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Vigorous Physical Activity in Psoriatic Arthritis

Thesis for the Degree of Philosophiae Doctor

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Knowledge comes, but wisdom lingers.

Alfred Lord Tennyson

Sammendrag

Psoriasis artritt (PsA) er en kronisk inflammatorisk leddsykdom assosiert til psoriasis. Sykdommen karakteriseres av leddbetennelse (artritt), betennelse i ryggsøylen (spondylitt), betennelse i senefester (entesitt), smerte og utmattelse (fatigue). Mange av pasientene er overvektige, noe som gir økt risiko for kardiovaskulær sykdom (CVD). I tillegg tyder forskning på at overvekt utgjør en egen risikofaktor for å utvikle psoriasis og PsA.

Det er forsket lite på trening ved PsA. Noen treningsstudier har inkludert PsA pasienter i grupper med revmatoid artritt og ankyloserende spondylitt, men ikke sett på PsA som en egen gruppe. PsA er forskjellig fra disse tilstander, blant annet ved den hyppige forekomst av entesitt. Det er usikkert om hard trening kan medføre økt sykdomsaktivitet fordi mekanisk stress kan utløse entesitt. Det finnes heller ikke gode retningslinjer for hvilken treningsform som bør anbefales ved psoriasis artritt. Videre er det lite kunnskap om hvordan trening påvirker risikoen for å utvikle PsA.

I denne avhandlingen har vi undersøkt effekten av hard fysisk trening på sykdomsaktivitet, kondisjon og kroppsmasse hos pasienter med etablert PsA. Videre har vi undersøkt om overvekt og fysisk aktivitet kan påvirke risikoen for utvikling av PsA. Avhandlingen er basert på data fra to forskjellige studier.

Artikkel 1 og 2 er basert på en randomisert kontrollert studie med inklusjon av 67 voksne PsA pasienter, som tilfeldig ble fordelt i enten en treningsgruppe eller kontrollgruppe. Treningsgruppen gjennomførte 11 uker med høy intensitets intervall trening (HIIT) på spinningssykkel tre ganger i uken. Deltakerne ble kondisjonstestet (VO_{2max}) og fikk målt sykdomsaktivitet (objektivt og selvopplevd) og kroppsmasse før oppstart med trening, samt etter 3 og 9 måneder. I perioden fra 3-9 måneder fikk hverken trenings- eller kontroll gruppen noen oppfølging eller treningsveiledning, men kontrollgruppen ble oppfordret til å komme i gang med kondisjonstrening.

Resultatene beskrevet i første artikkel viste at deltakernes totale opplevelse av sykdomsaktivitet og smerte ikke endrede seg vesentlig som følge av HIIT etter første studieperiode fra baseline til 3 måneder. Objektive mål for sykdomsaktivitet målt med blodprøve (CRP) og legens vurdering var også uendret. Dette stemmer godt overens med resultater fra tidligere studier, der man har trenet pasienter med artritt. Risikoen for å pådra seg entesitt var heller ikke større i treningsgruppen enn i kontrollgruppen. Imidlertid observerte vi en betydelig reduksjon i graden av fatigue etter HIIT. Aerob trening har også vist reduksjon av fatigue ved andre kroniske sykdomstilstander. Etter 9 måneder var det færre

som trente, og de som drev med trening trente med litt lavere intensitet enn under første studieperiode. Sykdomsaktiviteten var uendret og effekten på fatigue var ikke lengre til stede.

Resultatene fra den andre artikkelen viste etter første studieperiode at HIIT ga en betydelig forbedring av kondisjonsalder (VO_{2max}), noe som også er vist hos friske og blant pasienter med hjertekarlidelser. Samtidig fant vi en reduksjon i mengden av magefett. Etter 9 måneder hadde treningsgruppen fortsatt en betydelig høyere VO_{2max}.

