk of CVD and might seek medical attention more often than healthy individuals and likewise doctors might more often suspect CVD. This could lead to a difference in how often CVD is detected compared to in the general population and thus a detection bias. Data for comorbidities were collected from hospital records for the RA patients in FysKond2. These data are quite accurate for serious illnesses that usually lead to hospitalization such as myocardial infarction but may be less accurate for diseases diagnosed by the general practitioner such as hypertension or type II diabetes. Data from medical records are less prone to recall bias but can be affected by detection bias. Information about comorbidities

was not collected for the controls in FysKond2. Blood samples, weight, height, and blood pressure were collected through standardized procedures in HUNT (203).

The DAS28-CRP measure was the last recorded value in the hospital records in FysKond2. For 19 % of the RA patients in Study II this value was more than a year old. Ideally disease activity should have been measured by the research team. This was not done because the person recruiting patients for FysKond2 did not have experience with measuring joint counts, and because we did not have a recent acute-phase reactant measurement for all patients. Moreover, the same data were collected for those performing and not performing the 6MWT, and many of the participants in FysKond2 did not come for a physical visit at the hospital. We therefore included the patient global assessment in the questionnaire so that we collected a PROM related to disease activity for all RA patients. Data for disease duration and seropositivity were collected from hospital records and had reasonably high accuracy. Physical symptoms were rated on 10-point Likert scales. Physical symptoms are subjective and best captured with PROMs.

Depression, stress, and self-efficacy are constructs that can be hard to adequately capture, which can affect construct validity. Construct validity indicates how well a measure represents the underlying conceptual construct (222). HADS-D is a validated questionnaire of depressive symptoms that performs well as a screening tool in the general population, psychiatric patients, and patients with RA (213, 214). HADS-D has acceptable internal consistency and has been associated with several other measures of depression (213). HADS-D does not involve somatic aspects of depression, which could reduce overestimation of depression due to shared symptoms between RA and depression. On the other hand, this might also lead to an underestimation of the impact of depression for some individuals. A patient may be clinically depressed without scoring high on HADS-D or score high on HADS-D without being depressed, and thus it is not an ideal questionnaire for diagnosing depression.

As discussed earlier, psychological stress is a very wide concept. The perceived stress scale was developed to assess whether an individual in the past month has felt that life has been unpredictable, uncontrollable, or overloading (215). The perceived stress scale has been used and performed well in many different populations including students, teachers, psychiatric patients, cardiac patients, and parents of chronically ill children (216). There are 3 commonly used versions of the perceived stress scale, the original version with 14 items, the version

used in this thesis with 10 items, and a short version with 4 items. The psychometric properties appear to be best for the version with 10 items, which has good internal consistency and good test-retest reliability (216). A concern is whether is it appropriate with a single summary score as some studies have found a 2-factor structure and scalability issues for the perceived stress scale (216, 235). Nonetheless, it is a very popular measure in research that has been associated with several other measures of psychological stress, depression, and anxiety, as well as with physical fitness and mortality (198, 200, 216).

The scale to measure Exercise Self-Efficacy developed by Marcus et al. has demonstrated good test-retest reliability, internal consistency, and structural validity (217, 236). This scale has previously been associated with the Stages of exercise behaviour change, and with present and future exercise behaviour (217, 237). There are some variations of this questionnaire with 5 to 7 items, and 5-points, 7-points, or 11-points Likert scales for each item. This can make the comparison of studies using this measure a bit confusing. Moreover, there are several other scales that also measure self-efficacy for exercise (238). Some of these measures such as the Self-Efficacy for Exercise Scale developed by Resnick et al. are relatively similar to the measure by Marcus et al., whereas others are specific for certain types of exercises such as the Aquatic Exercise Self-Efficacy Scale (238, 239). We cannot rule out the possibility that the relationship between Exercise Self-Efficacy and 6MWD had been somewhat different if we had chosen a different measure of self-efficacy.

The 3 psychological constructs in this thesis, depression, stress, and self-efficacy for exercise, were assessed with frequently used questionnaires with acceptable psychometric properties available in Norwegian (211-217, 236). Although there may be some concerns regarding construct validity, these questionnaires do capture aspects relevant for the research aims and are relatively easy to administer both in research setting and in clinical practice.

### 5.2.3 Missing data

The sensitivity analysis with multiple imputation in Study I showed that exclusion of the participants with missing data for adjustment variables did not bias the results. However, the complete case analysis approach led to fewer included patients in the main analysis and therefore somewhat lower power. In Study II, 7 % of the patients who performed the 6MWT were excluded due to missing data for adjustment variables. This is a small proportion of those who performed the test and is unlikely to have biased the results. Approximately a quarter of the RA patients in Study III missed data to calculate eCRF, the dependent variable

in the SEM analyses. Even though SEM could include all participants with their available data, this is a limitation of Study III.

### 5.2.4 Confounding

A confounder is a variable that is associated with both the exposure and the outcome, but is not an effect of the exposure and is not on the causal pathway between the exposure and the outcome (224, 240). We adjusted for confounders in the statistical analyses to estimate the independent associations between the independent and dependent variables. Important confounders in this thesis were age and sex. For example, sex influences both the risk of developing RA and mortality rates, is not an effect of RA, and is not on the pathway between RA and excess mortality.

Residual confounding is confounding remaining after controlling for available adjustment variables in the analyses (222). Although we adjusted for many important factors in the mortality analysis like previous CVD and smoking habits, we did not have data on education, socioeconomic status, marital status, or physical activity habits. Some of these variables were collected in the HUNT study, but were not available in our dataset. That is unfortunate as for example socioeconomic status both impacts the risk of developing RA and mortality and is a relevant confounder is this context. Even so, the HR estimates for mortality only changed slightly after gradually adjusting for more variables in Cox regression Model 1 to 3, indicating that the results were reasonably robust.

Residual confounding can also be due to low construct validity of the variables included in the analyses (222). In Study I, we adjusted for smoking as current, previous, or former smoker. This categorization may not capture all aspects of smoking that influence the association between disease status and mortality as for example smoking intensity and years of smoking could matter. There could therefore be some residual confounding due to smoking even though a smoking variable was included in the analyses. However, more detailed variables could lead to more missing data and more uncertainty as many might not recall number of cigarettes smoked per day several decades ago.

There are several factors that probably influence the association between the presence of RA and eCRF that we did not explore. We did not adjust for factors like comorbidities, education, smoking, disease activity etc. Some of these were not available in the dataset, or only available for the RA patients. We could not include disease-related variables in the analysis because that would have led to collinearity with RA status. Further, some of these factors

may act as mediators in the pathways between RA, the latent variables, and eCRF. Smoking could for example be a mediator between negative emotions and eCRF, and therefore on the causal pathway in SEM Models 2b and 3. Moreover, the SEM Models were relatively complex, and we did not have the power to add many adjustment variables.

### 5.2.5 Statistical considerations

#### *5.2.5.1 Analyses of mortality*

Age was used as the time scale in the Cox regression analyses to compare participants of the same age. Alternatively, we could have set time of diagnosis as the entry time. This was deemed inappropriate as the time of diagnosis was found from hospital records for the RA patients and were self-reported for the diabetes patients, which could have led to a systematic error. In addition, no equivalent date was available for the controls. Moreover, both RA and diabetes often have a gradual debut, and some may have the disease for a long time before they are diagnosed.

There has been a steady improvement in the general health of the population and a steady reduction of mortality rates over the past decades (241, 242). We could have added an adjustment variable for year of baseline participation to account for the changes in mortality rates in the population. A 60-year-old who participated in HUNT2 between 1995 to 1997 had a somewhat different risk of mortality than a 60-year-old who participated in HUNT3 between 2006 and 2008. As the vast majority had their baseline observation in HUNT2 (86 %), this probably did not have a major influence on our results.

The higher relative risk for mortality observed in the younger individuals with diabetes compared to controls has previously been described (243, 244). The sensitivity analyses found higher HR in the younger diabetes patients, supporting the choice to calculate separate HR for diabetes patients ≤75 years and >75 years in the main Cox regression analyses. We did not find a similar age-related change in HR among the RA patients, which could be due to low power. Widdifield et al. reported higher standardized mortality ratios in younger RA patients, whereas a recent Norwegian study did not find a substantial difference in HR for all-cause mortality by age groups (96, 245).

Traditional risk factors such as smoking, lipids, and body mass index might have somewhat different relationships with mortality in individuals with RA or diabetes than in the general population. Dyslipidaemia is common in RA patients but has a different pattern than in the general population. The concentrations of total cholesterol, low-density lipoprotein

cholesterol, and high-density lipoprotein cholesterol tend to be lower than expected in recently diagnosed RA patients. These cholesterol measures increase after initiation of treatment, and decline during flares (246). Moreover, these lipids appear to have a U-shaped association with CVD risk in RA patients, with higher risk among those with low or high lipid levels as compared to those with moderate lipid levels (246, 247). RA patients with high levels of systemic inflammation tend to have lower lipid levels despite increased risk of CVD, and this is known as the lipid paradox (246, 247). It may therefore not be appropriate to adjust for total cholesterol as a continuous variable with similar hazard assumed among all participants. Nonetheless, as the Cox regression analyses were performed in steps that gradually included more adjustment variables, this is unlikely to have had a major impact on the overall results.

There were not enough events in the RA group to perform Cox regression analysis for each of the death causes. The observation period was long, median 18 years, which is a strength. As others have found that excess mortality first emerges 10 years after the time of diagnosis, long follow-up is necessary to evaluate the impact of RA on mortality (93, 94).

*5.2.5.2 Multivariable linear regression and structural equation modelling*

For both multivariable linear regression analysis and SEM, we were investigating associations in a cross-sectional setting and cannot draw conclusions about causation. Exercise Self-Efficacy and the patient global assessment were associated with the 6MWD, but it is not certain that these factors directly affect functional capacity. Exercise Self-Efficacy is a psychological concept that has been associated with current and maintained physical activity (121, 136). Increased Exercise Self-Efficacy may lead to changed physical activity behaviour which again could improve functional capacity. This may also go the other way; whereby good functional capacity leads to increased Exercise Self-Efficacy. Similarly, several factors with a potential bidirectional relationship were included in the SEM analysis in Study III. The conceptualized models were based on a discussion of what is likely the strongest effect, but the directions of these relationships are debatable.

The latent variables are derived from observed variables that represent a common concept. The indicator variables of a latent variable should be highly correlated, which they were (data not shown). Some advantages of using latent variables are that we can get insight into constructs that are not possible to observe directly, and the overall construct might be easier to understand than each individual observed variable. Further, we reduce the influence of

measurement errors. A disadvantage is that the results are not directly comparable to studies looking only at the observed variables. For example, the latent variable physical symptoms might have a different relationship with fitness than the observed variable morning stiffness.

We calculated unstandardized and standardized coefficients for both the multivariable linear regression analysis and the SEM. This gives information both into how much the dependent variable is expected to increase per unit increase in an independent variable, and per standard deviation increase in an independent variable. The latter allows us to compare the effect sizes of the independent variables directly. This may be demonstrated by Exercise Self-Efficacy, which had an unstandardized coefficient of 3 (95 % CI 1, 4) and a standardized coefficient of 0.26. Thus, 1 unit increase in Exercise Self-Efficacy was associated with walking 3 m longer. The standardized coefficient shows that the relative effect size for Exercise Self-Efficacy was greater than for example for sex.

### 5.2.6 External validity

External validity refers to whether the results from the study sample can be generalized to other populations or other settings (222).

The participation rates in HUNT2 and HUNT3 were reasonably high for a population-based study that requires quite a bit of effort from participants in terms of questionnaires, blood samples etc, but lower in HUNT3 than in HUNT2 (54 % versus 70 %) (203). Similar reduction in acceptance rates over time has been observed in other population-based studies (248). A study of non-participants in HUNT found that they had lower socioeconomic status, higher prevalence of CVD, lower prevalence of musculoskeletal pain, and higher mortality rates compared to participants (249). Thus, there were differences in the distribution of factors associated with disease status and mortality between participants and non-participants in Study I. As the prevalence of musculoskeletal pain was higher among participants, perhaps the prevalence of RA might have been similar in participants and non-participants. Moreover, the prevalence of RA in HUNT was close to the national estimate (2, 206). If the frailest RA and diabetes patients did not participate, the absolute mortality rates presented in Study I might underestimate the true mortality rates in these patient groups and perhaps underestimate the differences in mortality between the patient groups and the controls. However, it is likely that such volunteer response bias also would extend to the control group. This means that the relative mortality calculated with Cox regression analysis probably was

not extensively biased by the differences between participants and non-participants in Study I.

The acceptance rate to participated was 61 % for FysKond2 overall and 43 % for the 6MWT. The participants in Study II were reasonably representative of patients invited to perform the 6MWT, whereas the participants in Study III were a bit younger and more often female compared to non-participants. We did not have data on non-participants for the controls in Study III.

A higher percentage of the RA patients in Study II and Study III were seropositive as compared to Study I. This could be explained by the more sensitive classification criteria that were introduced in 2010 with somewhat higher weighting on seropositivity status (18). We did not have data to evaluate disease activity or medications for the RA patients in HUNT. The RA patients in FysKond2 were fairly representative of Norwegian RA patients in terms of the percentages of patients with either low disease activity or in remission according to last documented DAS28-CRP (84 % in Study II, 76 % in Study III, and 81 % among Norwegian RA patients overall) (250). Moreover, the average modified Health Assessment Questionnaire score for all Norwegian RA patients assessed in 2021 was 0.37, which is similar to the average scores among the patients in FysKond2 (mean modified Health Assessment Questionnaire 0.41 in both Study II and Study III). Overall, the RA patients who participated in FysKond2 seem representative of Norwegian RA patients in general.

Areas of residency may influence lifestyle, physical activity, and mortality. The region that the HUNT data was collected from is relatively similar to the Norway in general and consists of both rural and coastal areas, though it has no large cities and has less diverse ethnicities than other parts of Norway (203). FysKond2 recruited patients from St. Olavs Hospital and Levanger hospital and controls from the Blood Bank at St. Olavs Hospital. St. Olavs Hospital is located in the third largest city in Norway and Levanger Hospital is located in a small city. Both these hospitals cover rural and urban areas, and we therefore included individuals living in different regional areas.

The results regarding mortality in Study I are probably generalizable to prevalent RA cases in Caucasian populations with good access to healthcare services. The RA patient in Study II and Study III were relatively representative of Norwegian RA patients, and the findings from these studies are therefore likely relevant to other RA patients in Norway. It is more uncertain whether the results from Study II and Study III can be generalized to RA patients with high

disease activity and severe physical impairments, or to patients living in other countries. Nevertheless, one might speculate that the results from Study III would be even more evident in populations with larger differences in fitness between RA patients and the general population.

## 5.3 Interpretation of findings and comparison with the literature

### 5.3.1 Mortality

*5.3.1.1 Causes of death*

The distribution of death causes among the persons with RA was consistent with the literature (96, 245, 251, 252). As expected, the 3 major causes of death were diseases of the circulatory system, neoplasms, and diseases of the respiratory system. There were too few deaths from each cause to perform Cox regression analysis for the different causes, and the CIs for each percentage estimates were too wide to detect any differences compared in the distribution of deaths among the RA patients compared to diabetes patients or controls.

Caution is warranted when comparing the percentage of deaths due to a particular cause in groups that differ substantially in sex and age distribution at baseline, and in groups that have different mortality rates. In a recent Norwegian study by Kerola et al., the RA patients had relatively similar percentage of deaths due to diseases of the circulatory system, neoplasms, and diseases of the respiratory system as the general population, but significantly higher HR for each cause due to higher overall mortality rates (245). Similarly, the diabetes patients in Study I had significantly lower percentage of deaths due to neoplasms than the controls, but not lower neoplasm-specific mortality rate per 1,000 person year. The distribution of death causes among the persons with diabetes in Study I was similar to results from a large Swedish study, which also found diabetes-related causes to be the third most common cause of death (243).

*5.3.1.2 Mortality rates*

The present thesis found significantly higher mortality rates among RA patients and diabetes patients compared to the general population, and significantly higher mortality rates in diabetes patients ≤75 years than in RA patients.

Since Study I was published, a large study comparing the impact of RA and diabetes on mortality in a longitudinal setting has been published. Løgstrup et al. conducted a nationwide Danish study compared 15,032 incident RA cases to 75,160 matched controls and to 301,246 incident diabetes cases using data from 1996 to 2017 (253). They found mortality rates

similar to the general population for the RA patients (adjusted HR 1.02, 95 % CI 0.97, 1.06), and significantly higher mortality rates among the persons with diabetes compared to controls (adjusted HR 1.59, 95 % CI 1.56, 1.63). These analyses were adjusted for sex, age, and comorbidities. Løgstrup et al. excluded individuals with previous CVD, stopped follow-up at 10 years, and based the diagnoses on registry data for diagnostic codes and prescriptions for DMARDs and anti-diabetics. They only included patients who had initiated pharmacological treatment, thus excluding diabetes patients treated with diet restrictions. These inclusion criteria may limit how generalizable the results are for example to patients with previous CVD, RA patients with disease duration longer than 10 years, or diabetics treated with diet restrictions only. One may consider CV comorbidity as part of the disease burden associated with RA, and excluding all individuals with CVD may lead to a sample not representative for all RA patients. Moreover, excluding diabetes patients not treated with anti-diabetics may exaggerate the true differences in mortality between diabetes patients, RA patients, and the general population.

The finding of no excess mortality in incident RA cases has been reported in the past as well as in a recent Norwegian study by Provan et al. which reported no excess mortality in patients diagnosed after 2003 (89, 90, 254, 255). Provan et al. conducted an inception study that divided the RA patient into 3 cohorts by year of diagnosis: 1994 to 1998, 1999 to 2003, and 2004 to 2008 with 443, 479, and 469 patients in each cohort, respectively (255). Each patient was matched to 10 controls based on age, sex, and area of residency. The 10-year mortality was significantly higher in the RA patients in the 2 earliest cohorts (HR 1.28, 95 % CI 1.04, 1.28, and HR 1.37, 95 % CI 1.08, 1.73), but not in the latest cohort (HR 1.07, 95 % CI 0.77, 1.49). The all-cause mortality rates were lower in the later cohorts compared to the earliest for both patients and controls (255). These results are promising and can be interpreted as that RA patients diagnosed in more recent years no longer have higher mortality rates. A limitation was that this study only included RA patients from a single centre which has focused consistently on preventing CVD and may not be representative for all Norwegian patients. Furthermore, not all patients in the latest cohort were followed for 10 years.

On the other hand, the recent nationwide Norwegian study by Kerola et al. found excess mortality among the patients with RA (adjusted HR 1.45, 95 % CI 1.41, 1.48) (245). This is consistent with our results and with most previous research (87, 88, 92). Kerola et al. included both prevalent and incident cases of RA (in total 36,095 RA patients), had the entire Norwegian population as controls, and used similar statistical procedures as was used in

Study I, with age as the time scale in Cox regression analysis. They also adjusted for age group, sex, education, and health regions. Their RA definition was 2 entries with RA diagnostic codes as the primary or contributing diagnosis in a specialized healthcare setting within a 2-year period.

The difference of incident versus prevalent cases likely is the main reason why the results from the inception cohorts by Løgstrup et al. and Provan et al. differ from the results in Study I. As mentioned earlier, several manifestations of RA may first emerge several years after disease onset. Further, more than 10 years of follow-up could be needed to assess the impact of RA on mortality in recently diagnosed RA patients (93, 94). A nationwide Swedish study by Holmqvist et al. that used data from 1997 to 2015 reported lower mortality rates compared to matched controls the first year after onset of RA, though significantly higher mortality rates after 10 years (94). Løgstrup et al. stopped follow-up time at 10 years and Provan et al. did not have 10 year follow-up time for all patients in the latest cohort, which in both cases might have reduced the likelihood of detecting significant differences in mortality (253, 255).

A strength of Study I was that the RA diagnoses had been verified in hospital records. The large registry-based studies by Løgstrup et al. and Kerola et al. relied on diagnostic codes (245, 253). This approach is prone to including patients with osteoarthritis or other types of inflammatory arthritis in the RA group. The specificity of the RA definition improves when DMARD prescription is also included in the definition, which Løgstrup et al. did, but the RA diagnoses in these registry-based RA studies are still less accurate than studies applying diagnoses validated in medical records. An initial RA diagnosis can sometime be changed for example to psoriasis arthritis, but the patient might still be classified as an RA patient in registry-based studies. However, an advantage of the registry-approach is the ability to include many more individuals in a single study than what was feasible for Study I.

*5.3.1.3 Possible explanations for the excess mortality*

Some of the mechanisms that have been suggested to explain the excess mortality in RA are increased risk and prevalence of CVD and other comorbidities, systemic inflammation, disease-specific factors, lifestyle factors, and poor physical fitness (66, 67, 69, 93, 181-184, 247, 256-258).

