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Marthe Halsan Liff

Cardiorespiratory fitness and mortality in rheumatoid arthritis

Doctoral thesis

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

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Trondheim, June 2022

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Kondisjon og dødelighet hos pasienter med revmatoid artritt

Leddgikt, eller revmatoid artritt (RA), er mest kjent for å gi betennelse med hevelse og av og til ødeleggelser i ledd. Mindre kjent er at sykdommen også påvirker indre organer og kan føre til tidligere død hos personer med RA sammenliknet med den generelle befolkningen. Denne økte dødelighetsraten er delvis forklart ved at betennelse i kroppen bidrar til høyere forekomst av hjerte- og karsykdom.

I løpet av de siste tiårene har man tatt i bruk en rekke nye medikamenter i behandlingen av RA, som bl.a. reduserer betennelsesnivået i kroppen. Man håper derfor at dødelighetsraten i denne pasientgruppen på sikt vil reduseres.

I den generelle befolkningen er det nå mye kunnskap som viser at det fysiske kondisjonsnivået («kondisen») hos den enkelte har betydning for hvor lenge man lever. God kondisjon reduserer risikoen for tidlig død. Vi ønsket derfor å undersøke om kondisjonsnivået har betydning som risikofaktor for tidligere død også hos personer med RA.

Vi fant at personer med RA hadde dårligere kondisjon, og at deres kondisjon falt raskere ved økende alder sammenliknet med den generelle befolkningen. Dårlig kondisjon var en viktig årsak til den økte dødelighetsraten hos personer med RA, og var faktisk viktigere enn det å ha RA i seg selv.

Kondisjon kan vurderes uten en fysisk test ved å bruke en kondisjonsformel som bl.a. omfatter informasjon om treningsvaner, kjønn, alder, hvilepuls, livvidde eller kroppsmasseindeks. Våre studier viste at en kondisjonskalkulator utviklet for den generelle befolkningen ikke gav riktig kondisjonsnivå når den ble brukt for personer med RA. Vi utviklet derfor en ny kondisjonskalkulator tilpasset personer med RA (tilgjengelig på nettet, RA*fit*CALC: https://vev.medisin.ntnu.no/rafitcalc/). Kondisjonskalkulatoren ble brukt i våre studier, og kan også være et enkelt hjelpemiddel for personer med RA som ønsker å følge sin egen kondisjon.

Den viktigste konklusjonen fra våre studier er at tiltak for å bedre kondisjonen vil ha stor betydning for å gi personer med RA et lengre liv. Tiltak for å bedre kondisjonen bør derfor prioriteres selv om vi stadig får bedre medikamenter til behandling av denne sykdommen.

Metoder: I løpet av 2017 ble 93 voksne personer med RA rekruttert fra Revmatologisk avdeling ved St. Olavs hospital og kondisjonstestet på tredemølle. Videre ble deres kondisjonsnivå sammenliknet med 4631 deltakere som ble kondisjonstestet i Helseundersøkelsen i Trøndelag (HUNT3). Kondisjonsformelen vi utviklet ble brukt til å kalkulere kondisjonsnivåene til personer med RA i HUNT2 og HUNT3-materialet (188-436 personer i ulike artikler). Kondisjonsnivået, reduksjon av kondisjonen med økende alder og kondisjonsnivåets betydning for dødelighet ble sammenliknet med resultater fra deltakere i HUNT som ikke hadde RA (26202-67910 personer i ulike artikler).

Vi har benyttet ulike statistiske metoder som multippel lineær regresjonsanalyse, Cox regresjonsanalyse og medieringsanalyse. Prosjektet ble gjennomført i samarbeid med Revmatologisk avdeling ved St. Olavs Hospital, kjernefasiliteten for trening og bevegelse, NextMove, og HUNT.

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Marthe Halsan Liff,
Trondheim 2022

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RMD open. 2019;5(1):e000912.

Paper 2

An Estimation Model for Cardiorespiratory Fitness in Adults with Rheumatoid Arthritis.

Liff MH, Hoff M, Fremo T, Wisloff U, Videm V.

Med Sci Sports Exerc. 2020;52(6):1248-55.

Paper 3

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Liff MH, Hoff M, Wisløff U, Videm V.

Rheumatol Int. 2021;41(2):369-79.

Paper 4

Reduced cardiorespiratory fitness is a mediator of excess all-cause mortality in rheumatoid arthritis: the Trøndelag Health Study.

Liff MH, Hoff M, Wisloff U, Videm V.

RMD open. 2021;7(1):e001545.

SUMMARY OF THE THESIS

Background

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that affects synovial joints and internal organs. It affects around 1% of the population, and the disease is associated with increased all-cause mortality rates compared with the general population.

Through the last decades, medical treatment of RA has improved largely. Treatment strategies aim at early medical intervention to reduce inflammation and disease activity to improve function and inhibit joint destructions. As far as we know, there is still no robust evidence that improved medical treatment with modern drugs has reduced the mortality gap between RA patients and the general population.

Cardiorespiratory fitness (CRF) is an important modifiable predictor of all-cause mortality in the general population. Still, there is no robust evidence that this is true for RA patients. Some studies have demonstrated that RA patients have reduced CRF compared to healthy people, which may contribute to their increased mortality rates.

The gold standard test to quantify CRF is to measure a person's maximum oxygen uptake (VO_{2max}) during cardiopulmonary exercise testing (CPET) on a bicycle ergometer a treadmill. Less resource-intensive estimation equations for CRF (eCRF) without the need for a physical test have been developed for the general population, but have not been optimized for persons with RA. There is also a knowledge gap concerning which variables are associated with CRF in RA patients.

Aims

This study aimed to
- investigate which variables are associated with CRF in RA patients
- develop eCRF equations suitable for RA patients
- investigate differences in eCRF and age-related change in eCRF in RA patients and controls
- investigate which variables are associated with the eCRF change
- investigate which variables are associated with mortality in RA patients and controls
- study possible consequences from low eCRF on mortality in an RA population

Methods

During 2017, 93 RA patients from St. Olavs Hospital's rheumatology outpatient clinic were recruited for CPET to measure their VO_{2max}. We also collected RA-specific variables like presence of autoantibodies and various measures of disease activity along with vital measures like blood pressure, pulse, and body mass index (BMI). Multiple linear regression was then used to identify variables that were associated with CRF in RA patients and to develop new eCRF equations suitable for RA patients.

The new eCRF equations were used to calculate the eCRF of RA patients attending the second and third waves of the Trøndelag Health Study, HUNT2 (1995-1997) and HUNT3 (2006-2008). eCRF results were then compared with results from the general population in HUNT2 and HUNT3.

Multiple linear regression with change in eCRF from HUNT2 to HUNT3 as the dependent variable was used to investigate if CRF in RA patients decreased faster with increasing age

compared to the general population in HUNT. Furthermore, multiple linear regression was used to find variables associated with eCRF change.

All-cause mortality in RA patients and controls in HUNT2 and HUNT3 was analyzed using Cox proportional hazard regression. The analyses were stratified on sex, and age was the time variable. The date of the first participation in HUNT2 or HUNT3 was the baseline, and participants were followed until they died, or until the December 31st, 2018. To investigate the effect of having RA on mortality and to answer the question "How much of the associations of RA with all-cause mortality is caused by low eCRF?", a Cox regression-based mediation analysis was performed.

Results

BMI, physical activity, systolic blood pressure, resting heart rate, and smoking were associated with VO_{2max} in RA patients. The only RA-specific variable associated with VO_{2max} was the patient's global assessment.

Our investigations resulted in five new eCRF equations with some variations regarding variables to allow for the calculation of eCRF according to data availability. One eCRF equation for individual use (RA*fit*CALC) was published online.

eCRF in RA patients was lower and eCRF decreased more rapidly with increasing age in RA patients compared to the general population. In addition to sex and RA status, age, baseline eCRF, smoking, cardiovascular disease, BMI, high-density lipoprotein concentration, asthma, and hypertension were associated with the change in eCRF from HUNT2 to HUNT3.

Using Cox regression, low eCRF was associated with mortality both in RA patients and controls from the general population. This was also true after adjustment for hypertension, BMI, smoking, total cholesterol, diabetes, and creatinine concentration. The mediation analysis showed that RA patients had a 28% excess risk of all-cause mortality compared to controls. The direct effect of RA was 5%, the indirect effect of RA via low eCRF was 4%, and the effect from an interaction between RA and low eCRF accounted for 19%.

Conclusion and clinical implications

Low physical fitness is an underestimated risk factor for premature death in patients with RA, and its contribution to excess all-cause mortality by far exceeded the isolated effect of having RA. Along with medical treatment, measures to improve physical fitness in RA patients should be part of early intervention strategies to reduce the mortality gap between RA patients and the general population.

In addition to investigations about eCRF in RA patients attending large population-based studies, the new eCRF equations developed for RA patients make it possible for patients and physicians to follow eCRF improvements after a period of relevant physical training. Furthermore, physicians can easily identify if an RA patient has an eCRF level that needs to be addressed for better health. In this way the new eCRF equations can contribute to improved fitness in RA patients.

ABBREVIATIONS AND DEFINITIONS

ACC	American Colleague of Cardiology
ACPA	Anti-citrullinated protein antibody
ACSM	American College of Sports Medicine
ACR	American College of Rheumatology
AHA	American Heart Association
AS	Ankylosing spondylitis
bDMARDs	Biologic disease-modifying anti-rheumatic drugs
CDAI	Clinical Disease Activity Index
CI	Confidence interval
CPET	Cardiopulmonary exercise test
CRF	Cardiorespiratory fitness
CRP	C-reactive protein
csDMARDs	Conventional systemic disease-modifying anti-rheumatic drugs
CT	Computer tomography
CVD	Cardiovascular disease
CVR	Cardiovascular risk
DAS28	Disease activity score of 28 joints
DMARDs	Disease-modifying anti-rheumatic drugs
eCRF	Estimated cardiorespiratory fitness
ESR	Erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
HIIT	High intensity interval training
HLA	Human leucocyte antigen
HR	Heart rate
HuLARS	The HUNT Longitudinal Ankylosing Spondylitis and Rheumatoid Arthritis Study
HUNT	The Trøndelag Health study
hsCRP	C-reactive protein measured in high-sensitivity assays
MET	Metabolic equivalent
mHAQ	Modified Stanford Health Assessment Questionnaire
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
NorArtritt	The Norwegian arthritis registry

PA	Physical activity
PADI	Peptidyl arginine deaminase
PGA	Patient Global Assessment
PROM	Patient reported outcom measure
PTPN22	Protein tyrosine phosphatase non-receptor type 22 gene
RCT	Randomized controlled trial
RA	Rheumatoid arthritis
RER	Respiratory exchange ratio
RF	Rheumatoid factor
RHR	Resting heart rate
RPE Borg	Rated Perceived Exertion Scale 6-20
SCORE	European Society of Cardiology's Systematic coronary risk evaluation
SE	Shared epitope
SMR	Standard mortality ratio
TNF	Tumore necrosis factor
tsDMARDs	Targeted synthetic disease-modifying anti-rheumatic drugs
VAS	Visual Analogue Scale
VO_{2max}	Maximal oxygen ventilation
VO_{2peak}	Peak oxygen ventilation

BACKGROUND

1 Epidemiology and classification of rheumatoid arthritis

Rheumatoid arthritis (RA) has an overall incidence of approximately 50/100,000 per year (women 58/100,000 and men 36/100,000) and a prevalence of 768/100,000 (women 1,003/100,000 and men 513/100,000) in Norway, and the prevalence does not vary significantly in most regions of the world (1, 2). It is a chronic autoimmune rheumatic disease characterized by the presence of symmetric polyarthritis with a predisposition for small joints of the hands and feet (1, 3, 4). In theory, inflammation with synovitis can affect any synovial joint (3). As bursae and tendon sheaths have synovial linings, they are often affected as part of the disease. The inflammation with swelling of the joints is known as arthritis, whereas inflammation of bursae and tendon sheaths are denoted bursitis and tendinitis, respectively.

RA is often classified as being seropositive or seronegative, which reflects if the patient has tested positive or negative for rheumatoid factor (RF+/RF–) and/or anti-citrullinated protein antibodies (ACPA+/ACPA–). Whereas the specificity for RA of ACPA positivity is rather high, RF can be positive in a various of rheumatic diseases, as well as other diseases. Inflammation can lead to irreversible destructions of bone within joints (erosions) and eventually misalignments in joints that give reduced functionality. The degree of erosivity is affected by ACPA status, and choice and timing of medications (5).

With increasing knowledge and focus upon early medical treatment, classification criteria have changed over time. The former 1987 American College of Rheumatology (ACR) classification criteria (Table 1) (6) and the new ACR/European Alliance of Associations for Rheumatology (EULAR) 2010 classification criteria for RA (Table 2) (7) are both accepted tools for diagnosing RA. However, the ACR/EULAR 2010 version is now preferred, as it better detects RA at an early stage, allowing early treatment.

Table 1: The 1987 ACR revised criteria for the classification of rheumatoid arthritis (6)
For classification purposes, a patient has rheumatoid arthritis if he/she has satisfied at least 4 of these 7 criteria. Abbreviations: MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; PIP, proximal interphalangeal joint.

Criterion with definition	
1. ***Morning stiffness, lasting for ≥6 weeks*** Definition: Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement	1
2. ***Arthritis of 3 or more joint areas, lasting for ≥6*** **weeks** Definition: At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints	1
3. ***Arthritis of hand joints, lasting for ≥6 weeks*** Definition: At least 1 area swollen (as defined in 2) in a wrist, MCP, or PIP joint	1
4. ***Symmetric arthritis, lasting for ≥6 weeks*** Definition: Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPS, MCPs, or MTPs is acceptable without absolute symmetry	1
5. ***Rheumatoid nodules*** Definition: Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician	1
6. ***Serum rheumatoid factor*** Definition: Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in 4% of normal control subjects	1
7. ***Radiographic changes*** Definition: Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)	1

Table 2: 2010 RA classification criteria (7, 8)**: domains, categories, and point scores**

The points from each of domain A through D are added and the sum is the total score. A total score of ≥6 is needed to classify a patient as having definite rheumatoid arthritis. Abbreviations: ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IP, interphalangeal joint; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; PIP, proximal interphalangeal joint; RF, rheumatoid factor.

A. *Joint involvement* Definitions: Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. DIP joints, first CMC joints and first MTP joints are excluded from assessment. Large joints refer to shoulders, elbows, hips, knees, and ankles. Small joints refer to MCP joints, PIP joints, second through fifth MTP joints, thumb IP joints and wrists	
1 large joint	0
2-10 large joints	1
4-10 small joints (large joints not counted)	3
>10 joints including at least one small joint	5
B. *Serology* (at least one test needed for classification)	
Negative RF and negative ACPA (≤upper limit of normal)	0
Low positive RF or low positive ACPA (> upper normal limit)	2
High positive RF or high positive ACPA (>3 × upper normal limit)	3
C. *Acute-phase reactants* (at least one test needed for classification)	
Normal CRP and normal ESR (determined by local laboratory standards)	0
Abnormal CRP or abnormal ESR (determined by local laboratory standards)	1
D. *Duration of symptoms* (patient's self-report)	
< 6 weeks	0
≥ 6 weeks	1

2 Pathogenesis of RA

2.1 Phases in the development of established RA

The pathogenesis of RA results from an interplay between genetic and environmental factors. Clinical disease onset comes after a preclinical phase (preclinical RA) lasting from months to years, in which many persons develop ACPA, RF or other autoantibodies without having joint symptoms (9). Preclinical RA also consists of a phase with general symptoms like fatigue and arthralgia without arthritis (9, 10). Mice injected with ACPA developed pain-like behavior, supporting that ACPA may contribute to arthralgia without arthritis (11). Undifferentiated arthritis or "early RA" is often the last phase of preclinical RA before established classifiable RA evolves (9, 12).

2.2 Immunology and genetics

A cascade of immunologic events eventually leads to symptomatic RA. The pre-RA phase is dominated by immune processes outside the joints, e.g. at mucosal surfaces (9). Central to the development is the production of autoantibodies against post-translationally modified proteins that are presented for T-cells. T-cells further stimulate B-cell maturation into plasma cells that produce ACPA (9).

2.2.1 Post-translational modification processes in preclinical RA

Examples of post-translational modification processes of proteins are citrullination, carbamylation and acetylation (13, 14). In citrullination, the peptidyl arginine deiminase (PADI) enzyme that is located in mucosal surfaces converts arginine to citrulline while carbamylation is the conversion of a lysine into homocitrulline (15). In response to the citrullinated protein, ACPA+ RA individuals produce ACPA. In serum from ACPA- RA patients anti-carbamylated protein antibodies are present in 30% (16). Anti-carbamylated protein antibodies may also coexist with ACPA in ACPA+ patients (15). Autoantibodies against acetylated proteins are also identified (13). RF levels also during the preclinical stages of RA, and contribute to the pathogenesis by e.g., binding to the Fc part of immunoglobulins, forming immune complexes that trigger inflammation (17).

2.2.2 Antigen presentation in preclinical RA

The class II major histocompatibility complex (MHC) locus on chromosome 6 codes for important molecules called human leucocyte antigen (HLA) molecules. HLA molecules are involved in the antigen presentation to T-cells mentioned above. The MHC class II *HLA-DRB1* alleles constitute the single strongest genetic association for RA (18). In particular,

HLA-DRB1 alleles coding for particular amino acid residues 71-71 in the β-chain of the DRB1 molecule are associated with a high risk of developing RA (19). This amino acid sequence is also known as the shared epitope (SE) and contributes to a more effective binding of post-translationally modified proteins to the HLA molecule. This increases the risk of developing ACPA (20-22). Furthermore, the SE profile may have an impact on whether an ACPA+ person develops RA (23).

2.2.3 Non-MHC genes and different genetics of ACPA+ and ACPA- RA

More than 100 non-MHC single-nucleotide polymorphisms and genes are associated with ACPA+ RA. e.g., the coding variant of the protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) gene that affects the responsiveness of T-cell receptors (21, 24). The MHC class II HLA *DRB1* alleles are not associated with ACPA- RA, and the *PTPN22* gene is not often associated with ACPA- RA (24). However, genes located in the MHC class I HLA region are associated with ACPA- RA (24). Other RA-associated genes affect T- and B-cell function (24). In addition, epigenetic mechanisms like DNA methylation and histone modification play roles in the development of RA (12).

2.2.4 Symptomatic RA with autoimmune inflammation located in the joints

Eventually, the interplay between T- and B-cells, in many cases autoantibodies, and various cytokines leads to symptomatic RA with autoimmune processes in the joints giving rise to synovitis (19). Activated osteoclasts, fibroblasts and neutrophils are recruited as part of the inflammatory process leading to synovitis, degradation of cartilage, neoangiogenesis and destruction of bone (9).

2.3 Environmental risk factors

Genetic predisposition plays a role in RA, but only 10 % of monozygotic twins share ACPA+ RA, and 5% of monozygotic twins share ACPA- RA (23). This low concordance of RA in related persons implicates that environmental factors contribute to the development (25). Mucosal surfaces of the mouth, lungs and gastrointestinal tract are sites for exposure of environmental risk factors like toxins in addition to various bacteria. Cigarette smoking is perhaps the most well-known toxin. Other relevant substances are silica, textile dust, coal, and asbestos (21, 26, 27). Inhalation of toxic chemicals like cigarette smoke increases the expression of PADI, secondarily leading to increased protein citrullination. Heavy cigarette smoking in combination with carriage of two copies of the *HLA-DRB1* SE allele might increase the risk of RA 20-40 fold compared with non-smokers without these alleles (28, 29), and the risk declines slowly within 10 years of cessation (29).

Because more women than men suffer from RA, it has been investigated if factors affecting female sex hormones like breastfeeding and the use of oral contraceptives influence the risk of RA. These studies show conflicting results (21). Pregnancy is associated with reduced disease activity, while the post-partum period is associated with disease flares (30).

Periodontitis and certain bacteria of the oral mucosa are associated with higher risk of RA through mechanisms leading to hypercitrullination (31, 32), and stimulation of local differentiation of the T-helper 17 cells (33). Although there are differing bacterial patterns in gut flora of RA patients and healthy individuals, clear evidence for an association between certain bacteria in the gut flora and RA is still lacking. The gut microbiome may be changed because of an inflammatory disease, and anti-rheumatic medication may affect the gut flora as well (34).

3 Constitutional symptoms and extra-articular manifestations from RA

RA is a heterogenous disease with regards to symptoms and degree of symptoms that are expressed. The disease may vary over time and differ from one person to another regarding organ involvement and severity.

3.1 Constitutional symptoms

Pain is a common dominating symptom of RA, as swollen joins are tender, and cytokines released in the inflammation process stimulate nerve endings (nociceptive input) causing pain. In addition, peripheral and central sensitization may contribute to the complexity of pain in RA, i.e., with development of chronic pain despite adequate treatment of inflammation (35, 36).

Fatigue refers to a state of exhaustion that not necessarily improves with rest. It is a common symptom in RA, with 70% of RA patients suffering from fatigue at some time (37). Various scoring systems are used when diagnosing and grading fatigue (38). Fatigue is associated with pain, but disease activity, depression and sleep disturbances may also worsen fatigue (37, 39-41). By reducing disease activity, and when treating with biological agents such as the tumor necrosis factor (TNF) inhibitors, the level of fatigue may be reduced (42, 43). Physical functioning and work disability is associated with fatigue (37, 39, 44, 45), and exercise programs might reduce fatigue (46-48).

Rheumatoid cachexia is a condition of muscle wasting parallel with increased fat mass, in particular truncal fat. It is associated with disease activity leading to weight loss (49). BMI

could still be normal and even elevated, but with a higher share of fat at the expense of the proportion of muscle, also known as “cachectic obesity” (50, 51). Thus, it has been suggested that cut-offs for overweight and obesity should be lower in RA compared to the general population (50, 52). RA patients with weight loss of ≥3 kg/m^2 per year or shifting from obese (BMI >30 kg/m^2) to underweight (BMI < 20 kg/m^2) have dramatically increased risk of mortality (53), while with high BMI, mortality in RA is increased as well (50).

Malaise and fever are symptoms associated with rheumatoid vasculitis and hematological involvement, and can be signs of visceral involvement (4).

Morning stiffness is a common symptom of RA, and high disease activity is associated with longer duration of morning stiffness (54). It affects activities of daily living, including bathing and dressing (54), and is a common reason for early retirement (55).

3.2 Extraarticular RA

RA can affect many other extraarticular visceral organs, including the cardiovascular system, respiratory system, gastrointestinal system, urogenital system, skeletal system, exocrine glands, skin, and eyes.

Cardiovascular system: RA can lead to endothelial dysfunction and increased atherosclerosis resulting in ischemic cardiovascular disease (CVD) like angina, myocardial infarction, and ischemic heart failure (56-59). RA patients can suffer from RA myocarditis, pericarditis, and fibrosis, and have more non-ischemic heart failure compared to healthy controls (59-62). A multicenter study with 5630 RA patients demonstrated that interventions aiming to reduce disease activity may reduce CVD risk (63).

Pulmonary system: Typical RA-associated conditions affecting the airways are bronchiolitis, emphysema and asthma, and examples of interstitial lung disease associated with RA are organizing pneumonia, non-specific interstitial pneumonitis and usual interstitial pneumonia in addition to vascular and pleural affection (64).

Gastrointestinal system: RA may affect the gastrointestinal (GI) system directly (rheumatoid vasculitis) or indirectly for example from side effects from medical treatment (65).

Skeletal system: Osteoporosis caused by both the RA disease with activation of osteoclasts as part of RA, and secondary to the treatment with corticosteroids and inactivity might lead to painful fractures and contribute to reduction of function (66). Secondary osteoarthritis and joint damage because of erosive disease are known contributors to pain in RA (35).

Rheumatoid vasculitis may affect the intestine as well as other internal organs and the skin

(65, 67).

Hematological conditions: Felty's syndrome is seen in 1-3% of RA patients, characterized with seropositive RA, splenomegaly and neutropenia (68). Normocytic anemia is the most common hematological manifestation of RA, and thrombocytosis is seen as part of the acute-phase response (69).

Secondary Sjogren's syndrome may lead to discomfort and dryness of the mouth, esophagus, airways, genital system, skin and **eyes** (64, 70). Other RA effects on the eyes are scleritis, keratitis and maculopathy (70).

4 Medical treatment of RA

In the industrialized countries there have been great changes over the last 20 years regarding medical treatment of RA. New drugs are available and there is a shift towards treatment at higher doses of the older conventional drugs. "Tight control" and "Treat to target" are the strategies for treatment, emphasizing early start and increasing of the dose or adding drugs in situations of partial or non-responders (71-75). Remission is the main goal for medical treatment of RA, meaning no swollen joints, normalized C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) level and no progress of erosive changes (76).

Historically, drugs that suppress the immune response on a general basis were used, named as conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) (76). The most used is Methotrexate, but also Leflunomide, Hydroxychloroquine and Sulfasalazine are alternatives. Over the years, biologic disease-modifying anti-rheumatic drugs (bDMARDs) have been developed (76, 77). They target cytokines central to the cascade of inflammation or specific receptors on immune cells leading to a down-regulation of the RA immune response (76). Examples are TNF inhibitors, interleukin 6 inhibitors, B-cell inhibitors and T-cell moderators (76). The term biologic reflects the protein structures of these drugs, imitating antibodies (77). The last generation of DMARDs are not biologic, but still target specific molecules in the immune system. These drugs are known as targeted synthetic DMARDs (tsDMARDs) (76, 78), like the Janus Kinase inhibitors. Glucocorticoids are used as part of treatment regimens, in newly diagnosed RA patients until effect from csDMARDs (bridging), and later as a supplementary drug for disease flares (76, 79).

5 Monitoring of RA

It is important to limit irreversible changes like erosions and joint destructions by regular control of disease activity. In addition, effects and side effects from medications are monitored. Both subjective measures named patient-reported outcome measures (PROMs) as well as objective measures e.g., clinical examination, laboratory tests and imaging are used for this purpose.

5.1 Patient-Reported Outcome Measures

PROMs are defined as measures of a patient's health status or health-related quality of life at a single point in time (80). Scores derived from PROMs reflect e.g., the degree of reduction of functionality, the degree of pain, morning stiffness, and disease activity. They are important tools in detection of changes in the disease state and response to treatment at every visit at the outpatient clinic. In addition, PROMs capture symptoms from RA that are difficult to measure by laboratory tests and clinical examination.

The *Modified Stanford Health Assessment Questionnaire* (mHAQ) is a common PROM for detection of reduction of capacity to perform activities of daily living. It is a short version of the original 20 question Stanford Health Assessment Questionnaire. The mHAQ contains 8 questions about common daily activities, with graded options of response, i.e., "without any difficulty", "with some difficulty", "with much difficulty" or "unable to do" (81).

The *Visual Analogue Scales* (VAS) score is another group of PROMs where the patient's response on a line from 0 to 100 mm illustrates either degree of pain, degree of morning stiffness or disease complaints (disease activity). Alternatively, the scale is numerical from 0 to 10 (82).

The *Patient Global Assessment* (PGA) is an example of a VAS and is the second most frequently collected PROM after physical function (82, 83). It reflects disease activity as total disease complaints during the last week. Phrasing can be somewhat different and must therefore be considered when evaluating responses and comparing results from different studies (84). An example of phrasing of the PGA is "Please consider the activity of your rheumatic disease during the last week. Considering all the symptoms from your condition, how do you think your state is?" On the 100 mm response line, 0 mm corresponds to "Good, no symptoms" and 100 mm corresponds to "Very bad".

5.2 Laboratory tests

The most frequently considered laboratory tests reflect inflammation, like the ESR and CRP

measured in standard or high-sensitivity assays (hsCRP). Hematological and various organ-specific biochemical laboratory tests are used to detect possible side effects from medications in addition to effects caused by RA itself.

5.3 Composite scores

The *tender and swollen joint count* is central to the clinical examination, and the tender and swollen joint count is part of several composite scores for RA disease activity.

The *Disease Activity Index Score 28* (DAS28) (85), is a commonly used composite score including the tender and swollen joint count, the ESR or CRP, and the PGA.

The *Clinical Disease Activity Index* (CDAI) includes the tender and swollen joint count, the PGA, and the physician global assessment (86). The *Simple disease activity index* (SDAI) is a composite of the same variables as the CDAI, but in addition, CRP is included (86).

The scoring from DAS28 can be graded as *remission* (no disease activity), *low disease activity*, *moderate disease activity* and *high disease activity*. As there is increasing use of CRP and hsCRP at the expense of ESR as a laboratory test to monitor inflammation, there is also a shift from DAS28-ESR towards DAS28-CRP. Thus, the cut-offs for remission, low and high disease activity have been re-evaluated (87). As remission by the DAS28 can be achieved even with numerous swollen joints, improved remission criteria were developed, known as the *ACR/EULAR 2011 remission criteria*. These remission criteria also include swollen and tender joints of the ankles and feet and accept no more than 1 swollen joint and/or 1 tender joint at examination (72, 83, 88). Remission is the overall goal in the treatment of RA.

5.4 Imaging

Imaging is important both when diagnosing RA and when monitoring the disease. X-ray is the gold standard and is used for grading of the cumulative damage of bone; however, no changes may be visible on an X-ray in early RA (89). Computer tomography (CT) and magnetic resonance imaging (MRI) give earlier and more detailed information about joint erosions, and MRI is often used to find synovial inflammation with corresponding bone marrow edema as signs of arthritis (90). In addition, rheumatologists are trained to detect and score effusions (gray scale) and Power Doppler activity as signs of disease activity by ultrasonography (91).

6 Cardiorespiratory Fitness

6.1 Gold standard test for cardiorespiratory fitness

Cardiorespiratory fitness (CRF) is equivalent to the maximum uptake of oxygen (VO_{2max}) during physical activity (PA), measured as mL × min^{-1} or mL × min^{-1} × kg^{-1} when weight is considered (92, 93). CRF decreases with increasing age and on average men have higher CRF than women (94). The gold standard test to measure cardiorespiratory fitness (CRF) is through a cardiopulmonary exercise test (CPET) performed on a treadmill or bicycle ergometer (92). With increasing workload, the oxygen demand/consumption increases. Using an ergospirometry system, the increasing ventilation of oxygen is measured at specific intervals until the VO_2 uptake levels off at the point of maximal oxygen uptake (VO_{2max}) (93).

Over the years, various criteria for VO_{2max} have been established, and both primary and secondary criteria exist. Along with improvements of testing systems, standardization of protocols, and new knowledge about CPET in various populations, a debate is ongoing about criteria and verification methods to reassure that the correct VO_{2max} results are reached. The primary criterion for VO_{2max} is that the VO_2 levels off despite an increase in workload, also known as the O_2 plateau. If this criterion is not reached, secondary criteria can be used. Examples of secondary criteria are for example: blood lactate concentration >10 mmol/L, respiratory exchange ratio (RER) ≥ 1.05, heart rate (HR), and scores on the RPE Borg scale > 18 (95-98). Finally, a verification phase with a supramaximal workload performed following a short rest after the incremental test is one way of ensuring that the participants reach their VO_{2max} (99).

Often the expression metabolic equivalent (MET) is used. One MET is the amount of oxygen consumed while at rest and equals approximately 3.5 mL × min^{-1} × kg^{-1} (100, 101). Sedentary time is time spent with behavior of no more than 1.5 METs, while the expression “inactivity” refers to behavior of no more than 3 METs (100).

It is sometimes said that CRF mirrors our total health as it depends on an interwoven chain of physical processes and internal organs (102). Scientists and clinicians are increasingly becoming aware of CRF as an important measure in various risk evaluations. Perhaps the feature of CRF as a modifiable measure is what makes it important as most people have the potential to improve their CRF to reduce their risk of negative health outcomes. With PA, in particular high intensity interval training (HIIT) (103, 104), people can improve their own

CRF leading to better health outcomes like reduced mortality and reduced CVD (105, 106). A common variety of HIIT constitutes of four intervals of four minutes exercise at 90-95% of maximum heart rate (HR) interspersed by three minutes exercise at 70% of the maximum HR (103). Only a few studies with exercise at 90-95% of maximum HR are conducted in RA populations and the 2018 EULAR recommendations for PA in people with inflammatory arthritis and osteoarthritis use expressions like "moderate to vigorous PA" without explaining what intensity level these expressions represent (107, 108).

The increasing focus on CRF as an important clinical measure was confirmed in a scientific statement from the American Heart Association (AHA) in 2016 (102). This statement promotes CRF as being an equal or perhaps more important measure in the evaluation of risk for mortality, CVD and even some post-operative complications in the general population.

Most studies supporting this view are epidemiological, but results from two rather large randomized controlled trials (RCT), RAMIT and Look AHEAD, did not find an association between increased fitness and mortality or cardiovascular events in certain patient populations (109, 110). Results from these trials are discussed in the section "Discussion of findings and interpretations with other studies, subsection Hypothesis #5, page 90.

6.3 Estimated cardiorespiratory fitness

In the statement from the AHA the challenge of CPET as a resource-intensive method was discussed (102). Thus, in this same statement, alternative and less resource-intensive methods for estimating CRF (eCRF) without the need for a physical test are referred to as important tools during routine clinical visits. Such equations provide clinicians with the opportunity to counsel patients regarding the importance of performing regular PA. In particular, the ability of eCRF equations to predict long-term mortality has been emphasized as important (102, 106, 111). Various non-exercise models for eCRF have been published, and typically, these models are developed in healthy populations (112-116). One example is the equation from the Trøndelag Health Study (The HUNT Study) that was developed after CPET of 4,260 healthy participants as part of the HUNT3 Fitness study (93, 117). HUNT and the HUNT3 Fitness Study will be explained below. This equation is composed of the predictors sex, age, waist circumference or BMI, resting heart rate (RHR) and information about intensity, frequency and duration of PA habits (117). Prior to our study, no eCRF equation was developed in an RA population.

6.4 Physical tests substituting cardiopulmonary exercise tests

In order to reduce the impact on joints, studies evaluating CRF in RA patients often use sub-maximal tests or bicycle ergometer tests and then further calculation to estimate the likely CRF. Sub-maximal tests are not suitable as basis for development of equations for eCRF because they are not performed in line with gold standard CPET (92). Theoretically, even gold standard CPET may be restricted by arthritis pain leading to underperformance. Thus, to find eCRF equations for RA patients one must ensure that the CPET is valid and thereby provides a valid basis for further development of equations for CRF suitable for RA patients.

7 RA and physical activity

7.1 Former advice on physical activity in RA

Over the years, there has been a change in the field of preventive care in rheumatology with a shift towards "active rehabilitation", with "active patients" exercising at higher intensity (108). In the past, there was little knowledge about safety and effects of strenuous exercise like HIIT, jogging etc. in this group of patients. This is perhaps best illustrated with the 2007 EULAR Recommendations for treatment of early arthritis that give advice about non-pharmaceutical interventions like dynamic exercise, occupational therapy and hydrotherapy (118).

7.2 The latest recommendations for physical activity in RA

In contrast to former advice for PA in RA, the latest 2018 EULAR recommendations for PA in people with inflammatory arthritis and osteoarthritis are similar to the recommendations for the general population. Those recommendations are based upon The American College of Sports Medicine (ACSM) and AHA 2007 recommendations for PA (108, 119). The ACSM 2007 and the 2018 EULAR recommendations for aerobic PA are to perform either moderate-intensity PA ≥30 min on ≥5 days a week (≥150 min per week) or to perform vigorous-intensity aerobic activity ≥20 min ≥3 times a week (≥75 min per week) or combinations of PA at these intensity levels (108, 119). In other words, the 2018 EULAR recommendations substantiate the premises for PA in this group of patients, both regarding safety and extent. Further, the EULAR recommendations give detailed practical advice on level, frequency, and duration of PA (108). RA itself is not a contraindication to PA of any kind. Both HIIT and various forms for PA are regarded safe, illustrated with the contraindications being the same as with the general population (107, 108, 120-122).

7.3 Beneficial effects of physical activity and exercise on RA

The 2018 EULAR recommendations for PA in people with inflammatory arthritis and osteoarthritis were developed in response to increasing evidence of beneficial effects of PA in these conditions. In addition, the 2015/2016 EULAR update on recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis implemented PA and exercise as means for reducing CVD risk (108, 123).

Both improvement of RA outcomes and reduced impact of comorbidities are described as results from PA and exercise (124). For the general population, the beneficial effects of PA and exercise are common knowledge, and for many aspects, the evidence of similar effects in RA is established. Organized exercise programs combining strength and aerobic training can improve functional ability in RA (121, 122). Exercise improves strength and CRF as well as RA-related pain and fatigue (48, 125). RA is an autoimmune inflammatory disease, and a direct effect of exercise is reduction of inflammation by affecting levels of cytokines like TNF and IL-6. In a large systematic review and meta-analysis from the general population including 4,815 studies, exercise was important for reduction of visceral adiposity. It is likely that this effect is relevant in RA patients as well. Visceral adipose tissue has pro-inflammatory effects, so a consequence of reduced adipose tissue in RA may be a reduction in inflammation (126, 127). The reduction of inflammation from PA and exercise is followed by reduced ESR and CRP levels (128). Taken together, the reduction of pain and fatigue along with improved functional ability in combination with a reduction of inflammation may be reflected in improved RA disease activity composite sores (128).

Some comorbidities of RA are described in section 3.2 Extraarticular RA, page 20. A few beneficial effects from exercise that may reduce the impact of some comorbidities in RA are described here.

Hypertension is a risk factor for CVD. RA patients performing more PA and having higher CRF have lower blood pressure compared to RA patients who are less physically active and have lower CRF (129, 130). Insulin resistance is another risk factor for CVD. Studies describe that inactivity in RA is associated with increased insulin resistance, and on the contrary, higher CRF levels are associated with reduced insulin resistance (129, 130). PA and higher CRF in RA are also associated with a more favorable lipoprotein profile (129, 130).

The symptom of rheumatoid cachexia is described in section 3.1 Constitutional symptoms, page 19. Exercise training may partly counteract rheumatoid cachexia by increasing muscle mass and reducing adiposity (120).

7.4 Barriers for physical activity in RA

Despite new EULAR recommendations, it seems like lack of knowledge about safety and lack of strategies for improvement of cardiorespiratory fitness and strength, among physicians as well as patients, work as barriers for exercise in RA patients (120, 124, 131, 132). In addition, symptoms like fatigue and pain may limit RA patients from performing PA (133). Paradoxically, as described in the above section 7.3, there is increasing evidence that PA reduces fatigue and pain and improves sleep quality in RA patients (48, 131, 134).

8 Mortality in RA

8.1 Increased mortality in RA

Historically, all-cause mortality rates have been increased in RA patients compared to controls. In a review by Sokka and coworkers from 2008 (135), a range of standard mortality ratio (SMR) for RA patients of 1.2-1.3 was found in inceptive cohorts and 1.6-1.7 in non-inceptive cohorts, and the results were stable over 60 years of time. Another systematic review by Meune and coworkers from 2009 computed CVD-specific SMR and found a 60% overall increase in mortality rates caused by CVD in RA patients compared to controls (136). The consistency of findings was quite constant over the whole time period studied. Both RA-specific systemic inflammation that affects the vasculature and the internal organs and an unfavorable profile of general risk factors for CVD have been implicated (52, 57, 137).

8.1 Mortality gap

Lately, several studies claim that the mortality gap is narrowing (138-142), while a study using data from the Swedish arthritis registry concluded with no reduction of the mortality gap (143). In particular, the change of treatment regimens with higher doses of csDMARDs at time of diagnosis and the use of bDMARDs as part of the “Treat to target”- and “Tight control” strategies are regarded as possible mortality-reducing strategies in RA. Two large cohort studies by Widdifield et al. found that during follow-up both RA and controls had decreasing mortality rates, but that the gap remained equal (144). Like in the general population, the leading causes of death in RA were CVD, cancer, and diseases of the respiratory system. The difference was that symptoms from the CV and pulmonary system

developed at an earlier age in RA patients compared to the general population, hence, contributing to the increased preterm mortality in RA responsible for the mortality gap (145).

8.2 Considerations when evaluating mortality

When describing trends in mortality, one must consider the overall reduction in mortality in the general population as a whole, which may contribute to a false impression of reduction of the mortality gap. Studies have also pointed out that the increased mortality rates are seen only after 5-8 years of follow-up (146). Thus, perhaps some studies concluding with reduction of the mortality gap have too short follow-up. In addition, comparing populations that are included based upon classification criteria from different time periods and with incomparable treatment strategies, may give a false impression of reduction of mortality (135). For instance, those diagnosed using the ACR 1987 criteria in the late 1990s and early 2000s had more advanced disease at the time of diagnosis than people diagnosed after the introduction of the 2010 ACR/EULAR disease criteria (6, 7). Based upon these considerations, it is possible that an excess all-cause mortality risk still exists for RA patients of today. There is a need for more studies with longer follow-up to investigate trends in mortality after new treatment strategies were introduced.