Den andre studien danner grunnlag for artikkel 3, og er basert på data fra Helseundersøkelsen i Nord-Trøndelag (HUNT), en omfattende populasjonsstudie som inkluderer spørreskjema, klinisk undersøkelse og blodprøver. Vi utførte en longitudinell populasjonsstudie med utgangspunkt i HUNT2 (1995-97) og oppfølging i HUNT3 (2006-08). Vi innhentede baseline data om body mass index (BMI), livvidde og grad av fysisk aktivitet fra HUNT2. Deretter registrerte vi nye tilfeller av PsA, som oppsto i perioden mellom HUNT2 og HUNT3.

Resultatene viste at overvekt, og spesielt økt magefett, økte risikoen for utvikling av PsA. Samtidig indikerer resultatene at de som utførte hard fysisk aktivitet hadde en litt mindre risiko for utvikling av PsA uavhengig av BMI. Det var imidlertid ikke tegn til at hard fysisk aktivitet kunne redusere den økte risikoen for PsA hos de som allerede var overvektige.

Konklusjonen på denne avhandlingen er at trening med høy intensitet ikke medførte økt sykdomsaktivitet ved PsA. I tillegg økte kondisjonen og magefettet ble redusert, noe som kan redusere risiko for hjertesykdom. Det er derfor viktig at pasientene gis informasjon om nytten av hard fysisk trening. Videre er det viktig med forebygging av overvekt for å redusere risikoen for utvikling av PsA.

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Ruth Stoklund Thomsen

Acronyms and Abbreviations

ACPA	Anti-citrullinated peptide antigen
AS	Ankylosing Spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
axSpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BMI	Body mass index
BSA	Body surface area
cAMP	Cyclic adenosine monophosphate
CASPAR	ClASsification of Psoriatic ARthritis
CERG	Cardiac Exercise Research Group
CI	Confidence interval
CRP	C-reactive protein
CTLA-4	Cytotoxic T-Lymphocyte Associated Protein 4
CVD	Cardiovascular disease
DAPSA	Disease Activity index for Psoriatic Arthritis
DAS28	Disease activity score of 28 joints
DAS44	Disease activity score of 44 joints
DM	Diabetes mellitus
DMARDs	Disease-modifying anti-rheumatic drugs
DXA	Dual energy X-ray Absorptiometry
EULAR	European League Against Rheumatism
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ	Health assessment questionnaire
HIIT	High intensity interval training
HLA	Human leukocyte antigen
HR_{max}	Maximum heartrate
HRQoL	Health Related Quality of Life
HS-CRP	High sensitivity CRP
HUNT	Helseundersøkelsen i Nord-Trøndelag/The Nord-Trøndelag Health Study
IBD	Inflammatory bowel disease
IL	Interleukin
ITT	Intention to treat

JAK	Janus kinase
LEI	Leeds Enthesitis Index
MDA	Minimal disease activity
MET	Metabolic equivalent
MHC	Major histocompatibility complex
MICT	Moderate intensity continuous training
MRI	Magnetic Resonance Imaging
NSAID	Non-steroidal anti-inflammatory drugs
NTNU	Norwegian University of Science and Technology
OMERACT	Outcome Measures in Rheumatology Act
OR	Odds ratio
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area Severity Index
PGA	Patient global assessment
PROs	Patient reported outcomes
PsA	Psoriatic Arthritis
PsAID	Psoriatic Arthritis Impact of Disease
RA	Rheumatoid Arthritis
RCT	Randomized controlled trial
RER	Respiratory-exchange-ratio
RERI	Relative excess risk due to interaction
RR	Relative risk
SCORE	Systematic Coronary Risk Evaluation
SD	Standard deviation
SLE	Systemic lupus erythematosus
SpA	Spondyloarthropathy
SPARCC	Spondyloarthritis Research Consortium of Canada
TICOPA	Tight Control of inflammation in early Psoriatic Arthritis
TNF	Tumor necrosis factor
UK	United Kingdom
VAS	Visual analog scale
VO_{2max}	Maximal oxygen uptake
WHO	World Health Organization

List of Publications

The present PhD thesis is based on the following papers referred to as Paper I, Paper II and Paper III in the text.