The excess risk of CVD in RA has been compared to that in diabetes in several studies published after Study I. The study by Løgstrup et al. and a Pakistani study confirmed the finding from a nationwide Danish study that RA patients have similar excess risk of

myocardial infarction as diabetes patients (72, 253, 259). Løgstrup et al. also reported that RA patients had increased risk of heart failure, stroke, cardiac death, and major adverse CV events compared to controls, though lower relative risk than what was observed in diabetes patients (253). On the other hand, a Dutch study with median follow-up time of 11 to 12 years found higher risk of CV events in individuals with longstanding RA than in individuals with type II diabetes; age- and sex-adjusted HR of 2.07 (95 % CI 1.57, 2.72) in RA patients compared to controls and 1.51 (95 % CI 1.02, 2.22) in diabetes patients compared to controls (260). This study had considerably fewer participants than the study by Løgstrup et al., and the RA patients were recruited a decade later than the diabetes patients and the controls. In sum, RA is associated with significantly elevated risk of CVD, which is a in important contributor to increased mortality rates. Even so, apart from for myocardial infarction, this excess risk does not appear to be as high as in diabetes patients (72, 86, 253, 259).

Systemic inflammation increases the risk of CVD and mortality both in patients with RA and in patients with diabetes (181, 247, 261). An international study reported that 30 % of the CV events that occurred in a sample of 5,638 RA patients were attributable to RA-specific characteristics, in particular to seropositivity and disease activity (69). Seropositivity is generally associated with more severe RA and higher mortality rates (93, 94, 181). Furthermore, high disease activity is associated with higher risk of CVD and mortality in several studies (93, 256). These patients experience a higher inflammatory burden over time and have increased levels of proinflammatory cytokines, which might lead to oxidative stress, endothelial dysfunction, atherosclerosis, hypertension, CVD, and eventually excess mortality (67).

Several studies have reported that RA patients with poor physical fitness as measured with the Health Assessment Questionnaire, the modified Health Assessment Questionnaire, grip strength, or modified 25-foot walk time, have higher mortality rates (93, 181-184, 257). More recently, the 2 fitness measures applied in the present thesis have also been shown to predict long-term outcomes among RA patients (258, 262). In the fall of 2022, Ferreira et al. reported that 6MWD less than 345 m was associated with CV hospitalization or CV death in a sample of 387 Portuguese RA patients followed for median 1.5 years (HR 2.98, 95 % CI 1.37, 6.51) (262). As far as we know, this study is the largest to date that has evaluated the relationship between an objective measure of physical fitness and long-term outcomes in RA patients.

Moreover, a study published in 2021 by our group found that low eCRF explains most of the excess mortality in RA patients (258). Liff et al. used many of the same methods as the present thesis, such as data from HUNT2 and HUNT3 linked to the Norwegian Cause of Death Registry, age as the time scale in Cox regression analysis, and eCRF calculated with the fitness formulas as the measure of physical fitness. The participants were followed until the end of 2018. The RA patients had 28 % higher mortality rates than controls in a model adjusted for body mass index, smoking, hypertension, diabetes, total cholesterol, and creatinine, of which the direct effect of RA was only 5 %, and the direct and indirect effect of low eCRF was 23 %. A strength of the study by Liff et al. is that they also included 60,938 controls from the general population and could therefore provide more insight into the explanatory role of low physical fitness for excess mortality in RA. Most research of the association between physical fitness and long-term outcomes in RA patients has not had a control group. These 2 studies add to the literature that demonstrate the relevance of physical fitness for long-term outcomes in RA patients (258, 262).

### 5.3.2 Physical fitness

#### *5.3.2.1 Physical fitness in Study II and Study III*

The RA patients were relatively physically fit in terms of 6MWD and eCRF. The median 6MWD was in the expected range, and both lower and higher results have been reported in other studies of persons with RA. For example, mean 6MWD was 391 m at the start of follow-up in an observational study of 86 Brazilian RA patients and 549 m at baseline in a study of 124 Norwegian RA patients starting a rehabilitation programme (263, 264). In the study by Ferreira et al. the median 6MWD was 375 m and a third of the participants walked less than 345 m and a third walked more than 405 m (262). Our RA patients walked considerably longer than what was reported in a large study of patients with severe heart failure who had a median 6MWD at start of follow-up of 300 m (164). This indicates that many RA patients have good functional capacity, and that RA may not be as debilitating as for example severe heart failure. However, there could also some volunteer response bias in Study II whereby those agreeing to perform the 6MWT may be more fit than RA patients overall.

The eCRF estimates were comparable to previous CRF and eCRF results from Norwegian RA patients, but substantially higher than CRF results from the UK (178-180, 185). Most previous research testing CRF in RA patients has found fitness levels below the average in the general population (178, 179, 186). However, there are also some studies reporting fitness

levels similar as in the general population (188, 265). The test method may matter, as the latter studies calculated eCRF from submaximal exercise tests. Estimating methods based on formulas from the general population might not be directly applicable for patients with chronic diseases. For example, a study of 30 women with rheumatic diseases reported that calculating eCRF from a submaximal treadmill test often overestimated physical fitness (266). By contrast, a study of 27 RA patients found that the Åstrand test, a submaximal cycle ergometer test, underestimated CRF with approximately 10 % (267). However, the eCRF results were closer to the measured CRF when alternative prediction formulas for maximal heart rate were incorporated into the calculation. Regional differences and recruitment strategy may also explain parts of the variation in fitness results in different studies.

*5.3.2.2 Differences and correlations between physical fitness measures*

The different measures of physical fitness capture distinct though partly overlapping components of fitness. The 6MWD is related to overall functional capacity which is relevant for daily functioning. There may be a ceiling effect in the 6MWD, whereby patients who are rather fit do not necessarily walk longer during the test with further improvements in fitness. Because of this, the 6MWT probably perform best in patients with low physical fitness. A cardiopulmonary exercise test relies on the motivation of the individual to exert maximal effort, but the close monitoring of oxygen uptake and heart rate allows the test personnel to assess whether the individual reaches $VO_{2max}$. eCRF calculated with non-exercise formulas is less accurate than CRF, but easier to implement in clinical practice. A ceiling effect is less problematic for CRF and eCRF than for the 6MWD. Another measure that is sometimes referred to as a measure of functional capacity is the modified Health Assessment Questionnaire (210). There is a floor effect for the modified Health Assessment Questionnaire, as individuals with high function do not improve their scores substantially with improvements in physical fitness and many will score the lowest score of 0.00. Ceiling and floor effects could contribute to why some variables show different relationships with different measures of physical fitness.

Among the RA patients in Study II, eCRF and 6MWD were more closely correlated with each other than with the modified Health Assessment Questionnaire. This indicates that these 2 physical fitness measures capture aspects of physical fitness not captured by the modified Health Assessment Questionnaire. This is not a surprising finding given that the modified Health Assessment Questionnaire focuses on activities of daily living that healthy individuals usually do not have any difficulties performing. Activities like getting out of bed or picking

something up from the ground are probably first perceived as difficult when function is quite impaired.

The strength of the correlation between eCRF and 6MWD was somewhat lower than what has been reported between CRF measured with a cardiopulmonary exercise test and 6MWD in healthy adults ($R^2$=0.55), though within the wide range reported in patients with heart failure ($R^2$=0.20 to 0.71) (150, 152). Of note, the reported correlations between CRF and 6MWD have varied greatly. This may be related to differences between the tests and the variation in effort from the participants.

The correlation between the modified Health Assessment Questionnaire and the 6MWT among the patients in Study II was lower compared to the correlation previously reported between the Health Assessment Questionnaire and the 6MWT in RA patients from Brazil (r=-0.29, p=0.01 versus r=-0.50, p<0.001) (263). This may be due to the different properties of the Health Assessment Questionnaire and the modified Health Assessment Questionnaire, as well differences in patient characteristics (268).

*5.3.2.3 Patient-reported outcome measures and physical fitness*

Exercise Self-Efficacy was significantly associated with functional capacity as measured with the 6MWT. Self-efficacy has been associated with measures of physical fitness or physical activity in other studies as well. In patients undergoing elective surgery for abdominal aortic aneurism, self-efficacy for physical activity before the surgery was associated with postoperative 6MWD (269). In RA patients, self-efficacy for exercise has been associated with current physical activity habits, trajectory of physical activity over time, and sedentary behaviour (121, 136, 270, 271). Further, self-efficacy for managing the disease measured with the Arthritis Self-Efficacy Scale has been associated with eCRF calculated from a submaximal exercise test (188). Self-efficacy for exercise represents a potential intervention area that one can target to improve physical activity and exercise habits (139, 141).

According to Self-Efficacy Theory, the 4 sources of self-efficacy can all be addressed to improve the confidence that one can perform a specific task (138). Mastery of experience can be achieved by gaining positive experience with physical activity and exercise, for example by joining an exercise programme and experiencing success. Vicarious experience could be achieved by exercising with peers and seeing patients with similar abilities successfully engage in regular exercise. Verbal persuasion can involve encouragement from healthcare professionals, identification of barriers and facilitators, and motivational interviewing

techniques (140, 141). Education on the body's response to exercise and how to adjust exercises may help the patient interpret physiological feedback. Other behavioural change techniques that may improve self-efficacy are goal setting, problem solving, self-monitoring, feedback on performance, clear instructions, action planning, and reviewing goals (272).

The patient global assessment had an inverse association with the 6MWD. Likewise, previous research has demonstrated an inverse association between the patient global assessment and both CRF and physical activity among RA patients (179, 273). The patient global assessment is part of patient follow-up to incorporate the patient perspective. The patients are asked to rate their overall disease activity and may focus on aspects of their disease that they consider important, such as pain, fatigue, disability, or psychological aspects (24). The association between the patient global assessment and physical fitness may be related to RA symptoms, disability, habitual physical activity, and motivation. For example, disability can influence the patient global assessment and lead to shorter 6MWD (24, 263, 274). Another example could be mental health, which influences habitual physical activity behaviour and possibly also the motivation to walk far during the 6MWT (190, 191, 273). Poor mental health may also influence the patient global assessment especially in patients with well-controlled disease, like most of the patients in Study II (24, 274).

Depressive symptoms and perceived stress were not associated with the 6MWD. However, the latent variable negative emotions based on these 2 observed variables was associated with eCRF and acted as a mediator between RA status and eCRF. The physical fitness measures 6MWD and eCRF could have distinct relationships with mental health. Another explanation is how the analyses were performed. SEM Models 2b and 3 combined depressive symptoms and stress, involved more participants, and had no other psychological variables in the model as compared to the Multivariable linear regression Model 2. Depressive symptoms and stress might influence the motivation to walk as far as possible during the 6MWT, though perhaps this influence instead was captured by Exercise Self-Efficacy or the patient global assessment that also were included in Multivariable linear regression Model 2. As there were no physical test needed to calculate eCRF, psychological factors like depressive symptoms and stress could not directly impact the participants' performance during a test. Instead, perhaps the psychological factors influenced the eCRF measure indirectly through changes in physical activity levels and higher rating of the patient global assessment, which were variables in the non-exercise formulas.

Ferreira et al. reported that depressive symptoms measured with HADS-D were associated with the 6MWD in RA patients in unadjusted analyses, but not in multivariable analyses that also included age tertile, waist circumference, anemia etc. (262). This contrasts to findings in heart failure patients, though these heart failure patients had higher scores for HADS-D and considerably shorter 6MWD compared to our patients (mean 6MWD 222 m) (275). Perhaps the association between depression and 6MWD only is apparent in individuals with functional impairments and high levels of depressive symptoms. A systematic review reported that the severity of depressive symptoms had a modest unadjusted correlation (summary correlation coefficient -0.16, 95 % CI -0.21, -10) with CRF measured with a cardiopulmonary exercise test among healthy and depressed adults (197).

When it comes to the relationship between stress and physical fitness, the research in patients with RA is scarce and we will therefore focus on results from other patient groups and from the general population. A study in patients with pulmonary arterial hypertension reported that psychological stress was not correlated with the 6MWD (276). On the other hand, perceived stress has been associated with lower self-reported fitness in a large Danish study of the general population and with lower CRF in patients with type II diabetes (198, 277). A study of 44 healthy sedentary individuals found that individuals with high levels of mental stress had very low or no increase in $VO_{2peak}$ and maximal power after a 2-week exercise intervention programme, in contrast to the participants with low levels of stress (194). Although this was a small study with a short intervention period, this could indicate that stress is important for the response to exercise or for the commitment to an intervention. Similarly, a study of 135 undergraduate students reported that stress from negative life events was associated with smaller improvement in strength after a 12-week resistance programme (193). Different measures of stress and physical fitness, different settings, and different patient groups might explain why some studies have found a significant association between stress and fitness and others have not.

Depressive symptoms and stress appear to have a bidirectional association with physical activity and perhaps these psychological variables also have a bidirectional association with CRF (190-192, 196-198, 278). Improving mental health is important for overall wellbeing, adherence to treatment, long-term health, disease control etc. (40). Perhaps improvements in mental health can make changes in physical activity habits easier to achieve. On the other hand, lifestyle changes like increasing physical activity levels have positive effects on mental health, and a holistic approach targeting several aspects of living is probably most efficient in

order to improve mental health, fitness, and well-being (100, 278, 279). Mental health should be assessed regularly in patients with inflammatory arthritis, and cases of depression should be recognized and treated (59). Other strategies that can help to reduce stress and improve mood are sleep hygiene, balanced diet, maintaining social connections, avoiding risky substance abuse, spending time in the nature, and mind-body practices (279).

The latent variable physical symptoms, based on the observed variables joint pain in the past 6 months, morning stiffness, and pain in neck, back and hips, was associated with eCRF and acted as a mediator between RA status and eCRF. Stiffness has been associated with physical activity in a study of 30 RA patients, whereas the evidence of an association between pain and physical activity in individuals with RA is inconsistent (120, 130, 135, 280). Still, RA patients report symptoms of RA such as pain, fatigue, and stiffness as barriers to physical activity, and inactive patients might lack the confidence to be active despite their pain (133, 136, 281). A Danish study reported that among patients who met the ACSM/AHA aerobic physical activity recommendations in 2010, pain was associated with not meeting the recommendations at follow-up in 2017 (282). Pain has also been inversely associated with physical fitness in patients with fibromyalgia (283). Perhaps pain and stiffness influence exercise intensity more than the total amount of exercise per week (186). In Study III, a higher percentage of the RA patients than the controls reported to take it easy when engaging in physical activity (33 % versus 19 %, Table 11). Low intensity physical activity is better than no physical activity, but it leads to smaller improvements in CRF compared to high intensity physical activity (102, 169, 284).

Adequate pain management is an important part of patient management and could make it easier for inactive patients to start engaging in physical activity. Moreover, as exercise can lead to a reduction in pain it is an important part of self-management of RA (59, 115). Pain can be a challenging symptom that often persists even when the patient is in clinical remission. There are several strategies to manage pain, such as patient education, weight management, orthotics, pain medication, and psychological intervention (285). However, physical activity and exercise are something the patient can do themselves and should be encouraged by health professionals.

*5.3.2.4 Other correlates of physical fitness*

Older age and less favourable body composition were associated with shorter 6MWD in Study II whereas sex was not, which is consistent with results from the study by Ferreira et

al. (262). Sex, age, and body mass index were part of the eCRF formulas. Therefore, sex and age were only included as adjustment variables in Study III and the association between each of these variables and the eCRF cannot be directly interpreted.

None of the objective or composite disease measures were associated with the 6MWD in the Multivariable linear regression analyses. A Brazilian study reported that DAS28 had a significant association with 6MWD (Spearman's correlation coefficient -0.29, p=0.006), and Ferreira et al. reported that a significantly higher proportion of the RA patients walking <345 m had moderate to high disease activity compared to those walking ≥345 m (262, 263). But like in Study II, disease activity was no longer associated with 6MWD in the study by Ferreira et al. when variables like age tertile and a measure of body composition were included in multivariable analysis (262). Some studies have reported an association between CRF or eCRF and disease activity, whereas most studies have not (178, 179, 286). Ångstrøm et al. for example found a significant negative association between DAS28 and eCRF estimated from a submaximal cycle ergometer test, but this association was no longer significant when the analysis was adjusted for age and sex (286).

Ferreira et al. also found that CRP ≥3 mg/dl, NT-pro BNP >125 pg/mL, anaemia, and troponin T ≥14 pg/mL were associated with shorter 6MWD in RA patients (262). This is interesting, as it shows that functional capacity captured with the 6MWT reflects overall health. NT-pro BNP and troponin T are biomarkers associated with cardiac dysfunction and myocardial injury, whereas CRP and anaemia may represent an inflammatory response. Moreover, the 6MWD has been associated with CRP and NT-pro BNP in patients with systemic sclerosis, and with NT-pro BNP, troponin T, and haemoglobin in patients with heart failure (164, 287). CRP has also been associated with CRF in British RA patients (178). Likewise, Ångstrøm et al. reported that CRP and ESR were associated with eCRF in unadjusted analysis, and that the association between ESR and eCRF also was significant after adjusting for age and sex (286).

## 5.4 Clinical relevance and future perspectives

The individuals with RA in Study I had higher mortality rates than the general population, which is in line with most, but not all, previous reports (88, 91-94, 245, 253-255). Improved medical treatment of RA has led to many benefits for the patients, like better disease control, lower inflammatory burden, less joint damage, and less comorbidities (28, 67). However, medications alone can only do so much. Lifestyle, including physical activity habits, is crucial in the management of the disease (59, 126). As RA patients have lower fitness levels

compared to their healthy counterparts, physical activity and fitness are important targets (179, 185, 186). Exercise and physical activity can improve physical fitness, and improved fitness would likely reduce the excess mortality in RA patients (110, 112, 115, 258).

We have demonstrated that Exercise Self-Efficacy and the patient global assessment are associated with the 6MWD in RA patients. We have also demonstrated that physical symptoms and negative emotions explain some of their reduced eCRF. These PROMs could represent potential areas to assess and target in intervention programmes or in clinical practice. The RA fitness formula, the 6MWT, measures of self-efficacy for exercise, and screening tools for mental health status may be useful to identify patients who need additional attention. Patients with low eCRF or low 6MWD would benefit from increasing their physical activity levels. Moreover, individuals with low self-efficacy for exercise may need extra guidance, reassurance, and follow-up sessions to be able to adopt a more active lifestyle (141). Finally, improved mental health and symptom management might make it easier for patients to engage in physical activity.

In a clinical setting, clinicians should discuss physical activity habits with their patients and regularly assess physical fitness. It is also important to recognize and treat clinical cases of depression, and to discuss the symptoms of RA with the patients (59). Based on the individual patient and the factors important to him or her, interventions can be individualized. Clinicians can incorporate behavioural change techniques such goal setting, action planning, barrier identification, and problem-solving in their practice as means that may improve self-efficacy and support behavioural change (139-141, 272). Given the time constraints in clinical practice, it is important that health care professionals are aware of the available resources in the area - both in healthcare settings and outside. One can for example refer the patient to intervention programmes, physiotherapists, psychologists, exercise physiologists, or activity programmes led by public agencies or by patient organizations. Measures of physical fitness, together with the PROMs described in the present thesis, could be helpful when deciding whether to refer a patient to for example a physiotherapist.

Mortality among RA patients will continue to be an important research field in the coming years, requiring large studies of incident or prevalent RA cases with follow-up time for longer than 10 to 15 years. The relationship between physical fitness and mortality in RA patients should be further investigated, ideally with objective measures of CRF. Further research into factors explaining reduced physical fitness in RA patients is warranted, both in

cross-sectional and longitudinal studies. Some relevant factors to include in such research are rheumatoid cachexia, lung function, and physical activity habits. The association of physical symptoms and negative emotions with physical fitness should be investigated in other populations and in longitudinal settings. The present thesis identified several factors associated with physical fitness in individuals with RA. These factors may be useful to assess and perhaps target in exercise interventions, though this should be further evaluated in clinical exercise trials.

# 6 CONCLUSIONS

This thesis confirmed our main hypothesis that RA patients had higher mortality rates and lower eCRF than controls, and we identified several PROMs associated with physical fitness in RA patients.