9 Monitoring of comorbidities of RA

9.1 Standard follow-up

With symptoms of CVD, RA patients are referred to further objective investigations with electrocardiogram, exercise electrocardiogram and coronary angiography if necessary. Compared to the general population, RA patients report less symptoms from CVD. For example, angina pain could be attributed to musculoskeletal pain and RA patients tend to have "silent" myocardial infarctions (57, 147). There should be a low threshold for further objective investigations if in doubt about CVD. Spirometry and measures of lung diffusion capacity combined with either plain chest X-rays, CT or high-resolution CT can detect changes of the lungs associated with extraarticular RA or as side effects of DMARDs.

9.2 Prediction of risk

There is an increasing focus upon detection of risk for CVD. Due to the increased risk for CVD in RA patients, many outpatient clinics follow high-density lipoprotein and total cholesterol concentration on a regular basis, and often scoring systems for evaluating CVD risk are used (123, 148). In the general population, cardiovascular risk (CVR) may be calculated using various risk scores, typically including traditional CVR factors (age, sex, diabetes, hypertension, hyperlipidemia, smoking). Lately, models including variables reflecting RA disease activity (CDAI, mHAQ) and other aspects with RA (disease duration, use of DMARDs) have been developed (149). Another approach is to customize risk models developed for the general population to RA patients. For instance, EULAR recommends multiplying the American Colleague of Cardiology (ACC) and AHA's risk score and similar risk scores by 1.5 to find the 10 year CVR in RA patients (123), and the European Society of Cardiology's Systematic coronary risk evaluation (SCORE) has also been modified for an RA population (148, 150, 151). A previous study found that the RA SCORE algorithm does not provide sufficient improvement in risk prediction of future CVD in RA to serve as an alternative to the original SCORE (150). There are worries that those at moderate risk are not detected, something that is unfortunate, since they may benefit from lifestyle changes and medications (149). Thus, modified risk models for RA patients and risk models with RA-specific variables included as well as modified risk models developed in healthy populations have so far been somewhat inaccurate (152, 153).

9.3 eCRF for risk evaluation and as part of population-based studies

The field of preventive care in the general population is gradually accepting improvement of eCRF as an important measure. Equations for eCRF are being implemented in both clinical

practice and as self-evaluation tools (117). Implementing eCRF equations in large population-based studies allows for investigations of associations of eCRF with all-cause mortality, CVD-related mortality and other health outcomes like psychological symptoms and dementia (154-158).

9.4 eCRF equations for RA patients

For RA patients, studies have so far shown associations between the level of PA and CRF. Studies have also identified associations between CRF and level of specific CVD risk factors as well as associations between improvement of CRF with improvement of CVR (47, 120, 159-163). Some studies even demonstrate that improved CRF is associated with reduced CRP and disease activity (163, 164). Still, no eCRF equation customized for RA patients has been published; thus, no studies have investigated the association between RA and consequences of low eCRF in population-based studies.

10 The Trøndelag Health Study

The Trøndelag Health Study (HUNT) is one of the largest population-based studies in the world that aims to collect and store information for medical and health-related research. HUNT is designed as an open cohort and all inhabitants in the northern part of Trøndelag county aged 20 years or older are invited. Participants may be followed longitudinally. Data are linked to the national unique personal identification number which enables linking of data to local, regional and national health registries such as the Norwegian Cause of Death Registry (165). The HUNT study started in HUNT1 (1984-1986), addressing arterial hypertension, diabetes, screening of tuberculosis and quality of life. Over the years, more topics central to health have been included in HUNT2 (1995-1997), HUNT3 (2006-2008) and HUNT4 (2017-2019). In HUNT3 a biobank was established. HUNT data are gathered through questionnaires (socioeconomic conditions, health-related behaviors, symptoms, illness, and diseases), various measures, and samples of blood and urine. Data were collected in examination sites in each of the former 24 municipalities in the northern part of Trøndelag county.

The HUNT Longitudinal Ankylosing Spondylitis and Rheumatoid Arthritis Study (HuLARS) is an ongoing sub-project in HUNT which aims to investigate associations among different risk factors for CVD and mortality in RA or ankylosing spondylitis (AS). This project utilizes data from HUNT2 and HUNT3, particularly data from questionnaires screening for risk

factors for CVD, symptoms of musculoskeletal disease, data from clinical examination, and genetic risk variants. An important part of HuLARS was the identification of participants with either an RA or AS diagnosis, allowing for investigations of various aspects of RA and AS compared to controls in HUNT2 and HUNT3 (2, 166).

11 Knowledge gaps

The lack of an RA-specific eCRF formula limits the possibility for investigating topics related to eCRF in RA. Instead, such investigations must rely upon actual CPET testing, with the extra burden of time, cost, effort, and the uncertainty of whether RA patients perform maximally during a CPET. Thus, so far, no study has investigated associations between level of eCRF, age-related decrease of eCRF or associations between eCRF level and excess all-cause mortality in RA compared to controls in a population-based study. There is also a need for an eCRF equation for individual RA patients for easy calculation and follow-up of results for example after a period of exercise.

The present thesis is a sub-study in HuLARS, that focuses upon RA, cardiorespiratory fitness, and mortality. Parts of the thesis describe results from CPET of RA patients recruited from a similar area as the HUNT investigations, thus, permitting comparison with the CPET results from healthy controls in HUNT3 Fitness. Further, as the HUNT is an open cohort and participants take part in more than one wave of HUNT, parts of this thesis are follow-up studies of identified RA patients in HUNT.

HYPOTHESIS AND AIMS

Main hypothesis

Cardiorespiratory fitness (CRF) is lower in individuals with RA, this is associated with disease-specific variables, and has important health consequences.

Hypothesis 1

Cardiopulmonary exercise testing (CPET) using a treadmill is well tolerated in patients with RA and the results are not biased by arthritis pain**.**

Hypothesis 2

Equations for estimation of CRF developed for the general population need to be adjusted to become suitable for persons with RA.

Hypothesis 3

CRF in RA patients is lower than in a healthy age- and sex-matched population and the differences are also present in recent years.

Hypothesis 4

eCRF deteriorates faster by time in RA patients compared to controls.

Hypothesis 5

The increased mortality in RA compared to the general population is partly due to reduced eCRF in RA patients compared to controls.

Aims

1: (corresponding to hypothesis 1)

a- Perform CPET using a treadmill on RA patients from an outpatient clinic and evaluate the influence of arthritis pain on test performance.

2: (corresponding to hypothesis 2)

a- Investigate if existing eCRF models developed for healthy people accurately predict CRF in RA patients from the same geographical area.

b- If necessary, identify variables that are useful to improve CRF prediction in RA patients and develop customized models for individual patients and patients taking part in population-based studies.

3: (corresponding to hypothesis 3)

a- Compare eCRF between RA patients and controls participating in HUNT2 and/or HUNT3.

b- Compare recent CPET results from RA patients to CPET results from the HUNT3 Fitness study.

4: (corresponding to hypothesis 4)

a- Compare changes in eCRF from HUNT2 to HUNT3 in RA patients and controls.

b- Investigate whether increasing age affects the decline differently in the two groups and identify variables that are associated with the age-related decline in eCRF.

5: (corresponding to hypothesis 5)

a- Investigate which variables are associated with all-cause mortality in RA patients and controls.

b- Compare all-cause mortality in RA to all-cause mortality in the control group attending HUNT2 and/or HUNT3 and investigate if low eCRF is a mediator of excess all-cause mortality in RA.

PATIENTS AND METHODS

1 Ethics

Approval for HUNT was obtained from the Norwegian data safety Authorities and the Norwegian Department of Health, and participants provided written informed consent. The HUNT sub-studies in this thesis were approved by the Regional Committee for Medical Health Research Ethics (4.2009.1068 and 2018/1149) and performed in compliance with the Helsinki Declaration. Inclusion and CPET of RA patients was approved by the Regional Committee for Medical Health Research Ethics (2016/275) and performed in compliance with the Helsinki Declaration. CPET testing followed the ACC/AHA guidelines for exercise testing and all participants provided written informed consent (167). For practical reasons, only participants with CVR were monitored with an electrocardiogram during CPET.

2 Populations

2.1 RA population for cardiopulmonary exercise testing

To investigate whether CPET results from RA patients are valid (Aim 1, Paper 1) and to find variables associated with CRF in RA in order to develop new formulas for RA patients for estimating CRF (eCRF) without a physical test (Aim 2b, Paper 1 and Paper 2), 100 RA patients were recruited from the rheumatology outpatient clinic at St. Olavs Hospital in Norway. The RA patients had to be without contra-indications for CPET (chronic obstructive or chronic restrictive pulmonary disease with the need for oxygen, unstable heart conditions or disabilities preventing running/walking on a treadmill) and fulfilling the 2010 EULAR classification criteria for RA (7, 167). Forty patients were recruited in relation to a regular appointment at the outpatient clinic, 54 patients were recruited from the patient-centered follow-up program, and 6 were recruited after reading a newsletter from the local arthritis association. Inclusion and CPET took place from the 17th of February 2017 to the 4th of January 2018. After excluding those who did not meet for testing (n=2), had repetitive ventricular extrasystoles in the electrocardiogram (n=1), revealed a history of chest pain (n=2), or had untreated hypertension (n=1), a total of 94 RA patients performed a CPET.

Power calculation was based on the assumption that fitness-associated variables (e.g., RHR, sex, age, waist circumference and PA) explain 60% (R^2=0.60) of the variance of measured VO_{2peak}. With an α of 0.05, and a planned inclusion of 100 RA patients, we would be able to identify ≥1 RA-related variables that possibly could increase R^2 with another 5% with a corresponding power of 0.96. In our study, one test result was excluded because of atrial

fibrillation, resulting in a total of 93 (68 women and 25 men) valid CPET results. This equals a power of 0.95 to detect a 5% increase in R^2, considered satisfactory (Paper 1).

2.2 RA populations and controls in The Trøndelag Health Study

The participation rates in HUNT2 and HUNT3 were 69.5% (n=65,237) and 54.1% (n=50,807), respectively. By comparing information given in questionnaires in HUNT2 and HUNT3 to medical records, a previous study identified participants fulfilling the ACR/EULAR 2010 classification criteria for RA (2, 8). Based upon questionnaires in HUNT3, 30,513 participants were regarded suitable for a previously published sub-study in HUNT3, named the HUNT3 Fitness Study. This study aimed to establish a reference database for cardiorespiratory variables for healthy Norwegian men and women aged 20-90 years. Three municipalities were selected, thus leaving 12,609 candidates for CPET. After excluding those not fulfilling medical inclusion criteria using an interview (free from CVD, respiratory symptoms, cancer, and the use of anti-hypertensives) 4,631 completed a CPET (168, 169) (Figure 1).

To investigate if RA patients have reduced CRF compared to the general population (Aim 3a, Paper 3), eCRF for RA patients and controls participating in both HUNT2 and/or HUNT3 was compared. Those who received the diagnosis after participating in HUNT3 were excluded. Because eCRF formulas constitute of a set of variables, participants with missing variables for the eCRF formulas were excluded, leaving a total of 68,346 included participants (RA patients n=436, controls n=67,910). Comparison of the eCRF between RA patients and controls was also done in sex and 10-year age categories (30-89 years of age) (total=59,556, RA=432 and controls=59,124) (Figure 1 and Table 3).

To investigate if contemporary RA patients are deconditioned compared to a healthy population (Aim 3b, Paper 1), CRF in today's RA patients (n=93, CPET in 2017) was compared to a healthy population. A potential reduced CRF level in the 93 RA patients might support that any difference in eCRF level between RA patients and the general population in HUNT2 and HUNT3 is still relevant for today's RA population. The 93 valid CPET results (mean and 95% confidence interval (CI) from 68 women and 25 men) were compared to mean and 95% CIs of previously published CPET results from 4,631 healthy participants in the HUNT3 Fitness sub-study (Figure 1 and Table 3) (169). Our comparison was categorized by sex and 10-year age categories, except for the category covering those above 70 years which was placed in the category "70 years and over". Since few RA patients belonged to the

age categories 20-29 and 30-39 years, these categories were combined and compared to the HUNT3 Fitness category for 30-39 years of age.

When investigating if change in eCRF by increasing age differs in RA patients compared to the general population (Aim 4a, Paper 3) and identifying variables that are associated with the age-related decline in eCRF (Aim 4b, Paper 3), included participants had to attend both HUNT2 and HUNT3. Further, exclusion was made for persons missing variables in the eCRF formulas or missing in any of the adjustment variables in the regression analysis, leaving a total of n=26,390 persons who were included in the analysis (RA patients n=188 and controls n=26,202) (Figure 1 and Table 4). Power calculation was based on the following assumptions (2, 169): Approximately 33,000 participated in both HUNT2 and HUNT3 with a prevalence of RA of 0.75%; we expected about 15% missing data for calculation of eCRF; average 10-year decline in CRF in healthy people would be about 3.8 mL × min^{-1} × kg^{-1}; we presumed a 20% larger decline in RA patients; and used α=0.05 and a two-sided test. The calculated power was 82%, considered sufficient.

For the analysis of the association between eCRF, RA and mortality (Aim 5, Paper 4), 348 RA patients (women n=235, men n=113) and 60,938 controls (women n=31,729, men n=29,209) participants in HUNT2 and HUNT3 were included after exclusion of persons with missing variables for eCRF in both HUNT2 and HUNT3. If baseline variables were only missing in HUNT2, baseline was reclassified to HUNT3. Participants were followed until death or until end of observation on the 31st of December 2018 (Figure 1 and Table 3). Data from HUNT2 and HUNT3 were linked with the Norwegian Cause of Death Registry. This registry is a database for the official cause of death statistics for all Norwegian citizens living in Norway and abroad (165).

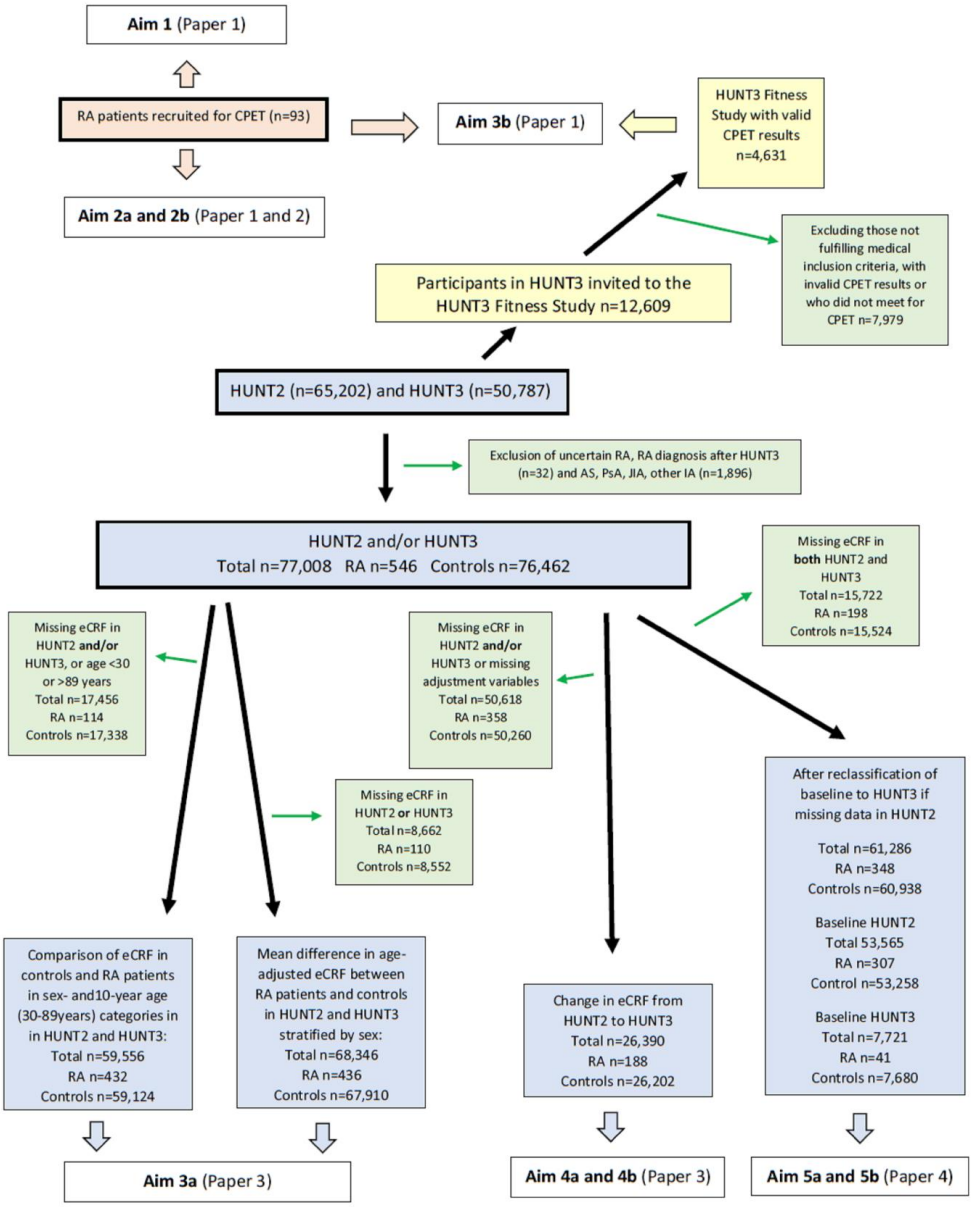


Figure 1: Recruitment to the studies
Abbreviations: CPET, cardiopulmonary exercise test; eCRF, estimated cardiorespiratory fitness, HUNT2 and HUNT3, Second and third wave of The Trøndelag Health Study; IA, inflammatory arthritis; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Aim		Population	Main methods	Supplementary methods	Paper
1	Perform CPET using a treadmill on RA patients from an outpatient clinic to evaluate the influence on test performance from arthritis pain	93 RA patients who performed CPET during 2017	CPET Scale for rating of arthritis-related pain RPE Borg scale		1
2a	Investigate if eCRF equations for healthy people accurately predict CRF in RA patients from the same area	93 RA patients who performed CPET during 2017	Equivalence test of the 90% CI for the difference between measured VO_{2peak} and predicted VO_{2peak} from HUNT3 equation	Scatterplot	2
2b	If necessary, identify variables that are useful to improve CRF prediction in RA patients and develop customized models for individual patients taking part in population-based studies		Multivariable linear regression with VO_{2peak} results as the dependent variable	Lasso for variable selection Residual plots Cook's distance Equivalence test Scatterplot Bootstrapping K-fold cross evaluation	1 and 2
3a	Compare eCRF between RA patients and controls participating in HUNT2 and/or HUNT3	HUNT2 and HUNT3 RA n=432 Controls n= 59,124	Two-sample t-test of mean eCRF of controls and RA patients in ten-year age categories (30-89 years) for each sex separately		3
		HUNT2 and HUNT3 RA n=436 Controls n=67,910	Age-adjusted linear regression stratified on sex to find mean sex-specific difference between RA patients and controls		3
3b	Compare recent CPET results from RA patients to CPET results from the HUNT3 fitness study	93 RA patients who performed CPET during 2017 HUNT3 Fitness n=4,631	Comparison of mean (95% CIs) VO_{2peak} to corresponding mean (95% CIs) in the HUNT3 Fitness population in gender and 10-year age categories		1
4a	Compare changes in eCRF from HUNT2 to HUNT3 in RA patients and controls	HUNT2 and HUNT3 RA n=188 Controls n= 26,202	Age-adjusted linear regression stratified by sex to find mean change of eCRF from HUNT2 to HUNT3 in RA patients compared to controls	Equivalence test	3
4b	Investigate whether increasing age affects the decline differently in the two groups and identify variables associated with the decline in eCRF		Multivariable linear regression with change of eCRF from HUNT2 to HUNT3 as the dependent variable and with stepwise inclusion of adjustment variables Use of interaction term RA*age	Lasso for variable selection	3
5a	Investigate which variables are associated with all-cause mortality in RA patients and controls	HUNT2 and HUNT3 RA n=348 Controls n=60,938	Cox proportional hazard regression	Residual plots Comparison of AIC/BIC	4
5b	Compare all-cause mortality in RA to all-cause mortality in the control group attending HUNT2 and/or HUNT3 and investigate if low eCRF is a mediator of the excess all-cause mortality in RA		Calculate mortality rate in the RA group and control group Cox regression-based mediation analysis		4

Table 3: Overview of aims with corresponding populations and methods

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CI, confidence interval; CPET, cardiopulmonary exercise test; eCRF, estimated cardiorespiratory fitness; HUNT2 and HUNT3, Second and third wave of The Trøndelag Health Study; Lasso, least absolute shrinkage and selection operator; RA, rheumatoid arthritis; RPE Borg scale, Scale for rating of perceived exertion

3 Cardiopulmonary Exercise test and data collection

The CPET and pre-test examinations were performed at the NeXtMove core facility at NTNU – Norwegian University of Science and Technology. Blood for hsCRP quantification was drawn. Questionnaires about PA habits with regard to frequency, duration and intensity (Table 4) (117) and motivation for PA were filled in, as well as the disease-specific PROMs mHAQ and the 100 mm VAS. This scale is known as the patient global assessment (PGA) and the same VAS was scored by the physician (the physician global assessment) (81, 84, 170). The PGA is also a part of the composite measures DAS28, CDAI, SDAI and the ACR/EULAR remission score, which were calculated as previously described (84-86, 88, 170). Further, heart and lungs were auscultated, and swollen and tender joints were counted. Weight, height, and waist circumference were measured, and after ten minutes of rest, RHR and blood pressure were registered. Information on year of diagnosis, smoking habits (never/ever, 0/1), comorbidity (CVD (angina, previous acute myocardial infarction, hypertension), stroke, arrythmias, chronic restrictive or obstructive pulmonary disease (CRPD/COPD), previous/present cancer, psoriatic skin disease, osteoporosis, gastrointestinal disease, osteoporosis and diabetes) and medications (β-blocking agents, non-steroid anti-inflammatory drugs (NSAIDs), corticosteroids and DMARDs) was collected during an interview and/or extracted from medical records.

After 6 minutes warm-up on the treadmill (Woodway PPS 55, Waukesha, Wisconsin, USA), the CPET protocols were individualized because of large individual variation in skills and fitness levels. Patients were fitted with a HR monitor (H7, Polar Electro, Kempele, Finland) and a facemask (7450 Series V2 CPET mask, Hans Rudolph, Shawnee, Kansas, USA). Common to all tests was a gradual increase in workload and repeated gas measurement every 10^{th} second using a mixed chamber ergospirometry system (Metalyzer II, Cortex, Biophysik Gmbh, Leipzig, Germany). The CPET was terminated at exhaustion or fulfillment of the criteria for VO_{2max} or VO_{2peak}.

A: How frequently do you exercise?	
a) Never	0
b) Less than once a week	0
c) Once a week	1
d) Two to three times a week	2
e) Almost every day	3
B: How hard do you push yourself?	
a) Take it easy	0
b) Heavy breath and sweat	5
c) Push near exhaustion	10
C: How long does each session last?	
a) < 15 min	1
b) 16-30 min	1
c) min	1.5
d) > 60 min	1.5

Table 4: The physical activity summary index (PA index)[1]

[1]Developed for the original HUNT equation. The index is calculated as the product of the points given for each question (117).

For this thesis, the following criteria were used : (1) VO_2 levelling off (<2 mL× min^{-1} × kg^{-1}) despite increase in workload and (2) RER ≥1.05 as a secondary criterion (93). If these criteria were not met, VO_{2peak} was used, defined as the mean of the three successive highest VO_2 registrations achieved during a CPET. In a sample with candidates reaching VO_{2peak} and other candidates reaching VO_{2max}, the average is termed VO_{2peak} is used for all, as in the present study.

In addition to standard rating of perceived exertion (RPE Borg scale 6-20) (Figure 2, Panel A) (98), pain caused from arthritis in the lower extremities was rated with a similar scale (Figure 3, Panel A). This was done to investigate whether RA patients were restricted because of arthritis pain, which secondarily could lead to underperformance and affect validity of the CPET results (Aim 1). Both scales were rated before, during, and at the peak of the CPET (Figure 2, Panel A and Panel B).

The ergospirometry system was calibrated regularly before the first test and after every fourth test if more tests in a row. Turbine change, sensor adjustment, check of ambient pressure, gas and flow was performed in accordance with an operating protocol. The ergospirometry

systems were validated regularly, both biologically (against the gold standard; Douglas bag) and mechanically (with a metabolic simulator) and the procedures are regularly validated.

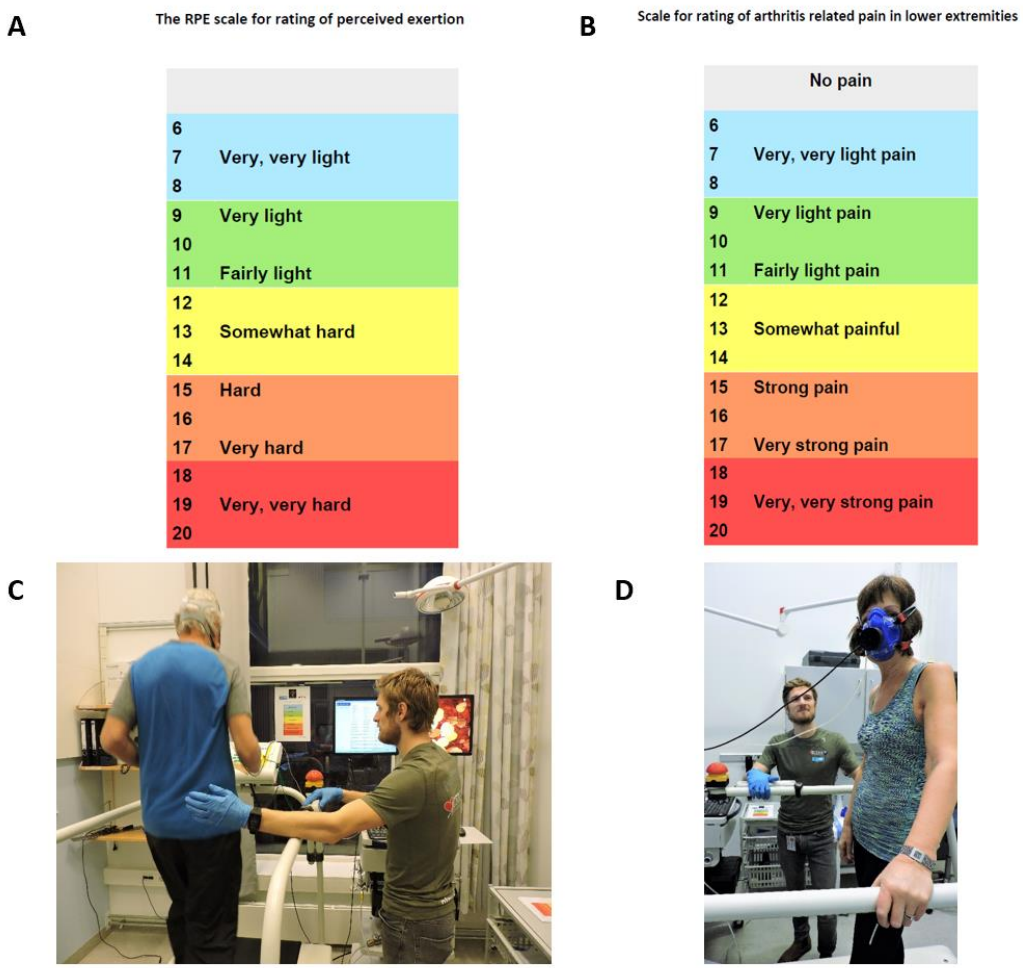


Figure 2: Cardiopulmonary exercise test
Panel A: RPE Borg scale for rating of perceived exertion (98). Panel B: Scale for rating of arthritis related pain in lower extremities. Panel C: Photo illustrating how the RPE scale is placed in front of the participant during CPET. Panel D: Photo illustrating the face mask used during CPET

4 Statistical analyses

Data are given as counts and percentages, mean with standard deviation (SD) or median with interquartile range (IQR) in parenthesis. *P*-values <0.05 were considered significant. Chi-square and two sample t-tests were performed for simple comparisons of baseline categorical and continuous variables, respectively. All statistical analyses were performed using STATA (Version 15.0, StataCorp, College Station, TX, USA).

Table 3 gives an overview of various statistical methods used for different aims of this study.

4.1 Multivariable linear regression analysis

Multivariable linear regression investigates the associations between several independent variables and one dependent variable, or outcome. The dependent variable is continuous, and the multivariable linear regression allows for the dependent variables to be expressed as a function of other continuous or categorical explanatory variables (also called covariates or predictors). The result from a multivariable linear regression analysis is expressed as the sum of a constant and the coefficients of every predictor. The constant is the value of the dependent variable if all coefficients are zero. The coefficients reflect the predicted increase in the dependent variable for every unit of increase of the explanatory variable.

4.1.1 Multivariable regression analysis in our study

Multivariable linear regression analyses were performed to find predictors for the dependent variable, VO_{2peak} (CPET of RA patients) (Aim 2b, Paper 1 and 2), and further to develop new equations for eCRF for RA patients (new RA equations) (Aim 2b, Paper 2). Based on previous literature, the following explanatory variables were chosen: age (years), sex, age*sex interaction, BMI (kg/m^2), smoking (ever/never=1/0), RHR (beats per minute, bpm) and the PA index. Other potential important variables included: comorbidity (cancer, CVD, diabetes, COPD/CRPD) coded as a single (yes/no, 1/0) variable, and SBP (mmHg). Common RA-specific variables were also considered: PGA (mm on a 100 mm-scale (170), physician global assessment, mHAQ (81), DAS28 (85), CDAI, SDAI (86), DAS28 remission criteria, ACR/EULAR remission criteria (88), time since RA diagnosis, seropositivity (ACPA and/or RF) and DMARDs. To develop RA equations for use in different situations with varying access to potential explanatory variables, series of multivariable regression analyses were repeated with somewhat different predictors for the dependent variable VO_{2peak}, resulting in 5 different RA equations (Aim 2b, Paper 2).

To identify variables associated with the age-related change in eCRF from HUNT2 to HUNT3 in both RA patients and controls (Aim 4b, paper3), the adjustment variables (age, sex, years from HUNT2 to HUNT3, baseline eCRF) and the predefined variables known to be associated with CRF were included in the regression, while variables with high number of missing, or that were highly correlated, were removed.

Mean eCRF levels in RA patients (n=436) and controls (n=67,910) in HUNT2 and/or HUNT3 were compared using age-adjusted linear regression stratified on sex (Aim 3a, Paper 3). New eCRF equations for RA patients were used for RA patients and HUNT equations were used for controls.

4.1.2 Methods supplementing the multivariable regression analysis

4.1.2.1 Least absolute shrinkage and selection operator regression

As a rule of thumb, the number of predictors should not be more than approximately 10 percent of the number of persons studied, because higher number of predictors may lead to over-fitting. Least absolute shrinkage and selection operator regression (Lasso regression) is a method that identifies the smallest useful set of variables among variables that might be highly correlated and is often used to reduce risk of overfitting when performing regression analysis (171). Lasso regression sets the coefficients of irrelevant variables to 0. The variables different from 0 can then be forced into a regression analysis where non-significant variables have been removed.

Lasso regression for sub-selection of variables was used during multivariable regression analysis to find new RA eCRF equations (Aim 2b, Paper 2) as well as in the multivariable linear regression to find variables associated with age-related change of eCRF from HUNT2 to HUNT3 (Aim 4b, Paper 3).

4.1.2.2 Standardization of coefficients

The size of coefficients in a final regression analysis may lead to misinterpretations of the importance of the various predictors. Larger coefficients give the impression that the variable is associated with larger changes in the dependent variable, because a coefficient does not take into account that different variables have different units. A multivariable linear regression analysis can be standardized to permit direct comparison of the coefficients. Following standardization, all variables in the analysis are measured in SD. Thus, the coefficient for an explanatory variable equals the change in SD of the dependent variable if the explanatory variable changes with 1 SD. The analyses of variables associated with

VO_{2peak} in RA patients (Aim, Paper 1) and eCRF change were standardized (Aim 4b, Paper 3).

4.1.2.3 The use of an interaction term

The interaction term age*sex was used in the regression analysis to find new RA equations for eCRF (Aim 2b, Paper 2) because age affects eCRF differently depending upon sex (94). The interaction term age*RA was introduced to investigate if age affected RA patients differently than controls regarding age-related change in eCRF (Aim 4b, Paper 3).

4.2 Cox proportional hazard regression

Cox regression is also called survival analysis. The Cox model estimates the ratio of the hazard (risk) of the event (i.e., death) between two groups. The hazard is the probability of experiencing the event in the next time interval among individuals who have not yet experienced the event by the start of the interval. The model assumes that the hazards are proportional in both groups (172, 173). A multivariable Cox proportional hazard regression model will yield an equation for the hazard as a function of several explanatory variables. Thus, makes it possible to estimate the hazard of death for an individual, given their prognostic variables.

To investigate if low eCRF was associated with mortality in RA patients and controls (Aim 5a, Paper 4), the control group not suffering from RA was set as the reference group, and the eCRF variable was dichotomized into eCRF above and below median eCRF for each sex and age group (Figure3). eCRF above median was set as the reference. To ensure that participants of same age were compared, age was used as the time variable in the Cox regression analysis. Adjustments for potential confounders were added in a stepwise manner.

As sensitivity analyses, we recategorized the eCRF variable into three categories before performing a similar Cox proportional hazard regression analysis. Alternatively, we used eCRF as a continuous variable in Cox regression. Finally, adding previous CVD as an adjustment variable was done to ensure that results were not biased when this variable was omitted.

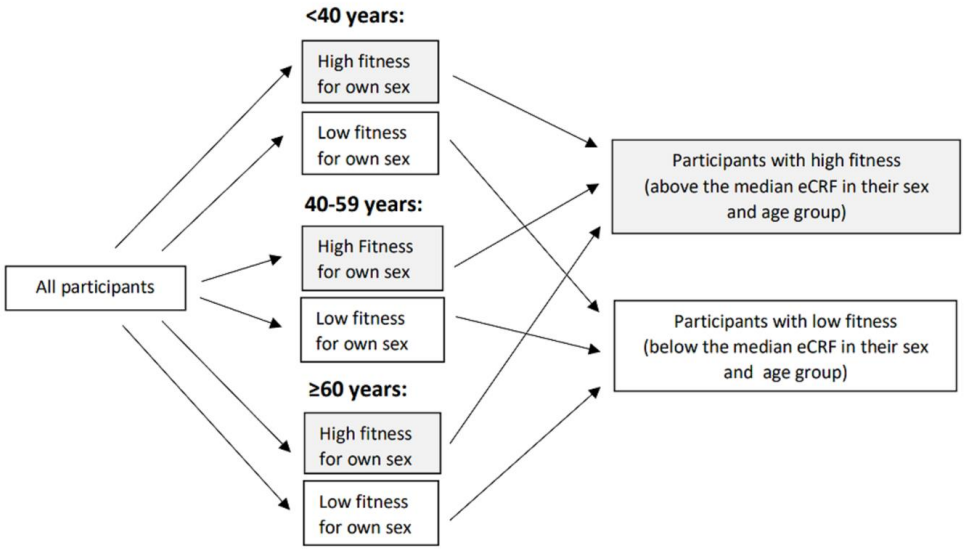


Figure 3: Categorization of fitness level above or below median eCRF for their sex and age group. Abbreviations: eCRF, estimated cardiorespiratory fitness. Age groups <40 years, 40-59 years, ≥60 years.

4.3 Cox regression-based mediation analysis

The total excess mortality risk in RA patients compared to controls (Aim 5b, Paper 4) was further investigated using a Cox regression-based mediation analysis.

To find to what extent low eCRF mediated the excess risk of all-cause mortality in RA patients (Aim 5b, Paper 4), we investigated the associations between the independent variable (RA diagnosis) and the dependent variable (excess all-cause mortality in RA) by including a mediator variable (low eCRF). The excess all-cause mortality risk was split into three pathways: the controlled direct effect of RA, the pure indirect effect of RA via low eCRF and the interaction between RA and low eCRF. All other variables were adjusted for in all three paths. The analyses were done using the Stata package med4way (174).

4.4 Comparison of models

In general, models were compared using the **Root Mean Square Error** (RMSE, i.e., standard error of the residuals, which tells how close the data lie around the line of best fit) and/or, **Akaike information criterion** and **Bayesian information criterion** (AIC and BIC, respectively). It is possible to increase the likelihood of a model by adding parameters but

doing so may result in overfitting. Lower numbers in both AIC and BIC when comparing alternative models for the same dataset means that the model better fits the data without being overfitted (Table 3).

4.5 Tests of method assumptions

4.5.1 In multivariable linear regression

For the new RA equations (Aim 2b, Paper 2), model assumptions were evaluated using **residual plots** including residual vs. predicted value plots to assess homoscedasticity. Multivariate outliers were assessed using **Cook's distance**, which is a method of measuring the effect of deleting a given observation, for instance the effect of deleting the data points with large residuals (outliers).

4.5.2 In Cox proportional hazard regression analysis

The proportional hazard assumption was evaluated using Stata's phtest based on **Schoenfeld residuals** (173), which are calculated for each regression variable to investigate if each variable independently satisfies the assumptions of the Cox proportional hazard regression model. Linearity of continuous variables was evaluated using **Martingale residuals** (173).

4.6 Methods illustrating and testing agreement

4.6.1 Scatterplots

When calculating the eCRF using the HUNT3 equation for the 93 RA patients, agreement was illustrated in a scatterplot with observed VO_{2peak} (CRF from CPET) versus predicted VO_{2peak} (eCRF from the HUNT equation) (Aim 2a, Paper 2).

After new RA equations were developed, scatterplots were used to illustrate agreement between the VO_{2peak} (CRF from CPET) and the estimated VO_{2peak} (CRF from the new RA equation) (Aim 2b, Paper 2).

4.6.2 Equivalence testing

Equivalence testing is a statistical method used to evaluate if methods can be considered equivalent or not (175). The mean and the 90% CI for the difference between the two methods are evaluated against a predefined equivalence region, which indicates how big the difference can be for the two measurements still to be considered equivalent. Equivalence testing can be illustrated with a graph with horizontal bars indicating the 90% CIs (with the

mean in the middle) for the differences between two methods, and with vertical lines indicating the predefined equivalence region. If the 90% CI for the difference cross the outer borders of the equivalence region, the tests are not considered equivalent.

To evaluate if the HUNT3 equation predicted CRF from CPET in RA patients (n=93) (Aim 2a, Paper 2), the 90% CI for the difference between measured VO_{2peak} (CRF from CPET) and predicted VO_{2peak} (eCRF from HUNT3-equation) for the 93 RA patients was evaluated against predefined equivalence regions. For this analysis we evaluated against three equivalence regions with decreasing accuracy ($\pm$ 1 MET, $\pm$ 1.5 MET and $\pm$2 MET).

When evaluating if the new RA equation was equivalent with the CRF from CPET in RA patients (n=93) (Aim 2b, Paper 2), the 90% CI represented the difference between the measured VO_{2peak} (CRF from CPET) and predicted VO_{2peak} (CRF from a new RA-equation) for the 93 RA patients. Since the same three equivalence regions ($\pm$ 1 MET, $\pm$ 1.5 MET and $\pm$2 MET) were used, it was possible to evaluate how the new RA equation performed in comparison with the HUNT equation. In other words, we tested which equation, the HUNT3 or the new RA equation was most equivalent to the gold standard method, CPET for RA patients.

In the analysis of eCRF in RA patients in HUNT (Aim 3, 4 and 5, Paper 3 and Paper 4), we chose the new RA equations that corresponded best with available data in HUNT. For example., eCRF equations in HUNT2 uses a dichotomized variable defining whether the ACSM/AHA 2007 recommendations for PA were fulfilled or not (yes=1/no=0) (106, 119), while eCRF equations in HUNT3 used PA index as the PA variable (Table 4) (117).

The predefined equivalence regions were $\pm$1 MET when we investigated if the two HUNT equations (HUNT2 and HUNT3 equations) for eCRF for the general population and if the two different RA equations for HUNT2 and HUNT3 were equivalent (Aim 4a, Paper 3). If equations were equivalent, the age-related change in eCRF from HUNT2 to HUNT3 could be calculated without being biased because of the use of different formulas (Aim 4a and Aim 4b, Paper 3).

When testing whether the "New alternative RA equation with SBP" was equivalent to CPET for healthy persons (Aim 2b, Paper 3), CPET results from the HUNT3 Fitness study (n=3,294) were used in the equivalence test (Paper 3). The 90% CI then reflected the difference between the VO_{2peak} (CRF from CPET) results for healthy people and VO_{2peak} (CRF from the new RA equation).

4.7 Methods for internal validation

Internal validation of new RA equations (n=1000) was done by bootstrapping and k-fold cross-validation (n=25) (Aim 2b, Paper 2). **Bootstrapping** is a method of randomly sampling data from the same population, or in this case, from the same coefficients, many times and then comparing original and bootstrapped CIs of the coefficients. **K-fold cross-validation** is a method with partitioning of data into subsets, performing the analysis in one subset and then validating the analysis in the other subset. We repeated this cycle 25 times and eventually used an average of the result of the prediction ability of the model as the result (Aim 2b, Paper 2).