Paper I

The impact of high intensity interval training on disease activity and patient disease perception in patients with psoriatic arthritis: a randomized controlled trial.
Thomsen, Ruth Stoklund; Nilsen, Tom Ivar Lund; Haugeberg, Glenn; Bye, Anja; Kavanaugh, Arthur; Hoff, Mari
Arthritis care & research. (2018)

Paper II

Effect of high-intensity interval training on cardiovascular disease risk factors and body composition in psoriatic arthritis: A randomised controlled trial.
Thomsen, Ruth Stoklund; Nilsen, Tom Ivar Lund; Haugeberg, Glenn; Bye, Anja; Kavanaugh, Arthur; Hoff, Mari
RMD Open (2018)

Paper III

Adiposity and physical activity as risk factors for developing psoriatic arthritis. Longitudinal data from the HUNT study.
Thomsen, Ruth Stoklund; Nilsen, Tom Ivar Lund; Haugeberg, Glenn; Gulati, Agnete Malm; Kavanaugh, Arthur; Hoff, Mari
Submitted, 2019

Summary

Psoriatic arthritis (PsA) is an inflammatory joint disease associated with psoriasis. The clinical presentation may be characterized by arthritis, spondylitis, enthesitis, pain and fatigue. Many patients are overweight, which increases the risk of cardiovascular disease (CVD). In addition, there is evidence that overweight increases the risk of developing psoriasis and PsA.

There is little evidence for the utility of physical exercise in PsA. Some studies of physical exercise included PsA patients in groups with mainly rheumatoid arthritis and ankylosing spondylitis patients. However, PsA was not evaluated as an own entity. PsA differs from these other inflammatory arthritides, e.g. by the increased freqeuncy of enthesitis. It is uncertain whether vigoruos exercise can increase disease activity since mechanical stress may induce enthesitis. Further, physical exercise is recommended in PsA, although the modality of physical activity is not specified. It is unknown whether physical activity can affect the ultimate development of PsA in susceptible individuals.

This thesis is focused on evaluating the effect of vigorous physical exercise on disease activity, cardiorespiratory fitness and body composition in established PsA. Further, we investigated wether obesity and physical activity could influence the risk of developing PsA. The thesis is based on data from two studies.

Paper I and II are based on a randomized controlled trial where 67 adult PsA patients were included and by random allocated to either an exercise group or a control group. The exercise group performed high intensity interval training (HIIT) on a spinning bicycle three times a week for 11 weeks. At baseline, and at three and nine months, the participants went through a cardiorespiratory fitness test, were evaluated for disease activity (objectively and self-perceived), and measured body mass. In the period from three to nine months none of the groups had any follow-up or supervised exercises. However, the control group was encouraged to start exercising.

In the first paper we reported that the patient's perception of disease activity and pain did not change due to HIIT measured after the first study period from baseline to three months. Objective measures of disease activity, such as the CRP and the physician's evaluation were also unchanged. The observations are in line with results from previous studies, where patients with arthritis performed physical exercise. The risk of increased enthesitis activity was not higher in the exercise group compared with the control group. However, we observed a considerable improvement in fatigue score after HIIT. There is also

evidence of a beneficial effect of aerobic exercise on fatigue in other chronic diseases. After nine months, less of the participants performed vigorous exercise and the exercises were performed with lower intensities compared to the first study period. The disease activity was unchanged and the effect on fatigue was no longer present.

The results from the second paper illustrated a considerable improvement of the cardiorespiratory fitness (VO_{2max}) after HIIT. A similar effect is also shown among healthy individuals and patients with CVD. In addition, we observed a reduction of the abdominal fat. After nine months, the effect on VO_{2max} was still present in the exercise group.