**Conclusion 1:** The mortality rates among persons with RA and/or diabetes were significantly higher than in the general population. The excess mortality in RA patients was comparable to in diabetes patients >75 years, but significantly lower than in diabetes patients ≤75 years

**Conclusion 2:** The CIs for the percentage estimates for the 3 main causes of deaths including diseases from the circulatory system among RA patients were overlapping with the estimates for diabetes patients and the general population, hence the distribution for causes of deaths were not significantly different

**Conclusion 3:** Exercise Self-Efficacy and the patient global assessment were significantly associated with functional capacity measured with the 6MWT in RA patients, whereas other RA disease measures were not

**Conclusion 4:** The physical fitness measures eCRF and 6MWD showed a statistically significant positive association in persons with RA

**Conclusion 5:** The RA patients had lower age- and sex-adjusted mean eCRF compared to healthy controls. Most of the association between the presence of RA and reduced eCRF was explained by physical symptoms and negative emotions

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# STUDY I

SCIENTIFIC REPORTS
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# Mortality is increased in patients with rheumatoid arthritis or diabetes compared to the general population – the Nord-Trøndelag Health Study

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**Persons with rheumatoid arthritis (RA) or diabetes have increased risk of cardiovascular disease (CVD) and higher death rates compared to the general population. This study used data from the population-based Nord-Trøndelag Health Study (HUNT) and the Norwegian Cause of Death registry to compare all-cause mortality rates for RA or diabetes patients to the general population. We used Cox regression with age as time variable, adjusting for sex, smoking, body mass index, hypertension, total cholesterol, creatinine and previous CVD. To achieve proportional hazards, an interaction term with an age group variable (≤75 years or >75 years) was included for diabetes, smoking and previous CVD. Median follow-up was 18.1 years. Mortality occurred for 123 (32%) of the RA patients, 1,280 (44%) of the diabetes patients, 17 (52%) of the patients with both diseases and 11,641 (18%) of the controls. Both diseases were associated with statistically significantly increased mortality rates. The hazard ratio (HR) for RA was 1.24 (95% CI: 1.03-1.44). The HR of diabetes was 1.82 (1.60-2.04) for individuals ≤75 years old and 1.49 (1.39-1.59) for individuals >75 years. Diabetes had a significantly higher HR for death than RA for participants ≤75 years, but not significantly different for participants >75 years.**

Rheumatoid arthritis (RA) is a systemic inflammatory disease causing inflammation in the synovia. It may lead to joint destruction and extra-articular manifestations such as pericarditis, vasculitis, osteoporosis, rheumatoid nodules and Sjögren's syndrome[1]. RA patients have increased risk of cardiovascular events, as well as have higher cardiovascular, respiratory, and all-cause mortality rates compared to the general population[2–10].

The risk of cardiovascular disease (CVD) associated with RA has been compared to that of diabetes, a well-known risk factor for CVD and premature death[11–13]. Recent evidence indicates that patients with either disease have increased risk of CVD compared to the general population, however, RA was associated with a lower increase in risk than diabetes[14]. This somewhat contradicts earlier studies indicating comparable risk in the two groups, and might be explained by changes in treatment of RA and differences in study populations[3,15,16].

In the past decades, the general population in the developed world has become healthier and lives longer[17–19]. This trend also seems to apply to patients with diabetes[20]. However, for RA patients the results over time are more conflicting, from widening mortality gap to better survival than the general population[2,4,5,7,21–28]. These contradictory findings might be explained by differences in genetics, demographics and health as well as differences in inclusion of incident or prevalent cases, in RA definition, and in follow-up time. However, most evidence based on large numbers of patients and long observation periods points towards lower absolute mortality rates among RA patients in recent years, though still higher than in the general population[4,5,7,24–26].

All-cause mortality among RA patients has been compared to that of diabetes patients in a perioperative setting[29]. However, to our knowledge it has not been compared in a longitudinal study in a general

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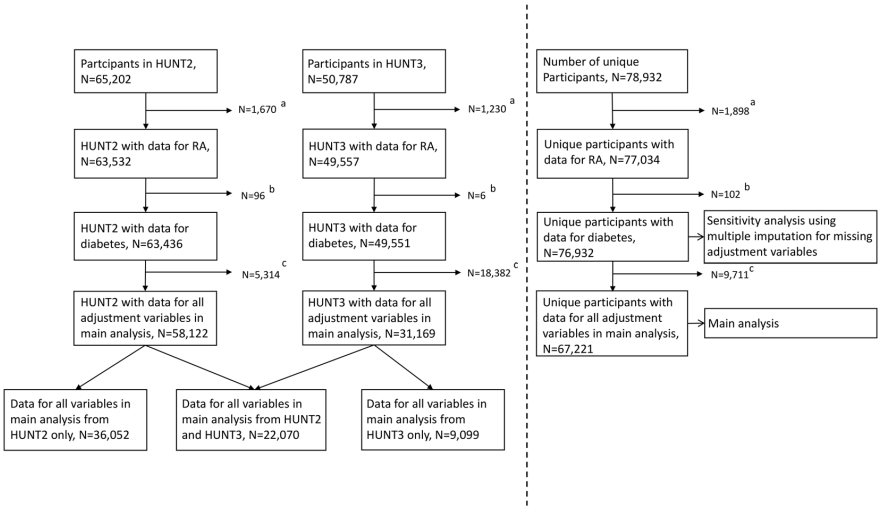


**Figure 1.** Participant inclusions and exclusions. Abbreviations: HUNT2 – second survey of Nord-Trøndelag Health Study, HUNT3 – third survey of Nord-Trøndelag Health Study, RA – rheumatoid arthritis. [a]Exclusions due to uncertainty regarding RA status, or presence of psoriasis arthritis, juvenile inflammatory arthritis, ankylosing arthritis or other forms of inflammatory arthritis. [b]Exclusions due to missing data to evaluate diabetes status. [c]Exclusions due to missing data regarding smoking, hypertension, previous cardiovascular disease, creatinine concentration, total cholesterol concentration or body mass index.

population, which would extend the implications of the findings. Awareness about the increased mortality risk associated with diabetes is high, whereas the increased risk associated with RA is less commonly considered by non-rheumatologists. Direct comparison would likely be of interest to patients and clinicians. Data from the longitudinal Nord-Trøndelag Health Study (HUNT) linked to the Norwegian Cause of Death Registry are ideal for such a comparison with detailed participant information and long follow-up time[30,31].

The hypothesis was that RA is a risk factor for increased mortality rates not significantly different in magnitude from diabetes, and that the percentage of deaths caused by CVD were increased in both patient groups. The primary aim of the study was to compare all-cause mortality rates in patients with RA and patients with diabetes to that of the general population. The secondary aim was to evaluate whether the causes of death differed among the groups.

## Materials and Methods

All methods were carried out in accordance with relevant guidelines and regulations.

**Participants and variable definitions.** This study utilized data from HUNT, a longitudinal population-based health study that invited all inhabitants of the Norwegian region Nord-Trøndelag aged ≥20 years to participate[30]. HUNT was designed to investigate the epidemiology of common diseases and quality of life in the general population with the first survey in 1984–1986. New surveys have been conducted with 11-year intervals, also including new individuals as they became adults. The present study included data from the second and third survey; HUNT2 and HUNT3. HUNT2 (1995–1997) had 65,202 participants (69.5% of those invited) and HUNT3 (2006–2008) had 50,787 participants (54.1% of those invited). Out of these, 37,056 individuals participated in both HUNT2 and HUNT3. Figure 1 shows inclusions and exclusions to the present study.

HUNT collected data from questionnaires, non-fasting blood sample and physical examination, as previously described[30]. Subjects were classified as having RA and/or having diabetes, or being controls. There are many false-positive RA diagnoses in self-reported surveys. Therefore, we applied validated RA diagnoses from a previous study[32]. In that study, hospital case notes of participants self-reporting to have RA in HUNT were reviewed and RA status, time of diagnosis, and status for immunoglobulin M rheumatoid factor and anti-citrullinated protein antibody (ACPA) were recorded. RA was defined according to American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria[33], documented in hospital case notes before the person participated in HUNT. With insufficient information to evaluate ACR/EULAR 2010 criteria, a previous diagnosis based on the ACR 1987 revised criteria qualified[34]. Seropositivity was defined as a positive test for rheumatoid factor or ACPA. We excluded participants with missing data to evaluate RA status, uncertainty whether the diagnosis was given after participation in HUNT, and patients with juvenile inflammatory arthritis, psoriasis arthritis, ankylosing spondylitis, or other forms of inflammatory arthritis (Fig. 1).

Diabetes was defined as self-reported diabetes, use of anti-diabetic medication, or having a non-fasting blood glucose level >11.1 mmol/L. Validation in HUNT1 found self-reported diabetes to be highly reliable compared

to the patients' hospital case notes, with a positive predictive value of 96.1% and a negative predictive value of 99.7%[35]. In the present study, we further increased the sensitivity of the definition as participants with high non-fasting blood sugar level or reporting to use anti-diabetics also were classified as having diabetes. Those fulfilling these criteria in HUNT2, and not in HUNT3, were assumed to still have diabetes in HUNT3 (N = 6). We excluded participants who lacked information to evaluate diabetes status. The remaining participants, who did not fulfil the criteria for RA or diabetes, served as controls.

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or being on blood pressure-lowering medication. Smoking habits were classified as never, former or current smoker. Previous CVD was defined as self-reported angina, stroke, or myocardial infarction. Body mass index (BMI) was categorized into 5 groups: <18.5 kg/m², 18–24.9 kg/m², 25–29.9 kg/m², 30–34.9 kg/m² and ≥35 kg/m².

The baseline of each participant was their first participation in HUNT2 or HUNT3. For those who participated in both surveys, the first observation with complete data on the variables included in the main analysis was considered the baseline observation. Hence, for those participating in both HUNT2 and HUNT3, HUNT3 was defined as baseline if there were missing data in HUNT2 and not in HUNT3 (N = 1,371). If a participant did not have any observations in HUNT with complete data for the variables included in the main analysis their baseline was set to the first time they participated.

Most baseline adjustment variables had <4% missing data, with some exceptions. Data on smoking was missing for 3,176 (8%) and 1,970 (13%) with HUNT2 and HUNT3 as baseline, respectively. Blood pressure measurement data were missing for 1,900 (13%) with baseline in HUNT3. Data for creatinine were lacking for 3,776 (27%) with baseline in HUNT3. We excluded participants with incomplete information for at least one observation on all adjustment variables used in the final model (Fig. 1).

The data from HUNT were linked with the Norwegian Cause of Death Registry[31]. The registry includes information regarding all deaths in Norway and death of Norwegian citizens abroad. The International Classification of Diseases revision 10 (ICD-10 or converted from ICD-9) codes listed as the underlying cause of death were used to evaluate causes of deaths. Among the participants who died, 110 (0.9%) lacked an ICD code (diabetes patients: n = 9, controls: n = 101). Participants were followed up from their baseline observation in HUNT until death or end of observation on 31.12.2014, whichever came first.

**Statistical analysis.** Data are given as medians with 25$^{th}$ and 75$^{th}$ percentiles, means with standard deviation, or numbers with percentage. Statistical analyses were performed using Stata (v. 15.1, StataCorp, College Station, TX, USA). P-values $< 0.05$ were considered statistically significant.

RA and diabetes were coded as yes/no variables; thus, those with both diseases were not coded as a separate group due to low number (N = 33). Kaplan-Meier survival curves were made to visualize survival in the groups. The few participants with both diseases were excluded from the plot.

Survival was evaluated using Cox proportional hazard regression modelling. Age was used as the time variable, with entry date at the baseline observation. This design ensured that participants were compared to other participants of the same age in all models. The alternative approach using time of diagnosis as the start of observation period was considered inappropriate. Firstly, there was no equivalent date for the controls. Secondly, age at time of diagnosis was self-reported for diabetes patients and collected from medical records in RA patients. This leads to a potential recall bias for the diabetes patients and a systematic error due to different data collection methods.

The proportional hazards (PH) assumption was assessed with Schoenfeld residuals, Cox-Snell residuals and log-minus-log plots. In order to meet the assumption, we included an interaction term between variables not initially fulfilling the assumptions and an age group variable; ≤75 years and >75 years. Participants turning 75 years in the observation period belonged to the first age group until they turned 75, and then changed to the second age group. The models were compared using log likelihood, Akaike information criteria and Bayesian information criteria. For subjects participating twice, data were updated at their second participation. The disease effects of RA and diabetes were compared by evaluating confidence intervals (CI) of the hazard ratios (HR).

Cox regression modelling was performed in three steps. Age was the time variable and thereby adjusted for in all models. On Step 1, the crude effects of RA and diabetes were investigated, with adjustment for sex. On Step 2, further adjustment for variables important for mortality was performed, i.e. hypertension, smoking, BMI, creatinine, total cholesterol. Cause-specific mortality rates attributed to CVD are elevated in RA and diabetes patients, compared to in the general population[2,6,7,12]. On Step 3, the analysis was therefore further adjusted for previous CVD. The main models included an interaction term between diabetes and the age group variable to meet the PH assumption, resulting in separate HR for diabetes patients ≤75 years and >75 years. Similarly, an interaction term with age group for smoking and previous CVD were also included. To avoid loss of statistical power to fewer deaths and because the PH assumption was not violated for RA, an interaction with age groups was not included for RA. In Sensitivity analysis 1, the analyses were repeated including the interaction term with age groups both for RA and diabetes.

In Sensitivity analysis 2, the Cox models were run following stratification by birth year into 10-year intervals instead of including the interaction term with age ≤75 years or >75 years. This approach provides the average HR over all age strata for RA and diabetes compared to controls, while permitting the baseline hazard to vary among strata. In Sensitivity analysis 3, the Step 1 models were run separately for diabetes and controls in each 10-year stratum. Similar analysis could not be run for RA due to fewer deaths.

Missing data may introduce bias in analyses only including complete cases. Sensitivity analysis 4 was performed to investigate the robustness of the result, using multiple imputation of missing data in adjustment variables. Multiple imputation (n = 50 datasets) was performed using chained equations assuming missing at random.

In the main analysis HR were calculated for each disease variable. Participants with both diseases contributed to the HR both for RA and diabetes, because the number with both diseases was considered too low to group them separately. To investigate whether this group influenced the result of the main models, Sensitivity analysis 5

| | RA N = 387 | Diabetes N = 2,898 | RA + Diabetes N = 33 | Controls N = 63,903 |
|---|---|---|---|---|
| Sex | | | | |
| Female | 261 (67) | 1,369 (47) | 20 (61) | 33,781 (53) |
| Male | 126 (33) | 1,529 (53) | 13 (39) | 30,122 (47) |
| Age (years) | 58 (49, 68) | 63 (51, 73) | 66 (59, 73) | 46 (34, 60) |
| Smoking status | | | | |
| Never smoker | 132 (34) | 1,263 (44) | 17 (52) | 29,426 (46) |
| Former smoker | 129 (33) | 682 (23) | 4 (12) | 19,010 (30) |
| Current smoker | 126 (33) | 953 (33) | 12 (36) | 15,467 (24) |
| Previous CVD[d] | 41 (11) | 594 (20) | 7 (21) | 4,094 (6) |
| Body mass index (kg/m$^2$) | 26.0 (23.7, 29.1) | 28.7 (25.9, 32.0) | 27.8 (24.4, 30.9) | 25.7 (23.4, 28.4) |
| Hypertension[e] | 199 (51) | 2,098 (72) | 26 (79) | 25,333 (40) |
| Waist/hip ratio | 0.84 (0.79, 0.90) | 0.90 (0.84, 0.95) | 0.88 (0.83, 0.93) | 0.85 (0.79, 0.90) |
| Non-fasting glucose (mmol/L) | 5.2 (4.8, 5.9) | 7.5 (5.8, 11.2) | 6.7 (5.6, 8.1) | 5.1 (4.7, 5.6) |
| Creatinine (µmol/L) | 84 (77, 92) | 89 (80, 99) | 89 (80, 98) | 85 (77, 94) |
| Triglycerides (mmol/L) | 1.4 (1.0, 2.0) | 2.1 (1.4, 3.0) | 1.5 (1.2, 2.2) | 1.4 (1.0, 2.1) |
| Total cholesterol (mmol/L) | 6.0 (5.3, 6.8) | 6.0 (5.1, 6.9) | 5.8 (5.0, 6.8) | 5.7 (4.9, 6.5) |
| HDL cholesterol (mmol/L) | 1.4 (1.1, 1.7) | 1.2 (1.0,1.4) | 1.4 (1.1, 1.7) | 1.3 (1.1, 1.6) |
| Total cholesterol/HDL cholesterol ratio | 4.3 (3.5, 5.5) | 5.1 (4.0, 6.5) | 4.3 (3.6, 5.4) | 4.2 (3.4, 5.3) |
| Observation time (years) | 18.1 (12.6, 18.8) | 17.1 (7.6, 18.6) | 16.8 (8.9, 18.2) | 18.1 (12.7, 18.8) |

**Table 1.** Baseline characteristics – cases with complete data[a,b,c]. [a]Number (%) or median (25$^{th}$ and 75$^{th}$ percentile) unless specified otherwise. [b]Abbreviations: RA - rheumatoid arthritis, CVD - cardiovascular disease, HDL - high-density lipoprotein. [c]Missing data: <4% missing for all variables. [d]Previous cardiovascular disease: self-reported angina, stroke, or myocardial infarction. [e]Hypertension: Systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥ 90 mmHg, or on blood pressure-lowering medication.

was a Step 3 model excluding participants with both diagnoses. The importance of missing data for diabetes medication or report of no diabetes treatment was investigated in Sensitivity analysis 6, adding a categorical variable indicating treatment/no treatment/missing information on medication to a Step 1 model.

The causes of death were evaluated by comparing the CI of the percentage estimates, which were calculated based on the Poisson distribution.

**Ethics.** Participants of HUNT gave written informed consent. Approval for the study was obtained from the Regional Committee on Medical Research Ethics, Central Norway (project 2009/661), the Norwegian Data Safety Authorities and the Norwegian Department of Health.

## Results

**Study population.** In total 67,221 participants had complete data for at least one time point, i.e. either HUNT2 or HUNT3 (Fig. 1). There were 420 RA patients, 2,931 diabetes patients and 63,903 controls. Among the patients 33 individuals had both RA and diabetes. Baseline participant characteristics are given in Table 1 and disease-specific characteristics are given in Table 2.

Participants with diabetes were slightly older than those with RA, and as a group controls were younger than diabetes and RA patients. There were more females in the RA group, and more RA patients were ever smokers. Diabetes patients more often had hypertension, had higher median BMI, waist/hip ratio, total cholesterol/HDL-cholesterol ratio, concentration of creatinine, glucose and triglycerides, and lower concentrations of HDL cholesterol. RA and diabetes patients had higher prevalences of previous CVD compared to controls, highest among diabetics. Baseline and disease-specific characteristics of participants in the first sensitivity analysis are presented in Supplementary Table S1.

**Mortality.** Throughout the follow-up period, 123 participants (32%) with RA, 1,280 participants (44%) with diabetes, 17 participants (52%) with RA and diabetes and 11,641 controls (18%) died. Total observation time was 1,034,596 person years; 5,999 person years in the RA group, 38,760 person years in the diabetes group, 445 person years in the RA and diabetes group, and 989,392 person years in the control group.

RA and diabetes were significantly associated with increased mortality compared to controls, and the association remained significant after adjustment for other variables. Figure 2a gives the results from the main Cox regression analysis calculating separate HR for the diabetes patients ≤75 and >75 years of age. The HR for death in patients with diabetes was higher for participants ≤75 years of age than for those >75 years of age. The HR estimates for diabetes patients in both these age groups were higher than for RA patients. However, the difference was only significantly different for the diabetes patients >75 years because the CI for the diabetes patients ≤75 years were overlapping with those of the RA patients.

| | RA N = 387 | Diabetes N = 2,898 | RA + Diabetes N = 33 |
|---|---|---|---|
| **RA-specific baseline variables** | | | |
| Seropositive[d] | 277 (72) | | 24 (73) |
| Age when diagnosed (years) | 55 (45, 64) | | 60 (53, 70) |
| RA duration before first HUNT participation with diagnosis (years) | 6 (3, 9) | | 7 (5, 10) |
| **Diabetes-specific baseline variables** | | | |
| Peroral diabetes medication | | 1,091 (38) | 11 (33) |
| Insulin | | 597 (21) | 10 (30) |
| Age when diagnosed (years) | | 59 (48, 67) | 64 (49, 69) |
| Diabetes duration before first HUNT participation with diagnosis (years) | | 5(2, 11) | 6 (4, 16) |

**Table 2.** Disease-specific baseline variables[a,b,c]. [a]Number (%) or median (25th and 75th percentile) unless specified otherwise. [b]Abbreviations: RA - rheumatoid arthritis, HUNT – Nord-Trøndelag Health Study. [c]Missing data: <4% missing for all variables except the diabetes-specific variables: peroral diabetes medication use missing for 755 (26%), insulin use missing for 761 (26%), duration of diabetes and age of diabetes onset missing for 192 (7%). [d]Seropositive: positive for rheumatoid factor and/or anti-citrullinated protein antibody.