4.8 Other statistical methods

To compare mean eCRF of RA patients and controls in HUNT2 and HUNT3 in 10-year age categories for each sex (Aim 3a, Paper 3), **two sample t-tests** with comparison of mean and 95% CIs were performed.

All-cause mortality rates with 95% CIs from baseline to end of follow-up were calculated for RA patients and controls (Aim 5b, Paper 4). With this method, non-overlapping CIs indicate that the rates are significantly different ($p<0.05$).

SUMMARY OF RESULTS

Aim 1 Results from CPET testing and data collection:

Results from questionnaires, interview, clinical examinations, and medical records are reported in Table 5. For CPET, the age span ranged from 26 to 78 years and the mean (95% CI) CRF for men (n=25) was 39.0 (32.0-43.8) $mL \times min^{-1} \times kg^{-1}$ and for women (n=68) was 29.7(25.8-30.6) $mL \times min^{-1} \times kg^{-1}$. CPET results for sex and 10-year age categories are reported in Table 6. At peak of the CPET, 13% of the RA patients reported disease complaints above 13 (somewhat painful) on the scale for rating of arthritis related pain in the lower extremities (Figure 3, Panel A), whereas 75% reported the test being ≥17 (very hard or above) on the RPE Borg scale (Figure 2, Panel A). Of the 93 completed tests, 83% fulfilled criteria for VO_{2max} and 17% for VO_{2peak}.

Aim 2a) Results from investigations to find if the HUNT3 fitness equation fits RA patients (n=93):

The scatterplot of VO_{2peak} from CPET vs. eCRF from the HUNT3 equation illustrates the deviation of results from the identity line (Figure 4). In particular, the deviation in the lower parts of the graph is of clinical importance because RA patients with the lower VO_{2peak} results had corresponding eCRF results that were too high. Results from equivalence testing of VO_{2peak} from CPET vs. eCRF from HUNT3 equation (n=93) showed that the HUNT3 equation was non-equivalent to VO_{2peak} measurement with respect to all equivalence regions, as seen by the CI falling above all region limits and below the 1 MET and 1.5 MET region limits (Figure 5).

Table 5: Patient characteristics

	Total n=93	**Women** n=68	**Men** n=25
Age median, (IQR)	60 (52-66)	60 (51-67)	60 (52-66)
Height (m), mean (SD)	1.69 (9.0)	1.66 (0.62)	1.80 (0.71)
Weight (kg), mean (SD)	76.4 (12.3)	72.7 (10.9)	86.8 (9.7)
Body mass index (kg/m^2), mean (SD)	26.7 (3.9)	26.6 (4.1)	26.9 (3.4)
Comorbidity, n (%)	38 (41)	30 (44)	8 (32)
Cardiovascular (HT, angina, MI)	21 (23)	17 (25)	4 (16)
Respiratory (COPD and/or CRPD)	18 (19)	15 (22)	3 (12)
Diabetes	4 (4)	3 (4)	1 (4)
Cancer (previous or present)	5 (5)	3 (4)	2 (8)
Smoking, n (%)[1]			
Never smoked	35 (38)	27 (40)	8 (32)
Previous smoker	51 (55)	37 (54)	14 (56)
Present smoker	7 (8)	4 (6)	3 (12)
Resting heart rate (beats per min), mean (SD)	66 (10)	67 (9)	65 (11)
Physical activity categories, n (%)			
Does not fulfill ACSM/AHA recommendations	64 (69)	44 (66)	19 (76)
Fulfills ACSM/AHA recommendations	29 (31)	23 (34)	6 (24)
Seropositivity (ACPA and/or RF), n (%)	75 (81)	54 (79)	21 (84)
Disease duration (years), median (IQR)	10 (5-19)	10 (5-20)	11 (6-16)
Patient global assessment (0-100 mm), median (IQR)	24 (10-36)	27 (16-42)	12 (5-24)
Physician global assessment (0-100 mm), median (IQR)	10 (0-12)	8 (0-18)	5 (0-10)
mHAQ, mean (SD)	0.26 (0.31)	0.29 (0.33)	0.17 (0.23)
hsCRP, median (IQR)	1.75 (0.75-3.13)	1.64 (0.71-3.13)	2.39 (0.98-3.20)
SDAI, n (%)			
Remission	22 (24)	12 (18)	10 (40)
Low disease activity	41 (44)	32 (47)	9 (36)
Moderate disease activity	24 (25)	21 (31)	3 (12)
High disease activity	6 (7)	3 (4)	3 (12)
Mean (SD)	10.2 (8.7)	10.6 (8.0)	9.3 (10.3)
DAS28 (hsCRP), n (%)			
Remission	39 (25)	25 (37)	14 (56)
Low disease activity	23 (25)	18 (27)	5 (20)
Moderate disease activity	28 (30)	23 (34)	5 (20)

High disease activity	3 (3)	2 (3)	1 (4)
Mean (SD)	2.56 (1.04)	2.67 (1.01)	2.27 (1.07)
ACR/EULAR remission, n (%)	25 (27)	13 (19)	12 (48)
Medication, n (%)			
bDMARDs (present)	54 (58)	41 (60)	13 (52)
cDMARDs (present)	74 (80)	54 (79)	20 (80)
Corticosteroids (any form during last year)	39 (42)	29 (43)	10 (40)

Abbreviations: ACPA, anti-citrullinated protein antibody; ACR, American College of Rheumatology; ACSM, American College of Sports Medicine; AHA, American Heart Association; bDMARDs, biological disease-modifying anti-rheumatic drugs; cDMARDs, conventional disease modifying anti rheumatic drugs; COPD, chronic obstructive pulmonary disease; CRPD, chronic restrictive pulmonary disease; DAS28, disease activity score index; EULAR, European Alliance of Associations for Rheumatology; hsCRP, C-reactive protein measured in high-sensitivity assays; HT, hypertension; mHAQ, modified Stanford Health Assessment Questionnaire; MI, myocardial infarction; PA index, physical activity summary index; RF, rheumatoid factor; SDAI, Simple Disease Activity Index. [1] Total sum is 101% due to rounding.

Table 6: Cardiopulmonary exercise test results for RA patients (n=93)

VO_{2peak} mL×min^{-1}×kg^{-1}, median (IQR)	**Women**	**Men**
All VO_{2peak} results	27.6 (24.7-33.7), n=68	37.5 (31.8-44.7), n=25
20-39 years	44.5 (43.5-50.6), n=7	54.9, n= 1
40-49 years	36.7 (31.7-41.1), n=8	44.1 (42.7-45.5), n=2
50-59 years	27.1 (24.1-31.9), n=16	42.2 (36.2-46.7), n=9
60-69 years	26.6 (25-28.4), n=25	32.3 (27.6-37.6), n=9
≥ 70 years	24.5 (18.6-28.0), n=12	31.9 (31.2-34.7), n=4

Abbreviations: IQR, inter quartile range; VO_{2peak}, peak ventilation of oxygen; RA, rheumatoid arthritis

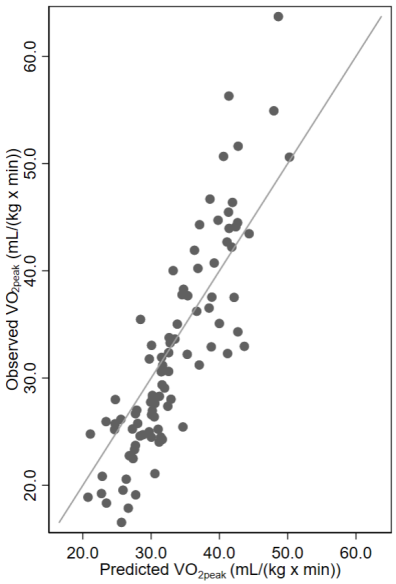


Figure 4: Scatterplot of observed VO_{2peak} (from CPET) vs predicted eCRF from HUNT3 equation (n=93)
Diagonal line indicates identity line. Abbreviations: CPET, cardiopulmonary exercise test; eCRF; estimated cardiorespiratory fitness; HUNT3, The third wave of the Norwegian population-based Trøndelag Health Study; RA, rheumatoid arthritis; VO_{2peak}, peak oxygen uptake

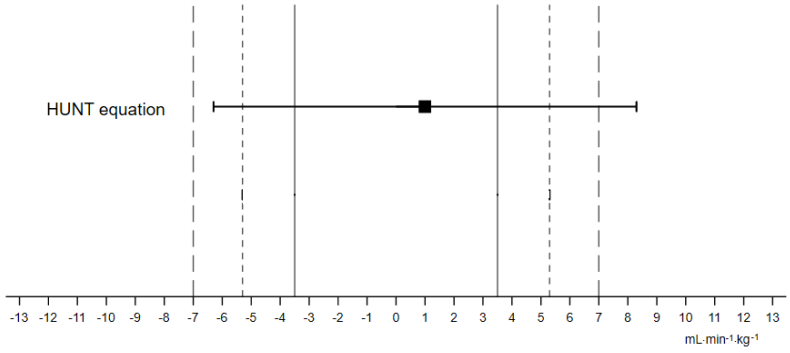


Figure 5: Equivalence testing of the HUNT equation vs VO_{2peak} results from RA patients (n=93)
The horizontal bars represent the 90% confidence interval of the mean (■).
The following equivalence regions are marked vertically:

———— ± 1 MET (± 3.5 mL·min^{-1}·kg^{-1})

- - - - - - - - ± 1.5 MET (± 5.3 mL·min^{-1}·kg^{-1})

– – – – – – ± 2 MET (± 7 mL·min^{-1}·kg^{-1})

Abbreviations: The Norwegian population-based Trøndelag Health Study; MET, metabolic equivalent of task; RA, rheumatoid arthritis; VO_{2peak}, peak oxygen uptake

Aim 2b) Results from investigations to find variables associated with eCRF in RA patients and new equations for eCRF in RA patients:

Results from the multivariable linear regression performed to find a new RA equation and four alternative new RA equations for use when certain variables are missing are described in Table 7. There were no outliers or overly-influential cases in the new RA equations.

PGA was the only RA-specific variable associated with eCRF, and standardization (Table 7, Column 4b) showed the relative importance of each predictor variable. Results for the alternative new RA equations are given in Table 7 and show only small variations in overall fit.

The scatterplots of VO_{2peak} from CPET vs. eCRF from the new RA equation (Table 7, Column 2) showed better fit with less deviation from the CPET results from RA patients for the lowest and highest values than in the scatterplot where the HUNT3 equation was used (Figure 6 compared to Figure 4).

Equivalence testing of eCRF from the new RA equation vs. VO_{2peak} from CPET showed that the new RA equation was equivalent to VO_{2peak} measurement when using the ±2 MET and ±1.5 MET equivalence regions (Figure 7). Bootstrapped CI for the new RA equation were very close to original CIs, indicating that the results were unbiased. The 25-fold cross-validation gave mean (SD) RMSE= 4.32 (1.68), which is close to the RMSE of the new RA equation, indicating that the data lie around the line of best fit.

	New RA equation RA*fit*CALC	New alternative RA equation	New RA equation with SBP	Standardization of variables in new RA equation with SBP	New alternative RA equation with SBP	New RA equation with PA recommend-dation
Column 1	Column 2	Column 3	Column 4a	Column 4b	Column 5	Column 6
Variables	Coefficients	Coefficients	Coefficients		Coefficients	Coefficients
Sex (female=0, male=1)	28.791*	25.460*	31.006*		28.053*	25.844*
Age (years)	-0.358*	-0.381*	-0.341*		-0.361*	-0.406*
Age × sex	-0.326**	-0.254***	-0.361**		-0.296**	-0.269***
Body mass index (kg/m^2)	-0.700*	-0.743*	-0.615*	-0.25*	-0.648*	-0.644*
Resting heart rate (beats per minute)	-0.125***	-0.115***	-0.107***	-0.11***	-0.095[b]	-0.094[c]
Smoking (never=0, ever=1)	-1.854[a]	-2.154**	-2.005***		-2.299***	-2.522***
Physical activity summary index	0.211*	0.209*	0.224*	0.21*	0.223*	
ACSM/AHA 2007 recommendations for PA (not fulfilled=0, fulfilled=1)						2.984***
Patient global RA assessment (mm)	-0.071***		-0.067**	-0.14**		
Systolic blood pressure (mmHg)			-0.073***	-0.12***	-0.079**	-0.071***
Constant	77.961*	77.851*	82.255*	-0.10***	82.487*	85.982*
R squared	0.81	0.79	0.82		0.80	0.79
RMSE	4.44	4.63	4.31		4.48	4.66

Table 7: Summary of the new RA equations to calculate eCRF in RA patients

It is possible to choose the RA equation with variables corresponding to the data available (column 2, 3, 4a, and 5). Column 4b represents standardized coefficients of the new RA equation with SBP. The standardized coefficient gives the change in the dependent variable in SD for one SD change in an explanatory variable.
*p < 0.001. **p < 0.01. ***p < 0.05.
[a]Smoking: p = 0.073 but was kept in the equation to avoid deterioration of overall model fit.
[b]Resting heart rate: p = 0.063 but was kept in the equation to avoid deterioration in the overall model fit.
[c]Resting heart rate: p = 0.078 but was kept in the equation to avoid deterioration in the overall model fit.
Abbreviations: ACSM, American College of Sports Medicine; AHA, American Heart Association; PA, physical activity; RA, rheumatoid arthritis; RA*fit*CALC, the online tool for calculation of cardiorespiratory fitness in RA patients; RMSE, root mean square error; R squared (R^2), proportion of variance explained by variables in the regression model; SBP, systolic blood pressure.

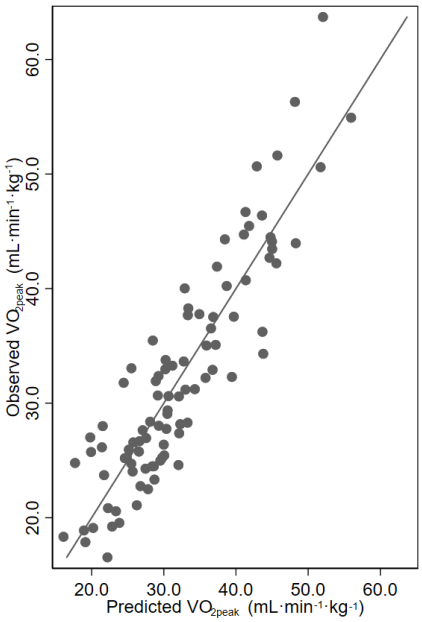


Figure 6: Scatterplot of observed VO_{2peak} (from CPET) vs predicted eCRF from the new RA equation (n=93)

Diagonal line indicates identity line. The new RA equation corresponds to the equation in column 2 in Table 7. Abbreviations: CPET, cardiopulmonary exercise test; eCRF; estimated cardiorespiratory fitness; RA, rheumatoid arthritis; VO_{2peak}, peak oxygen uptake

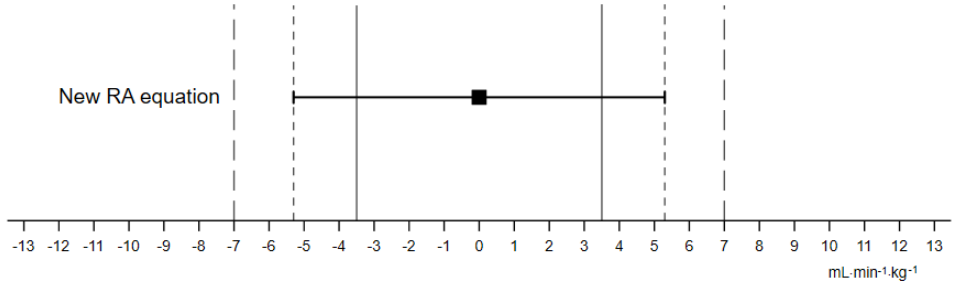


Figure 7: Equivalence testing of the new RA equation vs VO_{2peak} results from RA patients (n=93)

The new RA equation corresponds to the equation in column 2 in Table 7.
The horizontal bars represent the 90% confidence interval of the mean (■).
In The following equivalence regions are marked vertically:

———— ± 1 MET (± 3.5 mL·min⁻¹·kg⁻¹)

- - - - - - - - ± 1.5 MET (± 5.3 mL·min⁻¹·kg⁻¹)

– – – – – – ± 2 MET (± 7 mL·min⁻¹·kg⁻¹)

Abbreviations: MET, metabolic equivalent of task; RA, rheumatoid arthritis; VO_{2peak}, peak oxygen uptake

Aim 3a) Results from the comparison of eCRF in RA patients and controls participating in HUNT2 and/or HUNT3:

The mean age-adjusted difference in eCRF between RA patients (n=436) vs. controls (n=67,910) (p<0.001) was -3.2mL·min^{-1}·kg^{-1} in HUNT2 and -5.0mL·min^{-1}·kg^{-1} in HUNT3 for women, and -1.8mL·min^{-1}·kg^{-1} in HUNT2 and -4.0mL·min^{-1}·kg^{-1} in HUNT3 for men. In the comparison of sex-specific ten-year age categories, controls had significantly higher eCRF than RA patients in all age categories (p<0.05) except for men aged 30-49 years in HUNT2 and men aged 50-59 years, and women aged 40-49 years in HUNT3. Results from analyses in age categories with RA patients n<6 were disregarded (Table 8).

Table 8: Estimated cardiorespiratory fitness in controls and rheumatoid arthritis patients in sex and 10-year age categories (30-89 years) in HUNT2 and HUNT3

	Women			Men		
HUNT2	**Controls, eCRF[a]**	**RA patients, eCRF[b]**		**Controls, eCRF[a]**	**RA patients, eCRF[b]**	
Age	**Mean eCRF (CI), n**	**Mean eCRF (CI), n**	**p-value**	**Mean eCRF (CI), n**	**Mean eCRF (CI), n**	**p-value**
30-89 years	33.9(33.8-33.9), 24,033	29.1(28.2-30.0), 253	<0.001	43.2(43.1-43.3), 23,103	38.9(37.4-40.3), 129	<0.001
30-39 years	40.3(40.2-40.4), 5,623	38.4(36.4-40.2), 22	0.01	50.3(50.2-50.5), 5,134	55.9(46.6-55.4), 6	<0.01
40-49 years	36.6(36.5-36.7), 6,496	35.4(34.4-36.5), 68	0.01	46.2(46.1-46.3), 6,104	48.6(46.8-50.3), 20	0.026
50-59 years	32.9(32.8-33.1), 4,994	28.5(27.5-29.4), 69	<0.001	42.2(42.0-42.3), 4,910	40.3(39.0-41.6), 46	<0.01
60-69 years	29.0(28.9-29.1), 3,441	23.9(22.7-25.1), 60	<0.001	38.3(38.2-38.5), 3,600	34.8(33.2-36.3), 37	<0.001
70-79 years	25.3(25.2-25.5), 2,608	21.3(19.8-22.9), 30	<0.001	34.7(34.5-34.9), 2,678	28.2(26.5-30.0), 20	<0.001
80-89 years	22.1(21.9-22.4), 871	18.6(11.3-25.9), 4	0.06	30.4(30.0-30.8), 677	n=0	

HUNT3	**Controls, eCRF[c]**	**RA patients, eCRF[d]**		**Controls, eCRF[c]**	**RA patients, eCRF[d]**	
Age	**Mean eCRF (CI), n**	**Mean eCRF (CI), n**	**p-value**	**Mean eCRF (CI), n**	**Mean eCRF (CI), n**	**p-value**
30-89 years	31.4(31.3-31.4), 20,169	23.5(22.5-24.5), 149	<0.001	39.2(39.0-39.3), 16,249	31.2(29.4-32.9), 85	<0.001
30-39 years	37.1(36.9-37.2), 3,189	28.1(5.9-50.2), 3	<0.001	46.6(46.4-46.9), 2,069	49.1, 1	NA
40-49 years	34.8(34.7-34.9), 4,668	33.3(31.1-35.4), 7	0.34	43.3(43.1-43.5), 3,406	48.3, 1	NA
50-59 years	31.5(31.4-31.7), 4,994	28.0(26.6-29.4), 47	<0.001	39.5(39.4-39.7), 4,153	41.2(39.0-43.4), 15	0.22
60-69 years	28.2(28.1-28.4), 4,222	23.3(22.0-24.5), 47	<0.001	36.2(36.0-36.3), 3,764	31.2(29.1-33.2), 32	<0.001
70-79 years	24.9(24.8-25.1), 2,284	18.2(17.0-19.3), 31	<0.001	33.0(32.8-33.2), 2,149	27.8(26.0-29.7), 28	<0.001
80-89 years	22.6(22.3-22.8), 812	15.1(13.5-16.8), 14	<0.001	29.7(29.4-30.1), 708	19.7(16.8-22.6), 8	<0.001

eCRF of controls, estimated by [a)]general eCRF formula developed for HUNT2 (106) and [c)]general eCRF formula developed for HUNT3 (117), compared to eCRF of RA patients calculated by [b)]RA-specific formula developed for HUNT2, and [d)]RA-specific formula developed for HUNT3 (176). Comparison by two-sample t-test. Rows in gray when n<6.

Abbreviations: CI, 95% confidence interval; eCRF, estimated cardiorespiratory fitness; HUNT2 and HUNT3, The second and third wave of The Trøndelag Health Study; RA, rheumatoid arthritis

Aim 3b) Results from the comparison of recent CPET results from RA patients to CPET results from healthy participants in the HUNT3 Fitness study:

Comparisons of 10-year age categories (20-79) showed that the mean CRF level was below the 95% CI interval for corresponding age category for healthy participants in the HUNT3 Fitness study for all age categories, except 20-29 for both sexes, and 50-59 and 70-79 for men (Figure 8).

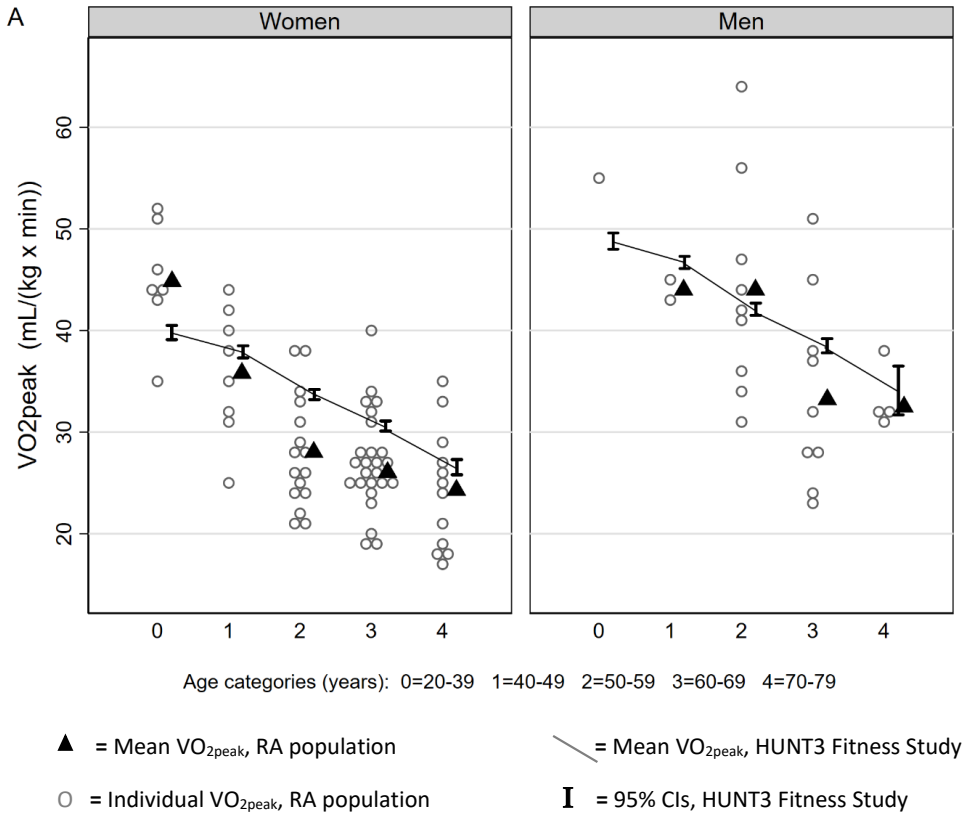


Figure 8: Comparison of sex-specific and 10-year categories of mean VO_{2peak} from CPET of 93 RA patients to mean and 95% CI for VO_{2peak} from the 4,631 participants in the HUNT3 Fitness Study
Abbreviations: CI, confidence interval; CPET, cardiopulmonary exercise test; HUNT3, The third survey of the Nord-Trøndelag Health Study; RA, rheumatoid arthritis; VO_{2peak}, peak oxygen uptake

Aim 4a) Results from the investigation of change in eCRF from HUNT2 to HUNT3:

The equivalence testing showed that the new RA equation was inequivalent to CPET for healthy persons for ±1, ±1.5 and ±2 METs as predefined equivalence regions (mean difference 0.3 $mL \times min^{-1} \times kg^{-1}$ and 90% CI -8.6, 6.0 $mL \times min^{-1} \times kg^{-1}$). The HUNT3 fitness equation was inequivalent with the CPET for RA for the same three predefined equivalence regions (mean difference 1.0 $mL \times min^{-1} \times kg^{-1}$ and 90% CI -6.3, 8.3 $mL \times min^{-1} \times kg^{-1}$) (Figure 5). Furthermore, equivalence testing of estimation methods for eCRF used in HUNT2 and HUNT3 showed that 90% CI intervals for difference between HUNT2 and HUNT3 equations (for controls) were equivalent for a predefined region of ±1 MET (mean difference 0.3 and 90% CI-1.4,2,0 $mL \times min^{-1} \times kg^{-1}$). The equivalence test of the RA equations used in HUNT2 and HUNT3 was equivalent for the same predefined equivalence region (mean difference -1.2 $mL \times min^{-1} \times kg^{-1}$ and 90%CI -1.3, -1,1 $mL \times min^{-1} \times kg^{-1}$).

Using the new eCRF estimation models for RA patients and the already existing eCRF models for healthy people, the change in eCRF from HUNT2 to HUNT3 for both RA patients and controls was calculated. The mean change in eCRF from HUNT2 to HUNT3 was -8.3 $mL \cdot min^{-1} \cdot kg^{-1}$ in RA patients compared to -6.7 $mL \cdot min^{-1} \cdot kg^{-1}$ in controls ($p<0.001$). For women with RA the mean (SD) eCRF change was -7.5 (3.7) $mL \cdot min^{-1} \cdot kg^{-1}$ vs. -6.0(3.4) $mL \cdot min^{-1} \cdot kg^{-1}$ for female controls. For men with RA the mean (SD) eCRF change was -9.6 (3.3) $mL \times min^{-1} \times kg^{-1}$ vs. -7.6 (4.1) $mL \times min^{-1} \times kg^{-1}$ for male controls.

Aim 4b) Results from investigations to find variables associated with the age-related change in eCRF from HUNT2 to HUNT3:

The results from the multiple linear regression with change in eCRF as the dependent variable are shown in Table 9. The final column of Table 9 represents the standardized coefficients. The interaction term for RA*age was significant ($p<0.001$). The decline in eCRF was faster in RA patients and larger with higher baseline age, and the association of higher age at baseline with faster decline in eCRF was more pronounced in RA patients compared to controls. The standardized regression coefficient for RA patients was (-0.482×age+0.044) compared to (-0.367×age) in controls.

Various analyses of model fit for new RA equations and the Cox proportional hazard regression models all showed acceptable fit.

Table 9: Variables associated to change of eCRF, with final standardization

	Step 1 model[a]	Step 2 model[b]	Step 3 model[c]	Step 4 model[d]
Age (years)	-0.053***	-0.110***	-0.110***	-0.367
RA status (no=0/yes=1)	0.421 (p=0.76)	2.138 (p=0.12)	2.011 (p=0.13)	0.044
Age and RA interaction	-0.060*	-0.101***	-0.096***	-0.115
Baseline eCRF (mL× min^{-1}×kg^{-1})	-0.271***	-0.475***	-0.473***	-0.964
Years from HUNT2 to HUNT3	-0.3771***	-0.334***	-0.339***	-0.050
Sex (male=0/female=1)	-0.965***	-3.361***	-3.320***	-0.431
Smoking (never=0/ever=1)		-0.474***	-0.518***	-0.068
Cardiovascular disease (no=0/yes=1)		-0.279*	-0.339**	-0.015
Body mass index (kg/(m^2))		-0.286***	-0.292***	-0.285
High-density lipoprotein concentration		0.336***	0.289***	0.029
Asthma (no=0/yes=1)		-0.253*	-0.216**	-0.015
Hypertension (no=0/yes=1)		-0.277***	-0.211***	-0.026
Pain (no=0/yes=1)		0.0310 (p=0.51)		
Cancer (no=0/yes=1)		0.0557 (p=0.70)		
Diabetes (no=0/yes=1)		-0.188 (p=0.36)		
Family CVD history (no=0/yes=1)		0.010 (p=0.83)		
Constant	11.561	30.706	30.893	
R squared	0.16	0.21	0.21	
RMSE	3.52	3.39	3.41	

*p<0.05, **p<0.01, ***p<0.001.

[a]After removal of variables because of collinearity and high number of missing. [b]After Lasso regression. [c]After removal of non-significant variables. [d]After standardization. The standardized coefficient gives the change in the dependent variable in SD for one SD change in an explanatory variable.

Abbreviations: RF, estimated cardiorespiratory fitness; RA, rheumatoid arthritis; HUNT2 and HUNT3, The second and third survey of the Nord-Trøndelag Health Study; CVD, cardiovascular disease; R-squared (R^2), the variation in the dependent variable explained by the independent variables; RMSE, Root mean square error; Lasso, least absolute shrinkage and selection operator regression.

Aim 5a) Results from the investigations to find variables that were associated with mortality in RA patients and controls:

Low eCRF (eCRF below median for sex and age group) was significantly associated with higher all-cause mortality in the final Step 3 of the Cox regression. Age was the time variable, and the models was adjusted for hypertension, BMI, smoking, cholesterol, diabetes, and creatinine ($P<0.001$) (Table 10).

Aim 5b) Results from the comparison of all-cause mortality in RA patients and controls, and the investigation if low eCRF is a mediator of excess all-cause mortality in RA:

During follow up from inclusion in HUNT2 or HUNT3 until end of observation, RA patients had a significantly higher mortality rate (n=127, 36.6%, CI 31.4-42.0) compared to controls (n=12,942, 21.2%, CI 20.9-21.6).

The Cox regression-based mediation analysis showed that the total excess risk of mortality for RA patients was 28% (95% CI: 2% to 55%, p=0.035), in which RA itself accounted for 5%, the interaction between RA and low eCRF (19%) in addition to low eCRF (4%) accounted for 23% (Figure 9 and Figure 10).

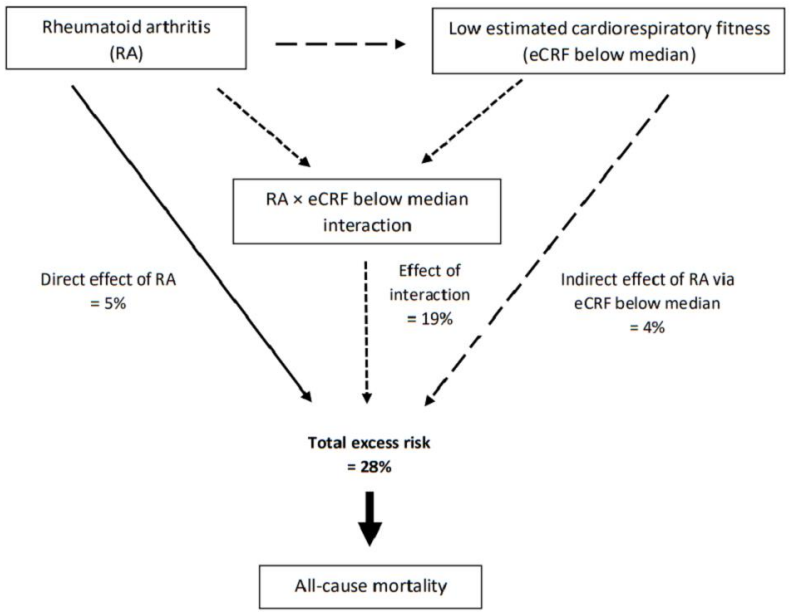
Table 10: Results from Cox regression analyses for all-cause mortality

	Variable	Hazard ratio(95% CI)	p-value
Step1a	RA (univariable)	Control: reference RA: 1.21(1.01-1.45)	 0.036
Step1b	eCRF-dichotomous (univariable)	eCRF above median: reference eCRF below median: 1.19(1.14-1.23)	 <0.001
Step 2	RA and eCRF-dichotomous (bivariable)	Control: reference RA: 1.15(0.96-1.37) eCRF above median: reference eCRF below median: 1.19(1.14-1.23)	 0.12 <0.001
Step 3	RA and eCRF-dichotomous, adjusted for hypertension, BMI, smoking, total cholesterol, diabetes, and creatinine	Control: reference RA: 1.10(0.93-1.32) eCRF above median: reference eCRF below median: 1.18(1.13-1.23)	 0.27 <0.001
Sensitivity analysis 1	RA and eCRF-tertiles, adjusted for hypertension, BMI, smoking, total cholesterol, diabetes, and creatinine	Control: reference RA: 1.09(0.91-1.30) eCRF higher tertile: reference eCRF middle tertile: 1.12(1.07-1.17) eCRF lower tertile: 1.24(1.18-1.31)	 0.34 <0.001 <0.001
Sensitivity analysis 2	RA and eCRF-continuous, adjusted for hypertension, BMI, smoking, total cholesterol, diabetes, and creatinine	Control: reference RA: 1.10 (0.93-1.32) eCRF-continuous: 0.99(0.989-0.997)	 0.25 0.001
Sensitivity analysis 3	RA and eCRF-dichotomous, adjusted for hypertension, BMI, smoking, total cholesterol, diabetes, creatinine, and previous cardiovascular disease	Control: reference RA: 1.08(0.91-1.29) eCRF above median: reference eCRF below median: 1.18(1.13-1.23)	 0.39 <0.001

Hypertension: Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or use of antihypertensive medication. Previous cardiovascular disease: Self-reported stroke and/or angina and/or myocardial infarction. Diabetes: Self-reported diabetes and/or use of anti-diabetic medication and/or having a non-fasting blood-glucose level>11 $mmol \times L^{-1}$.

Abbreviations: BMI, body mass index; 95% CI, 95 percent confidence interval; eCRF, estimated cardiorespiratory fitness; eCRF-continuous, eCRF as a continuous variable; eCRF-dichotomous, eCRF categorized as above or below the median eCRF for each participant's sex and age group (<40 years, 40-59 years, ≥60 years); eCRF-tertiles, eCRF categorized into higher, middle, and lower eCRF tertile for each participant's sex and age group; RA, rheumatoid arthritis.

A



B

Type of effect	%, 95% CI and *P*
——► = Controlled direct effect of RA on mortality when all other variables are adjusted for	5% (-16%, 26%) *P* = 0.63
— — — —► = Pure indirect effect of RA via eCRF below median when all other variables are adjusted for	4% (3%, 5%) *P* < 0.001
----------► = Portion attributable to interaction between RA and eCRF below median when all other variables are adjusted for	19% (-2%, 41%) *P* = 0.077
▬► = Total excess risk for all-cause mortality	28% (2%, 55%) *P* = 0.035

Figure 9: Mediation model

(A) The model is based on the Step 3 adjusted Cox regression model and shows how much of the association of RA with all-cause mortality was mediated by low estimated cardiorespiratory fitness (eCRF below median). (B) Details from results of the mediation analysis.

Abbreviations: 95% CI, 95 percent confidence interval; eCRF below median, estimated cardiorespiratory fitness below the sex- and age-specific eCRF median using age groups <40 years, 40-59 years, or ≥60 years.

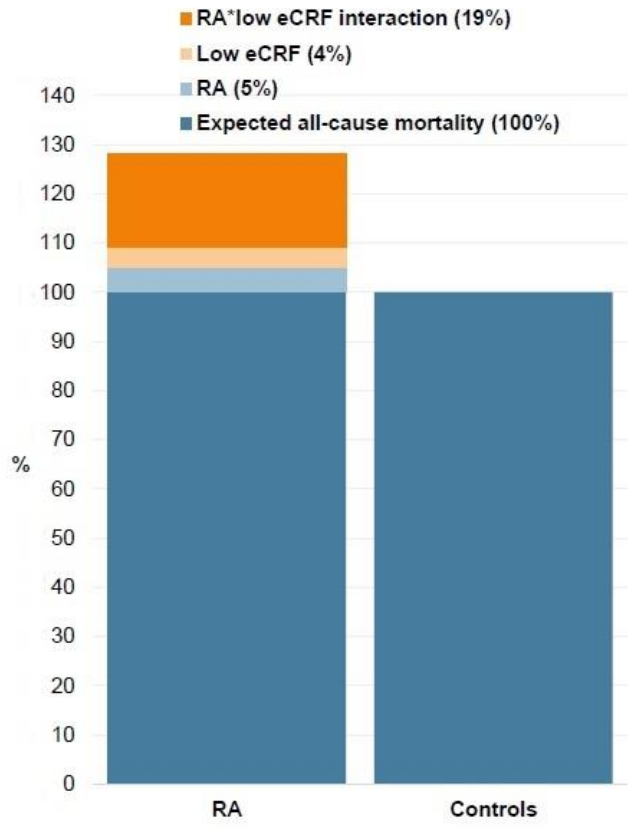


Figure 10: Excess all-cause mortality in RA
Total excess all-cause mortality in RA is 28%. RA itself accounted for 5%, the interaction between RA and low eCRF accounted for 19% and low eCRF alone accounted for 4%.
Abbreviations: Low eCRF, estimated cardiorespiratory fitness below median eCRF for sex and age group; RA, rheumatoid arthritis. The y-axis represents mortality rate (%)

DISCUSSION

We have demonstrated that cardiopulmonary exercise testing (CPET) on a treadmill was well tolerated in patients with RA, indicating that the results were not biased by arthritis pain. An eCRF model developed in a healthy population overestimated CRF in RA patients; thus, it was necessary to develop estimation models customized for RA patients. eCRF in RA patients was associated with slightly different explanatory variables, like PGA and smoking. Some explanatory variables resembled those of the eCRF equation for healthy people, but with coefficients weighted differently. We further calculated and compared eCRF level and eCRF change for RA patients and healthy controls attending a large population-based study (HUNT2 and HUNT3). RA patients were deconditioned and had larger age-related decrease in eCRF from HUNT2 to HUNT3 compared to age- and sex-matched controls. Finally, we found that RA patients had an excess all-cause mortality risk of 28% compared to controls of same age and sex. Low eCRF mediated more than two thirds of this excess risk.

1 Methodological considerations

1.1 Definitions

The design and population of the CPET study was very different from the studies using data from HUNT. Hence, whether random error, bias, and confounding affected the results and if internal and external validity exists is discussed in separate sections (1.3 and 1.4).

Some statistical methods for reducing or controlling for biases and confounding are mentioned in the following sections, while some methods are described in Section 4 "Statistical methods and their limitations and strengths".

1.1.1 Internal validity

When evaluating whether the observed results are true, meaning that the study has **internal validity**, it is important to address the possibilities of random errors, bias and confounding (177).

1.1.1.1 Random error

Random errors may lead to false associations between exposure and outcome and arise from an unpredictable process (177). Complete **precision** is the lack of random error (177). The degree/level of precision can be illustrated for example with CIs and SDs. To increase precision, the sample size can be increased and measurements or the whole study can be

repeated. **Measurement error** is the term often used to describe a random error (177) that for example arises if a instruments are defect or used incorrectly. A measurement error represents a systematic error for example if an instrument is not calibrated, thus, affecting all measures.

1.1.1.2 Bias

A bias can be introduced at any time during the study and represents a systematic error that results in an incorrect or invalid estimate of the measure of association (177).

1.1.1.2.1 Selection bias

Selection bias typically occurs during the selection and follow-up of participants; hence, selection bias occurs because of procedures used to select the study participants that result in systematic differences in characteristics between participants and non-participants (177).

Another type of selection bias results from **loss to follow-up** if this is **differential**, meaning that the loss is unequal between the RA patients and controls (178).

Voluntary response bias (or self-selection bias) occurs when individuals who volunteer for a study differ in relevant clinical characteristics from those who do not (178).

1.1.1.2.2 Observational bias

Observational bias, also known as **information bias**, occurs during data collection, and is caused by systematic differences in the way that the exposure or outcome is measured between study groups (178).

Misclassification occurs when there is an error of classification of for example of the exposure or other data. If misclassification is differential, it is more likely to occur in one of the groups studied (178). Both recall bias and interviewer bias contribute to misclassification. **Recall bias** occurs if there is a difference in accuracy of self-reported information between the exposed compared to the unexposed participants (178). **Interviewer bias** is a systematic difference in soliciting, recording or interpreting information in studies using interviews (178). An example is when exposed and unexposed are treated differently during data collection by the interviewers. The **Hawthorne effect** is bias where participants in a study change behavior simply because they are being studied (179).

1.1.1.3 Confounding

Confounding distorts the association between the exposure and outcome. To meet the **criteria of a confounder**, a variable must have an association with the outcome, it must be associated with the exposure, it must not be an effect of the exposure and not be an

intermediate step in a casual pathway between the exposure and outcome, i.e., a mediator (180). It is possible to control for a confounder by methods of design of a study and specific statistical methods are used to check for and control for confounding (180).