The third paper is based on data from the Nord-Trøndelag Health Study (HUNT), which is a large population-based health study and includes questionnaires, clinical examinations and blood samples. We performed a longitudinal observational study with baseline in HUNT2 (1995-97) and follow-up in HUNT3 (2006-08). Data on body mass index (BMI), waist circumference and level of physical activity was obtained from HUNT2. Then we registered new cases of PsA that had developed between HUNT2 and HUNT3.

We found that adiposity, and in particular central obesity, was associated with an increased risk of PsA. Further, the results indicated, that vigorous physical activity was associated with a somewhat lower risk of developing PsA, regardless of BMI. However, there was no modifying effect of vigorous physical activity on the risk of PsA among those with adiposity.

The conclusions from this thesis are that HIIT did not result in increased disease activity, the cardiorespiratory fitness improved, and the abdominal fat was reduced. Thus, in order to reduce the risk of CVD in PsA patients, it is important to inform them about the beneficial effects of vigorous physical exercise. Further, our observations highlight the importance of preventive work against obesity as well as encouraging physical activity in order to reduce the incidence of PsA.

1 Background

1.1 Epidemiology and classification of psoriatic arthritis

Psoriatic arthritis (PsA) is an inflammatory chronic joint disease associated with skin psoriasis, and the estimated occurrence in patients with psoriasis is 15-30 %.[1] It typically follows the onset of psoriasis by approximately 8-10 years[2] and affects both genders equally.[3] There is a geographic variance with prevalence's of PsA ranging from <0.01 to 0.67 % in different countries.[4 5] The highest prevalence is reported from Norway.[6] Over the last two decades it has become evident that PsA is a challenging condition, both diagnostically and therapeutically.[7]

In 1973, Moll and Wright published the first set of criteria to distinguish PsA from rheumatoid arthritis (RA) and defined it as "an inflammatory arthritis in the presence of psoriasis with a usual absence of rheumatoid factor".[8] Their work facilitated the development of other classification criteria that impart a better understanding of the nature of the disease. PsA is now considered as a disease entity in the spondyloarthropathy (SpA) group of diseases, which also include e.g. ankylosing spondylitis (AS), reactive arthritis, and arthritis associated with inflammatory bowel disease (IBD). These conditions share similar clinical characteristics and are associated with human leukocyte antigen (HLA) B27.[9] In 2006, the ClASsification of Psoriatic ARthritis (CASPAR) criteria (Table 1) were published taking into account the varied presentation of the disease.[10] CASPAR was designed for use in epidemiological research, but is widely applied also in ordinary clinical care.[11] CASPAR has a high specificity and sensitivity for PsA and has been found to be as high as 99.1 % and 87.4 %, respectively.[9 12]

Table 1 CASPAR criteria[10]

Application: Inflammatory articular disease (joint, axial or enthesitis) and ≥ 3 points:	**Score**
Skin psoriasis	
Present	2
Previous history – if patient unaffected	1
Family history – if patient unaffected	1
Nail lesions	1
Dactylitis or history of dactylitis	1
Rheumatoid factor negative	1
Juxta-articular new bone formation on radiograph	1

PsA is heterogeneous in its clinical presentation with possible manifestations including arthritis, nail disease with pitting, enthesitis, dactylitis and spondylitis (Figure 1).[13] A hallmark of PsA is the enthesitis that can occur in approximately 30-50 % of the cases.[14] Other distinctive features of PsA are dactylitis,[15] and the negative serology for rheumatoid factor and anti-citrullinated peptide antigen (ACPA) serology; the latter is lacking in 95 % of cases.[9] A diversity of radiographic features can be present such as erosions, periosteal new bone formation, enthesophytes, osteolysis and ankyloses.[9 16] Specific radiographic changes in PsA are the erosions in combination with new bone formation.[9] However, up to 50 % of the patients never develop erosions within the first ten years after disease onset.[17 18] In addition, extraarticular manifestations such as uveitis and IBD are associated with PsA.[13 19]