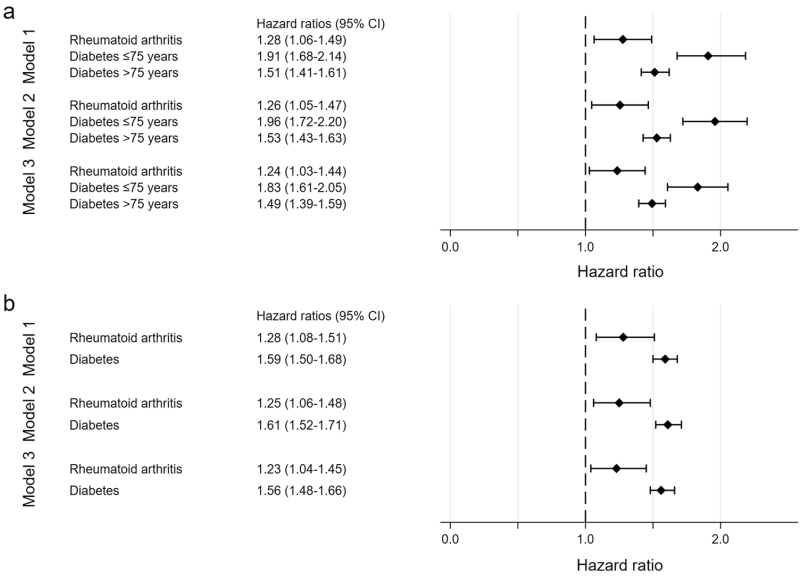


**Figure 2.** Cox regression models for mortality in rheumatoid arthritis and diabetes. Panel a: Main models. Panel b: Sensitivity analysis 2 – stratified by birth year intervals. Age was used as time axis in all models and is thereby adjusted for in all models. Model 1: Adjusted for sex. Model 2: Adjusted for sex, hypertension[1], smoking[2], BMI[3], creatinine, total cholesterol. Model 3: Adjusted for sex, hypertension[1], smoking[2], BMI[3], creatinine, total cholesterol, previous cardiovascular disease[4]. Abbreviations: 95% CI – 95% confidence interval, BMI – body mass index. [1]Hypertension: systolic blood pressure $\geq$ 140, diastolic blood pressure $\geq$ 90, or on blood pressure-lowering medication. [2]Smoking: never smoker, former smoker or current smoker. [3]BMI: categorised as $<18.5\,kg/m^2$, 18–24.9 $kg/m^2$, 25–29.9 $kg/m^2$, 30–34.9 $kg/m^2$ and $\geq 35\,kg/m^2$. [4]Previous cardiovascular disease: self-reported angina, stroke or myocardial infarction.

In Sensitivity analysis 1, the same age grouping was used for RA. The HR for RA compared to controls for patients $\leq$75 years and patients >75 were very similar to the HR without age grouping from to the main models, but the CI were wider due to fewer events in each group, especially in the lower age group. (Supplementary Table S2).

In Sensitivity analysis 2 stratified by birth year in 10-year intervals, the results for RA were very close to those from the main analysis at all three steps, as expected due to the PH (Fig. 2b). The HR for diabetes were between the estimates for the two age groups in the main model. Diabetes had significantly higher HR for mortality than RA at all steps. In Sensitivity analysis 3 a separate Step 1 model was run for diabetes and controls for each age stratum. The results confirmed that the HR for mortality tended to be lower in the older age strata, but the CI were much wider in the younger age strata due to fewer deaths (Fig. 3).

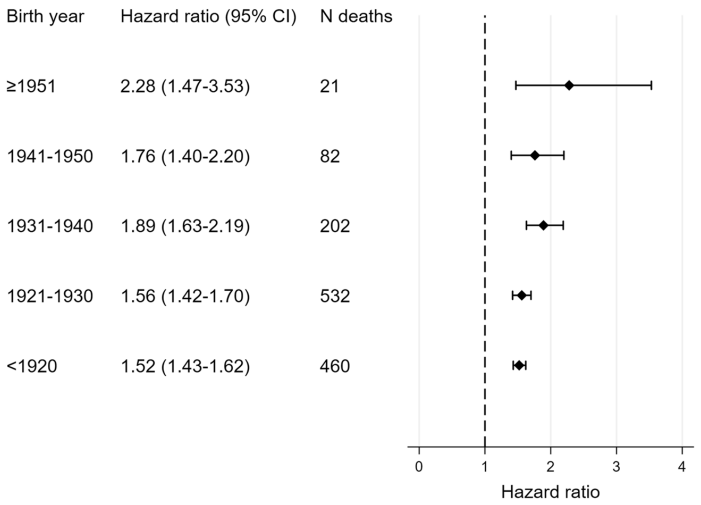


**Figure 3.** Cox regression models for mortality in diabetes according to birth year stratum. Age was used as time axis in all models and is thereby adjusted for in all models. Models were also adjusted for sex. Abbreviations: 95% CI – 95% confidence interval. Participants born in 1951 or later were pooled due to few deaths in the younger strata.

Figure 4 shows Kaplan-Meier survival estimates.

Sensitivity analysis 4 using multiple imputation of missing adjustment variables gave similar results as the main analysis, with essentially unchanged HR (Supplementary Table S2). Sensitivity analysis 5, in which the participants with both diseases were excluded in the Step 3 model, also resulted in essentially unchanged findings (Supplementary Table S2). Use of diabetes medication or not, or missing treatment information for diabetes patients (Sensitivity analysis 6), was not significant in the Step 1 model ($p = 0.66$).

The three main causes of death were diseases of the circulatory system (ICD10 I00-I99), neoplasms (ICD10 C00-D49) and diseases of the respiratory system (ICD10 J00-J99). Figure 5 shows the distribution of deaths from three main causes among patients with either RA or diabetes and controls. The third major cause of death in the diabetes group was diabetes-related (ICD10 E10-E14), accounting for 12% of the deaths in this group. Among the patients with diabetes, a significantly higher percentage died from circulatory disease and a significantly lower percentage died from cancer compared to controls.

## Discussion

The main finding of this study was that both diabetes and RA were associated with increased mortality rates. For diabetes, the HR tended to be higher in the younger participants as defined by 10-year strata by birth year. The average HR for death was significantly higher for diabetes than for RA, and significantly higher for participants $\leq$75 years when diabetes patients were grouped with a cut-off at 75 years. The increased death rates could not be explained by the lifestyle factors and other health parameters adjusted for in the analysis.

As expected, the main of causes of death in were circulatory disease, neoplasms, and respiratory disease in that order. For the patients with diabetes, diabetes-related deaths was the third main cause of death and respiratory diseases the fourth. Overall death rates were higher for patients with diabetes and/or RA, which explains how one may find higher death rates from a specific cause, but lower percentage of deaths due to that cause. The percentages of different death causes agree well with previous reports[6,7,9–12,22]. The controls were younger, so the interpretation of the comparison of death causes between the groups need some caution.

The main analysis and Sensitivity analysis 3 confirmed that the mortality risk among diabetes patients compared to controls was highest in the younger age group. This is consistent with a nationwide Swedish study, reporting that the HR for death among diabetics compared to healthy matched controls attenuated with age[12]. They reported an adjusted HR during or after 2005 of 2.59 (95% CI: 2.27–2.29) for those <55 years and of 1.03 (95% CI: 1.01–1.03) for those $\geq$75 years, hence a lower HR estimate than the present study for patients $\geq$75. The higher HRs in the younger diabetes patients might be due lower expected death rates in the general population, or a survival bias; those with most severe diabetes die earlier. Furthermore, disease with onset earlier in life might be more severe and cause more comorbidities over time. A similar increase in HR in the younger age group was not found for RA. This could be due to differences between RA and diabetes, such as the distribution of risk factors and comorbidities, or differences related to delay from disease onset to diagnosis. However, because a previous study reported higher relative risk in younger compared to older RA patients, the present study might lack the power to detect such a difference[7].

Previous studies have shown that all-cause death rates and cardiovascular-specific death rates are higher among patients with RA or diabetes than the general population[2,4,11,12]. There has been a focus on their risk of

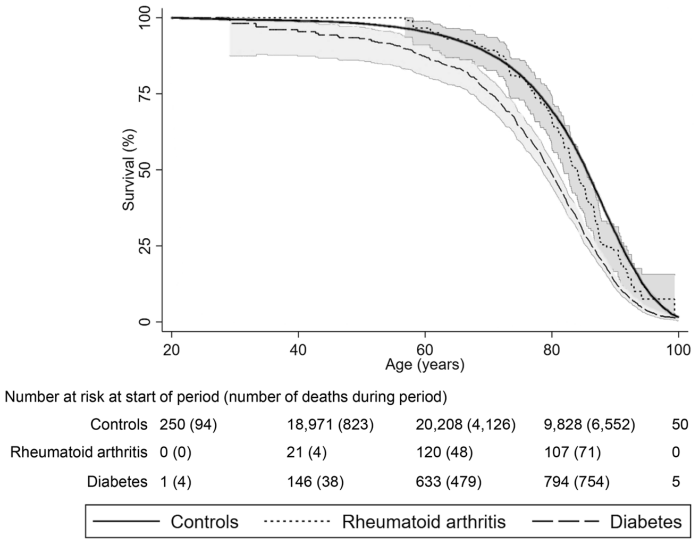


**Figure 4.** Kaplan-Meier survival curves. Kaplan-Meier survival estimates with 95% confidence intervals for rheumatoid arthritis patients, diabetes patients and controls. Participants with both diseases not presented.

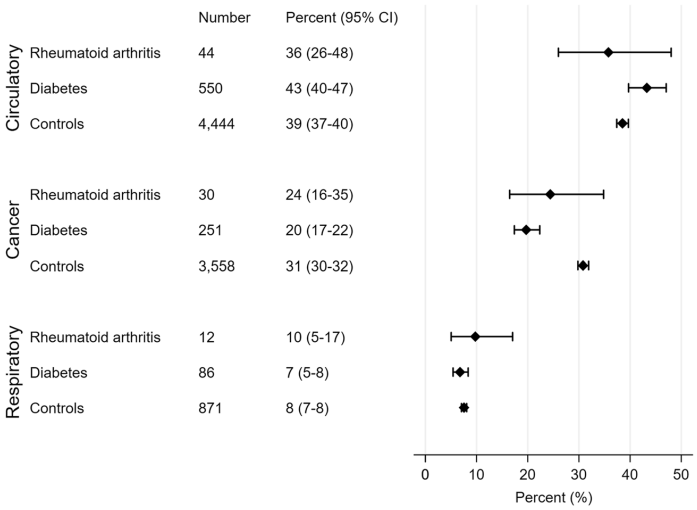


**Figure 5.** Distribution of causes of death. The number and percentages that died from each of the three main causes of deaths, for rheumatoid arthritis patients, diabetes patients and controls. Patients with both diseases not presented. Abbreviations: 95% CI – 95% confidence interval.

CVD, and on how to manage these patients[3,15,36,37]. A nationwide Danish study reported that the risk of myocardial infarction was comparable for diabetes and RA patients, with adjusted incidence rate ratios of 1.7 for both groups[3]. A large study from the US found that the risks of CVD were increased in both groups, although diabetes patients had a significantly greater risk than RA patients[14]. However, the magnitude, nature and consequence of a myocardial infarction may differ between the groups. In one study, RA patients had increased risk of silent ischemic heart disease, sudden death, and more often died shortly after developing heart failure compared to controls[38]. Another study from Taiwan found that RA patients more often than controls experienced adverse outcomes, including ischemic events and in-hospital mortality, following an acute cardiovascular event[39].

There have been contradictory results regarding mortality trends among RA patients in the new millennium; from reports of increasing mortality gap, to reports of lower rates than the general population, to the

more common reports of a reduction in absolute mortality rates though still higher rates than in the general population[4,7,21–24,27,28]. There has been a shift in treatment of RA patients with more emphasis on early intensive treatment, which has resulted in improved disease control[40–43]. Some of the RA specific-medications reduce CVD risk, and might contribute to reducing absolute mortality rates in RA patients[44–46].

Most large previous studies were registry-based and did not have information for smoking, BMI etc., thus, other factors may have acted as confounders. Smoking is an acknowledged risk factor for RA as well as for CVD and early death. Nevertheless, adjusting for these variables in the present study only changed the estimates slightly.

The strength of our study is the population-based design, the large registers, and a reasonably high participation approximately 70% in HUNT2 and 50% in HUNT3[30]. The HUNT study is considered as fairly representative for the Norwegian population[30], and there was a large number of relevant controls from the same population as the patients. We also had data not available from registries, like smoking habits and BMI. Another advantage is the long follow-up time, and that there were two surveys, making it possible to record changes over time.

Further, the RA diagnoses were validated from medical records, and can be considered accurate[32]. Data for vital status at the end of the observation period and date of death do also have very high accuracy. In contrast to previous studies where RA and diabetes have been compared with regards to perioperative mortality mortality[29], this longitudinal study format gives more information from a long-term perspective. Direct comparison of RA and diabetes, which both are associated with increased mortality rates, is useful when evaluating the importance of risk factors influencing overall health and longevity and planning appropriate interventions.

Our study does have some limitations. It may be argued that introducing the age group variable for diabetes and not for RA in the main analysis might bias the results. The sensitivity analyses demonstrated that the main models were acceptable and that they captured an important difference in diabetes mortality depending on age, even if the exact cut-off age should be interpreted cautiously. A similar age difference was not present for RA.

We were not able to distinguish between type I and type II diabetes. A Public Health Report estimated that there were 28,000 type I diabetes patients and 216,000 type II diabetes patients in Norway in 2014[47]. Thus, the majority in HUNT would have type II. Further, some participants may have developed RA or diabetes following their participation in HUNT. They would be controls in the present study, which could give an underestimation of the effect of RA or diabetes on mortality. The large number of controls makes that less likely.

Use of diabetes medication or not could potentially influence mortality rates in diabetes patients, but many participants had not answered the relevant questions. The sensitivity analysis indicated that treatment/no treatment/missing information was not associated with mortality in this patient group.

Further, there might have been a participation bias in HUNT. The proportion of participants among those invited was approximately 70% in HUNT2 and 50% in HUNT3[30]. A study of non-participants showed that they had reduced survival, lower socioeconomic status, higher prevalence of chronic diseases and higher proportion with diabetes than participants, though musculoskeletal pain was less common among non-participants[48]. If the sickest RA and diabetes patients did not participate, HR would be underestimated. Nevertheless, it is likely that such a bias would extend to the controls, hence not be excessive.

The adjustment variables in the models were registered at participation in HUNT. Ideally, they should have been registered before onset of disease, which was not possible due to HUNT's design. Some of the adjustment variables may act as mediators of mortality. To avoid drawing wrong conclusions due to erroneous adjustments the analyses were performed in a stepwise fashion with adjustment only for age and sex on Step 1. The study was not designed to identify mediators of the increased mortality in RA and diabetes, but the changes in HR from Step 1 to Step 3 in the main models were very small. We cannot exclude that other schemes for registration of adjustment variables, e.g. before diagnosis for all participants or with more frequent updates, could alter the results.

The self-reported data from HUNT have some uncertainty, particularly for smoking status and previous CVD. The underlying causes of death are in nature a bit uncertain and the low number of RA patients increased the uncertainty for their distribution of death causes.

In conclusion, the risk of death was higher for patients with either RA or diabetes compared to the general population. Diabetes patients had a significantly higher HR for death than RA patients for individuals 75 years of age or younger, but not for patients older than 75 years.

## Data availability

Data from HUNT are available upon reasonable request from the HUNT Research Centre (https://www.ntnu.edu/hunt/data), following approval from the Regional Research Ethics Committee. However, restrictions apply to the availability of the data for the present paper, which were used under license for the current study as detailed above (Ethics section) and are not publicly available in accordance with Norwegian law.

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## Author contributions

I.S.H. contributed to the conception of the study, acquisition and interpretation of the data and drafted the manuscript. M.H. and R.T. contributed to the conception of the study, interpretation of the data and substantially revised the manuscript. V.V. contributed to the conception of the study, analysis and interpretation of the data and substantially revised the manuscript. All authors have approved the submitted version and have agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

## Competing interests

The authors declare no competing interests.

## Additional information

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**SUPPLEMENTARY FILE**

# Mortality is increased in patients with rheumatoid arthritis or diabetes compared to the general population – the Nord-Trøndelag Health Study

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**Supplementary Table S1: Baseline and disease-specific characteristics including participants with missing covariates** [1,2,3]

| | RA N=475 | Diabetes N=3,820 | RA + Diabetes N=41 | Controls N=72,582 |
|---|---|---|---|---|
| **Baseline characteristics** | | | | |
| Sex | | | | |
| Female | 326 (69) | 1,852 (48) | 25 (61) | 38,571 (53) |
| Male | 149 (31) | 1,969 (52) | 16 (39) | 34,024 (47) |
| Age (years) | 58 (49, 68) | 62 (51, 73) | 66 (59, 73) | 46 (34, 60) |
| Smoking status | | | | |
| Never smoker | 152 (32) | 1,527 (40) | 18 (44) | 31,569 (43) |
| Former smoker | 160 (34) | 846 (22) | 9 (22) | 19,788 (27) |
| Current smoker | 140 (29) | 1,156 (30) | 14 (34) | 16,407 (23) |
| Previous CVD [4] | 51 (11) | 754 (20) | 10 (24) | 4,685 (6) |
| BMI (kg/m²) | 26.1 (23.8, 29.0) | 28.9 (26.1, 32.2) | 27.8 (24.4, 30.9) | 25.7 (23.4, 28.4) |
| Hypertension [5] | 233 (49) | 2,711 (71) | 29 (71) | 27,609 (38) |
| Waist/hip ratio | 0.84 (0.79, 0.90) | 0.90 (0.84, 0.96) | 0.88 (0.84, 0.93) | 0.85 (0.79, 0.90) |
| Non- fasting glucose | 5.2 (4.7, 5.9) | 7.3 (5.7, 10.7) | 6.7 (5.5, 9.6) | 5.1 (4.7, 5.6) |

| | | | | |
|---|---|---|---|---|
| (mmol/L) | | | | |
| Creatinine (µmol/L) | 83 (76, 92) | 89 (80, 99) | 85 (79, 96) | 85 (77, 94) |
| Triglycerides (mmol/L) | 1.4 (1.0, 2.0) | 2.1 (1.4, 3.1) | 1.6 (1.3, 2.4) | 1.4 (1.0, 2.1) |
| Total cholesterol (mmol/L) | 5.9 (5.2, 6.8) | 6.0 (5.2, 6.9) | 6.0 (5.2, 6.8) | 5.6 (4.8, 6.5) |
| HDL cholesterol (mmol/L) | 1.4 (1.1, 1.7) | 1.2 (0.9, 1.4) | 1.3 (1.1, 1.6) | 1.3 (1.1, 1.6) |
| Total cholesterol/HDL cholesterol ratio | 4.2 (3.4, 5.4) | 5.1 (4.1, 6.5) | 4.5 (3.6, 5.5) | 4.2 (3.3, 5.3) |
| Observation time (years) | 18.0 (12.1, 18.8) | 17.4 (7.5, 18.4) | 14.6 (7.2, 18.2) | 17.9 (8.0, 18.7) |
| **RA-specific variables** | | | | |
| Seropositive [6] | 348 (73) | | 31 (76) | |
| Age when diagnosed (years) | 55 (44, 65) | | 61 (53, 70) | |
| RA duration before first HUNT participation with diagnosis (years) | 6 (3, 9) | | 7 (4. 9) | |
| **Diabetes-specific variables** | | | | |
| Peroral diabetes medication | | 1,469 (38) | 15 (37) | |
| Insulin | | 722 (19) | 10 (24) | |
| Age when diagnosed (years) | | 59 (49, 68) | 61 (50, 69) | |

| | | |
|---|---|---|
| Diabetes duration before first HUNT participation with diagnosis (years) | 5 (2, 11) | 6 (3, 12) |

[1]Number (%) or median (25th and 75th percentile)

[2]RA: rheumatoid arthritis, CVD: cardiovascular disease, BMI: body mass index, HDL: high-density lipoprotein

[3]Missing data – <4% missing data except for smoking, blood pressure, creatinine, triglycerides and diabetes-specific variables. Smoking missing for 3,176 (5 %) and 1,970 (13%) with baseline in HUNT2 and HUNT3, respectively. Blood pressure missing for 1,900 (13%) with baseline in HUNT3. Creatinine and triglycerides missing for 3,777 (25%) with baseline in HUNT3. Diabetes-specific variables: peroral diabetes medication use missing for 1,058 (27%), insulin use missing for 1,072 (28 %), duration of diabetes and age of diabetes onset missing for 299 (8%).