Residual confounding is confounding from factors that are not controlled in the study or from factors that are controlled but are measured inaccurately (181).

1.1.2 External validity

External validity is the extent to which you can generalize the results of a study to other settings and people, i.e., in other words if the results are representative (177).

1.2 Methodological considerations: RA population for cardiopulmonary exercise testing

1.2.1 Study design

The CPET testing of the 93 RA patients from the outpatient clinic at St. Olavs Hospital represents a cross-sectional observational study.

1.2.2 Random error: Sample size and precision

CPET was performed at the certified NextMove test facilities. Highly qualified personnel at NextMove have performed thousands CPETs, and the equipment undergoes strict control, validation, and calibration on a regular basis. This reduces the chance of **systematic errors** to a minimum and reassures reproducibility of results. Still, it is impossible to eliminate **measurement error** during a CPET or when measuring SBP and pulse prior to CPET. As RA patients may have various physical limitations, individual protocols were used. For instance, if an RA patient had stiff ancle joints, the inclination of the treadmill could not be too steep. Some participants preferred higher speed with no inclination, while others preferred slower speed with steep inclination.

It is a strength that the number of participants needed for analysis was decided based upon pre-test power calculations, but one may speculate that because of the large age span and many traits of RA, the number was too low and gave rise to reduced precision. The low number of men (n=25) compared to women (n=68) may be regarded as **selection bias** and represents a weakness of the study. The low number of men probably affected the direct comparison of CPET results to age- and sex-matched healthy controls in the HUNT3 Fitness

Study (Aim 3b_Paper 1), because it resulted in reduced precision with wide CIs that overlapped with the HUNT results.

RA affects women approximately twice as often as men. One solution may have been to invite every second woman identified with RA but every man. This method of selection would probably be preferred if we were to perform a similar-sized study in the future. However, the best alternative to avoid bias because of sample size, would be to perform an even larger study with more participants.

1.2.3 Bias

It is possible to speculate that more fit people more often volunteer for a CPET, thus representing **voluntary response bias.** However, in this CPET study, most participants were not especially fit as they did not fulfill current ACSM recommendations for PA (119). Because some might believe that they had to jog or run, the information letter clearly described the possibility of walking during CPET. Travel expenses differ between patients recruited from rural compared to urban areas. To reduce the risk for this form of **selection bias**, rural participants with the highest travelling expenses were offered coverage of their costs. A **Hawthorne effect** cannot be ruled out because it is possible that RA patients who answered questions for example about disease activity or PA level unconsciously under- or overscored to meet investigators expectations. When possible, we tried to reduce the risk of a change in PA behavior before the CPET by scheduling it only a short time after participants had signed the informed written consent. Studies claim that RA patients may overestimate their own PA level because poor physical fitness may lead to the misinterpretation that PA with low intensity is vigorous (182). Hence, there is a possibility that questionnaires for the PA index may be misunderstood or filled out in a way leading to a wrong PA index, thus, representing **misclassification bias**. During warm-up before the CPET, the RBP Borg was rated, and a scoring around 12 indicated the correct workload to start off with for that particular participant. This approach probably contributed to more participants being able to reach their real VO_{2max} (183), which was important to reduce the possibility of **misclassification bias** reflected as only reaching a VO_{2peak} when a VO_{2max} was within reach. In addition, participants were carefully informed about the safety of CPET in RA, both in the information letter and while the participants were getting ready for the CPET. This was important as it may increase the patient's confidence to perform the CPET with maximal effort. There was no control group in this CPET study, so a differential recall bias was not an

issue. One can never eliminate recall bias leading to over- or under reported values in questionnaires for the RA group.

1.2.4 Confounding

Based upon previous knowledge about CRF and associated variables, a large number of variables were collected. Both multivariable linear regression and Lasso for variable selections reduced possible confounding. Still, it is possible that confounding variables associated with CRF in RA patients were omitted, giving rise to **residual confounding**.

1.2.5 External validity

As the RA population represents a broad range of ages and disease characteristics, and complaints vary largely within the population, the composition of an RA population needed to develop an RA customized eCRF equation was important. Both sexes had to be represented, and we wanted to include RA patients with variations in disease activity, time since diagnosis, and with different medication regimens. Thus, a strength of this study is that participants were included from both the outpatient clinic, the infusion unit, and from the group of RA patients attending patient-centered follow-up. Still, it is impossible to be certain that those who signed up for CPET were representative of RA patients as a group for example with respect to PA, medications, and disease activity. In other words, **external validity** may have been violated by **voluntary response bias**. The disease activity at baseline was high in only 3% of the participants, which is similar as the results reported in the Norwegian arthritis registry (NorArtritt) for 2017. At the same time, only 25% were in DAS28 remission and only 27% were in ACR/EULAR remission, which is less than in the NorArtritt reports for 2017 and 2019 (184, 185). Although a higher share of CPET participants used Methotrexate and/or bDMARDs compared to numbers from the 2017 NorArtritt report, the average DAS28 was the same for CPET participant and RA patients in NorArtritt in 2017 (185). Equal average DAS28 supports that the RA population was representative of Norwegian RA patients. The mHAQ score of 0.3 was close to the average of 0.4 in the Norwegian RA population in 2019, but one can speculate that the slightly better result represents **voluntary response bias** of RA patients with better physical function signing up for CPET (184). The overall impression is that the tested persons were quite representative for the Norwegian RA population. However, it is a concern whether results are valid in a foreign population of RA patients.

The finding that the only RA-specific variable associated with eCRF level in RA patients was the PGA supports that various disease activity levels and medications in other regions of the world perhaps are not so important for the generalizability of an eCRF equation for RA patients. However, we cannot exclude that the results could have been different in a patient group with higher disease activity.

The finding that more men had lower mHAQ and more often were in remission compared to women might represent **voluntary response bias** as one may speculate that men did not sign up for CPET unless they were feeling in shape.

It is a weakness that the new RA equations for eCRF results so far are not externally validated. Further CPET testing of an external group of RA patients to compare results to calculated results from the new RA equation could not be done within the timeline and economic boundaries of this thesis. Thus, to strengthen our results, analyses for internal validation like **bootstrapping** and **k-fold cross-validation** were performed with results supporting our findings. Another analysis showed that when CPET results from 3,294 non-RA controls were compared to calculated results using the RA equation, the eCRF results were non-equivalent with actual CPET results, meaning that the RA equation is not suitable for healthy people. The results from supplementary analyses strengthened the impression that the new RA equation performs well in an external RA population but cannot substitute external validation.

1.2.6 Missing data

The questionnaires were checked for missing data before they were handed in, and the participant was reminded to complete the question if possible. Thus, missingness was not an issue in this part of the study.

1.3 Methodological considerations: The Trøndelag Health Studies (HUNT2 and HUNT3)

1.3.1 Study design

Our investigations using data from the large open population-based HUNT studies (HUNT2 and HUNT3) were designed as **observational prospective cohort studies.** Parts of the studies were **cross-sectional comparisons**, e.g., the comparisons of eCRF level between RA patients and controls in sex specific and 10-year age categories in both HUNT2 and HUNT3.

The RA populations in HUNT2 and HUNT3 may differ regarding PA, thus the design with cross-sectional comparisons represents a strength because they may reveal such differences.

Other parts of the study were **longitudinal observational studies**, including persons who participated both in HUNT2 and/or HUNT3, which is a strength. In the longitudinal observational study of change in eCRF (Aim 4a, Paper 3), the mean follow-up time was 11 years and for investigations about excess mortality (Aim 5, Paper 4), mean follow-up was 19.3 years, which both represent long follow-up. This should be regarded as strengths. Increased mortality rates from RA may evolve years after the time of diagnosis (146), thus, the long follow up was important to be able to capture the excess all-cause mortality rate.

1.3.2 Random error: Sample size and precision

It is possible that random errors arose during data collection in HUNT, but the large number of participants reduces their potential effect. However, small numbers of exposed is a common problem in population-based studies. RA patients and controls with missing variables for the eCRF equations were excluded and this resulted in even smaller sample sizes in the RA patients in our investigations. To increase the number of RA patients in the investigations about mortality, participants with missing baseline variables in HUNT2 were instead included with baseline in HUNT3. Still, the small sample size of RA patients may be regarded as a weakness of our study. However, the large sample of controls in HUNT should be regarded as a strength because it improves the power (177). A larger sample of RA patients would probably increase the precision reflected in a smaller 95% CI. As an example, the result with 28% excess all-cause mortality in RA had a wide 95% CI (2% to 55%, p=0.035), and the result would probably have been more precise in a larger study.

1.3.3 Bias

In order to reduce **selection bias** because of expenses and travelling distance, HUNT was performed using several locations for data collection. Locations were distributed in both urban and rural parts of the northern part of Trøndelag county and questionnaires were distributed by mail. Still, as long as the response rates of the HUNT studies were below a 100%, we cannot rule out **voluntary response bias**. The response rate of HUNT3 was 15.4% lower than HUNT2. In a non-participation study of HUNT3, the lowest participation rates were found in age groups 20-39 years and 80 years and above (186). As the prevalence of RA increases with increasing age, low participation rates in the youngest age categories may be

contributing to the low number of RA patients in the age groups below 40 years, potentially leading to imprecise estimates.

We cannot rule out that the groups lost to follow-up were unrepresentative of RA patients or controls with particular characteristics, thus giving rise to differential **loss to follow-up bias.** However, approximately 70% of both men and women who attended HUNT2 also attended HUNT3, while 16.1 % had died. The largest loss to follow-up was among the youngest age groups with the lowest prevalence of RA (168).

One could speculate that RA patients with high disease activity are more prone to drop-out. However, the non-participation study concluded that a higher share of participants had musculoskeletal pain compared to the non-participants (186). This may support that not only RA patients with low disease activity attended HUNT3.

The RA equation for eCRF contained smoking as a variable and RA patients failing to report smoking status were excluded from analyses. These RA patients could potentially represent a sub-group with certain characteristics and the effect of excluding them from our analyses may potentially give rise to **selection bias** and differential **loss to follow-up bias**. Still, the number of participants who did not answer lifestyle questions in HUNT3 (including use of alcohol, smoking and exercise) was low, with only 2% in the youngest increasing to 12 % among those 80 years and above (186). Furthermore, results from the non-participation study from HUNT3 showed that responders and non-responders had reported the same rate of "daily smoking". This strengthens our results, as there was probably no strong selection bias for participants regarding smoking. However, there was a slightly higher number of "never smokers" among the participants of HUNT3 compared to non-participants (186).

Some studies on RA use diagnostic codes from registries without confirmation in hospital files. Thus, it is regarded as a strength that the diagnosis of RA in HUNT2 and HUNT3 was previously verified from hospital case files. The prevalence of RA in the HUNT studies was found to be comparable to other prevalence studies of RA (2). Potentially differential **misclassification bias** could arise if only participants in HUNT who reported symptoms suggestive of an arthritis diagnosis were subjects to the RA diagnosis validation process. However, during this process, a small, random selection of controls who did not report symptoms suggestive of an arthritis diagnosis were checked for an RA diagnosis. No true false-negative cases were found, hence, reducing the risk of misclassification regarding the RA diagnosis (2).

Participants in HUNT2 and HUNT3 may have misinterpreted their own PA when filling in questionnaires with rating of PA. This may lead to **misclassification bias**. If RA patients were deconditioned compared to the general population, it is possible that they more often rate low intensity activities as being vigorous (182). This could potentially give rise to **differential misclassification bias**. Because the PA classification used in HUNT is not validated in an RA population, it is impossible to rule out potential differential misclassification bias. In the non-participation study for HUNT3 a higher number of participants compared to non-responders reported exercise ≥2-3 times per week (162). This may potentially represent **selection bias** that may influence our results. As it is probable that both controls and RA patients attending HUNT3 reported more exercise than non-responders, this potential selection bias did not represent a differential selection bias.

For data collection, HUNT uses questionnaires, which reduces the chance of **interviewer bias**. When measuring, for example, blood pressure and HR, the examiner was not aware of the patients' state of either being RA patients or controls because this differentiation was not an issue at the time of data collection. This reduces the risk of interviewer bias.

1.3.4 Confounding

Compared to registry studies which often lack information about other lifestyle factors, the large amount of data accessible in HUNT is regarded as a strength. Information about comorbidities, lifestyle factors like smoking habits, and important measures like blood pressure and creatinine makes it possible to better evaluate associations by adjusting for possible confounders.

Socio-economic status and work status may affect PA habits (187). Unfortunately, work status was excluded from our analyses because of missingness, and we did not adjust for education level. This can be regarded as a weakness in our study. It is impossible to completely rule out other confounding variables associated with cardiorespiratory fitness and mortality. Thus, there is a possibility of residual confounding because of missing adjustment variables.

1.3.5 External validity

Ideally, a population-based study with large sample sizes, imitating the true population, with no missing variables and no bias would give results with 100% external validity in a similar population from the same geographical area. In previous sections, we have discussed that

small sample sizes, differential biases, and missing variables may reduce internal validity. Secondarily, this will give rise to reduced external validity.

The population of Norway is quite homogenic, thus, the population from Trøndelag studied in HUNT2 and HUNT3 is probably representative of populations elsewhere in Norway (186). An excess all-cause mortality in RA patients of 28% resembles results from other studies and strengthens the impression that the results were externally valid to a reasonable extent (135, 145). HUNT has no data on mHAQ or DAS28; thus, comparison of these variables with results from RA populations elsewhere in Norway was not possible.

1.3.6 Missing data

The size and design of the HUNT studies as population-based makes it impossible to contact participants directly to complete missing data. As mentioned earlier, some participants were excluded from our analyses because of missing eCRF variables (Figure 1). This may be regarded as a weakness of our study because it may represent a differential loss of participants. For example, the difference in eCRF equations between healthy and controls regarding smoking which is part of the RA equation but not the equation for controls may lead to **selection bias** because of differential missingness. As already mentioned, the missingness in lifestyle variables was rather low for HUNT3, indicating that this may not be a large problem (186).

1.4 Cardiopulmonary exercise testing

The concept of VO_{2max} was established early in the last century (188). Over the years, various CPET systems, test protocols, and criteria for VO_{2max} have existed. The debate is still ongoing about the validity of criteria, protocols and means to verify the VO_{2max} (95-97, 99, 189-192).

Although the O_2 plateau is a quite robust sign of reaching VO_{2max}, it has its limitations. The sampling interval is important, with fewer persons reaching VO_{2max} based on an O_2 plateau in studies with longer sampling intervals (190). Differences in sampling intervals are therefore important to consider when comparing percentages of participants reaching VO_{2max} among different studies. Furthermore, a person reaching VO_{2max} with a plateau in one experiment might reach the same VO_2 in a second CPET without an O_2 plateau (189). Another limitation is the various definitions given for the O_2 plateau (95).

Because not everyone reaches a VO_{2max} with an O_2 plateau, certain levels of blood lactate, RER, HR, and scoring of the RBP Borg scale were implemented as secondary criteria. The use of secondary criteria eventually led to further debate around their validity (96, 97, 189). For example, a study found that participants who reached the O_2 plateau still had a blood lactate concentration below the suggested cut-off for defining VO_{2max}. The lactate level in different populations studied varies substantially, making it difficult to define the correct cut-off (97). In the present study, we also considered that the prospect of further blood sampling might influence the patients' willingness to participate in CPET.

The RER criterion also has limitations. Studies have shown that an RER above 1.10 can occur before the O_2 plateau is reached (97, 189), and RER has a large natural span within a population (97). Although there are weaknesses with both blood lactate level and the RER as secondary criteria, the RER may be preferable because it is measured continuously during CPET, does not necessitate a blood test, and is correlated with the lactate level with RER increasing in response to an increasing blood lactate level (193).

A study from HUNT found that maximal HR calculation based upon age underestimated HR for those older than 30 years of age, and studies have shown that some participants reaching VO_{2max} with an O_2 plateau did not reach their pre-test calculated maximal HR (97, 194). This could potentially lead to misinterpretation of CPET results. The RPE Borg is a subjective scale. Although it largely corresponds with HR (98), it does not add extra information to guide whether a CPET qualifies as a VO_{2max} test or not. The RPE Borg score is a useful tool for easy communication of subjective effort and works as a guide for test personnel in deciding workload in individual CPET protocols.

In the first decade of this century, scientists focused upon the weaknesses of both the primary and the secondary criteria for VO_{2max}. In 2008, Poole et al. even concluded that the existing secondary criteria for VO_{2max} should be abandoned. A review in 2009 by Midgley et al. concluded that there was a need for new VO_{2max} criteria and mentioned the verification phase as a possible means for achieving a true VO_{2max} (189). A review from 2017 by Poole et al. clearly advocated the inclusion of a verification phase as part of the procedure to measure VO_{2max}. This verification phase was defined as a short phase of constant work with higher effort than what was achieved during the incremental test. By then, protocols including a verification phase had already been utilized in CPET studies of children, athletes, obese persons, healthy sedentary individuals, and some patient populations (99).

In our study, we planned to compare CPET results from RA patients with participants in the HUNT3 Fitness study. Thus, to avoid a differential misclassification bias the VO_{2max} criteria had to be equal to those used in HUNT3 Fitness. Data for the HUNT3 Fitness study were collected in 2008 (169). At that time, there was already a debate around the validity of the mentioned secondary VO_{2max} criteria, and the verification phase was not yet established as a standard part of CPET. The choice of RER as the only secondary criterion was based upon the argumentation above. In addition, RER can helps discriminate between a true O_2 plateau and a slope being close to flat because of low intensity.

Studies from the period when the present study was conducted stated that there was no consensus for how a verification phase test should be done and questioned if a verification phase added necessary information (191, 192, 195). In one study, the verification phase only showed minor inter-individual differences between the maximal VO_2 in the incremental test and the verification phase test (192, 195).

There are circumstances when a verification phase may be more important, for example for persons who are naïve to the test method or lack motivation, and for certain patient groups in which disease-related symptoms may limit achievement of a true VO_{2max} with an O_2 plateau (99). In RA patients one limiting factor might be arthritis-related pain in the lower extremities. This may be evaluated by a scale for rating of pain in the lower extremities. If a high percentage terminated the test because of pain in the lower extremities before reaching the plateau phase, the CPET results would be questionable. An important finding of our study was that RA-related arthritis pain was not an important reason for termination of the test, which supports that the lack of a verification phase may not have led to biased VO_{2max} results.

Finally, the extra cost in addition to extra time and effort for the participants must be considered, particularly in large-scale studies as the HUNT3 Fitness study (169). One may also speculate that if a person who for some reason performs submaximal in an incremental CPET would also do so in a verification phase test; thus, confirmation of the result is not the same as conformation of maximal effort.

Earlier studies on CRF in RA have used bicycle ergometer or treadmill tests, and there are pros and cons for both protocols. When evaluating which method to use, both safety and tolerability in addition to practicality was considered. Intuitively, a bicycle ergometer test seemed to give less load to the joints in the lower extremities, but a bicycle ergometer test

may give discomfort and fatigue of large muscle groups of the thighs in inexperienced subjects. This may cause termination of the test before VO_{2max} is reached (92). Studies have shown that people on average end up with lower VO_{2max} with the bicycle ergometer test, thus, conversion formulas exist (196). We also consulted physical therapists and occupational therapists who were familiar with RA patients being tested using both treadmills and bicycle ergometers. They argued that the treadmill test was better because it was well tolerated, and most people, including RA patients, are more familiar with walking. Only a few uses a bicycle on a regular basis. Thus, walking, jogging, or running on a treadmill would be more familiar for most participants.

The choice of a CPET with treadmill was also convenient because the HUNT equation used for comparison with our results was developed from regression analysis of results from treadmill CPET. Otherwise, this comparison could be biased because of differing test methods resulting in a differential **misclassification bias**.

1.5 Choice of eCRF equations

1.5.1 eCRF equations for the general population

For an eCRF equation to be accurate, the population where it was developed must be comparable to the population where the equation it is to be used (external validity). In addition, the included variables should be easy to collect with enough accuracy. Based on these criteria, most published eCRF equations were not adequate to include in our study. Using equations including registration of steps per day was not practically feasible (197-199). Equations developed in aerobically trained populations, using narrow age groups or recruitment schemes that might favor certain groups, or that did not distinguish between levels of eCRF were not appropriate (114, 200-202). Equations based on PA scoring systems that were not well defined or included questions that were not applicable to persons with RA (e.g., time to cover 1- and 3-mile walks) were not useful (112-114, 116). On the other hand, the HUNT equation was recommended in the Scientific statement from the AHA's listing of eCRF methods (102, 117). It has also been shown to predict long-term mortality and is therefore associated with a very important outcome. Furthermore, the HUNT equation was developed in a population of healthy participants from the same area of Norway (Trøndelag county) as the persons with RA included in our study. We also found it essential that the PA index used in the HUNT equation considered intensity, duration, and frequency, i.e., three

central aspects of activity. As mentioned, previous research has shown that persons with RA tend to rate PA as more strenuous than what it is (182), and we considered that this would better be illustrated using the three-dimensional scale in the HUNT equation (117).

1.5.2 eCRF equations for RA patients for analysis of data in HUNT

Five different eCRF equations for RA patients were developed from our regression analysis and these equations somewhat varied regarding included variables. For our further investigations using HUNT data, we chose eCRF equations developed for RA patients that best fit with available data in HUNT. Equations with SBP was preferred because RA is associated with higher frequency of hypertension (145). Depending on what PA scoring system was used in HUNT2 and HUNT3 equations with either the PA index or the categorical ACSM recommendations variable was used (117). No data on PGA were available in HUNT2 and HUNT3, thus, equations without this variable were used in our studies.

1.6 Statistical methods and their limitations and strengths

1.6.1 Multivariable linear regression

Associations, not causation

A limitation of the method is its inability to investigate causation, as a multivariable linear regression model only demonstrates associations between a dependent variable and its predictors. This is important to consider when interpreting results in this study.

Collinearity and overfitting

In the 94 RA patients who underwent CPET testing, more than one hundred variables were collected, but by rule of thumb, the regression should not contain more than approximately nine. Variables normally studied within one scientific field are often correlated and may give rise to problems with collinearity. To avoid over-fitting and reduce collinearity problems, Lasso regression was performed for variable selection. Thus, over-fitting was not a large concern and collinearity problems were avoided.

For Aim 4a (Paper 3), we originally planned to identify predictors from baseline in HUNT2 that would be associated to eCRF level in HUNT3. As eCRF is a composite variable calculated from an equation containing variables that naturally would be included in such a regression, a major collinearity problem arose. We therefore used the dependent variable change of eCRF from HUNT2 to HUNT3. Change of eCRF, as opposed to eCRF in HUNT3,

would not intrinsically be correlated to baseline variables in the regression, thus, the problem of collinearity by design was avoided.

Adjustment variables to reduce confounding and reduce problems with small sample size

As previously described, confounding in multivariable linear regression analysis is reduced by adjusting for possible confounders. Because both the CPET study and HUNT had data on many possible adjustment variables, multivariable linear regression analysis was suitable for various analyses in our study.

During the analysis to find eCRF equations suitable for RA patients, the problem with underrepresentation of men was handled by introducing a categorical sex variable. This resulted in similar eCRF equations for RA patients of both sexes, but at the same time ensuring that eCRF results differed by sex. By introducing this sex variable, we somewhat simplified the problem caused by underrepresentation of men, but like previously mentioned, this cannot eliminate possible biases and imprecision because the sample size was small.

Standardization

Larger coefficients give the impression that the variable is associated with larger changes in the dependent variable. However, **standardization** gave a more realistic impression when comparing the predictors. For instance, the importance of PGA as the only RA-specific explanatory variable associated with eCRF in RA patients was further strengthened by the finding that it was the third most important predictor. PGA had a coefficient of -0.14 (Table 7, Column 4b), only exceeded by BMI and the PA index.

1.6.2 Analysis of statistical agreement

Agreement analyses were important in many parts of this thesis. In the process of finding new equations for eCRF customized for RA patients, it was important to demonstrate whether already existing estimation models were useful in RA patients (agreement). In addition, different eCRF equations in HUNT2 and HUNT3 had to be proven interchangeable.

Despite well-known limitations in agreement analysis of regression models of the **Bland Altmann method** (203, 204), it is often used to evaluate agreement between regression models and variables in exercise science (205). The difference between the estimates (i.e., eCRF result) and criterion value (CPET result) and the means (mean of the eCRF value and CPET result) will always be correlated and will potentially introduce a bias to the BA plot, making the BA unfit for such agreement analysis (205). Instead, **ANOVA and t-tests** are sometimes used to investigate differences between measurement means. However, these tests

are not designed to test equivalence, but rather to detect difference. Demonstrating that two methods are not different is not the same as demonstrating that methods are equivalent (175).

One possible method to demonstrate agreement without introducing bias because of correlations, is by plotting the observed (criterion variable) vs. the estimated results with an identity line as in a **scatterplot** (206). This was done in the agreement analysis where observed VO_{2peak} from CPET was plotted vs. predicted VO_{2peak} from the New RA-specific eCRF equation. This method depends upon visual judgement. When there is a need for comparison of more than two methods (e.g., agreement of two different eCRF equations with actual CPET results), it may be difficult to compare results. Thus, for the remining agreement analyses, we decided to use **equivalence testing** (175). Equivalence testing is an accepted method for both agreement analysis between an estimate (eCRF equation) vs a criterion value (CPET result) as well as one estimate vs. another estimate (e.g., agreement of two eCRF equations). In the field of exercise science, there is an increasing need for reliable measures as well as surrogate estimates without bias. With knowledge about the limitations of the BA method, equivalence testing is used more and more frequently for analyzing agreement in this field (175).

A limitation of the method is that results are dependent upon which equivalence region is chosen. We decided to use equivalence regions of ± 1 MET (± ~3.5 mL × min^{-1} × kg^{-1}), ± 1.5 MET and ± 2 METs. 1 MET was chosen because studies have shown that changes as small as 1 MET may give 21% reduced mortality from CVD in the general population (207). This may not be true for an RA population, but there were no available relevant data. Even with too wide equivalence regions, one can visually evaluate what estimation model better predicts the CPET results. Results from equivalence testing demonstrated that the eCRF methods for HUNT2 and HUNT3 were equivalent, and the eCRF methods developed for healthy persons were non-equivalent for RA patients and vice versa. This ensured that adequate eCRF models were used for the right populations. Thus, the difference in eCRF between HUNT2 and HUNT3 was real, and not a result from using different equations.

1.6.3 Cox proportional hazard regression analysis

Performing Cox regression with age as time variable ensured that possible bias because of different ages at baseline was eliminated. Another alternative would have been adjustment for age. We chose not to use this approach, which may introduce multicollinearity because age is

part of the composite variable eCRF. Furthermore, age at inclusion to HUNT (baseline) does not correspond to the time of diagnosis of RA.

After adjusting for variables known to be associated with preterm mortality, the association between eCRF below mean and excess mortality remained significant. It is a strength that HUNT provides many variables that are known to be associated with excess mortality, because it allowed for control for confounding to a certain degree. In addition, results from three sensitivity analyses strengthened the impression that the Step 3 Model represented the best model for evaluation of associations between eCRF below mean and excess mortality in this study.

1.6.4 Mediation analysis

We found 28% excess all-cause mortality risk when the Cox-based mediation analysis was performed based on the final model from the Cox regression analysis. A limitation for this analysis may be the low number of RA patients, and in particular the low number of RA patient with high fitness. This problem is not unusual in population-based studies, because with a prevalence of RA of approximately 1%, the study needs to be very large to include many RA patients. Ordinary Cox regression is unable to evaluate mediation effects. It is a strength that we included the Cox-based mediation analysis that allowed for analysis of mediation effects and relations between more than one variable associated with mortality (174).

2 Discussion of findings and interpretation with other studies

HYPOTHESIS #1: *Cardiopulmonary exercise testing using a treadmill is well tolerated in patients with RA and the results are not biased by arthritis pain*

Aim 1: Perform CPET using a treadmill on RA patients from an outpatient clinic and evaluate the influence of arthritis pain on test performance

As nobody terminated CPET because of arthritis complaints in the lower extremities and most participant had high scores in the RPE Borg scale for exhaustion at the time of termination, we demonstrated that RA patients tolerated CPET on a treadmill well. Compared to the HUNT3 Fitness Study that tested healthy participants (169), the same share of participants managed to reach VO_{2max} in our CPET study, which serves as another indicator that RA patients tolerated the test well.

Furthermore, for this study, the RPE Borg scores were important measures as they were compared to scores from a similar scale for evaluation of arthritis-related pain in the lower extremities. For easy comparison, the scale for evaluation of arthritis-related pain in the lower extremities used similar grading and colors as the RPE Borg scale, but one may criticize that the scale for arthritis pain was not validated. Even so, in lack of other tools, by using this scale we demonstrated that only a few participants experienced pain in the lower extremities at peak (13%), while most participants rated the test as being very hard or above (75%). Thus, our finding substantiated that CPET was not terminated because of pain in lower extremities, but rather stopped because of exhaustion.

There are not many studies in RA patients to compare with, as most previous studies are performed either as submaximal tests or as CPET on a bicycle ergometer (164, 208). Average VO_{2peak} in our study was higher compared to a study published in 2015 with treadmill CPET results from a group of British RA patients (129). A Swedish study published in 2014, showed slightly better mean VO_{2max} results (209). Differences when comparing with populations in other countries might be explained by the fact that Norwegians in general tend to live active lives. This is reflected in results from studies from the general population in Norway that show better CRF compared to results from other parts of the world (93, 210).

Differences in medical treatment throughout the world may reduce the external validity of our CPET results. However, we found no significant associations between CRF and various

DMARDs, supporting that variations in medical regimens may not be important for CPET results in RA patients.

HYPOTHESIS #2: *Equations for estimation of CRF developed for the general population need to be adjusted to become suitable for persons with RA*

Aim 2a: Investigate if existing eCRF models developed for healthy people accurately predict CRF in RA patients from the same geographical area.

Our results showed that if the HUNT3 equation is used in RA patients (117), it would lead to falsely high eCRF in those that are least fit. This could possibly lead to missed opportunities to improve eCRF in the most vulnerable group of patients. We also showed that it was necessary to use eCRF equations suitable for RA patients to investigate aspects and differences of eCRF in RA patients and controls in HUNT. A calculation bias would be introduced if eCRF were calculated using the same equations for RA patients and controls in HUNT.

Aim 2b: If necessary, identify variables that are useful to improve CRF prediction in RA patients and develop customized models for individual patients and patients taking part in population-based studies.

We developed a total of five equations for eCRF in RA patients. This allows scientists to choose the equation that best fits with available data. As previously described in the discussion, section 3 “Choice of eCRF equations”, most other alternative eCRF methods were not suitable for our study. Compared to the HUNT3 equation (117), which could have been adequate, the new RA-specific equations developed in the present study had better fit. As already mentioned, various agreement methods were used to investigate whether the new RA specific eCRF equations fit better for RA patients. To our knowledge, no other eCRF equations exist for RA patients developed from VO_{2peak} results from CPET on a treadmill. Another test found valid for prediction of CRF in RA, the Åstrand cycle test was found to be valid for prediction of CRF in RA patients is a sub-maximal physical test (209, 211). Our RA eCRF equations do not depend on a physical test, which is a strength, as it saves time and resources and may be used in population-based studies.

Despite carefully performed Lasso and multivariable regression analysis to develop these equations, there may be concerns about variable selection. We cannot exclude that other variables may perform equally well or better. Because CRF is associated with age and sex (94), all RA-specific eCRF equations included adjustment for age and sex.

When starting this study, we discussed what RA-specific variables that most probably could be associated with eCRF. For example, disease duration was a possible variable for an eCRF equation for RA because it affects the amount of irreversible changes in joints that eventually could affect the patients' ability to perform PA. Disease activity measured for example as *DAS28*, *CRP*, *SDAI*, *CDAI* or the number of swollen and tender joints was suggested as possible variables associated with level of eCRF, because disease activity may lead to pain and fatigue that may work as barriers for PA (131). Regardless of these potential mechanisms, the only RA-specific variable associated with eCRF was the PGA (212), in addition to well-known variables associated with eCRF in the general population like systolic blood pressure, RHR, BMI, smoking and level of PA.

The PGA score is subjective and has been described as an important tool in other studies because it covers aspects of a patient's health that clinicians tend to overlook (84). Psychosocial aspects, pain, fatigue and other qualities of a person's health and disease state may be reflected in the PGA (84). These factors will most likely affect motivation for PA as well as intensity of PA. Thus, it may not be surprising that the PGA was associated with eCRF level in RA patients, while e.g., the physician's VAS global, CRP, DAS28, SDAI, CDAI and disease duration were not. Based on our findings, one may speculate whether including a PGA or similar scoring of global health in already existing eCRF equations could lead to better prediction of eCRF, even in equations developed for healthy populations.

As previously mentioned, cigarette smoking contributes to development of RA at an earlier age and is associated with a more severe disease course (21). Hence, it was important to include smoking as a predictor of eCRF in our RA-specific equations.

Many population-based studies include systolic blood pressure. As RA patients may be more prone to hypertension (145, 213), we assumed it would be reasonable to have equations including a systolic blood pressure variable as well.

For easy calculation and easy access, the new RA equation for individual RA patients is published as an open access online calculator (RA*fit*CALC) on NTNU - Norwegian University of Science and Technology's website (214). For this calculator, we preferred the

equation without any measurements that would trigger the need for equipment like a blood pressure monitor or a visit to a healthcare provider to complete eCRF calculation. The use of BMI instead of waist circumference makes the equation user-friendly as most people have their own bathroom scale and know their height. Measuring the waist circumference may introduce measurement bias because there is so much variation in shapes of the waist, in particular because of variations of location of measurement (215), differences in sex and age, variations due to number of childbirths and variations in ability to relax when measuring.

HYPOTHESIS #3: *CRF in RA patients is lower than in a healthy age- and sex-matched population and the differences have not been reduced in recent years*

Aim 3a: **Compare eCRF between RA patients and controls participating in HUNT2 and/or HUNT3**

Aim 3b: Compare recent CPET results from RA patients to CPET results from the HUNT3 Fitness study

RA patients of both sexes had significantly lower eCRF compared to controls in both HUNT2 and HUNT3. In the comparison performed in 10-year age categories from 30-89 years, we found that for women, controls had significantly better eCRF compared to RA patients in 11 out of 12 categories and male controls had significantly higher eCRF compared to controls in 7 out of 10 categories.

One may argue that these findings are irrelevant for today's RA population as one could expect that improved treatment strategies and medication for RA patients would lead to fitness levels in line with those of controls. On the contrary, we showed that most age groups of RA patients who performed CPET in 2017 had reduced CRF compared to a healthy population (93). This finding supports that our results with low eCRF in RA patients compared to controls in HUNT2 and HUNT3 still are relevant today. Results from studies from Britain and Sweden demonstrate the same (129, 208, 216).

The finding that disease activity and the use of bDMARDs and/or csDMARDs were not associated with CPET results illustrate that change in treatment strategies do not necessarily affect the eCRF level. However, a study from The Netherlands demonstrated that improvement of DAS28 from medical treatment was associated with improvement in PA in early arthritis patients (217). We performed a cross-sectional observational CPET study and

only included a few early arthritis patients that were on DMARDs. Thus, we cannot rule out that a study with mostly early RA patients with high disease activity and only partial DMARD treatment would give different results. However, in Norway as well as in other industrialized parts of the world, treatment with DMARDs from time of diagnosis is the standard. A study of associations of eCRF in DMARD naive RA patients would be interesting, but the results would perhaps be less relevant for the average RA patients of today.

HYPOTHESIS #4: *eCRF deteriorates faster by time in RA patients compared to controls*

Aim 4a: Compare changes in eCRF from HUNT2 to HUNT3 in RA patients and controls

Aim 4b: Investigate whether increasing age affects the decline differently in the two groups and identify variables that are associated with the age-related decline in eCRF

The age- and sex-adjusted change of eCRF was significantly larger among RA patients of both sexes compared to controls. Higher age at baseline was associated with a faster decline in eCRF that was more pronounced in RA patients.

To our knowledge, no previous study has demonstrated faster age-related decline of eCRF in RA compared to controls. One may speculate that this is related to differences in the ageing process with including preterm ageing of the immune system and other organs in RA patients compared to the general population (218). Rheumatoid cachexia may add to the natural wasting of muscle mass associated with increasing age (51). With potentially accelerated ageing and rheumatoid cachexia, RA patients may be more prone to the frailty syndrome. Frailty is associated with negative health outcomes like decreased functional capacity and reduced mobility (218). In addition, other possible confounding variables could partly be responsible for the faster age-related decline in eCRF in RA, i.e., work status and sedentary time.

Some jobs may be associated with PA, as part of the job and/or because transportation to/from the job requires PA. A contributing factor to increased age-related change in eCRF in RA may be the reduced work capacity reflected in early retirement and a higher share of part-time work (219-221). It may be considered a weakness that work status was not included in

our study because of missing data, thus, a potential confounding effect of work status could not be investigated.

With more sedentary jobs, there are concerns that increasing sedentary time and inactivity contribute to negative health outcomes in the general population. Studies have demonstrated that prolonged sedentary time is associated with CVR factors and all-cause mortality in the general population. At the same time, high eCRF may offset the odds for risk clustering for CVD caused by sedentary time (100, 222, 223). Studies have demonstrated that RA patients have increased sedentary time compared to controls (224, 225), and this could potentially contribute to the increased age-related decrease in eCRF in RA patients. Unfortunately, data on sedentary time were not available in the present study.

There are conflicting results from studies with various exercise interventions in RA patients. Some studies have demonstrated improved CRF (107, 162, 164), while another study demonstrated no improvement of CRF after a period of PA intervention (216). One study in RA patients at increased 10-year risk of CVD found a positive association between CRF and moderate to vigorous PA and it demonstrated a positive association between CRF and step count (226). Increasing number of steps per day is most likely manageable for most RA patients regardless of disease activity and other barriers for PA and could work as an introduction to PA. However, studies in healthy subjects have found that HIIT is best at improving CRF (103), but not many studies with RA patients have followed strict HIIT protocols.

In addition to improvement of several CV risk factors, the lower body strength improved with an eight-week exercise program aiming to improve CRF in RA patients (47). Another study demonstrated that “Treat to target”/ “Tight control” alone was not associated with increase in muscle mass, thus, not leading to reduced rheumatoid cachexia (49). These findings are interesting as they may add to the impression that it is increased PA, and not reduced disease activity, that leads to better physical function and maintenance of CRF level despite ageing. These findings are in line with our study demonstrating that disease activity was not necessarily related to CRF level.

HYPOTHESIS #5: ***The increased mortality in RA compared to the general population is partly due to reduced eCRF in RA patients***

Aim 5a: Investigate which variables are associated with all-cause mortality.

Aim 5b: Compare all-cause mortality in RA to all-cause mortality in the control group attending HUNT2 and/or HUNT3 and investigate if low eCRF is a mediator of excess all-cause mortality in RA.

Based upon previous results regarding mortality rates in RA, our findings with 28% excess risk of all-cause mortality are in line with other data from many parts of the world from the same time period (135). However, a study from the Netherlands that followed 155 RA patients on strict DMARDs regimen for 23 years from time of diagnosis until 2017 found an equal mortality rate in the RA patients as the control group from the general population (138). Other studies with updates on mortality rates still demonstrate a mortality gap in RA patients compared to the general population (143, 227). This is an indication that our finding is still relevant today.

The baseline age was significantly higher in the RA population compared to controls in HUNT. This probably contributed to the higher share of deaths among RA patients compared to controls during follow-up. But as the survival analyses and the mediation analysis used age as time variable, age at baseline did not bias the results.

Already at the turn of this century, grip strength, walk test and the mHAQ score were measures described as predictors of mortality in RA (212, 228). To our knowledge, no previous study has investigated associations between low eCRF and mortality in RA in a population-based study. Our finding that low eCRF was associated with all-cause mortality and that almost three quarters of the excess risk was mediated by low eCRF or low eCRF in interaction with RA may seem controversial. However, the association between low eCRF and mortality is well-known in preventive care in the general population. One study in the general population in HUNT showed that eCRF was independently associated with CVD and all-cause mortality. Adding other traditional CVR factors hardly improved risk discrimination, nor did it improve classification of risk beyond eCRF alone (106). These findings substantiate the importance of improving CRF in the general population (106), and our findings indicate that this applies for RA patients as well.

Challenges of calculating CVD risk in RA patients was discussed in the introduction. None of the published models have included eCRF or CRF. With the result from our study in mind and the increasing knowledge about the importance of PA in preventive care in RA, it is somewhat surprising that risk calculation models for negative health outcomes in RA patients completely lack questions about PA or measurements of CRF.

In the scientific statement from AHA from 2016, Ross et al. proposed that CRF and eCRF page could increase the predictive ability of risk scoring systems for negative outcomes like mortality and CVD in the general population (102). A recent study demonstrated that the predictive power of three known prediction scores for CVD mortality improved when CRF was added into the calculation, and CRF alone was better at predicting CVD-related mortality than other risk scores (229). Our findings support that similar results may well be expected in the RA population.