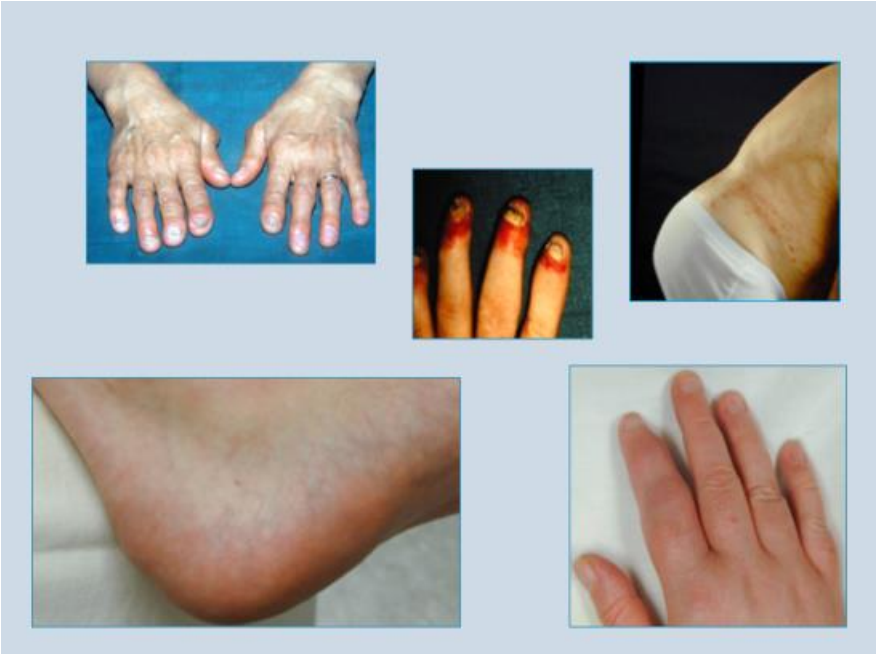

Figure 1 Clinical manifestations of psoriatic arthritis: poly/oligo arthritis, nail disease, spondylitis, enthesitis and dactylitis.
Printed with permission from Dr. Dafna Gladman and Group for Research and Assessment of Psoriatic Arthritis (GRAPPA)

The prognosis of PsA differ due to the heterogeneous character of the disease, and both disease activity and phenotype can change during the course of the disease.[20] Factors associated with an adverse prognosis are polyarticular disease, female sex and raised inflammatory markers.[9] Thus, it is a chronic condition, in which irreversible joint damage can occur within the first two years of disease onset.[21] However, early and intensive treatment can improve the outcome of the disease.[22] Hence, it is important to distinguish between the

diagnosis of PsA and RA or osteoarthritis, as the correct diagnosis of PsA determines the treatment options and prognosis of the disease.

1.2 Pathogenesis

The pathogenic mechanisms in PsA are related to both genetics, environmental risk factors and immunology.

1.2.1 Genetics

There is evidence of a hereditable component in PsA with a recurrence ratio of PsA among first-degree relatives that is higher than in psoriasis.[9 23] Approximately 50 % of PsA patients have a family history, suspecting a strong genetic role in causality.[16] Also the hereditability is greater than for other rheumatic diseases such as RA and Sjøgrens disease.[24]

Several genetic factors are implicated in PsA susceptibility with strong associations to HLA alleles and haplotypes such as HLA-B27, HLA-B08, HLA-B38, HLA-B39 and HLA-C06. Genetically, PsA is more heterogenous than psoriasis. There is also evidence that genotype to some degree can predict the phenotype: HLA-B27 is associated with axial disease and enthesitis, HLA-B08 is associated with synovial affection, and dactylitis is associated with both.[18] In addition, it seems like genotype defines the time span from the first skin lesions to development of PsA. HLA-B27 and HLA-B39 subsets of PsA cases develop much closer to the appearance of psoriasis than HLA-C06 subset of cases. One third of the HLA-B27 subset of PsA cases develop before skin disease, i.e. PsA *sine* psoriasis.[16] The explanation behind the genotype association with phenotype could be that different HLA molecules bind different peptides and thus exhibit distinct autoimmune responses that imply development of different phenotypes.[16] This knowledge is important when tailoring the choice of medical treatment at an individual level.