[4]Previous cardiovascular disease: self-reported angina, stroke, or myocardial infarction

[5]Hypertension: Systolic blood pressure ≥ 140, diastolic blood pressure ≥ 90, or on blood pressure-lowering medication

[6]Seropositive – positive for either rheumatoid factor and/or anti-citrullinated protein antibodies

**Supplementary Table S2: Sensitivity analyses 1, 4, and 5**

| | Hazard ratio | 95 % Confidence interval | P-value |
|---|---|---|---|
| **Sensitivity analysis 1: Cox regression for mortality by age groups** | | | |
| Rheumatoid arthritis ≤75 years | 1.21 | 0.79-1.62 | 0.25 |
| Rheumatoid arthritis >75 years | 1.24 | 1.01-1.48 | 0.035 |
| Diabetes age ≤75 years | 1.83 | 1.61-2.05 | <0.001 |
| Diabetes age >75 years | 1.49 | 1.39-1.59 | <0.001 |
| **Sensitivity analysis 4: Cox regression for mortality after multiple imputation of missing adjustment variables** | | | |
| Rheumatoid arthritis | 1.20 | 1.03-1.40 | 0.021 |
| Diabetes age ≤75 years | 1.90 | 1.70-2.12 | <0.001 |
| Diabetes age >75 years | 1.43 | 1.27-1.62 | <0.001 |
| **Sensitivity analysis 5: Cox regression for mortality excluding patients with both diseases** | | | |
| Rheumatoid arthritis | 1.24 | 1.02-1.46 | 0.017 |
| Diabetes age ≤75 years | 1.83 | 1.61-2.06 | <0.001 |
| Diabetes age >75 years | 1.52 | 1.39-1.59 | <0.001 |

All models are from Step 3, i.e. adjusted for sex, hypertension [1], smoking [2], BMI [3], creatinine, total cholesterol, and previous cardiovascular disease [4]

Age was used as the time variable and was thereby adjusted for in all models

Abbreviations: BMI – body mass index

[1]Hypertension: Systolic blood pressure ≥ 140, diastolic blood pressure ≥ 90, or on blood pressure-lowering medication

[2]Smoking: never smoker, current smoker or former smoker

[3]BMI: categorised as <18.5 kg/m², 18.5-24.9 kg/m², 25-29.9 kg/m², 30-34.9 kg/m² and ≥35 kg/m²

[4]Previous cardiovascular disease: self-reported angina, stroke, or myocardial infarction

# STUDY II

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ORIGINAL ARTICLE

# Exercise Self-Efficacy and patient global assessment were associated with 6-min walk test distance in persons with rheumatoid arthritis

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## Abstract

**Introduction** Low functional capacity is related to future loss of daily function and cardiovascular events. The present study explored the associations of patient-reported outcome measures (PROMs) and disease-specific measures with functional capacity as measured by the 6-min walk test (6MWT) in persons with rheumatoid arthritis (RA).

**Methods** Seventy-nine participants from rheumatology outpatient clinics were included. The distance walked during the 6MWT (6MWD) was the dependent variable in multivariable regression analyses. Model 1 included the independent variables sex, age (in tertiles to improve model fit), and body mass index (BMI). Building on Model 1, Model 2 added smoking, patient global assessment (PGA), Exercise Self-Efficacy, Hospital Anxiety and Depression Scale's Depression score, and Cohen's Perceived Stress Scale score, whereas Model 3 added smoking, disease duration, present use of glucocorticosteroids, seropositivity, Disease Activity Score 28—C-Reactive Protein (DAS28-CRP), and a comorbidity variable.

**Results** Median age was 65 years, 76% were female, and median 6MWD was 493 m. In Model 1, BMI and age were significantly associated with the 6MWD ($R^2 = 0.42$). In Model 2, PGA and Exercise Self-Efficacy were also significantly associated with the 6MWD, with standardized regression coefficients of −0.21 ($p = 0.03$) and 0.26 ($p = 0.004$) respectively ($R^2 = 0.54$). The RA-specific variables in Model 3 were not significantly associated with the 6MWD ($R^2 = 0.49$).

**Conclusion** The PROMs PGA and Exercise Self-Efficacy were significantly associated with functional capacity as measured by the 6MWT in persons with RA, whereas disease-specific measures such as DAS28-CRP and disease duration were not.

**Key Points**

- *Functional capacity measured with the 6-minute walk test was significantly associated with body massindex, age, patient global assessment, and Exercise Self-Efficacy in persons with RA.*
- *Patient-reported outcome measures explained more of the variation in functional capacity than objectiveor composite measures of disease and are relevant measures in clinical follow-up.*
- *Techniques that enhance self-efficacy for exercise should be incorporated into clinical practice topromote physical activity.*

Keywords "6-min walk test · "Functional capacity · "Patient-reported outcome measures · "Rheumatoid arthritis

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## Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory joint disease, affecting 0.5–1.0% of the adult population, and is associated with depression, hypertension, cardiovascular disease (CVD), pulmonary disease, and increased mortality rates [1–3]. Low cardiorespiratory fitness (CRF) is an important mediator of the excess mortality among persons with RA, and increasing the physical activity (PA) and fitness levels in this group is a central part of CVD risk management [4]. The European Alliance of Associations for Rheumatology (EULAR) recommends that PA and exercise should be an integral part of standard care for persons with RA [5]. Healthcare professionals should promote PA, refer to interventions if necessary, and emphasize to the patients that the PA recommendations for the general population are safe and applicable for persons with RA [5–7].

Compared to the general population, fewer persons with RA meet the PA recommendations [8, 9]. Interventions targeting persons with low PA level and low CRF are therefore needed. Cardiopulmonary exercise testing is the gold standard method for assessing CRF. However, as testing requires personnel and special equipment, and has several contra-indications, it is not practical in clinical settings. Non-exercise formula may be applied to estimate CRF (eCRF), which is a quick method that does not depend on a physical test [10, 11]. The 6-min walk test (6MWT) is another method to assess overall functional capacity with an objective test, in which the distance walked in 6 min (6MWD) is registered [12]. The 6MWT is safe to perform, requires few resources, and gives information relevant to daily function. A recent large study found that the 6MWD could predict very low CRF in the general population, thereby identify persons in which interventions are most strongly needed [13].

Patient-reported outcome measures (PROMs) are calculated from questionnaires which the patients complete. Such measures capture the impact of disease in different and complementary manners compared to the objective measures of disease. The inclusion of PROMs in standard care reflects the focus on patient-centered follow-up. A vast number of PROMs exist in rheumatology, related to disease activity, function, psychological aspects etc. One of the most widely used is the patient global assessment (PGA), in which the patients rate their disease activity and indirectly the burden of RA, which may include consideration of symptoms, joint damage, function, disease activity, as well as psychological and societal aspects [14]. In a study testing CRF in persons with RA, the PGA was associated with CRF, whereas other RA-specific measures such as physician global assessment and swollen joint counts were not [15]. Exercise Self-Efficacy is a PROM assessing the psychological concept of self-efficacy for exercise; the belief in one's ability to perform exercise under different circumstances [16]. Previous studies have found that Exercise Self-Efficacy correlated with actual PA behaviour and the ability to change behaviour, and that interventions could increase self-efficacy [17–20].

The hypotheses for the present study were that PROMs would have a stronger association with functional capacity measured by the 6MWT than objective or composite disease measures, and that the eCRF would be significantly associated with the 6MWD in persons with RA. The primary aim was to investigate the association between several different factors and the 6MWD in persons with RA. The secondary aim was to explore the relationship between the eCRF and the 6MWD in persons with RA.

## Participants and methods

### Participants

The present investigation was part of a larger study regarding PROMs and PA in patients with inflammatory arthritis, FysKond2. Participants fulfilling the American College of Rheumatology/EULAR 2010 criteria for RA were recruited from the Rheumatology outpatient clinics at Levanger Hospital and St. Olavs University Hospital in Norway in 2019 and 2021 [21]. The participants received an information letter before an appointment and were approached about the project when they came to the hospital. The participants were asked to perform the 6MWT, which was an optional part of their participation.

### Questionnaires and measurements

The participants filled in previously published questionnaires (further described below) related to psychological and disease-specific PROMs. They also responded to questions regarding PA and background information. Resting heart rate was measured after the participants had been sitting for at least 5 min.

The Exercise Self-Efficacy score is based on 5 questions regarding ability to perform regular PA under different circumstances; when tired, when in a bad mood, when there is lack of time, during holidays, and when it rains/snows [16]. Each question was rated on a Likert scale from 1 to 7, where 1 was anchored as "completely disagree" and 7 as "completely agree". The scores for each question were added, giving an overall possible range of 5 to 35. Higher scores indicate higher self-efficacy for exercise.

Presence of depressive symptoms in the past week was measured with the 7 questions in the Hospital Anxiety and Depression Scale's Depression score (HADS-D). HADS-D ranges from 0 to 21; higher scores imply more depressive symptoms [22].

Level of stress in the past month was assessed with Cohen's scale for perceived stress, which is based on 10 questions [23]. The score ranges from 0 to 40; higher scores indicate more stress.

The PGA where the participants rated overall disease activity on a 100-mm visual analogue scale was assessed using the following phrasing: "Please consider the activity of your rheumatic disease in the past week. When considering all the symptoms, how do you think your state is?" A higher score implies more symptoms.

The modified Stanford Health Assessment Questionnaire (mHAQ) was used to measure self-reported physical function in the past week [24]. The mHAQ score is calculated from 8 questions, the final score ranges from 0 to 3, and a lower score indicates better physical function.

Information about duration, frequency, and intensity of the participants' habitual PA was used to evaluate whether they fulfilled the 2007 recommendations for PA from the American College of Sport Medicine and the American Heart Association (ACSM/AHA) [6]. The information about the participants' habitual PA was also applied to calculate a PA index as previously described [11]. A non-exercise model specific for persons with RA was used to estimate CRF based on sex, body mass index (BMI), smoking habit, PGA, resting heart rate, and the PA index [10].

The 6MWT was performed using standardized instructions from the American Thoracic Society [12]. The participants walked back and forth along a 25-m stretch and were instructed to walk as far as possible for 6 min. The participants were allowed to use their normal walking aids, choose their walking pace, and could stop to rest if necessary. They assessed their level of perceived exertion before and after the test using a Borg scale from 6 (no exertion) to 20 (maximum exertion), which is a scale closely related to physiological measures of exercise intensity like heart rate [25, 26]. The participants also rated their level of dyspnoea and lower extremity pain on similar scales from 6 (none) to 20 (maximum) before and after the test. The heart rate was measured immediately after the test.

## Hospital records

A review of hospital records was performed to collect information regarding the diagnosis, use of disease modifying anti-rheumatic drugs (DMARDs) and glucocorticosteroids, comorbidities, seropositivity status, and disease activity. Seropositivity was defined as a positive test for rheumatoid factor and/or anti-citrullinated protein antibody. Disease activity was assessed using the last documented Disease Activity Score 28—C-Reactive Protein (DAS28-CRP). DAS28-CRP is a composite score incorporating both subjective and objective measures of disease activity, namely, swollen and tender joint counts, CRP, and PGA. For 19% of the participants, the last recorded DAS28-CRP value was from more than one year before inclusion to the study.

## Statistics

Normality of continuous variables was assessed visually and with the Shapiro–Wilk test. As most of the continuous variables were not normally distributed, continuous data are presented as median with $25^{th}$ and $75^{th}$ percentile and compared with the Mann–Whitney *U*-test. Categorical variables are presented as number with percentage and were compared with the Chi-square test. Statistical analyses were performed using Stata (v16, StataCorp). $p$-values $< 0.05$ were considered statistically significant.

The associations between the different variables and the 6MWD were analysed using multivariable linear regression, with the 6MWD as dependent variable. Model 1 included variables known to be associated with the 6MWD; sex, age, and BMI. Model 2 explored the additional associations of several PROMs while Model 3 focused on more objective and composite RA measures. Model 2 added smoking habit (dichotomized as never or ever smoker), Cohen's scale of perceived stress, HADS-D, Exercise Self-Efficacy, and PGA to Model 1. Model 3 added smoking habit, duration of RA, DAS28-CRP, seropositivity, present use of glucocorticosteroids, and comorbidities to Model 1. The comorbidity variable was coded "yes" if the participants had a history of any of the following: hypertension, angina, myocardial infarction, arrythmia, stroke, chronic obstructive respiratory disease, chronic restrictive respiratory disease, asthma, diabetes, or cancer; or "no" if not.

Age was categorized into tertiles to improve model fit ($< 59$, 59–69, or $\geq 70$ years). Participants with missing data for variables in the models were excluded. Residual plots, Akaike and Bayesian information criteria, and $R^2$ were applied to evaluate model assumptions and model fit. Standardized regression coefficients, which is the number of standard deviations the dependent variable changes per standard deviation increase in each of the independent variables, were calculated to allow for direct comparison of the coefficients of the variables in the models.

A sensitivity analysis assessed whether recruitment at Levanger Hospital (2019) or at St. Olavs University Hospital (2021) had a significant impact on the 6MWD, as the COVID-19 pandemic started between the two data collection periods. A regression model was performed with the 6MWD as the dependent variable, and the independent variables sex,

age (in tertiles), BMI, and hospital (Levanger or St. Olavs University Hospital).

In the secondary analysis, the relationship between the eCRF and the 6MWD was assessed with Pearson's correlation coefficients and a scatterplot. Several variables like sex and age are part of the eCRF formula, and multivariable regression was not considered an appropriate analytical method due to collinearity issues.

### Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (#23,420). All participants gave informed consent. The study was performed in accordance with the principles of the Helsinki declaration.

## Results

Out of the 200 persons that were invited to participate, 139 completed the questionnaires (70%) and 86 performed the 6MWT (43%). The participants in the overall study were somewhat younger than those who declined the invitation (median age 64 versus 67 years, $p=0.03$), and the proportion of females was similar (71% versus 82%, $p=0.11$). Inclusions and exclusions to the study are presented in Fig. 1. Table 1 presents participant characteristics for the RA patients invited to perform the 6MWT, comparing the participants included in the analysis ($N=79$) with participants who either declined to perform the 6MWT or were excluded from analysis for other reasons ($N=54$).

The median distance walked during the 6MWT was 493 m (range 248–738 m). The median values for perceived exertion, dyspnoea, lower extremity pain, and heart rate increased during the test (Table 2).

Results from the multivariable regression models are presented in Table 3. In Model 1, age and BMI were significantly associated with the 6MWD, whereas sex was not ($R^2=0.42$). Among the additional variables in Model 2, Exercise Self-Efficacy and PGA were significantly associated with the 6MWD ($R^2=0.54$). None of the additional variables in Model 3 was significantly associated with the 6MWD ($R^2=0.49$). Compared to Model 1, Models 2 and 3 further explained 12% and 7% of the variation in the 6MWD, respectively.

In the Sensitivity analysis there was no significant association between which hospital the participants were recruited from and the 6MWD ($p=0.39$), indicating that whether they participated in 2019 or 2021 did not have a major effect on the distance walked.

The secondary analysis demonstrated that the eCRF was significantly associated with the 6MWD among persons with RA (Fig. 2). Pearson's correlation coefficient was 0.61 ($p<0.0001$). Three persons were excluded before the secondary analysis because of missing data for resting heart rate, which is needed to calculate eCRF.

## Discussion

The main finding of the present study was that Exercise Self-Efficacy and PGA, in addition to age and BMI, were significantly associated with functional capacity in persons with RA.

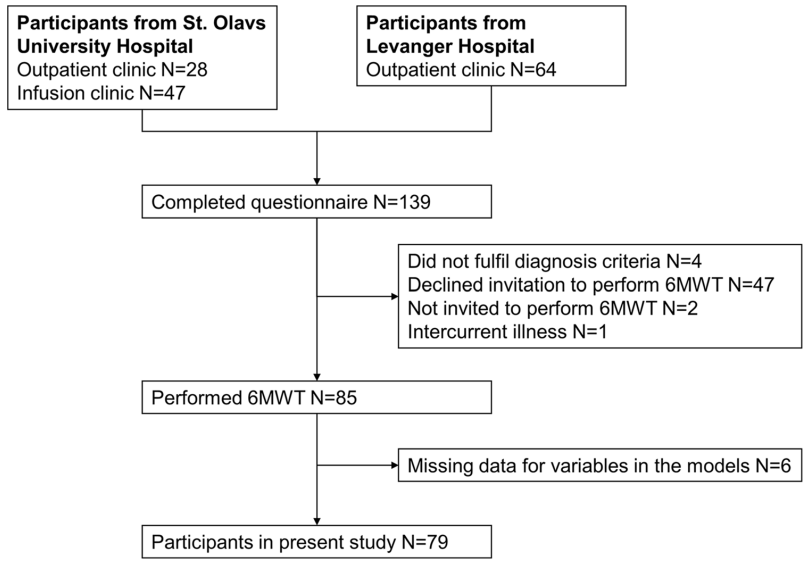


**Fig. 1** Inclusion and exclusions to the present study. Abbreviation: 6MWT: 6-min walk test. Two participants were not invited to perform the 6MWT for practical reasons. One participant was excluded due to an intercurrent disease that affected the result of the 6MWT

**Table 1** Participant characteristics for those invited to perform the 6-min walk test [a,b,c,d]

| | Included in analysis ($N=79$) | Not included in analysis ($N=54$) | $p$-value |
|---|---|---|---|
| Female sex | 60 (76) | 36 (67) | 0.24 |
| Age (years) | 65 (55, 71) | 62 (53, 71) | 0.44 |
| Smoking status | | | 0.56 |
| Current smoker | 7 (9) | 3 (6) | |
| Former smoker | 42 (53) | 34 (63) | |
| Never smoker | 30 (38) | 17 (31) | |
| Body mass index ($kg \times m^{-2}$) | 26.3 (23.6, 28.9) | 27.7 (23.7, 31.5) | 0.09 |
| Resting heart rate (beats per minute) | 68 (63, 76) | 71 (68, 80) | 0.06 |
| Rheumatoid arthritis duration (years) | 10 (5, 23) | 6 (2, 15) | 0.03 |
| Age when diagnosed (years) | 48 (35, 58) | 50 (39, 61) | 0.26 |
| Seropositive (ACPA and/or RF) | 68 (86) | 48 (89) | 0.63 |
| Medication, current use | | | |
| Conventional DMARDs | 67 (85) | 42 (78) | 0.30 |
| Biological DMARDs | 42 (53) | 30 (56) | 0.79 |
| Glucocorticosteroids | 21 (27) | 14 (26) | 0.93 |
| Comorbidity | | | |
| Hypertension | 32 (41) | 16 (30) | 0.20 |
| Osteoporosis | 23 (29) | 12 (22) | 0.38 |
| Respiratory disease [e] | 20 (25) | 9 (17) | 0.24 |
| Cardiovascular disease [f] | 13 (16) | 12 (22) | 0.40 |
| Diabetes | 7 (9) | 3 (6) | 0.48 |
| Cancer | 5 (6) | 5 (9) | 0.52 |
| DAS28-CRP | | | 0.19 |
| Remission | 52 (66) | 27 (50) | |
| Low disease activity | 14 (18) | 10 (18) | |
| Moderate disease activity | 12 (15) | 15 (28) | |
| High disease activity | 1 (1) | 2 (4) | |
| Overall score DAS28-CRP | 2.3 (1.7, 2.9) | 2.7 (1.8, 3.6) | 0.14 |
| Modified Stanford Health Assessment Questionnaire | 0.38 (0.13, 0.63) | 0.25 (0.00, 0.75) | 0.46 |
| Patient global assessment (mm) | 27 (12, 40) | 30 (14, 56) | 0.16 |
| Hospital Anxiety Depression Scale's Depression score | 3 (1, 4) | 3 (1, 6) | 0.26 |
| Cohen's Perceived Stress Scale | 15 (9, 19) | 15 (11, 19) | 0.51 |
| Exercise Self-Efficacy | 25 (17, 30) | 22 (17, 25) | 0.07 |
| Fulfills ACSM/AHA 2007 recommendations | 23 (32) | 11 (20) | 0.28 |
| Estimated cardiorespiratory fitness ($mL \times kg^{-1} \times min^{-1}$) | 29.0 (22.3, 35.5) | 26.6 (22.6, 35.8) | 0.79 |

[a]Number with percentage or median with 25th and 75th percentiles

[b]*ACSM/AHA*, American College of Sport Medicine/American Heart Association; *ACPA*, anti-citrullinated protein antibody; *DAS28-CRP*, Disease Activity Score 28—C—Reactive Protein; *DMARDs*, disease-modifying antirheumatic drugs; *RF*, rheumatoid factor

[c]Chi-square test or Mann–Whitney *U*-test

[d]Missing data: < 5% for all variables, with the following exceptions: estimated cardiorespiratory fitness (17% missing for those not included in the analysis), heart rate (11% missing for those not included in the analysis), mHAQ and HADS-D (7% missing data in the group not included in the analysis)

[e]Respiratory disease: chronic obstructive pulmonary disease, chronic restrictive pulmonary disease, or asthma

[f]Cardiovascular disease: angina, myocardial infarction, arrhythmia, or stroke

Sex, smoking, level of depressive symptoms, level of perceived stress, seropositivity, disease duration, DAS28-CRP, use of glucocorticosteroids, and comorbidities had little impact on the distance walked. The eCRF was significantly associated with the 6MWD. The results confirmed the hypothesis that PROMs explained functional capacity better than more objective or composite measures of disease in this sample of RA patients.