Overweight and diabetic patients and patients with prior acute myocardial infarction have increased cardiovascular morbidity and mortality. Increased fitness was not associated with a reduction in mortality or cardiovascular events in two large RCT in these patient groups (109, 110). The Look AHEAD trial included overweight or obese or patients with Type 2 Diabetes. The active arm included a lifestyle intervention aiming to achieve and maintain a weight loss of at least 7% through reduction of calorie intake and increasing PA (109, 230). The PA goal was 175 min of moderate activity per week. Participants attended weekly sessions during the first six months, gradually decreasing to monthly sessions (230, 231). The control group received their usual medical care, plus three group educational sessions per year for four years (230). Fitness increased significantly in the intervention group compared to the control group; 20.9% vs 5.7% after one year, and 5.4% vs -0.83% after four years (231, 232). After one year the intervention group and control group had weight loss of 8.5% vs. 0.6%, respectively, and after eight years the corresponding levels were 4.7% vs. 2.1% (233). Still, no significant reduction in the primary outcome of cardiovascular mortality and morbidity was demonstrated after ten years, with a hazard ratio of 0.95 (95% CI 0.83-1.09) in the intervention group relative to the control group (109, 231).

Several reasons have been put forward to explain these negative results. A large percentage was excluded during the screening process, and only 5,145 of 15,561 eligible persons at prescreen were included in the RCT (230). All participants had to pass a maximal cardiovascular stress test to be included and only 14% of the participants had prior CVD,

which perhaps is less than expected in a group of diabetic patients (230, 231). This may indicate selection bias. Patients had an average BMI of 36 kg/m^2, which is rather high, and the study did not reach the goal of 7% weight loss. Perhaps the average achieved loss was not enough to reduce mortality and CVD morbidity in patients with this high BMI at baseline despite improved fitness (231). This hypothesis is supported by post hoc analyses showing evidence that participants with the greatest weight losses (>10%) after one year had a significant reduction of the primary outcome from year 2 to year 10 (231). Similar findings have been demonstrated in subgroups with the largest improvement in CRF (231). The PA protocol focused on unsupervised, home-based exercise of moderate intensity, which may not be a very effective PA intervention, and a weakness may be that change in fitness was assessed with a submaximal rather than a maximal graded exercise test (230, 232). In addition, the PA intervention was combined with other lifestyle interventions, which may have reduced the focus on PA. Blood tests were done in both groups and the physicians receiving these results could change medications in response (230, 231). During the same time-period, there was a change in medical treatment strategies for diabetic patients, with increased use, for example of statins (231). Thus, medication and tighter control of the diabetic patients, may have contributed to the small difference in cardiovascular events between the groups (231).

All these factors may potentially have resulted in the amount and intensity of PA not being sufficient to bring about a decrease in CV events in the intervention group compared to the control group receiving improved regular care.

The other RCT, RAMIT, was a multicenter study of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. The study aimed to determine the effect of cardiac rehabilitation, and the primary endpoint was mortality after two years. Participants were randomized to either cardiac rehabilitation or routine care (110). Participating centers had to have an established cardiac rehabilitation program and be willing to randomize patients out of rehabilitation (110). This trial demonstrated no significant difference in mortality between patients in the cardiac rehabilitation group and controls after 2 years (RR 0.98, 95% CI 0.74-1.30) or after 7-9 years (RR 0.99, 95% CI 0.85 to 1.15) (110).

The final design of the RAMIT study has been questioned. Only 1,813 of a planned number of 6,000 patients were included. This happened partly because the sponsors requested early

closure, but the reasons are not known, and not much information about the losses to follow-up is known (110, 234).

There is little information about the exercise intervention, other than that it had to consist of exercise training, health education and counselling in line with the British Association for Cardiac rehabilitation for phase three (outpatient) rehabilitation (110). The sessions were weekly or bi-weekly and lasted for 6-8 weeks (110). Information is given about frequencies of participants in the control and intervention group who exercised with more than a daily average of 100 kcal of energy expenditure, but as no CPET was performed, it is unclear whether this exercise improved CRF (110). The lack of information about what intensity exercise training was performed at and change in CRF is important because too low intensities not giving rise to improved CRF may contribute to the negative result regarding mortality (110, 234).

RAMIT has been criticized because the quality of cardiac rehabilitation differed between the various centers, both with regard to staffing level and multi-disciplinary involvement (234). Patients were free to attend support groups, thus, one can speculate that some patients in the control group may have attended cardiac rehabilitation organized in these support groups (110). At the time of RAMIT, cardiac rehabilitation was regarded as an intervention that reduced mortality, hence, centers that were willing to randomize participants to the control group may represent a group of centers with cardiac rehabilitation programs differing from other centers (234).

In conclusion, design issues with both the Look AHEAD and RAMIT studies may have contributed to the negative results. Hopefully, future RCT studying the effect of improved CRF on mortality in RA will avoid making the same mistakes when recruiting, conducting, and evaluating the trials.

Studies demonstrate reduction of fatigue and pain as well as improved sleep quality and cognitive function from PA intervention in RA (134, 164). By including eCRF or PA-related questions into risk calculations, an additional gain may be that patients become aware of the need for PA to improve their health and interrupt the vicious circle of disease-related barriers like fatigue and pain that lead to reduced PA.

A study from Britain compared effects from TNF inhibitor treatment to effects from exercise. This study demonstrated that treatment with a TNF inhibitor improved RA-specific disease activity scores but did not reduce the overall CVD risk. On the contrary, the exercise group

reduced the overall risk of CVD and improved vascular function (235). This was a short-term study, and results may be different with longer follow-up. Another study from Britain demonstrated that CRF was a strong predictor of improvement in endothelial function after a six-month period of exercise in RA patients (163). Yet, a third British study found that six months of high-intensity training three times per week significantly reduced disease activity and specific CVR factors as well as the 10-year CVD risk compared to controls that only received advice on exercise and lifestyle changes (162). These results contribute to the impression that medication alone does not reduce CVR sufficiently. Thus, combined treatment including both adequate medication and PA are necessary and in line with our finding that low eCRF is an important mediator of increased all-cause mortality rates in RA

It would be interesting to study associations between low eCRF and specific CV mortality in RA, but because of too few RA patients in our study, data were not sufficient to analyze this.

CONCLUSIONS

The study confirmed our main hypothesis that CRF is lower in individuals with RA, that this is associated with disease-specific variables, and has important health consequences.

- **Aim 1:** RA patients tolerated CPET on a treadmill and their CPET results were valid.
- **Aim 2a:** eCRF equations developed for healthy individuals overestimated eCRF in RA patients with low CRF.
- **Aim 2b:** We developed five new eCRF equations for RA patients which were better at predicting CRF in RA patients than already existing equations for healthy individuals. The new eCRF equations for RA patients had slightly different explanatory variables than eCRF equations for healthy people. When explanatory variables resembled those of the eCRF equation for healthy people, the coefficients were weighted differently. The PGA was the only RA specific variable included in the new eCRF equations for RA patients.
- **Aim 3a:** In the Trøndelag Health Study, RA patients had lower eCRF compared to a sex- and age-matched population from the same geographical area.
- **Aim 3b:** RA patients of today had reduced measured CRF compared to a sex- and age-matched population from the same geographical area.
- **Aim 4a:** RA patients had a faster age-related decrease in eCRF compared to the general population.
- **Aim 4b:** The variables age, age*RA interaction, baseline eCRF, sex, smoking, cardiovascular disease, body mass index, high-density lipoprotein, asthma, and hypertension were associated with eCRF change from HUNT2 to HUNT3. The decline in eCRF was larger with higher age at baseline, and this association was more pronounced in RA patients compared to controls.
- **Aim 5a:** Low eCRF was associated with all-cause mortality in both RA patients and controls. This was still true after adjusting for hypertension, body mass index, smoking, total cholesterol, diabetes, and creatinine.
- **Aim 5b:** Compared to the general population, RA patients had an excess all-cause mortality rate of 28% (95% CI: 2% to 55%, p=0.035), in which RA itself accounted for 5%, the interaction between RA and low eCRF (19%) in addition to low eCRF (4%) accounted for 23%.

CLINICAL IMPLICATIONS

The decreased CRF in RA patients compared to controls and the association between low eCRF and excess risk of all-cause mortality in RA patients underlines the importance of an early introduction of PA along with DMARDs. Improved CRF can potentially contribute to preventing preterm mortality in RA patients and reducing the mortality gap.

With the new eCRF equations, physicians can identify if an RA patient has an eCRF level that needs to be addressed for better health, and patients can follow eCRF improvements after a period of relevant physical training. Thus, the new eCRF equations can contribute to improved fitness in individual RA patients as well as making it possible to investigate aspects of eCRF in RA patients in population-based studies.

FUTURE STUDIES

It would be a strength if we could validate the RA*fit*CALC externally in another group of RA patients.

To investigate if PA behavior changes after RA is diagnosed, it would be interesting to evaluate the PA Index and eCRF before and after participants are given a diagnosis of RA in HUNT.

HUNT4 is the fourth wave of HUNT, and data collection for HUNT4 was finished in 2019. It is important to investigate if the mortality gap between RA patients and controls still exists in HUNT4 and investigate associations between eCRF and mortality in HUNT4. This is important because RA patients in HUNT4 have had longer follow-up with tight control regimens using more bDMARDs and tsDMARDs than in HUNT3, which may affect the mortality gap. Furthermore, by including RA patients from HUNT4 in addition to those from HUNT2 and HUNT3, the statistical power is higher to investigate if eCRF level is associated with specific CV mortality and CV events in RA patients.

HUNT4 included data on sedentary time, bio-impedance, and accelerometer data in RA patients, which makes it possible to investigate associations of these important variables with mortality and other health outcomes in RA.

It would be interesting to investigate if inclusion of eCRF results may improve prediction of negative health outcomes in already existing risk calculation models for RA patients.

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Paper 1

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ORIGINAL ARTICLE

Cardiorespiratory fitness in patients with rheumatoid arthritis is associated with the patient global assessment but not with objective measurements of disease activity

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ABSTRACT

Objective Patients with rheumatoid arthritis (RA) suffer from more cardiovascular disease (CVD), and develop cardiovascular risk factors at an earlier age than the general population. Cardiorespiratory fitness (CRF) is an important predictor of cardiovascular health. There are few data regarding CRF of RA patients, measured as peak oxygen uptake (VO_{2peak}) by the gold standard method; cardiopulmonary exercise testing. We compared CRF in RA patients to those from a healthy population, and investigated if risk factors for CVD and RA-specific variables including subjective and objective disease activity measures were associated with CRF in RA patients.

Methods VO_{2peak} tests of RA patients (n=93) were compared to those of an age-matched and gender-matched healthy population (n=4631) from the Nord-Trøndelag Health Study. Predictors of VO_{2peak} were found using Lasso (least absolute shrinkage and selection operator) regression, followed by standardised multiple linear regression.

Results Women with RA ≥40 years and men with RA aged 40–49 years or 60–69 years had up to 20% lower CRF than the healthy population in the same age groups. By relative importance, body mass index (standardised coefficient=−0.25, p<0.001), physical activity level (coefficient=0.21, p<0.001), patient global assessment (PGA; coefficient=−0.14, p=0.006), systolic blood pressure (coefficient=−0.12, p=0.016), resting heart rate (coefficient=−0.11, p=0.032) and smoking (coefficient=−0.10, p=0.046) were significant predictors of CRF (R^2=0.82, gender-adjusted and age-adjusted).

Conclusion CRF in RA patients was lower than in a healthy population. CRF was associated with common risk factors for CVD and the PGA score. Focusing on fitness in RA patients may improve cardiovascular health.

Key messages

What is already known about this subject?

- Cardiovascular disease (CVD) is inversely associated with cardiorespiratory fitness (CRF), and patients with rheumatoid arthritis (RA) suffer from more CVD and develop cardiovascular risk factors at an earlier age than the general population.

What does this study add?

- The variables most strongly associated with the CRF level in RA patients were body mass index (BMI), physical activity level and the patient global assessment (PGA).
- Contradictory to earlier suggestions that objective measures of RA disease activity are related to CRF, the subjective patient assessment captured as the PGA was the only RA-related variable associated with CRF in this study.

How does this impact on clinical practice?

- Physical activity should be assessed and acted on in RA patients because it may positively change both their BMI and CRF level.
- Assessing the PGA may be a simple method to capture the patient's subjective factors influencing the physical activity level.

INTRODUCTION

Cardiorespiratory fitness (CRF) is inversely associated with the risk for cardiovascular disease (CVD) in the general population.[1–6] The CRF level influences prognosis after myocardial infarction and coronary artery bypass surgery,[7 8] and the American Heart Association now regards CRF as a clinical vital sign which associates inversely with prognosis after several diseases and conditions.[9] Patients with rheumatoid arthritis (RA) also suffer from more CVD, develop cardiovascular risk factors at an earlier age,[10 11] and have an increased death rate due to CVD compared with age-matched controls.[11–15] Both RA-specific and general risk factors have been implicated, including the RA-associated

systemic inflammation process that affects the vasculature of internal organs.

Studies suggest that RA patients might be less physically active due to fatigue, incomplete RA disease control, pain and/or structural changes of the joints.[16 17] In practice, changing frequency, duration and/or intensity of physical activity is the only way to improve CRF. Physical inactivity might therefore contribute to worsened CRF and greater prevalence of CVD.[18 19] Thus, low CRF may contribute to the risk of CVD in RA patients in addition to an increased burden of known cardiovascular risk factors, such as smoking, lipid levels and hypertension.[11–15]

Cardiopulmonary exercise testing with direct measurement of peak oxygen uptake (VO_{2peak}) is the gold standard method for CRF assessment. However, VO_{2peak} in RA patients has rarely been compared with VO_{2peak} in healthy age-matched and gender-matched controls from the same population.[18 20 21] Moreover, many studies were performed before biological disease-modifying anti-rheumatic drugs (DMARDs) became part of standard treatment regimens.

Given the excess of CVD and indications of limited physical activity in RA patients, we hypothesised that CRF in RA patients is lower than in a healthy age-matched and gender-matched population. This study therefore had three aims: (1) to measure VO_{2peak} in RA patients and compare the results with VO_{2peak} measurements from a healthy age-matched and gender-matched population; (2) to investigate variables that potentially were associated with VO_{2peak} in RA patients, including both RA-specific variables and general risk factors for CVD, and evaluate their relative importance in our population.

PATIENTS AND METHODS

RA patients fulfilling the 1987 American College of Rheumatology (ACR)[22] and/or the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA[23 24] were recruited from St. Olavs Hospital's Rheumatology outpatient clinic from 17 February 2017 to 04 January 2018. Since 01 May 2013, RA patients with stable disease activity have been transferred to a patient-centred follow-up programme where the patient's general practitioner (GP) performs check-ups. If necessary, either the GP or the patient may contact the rheumatology clinic for an appointment. The remaining RA patients attend regular visits at the outpatient clinic. To include participants representing different disease activities, both types of patients were recruited to the present study. Exclusion criteria were unstable heart conditions, chronic obstructive/restrictive pulmonary disease (COPD/CRPD) necessitating use of oxygen therapy, or physical disability making a treadmill test impossible.

Three different recruitment schemes were used (figure 1): (1) RA patients attending regular visits were recruited during an appointment at the clinic; (2) a random selection of RA patients from the patient-centred follow-up list were contacted by mail; (3) a few RA patients signed up after reading information from the local arthritis association.

Power calculations were based on the following assumptions: from the literature, we assumed that the most relevant variables associated with fitness in the general population (ie, age, gender, waist circumference, resting heart rate [RHR] and an index of physical activity)[25] would explain 60% of the variance in measured VO_{2peak} (ie, R^2=0.60). Given α=0.05 and a planned inclusion of 100 RA patients, we would be able to identify one or more RA-related variables that would increase R^2 to 0.65 with a power of 0.96, which was considered very satisfactory. In reality, useful data were available from 93 patients, which resulted in a power of 0.95 to detect this increase in R^2.

Cardiopulmonary exercise testing to measure VO_{2peak} was performed at the NeXt Move core facility at NTNU—Norwegian University of Science and Technology. Because RA patients sometimes exhibit physical limitations, experienced personnel determined the best individual cardiopumonary exercise testing (CPET) regimen during a 6 min warm-up on a treadmill (Woodway PPS 55, Waukesha, Wisconsin, USA), by detecting functional walking or running speed and inclination, as well as subjective moderate aerobic intensity based on rated perceived exertion (RPE Borg scale 6–20).[26] Participants were then fitted with a heart rate monitor (H7, Polar Electro, Kempele, Finland) and facemask (7450 Series V2 CPET mask, Hans Rudolph, Shawnee, Kansas, USA). During an initial period of 4 min at fixed submaximal workload serving as an extended warm-up, work economy measurements were made.

An individualised ramp protocol was used, until either exhaustion or fulfilment of the criteria for VO_{2max} or VO_{2peak}. Workload was gradually increased, and gas measurements were recorded every 10th second using a mixing chamber ergospirometry system (Metalyzer II, Cortex Biophysik Gmbh, Leipzig, Germany). Maximal oxygen uptake (VO_{2max}) was defined using the following criteria: (1) VO_2 levelling off (<2 mL/(kg x min)) despite increase in workload and (2) respiratory exchange ratio ≥1.05. If these criteria were not met, the term VO_{2peak} was used. A participant's VO_{2peak} was defined as the mean of the three successive highest VO_2 registrations achieved during the CPET. Of the 93 patients tested, 17.2% qualified for VO_{2peak}. For simplicity, the term VO_{2peak} is used for all patients.

Participants rated their RPE on the Borg scale before, during and at the peak of the test, using a 6–20 scale.[26] At the same time points, they also graded their lower extremities joint pain due to RA. Grading was similar to the RPE Borg scale, but instead focusing on pain: 6='Very, very light pain,' 9='Very light pain,' 11='Fairly light pain,' 13='Somewhat painful,' 15='Strong pain,' 17='Very strong pain' and 20='Very, very strong pain.' Ratings below 6 were equivalent to 'no pain.' Age-predicted maximal heart rate was not used because it is does not account for the large normal variation. Lactate measurements were considered unnecessary because we

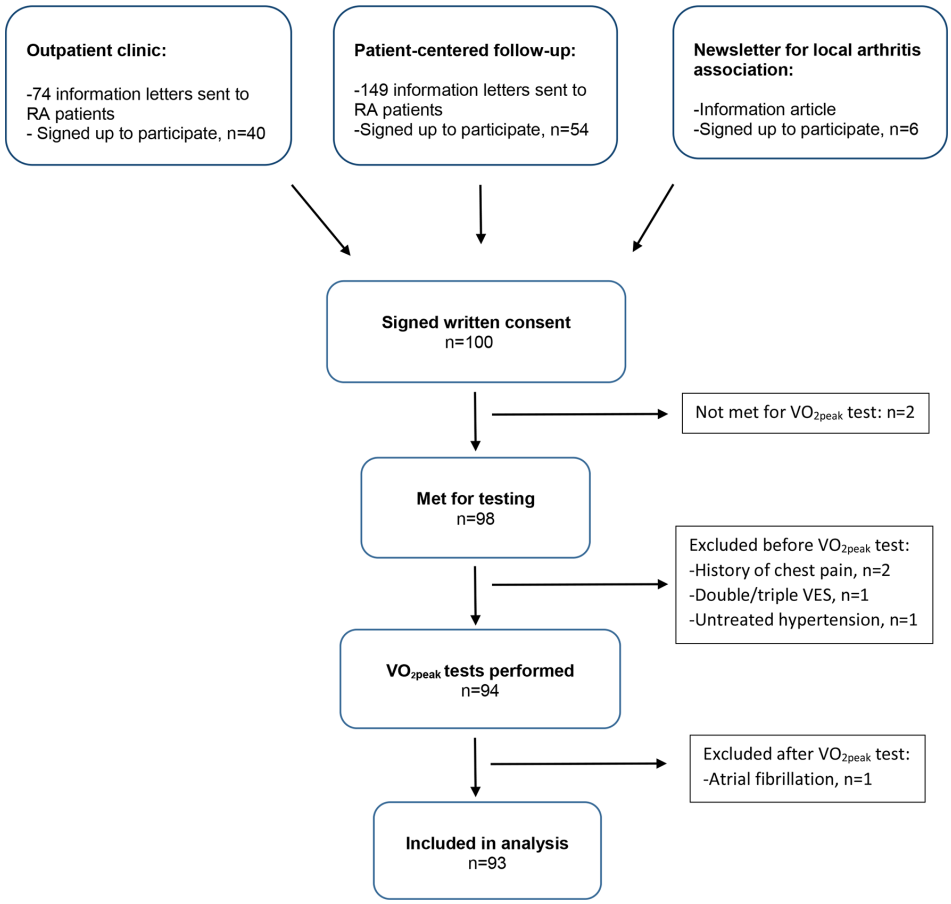


Figure 1 Recruitment to the study. RA, rheumatoid arthritis; VES, ventricular extrasystoles.

measured the increase in respiratory exchange ratio, which is caused by and strongly correlated to lactate. The protocol for VO_{2peak} testing did not include a verification phase because there is no general agreement on how it should be performed.

Before the physical test, a blood sample for measurement of high sensitivity C reactive protein (hsCRP) was drawn. A rheumatologist recorded the number of tender and swollen joints, height, weight, physician global assessment,[27] rheumatoid factor (RF), anti-citrullinated protein antibody, present/previous RA medication, disease duration and information on comorbidity (cancer, CVD, diabetes, COPD/CRPD) from an interview and medical records. Blood pressure (BP) and RHR were measured after 10 min of rest. RHR was electronically measured using a pulse watch, and compared with manually counted RHR in 15 randomly selected participants to ensure that readings were correct. Participants filled in the modified Health Assessment Questionnaire (mHAQ)[28] and the patient global assessment (PGA),[27] as well as self-reported smoking (never vs ever). A questionnaire from the Nord-Trøndelag Health Study[29] on physical activity habits, grading frequency, duration and intensity of physical activity was completed, and a physical activity summary index (PA index) was calculated from a previously published formula.[25] In the statistical analysis, the PA index was used as a continuous variable. For descriptive purposes, patients were categorised into two physical activity categories, depending on whether they fulfilled the American College of Sports Medicine and American Heart Association's recommendations for physical activity or not (table 1).[30] The Disease Activity Score 28 (DAS28),[31] Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI)[32] were also calculated.

We compared our results with VO_{2peak} measurements from the general population using published data from the HUNT3 Fitness study, which was part of the third survey of the Nord-Trøndelag Health Study (HUNT3, ntnu.edu/hunt).[29] In HUNT3 (2006–2008), the entire population ≥20 years old in the northern region of Trøndelag (previously, Nord-Trøndelag county), Norway, were

Table 1 Patient characteristics

Patient characteristics	Total n=93	Women n=68	Men n=25
Age median, (IQR)	60 (52–66)	60 (51–67)	60 (52–66)
Height (m), mean (SD)	1.69 (0.90)	1.66 (0.63)	1.80 (0.71)
Weight (kg), mean (SD)	76.4 (12.3)	72.7 (10.9)	86.8 (9.7)
Body mass index (kg/m^2), mean (SD)	26.7 (3.9)	26.6 (4.1)	26.9 (3.4)
Comorbidity, n (%)	38 (41)	30 (44)	8 (32)
Cardiovascular (HT, angina, MI)	21 (23)	17 (25)	4 (16)
Respiratory (COPD and/or CRPD)	18 (19)	15 (22)	3 (12)
Diabetes	4 (4)	3 (4)	1 (4)
Cancer (previous or present)	5 (5)	3 (4)	2 (8)
Smoking, n (%)*			
Never smoked	35 (38)	27 (40)	8 (32)
Previous smoker	51 (55)	37 (54)	14 (56)
Present smoker	7 (8)	4 (6)	3 (12)
Resting heart rate (beats per min), mean (SD)	66 (10)	67 (9)	65 (11)
Physical activity categories, n (%)			
Does not fulfil ACSM/AHA recommendations	64 (69)	44 (66)	19 (76)
Fulfils ACSM/AHA recommendations	29 (31)	23 (34)	6 (24)
Seropositivity (ACPA and/or RF), n (%)	75 (81)	54 (79)	21 (84)
Disease duration (years), median (IQR)	10 (5–19)	10 (5–20)	11 (6–16)
Patient global assessment (0–100 mm), median (IQR)	24 (10–36)	27 (16–42)	12 (5–24)
Physician global assessment (0–100 mm), median (IQR)	10 (0–12)	8 (0–18)	5 (0–10)
mHAQ, mean (SD)	0.26 (0.31)	0.29 (0.33)	0.17 (0.23)
hsCRP, median (IQR)	1.75 (0.75–3.13)	1.64 (0.71–3.13)	2.39 (0.98–3.20)
SDAI, n (%)			
Remission	22 (24)	12 (18)	10 (40)
Low disease activity	41 (44)	32 (47)	9 (36)
Moderate disease activity	24 (25)	21 (31)	3 (12)
High disease activity	6 (7)	3 (4)	3 (12)
Mean (SD)	10.2 (8.7)	10.6 (8.0)	9.3 (10.3)
DAS28 (hsCRP), n (%)			
Remission	39 (42)	25 (37)	14 (56)
Low disease activity	23 (25)	18 (27)	5 (20)
Moderate disease activity	28 (30)	23 (34)	5 (20)
High disease activity	3 (3)	2 (3)	1 (4)
Mean (SD)	2.56 (1.04)	2.67 (1.01)	2.27 (1.07)
ACR/EULAR remission, n (%)	25 (27)	13 (19)	12 (48)
Medication, n (%)			
bDMARDs (present)	54 (58)	41 (60)	13 (52)
cDMARDs (present)	74 (80)	54 (79)	20 (80)
Corticosteroids (any form during last year)	39 (42)	29 (43)	10 (40)

*Total sum is 101% due to rounding.
ACPA, anti-citrullinated protein antibody; ACR, American College of Rheumatology; ACSM, American College of Sports Medicine; AHA, American Heart Association; bDMARDs, biological disease-modifying anti-rheumatic drugs; cDMARDs, conventional disease-modifying anti-rheumatic drugs; COPD, chronic obstructive pulmonary disease; CRPD, chronic restrictive pulmonary disease; DAS28, disease activity score index; EULAR, European League Against Rheumatism; hsCRP, high-sensitivity C reactive protein; HT, hypertension; mHAQ, modified Health Assessment Questionnaire; MI, myocardial infarction; PA index, physical activity summary index; RF, rheumatoid factor; SDAI, Simple Disease Activity Index.

invited, with a participation rate of 54%. In the HUNT3 Fitness sub-study 4631 participants of both genders free from CVD, respiratory symptoms, cancer and the use of anti-hypertensives also completed VO_{2peak} tests.[1 33]

Statistical analysis

Data are given as counts and percentages, mean with SD or median with IQR in parenthesis.

Mean VO_{2peak} in 10 years age and gender categories in our study were compared with the corresponding mean and 95% CI in the HUNT3 Fitness population. Due to small numbers in our study, age groups 20–29 years and 30–39 years were combined, and compared with the HUNT3 Fitness age group 30–39 years. The results were similar if the RA patients from 20 to 29 years were omitted from the comparison.

To evaluate variables associated with VO_{2peak} in RA patients, multivariable linear regression analyses with VO_{2peak} (mL/(kg x min)) as the dependent variable were performed. The following explanatory variables were included based on previous literature: age, gender and the age×gender interaction, body mass index (BMI, calculated as weight in kg/height in m^2), smoking (present or previous vs never smoker), RHR and the PA index. Other potential explanatory variables included the systolic blood pressure (SBP), comorbidity (cancer, CVD [hypertension/angina/myocardial infarction], diabetes, COPD/CRPD) coded as a single yes/no variable. The following RA-specific variables were then considered: PGA and the physician global assessment, mHAQ, DAS28, SDAI, CDAI, remission criteria (DAS28 or ACR/EULAR),[34–36] time since diagnosis, seropositivity and medication (present use of biological DMARDs and conventional DMARDs, and corticosteroids used during the last year). In order not to overfit the linear regression model, variable selection for these variables was first performed using Lasso (least absolute shrinkage and selection operator) regression using n=1000 repetitions. Lasso regression identifies the smallest useful set of variables among variables that may be highly correlated, setting the coefficients of irrelevant variables to 0. Only variables with a coefficient different from 0 in the Lasso regression were included in the multivariable linear regression model. The full model was then reduced to the final model by removal of non-significant variables. Finally, the reduced model was standardised in order to permit direct comparison of the importance of the included variables by the size of their coefficients, which are all measured on the same scale (ie, SD). P values <0.05 were considered significant and assumptions were evaluated using residual plots.

RESULTS

A 100 RA patients signed up for the project, and 93 patients completed a valid VO_{2peak} test (figure 1). From those receiving an invitation letter by mail, a higher percentage of men (40%) compared with women (34%) replied when recruited from the patient-centred follow-up lists, whereas a higher percentage of women (62%) compared with men (33%) signed up from patients attending regular visits. More women (n=68) than men (n=25) entered.

Patient characteristics are given in table 1.

Approximately 2/3 of the women and 3/4 of the men did not fulfil the current recommendations for physical activity. Higher proportions of men were in DAS28 and ACR/EULAR remission, and men had lower disease activity compared with women. At the test peak, only 10% of participants reported complaints above 13='Somewhat painful' due to RA in the lower extremities, whereas 75% of participants reported the test being 17='Very Hard' or above (RPE Borg scale).[26]

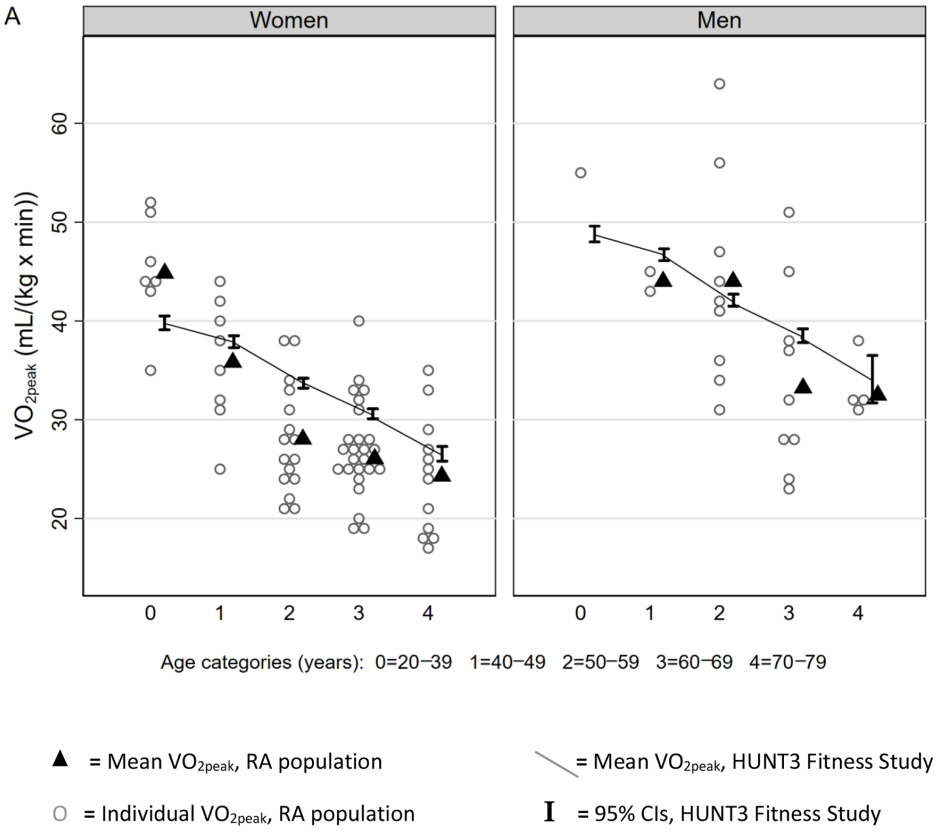
VO_{2peak} was lower in older age groups, and women had lower VO_{2peak} than men (figures 2 and 3A). Compared with the general population, women with RA aged ≥40 years had significantly lower VO_{2peak} as indicated by group means below the 95% CI for the HUNT3 Fitness population, and men with RA in the age groups 40–49 and 60–69 years had a significantly lower VO_{2peak} (figure 2). In most age groups, patients recruited from the patient-centred follow-up list had higher VO_{2peak} compared with the other patients (age group <70 years: p=0.02 for patient-centred follow-up vs other patients in linear regression adjusted for gender).

In the Lasso regression with VO_{2peak} as the dependent variable, five explanatory variables were significant: comorbidity (yes/no), disease duration, SBP, ACR/EULAR remission (yes/no) and the PGA. These variables were included in the full regression model in addition to explanatory variables included based on previous literature; that is, age, gender, the age×gender interaction, BMI, smoking, RHR and the PA index. After stepwise removal of non-significant variables (disease duration [p=0.90], comorbidity [p=0.33] and ACR/EULAR remission [p=0.25]), and after adjusting for age (p<0.001), gender (p<0.001) and the age×gender interaction term (p=0.001), the final reduced model explained 82% of the variation in VO_{2peak}. The final predictors in the multiple linear regression model and their standardised coefficients are shown in table 2. The influence of each variable on VO_{2peak} is shown in figure 3.

DISCUSSION

The main finding in this study was that in most age groups, patients with RA had significantly lower CRF measured as VO_{2peak} compared with healthy controls of similar age and gender. The difference in CRF level between RA patients and the general population was more pronounced in women. CRF was associated with common risk factors for CVD, with BMI having the strongest association, followed by physical activity measured by the PA index, and the patients' own impression of RA disease activity measured as the PGA. The only RA-specific variable associated with CRF was the PGA.

A



B

VO_{2peak} (mL/(kg x min)), median (IQR)	Women	Men
All VO_{2peak} results	27.6 (24.7–33.7), n=68	37.5 (31.8–44.7), n=25
20–39 years	44.5 (43.5–50.6), n=7	54.9, n= 1
40–49 years	36.7 (31.7–41.1), n=8	44.1 (42.7–45.5), n=2
50–59 years	27.1 (24.1–31.9), n=16	42.2 (36.2–46.7), n=9
60–69 years	26.6 (25–28.4), n=25	32.3 (27.6–37.6), n=9
≥ 70 years	24.5 (18.6–28.0), n=12	31.9 (31.2–34.7), n=4

Figure 2 VO_{2peak} in RA patients compared with healthy controls. (A) Mean VO_{2peak} in RA population compared with means and 95% CIs of HUNT3 Fitness study. (B) VO_{2peak} results for RA population, median (IQR). RA, rheumatoid arthritis.

Predictors of VO_{2peak}

The associations between CRF and common risk factors for cardiovascular health in RA patients (high BMI, high RHR, high SBP and previous/present smoking) are supported by other studies.[18 21] CRF is a predictor of cardiovascular health, and improvement of CRF strengthens cardiovascular health in the general population[6] and improves risk factors for CVD in RA patients.[21] Thus, improvement of CRF could probably contribute to better cardiovascular health in RA patients.[1–8 18]

The degree of physical activity, measured as the PA index, contributed strongly to the prediction of CRF. Increased physical activity might also reduce BMI. These two factors showed the highest relative importance for

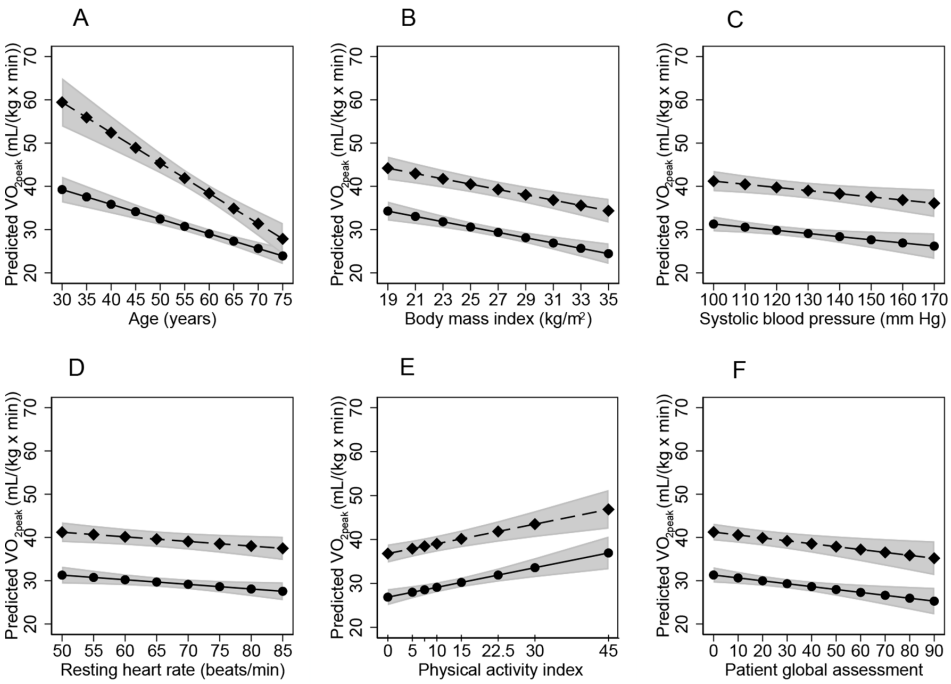


Figure 3 Associations of VO_{2peak} to significant predictors. Influence of age (A), body mass index (BMI) (B), systolic blood pressure (SBP) (C), resting heart rate (RHR) (D), physical activity index (E) and patient global assessment (PGA) (F) on VO_{2peak}, based on the multivariable model including age, gender, BMI, RHR, smoking, SBP, physical activity index and PGA. Circles: women; diamonds: men; grey areas: 95% CIs.

the CRF, supporting the view that physical activity should be assessed and acted on in RA patients. Information on the degree of physical activity might reveal possibilities and barriers for improving CRF, which is associated with cardiovascular health.

Contradictory to our hypothesis, CRF was not associated with objective RA-specific variables. The PGA score is strongly subjective, and completely determined by the patient's own impression of disease impact. In addition to disease activity, pain and functional incapacity, the PGA is driven by factors like fatigue, psychological distress and the coexistence of fibromyalgia.[37] Such factors may represent aspects of RA that are difficult for physicians to capture, and might partly explain the discrepancy between the patient and physician global assessment (table 1). Physicians tend to examine joints and evaluate markers of inflammation before deciding on the global assessment, and joint counts and CPR concentrations are not strong drivers of the PGA.[37] Perhaps disease activity is not what stops RA patients from being physically active, but rather symptoms like fatigue, psychological distress and coexistence of fibromyalgia that influence motivation for physical activity. The association between the PGA with CRF merits further investigation.

In the HUNT Fitness Study, patients were excluded if they had comorbidities and the participants therefore represent a selected, healthy population. In the present study, no such exclusions were made. The results indicate that the reason for lower fitness in the RA patients was not the coexistence of CVD, diabetes, cancer or pulmonary disease, but was rather related to other differences from the healthy population. However, the study was not designed to investigate the mechanisms behind the observed fitness level. Further, a larger study would

Table 2 Variables associated with VO_{2peak} in the standardised regression model*

Variable	P value	Standardised coefficient
Body mass index	<0.001	−0.25
Physical activity summary index	<0.001	0.21
Patient global assessment	0.006	−0.14
Systolic blood pressure	0.016	−0.12
Resting heart rate	0.032	−0.11
Smoking	0.046	−0.10

*The model was adjusted for age and gender. The standardised coefficient gives the change of VO_{2peak} (mL/(kg x min)) for one SD increase in each variable.

enable investigating the influence of separate comorbidities, avoiding possible biases from using a combined and dichotomised comorbidity variable.

Patient representability

Disease activity in the present RA population was comparable with disease activity in other Norwegian RA patients,[38] but the mHAQ was slightly lower. The discrepancy in mHAQ may be due to biassed selection of participants with fewer physical restraints to the VO_{2peak} test. Due to few included women <40 years and men in all age groups, the results for these groups should be evaluated cautiously. A higher proportion of men from the patient-centred follow-up programme agreed to participate, to a large extent representing patients with more stable disease than those with regular clinical appointments. This selection bias may explain why the findings of lower fitness were clearer for women than men when comparing to the healthy population and limits the generalisability of the results for men. We cannot exclude that a bigger study with more patients with moderate or high disease activity would have resulted in different findings regarding the importance of disease activity. However, the study was well powered to identify the most important variables among a large selection of potentially relevant disease-related variables. Furthermore, reaching an R^2 of ~0.80, only a small part of the variance in the data remained unexplained.

It is difficult to evaluate whether the participants were representative of Norwegian RA patients with respect to physical activity, because the PA index of those who declined to attend is unknown. Physical activity was based on self-report and could be both underestimated and overestimated by the participants. The PA index used in our study has not been validated in RA patients. Objective measures like accelerometry would have been useful, but were not available in our setting. We may speculate that RA patients who are familiar with working out might be more likely to sign up for a study with CRF testing. However, most participants did not fulfil the current recommendations for physical activity.[30]

Validity of VO_{2peak} test results

In comparison to some studies measuring VO_{2peak} in RA patients, our results are quite high, but many studies are old, and have different inclusion criteria. For instance, some interventional studies excluded participants not leading a sedentary life[21 39] or those undertaking more than 30 min aerobic exercise three times a week.[40] The baseline of VO_{2peak} results of such studies are therefore not comparable to those of our study where no such exclusions were made. In addition, over the years, there has been a tremendous change in treatment strategies for RA,[41 42] and treatment strategies and traditions of physical activity might differ between countries. This further complicates comparisons with VO_{2peak} results of other studies. In one Swedish study from 2014, RA patient's mean (SD) VO_{2peak} was 31.2 (7.0) in women and 40.0 (8.2) in men,[43] which closely resembles the results of our study. The RA population of Sweden is expected to be comparable to that of Norway.