1.2.2 Environmental risk factors

Environmental factors, including infections,[25 26] obesity,[27-30] smoking,[31-34] trauma,[35 36] and stress have been implicated in the triggering of PsA in genetically susceptible individuals.[35]

In PsA patients, an increased prevalence of streptococcal antibodies have been observed, indicating that infection plays a pathogenetic role due to gene-environment interaction.[26] A viral etiology has also been hypothesized, however, study results are conflicting.[25]

Obesity has in several studies been identified as a risk factor for developing PsA.[27-30] Evidence has demonstrated that adipose tissue act as an endocrine organ producing inflammatory mediators like several different adipokines and pro-inflammatory cytokines, which influence the pathophysiology of inflammation in psoriatic diseases.[37] Adipocytes and recruited macrophages produce cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-6 and adipokines such as adiponectin, leptin, and resistin, which are thought to be associated with obesity, insulin resistance, and related inflammatory disorders.[38] Adiponectin is primarily anti-inflammatory, and leptin and resistin are pro-inflammatory.[39] TNF is involved with the pathophysiology of PsA[27] and leptin with psoriasis.[40] Thus, the emerging idea is that obesity can be considered as a low-grade chronic systemic inflammatory disease.[27] Further, several studies indicate that high body mass index (BMI) is a cause of PsA rather than a consequence[27 41 42] and that obesity already at young age seems to increase the risk.[40] In addition, BMI is higher in patients with PsA, compared to patients with psoriasis and RA, and the general population.[43 44] A recent study indicate that by weight reduction the risk of incident PsA can be modified among patients with psoriasis.[45]

Trauma is a known risk factor for the development of psoriatic skin lesions, a mechanism known as the Koebner phenomenon.[46] There is evidence that this phenomenon also plays a role in the development of PsA. A longitudinal study reported evidence of local trauma before the development of PsA in 25 % of patients.[35] More recently, a study described that preceding bone or joint trauma was associated with PsA.[36]

Smoking appears to increase the risk of developing PsA in healthy controls,[32] but not in patients with psoriasis.[33] Smoking has been suggested to be protective in psoriasis,[32] named the smoking paradox. However, the conflicting results may relate to different study designs and timing of smoking measurement.[34 45]

1.2.3 Immunology

There are several hypotheses explaining the pathogenic mechanisms in PsA. The first hypothesis suggests an autoimmune process related to class I major histocompatibility complex (MHC) genes, with an inflammatory cascade triggered by CD8-T cells binding to self-peptides through MHC class 1 molecules. CD8-T cells are predominating in synovial tissue in PsA compared with CD4-T cells in RA.[9 16] In diseases with CD4-T cell depletion, such as HIV, both psoriasis and PsA occur more frequently and severely, suggesting that persisting memory-effector CD8-T cells drive the disease.[16]

Further, there is increased expression of pro-inflammatory cytokines, including TNF, IL-1 and IL-6,[35] which stimulates further proliferation of inflammatory cells, such as IL-23, as well as the maturation and activation of osteoclast progenitors in peripheral blood of PsA. The latter is causing cartilage loss and bone lesions observed in PsA.[9] IL-23 target the T-helper-17 (Th17) cells to differentiation. Th17 cells are effector cells in inflammation and tissue damage and play an important role in the pathophysiology of psoriatic disease.[47] Increased levels of Th17 cells are found in blood and synovial fluid of patients with PsA. In addition, Th17 cells are the major contributor of IL-17A that plays a key role in psoriatic diseases.[48]