The included participants had relatively high self-reported function and low disease activity levels, comparable to previous results from Norwegian RA patients on stable treatment [15, 27]. The median 6MWD for our patients was 493 m, which was relatively long compared to results from persons with other chronic diseases [28, 29]. The mean 6MWD in a study in heart failure patients was 222 m and 73% of the

**Table 2** Results from 6-min walk test [a,b]

| Measures | Included patients ($N=79$) |
|---|---|
| Distance walked (m) | 493 (447, 576) |
| Heart rate | |
| Before the 6MWT | 68 (63, 73) |
| After the 6MWT | 92 (84, 104) |
| Level of perceived exertion [c] | |
| Before the 6MWT | 9 (6, 11) |
| After the 6MWT | 11 (9, 12) |
| Level of dyspnea [c] | |
| Before the 6MWT | 6 (6, 9) |
| After the 6MWT | 11 (9, 13) |
| Level of pain in lower extremities [c] | |
| Before the 6MWT | 8 (6, 11) |
| After the 6MWT | 9 (7, 13) |
| Walking aids | 3 participants used one crutch (4) |

[a]Number with percentage or median with 25th and 75th percentiles

[b]Abbreviation: *6MWT*, 6-min walk test

[c]Rated on a Borg scale from 6 (nothing) to 20 (maximum)

participants walked less than 300 m [28]. The mean 6MWD in cardiac surgery patients admitted to rehabilitation was 248 m, which increased to 374 m before discharge [29]. Among persons with RA, the initial mean 6MWD in two different studies were 391 m and 549 m, shorter and longer than the results in the present study, respectively [30, 31]. This suggests that the results from the 6MWT were in the expected range for persons with RA.

## Importance of PROMs

Exercise Self-Efficacy was significantly positively associated with the 6MWD in persons with RA, in line with results from other fields [32]. Interestingly, participants who performed the 6MWT had a trend towards higher Exercise Self-Efficacy compared to those who declined, indicating stronger beliefs in their ability to perform the test. Increasing self-efficacy may be a necessary step to turn intentions to increase PA into actual change of behaviour and thereby improvement of functional capacity. Examples of approaches that may increase self-efficacy are motivational interviewing techniques, self-regulation sessions, learning by doing, role modelling, positive feedback, problem solving, goal-setting, and education on body responses [19, 20]. To be able to engage in PA, persons with low self-efficacy for exercise may need supervision, more positive feedback and assurance, the option to exercise with peers, and an individualized exercise program, whereas persons with high self-efficacy may be less dependent on external factors [20].

The PGA is a subjective measure of disease activity that has been associated with CRF, and the present study found a significant negative association with the 6MWD [15]. The PGA is more closely related to the subjective impact of RA than to objective measures such as swollen joint count and inflammation [14, 33]. Furthermore, disease activity may affect which factors the PGA reflects. For example, health distress may only surface at lower disease activity [34]. As RA was relatively well controlled in most of our participants, their assessment may reflect a wider range of factors than pain and self-reported function. Several factors may affect both the PGA and PA behaviour, and some patient-reported barriers to PA including pain and fatigue may be improved by PA [14, 34–36].

Depressive symptoms may lead to a reduction in PA and thereby loss of functional capacity. However, our study did not find a significant association between depressive symptoms and the 6MWD in persons with RA. This is similar to findings among breast cancer survivors, but in contrast to results in heart failure patients [28, 37]. Potential explanations may be differences in patient characteristics, such as age, physical impairment, and level of depression. Compared to our participants, the heart failure patients were older, had higher scores for HADS-D (mean score 7), and walked shorter (mean 6MWD 222 m), whereas the breast cancer survivors were younger, had slightly higher HADS-D scores (mean score 5), and walked similar distances (mean 6MWD 511 m).

Perceived stress was not associated with the 6MWD in the present study. This was surprising as perceived stress has been negatively associated with PA in the general population and CRF in persons with diabetes [38, 39]. Maybe the association with stress would have been stronger in a sample with less variation in age. Participants with small children at home and a full-time job might experience more stress than a person who recently retired, but still walk further. Stress might interact with other psychological domains such as self-efficacy, and perhaps, the impact of stress was mediated through other variables in the model.

## Objective and composite disease measures

There were no significant associations between the 6MWD and the objective or composite RA measures. One study reported a significant negative association between DAS28 and the 6MWD (Spearman's correlation coefficient − 0.294, $p=0.006$); however, this was not further explored in multivariable analyses [30]. Perhaps the association between objective measures and the 6MWD would have been stronger in a population with higher disease activity or lower self-reported function.

## Clinical implications

Busy clinicians may prioritize objective over subjective measures of disease activity. Nevertheless, the fact that the

**Table 3** Variables associated with the 6-min walk test distance in multivariable regression analyses [a]

| | Regression coefficient (95% CI) | Standardized regression coefficient | *p*-value |
|---|---|---|---|
| Model 1 ($R^2 = 0.42$) | | | |
| Male sex | 27 (−9, 64) | 0.13 | 0.14 |
| Age | | | |
| Middle versus youngest tertile | −35 (−72, 1) | −0.20 | 0.06 |
| Oldest versus youngest tertile | −115 (−155, −76) | −0.59 | <0.001 |
| Body mass index | −8 (−12, −5) | −0.39 | <0.001 |
| Model 2 ($R^2 = 0.54$) | | | |
| Male sex | 15 (−22, 53) | 0.08 | 0.42 |
| Age | | | |
| Middle versus youngest tertile | −39 (−74, −3) | −0.22 | 0.03 |
| Oldest versus youngest tertile | −117 (−155, −79) | −0.60 | <0.001 |
| Body mass index | −6 (−10, −2) | −0.28 | 0.002 |
| Exercise Self-Efficacy | 3 (1, 4) | 0.26 | 0.004 |
| Patient global assessment | −1 (−2, 0) | −0.21 | 0.03 |
| Cohen's scale of perceived stress | −2 (−5, 1) | −0.15 | 0.25 |
| HADS-D | 3 (−4, 9) | 0.11 | 0.38 |
| Ever smoker | −6 (−39, 26) | −0.03 | 0.71 |
| Model 3 ($R^2 = 0.49$) | | | |
| Male sex | 28 (−9, 66) | 0.14 | 0.13 |
| Age | | | |
| Middle versus youngest tertile | −26 (−64, 12) | −0.15 | 0.17 |
| Oldest versus youngest tertile | −97 (−142, −53) | −0.50 | <0.001 |
| Body mass index | −7 (−11, −3) | −0.32 | 0.002 |
| Ever smoker | −27 (−60, 7) | −0.15 | 0.12 |
| Comorbidity (yes/no)[b] | −23 (−60, 15) | −0.13 | 0.23 |
| DAS28-CRP | −12 (−29, 5) | −0.13 | 0.17 |
| Present glucocorticosteroid use | −24 (−61, 12) | −0.12 | 0.19 |
| Seropositive (positive RF and/or ACPA) | 8 (−38, 55) | 0.03 | 0.72 |
| Rheumatoid arthritis duration | 0 (−1, 1) | −0.01 | 0.94 |

[a]Abbreviations: *ACPA*, anti-citrullinated protein antibody; *CI*, confidence interval; *DAS28-CRP*, Disease Activity Score 28—C—Reactive Protein; *DMARD*, disease-modifying antirheumatic drugs; *HADS-D*, Hospital Anxiety and Depression Scale's Depression score; *RF*, rheumatoid factor

[b]Comorbidity defined as having a history of hypertension, angina, myocardial infarction, arrythmia, stroke, chronic obstructive respiratory disease, chronic restrictive respiratory disease, asthma, diabetes, or cancer

objective and composite disease measures were not related to functional capacity underlines the importance of including PROMs in clinical evaluations. PGA is often used in the follow-up of persons with RA to represent the patient's perspective regarding disease impact, whereas scoring of Exercise Self-Efficacy is not a common tool in rheumatology. Exercise Self-Efficacy assesses a psychological dimension that clinicians can target. One may include motivational interviewing techniques, goal-setting, and positive feedback as part of regular follow-up, or refer to exercise programs, physiotherapist etc. Interventions that target self-efficacy are probably most efficient when combined with some sort of exercise intervention [19]. In addition to prescribing medications, active promotion of PA and exercise is important as that is something the patients can do themselves to reduce symptoms and improve function [5, 7, 36].

## Functional capacity

The 6MWD was significantly associated with the eCRF in our study, similar to previous results showing moderate to high correlation with measured CRF in the general population and in persons with heart failure [13, 40]. The 6MWD is an objective measure of physical capacity that has been associated with important clinical outcomes like mortality and major cardiac events in other patient groups [29, 41, 42]. Furthermore, we have now shown that it is related to PGA, Exercise Self-Efficacy, and eCRF. The 6MWT is most often used to assess the effect of interventions, for example physical rehabilitation, exercise programs, or surgical procedures, but can also be part of initial clinical assessments. The testing itself may lead to conversations on aspects the patients perceive as important. A 6MWT is not equivalent to a cardiopulmonary exercise test

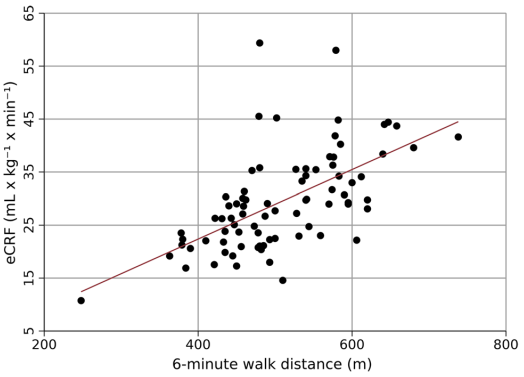


**Fig. 2** Estimated cardiorespiratory fitness versus 6-min walk distance. Abbreviation: eCRF: estimated cardiorespiratory fitness. Linear regression line presented. Note that the X and Y axes do not start at 0

as it does not measure CRF or give detailed information of cardiac and pulmonary function. Regardless, the test is simple, safe, and inexpensive to perform, and can help identify persons needing additional follow-up.

Another alternative to estimate physical capacity is using non-exercise formulas for eCRF [10]. Advantages of the formula approach is that it is quick, requires few measurements, and can be completed by the patients themselves [43]. A limitation of non-exercise formulas, at least in the general population, is that they may classify a large proportion of participants into a wrong fitness group [44].

## Representativeness

As 60% of those invited were not included in the analysis, a concern is whether the results are applicable to other persons with RA. The participants who performed the 6MWT and were included in the analysis were representative for those agreeing to participate in the study, apart from slightly longer disease duration. The persons who agreed to participate in the project (with or without performing the 6MWT) were slightly younger than those who declined. Only a third of the participants included in the analysis fulfilled the ACSM/AHA 2007 recommendations for PA, which is comparable to other Scandinavian studies of persons with RA [8, 9]. The results from the present study may not be applicable to patients with high disease activity and/or who live outside of Scandinavia.

## Strengths and weaknesses

A strength of the present study is the wide range of variables recorded, permitting investigation of several factors known to influence functional capacity. The participants varied in age, sex, disease activity level, and disease duration. The RA diagnoses were validated using hospital records, and information regarding comorbidity and medications had high accuracy. To our knowledge, this is the first study to thoroughly explore the association between different PROMs and disease-specific measures with the 6MWD in persons with RA.

A weakness is that the DAS28-CRP value might not reflect the present disease activity level for all participants. Evaluation of causation is not possible due to the cross-sectional design. A larger sample size would have increased the power of the study. For practical reasons the walking course for the 6MWT was 25 m, shorter than the recommended 30 m, which possibly led to a shorter distance walked due to more turns [45]. However, it is unlikely that this had a major impact on the associations between the investigated variables and the 6MWD. Lastly, as weight and height were self-reported, BMI estimates may be imprecise.

## Conclusion

The PROMs Exercise Self-Efficacy and PGA were significantly associated with functional capacity measured with the 6MWT in persons with RA, whereas objective and composite disease measures were not. Applying techniques that may enhance Exercise Self-Efficacy could help patients increase their PA level and thereby improve functional capacity. The present study also demonstrated that the eCRF was significantly associated with the 6MWD. The 6MWT is a cheap, objective, and feasible test that can help identify patients who could benefit from more comprehensive follow-up.

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**Author contribution** Study conception and design: VV, MH, ISH. Data collection: ISH, MH, OH. Data analysis: VV, ISH. Data interpretation: ISH, VV, MH, OH. Drafting the manuscript: ISH. Revising the manuscript critically for important intellectual content: VV, MH, OH. All authors approved the final version of the manuscript.

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## Declarations

**Conflict of interest** The authors declare no competing interests.

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# STUDY III

Clinical Rheumatology
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ORIGINAL ARTICLE

# The association between rheumatoid arthritis and reduced estimated cardiorespiratory fitness is mediated by physical symptoms and negative emotions: a cross-sectional study

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## Abstract

**Objectives** Persons with rheumatoid arthritis (RA) have lower cardiorespiratory fitness (CRF) than healthy individuals. We sought to identify variables explaining the association between RA status and reduced CRF.

**Methods** RA patients recruited from two Norwegian hospitals and blood donors recruited as controls filled in questionnaires about physical activity, physical symptoms, and psychological factors. Estimated CRF (eCRF) was calculated from non-exercise models. The relationship between RA status and reduced eCRF was explored with structural equation modelling. The latent variables physical symptoms (based on morning stiffness, joint pain, and pain in neck, back, or hips) and negative emotions (based on Hospital Anxiety and Depression Scale's Depression score and Cohen's perceived stress scale) were included as possible mediators between RA status and eCRF in separate and combined models adjusted for age and sex.

**Results** Two-hundred-and-twenty-seven RA patients and 300 controls participated. The patients were older and had lower eCRF than controls (age- and sex-adjusted mean difference: 1.7 mL/kg/min, p=0.002). Both latent variables were significant mediators of the association between RA and reduced eCRF when included in separate models. The latent variables mediated 74% of the total effect of RA on eCRF in the combined model. Standardized coefficients: direct effect of RA -0.024 (p=0.46), indirect effect through physical symptoms -0.034 (p=0.051), and indirect effect through negative emotions -0.034 (p=0.039).

**Conclusion** Both physical symptoms and negative emotions mediated the association between RA and reduced eCRF with similar effect sizes. To successfully increase CRF in RA patients, both physical and psychological factors should be addressed

**Key Points**

- *The RA patients in the present study had 1.7 mL/kg/min lower mean estimated cardiorespiratory fitness (CRF) compared to healthy controls.*
- *Mediation analysis demonstrated that physical symptoms and negative emotions mediated 74% of the total negative effect of RA on estimated CRF in a combined, adjusted model.*
- *This suggests that both physical and psychological factors should be addressed when supporting RA patients in improving their CRF.*

**Keywords** Cardiorespiratory fitness · Depressive symptoms · Mental health · Psychological stress · Rheumatoid arthritis

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## Introduction

Cardiorespiratory fitness (CRF) is an important indicator of health and can be measured with a cardiopulmonary exercise test, or estimated using sub-maximal exercise tests or non-exercise models [1]. Low CRF is associated with increased risk of cardiovascular disease (CVD), depression, and diabetes, and with higher mortality rates [1, 2]. Rheumatoid arthritis (RA) is characterized by painful and swollen joints, morning stiffness, fatigue, and inflammation [3]. RA is also associated with increased risk of CVD and depression, and despite several reports

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of improved survival and some indicating similar survival as in the general population, RA was still associated with excess mortality in a recent nationwide Norwegian study [4–6]. RA patients with low CRF have more CVD risk factors and higher mortality rates than patients who are more physically fit [7, 8]. As RA patients have lower mean CRF compared to the general population, improving their fitness levels is an important part of managing their CVD risk profile [7, 9, 10].

Determinants of and correlates with CRF include sex, age, body composition, resting heart rate, physical activity (PA) habits, education, smoking habits, alcohol consumption, and genetics [11, 12]. Although the response to exercise may be influenced by individual factors, performing aerobic exercise is essential to improve and maintain CRF [1, 13]. Interventions involving regular aerobic exercise are associated with improved aerobic capacity, improved functional ability, reduced pain, and improved CVD risk profile in persons with RA [14, 15].

The European Alliance of Associations for Rheumatology (EULAR) emphasizes that PA and exercise should be an integrated part of standard care for persons with RA [16]. Consistent with the aerobic PA recommendations for the general population, EULAR recommends performing ≥150 minutes of PA at moderate intensity, or ≥75 minutes at vigorous intensity, or a combination of these, per week [16]. Psychological, physical, social, and environmental factors may affect PA behaviour and in turn CRF. RA patients have more joint symptoms and increased prevalence of depression compared to healthy individuals [4, 17]. Furthermore, RA patients tend to experience more work stress and interpersonal stressors than the general population, and the presence of RA can also be considered a stressor [18]. These factors may explain some aspects of the lower CRF estimates among RA patients compared to controls. For example, as psychological stress has been associated with a reduction in PA and exercise in longitudinal settings, it is plausible that higher levels of stress over time also lead to a reduction in fitness [19].

More knowledge on why RA patients have lower CRF levels than healthy individuals may identify areas that can be targeted in interventions or addressed in clinical practice. The hypothesis for the present study was that more physical symptoms and more negative emotions in RA patients would explain some of the association between RA status and lower estimated CRF (eCRF). The aim was to evaluate whether physical symptoms and/or negative emotions mediated the relationship between RA status and eCRF and to compare the relative effect of these two factors.

## Participants and methods

### Participants

The present study is part of a larger study, FysKond2, investigating the relationship between different patient-reported outcome measures and PA in patients with inflammatory joint diseases. Results from a subgroup of the participants who performed an optional 6-minute walk test have previously been published [20]. The present study included an RA group and a control group. To have large enough sample size to perform structural equation modelling (SEM), we aimed for at least 200 participants in each group.

Persons with an RA diagnosis according to the American College of Rheumatology/EULAR 2010 criteria were recruited at the Rheumatology Outpatient Clinics at Levanger Hospital and St. Olavs hospital, Trondheim University Hospital, Norway, in 2019 and 2021 [3]. All patients received an information letter about the study before they were contacted. At St. Olavs hospital, patients with well-controlled disease may be transferred to a patient-centred follow-up programme with regular controls at their general practitioner. To recruit a representative sample of RA patients, two recruitment strategies were used. We contacted a random selection of those in the patient-centred follow-up programme as well as patients with scheduled physical or digital appointments at the Rheumatology Outpatient Clinics during the recruitment periods, see Fig. 1. Persons with physical appointments were recruited during their visits. Those without a physical appointment were contacted by telephone and the questionnaires and a return envelope were sent to the participants by mail.

Blood donors were chosen as the control group because they are relatively easy to recruit and consist of persons of different ages and backgrounds. They fulfilled the national criteria for blood donors and were recruited in 2019 during an appointment at the Blood Bank at St. Olavs hospital [21].

### Questionnaires and data sources

All participants filled in questionnaires regarding PA, psychological factors, and physical symptoms, as further described below. Questions about frequency, duration, and intensity of performed PA were used to evaluate fulfilment of the aerobic PA recommendations and to calculate a PA index [16, 22]. Data regarding the rheumatic disease, use of anti-rheumatic medication, and comorbidities were collected from hospital records for the participants with RA. Due to the recruitment strategy explained above, many patients had not recently seen a rheumatologist and did not have a recent disease activity score of 28 joints (DAS28).

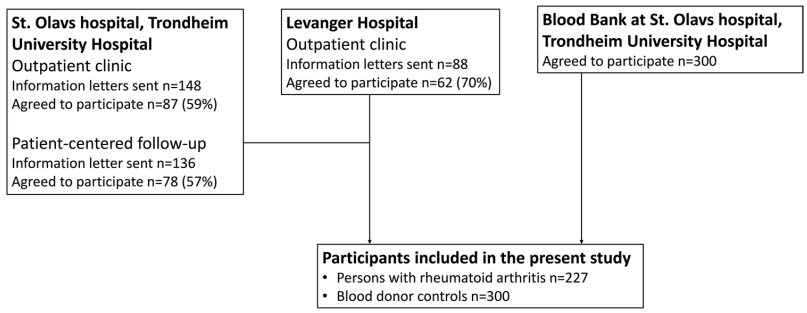


**Fig. 1** Inclusions to the study

Non-exercise models developed in the same region of Norway were applied to calculate eCRF. An RA-specific model was used for the participants with RA and a model developed in healthy individuals was used for the controls [22, 23]. Both models include data on sex, age, body mass index, resting heart rate, and the PA index, and the RA model further includes smoking status and the patient global assessment [23, 24].

Degree of morning stiffness, intensity of joint pain in the past 6 months, and degree of pain in the neck, back, or hips were rated on a Likert scale from 0 to 10. A higher score indicates more severe symptoms.

The 10-item version of Cohen's perceived stress scale was applied to assess level of stress [25]. The items include questions about the ability to handle stressors and emotional response to stressors in the past month. The scale ranges from 0 to 40, with higher scores indicating more perceived stress. The Hospital Anxiety and Depression Scale's Depression score (HADS-D) was applied to assess the level of depressive symptoms [26]. The items include questions about mood, enjoyment etc. in the past week. HADS-D is based on 7 items and has a possible range of 0-21, with higher scores implying more depressive symptoms.