Previous studies have shown benefits of exercise and few safety issues in RA patients.[20 21 39 44 45] The present study demonstrated that RA patients are able to complete treadmill tests without premature termination due to disease complaints. At peak, only a small proportion of participants reported RA-associated joint pain in the lower extremities, supporting that RA patients probably terminated the VO_{2peak} test because of cardiorespiratory limitations, rather than RA complaints. Adequate VO_{2peak} test using a cycle ergometer requires cycling experience and may lead to lower measured VO_{2peak} due to local fatigue.[46 47] On the other hand, everyone is familiar with walking. The NeXt Move core facility has strict routines for calibration and maintenance of the testing equipment. We therefore consider the VO_{2peak} test results to be reliable.

In summary, RA patients had decreased CRF compared with a healthy population of similar age and gender. Their CRF was associated with common risk factors for CVD, implying that life-style changes may improve CRF, which is associated with improved cardiovascular health. Reduction of BMI and increased physical activity would most strongly improve the CRF. The CRF level adds important information to the evaluation of RA patients, but the VO_{2peak} test is a resource-intensive method. Models for estimation of CRF without a physical test have been developed for healthy people. Until similar tools exist for RA patients, increasing and monitoring physical activity, advice on smoking cessation, measurement of BP, RHR and BMI are practical interventions for CVD prevention. RA-specific variables were not of importance for CRF, except for PGA, indicating that subjective factors have a stronger bearing on CRF than objective measures of disease activity in RA patients. Future studies are warranted that test the use of CRF to identify RA patients at increased risk of CVD, and whether effective prevention strategies including reduction of sedentary behaviour and improvement of fitness may be developed and implemented in this population.

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Contributors Study conception and design: MHL, MH, UW, RT, VV. Acquisition and analysis of data: MHL, TF, VV. Interpretation of data: MH, UW, RT, VV. Drafting the manuscript: MHL, TF, VV. Revising the manuscript critically for important intellectual content: MH, TF, UW, RT, VV. All authors approved the final version of the manuscript.

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Competing interests None declared.

Patient consent for publication All participants provided written informed consent.

Ethics approval The Regional Committee for Medical and Health Research Ethics approved the study (2016/275), which was performed in compliance with the Declaration of Helsinki.

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Paper 2

OPEN

An Estimation Model for Cardiorespiratory Fitness in Adults with Rheumatoid Arthritis

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ABSTRACT

LIFF, M. H., M. HOFF, T. FREMO, U. WISLØFF, and V. VIDEM. An Estimation Model for Cardiorespiratory Fitness in Adults with Rheumatoid Arthritis. *Med. Sci. Sports Exerc.*, Vol. 52, No. 6, pp. 1248–1255, 2020. **Purpose:** Cardiopulmonary exercise testing of peak oxygen uptake ($\dot{V}O_{2peak}$) is the gold standard to measure cardiorespiratory fitness (CRF). For resource-intensive evaluation, equations estimating CRF (eCRF) may be used. The purpose was to investigate if an eCRF equation from a healthy population is useful in persons with rheumatoid arthritis (RA), and if necessary, develop new equations for eCRF in this group. **Methods:** $\dot{V}O_{2peak}$ results from 93 persons with RA were compared with eCRF calculated by an established equation for healthy individuals including age, sex, physical activity (PA index), resting HR (RHR), and waist circumference. Because of deviation from the observed $\dot{V}O_{2peak}$, new equations for eCRF in persons with RA were developed from regression analysis of variables associated with observed $\dot{V}O_{2peak}$. **Results:** The established equation overestimated CRF ($R^2 = 0.48$, root mean square error [RMSE] = 7.07). The new RA equation more accurately estimated CRF ($R^2 = 0.81$, RMSE = 4.44) (female = 0, male = 1; never smoked = 0, ever smoked = 1): eCRF = 77.961 + (sex × 28.791) − (age × 0.358) − (age–sex interaction × 0.326) − (body mass index [BMI] × 0.700) − (RHR × 0.125) − (smoking × 1.854) + (PA index × 0.211) − (patient global RA assessment × 0.071). Alternative new RA equation (R^2 = 0.79, RMSE = 4.63): eCRF = 77.851 + (sex × 25.460) − (age × 0.381) − (age–sex interaction × 0.254) − (BMI × 0.743) − (RHR × 0.115) − (smoking × 2.154) + (PA index × 0.209). **Conclusions:** The new RA equations better predicted CRF in individuals with RA, preventing overestimation in low-fit persons. The new equation should be preferred when estimating CRF in individuals with RA. The alternative equation, without patient global assessment, is useful for individuals with RA in population-based studies. **Key Words:** $\dot{V}O_{2PEAK}$, PREDICTED FITNESS, PERSON-SPECIFIC MEDICINE, INFLAMMATORY ARTHRITIS

The gold standard method for measuring cardiorespiratory fitness (CRF) is by cardiopulmonary exercise testing (CPET) of maximal or peak oxygen uptake ($\dot{V}O_{2peak}$), where peak uptake denotes the situation where the criteria for a maximal test were not met (1,2). Cardiorespiratory fitness is inversely associated with cardiovascular disease (CVD) in the general population (2–7). Thus, there is an increasing focus on exercise that increases CRF in prevention and treatment of lifestyle-related diseases (2). Higher demands on the cardiorespiratory and musculoskeletal system, particularly with exercise of high intensity, have the effect of improving CRF (2,7), which in turn is associated with reduced cardiovascular risk factors (7,8).

Despite the importance of CRF for health, measurements of $\dot{V}O_{2peak}$ in health care settings is rare for different reasons, including the cost and time consumption of the methods, as well as the potential risks related to maximal physical efforts. Therefore, various equations for estimated CRF (eCRF) have been developed (2,9–11). In a previous study in a general healthy population, low eCRF was independently associated with CVD and all-cause mortality (12). Compared with CPET, eCRF equations are easily accessible, save time, and reduce cost (2,13). An example is the The Norwegian population-based

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Nord-Trøndelag Health Study (HUNT) equation (11), which was developed from the $\dot{V}O_{2peak}$ results of 4631 healthy participants of the fitness study of the third survey of the Nord-Trøndelag Health Study (HUNT3 Fitness study) (14,15). The HUNT equation has been implemented in other studies regarding fitness and is one of the equations of choice for nonexercise estimation of CRF during routine clinical visits for healthy people in a scientific statement from the American Heart Association (AHA) (2,16). The variables included in the HUNT equation are age, sex, resting HR (RHR), waist circumference and a physical activity summary index (PA index) score (Table 1) (11). Equations for eCRF also make investigation of fitness easier in population-based studies, where simple measurements and questions can be included (2,16).

Equations for eCRF are often developed from measurements of $\dot{V}O_{2peak}$ in relatively healthy populations without specific diseases. It is not obvious that such equations are valid for people suffering from rheumatoid arthritis (RA) and to our knowledge, no eCRF equation has previously been developed particularly for persons with RA. Rheumatoid arthritis is the most common autoimmune rheumatic disease with a prevalence of approximately 1% (17,18) and a life time risk close to 4% in women and 2% in men (19). Persons with RA have an increased burden of CVD, cardiovascular risk factors, and higher mortality rates from CVD compared with age-matched controls (18), and those with higher CRF have lower blood pressure, reduced insulin resistance and significantly better lipid profiles compared with persons with reduced CRF (20). Improvement of CRF in persons with RA is associated with reduction of risk factors for CVD (21).

Rheumatoid arthritis affects joints (arthritis) and internal organs, including the vasculature. Furthermore, body composition may be altered in persons with RA (18). Such pathophysiological changes may alter the associations of CRF to RHR and/or waist circumference, which are used in the HUNT eCRF equation. We have previously found that CRF in persons with RA was associated not only with some of the same variables as in the general healthy population but also with other variables including smoking habits and the patient global assessment of RA disease activity (patient global RA assessment [PGA]) (22).

TABLE 1. The PA summary index.[a]

How Frequently Do You Exercise?	
Never	0
Less than once a week	0
Once a week	1
Two to three times a week	2
Almost everyday	3
How hard do you push yourself?	
Take it easy	0
Heavy breath and sweat	5
Push near exhaustion	10
How long does each session last?	
<15 min	1
16–30 min	1
30–60 min	1.5
>60 min	1.5

[a]Developed for the original HUNT equation. The index is calculated as the product of the points given for each question (11).

The American College of Sports Medicine (ACSM) and AHA 2007 recommendations for PA to promote and maintain health in healthy adults (23) are central to the 2018 European League Against Rheumatism (EULAR) recommendations for PA in people with arthritis (24). With the increasing focus on PA as an important contributor to health in people with RA and the association of low CRF to CVD in the healthy population, estimating CRF levels in persons with RA is of practical importance.

On this background, we hypothesized that an equation for eCRF suitable for persons with RA (new RA equation) would need to be adjusted compared with equations developed for the general population. Thus, the purpose of this study was to develop a new RA equation that best represents the actual $\dot{V}O_{2peak}$ in persons with RA by: 1) comparing $\dot{V}O_{2\ peak}$ test results with the eCRF calculated by the HUNT equation in persons with RA; 2) if there were deviations between the observed and estimated results of CRF, developing a specific equation for persons with RA; 3) developing a new alternative RA equation for eCRF in persons with RA in population-based studies without access to RA-specific variables. The HUNT equation was selected because it was developed using data from the same region of Norway as the persons with RA that would be included in our study. Furthermore, it takes three important aspects of PA into account when calculating the eCRF, that is, frequency, duration, and intensity, which we found would be relevant in persons who may have physical limitations to movement.

METHODS

As previously described (22), a convenience sample of adults with RA (n = 93) fulfilling the 1987 American College of Rheumatology (ACR) (25) and/or the 2010 ACR/EULAR classification criteria for RA (26), were recruited from February 17, 2017, to January 4, 2018, from the outpatient clinic at the Rheumatology Department at St. Olavs University Hospital and from the group of persons with RA attending patient-centered follow-up.

Power calculations were based on the following assumptions (22): from the literature, we assumed that the most relevant variables associated with fitness in the general population would explain 60% of the variance in measured $\dot{V}O_{2peak}$ (i.e., $R^2 = 0.60$). Given $\alpha = 0.05$, with inclusion of 100 persons with RA, the power to identify one or more RA-related variables that would increase R^2 to 0.65 would be 0.96. Useful data were available from 93 participants, which resulted in a power of 0.95 to detect this increase in R^2, considered as satisfactory.

Testing of $\dot{V}O_{2max}$ was performed on a treadmill identical to that used in previous studies in our group and followed the American College of Cardiology/AHA (ACC/AHA) guidelines for exercise testing (27). The relevant exclusion criteria in our study were unstable heart conditions, chronic obstructive/restrictive pulmonary disease necessitating use of oxygen therapy, or physical disability making a treadmill test impossible.

Because RA patients sometimes exhibit physical limitations, experienced personnel at the *NeXt Move* core facility at NTNU - Norwegian University of Science and Technology determined the best individual CPET regimen during a 6-min

warm-up on a treadmill (Woodway PPS55; USA Inc., Waukesha, WI). They detected inclination and functional running or walking speed, in addition to subjective moderate aerobic intensity based on rated perceived exertion (RPE Borg scale 6–20) (22,28). Participants were fitted with an HR monitor (H7, Polar Electro, Kempele, Finland) and facemask (7450 Series V2 CPET mask, Hans Rudolph Inc., Shawnee, KS). An individualized ramp protocol with gradual increase in workload was used, until either exhaustion or fulfillment of the criteria for $\dot{V}O_{2max}$ or $\dot{V}O_{2peak}$ ($mL \cdot min^{-1} \cdot kg^{-1}$). Gas was measured every tenth second using a mixing chamber ergospirometry system (Metalyzer II; Cortex Biophysik Gmbh, Leipzig, Germany). Maximal oxygen uptake ($\dot{V}O_{2max}$) was defined using the following criteria: 1) $\dot{V}O_2$ leveling off (<2 $mL \cdot min^{-1} \cdot kg^{-1}$) despite increase in workload and 2) respiratory exchange ratio ≥1.05. If the criteria for $\dot{V}O_{2max}$ were not met, the term $\dot{V}O_{2peak}$ was used instead. $\dot{V}O_{2peak}$ was defined as the mean of the participant's three successive highest $\dot{V}O_2$ registrations achieved during the CPET. There were 17.2% of the 93 patients that qualified for $\dot{V}O_{2peak}$. For simplicity, the term $\dot{V}O_{2peak}$ is used for all patients.

The ergospirometry system was calibrated according to a standardized protocol every day before use and subsequently before every fourth test if performing multiple tests on the same day. The operating protocol also details the methods for turbine change, check of ambient pressure, gas, and flow. Turbine change and sensor adjustment to ambient conditions were performed before every test to ensure accurate flow and gas measurements, and the system is regularly validated biologically against the gold standard (Douglas bag) and mechanically using a metabolic simulator.

Information collected at the same visit or extracted from medical records covered smoking habits, medications, comorbidities (cancer, CVD (hypertension/angina/myocardial infarction), diabetes, chronic obstructive pulmonary disease/chronic restrictive pulmonary disease [COPD/CRPD]), as well as the RA-specific variables year of RA diagnosis, anticitrullinated protein antibody, rheumatoid factor, the modified Health Assessment Questionnaire (mHAQ) (29), the physician global RA assessment (0–100 mm scale) (30), Disease Activity Score 28 (31), EULAR remission criteria (32), and the PGA (30). The question asked in the PGA was: "Considering all the symptoms from your rheumatic disease during the last week, how do you think your state is?" They then responded on a 0- to 100-mm visual analog scale; "0" meaning, "Good, no symptoms; and "100" meaning, "very bad." High-sensitivity C-reactive protein ($mg \cdot L^{-1}$), blood pressure (mm Hg), RHR (bpm), waist circumference (cm), height (m), and weight (kg) were measured (22). Body mass index (BMI) was calculated as the body weight (kg) divided by the squared value of height (m).

The RHR and blood pressure were measured after 10 min of rest in a comfortable chair. Smoking status was defined as smoker (previous and present) versus never smoker. The PA index used was developed for the HUNT equation, based on answers to separate questions on PA (frequency, duration, and intensity) (Table 1) (11). Participants were also categorized in two categories, depending on whether they fulfilled the ACSM/AHA 2007 recommendations for PA (23).

All participants provided written informed consent. The Regional Committee for Medical and Health Research Ethics approved the study (2016/275), which was performed in compliance with the Helsinki Declaration.

Statistical analysis. Data are given as counts and percentages, mean with standard deviation (SD) or median with interquartile range in parenthesis. All Statistical analyses were performed using STATA (Version 15.0; StataCorp, College Station, TX).

The eCRF was calculated with the HUNT equation in all 93 participants, and the agreement of the observed and the calculated $\dot{V}O_{2peak}$ from the HUNT equation was analyzed using scatterplots of observed versus predicted $\dot{V}O_{2peak}$ and by equivalence testing (33). With this method, the difference between the observed and predicted $\dot{V}O_{2peak}$ is calculated for all participants. The mean and 90% confidence interval (CI) of this difference is evaluated against a predefined equivalence region, which indicates how big the difference may be for the two measurements still to be considered equivalent. Because there is no generally accepted equivalence region for eCRF versus measured $\dot{V}O_{2peak}$, we evaluated against an equivalence region of 1 metabolic equivalent of task (MET) (3.5 $mL \cdot min^{-1} \cdot kg^{-1}$), 1.5 MET (5.3 $mL \cdot min^{-1} \cdot kg^{-1}$) or 2 MET (7.0 $mL \cdot min^{-1} \cdot kg^{-1}$). Evaluation was performed for all participants as well as for participants with measured $\dot{V}O_{2peak} < 30\ mL \cdot min^{-1} \cdot kg^{-1}$ ($n = 45$) because these participants were considered more vulnerable if their eCRF was inaccurate.

Variables associated with $\dot{V}O_{2peak}$ in persons with RA were assessed using multivariable linear regression analyses with $\dot{V}O_{2peak}$ as the dependent variable. Explanatory variables were selected based on previous literature: age, sex, and the age–sex interaction, BMI, smoking (present or previous vs never smoker), RHR and the PA index. Body mass index was considered easier to measure accurately than alternative variables, including waist circumference. Other potential explanatory variables that might be important in RA patients included comorbidity (cancer, CVD, diabetes, COPD/CRPD), coded as a single yes/no variable, and systolic blood pressure (SBP). We also considered a selection of common RA-specific variables: PGA and the physician global RA assessment, mHAQ, various disease activity scores, including the Disease Activity Score 28 (DAS28), remission criteria (DAS28 or ACR/EULAR), time since diagnosis, seropositivity, and disease-modifying antirheumatic medication.

Subselection of these variables was performed first using Lasso (least absolute shrinkage and selection operator) regression (34) with 1000 repetitions. This procedure reduces the risk of overfitting. By setting the coefficients of irrelevant variables to 0, Lasso regression identifies the smallest useful set of variables among variables that may be highly correlated. We therefore only selected the variables with a coefficient different from 0 in the Lasso regression for inclusion in the multivariable linear regression models. All selected variables were forced into the models resulting in full models, which were then reduced to the final models by removal of nonsignificant variables. The final variables in the new RA equation were age,

TABLE 2. Participant characteristics.

	Total, $N = 93$
Age (yr), median (IQR)	60 (52–66)
Women, *n* (%)	68 (73)
Height (m), mean (SD)	1.69 (0.09)
Weight (kg), mean (SD)	76.4 (12.3)
BMI (kg·m^{-2}), mean (SD)	26.7 (3.9)
Comorbidity, *n* (%)	38 (41)
Cardiovascular (HT, angina, MI)	21 (23)
Respiratory (COPD and/or CRPD)	18 (19)
Diabetes	4 (4)
Cancer (previous or present)	5 (5)
Smoking, *n* (%)[a]	
Never smoked	35 (38)
Previous smoker	51 (55)
Present smoker	7 (8)
SBP (mm Hg), median (IQR)	122 (114–131)
RHR (bpm), mean (SD)	66 (10)
ACSM/AHA 2007 recommendations for PA, *n* (%)	
Does not fulfill ACSM/AHA 2007 recommendations	64 (69)
Fulfills ACSM/AHA 2007 recommendations	29 (31)
Seropositivity (ACPA and/or RF), *n* (%)	75 (81)
Disease duration (yr), median (IQR)	10 (5-19)
Patient global RA assessment (0–100 mm), median (IQR)	24 (10-36)
Physician global RA assessment (0–100 mm), median (IQR)	10 (0-12)
mHAQ, median (IQR)	0.13 (0-0.38)
mHAQ, mean (SD)	0.26 (0.31)
hsCRP, median (IQR)	1.75 (0.75-3.13)
DAS28 (hsCRP), *n* (%)	
Remission	39 (42)
Low disease activity	23 (25)
Moderate disease activity	28 (30)
High disease activity	3 (3)
Mean (SD)	2.56 (1.04)
ACR/EULAR remission, *n* (%)	25 (27)
Medication, *n* (%)	
bDMARD (present)	54 (58)
cDMARD (present)	74 (80)
Corticosteroids (any form during last year)	39 (42)
$\dot{V}O_{2peak}$ (mL·min^{-1}·kg^{-1}), median (IQR)	30.6 (25.2–37.7)
20–39 yr	45.4 (43.8–51.1)
40–49 yr	39.3 (32.2–42.7)
50–59 yr	31.2 (26.2–37.8)
60–69 yr	27.2 (25.0–32.4)
≥70 yr	26.4 (19.7–31.9)

ACPA, anticitrullinated protein antibody; bDMARD, biological disease modifying anti rheumatic drugs; cDMARD, conventional disease modifying anti rheumatic drugs; hsCRP, high sensitivity C-reactive protein; HT, hypertension; IQR, interquartile range; MI, myocardial infarction; RF, rheumatoid factor.
[a]Total sum is 101% due to rounding.

sex, BMI, RHR, smoking, PA index, patient global RA assessment. A new alternative RA equation was made by removing the only RA-specific variable that remained in the new RA equation, that is, the patient global RA assessment. To identify the best variable to represent body composition, we performed a sensitivity analysis substituting BMI with the waist-to-height ratio in the new RA equation.

Model assumptions were evaluated using residual plots including residual versus predicted value plots to assess homoscedasticity. Multivariate outliers were assessed using Cook's distance. The models were compared using the R^2, root mean square error (RMSE) (i.e., the standard deviation of the unexplained variance), Akaike information criterion, and Bayesian information criterion. P values <0.05 were considered significant. The agreement of the observed and the calculated $\dot{V}O_{2peak}$ from eCRF calculated by the new RA equation and the alternative new RA equation were analyzed using scatterplots of observed versus predicted $\dot{V}O_{2peak}$ and by equivalence testing with equivalence regions as described above (33). Internal validation of the new RA equation was performed by bootstrapping (n = 1000) to compare original and bootstrapped CI of the coefficients, and by k-fold cross validation (n = 25 folds). Bivariate Pearson's correlation coefficients were also calculated.

In addition, two RA equations including SBP and one RA equation where the PA index was substituted with fulfillment or not of the ACSM/AHA 2007 PA recommendations (23) were developed through a similar process as described above.

RESULTS

Participant characteristics and $\dot{V}O_{2peak}$ results are shown in Table 2. Using the HUNT equation, RMSE was 7.07 and R^2 was 0.48. The corresponding RMSE and R^2 values using the best-fitting RA equations are shown in Table 3. There were no outliers or overly influential cases in the new RA models.

When comparing the observed $\dot{V}O_{2peak}$ results to those estimated by the HUNT equation and the new RA equation (Fig. 1), there were some discrepancies between observed and estimated CRF for both models. However, the smallest differences between measured and estimated CRF was found with the new RA equation. These findings are illustrated in the scatterplots for observed versus calculated eCRF for the HUNT and new RA equation (Fig. 1).

Figure 2 shows the results from equivalence testing of the HUNT equation and new RA equation versus observed $\dot{V}O_{2peak}$, respectively. The mean and 90% CI for the difference from measured $\dot{V}O_{2peak}$ using the HUNT equation were 1.0 (−6.3 to 8.3) mL·min^{-1}·kg^{-1} for all participants (n = 93), and 3.7 (−5.0 to 12.4) mL·min^{-1}·kg^{-1} for participants with measured $\dot{V}O_{2peak}$ < 30 (n = 43). For the new RA equation, the mean and CI were 0 (−5.3 to 5.3) mL·min^{-1}·kg^{-1} for all participants

TABLE 3. The best-fitting new RA equations.

RA Equation				
R^2 = 0.81, RMSE = 4.44	**Coefficient**	**SE**	***P***	**CI**
Sex (female = 0, male = 1)	28.791	6.431	<0.001	15.990 to 41.592
Age (yr)	−0.358	0.050	<0.001	−0.456 to −0.260
Age and sex interaction	−0.326	0.109	0.004	−0.542 to −0.110
BMI (kg·m^{-2})	−0.700	0.125	<0.001	−0.949 to −0.451
RHR (bpm)	−0.125	0.050	0.013	−0.224 to −0.027
Smoking (never = 0, ever = 1)	−1.854	1.019	0.073[a]	−3.881 to 0.173
PA summary index	0.211	0.058	<0.001	0.096 to 0.325
Patient global RA assessment (mm)	−0.071	0.025	0.005	−0.120 to −0.022
Constant	77.961	5.439	<0.001	67.144 to 88.779
Alternative RA Equation				
R^2 = 0.79, RMSE = 4.63	**Coefficient**	**SE**	***P***	**CI**
Sex (female = 0, male = 1)	25.460	6.602	<0.001	12.333 to 38.589
Age (yr)	−0.381	0.051	<0.001	−0.483 to −0.280
Age and sex interaction	−0.254	0.110	0.024	−0.473 to −0.034
BMI (kg·m^{-2})	−0.743	0.130	<0.001	−1.000 to −0.485
RHR (bpm)	−0.115	0.052	0.029	−0.217 to −0.012
Smoking (never = 0, ever = 1)	−2.154	1.057	0.045	−4.256 to −0.052
PA summary index	0.209	0.060	0.001	0.089 to 0.328
Constant	77.851	5.670	<0.001	66.577 to 89.125

[a]Smoking in the RA equation had P = 0.073 but was kept in the equation to avoid deterioration of overall model fit.

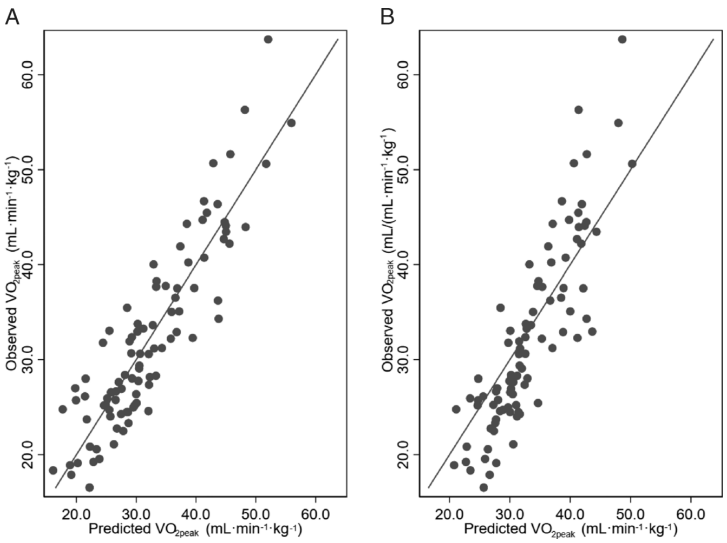

FIGURE 1—Observed vs predicted $\dot{V}O_{2peak}$ in persons with RA. Observed vs predicted $\dot{V}O_{2peak}$ ($mL \cdot min^{-1} \cdot kg^{-1}$) using Panel A: The RA equation. Panel B: The HUNT equation (11). The diagonal lines indicate identity between observed and predicted $\dot{V}O_{2peak}$. With the HUNT equation, there was a systematic tendency to overestimation of low observed $\dot{V}O_{2peak}$ and underestimation of high observed $\dot{V}O_{2peak}$.

(n = 93), and 1.4 (−4.4 to 7.2) $mL \cdot min^{-1} \cdot kg^{-1}$ for participants with measured $\dot{V}O_{2peak}$ < 30 $mL \cdot min^{-1} \cdot kg^{-1}$.

Bootstrapped (n = 1000) CI for the new RA equation were very close to original CI, indicating that the results were unbiased. Furthermore, the 25-fold cross-validation gave a mean (SD) RMSE of 4.32 (1.68), which is close to that of the new RA equation. The bivariate correlations for the variables in the new RA equation are given in a correlation matrix (see Table, Supplemental Digital Content 1, describing the correlation matrix for variables in the new RA equation, http://links.lww.com/MSS/B872).

In the new alternative RA equation, where the only RA-specific variable (PGA) was omitted, the graphs were very similar to those of the complete new RA equation (see Figure, Supplemental Digital Content 2, describing observed vs predicted $\dot{V}O_{2peak}$ in persons with RA, http://links.lww.com/MSS/B873 and Figure, Supplemental Digital Content 3, describing the results from equivalence testing of the HUNT equation and the new alternative RA equation vs measured $\dot{V}O_{2peak}$, http://links.lww.com/MSS/B874). The eCRF model from sensitivity analysis where BMI in the new RA equation was substituted with the waist-to-height ratio showed a somewhat reduced fit (R^2 = 0.80, RMSE 4.51).

Two additional new RA equations including SBP (see Table, Supplemental Digital Content 4, describing a new RA equation and new alternative RA equation when the SBP is known, http://links.lww.com/MSS/B875), and one new RA equation where the PA index was substituted with fulfillment or not of the ACSM/AHA 2007 recommendations for PA (23) (see Table, Supplemental Digital Content 5, describing a new RA equation based on fulfillment or not of ACSM/AHA 2007 recommendations for PA, http://links.lww.com/MSS/B876) were developed to allow for the use of the equation in settings lacking more detailed PA information.

DISCUSSION

In this study, we developed an equation for the estimation of CRF for persons with RA, with better fit than a previously published equation from a healthy population. The new RA equation included these self-reported variables: age, sex, smoking status, PA index, and patient global RA assessment, as well as measurements of BMI and RHR. The accessibility of the variables of the new RA equation makes it resource saving in a clinical setting, especially if a web-based calculator becomes available which may also be used by the person with RA. A new alternative RA equation without the patient global RA assessment permits investigation of CRF in persons with RA based on general information in population-based studies.

New RA equation instead of HUNT equation for persons with RA. The new RA equation explained 81% of the variability of the $\dot{V}O_{2peak}$ in persons with RA in the present study, whereas the HUNT equation (11) explained 48% of the variability of $\dot{V}O_{2peak}$. The scatterplot of eCRF clearly showed better fit with the new RA equation than the HUNT equation, with less deviation from the measured $\dot{V}O_{2peak}$ for the lowest and highest values. This substantiates that eCRF for persons with RA should be calculated using the new RA equation, even if equivalence testing showed that it did not perfectly predict the measured $\dot{V}O_{2peak}$.

The discrepancy between the actual $\dot{V}O_{2peak}$ test results (observed CRF) and the estimated CRF (eCRF) using the HUNT

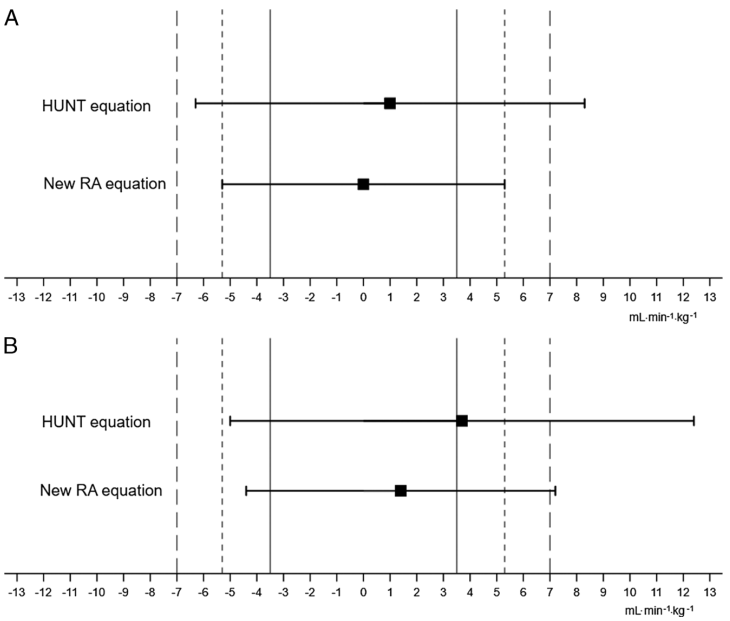

FIGURE 2—Equivalence testing of the new RA equation and the HUNT equation vs measured $\dot{V}O_{2peak}$. Panel A: Equivalence testing including all participants (n = 93). The HUNT equation was nonequivalent to $\dot{V}O_{2peak}$ measurement with respect to all equivalence regions, as seen by the CI falling above all region limits and below the 1 MET and 1.5 MET region limits. The new RA equation was equivalent to $\dot{V}O_{2peak}$ measurement when using the 2 MET and 1.5 MET equivalence regions. Panel B: Equivalence testing including participants with measured $\dot{V}O_{2peak}$ < 30 mL·min^{-1}·kg^{-1} (n = 45). Both the HUNT equation and the new RA equation were nonequivalent to $\dot{V}O_{2peak}$ measurement with respect to all equivalence regions, as seen by the CI falling above all region limits and below the 1 MET region limit. The HUNT equation more strongly tended to over-estimate $\dot{V}O_{2peak}$ in this group of participants. The horizontal bars represent the 90% CI of the mean (square). In both figures, the following equivalence regions are marked vertically: Solid line ± 1 MET (±3.5 mL·min^{-1}·kg^{-1}), short dashed line ± 1.5 MET (±5.3 mL·min^{-1}·kg^{-1}), long dashed line ± 2 MET (±7 mL·min^{-1}·kg^{-1}).

equation is of particular importance for persons with RA with the lowest observed CRF. This was the main reason to develop a new RA equation. As previously reported for healthy individuals (11), the HUNT equation tended to overestimate CRF for persons with RA with the lowest observed $\dot{V}O_{2peak}$ test results. In a previous study, CVD mortality was reduced by 20% to 22% per $\dot{V}O_{2peak}$ increase of 3.5 mL·min^{-1}·kg^{-1} in both men and women (1). This substantiates the possible negative consequence of overestimating CRF to the extent that was seen using the HUNT equation for those in the subgroup with measured CRF below 30 mL·min^{-1}·kg^{-1}. Because of this overestimation, the HUNT equation might give the impression that improving CRF is not very important in persons with RA belonging to the group where improvement is most important. The new RA equation showed less overestimation in these most vulnerable persons. Underestimation of high fitness with the HUNT equation, where the new RA equation was also more accurate, is of less clinical importance.

Considerations regarding variable selection. BMI is implemented in the new RA equation, whereas the HUNT equation uses waist circumference instead. Both BMI and waist circumference were significant predictors (P < 0.001), but accurate measurement of waist circumference may be difficult because it depends on body shape. The sensitivity analysis substituting BMI with waist-to-height ratio indicated that using this variable did not lead to improved prediction. We, therefore, chose BMI, which is a familiar measurement for both physicians and people with RA. Electronic apps for BMI are available, where you key in height and weight, and the app does the calculation.

The patient global RA assessment (30) was the only significant RA-specific variable. Persons with RA were asked to evaluate the disease activity of their RA during the last week. Adults with RA are used to this score when evaluated at the Rheumatology department, as part of the commonly used Disease Activity Score of 28 (31), or as an independent scale. The phrasing of the question might vary slightly, and there are some concerns that various phrasings might give different responses (35). Therefore, it is of importance to use a phrasing similar to that given in the present study.

When to use the new RA equation. Because previous findings suggest that improvement of CRF reduces cardiovascular risk factors in persons with RA (21), the possibility to estimate CRF in this group may improve care by guiding and stimulating PA. For instance, repeated measurement and recalculation can give important information when evaluating the effect of changes in PA. The eCRF improvement might inspire continuation of workout, whereas equal or decreased eCRF indicates lack of effective training and could lead to change of exercise training regimens. The new RA equation may, therefore,

contribute to planning and inspire to PA, both in pretraining and posttraining periods, and at clinical visits. Health professionals like the patient's general practitioner, rheumatologist, physical therapist, or nurse, in addition to the patient herself or himself, may calculate the eCRF. In addition to being a less resource-intensive method than $\dot{V}O_{2peak}$ testing by CPET, a potential web-based calculator for eCRF for persons with RA would make the calculation even easier.

Generalizability of the new RA equation. The eCRF equations developed for healthy people are used in various countries, regardless of different socioeconomic status and different cultures (16). The ACR and EULAR have developed common classification criteria for RA (26), and these criteria are also accepted in other regions of the world. As long as RA is diagnosed using the same criteria, the new RA equation is probably generalizable to other countries. As expected, persons with RA had reduced $\dot{V}O_{2peak}$ test results compared with the healthy HUNT population (22), and this is a finding similar to what other studies on RA and cardiorespiratory fitness have found (36), which further strengthens the impression that the participants were representative of other persons with RA. The fact that only one third of the persons with RA fulfilled the ACSM/AHA 2007 recommendations for PA (23) indicates that the included participants were not especially physically active. The new RA equation should be externally validated; however, internal validation showed that the equation is not strongly biased. The finding that the eCRF equation developed from a healthy population did not have an adequate fit in the most vulnerable persons with RA raises the question if similar discrepancies are relevant in other chronic conditions.

CONCLUSIONS

The new RA equation gives more precise estimates of eCRF than the previously published equation developed for a healthy population. This prevents overestimation of the eCRF in persons with RA having the lowest $\dot{V}O_{2peak}$ test results. The new RA equation may, therefore, become an important tool in the care for individual persons with RA to reduce cardiovascular risk. For use in population-based studies, the new alternative RA equation without RA-specific variables is a useful alternative.

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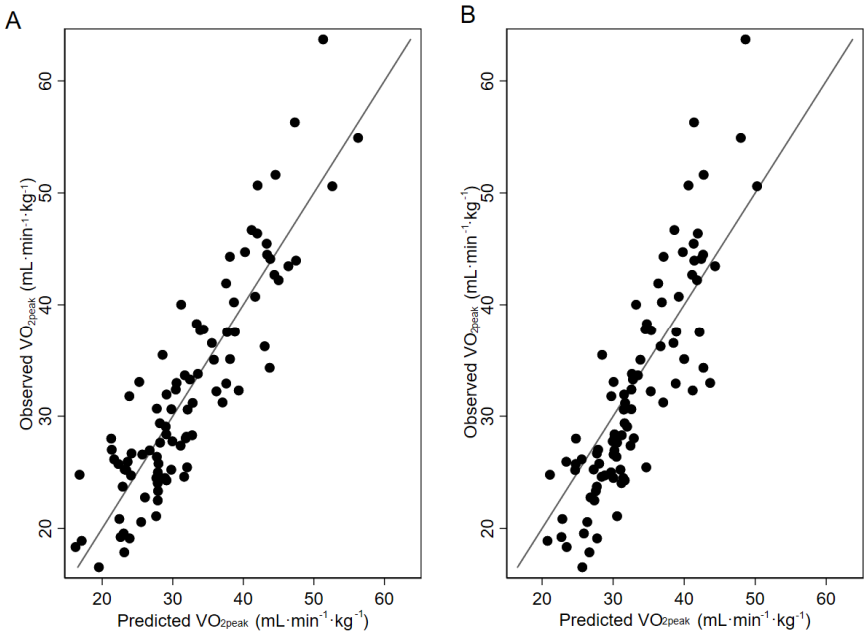
Supplemental Digital Content 1: Correlation matrix for variables in the new RA equation

	Estimated cardio-respiratory fitness (eCRF)	Gender	Age	Body mass index (BMI)	Resting heart rate (RHR)	Smoking	Physical activity summary index (PA Index)	Patient global RA assessment (PGA)
Estimated cardio-respiratory fitness (eCRF)	1.0000							
Gender	0.4304	1.0000						
Age	-0.6200	0.0110	1.0000					
Body mass index (BMI)	-0.3853	0.0449	0.0492	1.0000				
Resting heart rate (RHR)	-0.2497	-0.0657	-0.0004	0.2264	1.0000			
Smoking	-0.2997	0.0705	0.2890	0.0731	0.1723	1.0000		
Physical activity summary index (PA index)	0.3266	-0.2120	-0.3301	-0.2079	-0.0118	-0.1630	1.0000	
Patient global RA assessment (PGA)	-0.3243	-0.2595	0.1096	0.0858	-0.0324	0.0943	-0.0283	1.000

Supplemental Digital Content 2

Figure: Observed vs. predicted VO_{2peak} in persons with RA



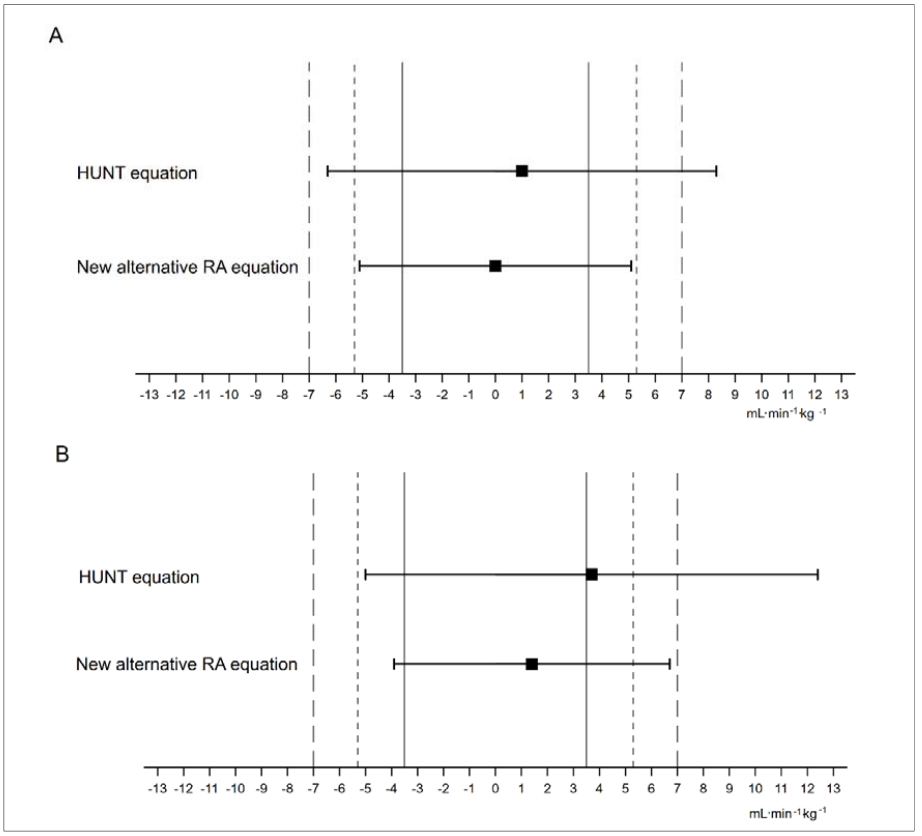
Observed vs. predicted VO_{2peak} ($mL \cdot min^{-1} \cdot kg^{-1}$) using
Panel A: The new alternative RA equation without the patient global RA assessment.
Panel B: The HUNT equation (1).
The diagonal lines indicate identity between observed and predicted VO_{2peak}. With the HUNT equation, there was a systematic tendency to overestimation of low observed VO_{2peak} and underestimation of high observed VO_{2peak}.
Abbreviations: HUNT, The Norwegian population-based Nord-Trøndelag Health Study; RA, rheumatoid arthritis; VO_{2peak}, peak oxygen uptake.