The participants with RA responded to the patient global assessment on a 100 mm visual analogue scale with the phrasing "Please consider the activity of your rheumatic disease in the past week. When considering all the symptoms, how do you think your state is?" Self-reported function in the past week was assessed with the modified Stanford Health Assessment Questionnaire (mHAQ) in the RA patients [27]. The mHAQ score has a possible range from 0.00 to 3.00, with higher scores indicating worse physical function. The RA patients also rated the degree of joint tenderness or swelling on a Likert scale from 0-10, with a higher score indicating more symptoms.

For participants who were recruited during a physical visit, resting heart rate was measured after the participant had been sitting for at least 5 minutes. Participants who mailed in their questionnaire were encouraged to count their resting heart rate after sitting for 10 minutes.

## Statistical analysis

Statistical analyses were performed using Stata (v16, StataCorp, College Station, TX, USA). P-values $<0.05$ were considered statistically significant. Normality was assessed with histograms and the Shapiro-Wilk test. Continuous data are presented as median with interquartile range or as mean with standard deviation as appropriate. Categorical data are presented as number with percentage. Comparisons of descriptive data were performed with the Mann-Whitney U test for non-normally distributed continuous data, the t-test for normally distributed continuous data, and the chi-square test for categorical data.

SEM was applied to evaluate the relationship between RA status and eCRF, including different potential mediators. SEM is a statistical method that tests whether a hypothesized model fits the observed data, and is suitable for mediation analysis, complex models, and models with latent variables. Mediation analysis tests whether some of the effect of the independent variable on the dependent variable is mediated by an intermediary variable (a mediator), meaning that the independent variable influences the mediator which in turn influences the dependent variable. A latent variable is not measured directly, but rather derived from numerous observed variables representing a common concept. SEM can include participants with missing data in the analysis, utilizing the available data. Furthermore, several dependent variables may be included in the same SEM model, and variables may correlate. In SEM several fit indices are used when evaluating whether the observed data fit with the proposed model. A model with good fit should have a non-significant chi-square test, root mean square error of approximation (RMSEA) $<0.10$, comparative fit index (CFI) $\geq 0.90$, and Tucker-Lewis Index (TLI) $\geq 0.90$ [28]. Several hypothesized models might fit the data adequately. Further details regarding SEM are provided in Online Resource Text 1. Both the unstandardized and standardized path coefficients were calculated. Following standardization, all coefficients in the model are given on the same scale, namely standard deviations for each included variable.

All SEM models were adjusted for sex and age and are presented in Figs. 2 and 3. Model 1 investigated the direct effect of RA status on eCRF. Model 2a builds on Model 1 by adding the latent variable "physical symptoms" as a possible mediator of the relationship between RA status and eCRF. The physical symptoms latent variable was derived from three observed variables: morning stiffness, joint pain in the past 6 months, and pain in neck, back, or hips. Model 2b added a different possible mediator of the relationship between RA status and eCRF to Model 1, namely "negative emotions". The negative emotions latent variable was derived from the observed variables depressive symptoms and perceived stress. Model 3 combined Model 2a and 2b to explore how including both physical symptoms and negative emotions as mediators of the relationship between RA status and eCRF in the same model would impact the mediating role of each latent variable. We did not adjust for smoking habits because of the complex relationship between smoking, mental health, and physical fitness. For example, smoking is a risk factor both for developing RA and reduced eCRF but might also be a mediator of the relationship between negative emotions and eCRF.

## Ethics

The Regional Committee for Medical and Health Research Ethics approved the project (#23420). The project was performed in accordance with the Helsinki declaration. All participants provided informed consent.

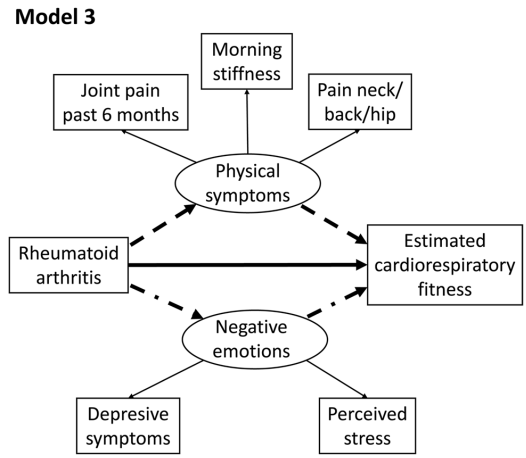


**Fig. 3** Pathway diagram for Model 3. Structural equation model investigating the direct effect of the presence rheumatoid arthritis on estimated cardiorespiratory fitness (——), and the indirect effect through physical symptoms (----) and through negative emotions (— · —). Latent variables are represented as circles, observed variables as squares, and pathways with arrows

## Results

In total, 227 persons with RA and 300 blood donors were included the present study, see Fig. 1. In the RA group, the overall acceptance rate to participation was 61%. RA

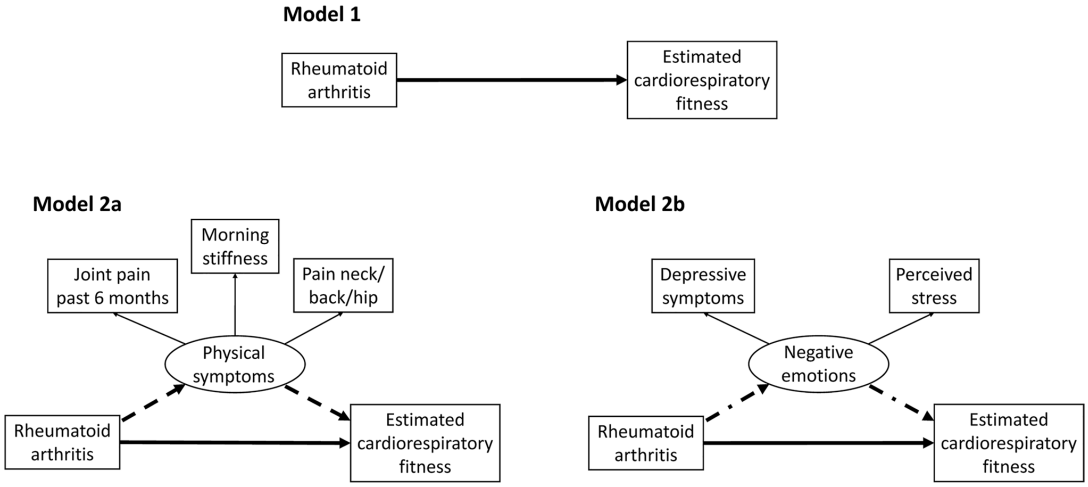


**Fig. 2** Pathway diagrams for Model 1, 2a and 2b. Structural equation models investigating the direct effect of the presence of rheumatoid arthritis on estimated cardiorespiratory fitness (——), and the indirect effect through either physical symptoms (----) or negative emotions (— · —). Latent variables are represented as circles, observed variables as squares, and pathways with arrows

participants were less often female (67% versus 78%, p=0.03) and younger (median age 64 versus 66 years, p=0.004) compared to the RA patients who declined or did not respond to the invitation to participate. Data to calculate acceptance rate were not collected for the controls.

The age range was 21 to 83 years for the RA patients and 19 to 75 years for the controls. Participant characteristics are presented in Table 1. The persons with RA were older, more often female, more often ever smokers, had lower eCRF, more joint symptoms, and more negative emotions compared to controls. Approximately one fourth of the RA patients and one third of the controls fulfilled the aerobic PA recommendations. Although there was no statistically significant difference in the proportion who fulfilled the aerobic PA recommendations, the RA group performed PA less frequently and at lower intensity compared to the control group. Data to calculate eCRF were missing for 27% of the RA patients, largely due to missing data for resting heart rate for 51% of the patients who mailed their questionnaire. The percentage of data missing was ≤4% for all other variables. The RA patients with missing data to calculate eCRF were not significantly different from the patients with sufficient data to calculate eCRF in terms of age, gender, disease duration, physical function, negative emotions, and physical symptoms (p>0.10 for all variables).

Results from the SEM models are presented in Table 2 and in more detail in Online Resource Table S1-4. The unstandardized coefficient for the direct effect of RA on eCRF in Model 1 was -1.7 (95% confidence interval: -2.8 to -0.6, p=0.002). Thus, having RA was associated with statistically significantly lower eCRF and the age- and sex-adjusted mean difference in eCRF was -1.7 mL/kg/min. The indirect pathways between RA status and eCRF through physical symptoms and negative emotions were statistically significant in Model 2a and 2b, respectively. When both latent variables were included in Model 3, the standardized coefficients for both indirect pathways were -0.034 with p-values close to 0.05 (p=0.051 for physical symptoms, p=0.039 for negative emotions). Of the total effect of RA on eCRF in Model 3, 26% was the direct effect, 37% was mediated through physical symptoms, and 37% was mediated through negative emotions. In other words, 74% of the total effect of RA on eCRF was mediated by the latent variables in the final model. The fit indices for each SEM model are presented in Online Resource Table S5. The models had non-significant chi square tests, RMSEA <0.04, CFI >0.99 and TLI >0.98. The only exception was the chi-square test for Model 3, with p=0.047. As the chi-square test often is significant in large samples, model fit was considered acceptable [28].

## Discussion

The main finding was that both physical symptoms and negative emotions acted as mediators of the association between RA status and eCRF in the present study. As expected, the RA patients had significantly lower eCRF compared to the controls, also when adjusting for sex and age. The indirect effect through physical symptoms and the indirect effect through negative emotions were of similar effect size. To our knowledge this is the first study to explore factors mediating the relationship between RA status and physical fitness.

### Cardiorespiratory fitness

The RA patients had comparable CRF estimates to previous CRF results in Norwegian RA patients, though higher than results in British RA patients [7, 9, 15]. The differences may be explained by recruitment strategy, recruitment year, regional and cultural factors related to PA habits, disease activity, and comorbidities. The mean difference in eCRF between RA patients and controls was smaller than expected, but in the expected direction and statistically significant. In a large Norwegian population-based cohort, the age-adjusted mean eCRF in RA patients was 3.2-5.0 mL/kg/min lower in women and 1.8-4.0 mL/kg/min lower in men compared to controls [10]. Perhaps the fitness level among Norwegian RA patients has improved over the past decade with better medical treatment. Another explanation may be participation bias in the present study. Inactive patients are less likely to participate in a study about PA especially if it involves a physical test, and perhaps the invitation to the optional 6-minute walk test for a subgroup of the RA patients made some more reluctant to participate. However, many participants with low PA levels agreed to participate as only 28% of RA patients fulfilled the aerobic PA recommendations. The eCRF results among the controls were comparable to CRF results published in healthy individuals of similar mean age in the same region of Norway [29].

The standardized coefficients for the effect of RA status on eCRF might appear small. However, the size of standardized coefficients depend on the underlying distribution and relative importance of each variable. This association is still of clinical interest as even small improvements in CRF have positive effects on long-term health [1].

As the RA participants in the present study had high self-reported function and relatively high eCRF estimates, they might not be representative for all RA patients or RA patients in other countries. However, we expect that the role of mediating variables would be even more prominent in a population with larger differences in CRF between RA patients and controls.

**Table 1** Participant characteristics[a,b]

| | RA patients n=227 | Controls n=300 | P-value[c] |
|---|---|---|---|
| Age (years) | 64 (53, 71) | 46 (35, 55) | <0.0001 |
| Female sex | 153 (67) | 161 (54) | 0.001 |
| Body mass index (kg/m$^2$) | 26 (23, 29) | 26 (23, 29) | 0.96 |
| Ever smoker | 150 (66) | 105 (35) | <0.001 |
| Resting heart rate (beats per minute) | 68 (62, 76) | 68 (63, 73) | 0.62 |
| Degree of morning stiffness (scale 0-10) | 4 (1, 6) | 1 (0, 2) | <0.0001 |
| Intensity of joint pain past 6 months (scale 0-10) | 4 (2, 6) | 0 (0, 2) | <0.0001 |
| Degree of pain in neck/back/hips (scale 0-10) | 4 (1, 7) | 2 (0, 4) | <0.0001 |
| Physical activity frequency | | | 0.009 |
| Less than once per week | 24 (11) | 19 (6) | |
| Once per week | 36 (16) | 28 (9) | |
| 2-3 times per week | 98 (43) | 130 (44) | |
| Almost every day | 68 (30) | 122 (41) | |
| Physical activity average intensity[d] | | | <0.001 |
| Take it easy | 76 (33) | 58 (19) | |
| Heavy breathing or sweat | 117 (52) | 211 (70) | |
| Near exhaustion | 7 (3) | 11 (4) | |
| Physical activity average duration[d] | | | 0.27 |
| Less than 15 minutes | 5 (2) | 3 (1) | |
| 15-29 minutes | 33 (15) | 56 (19) | |
| 30-60 minutes | 115 (51) | 168 (56) | |
| More than 60 minutes | 48 (21) | 53 (18) | |
| Fulfilled the EULAR aerobic physical activity recommendations | 63 (28) | 104 (35) | 0.11 |
| Estimated cardiorespiratory fitness (mL/kg/min) | | | |
| Overall | 30.9 (±10.1) | 39.8 (±7.2) | <0.0001 |
| Women | 27.8 (±7.8) | 36.3 (±5.8) | <0.0001 |
| Men | 37.2 (±11.5) | 44.0 (±6.5) | <0.0001 |
| Cohen's perceived stress scale (scale 0-40) | 14 (9, 18) | 10 (7, 14) | <0.0001 |
| HADS-D (scale 0-21) | 3 (1, 5) | 1 (0, 3) | <0.0001 |
| RA specific information | | | |
| Age when diagnosed (years) | 48 (±15) | | |
| Disease duration (years) | 11 (5, 20) | | |
| Positive for anti-citrullinated protein antibody | 167 (74) | | |
| Positive for rheumatoid factor | 159 (70) | | |
| Patient global assessment (mm, scale 0-100) | 29 (14, 48) | | |
| mHAQ (scale 0.00-3.00) | 0.25 (0.00, 0.63) | | |
| Degree of joint tenderness or swelling (scale 0-10) | 2 (1, 5) | | |
| Medication - current use | | | |
| Conventional DMARDs | 186 (82) | | |
| Biological DMARDs | 116 (51) | | |
| Glucocorticoids | 51 (22) | | |
| Comorbidities | | | |
| Hypertension | 68 (30) | | |
| Respiratory disease[e] | 43 (19) | | |

**Table 1** (continued)

| | RA patients n=227 | Controls n=300 | P-value[c] |
|---|---|---|---|
| Cardiovascular disease[f] | 42 (19) | | |
| Cancer | 22 (10) | | |
| Diabetes | 14 (6) | | |

[a]Presented as number with percentage, median with 25$^{th}$ and 75$^{th}$ percentile, or mean with standard deviation as appropriate

[b]Abbreviations: DMARDs disease-modifying antirheumatic drugs, EULAR European Alliance of Associations for Rheumatology, HADS-D Hospital Anxiety and Depression Scale's Depression Score, mHAQ modified Health Assessment Questionnaire, RA rheumatoid arthritis

[c]Chi-square test, Mann Whitney U-test or t-test as appropriate

[d]Only participants performing physical activity at least weekly were asked to report intensity and duration

[e]Respiratory disease: chronic obstructive pulmonary disease, chronic restrictive pulmonary disease, or asthma

[f]Cardiovascular disease: myocardial infarction, angina, heart failure, arrhythmia, or stroke

**Table 2** Results from the structural equation models[a]

| | Associations between rheumatoid arthritis status and estimated cardiorespiratory fitness | Unstandardized coefficient (95 % confidence interval) | Standardized coefficient | P-value |
|---|---|---|---|---|
| Model 1 | Direct effect | -1.7 (-2.8, -0.6) | -0.089 | 0.002 |
| Model 2a | Direct effect | -0.9 (-2.0, 0.3) | -0.045 | 0.14 |
| | Indirect effect via physical symptoms | -0.8 (-1.3, -0.3) | -0.042 | 0.002 |
| | Total effect | -1.7 (-2.8, -0.6) | -0.087 | 0.003 |
| Model 2b | Direct effect | -0.8 (-2.0, 0.4) | -0.041 | 0.20 |
| | Indirect effect through negative emotions | -0.9 (-1.5, -0.4) | -0.048 | 0.002 |
| | Total effect | -1.7 (-2.8, -0.6) | -0.089 | 0.002 |
| Model 3 | Direct pathway | -0.5 (-1.3, 0.0) | -0.024 | 0.46 |
| | Indirect effect through physical symptoms | -0.7 (-1.3, 0.0) | -0.034 | 0.051 |
| | Indirect effect through negative emotions | -0.6 (-1.3, 0.0) | -0.034 | 0.039 |
| | Total effect | -1.8 (-2.8, -0.7) | -0.092 | 0.001 |

[a]Model 1: The effect of rheumatoid arthritis status on estimated cardiorespiratory fitness. Model 2a: The effect of rheumatoid arthritis status on estimated cardiorespiratory fitness, directly and indirectly through physical symptoms. Model 2b: The effect of rheumatoid arthritis status on estimated cardiorespiratory fitness, directly and indirectly through negative emotions. Model 3: The effect of rheumatoid arthritis status on estimated cardiorespiratory fitness, directly and indirectly through physical symptoms and negative emotions. All models were adjusted for age and sex

## Physical symptoms

Physical symptoms, represented by a latent variable based on the observed variables morning stiffness, joint pain, and pain in neck, back, or hips, explained 37% of the association between RA status and eCRF in the final model. Both pain and stiffness have been reported as important barriers to PA by RA patients [30]. Stiffness has been associated with PA habits in one study, whereas the association between pain and PA habits appears to be non-significant in most studies of RA patients [31, 32]. In patients with fibromyalgia more pain has been associated with lower fitness [33]. We may speculate that pain mainly affects exercise intensity, as our RA patients reported lower PA intensity than controls and as PA at low intensity would lead to lower CRF compared to PA at higher intensity. Regardless, exercise may lead to some reduction in pain among persons with RA. Thus, exercise can affect pain and pain can affect exercise habits [14, 30]. As the physical symptoms variable was based on three distinct symptoms, the results are not directly comparable to previous studies. The symptoms included were chosen as they are closely related to each other and therefore fit as indicators of the same latent variable. Furthermore, musculoskeletal symptoms are common both in RA patients and in healthy individuals.

Pain and morning stiffness may be prominent symptoms even when the patient is in clinical remission. EULAR recommends a patient-centred approach to pain management that involves proper assessment, a personalized management plan, and patient education [34]. Treatment of pain may involve non-pharmacological options such as PA, cognitive-behavioural therapy, and weight management, and if necessarily also pharmacological options. Some patients fear that PA can lead to disease exacerbation and joint damage [30]. This concern should be addressed with patient education, clear exercise advice, and possibly referral to a physiotherapist or other interventions that can further increase the patients' knowledge and confidence regarding PA and exercise [16, 35].

### Negative emotions

Negative emotions, represented by a latent variable combining depressive symptoms and perceived stress, explained 37% of the association between RA status and eCRF in the final model. The relationship between RA, depression, stress, and CRF is complex. RA itself increases the risk of depression and some types of stress, however both depression and stress may increase the risk of developing RA [17, 18, 36, 37]. Both depression and stress have been associated with a reduction in PA over time, and stress has been associated with lower self-reported fitness levels [19, 38, 39]. However, high CRF protects against developing depressive symptoms [2].

Depression has several detrimental effects in RA patients, including lower chance of remission, lower adherence to treatment, higher pain levels, lower quality of life, and even increased mortality rates [17]. Stress in RA patients is associated with more pain, anxiety, and reduced quality of life [40, 41]. Active behaviour coping strategies might buffer some of the impact of perceived stress on depressive symptoms in RA patients [41]. EULAR recommends regular assessment of mental health in persons with inflammatory joint diseases and initiation of interventions if necessary, as better mental health can lead to better self-management [35]. The present study demonstrated that negative emotions are associated with lower eCRF. We speculate that improvements in mental health, particularly if the individual has high levels of depressive symptoms and perceived stress, could lead to increased PA engagement, which again may increase CRF levels. Healthy lifestyle choices such as a healthy diet, regular PA, enough sleep, strong social connections, and avoidance of risky substance intake, are beneficial for mental health [42]. Persons with clinical depression might need psychological and pharmacological interventions as well. Spending time in nature and mind-body practices are other strategies that may alleviate stress [42].

### Other mediating factors

Other factors than physical symptoms and negative emotions probably also mediate the relationship between RA and low CRF. Potential mediators might include fatigue, comorbidities, lung function, body composition, inflammation, exercise habits, anxiety, motivation, self-efficacy, coping strategies, and sarcopenia [11, 32, 43, 44]. We focused on factors that are common both in RA patients and the general population, though generally more prevalent in RA patients. Including too many potentially mediating factors will lead to a very complex model and is only feasible in very large studies. RA-specific variables such as disease duration, seropositivity, tender and swollen joint counts, or disease activity, could not be included as potential mediators due to collinearity with RA status. For example, we would not expect the controls to have swollen joints, so including swollen joint count as part of the physical symptoms latent variable would lead to collinearity with RA. Although the presence of RA in the present study was associated with lower eCRF, other factors like sex, age, PA habits, and genetics probably have a larger impact on an individual's CRF than RA status [11, 12].