Reference:

1. Nes BM, Janszky I, Vatten LJ, Nilsen TI, Aspenes ST, Wisloff U. Estimating V.O 2peak from a nonexercise prediction model: the HUNT Study, Norway. *Med Sci Sports Exerc.* 2011;43(11):2024-30.

Supplemental Digital Content 3

Figure: Equivalence testing of the new alternative RA equation and the HUNT equation vs. measured VO_{2peak}



Panel A: Equivalence testing including all participants (n=93)

The HUNT equation was non-equivalent to VO_{2peak} measurement with respect to all equivalence regions, as seen by the confidence interval falling above all region limits and below the 1 MET and 1.5 MET region limits. The new alternative RA equation was equivalent to VO_{2peak} measurement when using the 1.5 and 2 MET equivalence regions.

Panel B: Equivalence testing including participants with measured VO_{2peak} <30 $mL \cdot min^{-1} \cdot kg^{-1}$ (n=45)

The HUNT equation was non-equivalent to VO_{2peak} measurement with respect to all equivalence regions, as seen by the confidence interval falling above all region limits and below the 1 MET region limit. The equation more strongly tended to over-estimate VO_{2peak} in this group of participants. The new alternative RA equation was equivalent to VO2peak measurement when using the 2 MET equivalence region, and showed less tendency to CRF over-estimation.

The horizontal bars represent the 90% confidence interval of the mean (■).
In both figures, the following equivalence regions are marked vertically:

———— ± 1 MET (± 3.5 mL·min^{-1}·kg^{-1})

- - - - - - - - ± 1.5 MET (± 5.3 mL·min^{-1}·kg^{-1})

– – – – – – ± 2 MET (± 7 mL·min^{-1}·kg^{-1})

Abbreviations: CRF, cardiorespiratory fitness; HUNT, The Norwegian population-based Nord-Trøndelag Health Study; MET, metabolic equivalent of task; RA, rheumatoid arthritis; VO_{2peak}, peak oxygen uptake.

Supplemental Digital Content 4

New RA equation with SBP and new alternative RA equation with systolic blood pressure

In the process of developing the final RA equation and alternative RA equation, we also developed two equations containing the systolic blood pressure (SBP). We chose not to use these equations in the final estimation model, since the SBP makes the equation less relevant for persons with RA not having easy access to their SBP. Because R^2 was somewhat higher and graphs of observed vs. predicted VO_{2peak} and Bland-Altman plots were almost similar to the graphs from our final model, these equations are included here. Details are given in the Supplemental Table 1.

The final new RA equation with SBP (female=0, male=1; never smoked=0, ever smoked=1) (R^2=0.82, RMSE=4.31): eCRF = 82.255 + (sex × 31.006) - (age × 0.341) - (age x sex interaction × 0.361) - (body mass index (BMI) × 0.615) - (RHR × 0.107) - (smoking × 2.005) + (PA index × 0.224) - (systolic blood pressure(SBP) × 0.073) - (patient global RA assessment (PGA) × 0.067).

The alternative new RA equation with SBP (for use in population-based studies where SBP is known) (female=0, male=1; never smoked=0, ever smoked=1) (R^2=0.80, RMSE=4.48): eCRF = 82.487 + (sex × 28.053) - (age × 0.361) - (age × sex interaction × 0.296) - (BMI × 0.648) - (RHR × 0.095) - (smoking × 2.299) + (PA index × 0.223) - (SBP × 0.079).

Table: New RA equation and new alternative RA equation when the systolic blood pressure is known

New RA equation with SBP (R^2=0.82, RMSE=4.31)	**Coefficient**	**SE**	***P***	**Confidence interval**
Sex (female=0, male=1)	31.006	6.315	<0.001	18.445 - 43.567
Age (years)	-0.341	0.049	<0.001	-0.437 - -0.244
Age × sex	-0.361	0.107	0.001	-0.573 - -0.149
Body mass index (m/kg^2)	-0.615	0.126	<0.001	-0.867 - -0.364
Resting heart rate (beats per minute)	-0.107	0.049	0.032	-0.204 - -0.010
Smoking (never=0, ever=1)	-2.005	0.992	0.046	-3.978 - -0.033
Physical activity summary index	0.224	0.056	<0.001	0.112 - 0.335
Systolic blood pressure (mm Hg)	-0.073	0.030	0.016	-0.132 - -0.014
Patient global RA assessment	-0.067	0.024	0.006	-0.115 - -0.020
Constant	82.255	5.562	<0.001	71.193 - 93.316
Nev alternative RA equation with SBP (R^2=0.80, RMSE=4.48)	**Coefficient**	**SE**	***P***	**Confidence interval**
Sex (female=0, male=1)	28.053	6.476	<0.001	15.175 - 40.931
Age (years)	-0.361	0.050	<0.001	-0.461 - -0.262
Age × sex	-0.296	0.108	0.008	-0.511 - -0.081

Body mass index (m/kg^2)	-0.648	0.131	<0.001	-0.909 - -0.388
Resting heart rate[1] (beats per minute)	-0.095	0.051	0.063	-0.196 - 0.005
Smoking (never=0, ever=1)	-2.299	1.026	0.028	-4.338 - -0.259
Physical activity summary index	0.223	0.059	<0.001	0.106 - 0.339
Systolic blood pressure (mm Hg)	-0.079	0.031	0.012	-0.140 - -0.018
Constant	82.487	5.783	<0.001	70.986 - 93.988

[1]Resting heart rate had $P = 0.063$ in the alternative RA equation but was kept in the equation to avoid deterioration in the overall model fit.
Abbreviations: RA, rheumatoid arthritis; SBP, systolic blood pressure.

Supplemental Digital Content 5

New RA equation where the PA index was substituted with fulfillment or not of the ACSM/AHA 2007 recommendations for PA

Sometimes information about intensity, frequency, and duration of physical activity (PA) is lacking and the physical activity summary index (PA index) cannot be calculated. Instead the following equation may be used if information regarding fulfillment or not of the American Colleague of Sports Medicine (ACSM) and the American Heart Association's (AHA) 2007 recommendations for PA (1) is available.

New RA equation based on ACSM/AHA 2007 recommendations for PA (female=0, male=1; never smoked=0, ever smoked=1; not fulfilled ACSM/AHA 2007 recommendations for PA =0, fulfilled ACSM/AHA 2007 recommendations for PA =1) (R^2=0.79, RMSE=4.66):

eCRF = 85.982+ (sex × 25.844) - (age × 0.406) - (age × sex interaction × 0.269) - (BMI × 0.644) - (RHR × 0.094) - (smoking × 2.522) + (PA recommendations fulfilled × 2.984) - (SBP × 0.071).

Table: New RA equation based on fulfillment or not of ACSM/AHA 2007 recommendations for PA

New RA equation (R^2=0.79, RMSE=4.66)	**Coefficient**	**SE**	***P***	**Confidence interval**
Sex (female=0, male=1)	25.844	6.682	<0.001	12.557 - 39.131
Age (years)	-0.406	0.049	<0.001	-0.504 - -0.308

Age × sex	-0.269	0.112	0.019	-0.492 - -0.046
Body mass index (m/kg^2)	-0.644	0.140	<0.001	-0.921 - -0.366
Resting heart rate[1] (beats per minute)	-0.094	0.053	0.078	-0.198 - 0.011
Smoking (never=0, ever=1)	-2.522	1.066	0.020	-4.641 - -0.403
ACSM/AHA 2007 recommendations for PA (not fulfilled=0, fulfilled=1)	2.984	1.127	0.010	0.744 - 5.224
Systolic blood pressure (mm Hg)	-0.071	0.032	0.029	-0.134 - -0.008
Constant	85.982	5.864	<0.001	74.321 - 97.643

[1]Resting heart rate had a *P* value = 0.078 in this RA equation but was kept in the equation to avoid deterioration of overall model fit.
Abbreviations: ACSM, American College of Sports Medicine; AHA, American Heart Association; PA, physical activity; RA, rheumatoid arthritis.

Reference:

1. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation.* 2007;116(9):1081-93.

Paper 3

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Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Faster age-related decline in cardiorespiratory fitness in rheumatoid arthritis patients: an observational study in the Trøndelag Health Study

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Abstract

Primary aim: Compare change in estimated cardiorespiratory fitness (eCRF change) in rheumatoid arthritis (RA) patients with population-based age- and sex-matched controls during ~ 11-year follow-up and identify variables associated with eCRF change. Secondary aim: Compare eCRF level in RA patients and controls. eCRF change from the second (HUNT2 1995–1997) to the third (HUNT3 2006–2008) surveys of the Norwegian Trøndelag Health Study was compared between RA patients ($n = 188$) and controls ($n = 26{,}202$) attending both surveys. Predictors of eCRF change were identified by Lasso regression followed by multiple linear regression. Mean eCRF level in RA patients ($n = 436$) and controls ($n = 67{,}910$) was compared using age-adjusted linear regression stratified on sex, as well as two-sample t tests including RA patients ($n = 432$) and controls ($n = 59{,}124$) who attended either HUNT2, HUNT3 or both HUNT2 and HUNT3. The mean eCRF decline from HUNT2 to HUNT3 in RA patients was 8.3 mL min^{-1} kg^{-1} versus 6.7 mL min^{-1} kg^{-1} in controls ($p < 0.001$). The decline was faster in RA patients and larger with higher baseline age (standardized regression coefficient for RA patients: $(-0.482 \times \text{age} + 0.044)$; controls: $(-0.367 \times \text{age}$, $p < 0.001)$. The decline was also associated with smoking, cardiovascular disease, increasing body mass index, asthma, and hypertension. Mean differences in age-adjusted eCRF level for RA patients versus controls ($p < 0.001$): women HUNT2: − 3.2 mL min^{-1} kg^{-1}; HUNT3: − 5.0 mL min^{-1} kg^{-1}; men HUNT2: − 1.8 mL min^{-1} kg^{-1}; HUNT3: − 4.0 mL min^{-1} kg^{-1}. Higher age at baseline was associated with faster decline in eCRF. This change was more pronounced in RA patients than controls, indicating a larger negative effect on fitness of aging in RA. RA patients had lower eCRF compared to healthy individuals.

Keywords Cardiorespiratory fitness · Rheumatoid arthritis · Aging · Population-based study

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00296-020-04713-2) contains supplementary material, which is available to authorized users.

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Introduction

Rheumatoid arthritis (RA) is an inflammatory disease of the joints [1], but it also affects internal organs, including the vasculature. RA patients are younger when they develop cardiovascular risk factors, suffer from more cardiovascular disease (CVD), and have higher mortality rates due to CVD than the general population [2–5]. Evidence supports that the chronic systemic inflammation associated with RA is an important driver of excess CVD in RA patients, particularly by causing accelerated atherosclerosis [6]. In addition, it has become evident that factors like reduced physical activity (PA) and increased levels of traditional risk factors for CVD contribute to the differences. PA affects cardiorespiratory fitness (CRF) [7, 8], and CRF is inversely associated with cardiovascular risk [7]. CRF is viewed as an independent risk factor for CVD and mortality [7, 9, 10], and has recently received much attention because it may be modified.

The gold standard method of measuring CRF is by testing maximum oxygen uptake during cardiopulmonary exercise testing (CPET), which is rather resource intensive [7]. For easier evaluation, equations for estimated cardiorespiratory fitness (eCRF) may be used, making it possible to investigate eCRF in big population-based studies without the need for a physical test [7]. eCRF equations are usually developed by multivariable regression analysis of variables expected to be associated with the maximum oxygen uptake measured by CPET, followed by removal of non-significant variables to achieve a simplified, yet appropriate regression model. Selected variables should be easily accessible, e.g., height, weight, waist circumference, resting heart rate (RHR) and/or answers to questionnaires describing PA habits. In this way, CRF may be calculated from the model with acceptable accuracy without performing CPET [11].

In the second and third surveys of the Norwegian population-based Trøndelag Health Study (HUNT2 and HUNT3) conducted in 1995–1997 and 2006–2008 [12], formulas for eCRF for healthy participants were developed [10, 11]. Using these eCRF equations, the associations of eCRF to various risk factors and outcomes have been investigated [10, 13, 14]. After demonstrating that these formulas overestimated eCRF in RA patients with the lowest measured CRF, our group developed eCRF equations that more correctly calculate eCRF in RA patients [15]. Previous studies suggest that RA patients are deconditioned and on average have decreased CRF compared to the general population [16–18]. To our knowledge, no studies have compared age-related changes in eCRF of RA patients and healthy people in a population-based setting. The design of the large population-based HUNT study with long follow-up makes this possible.

On this background, we hypothesized that eCRF in RA patients deteriorates faster by time compared to controls, and that RA patients in HUNT2 and HUNT3 are deconditioned and have lower eCRF than controls. Thus, the primary aim of the present study was to investigate the change of eCRF by time from HUNT2 to HUNT3 in RA patients compared to controls and identify variables associated with the potential difference in this change between the two groups. The secondary aim was to compare eCRF levels between RA patients and controls in HUNT2 and HUNT3.

Methods

The present work was a sub-study of HuLARS (HUNT Longitudinal Ankylosing spondylitis and Rheumatoid Arthritis Study). In the HUNT study [12], all inhabitants ≥ 20 years old from the northern part of the Norwegian county of Trøndelag were invited. The HUNT study is an open cohort study and data, including results from questionnaires and blood samples from participants from HUNT2 (1995–1997) and HUNT3 (2006–2008), were used in the present observational study.

Power was calculated based on the following assumptions using data from previous HUNT publications [19, 20]: Approximately 33,000 persons participated in both HUNT2 and HUNT3 and the prevalence of RA was ~ 0.75%; we expected ~ 15% missing data for calculation of eCRF; the average 10-year decline in CRF in healthy people would be ~ 3.8 mL min^{-1} kg^{-1}; we presumed a 20% larger decline in individuals with RA; and used alpha = 0.05 and a two-sided test. The calculated power was 82%, which was considered sufficient to perform the study.

Patients

Based on the information in hospital case files and using the standardized 2010 ACR/European League Against Rheumatism classification criteria for rheumatoid arthritis [20–22] or for some cases diagnosed before 2010 the 1987 American College of Rheumatology (ACR) classification criteria due to insufficient information [21], a previous study identified those with a valid RA diagnosis ($n = 578$) out of all participants in HUNT2 and HUNT3 who self-reported RA. We excluded those who received an RA diagnosis after HUNT3 ($n = 32$) and participants with ankylosing spondylitis, psoriasis arthritis, juvenile idiopathic arthritis, or other inflammatory arthritis. The remaining participants were included as controls. The primary aim was to investigate the change in eCRF from HUNT2 to HUNT3; thus, we only included controls and RA patients with valid eCRF in both HUNT2 and HUNT3 and with no missing adjustment variables in the regression analysis (188 RA patients and 26,202 controls) in this analysis (Fig. 1). For the secondary aims comparing

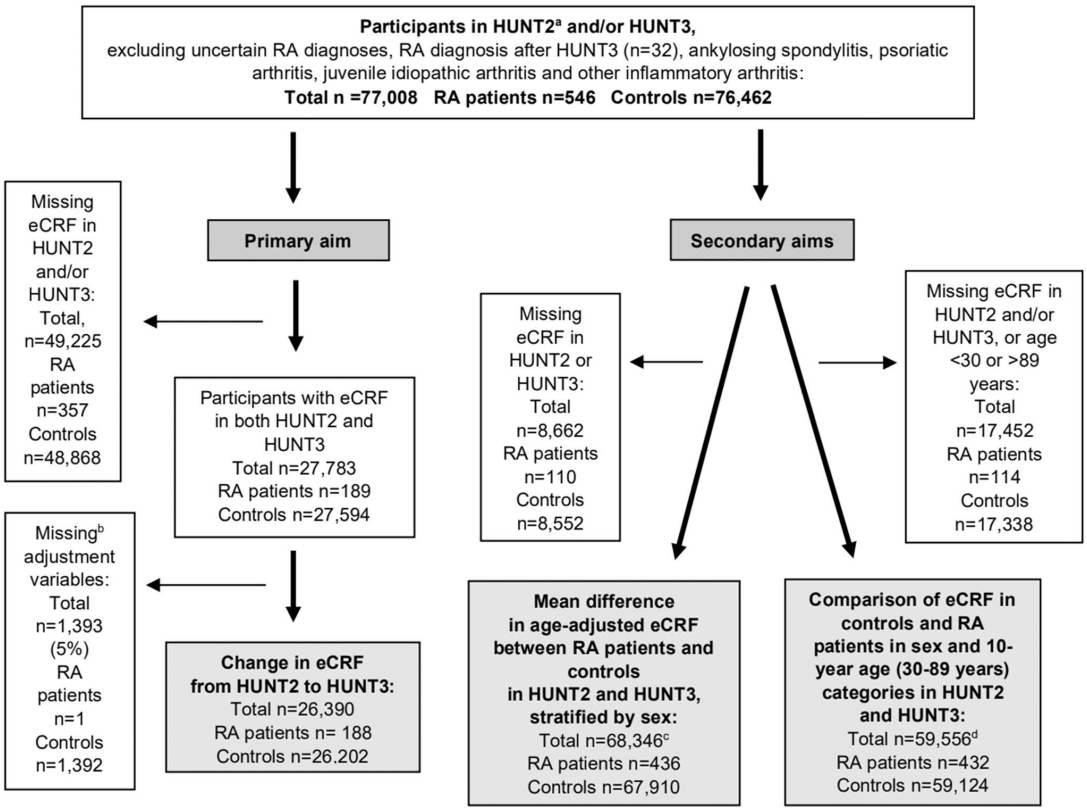

Fig. 1 Recruitment to the study. **a** *HUNT2 and HUNT3* Second and third surveys of the Trøndelag Health Study, *RA* rheumatoid arthritis, *eCRF* estimated cardiorespiratory fitness, *HUNT3 Fitness* Substudy of HUNT3. **b** Missing data: < 0.1% for body mass index and asthma, < 0.2% for cardiovascular disease and hypertension, and 4.5% for smoking. Remaining variables complete. **c** Numbers represent unique participants. Because persons participating both in HUNT2 and HUNT3 were included in the analysis for both timepoints, the actual n was higher (total $n = 96{,}129$, RA patients $n = 625$, controls $n = 95{,}504$). **d** Numbers represent unique participants. Because persons participating both in HUNT2 and HUNT3 were included in the analysis for both timepoints, the actual n was higher (total $n = 84{,}170$, RA patients $n = 616$, controls $n = 83{,}554$)

eCRF levels in controls and RA patients, we included participants attending either HUNT2 only, HUNT3 only, or HUNT2 and HUNT3, resulting in a higher number of participants for these comparisons as detailed in Fig. 1. Method validation was performed in participant subsets as further described below.

Main outcome variable

eCRF (mL kg^{-1} min^{-1}) was calculated using the previously published eCRF equations for healthy controls [10, 11], and the RA-specific equation for RA patients [15]. Due to collinearity, variables present in eCRF equations cannot be used as explanatory variables for eCRF in a novel regression analysis. This problem was avoided for the primary aim in the present study because the outcome variable was the change in eCRF from HUNT2 to HUNT3.

Study factors

The primary and secondary outcomes were compared among RA patients and controls as defined above.

Other variables

Variables known from the literature to be associated with eCRF change and available in the HUNT surveys were used. The following variables and definitions were used: CVD (yes/no)—self-reported prior or present angina pectoris and/or myocardial infarction and/or stroke. Family CVD

history (yes/no)—previous/present stroke and/or hypertension and/or myocardial infarction (MI) before age 60 years in a first-degree relative. Hypertension (yes/no)—blood pressure ≥ 140/90 mm Hg and/or self-reported use of antihypertensive medication. Hypertension and systolic blood pressure (SBP) are correlated, and only hypertension was used because those treated with anti-hypertensive medication might have normalized SBP despite a diagnosis of hypertension. Smoking (yes/no)—self-reported prior or present smoking. Asthma (yes/no)—self-reported prior or present asthma. Diabetes (yes/no)—self-reported diabetes and/or the use of anti-diabetic medication and/or having a non-fasting blood-glucose level > 11 mmol × L^{-1}. Cancer (yes/no)—self-reported prior or present cancer. Pain (yes/no)—pain and/or stiffness that had lasted for ≥ 3 of the 12 latest months. Body mass index—weight/squared height (kg/m^2). High-density lipoprotein (HDL) cholesterol measured in mmol/L.

PA strongly influences CRF [7, 8]. The American College of Sports Medicine and American Heart Association's (ACSM/AHA) recommendations for aerobic PA are to perform either moderate-intensity physical activity ≥ 30 min on ≥ 5 days each week (≥ 150 min per week) or to perform vigorous-intensity aerobic activity ≥ 20 min ≥ 3 days a week (≥ 75 min per week). PA at these two intensities may also be combined [10, 23]. To describe the level of PA, the proportions of RA patients and controls fulfilling the ACSM/AHA recommendations for aerobic PA at HUNT2 (baseline) and HUNT3 were calculated from responses to questions about frequency, intensity and duration of weekly performed PA [10, 11, 23].

Ethics statement

All participants in HUNT2 and HUNT3 provided written informed consent. The present study was approved by The Regional Committee for Medical and Health Research Ethics (4.2009.1068 and 2018/1149) and was performed in compliance with the Helsinki Declaration.

Statistical analysis

Data are given as counts or mean with percentages or standard deviation (SD) in parenthesis. p values < 0.05 were considered significant. Analyses were performed using STATA (Version 15.0, StataCorp, College Station, TX, USA).

To evaluate the decline in eCRF from HUNT2 to HUNT3 for the primary aim, regression models were performed in steps with different adjustments. In Step 1, we performed multiple linear regression with change in eCRF as the dependent variable and age (continuous), RA status (yes/no), and the interaction term for age and RA status as independent variables, which permitted investigation of whether eCRF reduction by time was different between RA patients and controls depending on age. Inclusion of age in the model ensured that differences in baseline age between RA patients and controls were adjusted for. We also included the following predefined adjustment variables: baseline eCRF, sex (male = 0 and female = 1), and time from participation in HUNT2 to participation in HUNT3 (years). Baseline eCRF, sex and age were included because the change in eCRF may depend on the starting level, and CRF varies with sex and age. Adjustment for time between the HUNT2 and HUNT3 was included because time varied from 10 to 12 years among individual participants.

The Step 1 model was then further modified to investigate other associations to the decline in eCRF from HUNT2 to HUNT3 (Step 2–4). Based upon literature, further baseline variables possibly relevant for the change in eCRF were considered as detailed above (CVD, family CVD history, hypertension, smoking, asthma, diabetes, cancer, pain, BMI, and HDL cholesterol). PA and RHR could not be included in the main analysis of change of eCRF because of collinearity with the dependent variable.

To reduce the risk of overfitting and promote reliable variable selection, the mentioned explanatory variables were first analyzed by Lasso (least absolute shrinkage and selection operator) regression (n = 1000 repetitions). Lasso identifies the smallest useful set of variables among variables that may be highly correlated, and gives irrelevant variables a coefficient of 0 [24]. Variables with a coefficient different from 0 in the Lasso regression were, therefore, added to the Step 1 model to achieve the Step 2 model. The Step 2 model was then reduced to the final Step 3 model by removal of non-significant variables. In Step 4, the Step 3 model was standardized to compare the effect sizes of the predictors.

The models were compared using the R^2 (i.e., the variation in the dependent variable explained by the independent variables), root mean square error (RMSE, i.e., standard error of the residuals, which tells how close the data lie around the line of best fit), Akaike information criterion (AIC) and Bayesian information criterion (BIC), where low numbers mean that the model better fits the data. Assumptions were evaluated using residual plots.

For the secondary aims, analysis was performed separately for HUNT2 and HUNT3 and each participant was included wherever she/he had participated (Fig. 1). Linear regression was used to find the mean sex-specific age-adjusted difference in eCRF between RA patients and controls. Mean eCRF of controls and RA patients aged 30–89 years were further compared with two-sample t tests in ten-year age categories for each sex separately.

As a sensitivity assay, we validated whether the eCRF calculation methods used in the study were comparable employing equivalence testing. With this method, the mean and 90% confidence interval (CI) of the difference between

two methods, e.g., the calculated eCRF and measured CRF are evaluated against a predefined equivalence region [25]. The equivalence region indicates how big the difference may be for the two methods still to be considered equivalent. As there is no generally accepted equivalence region for eCRF vs. measured CRF, we evaluated against an equivalence region of ± 1 Metabolic Equivalent (MET) (± 3.5 mL min^{-1} kg^{-1}).

The eCRF equation for the general population was developed from a sub-study of HUNT3 (HUNT3 Fitness) [11, 19], which ensures that the eCRF equation for the general population fits the controls of our study. To evaluate whether the RA-specific eCRF equation would be adequate for the controls, an equivalence test was performed to compare the calculated eCRF by the RA-specific equation to the measured CRF from CPET in 3,294 of the controls in our study (women, $n = 1754$ and men, $n = 1540$), who had also participated in the HUNT3 Fitness study.

The equations for estimation of the RA-specific eCRF in HUNT2 and HUNT3 were slightly different due to the registered variables concerning PA in each survey. In a second equivalence test, we, therefore, compared these two RA equations in 189 RA patients where data for both methods were available. There are similar differences in the eCRF equations used in controls in HUNT2 and HUNT3. Thus, a third equivalence test of the general eCRF equations for HUNT2 and HUNT3 in 27,594 controls was also performed.

Results

Baseline characteristics, including mean eCRF in HUNT2 and the frequencies of RA patients and controls fulfilling the ACSM/AHA recommendation for aerobic PA at baseline are given in Table 1. Table 1 presents baseline characteristics for RA patients ($n = 188$) and controls ($n = 26,202$), after exclusion of those with missing data for variables in the main regression analysis of change of eCRF. In HUNT2, 48% of the women with RA and 58% of the control women fulfilled aerobic PA recommendations, and the corresponding figures for men were 61% and 66%, respectively. In HUNT3, 31% of the women with RA and 40% of the control women fulfilled aerobic PA recommendations, and the corresponding figures for men were 29% and 41%, respectively.

Primary aim

The mean change in eCRF from HUNT2 to HUNT3 was − 8.3 mL min^{-1} kg^{-1} in RA patients compared to − 6.7 mL min^{-1} kg^{-1} in controls ($p < 0.001$); for women: − 7.5 (3.7)

Table 1 Baseline characteristics for the main analysis

Total, $n = 26,390$	Women			Men		
	Controls $n = 14,466$	RA patients $n = 119$	p value	Controls $n = 11,736$	RA patients $n = 69$	p value
Age, mean (SD) (years)	44.9 (12.8)	52.4 (10.5)	< 0.001	46.8 (12.7)	55.6 (9.7)	< 0.001
Systolic blood pressure, mean (SD) (mm Hg)	129.6 (19.0)	134.0 (16.4)	0.01	137.0 (16.4)	141.0 (19.8)	0.06
Resting heart rate, mean (SD) (bpm)	72.2 (12.2)	73.1 (10.8)	0.42	67.0 (12.3)	68.4 (12.7)	0.33
Body mass index, mean (SD) (kg/m^2)	25.6 (4.1)	26.7 (4.0)	0.006	26.4 (3.2)	26.3 (3.3)	1.00
Waist circumference, mean (SD) (cm)	79.4 (10.3)	83.0 (10.6)	< 0.001	91.0 (8.4)	91.6 (9.2)	0.57
High-density lipoprotein mean (SD) (mmol/L)	1.53 (0.38)	1.50 (0.45)	0.42	1.25 (0.33)	1.23 (0.33)	0.53
Ever smoker, n (%)	7191 (50)	69 (58)	0.07	6359 (54)	48 (70)	0.01
Cardiovascular disease[a], n (%)	237 (2)	3 (3)	0.45	575 (5)	8 (12)	0.01
Asthma[b], n (%)	1084 (8)	9 (8)	1.00	933 (8)	3 (4)	0.27
Hypertension[c], n (%)	3994 (28)	46 (39)	0.01	4923 (42)	39 (57)	0.02
Diabetes[d], n (%)	144 (1)	3 (3)	0.10	183 (2)	4 (6)	0.005
Fulfills ACSM/AHA recommendations for aerobic PA, n (%)	8522 (59)	57 (48)	0.02	7768 (66)	42 (61)	0.35
eCRF in HUNT2, mean (SD) (mL min^{-1} kg^{-1})	36.81 (5.8)	31.19 (6.2)	< 0.001	46.10 (6.8)	40.95 (8.2)	< 0.001

RA rheumatoid arthritis, *bpm* beats per minute, *ACSM* American College of Sports Medicine; *AHA* American Heart Association, *PA* physical activity, *eCRF* estimated cardiorespiratory fitness, *HUNT2* The second survey of the Trøndelag Health Study

[a]Cardiovascular disease: Self-reported prior or present angina pectoris and/or myocardial infarction and/or stroke

[b]Asthma: Self-reported prior or present asthma

[c]Hypertension: Blood pressure ≥ 140/90 and/or self-reported use of anti-hypertensive medication

[d]Diabetes: Self-reported diabetes and/or the use of anti-diabetic medication and/or having a non-fasting blood-glucose level > 11 mmol × L^{-1}

mL min^{-1} kg^{-1} for RA patients vs. − 6.0 (3.4) mL min^{-1} kg^{-1} for controls; for men: − 9.6 (3.3) mL min^{-1} kg^{-1} in RA patients vs. − 7.6 (4.1) mL min^{-1} kg^{-1} for controls.

The Step 1 regression model for change in eCRF from HUNT2 to HUNT3 showed that the decline was larger in RA patients compared to controls and increasing with older age at baseline (Table 2, Fig. 2, panel a and b). No potential adjustment variables had a coefficient of 0 in the Lasso regression, so all variables were included in the Step 2 model. Cancer, diabetes, pain, and family CVD history were non-significant in Model 2 and were removed from Model 3. Removal of these variables hardly influenced model fit. The adjustment provided by smoking, CVD, BMI, HDL cholesterol, asthma and hypertension in the Step 3 model (Table 2) rendered the decline in eCRF from HUNT2 to HUNT3 even more pronounced (Fig. 2, panel c and d). Based on the Step 4 model, the age-related eCRF decrease in RA patients was (− 0.482 × age + 0.044) mL min^{-1} kg^{-1} compared to (− 0.367 × age) mL min^{-1} kg^{-1} in controls.

Secondary aims

eCRF in RA patients was lower than eCRF in controls. Mean differences in age-adjusted eCRF for RA patients versus controls were: women HUNT2: − 3.2 mL min^{-1} kg^{-1}; women HUNT3: − 5.0 mL min^{-1} kg^{-1}; men HUNT2: − 1.8 mL min^{-1} kg^{-1}; men HUNT3: − 4.0 mL min^{-1} kg^{-1}) ($p < 0.001$ for all comparisons). Online Resource 1 provides further details regarding eCRF in RA patients and controls in 10-year categories for both sexes.

Sensitivity analyses for method validation

The RA-specific equation was non-equivalent with measured CRF when used for healthy persons, confirming that eCRF in controls and RA patients cannot be calculated using the same equation (Fig. 3). The RA equations for HUNT2 and HUNT3 were equivalent, and so were the general eCRF equations for HUNT2 and HUNT3, demonstrating that

Table 2 Regression models for eCRF change (mL min^{-1} kg^{-1}) with standardization

	Step 1 model[a]	Step 2 model[b]	Step 3 model[c]	Step 4 model[d]
Age (years)	− 0.053***	− 0.110***	− 0.110***	− 0.367
RA status (no = 0/yes = 1)	0.421 ($p = 0.76$)	2.138 ($p = 0.12$)	2.011 ($p = 0.13$)	0.044
Age and RA interaction	− 0.060*	− 0.101***	− 0.096***	− 0.115
Baseline eCRF (mL min^{-1} kg^{-1})	− 0.271***	− 0.475***	− 0.473***	− 0.964
Years from HUNT2 to HUNT3	− 0.3771***	− 0.334***	− 0.339***	− 0.050
Sex (male = 0/female = 1)	− 0.965***	− 3.361***	− 3.320***	− 0.431
Smoking (never = 0/ever = 1)		− 0.474***	− 0.518***	− 0.068
Cardiovascular disease (no = 0/yes = 1)		− 0.279*	− 0.339**	− 0.015
Body mass index (kg/(m^2))		− 0.286***	− 0.292***	− 0.285
High-density lipoprotein concentration		0.336***	0.289***	0.029
Asthma (no = 0/yes = 1)		− 0.253*	− 0.216**	− 0.015
Hypertension (no = 0/yes = 1)		− 0.277***	− 0.211***	− 0.026
Pain (no = 0/yes = 1)		0.0310 ($p = 0.51$)		
Cancer (no = 0/yes = 1)		0.0557 ($p = 0.70$)		
Diabetes (no = 0/yes = 1)		− 0.188 ($p = 0.36$)		
Family CVD history (no = 0/yes = 1)		0.010 ($p = 0.83$)		
Constant	11.561	30.706	30.893	
R squared	0.16	0.21	0.21	
RMSE	3.52	3.39	3.41	

The standardized coefficient gives the change in eCRF for one SD increase in each continuous variable, and the change in eCRF for the change from 0 to 1 in each categorical variable

eCRF estimated cardiorespiratory fitness, *RA* rheumatoid arthritis, *HUNT2 and HUNT3* The second and third surveys of the Trøndelag Health Study, *CVD* cardiovascular disease, *R−squared* the variation in the dependent variable explained by the independent variables, *RMSE* root mean square error; *Lasso* least absolute shrinkage and selection operator regression

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[a]After removal of variables because of collinearity and high number of missing

[b]After Lasso regression

[c]After removal of non-significant variables

[d]After standardization

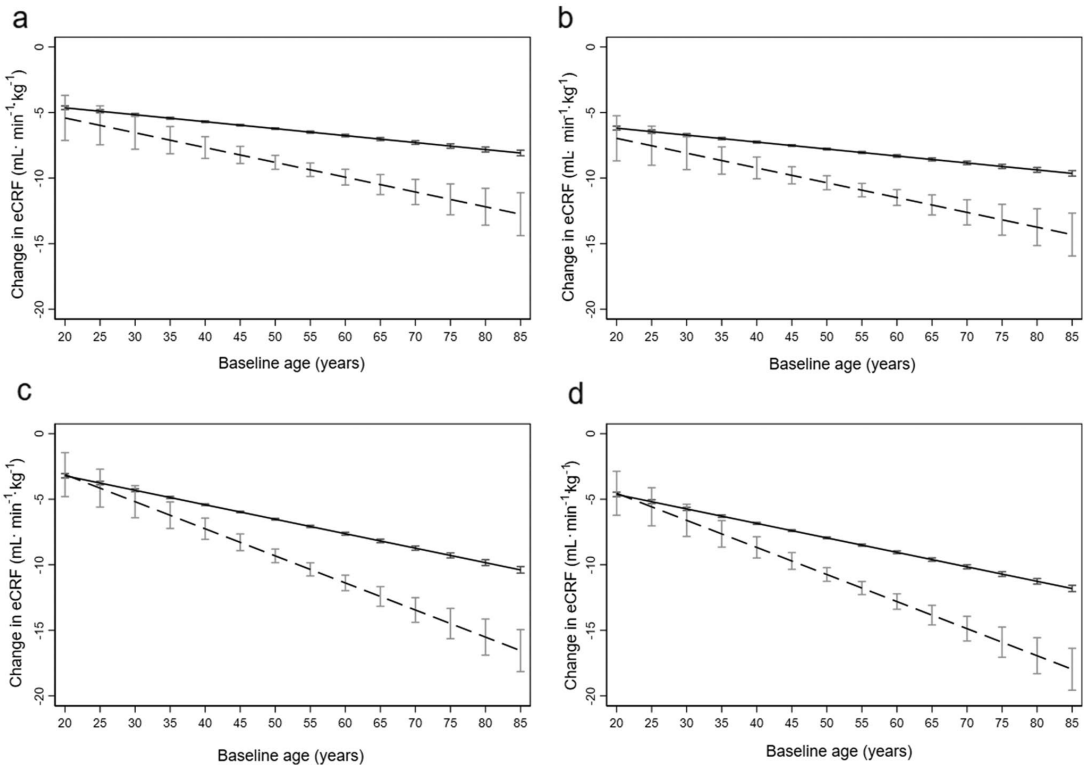

Fig. 2 Change of eCRF[a] from HUNT2 to HUNT3. Change of eCRF from HUNT2 to HUNT3 for RA patients (------) and controls (——) with 95% confidence intervals. Panels **a** (women) and **b** (men) represent the Step 1 model including RA status (yes/no), age, and the interaction term for age and RA status with adjustment for baseline eCRF, sex and time between HUNT2 and HUNT3. Panels **c** (women) and **d** (men) represent the Step 3 model, additionally adjusted for smoking (never vs. ever), cardiovascular disease, body mass index, high-density lipoprotein, asthma and hypertension. [a]*eCRF* estimated cardiorespiratory fitness, *HUNT2 and HUNT3* The second and third surveys of the Trøndelag Health Study, *RA* rheumatoid arthritis

change in eCRF from HUNT2 to HUNT 3 was not biased by the use of slightly different equations (Fig. 3).

Discussion

Having an RA diagnosis was associated with a faster age-related decline in eCRF compared to controls, and this effect was larger with higher age at baseline. RA patients also had lower eCRF than controls, especially in the older age categories.

There has been much focus upon the fact that RA patients have worse cardiovascular risk factor profiles, excess CVD and excess mortality from CVD compared to the general population [3]. In theory, the faster decline in CRF associated with RA might be explained by their less favorable cardiovascular risk factors and higher incidence of CVD at an earlier age, contributing to a vicious cycle. In this study, women with RA had higher BMI and more often had hypertension compared to controls; whereas, more men with RA more often were ever smokers, had diabetes, CVD, or hypertension compared to controls. However, by adjusting for known risk factors for cardiovascular disease like BMI, smoking, and lower HDL cholesterol in addition to hypertension, asthma, and previous CVD, the faster decline in eCRF of RA patients compared to controls became even more pronounced, indicating that other factors were also involved. The association between CVD, risk factors, and CRF substantiates the importance of CRF improvement as a preventive measure of CVD in RA patients. The findings that fewer RA patients met the general recommendations for aerobic PA compared to controls and that fewer participants met the recommendations in HUNT3 than in HUNT2 are important from

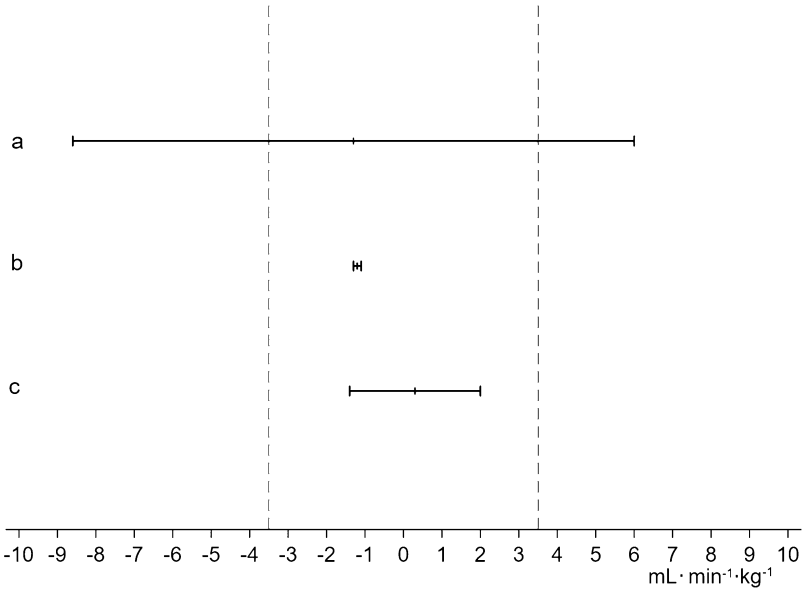

Fig. 3 Equivalence testing for method validation. Methods are regarded equivalent when the 90% confidence interval (CI) of the difference between measurement with the two methods (horizontal bars) lie within the equivalence region (vertical dashed lines), defined as ± 1 MET (± 3.5 mL min^{-1} kg^{-1}). Bar a: RA[d] -specific equation used for healthy participants in HUNT3 Fitness compared to measured CRF. Mean difference: − 1.3 min^{-1} kg^{-}1, 90% CI − 8.6, 6.0 mL· min^{-1} kg^{-1}. Methods were non-equivalent. Bar b: RA-specific equation for HUNT3 compared to RA-specific equation for HUNT2. Mean difference: − 1.2 mL kg^{-1} min^{-1}, 90% CI − 1.3, − 1.1 mL kg^{-1} min^{-1}. Methods were equivalent. Bar c: General eCRF equation for HUNT3 compared to general eCRF equation for HUNT2. Mean difference: 0.3 mL min^{-1} kg^{-1}, 90% CI − 1.4, 2.0 mL min^{-1} kg^{-1}. Methods were equivalent. [d]*RA* rheumatoid arthritis, *HUNT3 Fitness* Sub-study of HUNT3, *CRF* cardiorespiratory fitness, *HUNT2 and HUNT3* The second and third surveys of the Trøndelag Health Study, *eCRF* estimated cardiorespiratory fitness

this perspective because the level of PA is a well-known predictor of CRF.

It could be important for interpretation of the results that advice and information about PA given to RA patients have changed in recent years. Advice recommending exercise with low intensity has gradually shifted towards advice about high-intensity exercise. Thus, more recent exercise regimens for RA patients could potentially have counteracted the decline in eCRF from HUNT2 to HUNT3. This does not seem to have had a strong effect because a study from our group showed that RA patients tested in 2017 still had reduced CRF compared to the healthy population [16].

For better care and follow-up of the general population, the AHA has recommended use of estimation models for eCRF [7], and the ACSM/AHA recommendations for PA are implemented as important aims for the level of physical activity in RA patients [23, 26]. However, development and implementation of suitable exercise programs for RA patients still need higher priority. Estimating CRF in RA patients can contribute to better follow-up. To facilitate correct estimation of eCRF, we have recently published equations that are customized for RA patients [15]. Uptake of these formulae in rheumatology practice may contribute to better patient care.

The proportion of healthy controls that fulfill the recommendations for PA has not changed much over the years. On the contrary, there is a trend of major concern for public health that inactivity at work has increased. Analyzing the effect of type of work (physical vs. non-physical) could be of interest in the present study as well, but due to missing data, this variable could not be included.

Other possible explanations for increased deterioration of eCRF by time in RA patients need to be considered. The natural process of aging contributes to deterioration of CRF by time. As RA is associated with accelerated aging of the immune system, including insufficiency of telomerase activity and deficiency of DNA repair mechanisms [27], one may speculate that such mechanisms contributed to the faster decline in eCRF. Further, RA is associated with rheumatoid cachexia, with reduced muscle mass and increased fat mass [6], which adds to the natural wasting of musculature by increasing age. This may render RA patients more

susceptible to the frailty syndrome. An individual is considered frail if three out of these five phenotypes are present: weakness, unintentional weight loss, exhaustion, low PA and slower walking speed [28]. Frail persons have an increased frequency of negative health outcomes, including accidental falls, reduced mobility and decreased functional capacity [27]. Frailty could potentially contribute to reduced eCRF in RA patients, but unfortunately, we did not have data to assess frailty in the present study.

The present study has several strengths. It was population-based and included a substantial number of participants with ~ 11 years of follow-up. Furthermore, the RA diagnoses were validated from information in hospital case files [20]. A potential weakness is that eCRF for controls and RA patients were calculated using different equations, but the sensitivity analyses clearly showed that this did not bias the results. Our study confirmed that the RA-specific equations should only be used in RA patients. Another study from our group showed that the general eCRF equation is not adequate for RA patients because of a tendency towards underestimation in RA patients at highest risk of CVD [15]. The equations used in HUNT2 and HUNT3 were equivalent, both for RA patients and healthy controls. Taken together, our study supports that eCRF in RA patients and the general population should be calculated using different equations.

Because HUNT is a large population-based study, RA disease-related variables that would not be relevant for controls such as disease activity, swollen and tender joint counts, or the patient's global disease assessment were not collected. Previously, our group found that a number of variables describing physical function and disease activity were not associated with measured CRF at CPET in RA patients and did not improve the RA-specific eCRF equation [15, 16]. Thus, the results of the present study are probably not biased because such variables were missing.

Since HUNT3 was performed in 2006–2008, there has been a change in treatment strategies for RA with more medications to choose from and use of higher doses of antirheumatic drugs like methotrexate. Thus, results from this study might not be representative for today's RA population. In a former study [16], we investigated various predictors for the measured CRF in RA patients. Disease modifying antirheumatic drugs, comorbidities, and disease activity scores other than the patient global assessment were not significant predictors for CRF. These findings support that despite changes in treatment strategies the start of the present study, the results may still be representative.

A limitation of this study may be the use of estimation models for CRF instead of direct measurement. CPET of all participants would not easily be feasible in a study as large as HUNT, but a smaller future study using CPET could provide more accurate data. The low number of RA patients may represent a limitation, but the very large control group reduces selection bias and thereby improves the validity of the results.

In conclusion, the present study showed that age-related eCRF deterioration was faster in RA patients compared to healthy controls. This finding may add to the explanation of the increased frequency of CVD in RA patients at an earlier age compared to healthy controls. The study also found that a lower percentage of RA patients fulfilled recognized PA recommendations, and that RA patients had lower CRF at baseline. Thus, increasing PA in RA patients seems to be an important measure to improve cardiovascular health by reducing the age-related decline in eCRF, in addition to modern medical treatment.

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Author contributions MHL: contributed to the study conception and design, performed data analysis, wrote the first manuscript draft, and contributed to interpretation of the results and critical revision for important intellectual content. MH: contributed to the study conception and design, interpretation of the results, and critical revision for important intellectual content. UW: contributed to the study conception and design, interpretation of the results, and critical revision for important intellectual content. VV: contributed to the study conception and design, performed data analysis, and contributed to interpretation of the results and critical revision for important intellectual content. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability Data from HUNT are available upon reasonable request from the HUNT Research Centre (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 and are not publicly available in accordance with Norwegian law.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest.

Ethical approval This study was approved by The Regional Committee for Medical and Health Research Ethics (4.2009.1068 and 2018/1149) and was performed in compliance with the Helsinki Declaration.

Informed consent All participants in HUNT provided written informed consent.

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Title: Faster age-related decline in cardiorespiratory fitness in rheumatoid arthritis patients – an observational study in the population-based Trøndelag Health Study

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Online Resource 1: Estimated cardiorespiratory fitness (eCRF) in controls and rheumatoid arthritis (RA) patients in sex and 10-year age categories (30-89 years) in HUNT2 and HUNT3

	Women			**Men**		
HUNT2	**Controls, eCRF[a]**	**RA patients, eCRF[b]**		**Controls, eCRF[a]**	**RA patients, eCRF[b]**	
Age	**Mean eCRF (CI), n**	**Mean eCRF (CI), n**	***p*-value**	**Mean eCRF (CI), n**	**Mean eCRF (CI), n**	***p*-value**
30-89 years	33.9(33.8-33.9), 24,033	29.1(28.2-30.0), 253	<0.001	43.2(43.1-43.3), 23,103	38.9(37.4-40.3), 129	<0.001
30-39 years	40.3(40.2-40.4), 5,623	38.4(36.4-40.2), 22	0.01	50.3(50.2-50.5), 5,134	55.9(46.6-55.4), 6	<0.01
40-49 years	36.6(36.5-36.7), 6,496	35.4(34.4-36.5), 68	0.01	46.2(46.1-46.3), 6,104	48.6(46.8-50.3), 20	0.026
50-59 years	32.9(32.8-33.1), 4,994	28.5(27.5-29.4), 69	<0.001	42.2(42.0-42.3), 4,910	40.3(39.0-41.6), 46	<0.01
60-69 years	29.0(28.9-29.1), 3,441	23.9(22.7-25.1), 60	<0.001	38.3(38.2-38.5), 3,600	34.8(33.2-36.3), 37	<0.001
70-79 years	25.3(25.2-25.5), 2,608	21.3(19.8-22.9), 30	<0.001	34.7(34.5-34.9), 2,678	28.2(26.5-30.0), 20	<0.001
80-89 years	22.1(21.9-22.4), 871	18.6(11.3-25.9), 4	0.06	30.4(30.0-30.8), 677	n=0	
HUNT3	**Controls, eCRF[c]**	**RA patients, eCRF[d]**		**Controls, eCRF[c]**	**RA patients, eCRF[d]**	
Age	**Mean eCRF (CI), n**	**Mean eCRF (CI), n**	***p*-value**	**Mean eCRF (CI), n**	**Mean eCRF (CI), n**	***p*-value**
30-89 years	31.4(31.3-31.4), 20,169	23.5(22.5-24.5), 149	<0.001	39.2(39.0-39.3), 16,249	31.2(29.4-32.9), 85	<0.001
30-39 years	37.1(36.9-37.2), 3,189	28.1(5.9-50.2), 3	<0.001	46.6(46.4-46.9), 2,069	49.1, 1	NA
40-49 years	34.8(34.7-34.9), 4,668	33.3(31.1-35.4), 7	0.34	43.3(43.1-43.5), 3,406	48.3, 1	NA
50-59 years	31.5(31.4-31.7), 4,994	28.0(26.6-29.4), 47	<0.001	39.5(39.4-39.7), 4,153	41.2(39.0-43.4), 15	0.22
60-69 years	28.2(28.1-28.4), 4,222	23.3(22.0-24.5), 47	<0.001	36.2(36.0-36.3), 3,764	31.2(29.1-33.2), 32	<0.001
70-79 years	24.9(24.8-25.1), 2,284	18.2(17.0-19.3), 31	<0.001	33.0(32.8-33.2), 2,149	27.8(26.0-29.7), 28	<0.001
80-89 years	22.6(22.3-22.8), 812	15.1(13.5-16.8), 14	<0.001	29.7(29.4-30.1), 708	19.7(16.8-22.6), 8	<0.001

eCRF of controls, estimated by [a)]general eCRF formula developed for HUNT2 [1] and [c)]general eCRF formula developed for HUNT3 [2], compared to eCRF of RA patients calculated by [b)]RA-specific formula developed for HUNT2, and [d)]RA-specific formula developed for HUNT3 [3]. Rows in gray when n<6.

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Paper 4

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Reduced cardiorespiratory fitness is a mediator of excess all-cause mortality in rheumatoid arthritis: the Trøndelag Health Study

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ABSTRACT

Objectives Investigate if low cardiorespiratory fitness (CRF) was associated with and acted as a mediator of excess all-cause mortality rate in persons suffering from rheumatoid arthritis (RA) compared with the general population.

Methods All-cause mortality was analysed using Cox regression modelling in patients with RA (n=348) and controls (n=60 938) who took part in the second (1995–1997) and third (2006–2008) waves of the longitudinal population-based Trøndelag Health Study in Norway. A mediation analysis was performed to investigate if excess relative risk of mortality in RA was mediated by low estimated CRF (eCRF).

Results During the follow-up until 31 December 2018 (mean 19.3 years), the mortality rate among patients with RA (n=127, 36.5%) was higher than among controls (n=12 942, 21.2%) (p<0.001). Among controls and patients with RA, 51% and 26%, respectively, had eCRF above the median for their age and sex (p<0.001). The final Cox model included RA status and eCRF, adjusted for hypertension, body mass index, smoking, cholesterol, diabetes and creatinine. eCRF below median for sex and age category was associated with increased mortality (p<0.001). The total excess relative risk of mortality in patients with RA was 28% (95% CI 2% to 55%, p=0.035), in which RA itself contributed 5% and the direct and indirect contributions of low eCRF accounted for 23%.

Conclusions Low eCRF was an important mediator of the increased all-cause mortality rate found in RA. Our data indicate that patients with RA should be given advice to perform physical activity that increases CRF, along with optimised treatment with antirheumatic drugs, from the time of diagnosis.

Key messages

What is already known about this subject?

- Low cardiorespiratory fitness (CRF) is independently associated with all-cause mortality in the general population.
- Patients suffering from rheumatoid arthritis (RA) have increased mortality rates compared with the general population.

What does this study add?

- Participants with RA had a 28% excess relative risk of mortality compared with controls in the large population-based Trøndelag Health Study.
- In mediation analysis, RA itself contributed 5% and the direct and indirect contributions of low estimated CRF accounted for 23% of this excess mortality risk.

How might this impact on clinical practice?

- Together with optimal medical treatment, both information and implementation of strategies for improving CRF should be introduced early in the management of RA to reduce the risk of premature mortality.

INTRODUCTION

Rheumatoid arthritis (RA) is a common chronic systematic rheumatic disease affecting joints, tendons, bursae and internal organs including the cardiovascular and respiratory systems.[1] In Norway, RA has a prevalence of 768/100 000 (women 1003/100000, men 513/100 000).[2] The prevalence of RA is quite stable around the world, around 0.5%–1%.[1]

Patients with RA often show more unfortunate cardiovascular risk profiles, with higher frequencies of the metabolic syndrome and smoking compared with the general population.[3 4] In addition, chronic inflammation in RA is regarded as an important contributor to accelerated atherosclerosis leading to increased cardiovascular disease (CVD) that eventually leads to increased rates of premature death in RA.[5–11] There are indications that improved medical treatment with new biological disease modifying antirheumatic drugs (DMARDs) and targeted synthetic DMARDs in addition to use of conventional DMARDs at higher doses and an earlier disease stage led to reduced inflammation,[12–14] which in turn has contributed to reduced mortality in patients with RA in short-term studies.[15 16]

However, robust evidence of improved survival rates in long-term studies in persons with RA is lacking.[17]

There is strong evidence that the cardiorespiratory fitness (CRF) level affects cardiovascular health, and low CRF is a stronger predictor of adverse cardiovascular outcomes than traditional risk factors.[18] CRF is measured as a person's maximum oxygen uptake (VO_{2max}), and is now regarded as a clinical vital sign.[18] Exercise training, particularly at high intensities, leads to improved CRF.[19] CRF is, therefore, an important modifiable risk factor because it may be improved by increasing relevant physical activity (PA).[20]

Studies have shown that patients with RA have reduced CRF compared with the healthy population,[21–23] whereas PA interventions that improve CRF are associated with increased function and reduction of cardiovascular risk in RA.[24 25]

The gold-standard method to measure VO_{2max} is by cardiopulmonary exercise testing (CPET) either on a treadmill or bicycle ergometer.[18] With gradually increasing workload, oxygen expenditure increases until the oxygen ventilation curve flattens as the person reaches physical exhaustion. VO_{2max} is the measured level of oxygen ventilation at this point. CPET is a resource-intensive method. Various mathematical models have therefore been developed to estimate VO_{2max} (eCRF) without the need for a physical test.[18 26–28] One example is the eCRF equation developed by regression analysis with the CPET results from 4260 participants in the third wave of the Trøndelag Health Study (HUNT3) as the dependent variable. The predictors in this model are age, gender, resting heart rate and waist circumference, as well as information about frequency, duration and intensity of PA performed by the participants.[26]

High eCRF can counteract the increased cardiovascular risk factor clustering caused by long sedentary time,[29] and in one study the risk of acute myocardial infarction (MI) in women was inversely associated with the level of eCRF.[30] In addition, several studies have shown that eCRF serves as an independent predictor of mortality in the general population.[28 31 32] A previous study showed that a 3.5 mL/(min x kg) higher eCRF was associated with a 21% lower HR for CVD mortality in both men and women.[31]

Despite the strong association between low CRF and mortality found in the general population, evidence is still lacking for importance of the same association in patients with RA. To our knowledge, no population-based studies have analysed CRF level in relation to excess mortality in an RA population. Focus so far has rather been on medication reducing inflammation to prevent excess mortality in RA, and thereby perhaps overlooking the potential additional importance of low CRF as a mediator of increased mortality rates in RA. The hypothesis of this study was that low CRF contributes to the increased mortality in patients with RA compared with the general population. The aims were to investigate if low eCRF was associated with and acted as a mediator of increased all-cause mortality in patients with RA, using data from a large population-based cohort.

METHODS

Participants

HUNT is a longitudinal population-based health study using an open cohort design. All present inhabitants ≥20 years of age in the northern region of Trøndelag county in Norway are invited to each wave of the study, independent of whether they have previously participated in HUNT. In this study data from the second (HUNT2, 1995–1997, n=65 202, 69.5% of invited) and third (HUNT3, 2006–2008, n=50 787, 54.1% of invited) waves were used.[33] Data from the first wave (HUNT1, 1984–1986) could not be included because there was no question regarding RA. All participants in HUNT provided written informed consent.

Based on information in hospital case files, a previous study identified those with a valid RA diagnosis (n=546) out of all participants in HUNT2 and HUNT3 who self-reported RA.[2] The standardised 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria for RA were used during diagnosis validation.[34] Those with uncertain RA, given an RA diagnosis after HUNT3 and/or having psoriatic arthritis, juvenile inflammatory arthritis, ankylosing spondylitis or other forms of inflammatory arthritis, were excluded. Following exclusion of participants with missing variables for eCRF calculation, 348 patients with RA (235 women and 113 men) and 60 938 controls were included (figure 1).

Variables

The following variables and definitions were used: eCRF (mL/(min x kg)) in controls and patients with RA was calculated as previously described and detailed in online supplemental data 1.[26–28] Body mass index (BMI) was divided into three categories: <18.5, 18.5–24.9, ≥30.0 kg/m^2; hypertension (yes/no): systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mm Hg and/or self-reported use of antihypertensive medication; previous CVD (yes/no): self-reported stroke and/or angina and/or MI; smoking: self-reported never, previous or present smoking; diabetes (yes/no): self-reported diabetes and/or the use of antidiabetic medication and/or having a non-fasting blood-glucose level >11 mmol/L; creatinine (µmol/L); total cholesterol (mmol/L); seropositive RA: presence of rheumatoid factor and/or anticitrullinated peptide antibody; duration of RA: three categories: <3 years, 4–9 years and ≥10 years.

Data from HUNT2 and HUNT3 were linked with the Norwegian Cause of Death Registry,[35] which registers information about all deaths of Norwegian citizens in Norway or abroad.

Patient and public involvement

There was no direct patient and public involvement (PPI) involvement in the design of this study. Two PPI

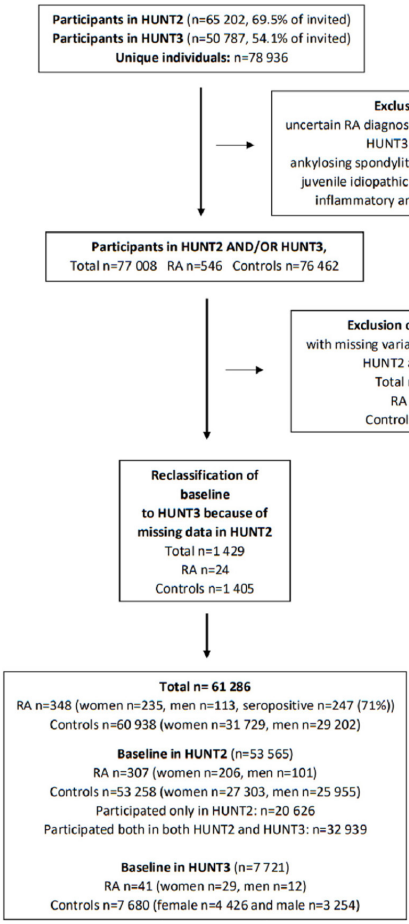


Figure 1 Recruitment to the study. All inhabitants ≥20 years of age are invited to participate. eCRF, estimated cardiorespiratory fitness; HUNT2 and HUNT3, the second and third wave of the longitudinal population-based Trøndelag health study; RA, rheumatoid arthritis.

representatives will help select and design material for dissemination of results to their peers and patient groups.

Statistics

Data are given as counts and percentages or mean with SD. P values <0.05 were regarded significant. Statistical analyses were performed using Stata (V.15.1, StataCorp). Normal distribution of continuous variables was evaluated using histograms.

Because HUNT2 and HUNT3 took place approximately 11 years apart, baseline characteristics of the participants could have changed between them. Baseline comparisons for patients with RA and controls were therefore performed separately for HUNT2 and HUNT3, using χ^2 tests or t-tests.

In brief, the associations of RA and low fitness were analysed using Cox regression. Adjustments for potential confounders were added in steps to better permit evaluation of whether the associations found for RA and low fitness were independent from each other and from the adjustment variables. To investigate the total excess relative risk of mortality in RA and whether it was mediated through low fitness, a Cox regression-based mediation analysis was performed. The details of the analyses are described in the following paragraphs.

All-cause mortality in patients with RA and controls was analysed employing Cox proportional hazard regression modelling in several steps as detailed below. Age was used as the time variable, thereby ensuring that participants were compared with other participants of the same age in all models. This design safeguards against introducing bias due to age differences between patients with RA and controls. The analyses were stratified by sex, and entry was the date for the first participation in HUNT (baseline), that is, either HUNT2 or HUNT3. For those who participated twice, the first observation with complete data for the fully adjusted model (Step 3) was considered the baseline observation; thus those who took part in both HUNT2 and HUNT3 but had missing variables for HUNT2 were included with their baseline defined as HUNT3. For participants in both HUNT2 and HUNT3, relevant variable values were updated in HUNT3. Participants were followed from their baseline until they died, or observation ended on 31 December 2018.

In the main analysis, eCRF was categorised as above or below the median for each participant's sex and age group (<40 years, 40–59 years, ≥60 years, variable denoted eCRF-dichotomous, using eCRF above the median as reference group) (figure 2). This was done because fitness is strongly associated with age and significantly higher in men than women. Using eCRF-dichotomous in the main model had two reasons: The Step 3 Cox model was directly comparable to the model used to test eCRF as a mediator of excess mortality in RA (second study aim), for which using more than two eCRF categories was not possible; and because there is some variability in measured CRF compared with eCRF.

The first analytic step (Step 1) consisted of univariable models for RA status (yes/no) (Step 1a) and

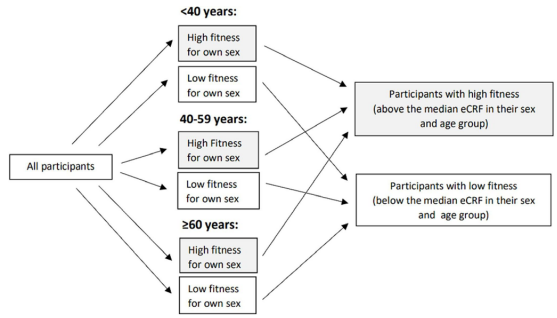


Figure 2 Categorisation of fitness level above or below median eCRF for their sex and age group. eCRF, estimated cardiorespiratory fitness.

Table 1 Baseline characteristics*

	HUNT 2			HUNT 3		
	RA (n=307)	Controls (n=53 258)	RA versus controls, p value	RA (n=41)	Controls (n=7680)	RA versus controls, p value
Female sex, n (%)	206 (67)	27 303 (51)	<0.001	29 (71)	4426 (58)	0.090
Age (years), mean (SD)	56.3 (12.0)	47.6 (16.1)	<0.001	65.0 (14.2)	43.7 (17.3)	<0.001
Systolic blood pressure (mm Hg), mean (SD)	138 (20)	136 (21)	0.23	142 (20)	126 (17)	<0.001
Body mass index (kg/m^2), mean (SD)	26.5 (4.1)	26.2 (4.0)	0.15	29.0 (5.2)	26.6 (4.6)	0.041
eCRF-dichotomous			<0.001			<0.001
Below median, n (%)	223 (72.6)	26 385 (49.5)		34 (82.9)	3660 (47.7)	
Above median, n (%)	84 (27.4)	26 873 (50.5)		7 (17.1)	4020 (52.3)	
eCRF-tertiles			<0.001			<0.001
Lower tertile, n (%)	181 (59.0)	17 488 (32.8)		31 (75.6)	2449 (31.9)	
Middle tertile, n (%)	69 (22.5)	17 851 (33.5)		6 (14.6)	2525 (32.9)	
Higher tertile, n (%)	57 (18.6)	17 919 (33.7)		4 (9.8)	2706 (35.2)	
eCRF-continuous (mL/(min x kg)), mean (SD)	32.4 (9.2)	40.2 (9.0)	<0.001	24.7 (8.7)	38.5 (9.1)	<0.001
Creatinine (µmol/L), mean (SD)	85 (13)	88 (15)	0.004	85 (22)	82 (15)	0.13
Total cholesterol (mmol /L), mean (SD)	6.0 (1.2)	5.8 (1.2)	0.014	5.6 (1.0)	5.2 (1.1)	0.031
Smoking			<0.001			0.42
Never, n (%)	107 (34.9)	23 955 (45.3)		18 (43.9)	4157 (54.1)	
Previous, n (%)	107 (34.9)	12 782 (24.2)		13 (31.7)	1977 (25.7)	
Present, n (%)	93 (30.3)	16 119 (30.5)		10 (24.4)	1546 (20.1)	
Previous cardiovascular disease, n (%)	30 (9.8)	3348 (6.3)	0.010	9 (22)	395 (5.1)	<0.001
Hypertension, n (%)	155 (50.5)	21 244 (39.9)	<0.001	28 (68.3)	2015 (26.2)	<0.001
Diabetes, n (%)	13 (4.2)	1402 (2.6)	0.14	3 (7.3)	280 (3.7)	0.008

Hypertension: systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication. Previous cardiovascular disease: self-reported stroke and/or angina and/or myocardial infarction. Diabetes: self-reported diabetes and/or the use of antidiabetic medication and/or having a non-fasting blood-glucose level>11 mmol/L. eCRF, estimated cardiorespiratory fitness; eCRF-continuous, eCRF as a continuous variable; eCRF-dichotomous, eCRF categorised as above or below the median eCRF for each participant's sex and age group (<40 years, 40–59 years ≥60 years); eCRF-tertiles, eCRF categorised into higher, middle and lower eCRF tertile for each participant's sex and age group.
*There were no missing data in patients with RA. Missingness for controls, HUNT2: hypertension 0.03%, smoking 0.08%, body mass index 0.002%, systolic blood pressure 0.01%; HUNT3: systolic blood pressure 0.9%. Comparisons between patients with RA and controls were performed using the χ^2 test or t-test.
eCRF, estimated cardiorespiratory fitness; HUNT2 and HUNT3, The second and third wave of the longitudinal population-based Trøndelag Health study; RA, rheumatoid arthritis.

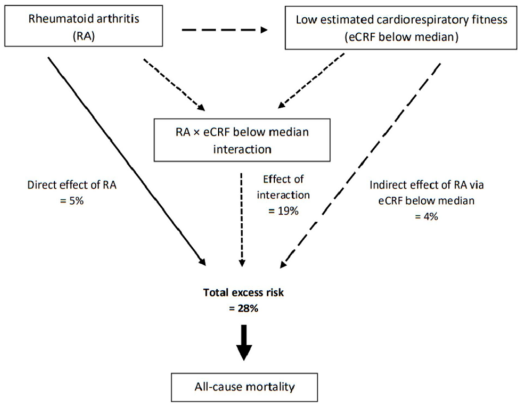
eCRF-dichotomous (Step 1b) for the relevant age group and sex, respectively. Step 2 was a bivariable model including both RA status and eCRF-dichotomous. Step 3 was a multivariable model including RA status, eCRF-dichotomous and the following adjustment variables: hypertension, BMI, smoking status, total cholesterol, diabetes status and serum creatinine. They were chosen based on published associations with mortality.

Because missingness was very low (table 1), the analysis was performed on complete cases. The proportional hazard assumption was evaluated using Stata's phtest based on Schoenfeld residuals. For models with violation of the proportional hazard assumption, a corresponding flexible parametric survival model was fitted. If the HRs (mean with 95% CI) were similar, the Cox models were considered acceptable. Linearity of continuous variables was evaluated using Martingale residuals. Models were compared using the Akaike and Bayesian information criteria (AIC and BIC), where a lower numerical value indicates better fit.

Two sensitivity analyses for the Step 3 (adjusted) model were performed to ascertain whether dichotomisation of eCRF introduced bias. First, categorisation was performed in tertiles for each participant's sex and age group (variable denoted eCRF-tertiles, using the higher eCRF tertile as reference group). Another sensitivity analysis used eCRF as a continuous variable, denoted as eCRF-continuous. A third sensitivity analysis included adjustment for previous CVD in addition to the adjustments used in the Step 3 model.

To investigate whether an increased mortality rate in RA is mediated by low eCRF, we performed a mediation analysis using the Stata package med4way.[36] In this Cox regression-based analysis, the total effect on mortality of

A



B

Type of effect	%, 95% CI and *P*
——→ = Controlled direct effect of RA on mortality when all other variables are adjusted for	5% (-16%, 26%) *P* = 0.63
— — — —▶ = Pure indirect effect of RA via eCRF below median when all other variables are adjusted for	4% (3%, 5%) *P* < 0.001
----------▶ = Portion attributable to interaction between RA and eCRF below median when all other variables are adjusted for	19% (-2%, 41%) *P* = 0.077
▬▬▶ = Total excess risk for all-cause mortality	28% (2%, 55%) *P* = 0.035

Figure 3 Mediation model. (A) The model is based on the Step 3 adjusted Cox regression model and shows how much of the association of RA with all-cause mortality was mediated by low fitness (eCRF below median). (B) Details from results of the mediation analysis. eCRF below median, estimated cardiorespiratory fitness below the sex-specific and age-specific eCRF median using age groups <40 years, 40–59 years or ≥60 years.

having RA is calculated as the total excess relative risk of mortality. This excess risk was then split into three paths and the mediator effect of eCRF was calculated fixing eCRF-dichotomous to low, that is, below the sex-specific and age-specific median. In other words, the mediation analysis sought to answer the following question: How much of the association of RA with all-cause mortality is mediated by low eCFR? The three different paths were the controlled direct effect of RA on all-cause mortality (ie, when all other variables are adjusted for), the pure indirect effect of RA via eCRF below the median, and the portion attributable to interaction between RA and eCRF below the median when all other variables are adjusted for (figure 3). The mediation model used Cox regression based on the Step 3 (adjusted) model above. eCRF was not used as a continuous variable in the mediation analysis because there is no clear definition of what the relevant value of eCRF would be at which to analyse the mediation effect. As a sensitivity analysis, the mediation analysis was also performed after inclusion of previous CVD as an additional adjustment variable.

RESULTS

The baseline characteristics and results from comparisons between patients with RA and controls for participants with baseline in HUNT2 (RA n=307, controls n=53 258) and HUNT3 (RA n=41, controls n=7680) are presented in table 1. BMI was not significantly different between patients with RA and controls for participants with baseline in HUNT2, but the patients with RA with baseline in HUNT3 had significantly higher BMI than controls. Baseline total cholesterol was significantly higher in patients with RA than controls in HUNT2, but not in HUNT3. Higher frequencies of patients with RA were smokers or previous smokers in HUNT2, and had hypertension or previous CVD compared with controls at both baseline time points (table 1).

Out of 348 patients with RA, 247 (71.0%) were seropositive, 93 (26.7%) were seronegative and 8 (2.3%) had unknown serologic status. RA disease duration (<3 years, 4–9 years and ≥10 years) was 27.9%, 49.7% and 19.8%, respectively, and 2.6% lacked information about the duration of RA.

Mean follow-up was 19.3 years (min. 0.2 to max. 23.4 years), during which 13 069 participants died. The all-cause mortality rate was significantly higher among patients with RA (n=127, 36.5%) compared with controls (n=12 942, 21.2%) (p<0.001). Among controls and patients with RA, 51% and 26%, respectively, had baseline eCRF above the median for their age and sex (p<0.001).

Low fitness was strongly associated with mortality in both groups. Of the 127 patients with RA who died, only 4% (n=5) belonged to the high fitness category, in contrast to 8.8% (n=12 942) of the controls (p=0.054). Total time at risk was 1 158 878 person years, that is, 5596 person years for patients with RA and 1 153 281 person-years for controls.

Detailed results from the stepwise Cox regressions and sensitivity analyses are given in table 2.

In the univariable Step 1 Cox analyses, either having RA (p=0.036) (Step 1a) or having eCRF below the median (p<0.001) (Step 1b) were associated with increased mortality. In the bivariable Step 2 model with RA and eCRF-dichotomous, RA status became non-significant (p=0.12) whereas eCRF below the median remained significant (p<0.001). This finding is compatible with the hypothesis that part of the excess mortality risk of RA in the univariable model was in fact explained by the lower eCRF among patients with RA compared with controls. Following adjustment for hypertension, BMI, smoking, total cholesterol, diabetes and creatinine in the Step 3 model, eCRF below the median remained significant (p<0.001) (table 2). The sensitivity analyses showed that results and model fit using eCRF-dichotomous in Step 3 (AIC=213 717.9 and BIC=213 829.7) were comparable to models using eCRF-tertiles (AIC=213 714.4 and BIC=213 835.5) and better than eCRF as a continuous variable (AIC=213 768.0 and BIC=213 879.8). Inclusion of adjustment for previous CVD in the third sensitivity analysis

Table 2 Results from Cox regression analyses for all-cause mortality

	Variable	HR (95% CI)	P value
Step1a	RA (univariable)	Control: reference	
		RA: 1.21 (1.01 to 1.45)	0.036
Step1b	eCRF-dichotomous (univariable)	eCRF above median: reference	
		eCRF below median: 1.19 (1.14 to 1.23)	<0.001
Step 2	RA and eCRF-dichotomous (bivariable)	Control: reference	
		RA: 1.15 (0.96 to 1.37)	0.12
		eCRF above median: reference	
		eCRF below median: 1.19 (1.14 to 1.23)	<0.001
Step 3	RA and eCRF-dichotomous, adjusted for hypertension, BMI, smoking, total cholesterol, diabetes and creatinine	Control: reference	
		RA: 1.10 (0.93 to 1.32)	0.27
		eCRF above median: reference	
		eCRF below median: 1.18 (1.13 to 1.23)	<0.001
Sensitivity analysis 1	RA and eCRF-tertiles, adjusted for hypertension, BMI, smoking, total cholesterol, diabetes and creatinine	Control: reference	
		RA: 1.09 (0.91 to 1.30)	0.34
		eCRF higher tertile: reference	
		eCRF middle tertile: 1.12 (1.07 to 1.17)	<0.001
		eCRF lower tertile: 1.24 (1.18 to 1.31)	<0.001
Sensitivity analysis 2	RA and eCRF-continuous, adjusted for hypertension, BMI, smoking, total cholesterol, diabetes and creatinine	Control: reference	
		RA: 1.10 (0.93 to 1.32)	0.25
		eCRF-continuous: 0.99 (0.989 to 0.997)	0.001
Sensitivity analysis 3	RA and eCRF-dichotomous, adjusted for hypertension, BMI, smoking, total cholesterol, diabetes, creatinine and previous cardiovascular disease	Control: reference	
		RA: 1.08 (0.91 to 1.29)	0.39
		eCRF above median: reference	
		eCRF below median: 1.18 (1.13 to 1.23)	<0.001

Hypertension: systolic blood pressure ≥140 mm Hg and/or diastolic bloodpressure ≥90 mm Hg and/or use of antihypertensive medication. Previous cardiovascular disease: self-reported stroke and/or angina and/or myocardial infarction. Diabetes: self-reported diabetes and/or use of antidiabetic medication and/or having a non-fasting blood-glucose level >11 mmol/L.
BMI, body mass index; eCRF, estimated cardiorespiratory fitness; eCRF-continuous, eCRF a a continuous variable; eCRF-dichotomous, eCRF categorised as above or below the median eCRF for each participant's sex and age group (<40 years, 40-59 years, ≥ 60 years); eCRF-tertiles, cCRF categorised into higher, middle and lower eCRF tertile for each participant's sex and age group; RA, rheumatoid arthritis.

had minimal influence on the Cox regression results (table 2).

Some adjustment variables violated the proportional hazard assumption. However, the coefficients hardly changed when using a flexible parametric survival model instead, so the Cox models were considered acceptable.

Results from the mediation analysis are given in figure 3. The results showed that having an eCRF below the sex-specific and age-specific median if one suffered from RA acted as a mediator for mortality, which explained 23% (4% plus 19%) of the total increased risk of all-cause mortality of 28%. Thus, the effects of low eCRF exceeded the isolated contribution of RA itself of 5% in this setting. In the sensitivity analysis with additional adjustment for previous CVD, the total increased risk of all-cause mortality was 27%, of which 21% were explained by having an eCRF below the sex-specific and age-specific median. Thus, previous CVD had little influence on the results.

DISCUSSION

This study showed that patients with RA had significantly increased long-term all-cause mortality rates compared with controls. When adjusting for other risk factors for mortality, the excess relative risk of 28% was partly associated with the RA disease itself, but the major part, that is, 23%, was mediated by low eCRF combined with the interaction between RA and low eCRF. The contribution of the interaction to the total increased relative risk of mortality was not significant (p=0.077), but this is likely a false-negative result due to low power because very few of the patients with RA who died had eCRF above the median. However, residual confounding due to missing adjustment variables cannot be excluded. Because eCRF is modifiable, results from this study are particularly interesting as increasing PA that leads to improved CRF may translate to reduced mortality rates in patients with RA.

Already at the turn of this century, tests of physical function (ie, walk test and grip strength) in addition to

patient-reported measures reflecting physical function (ie, the modified health assessment questionnaire and the patient global assessment) were described as predictors of mortality, whereas radiographic change, RF positivity and inflammation markers were not.[37–41] In the following years, new treatment strategies like 'Treat to target' with new drugs have been in focus.[12 42] An unintended consequence might be that registration of inflammation levels and radiographic changes may have been performed almost at the expense of other outcomes like CRF and other measures of physical function.

New and better drugs increase quality of life, reduce inflammation and radiographic change, and thereby help patients with RA exercise; however, drugs alone do not increase CRF. There is no doubt that higher CRF is associated with longer survival in the general population,[18 28 31 43] and the present study gives evidence that this also applies to patients with RA. Thus, increasing fitness may be an important tool for reduction of preterm mortality, counteracting the increased age-related decline in eCRF described in RA.[44] In addition to early medical treatment, encouragement and information about suitable PA and exercise training, in particular at high intensity,[24] should therefore be an obligatory part of RA treatment strategies from the time of diagnosis.

An increasing focus on PA is reflected in the latest 2017 EULAR recommendations for PA in arthritis. They state that arthritis patients should follow the same recommendations for PA as the general population and that PA in RA is safe.[45 46] Perhaps because of lacking evidence, The EULAR recommendations for prevention of CVD recommend PA because it might reduce inflammation and prevent CVD, but CRF and related terms are not mentioned.[47] The present finding that low eCRF clearly acts as a mediator of excess mortality in RA contributes to the evidence supporting improvement of CRF as an important tool for preventive care also in patients with RA.

Some studies have indicated that the mortality gap between patients with RA and the general population is narrowing.[15 16] However, comparison of RA populations diagnosed in different time periods using different criteria and various follow-up strategies may result in a false impression of a narrowing mortality gap.[6] Cigarette smoking is associated with earlier debut of seropositive and more severe RA and is a well-known risk factor for atherosclerosis and increased mortality rates.[4 48] One may ask whether the overall observed reduction of smoking in most industrialised countries has a more positive effect in patients with RA compared with the general population and is possibly contributing to narrowing of the mortality gap. However, low eCRF remained a strong risk factor for mortality in our study after adjustment for smoking and other variables associated with mortality and CVD.

Access to lifestyle-related and other relevant adjustment variables in HUNT, and the long follow-up should be regarded as strengths of our study. The low number of patients with RA may represent a weakness, but the very large population-based control group reduces selection bias and thereby improves the validity of the results.

Another strength of the present study is that RA diagnoses were confirmed from medical records and not based on self-report or diagnostic codes in various registries.[2] Given that many of our study participants were diagnosed with RA several years ago and that their eCRF was not recently updated, it may be argued that the findings are no longer relevant. A previous study from our group found that patients with RA who performed CPET in 2017 were deconditioned compared with the healthy population and use of various conventional and biological DMARDs was not associated with CRF.[21] The results are therefore probably relevant for today's RA population as well, even if there have been large changes in medication and treatment strategies.

Using eCRF instead of the measured CRF from CPET may be regarded as a limitation of this study. However, using CPET may introduce selection bias, as those more used to PA may be more motivated for participation. Using eCRF calculated from other data makes it possible to include a wider range of participants. Furthermore, performing CPET in such a large population-based study would have been practically and economically impossible.

Because HUNT has an open cohort design, participants in our study had different baselines. This permitted inclusion of more participants and thereby provided higher statistical power, as well as the possibility of updating the data for those who participated twice. However, we cannot exclude that studying participants having different baselines could have influenced the results.

In conclusion, this study showed that low CRF was an important mediator of the increased mortality found in patients with RA. In addition to optimal medical treatment, focus on improvement and follow-up of CRF should be an integral part of standard treatment of RA already from the time of diagnosis.

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Competing interests None declared.

Patient consent for publication Not required.

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Data availability statement Data may be obtained from a third party and are not publicly available. Data from HUNT are available on reasonable request from the HUNT Research Centre (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 licence for the current study and are not publicly available in accordance with Norwegian law.

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