### Strengths and limitations

A strength of this study is that we included a relatively large sample of RA patients and controls recruited from the same geographical region. Even if the blood donors are a healthy sample of the population with few comorbidities and might not be directly comparable to persons with RA, both groups consisted of persons with a wide age range with varying levels of PA, and the analyses were adjusted for age and sex. The models had good fit. Nevertheless, there are likely other SEM models with acceptable fit, especially since several of the factors in the model may act bidirectionally.

Missing data for eCRF in 27% of the RA patients is a weakness. This was due to changes in the recruitment process to also include mail-only participation during the COVID-19 pandemic, which resulted in missing data for resting heart rate and consequently eCRF. However, all participants were included in the SEM models with their available data, which is a recognized strategy to deal with missing data that generally introduces less bias than for example listwise deletion [45]. Using non-exercise models to calculate eCRF can lead to both over- and underestimation of physical fitness. A cardiopulmonary exercise test would have given more accurate CRF results. Nevertheless, we did not have the resources to perform such testing. Moreover, by not including such testing less effort was required to participate, which probably resulted in a more representative

and larger sample. Physical symptoms, depressive symptoms, and perceived stress are subjective variables and there is inevitably some uncertainty with these measures. HADS-D and Cohen's perceived stress scale were chosen to assess the negative emotions because they are well-known, validated, and frequently used instruments [25, 26]. Due to the cross-sectional design, evaluation of causality was not possible.

## Conclusion

Both physical and emotional factors mediated the association between RA and low eCRF. It is important to assess or estimate CRF, or alternatively PA levels, and support persons with low eCRF in increasing their PA engagement. Both physical and psychological factors impact human behaviour, and both aspects need to be addressed for optimal care.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10067-023-06584-x.

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**Author contributions** Study conception and design: VV, MH, ISH. Data collection: ISH, VV, MH. Data analysis: VV, ISH. Data interpretation: ISH, VV, MH. Drafting the manuscript: ISH. Critically revising the manuscript: VV, MH. All authors approved the final version of the manuscript.

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**Data availability** No additional data are available.

## Declarations

**Conflicts of interest** No conflicts of interest, financial or otherwise, are declared by the authors.



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# Online Resource Text 1

Article: The association between rheumatoid arthritis and reduced estimated cardiorespiratory fitness is mediated by physical symptoms and negative emotions: a cross-sectional study

Journal: Clinical Rheumatology.

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**Model fit indices and estimation method**

Common model fit indices in structural equation modelling (SEM) are the chi-square test, root mean error of approximation (RMSEA), comparative fit index (CFI), and Tucker-Lewis index (TLI) [1]. The chi square test compares the SEM model to a model that fits the data perfectly. RMSEA is related to the residual between the model and the observed data, accounting for sample size and model complexity. CFI and TLI estimates how much better the SEM model fits the data compared to the baseline model that assumes no correlation between the variables, penalizing for complex models in different ways. A model with that fit the data well should have a non-significant chi-square test, RMSEA $<0.10$, CFI $\geq 0.90$, and TLI $\geq 0.90$ [1].

The estimation method maximum likelihood with missing values was chosen in the present study as many participants missed data for one or more variables. This method includes all participants in the analysis with each participant contributing with their available data.

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# Online Resource Table S1

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Journal: Clinical Rheumatology.

Authors: Ingrid Sæther Houge, Mari Hoff, Vibeke Videm

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**Online Resource Table S1: Detailed results from Structural Equation Model 1 [a,b]**

| | **Unstandardized coefficients (95% confidence interval)** | | | **Standardized coefficients** | | |
|---|---|---|---|---|---|---|
| | Direct effect | Indirect effect | Total effect | Direct effect | Indirect effect | Total effect |
| Effect on eCRF | | | | | | |
| Rheumatoid arthritis | -1.70 (-2.79, -0.61)* | - | -1.70 (-2.79, -0.61)* | -0.089* | - | -0.089* |
| Male sex | 9.45 (8.51, 10.38)* | 0.25 (0.05, 0.46)† | 9.70 (8.76, 10.63)* | 0.488* | 0.013† | 0.501* |
| Age | -0.38 (-0.42, -0.35)* | -0.03 (-0.05,-0.01)* | -0.41 (-0.44, -0,38)* | -0.645* | -0.046* | -0.691* |
| Effect on rheumatoid arthritis | | | | | | |
| Male sex | -0.15 (-0.22, - 0.08)* | - | -0.15 (-0.22, - 0.08)* | -0.148* | - | -0.148* |
| Age | 0.02 (0.01, 0.02)* | - | 0.02 (0.01, 0.02)* | 0.516* | - | 0.516* |

[a] Abbreviations: eCRF estimated cardiorespiratory fitness. †<0.05, *<0.01.

[b] Model 1: The effect of rheumatoid arthritis status on estimated cardiorespiratory fitness in a model adjusted for age and sex.

# Online Resource Table S2

Article: The association between rheumatoid arthritis and reduced estimated cardiorespiratory fitness is mediated by physical symptoms and negative emotions: a cross-sectional study

Journal: Clinical Rheumatology.

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**Online Resource Table S2: Detailed results from Structural Equation Model 2a [a,b]**

| | Unstandardized coefficients (95% confidence interval) | | | Standardized coefficients | | |
|---|---|---|---|---|---|---|
| | Direct effect | Indirect effect | Total effect | Direct effect | Indirect effect | Total effect |
| Effect on eCRF | | | | | | |
| Rheumatoid arthritis | -0.87 (-2.03, 0.30) | -0.81 (-1.33, -0.29)* | -1.68 (-2.77, -0.59)* | -0.045 | -0.042* | -0.087* |
| Male sex | 9.26 (8.34, 10.19)* | 0.25 (0.05, 0.45)† | 9.51 (8.59, 10.43)* | 0.480* | 0.013† | 0.493* |
| Age | -0.38 (-0.41, -0.35)* | -0.03 (-0.05, -0.01)* | -0.41 (-0.44, -0.38)* | -0.640* | -0.055* | -0.695* |
| Physical symptoms | 1 (constrained) | - | 1 (constrained) | 0.095* | - | 0.095* |
| Effect on rheumatoid arthritis | | | | | | |
| Male sex | -0.15 (-0.22, -0.08)* | - | -0.15 (-0.22, -0.08)* | -0.148* | - | -0.148* |
| Age | 0.02 (0.01, 0.02)* | - | 0.02 (0.01, 0.02)* | 0.516* | - | 0.516* |
| Effect on physical symptoms | | | | | | |
| Rheumatoid arthritis | -0.81 (-1.33, -0.29)* | - | -0.81 (-1.33, -0.29)* | -0.444* | - | -0.444* |
| Male sex | - | 0.12 (0.02, 0.22)† | 0.12 (0.02, 0.22)† | - | 0.066† | 0.066† |
| Age | -0.01 (-0.01, 0.00) | -0.01 (-0.02, 0.00)* | -0.02 (-0.03, -0.01)* | -0.099 | -0.229* | -0.328* |
| Effect on joint pain past six months | | | | | | |
| Rheumatoid arthritis | - | 2.42 (1.94, 2.91)* | 2.42 (1.94, 2.91)* | - | 0.423* | 0.423* |
| Physical symptoms | -2.99 (-4.83, -1.15)* | - | -2.99 (-4.83, -1.15)* | -0.952* | - | -0.952* |
| Sex | - | -0.36 (-0.55, -0.17)* | -0.36 (-0.55, -0.17)* | - | -0.062* | -0.062* |
| Age | - | 0.06 (0.04, 0.07)* | 0.06 (0.04, 0.07)* | - | 0.313* | 0.313* |
| Effect on morning stiffness | | | | | | |
| Rheumatoid arthritis | - | 2.26 (1.81, 2.71)* | 2.26 (1.81, 2.71)* | - | 0.399* | 0.399* |
| Physical symptoms | -2.79 (-4.51, -1.08)* | - | -2.79 (-4.51, -1.08)* | -0.899* | - | -0.899* |
| Male sex | - | -0.34 (-0.51, -0.16)* | -0.34 (-0.51, -0.16)* | - | -0.060* | -0.060* |
| Age | - | 0.05 (0.04, 0.06)* | 0.05 (0.04, 0.06)* | - | 0.295* | 0.295* |
| Effect on pain in neck/back/hips | | | | | | |
| Rheumatoid arthritis | - | 1.71 (1.22, 2.19)* | 1.71 (1.22, 2.19)* | - | 0.287* | 0.287* |
| Physical symptoms | -2.11 (-3.33, -0.89)* | - | -2.11 (-3.33, -0.89)* | -0.647* | - | -0.647* |
| Male sex | - | -0.25 (-0.40, -0.11)* | -0.25 (-0.40, -0.11)* | - | -0.042* | -0.042* |
| Age | - | 0.04 (0.03, 0.05)* | 0.04 (0.03, 0.05)* | - | 0.212* | 0.212* |

[a] Abbreviations: eCRF estimated cardiorespiratory fitness. †<0.05. *<0.01.

[b] Model 2a: The effect of rheumatoid arthritis status on estimated cardiorespiratory fitness, directly and indirectly through physical symptoms, in a model adjusted for age and sex.

# Online Resource Table S3

Article: The association between rheumatoid arthritis and reduced estimated cardiorespiratory fitness is mediated by physical symptoms and negative emotions: a cross-sectional study

Journal: Clinical Rheumatology.

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**Online Resource Table S3: Detailed results from Structural Equation Model 2b [a,b]**

| | Unstandardized coefficients (95% confidence interval) | | | Standardized coefficients | | |
|---|---|---|---|---|---|---|
| | Direct effect | Indirect effect | Total effect | Direct effect | Indirect effect | Total effect |
| Effect on eCRF | | | | | | |
| - Rheumatoid arthritis | -0.78 (-1.99, 0.42) | -0.93 (-1.50, -0.35)* | -1.71 (-2.81 -0.62)* | -0.041 | -0.048* | -0.089* |
| - Male sex | 9.50 (8.56, 10.44)* | 0.25 (0.05, 0.46)† | 9.75 (8.82, 10.69)* | 0.490* | 0.013† | 0.503* |
| - Age | -0.39 (-0.43, -0.36)* | -0.02 (-0.04, 0.00) | -0.41 (-0.44, -0.38)* | -0.661* | -0.029 | -0.690* |
| - Negative emotions | 1 (constrained) | - | 1 (constrained) | 0.107* | - | 0.107* |
| Effect on rheumatoid arthritis | | | | | | |
| - Male sex | -0.15 (-0.22, -0.08)* | - | -0.15 (-0.22, -0.08)* | -0.148* | - | -0.148* |
| - Age | 0.02 (0.01, 0.02)* | - | 0.02 (0.01, 0.02)* | 0.516* | - | 0.516* |
| Effect on negative emotions | | | | | | |
| - Rheumatoid arthritis | -0.93 (-1.50, -0.35)* | - | -0.93 (-1.50, -0.35)* | -0.453* | - | -0.453* |
| - Male sex | - | 0.14 (0.03, 0.25)† | 0.14 (0.03, 0.25)† | - | 0.067† | 0.067† |
| - Age | 0.01 (0.00, 0.02)† | -0.02 (-0.02, -0.01)* | -0.01 (-0.01, 0.00) | 0.157† | -0.234* | -0.077 |
| Effect on HADS-D | | | | | | |
| - Rheumatoid arthritis | - | 2.35 (1.80, 2.89)* | 2.35 (1.80, 2.89)* | - | 0.406* | 0.406* |
| - Negative emotions | -2.52 (-4.00, 1.05)* | - | -2.52 (-4.00, -1.05)* | -0.897* | - | -0.897* |
| - Sex | 0.23 (-0.24, 0.71) | -0.35 (-0.54, -0.16)* | -0.12 (-0.61, 0.38) | 0.040 | -0.060* | -0.020 |
| - Age | - | 0.01 (0.00, 0.03) | 0.01 (0.00, 0.03) | - | 0.069 | 0.069 |
| Effect on perceived stress scale | | | | | | |
| - Rheumatoid arthritis | - | 4.18 (2.99, 5.37)* | 4.18 (2.99, 5.37)* | - | 0.334* | 0.334* |
| - Negative emotions | -4.50 (-7.03, -1.96)* | - | -4.50 (-7.03, -1.96)* | -0.737* | - | -0.737* |
| - Male sex | -1.30 (-2.34, -0.26)† | -0.62 (-0.98, -0.27)* | -1.92 (2.99, -0.85)* | -0.103† | -0.049* | -0.152* |
| - Age | - | 0.02 (0.00, 0.05) | 0.02 (0.00, 0.05) | - | 0.057 | 0.057 |

[a] Abbreviations: eCRF estimated cardiorespiratory fitness, HADS-D Hospital Anxiety and Depression Scale' Depression Score. †<0.05. *<0.01.

[b] Model 2b: The effect of rheumatoid arthritis status on estimated cardiorespiratory fitness, directly and indirectly through negative emotions, in a model adjusted for age and sex.

# Online Resource Table S4

Article: The association between rheumatoid arthritis and reduced estimated cardiorespiratory fitness is mediated by physical symptoms and negative emotions: a cross-sectional study

Journal: Clinical Rheumatology.

Authors: Ingrid Sæther Houge, Mari Hoff, Vibeke Videm

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**Online Resource Table S4: Detailed results from Structural Equation Model 3** [a,b]

| | Unstandardized coefficients (95% confidence interval) | | | Standardized coefficients | | |
|---|---|---|---|---|---|---|
| | Direct effect | Indirect effect | Total effect | Direct effect | Indirect effect | Total effect |
| Effect on eCRF | | | | | | |
| - Rheumatoid arthritis | -0.46 (-1.70, 0.77) | -1.30 (-1.98, -0.62)* | -1.76 (-2.85, -0.68)* | -0.024 | -0.068* | -0.092* |
| - Male sex | 9.30 (8.37, 10.22)* | 0.26 (0.06, 0.47)† | 9.56 (8.64, 10.48)* | 0.480* | 0.014† | 0.494* |
| - Age | -0.39 (-0.42, -0.35)* | -0.02 (-0.05, 0.00)† | -0.41 (-0.44, -0.38)* | -0.652* | -0.043† | 0.695* |
| - Physical symptoms | 1 (constrained) | - | 1 (constrained) | 0.072† | - | 0.072† |
| - Negative emotions | -0.27 (-0.53, -0.02)† | - | -0.27 (-0.53, -0.02)† | -0.074† | - | -0.074† |
| Effect on rheumatoid arthritis | | | | | | |
| - Male sex | -0.15 (-0.22, -0.08)* | - | -0.15 (-0.22, -0.08)* | -0.148* | - | -0.148* |
| - Age | 0.02 (0.01, 0.02)* | - | 0.02 (0.01, 0.02)* | 0.516* | - | 0.516* |
| Effect on physical symptoms | | | | | | |
| - Rheumatoid arthritis | -0.65 (-1.31, 0.00) | - | -0.65 (-1.31, 0.00) | -0.471 | - | -0.471 |
| - Male sex | - | 0.10 (-0.01, 0.21) | 0.10 (-0.01, 0.21) | - | 0.070 | 0.070 |
| - Age | -0.01 (-0.01, 0.00) | -0.01 (-0.02, 0.00) | -0.02 (-0.03, 0.00) | -0.101 | -0.243 | -0.344 |
| Effect on joint pain past six months | | | | | | |
| - Rheumatoid arthritis | - | 2.38 (1.90, 2.86)* | 2.38 (1.90, 2.86)* | - | 0.416* | 0.416* |
| - Physical symptoms | -3.65 (-7.28, -0.03)† | - | -3.65 (-7.28, -0.03)† | -0.882† | - | -0882† |
| - Sex | - | -0.36 (-0.54, -0.17)* | -0.36 (-0.54, -0.17)* | - | -0.061* | -0.061* |
| - Age | - | 0.05 (0.04, 0.07)* | 0.05 (0.04, 0.07)* | - | 0.304* | 0.304* |
| Effect on morning stiffness | | | | | | |
| - Rheumatoid arthritis | - | 2.25 (1.80, 2.71)* | 2.25 (1.80, 2.71)* | - | 0.398* | 0.398* |
| - Physical symptoms | -3.46 (-6.89, -0.03)† | - | -3.46 (-6.89, -0.03)† | -0.845† | - | -0.845† |
| - Sex | - | -0.34 (-0.51, -0.16)* | -0.34 (-0.51, -0.16)* | - | -0.059* | -0.059* |
| - Age | - | 0.05 (0.04, 0.06)* | 0.05 (0.04, 0.06)* | - | 0.291* | 0.291* |
| Effect on pain in neck/back/hips | | | | | | |
| - Rheumatoid arthritis | - | 1.94 (1.49, 2.40)* | 1.94 (1.49, 2.40)* | - | 0.327* | 0.327* |
| - Physical symptoms | -2.98 (-5.90, -0.07)† | - | -2.98 (-5.90, -0.07)† | -0.694† | - | -0.694† |
| - Sex | - | -0.29 (-0.45, -0.13)* | -0.29 (-0.45, -0.13)* | - | -0.048* | -0.048* |
| - Age | - | 0.04 (0.03, 0.06)* | 0.04 (0.03, 0.06)* | - | 0.239* | 0.239* |
| Effect on negative emotions | | | | | | |
| - Rheumatoid arthritis | 2.36 (1.82, 2.91)* | - | 2.36 (1.82, 2.91)* | 0.456* | - | 0.456* |
| - Male sex | - | -0.35 (-0.54, -0.16)* | -0.35 (-0.54, -0.16)* | - | -0.067* | -0.067* |

| | | | | | | |
|---|---|---|---|---|---|---|
| - Age | -0.03 (-0.04, -0.01)* | 0.04 (0.03, 0.05)* | 0.01 (0.00, 0.03) | -0.159* | 0.236* | 0.077 |
| Effect on HADS-D | | | | | | |
| - Rheumatoid arthritis | - | 2.36 (1.82, 2.91)* | 2.36 (1.82, 2.91)* | - | 0.409* | 0.409* |
| - Negative emotions | 1 (constrained) | - | 1 (constrained) | 0.897* | - | 0.897* |
| - Sex | 0.34 (-0.11, 0.79) | -0.35 (-0.54, -0.16)* | -0.01 (-0.48, 0.46) | 0.058 | -0.060* | -0.002 |
| - Age | - | 0.01 (0.00, 0.03) | 0.01 (0.00, 0.03) | - | 0.069 | 0.069 |
| Effect on perceived stress scale | | | | | | |
| - Rheumatoid arthritis | - | 4.23 (3.02, 5.43)* | 4.23 (3.02, 5.43)* | - | 0.338* | 0.338* |
| - Negative emotions | 1.79 (1.39, 2.18)* | - | 1.79 (1.39, 2.18)* | 0.740* | - | 0.740* |
| - Male sex | -1.11 (-2.10, -0.11)† | -0.63 (-0.99, -0.27)* | -1.73 (-2.77, -0.70)* | -0.088† | -0.050* | -0.138* |
| - Age | - | 0.02 (0.0, 0.05) | 0.02 (0.00, 0.05) | - | 0.057 | 0.057 |

[a]Abbreviations: eCRF estimated cardiorespiratory fitness, HADS-D Hospital Anxiety and Depression Scale' Depression Score. †<0.05. *<0.01.

[b]Model 3: The effect of rheumatoid arthritis status on estimated cardiorespiratory fitness, directly and indirectly through physical symptoms and negative emotions, in a model adjusted for age and sex

# Online Resource Table S5

Article: The association between rheumatoid arthritis and reduced estimated cardiorespiratory fitness is mediated by physical symptoms and negative emotions: a cross-sectional study

Journal: Clinical Rheumatology.

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**Online Resource Table S5: Model fit indices for the structural equation models** [a]

| | **P-value for the chi-square test** | **Root mean square error of approximation** | **Comparative fit index** | **Tucker Lewis Index** |
|---|---|---|---|---|
| Model 1 | Not applicable | <0.001 | 1.000 | 1.000 |
| Model 2a | 0.15 | 0.032 | 0.998 | 0.993 |
| Model 2b | 0.25 | 0.026 | 0.999 | 0.995 |
| Model 3 | 0.047 | 0.037 | 0.995 | 0.987 |

[a]Model 1: The effect of rheumatoid arthritis status on estimated cardiorespiratory fitness. Model 2a: The effect of rheumatoid arthritis status on estimated cardiorespiratory fitness, directly and indirectly through physical symptoms. Model 2b: The effect of rheumatoid arthritis status on estimated cardiorespiratory fitness, directly and indirectly through negative emotions. Model 3: The effect of rheumatoid arthritis status on estimated cardiorespiratory fitness, directly and indirectly through physical symptoms and negative emotions. All models were adjusted for age and sex.

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