The second hypothesis relates to the auto-inflammatory theory, that the enthesis is the primary site of inflammation in SpA including PsA.[14 49] Entheseal tissue releases pro-inflammatory cytokines, and both CD68 macrophages and CD8-T-cell infiltration have been observed at sites of entheseal inflammation. The enthesis is continuous with the joint structure and merges into the nail bed. Microtrauma and biomechanical stress at entheseal sites in genetically susceptible individuals leads to inflammation, which could spread secondarily to structures such as the synovium or the nail.[9 16 50]

The third hypothesis involves the microbiome and its association with inflammatory diseases. PsA patients have lower levels of certain gut microbes (*Akkermansia* and *Ruminococco*) compared with psoriasis patients and normal controls, which is similar to lack of gut microbe diversity in IBD.[51] Altered intestinal microbe diversity may alter immune system leading to inflammatory diseases.[9]

Knowledge about genetic risk factors and environmental stimuli that can trigger the onset of PsA is important to make an attempt to modify the risk of incident PsA.[30]

1.3 Treatment

Due to the large variation in clinical phenotypes, treatment of PsA is challenging. When treatment strategies are chosen, it is necessary to consider different manifestations such as enthesitis, dactylitis and spondylitis as well as extraarticular manifestations such as IBD and uveitis. The diversities of phenotypes represent different immunological pathways. Treat-to-target is a treatment strategy that primarily has proven to be useful in RA. However, it has been demonstrated, by the TICOPA study, to be a useful tool in PsA as well.[22] Nevertheless, the medical treatment options are fewer in PsA than RA.[9] New treatment recommendations for PsA were updated in 2015 by both the European League Against Rheumatism (EULAR)[52] and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).[53]

In patients with mild oligoarticular disease, non-steroidal anti-inflammatory drugs (NSAIDs) is a temporary treatment option.[9] Glucocorticoids are useful as local injections in specific swollen joints and in enthesitis.[9] Systemic glucocorticoids such as per oral treatment and intramuscular injections are useful in PsA flares due to their rapid anti-inflammatory effect.[13] However, there is a concern about flaring of skin psoriasis associated with tapering or withdrawal of systemic glucocorticoids.[54 55] Nevertheless, this flare is mainly related to use of high doses of systemic glucocorticoids.[22]

1.3.1 Conventional synthetic disease-modifying anti-rheumatic drugs

Conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs) include methotrexate, leflunomide and sulphasalazine.[21 22]

Methotrexate is widely used although study results on effect have been conflicting.[56-58] Nevertheless, a dose-response effect seems to be present,[7 22] although an effect on radiologic damage has not been proven.[59 60] The immunopathophysiologic effects of methotrexate are not fully understood.[61] Leflunomide has some beneficial effect on both peripheral arthritis and skin lesions.[21 62] A small beneficial effect has been suggested for peripheral synovitis using sulphasalazine.[21] There is no evidence of an effect of csDMARDs on other domains of PsA such as enthesitis and spondylitis, although leflunomide may improve dactylitis.[63]

1.3.2 Biological disease-modifying anti-rheumatic drugs

Biological (b) DMARDs encompass e.g. the TNF inhibitors, IL inhibitors (e.g. IL-17, IL12/23) and abatacept.

If a treatment failure on csDMARDs is evident, TNF inhibitors or IL inhibitors are indicated.[9] Studies on TNF inhibitors (e.g. etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol) have proven consistent efficacy in short-term and long-term treatment of patients with active PsA, and TNF inhibitors are currently approved for the treatment of moderate to severe PsA.[64-68] TNF inhibitors are effective on all modalities of the disease, including radiographic progression.[13 52 53] Drug survival in TNF inhibitors due to immunogenicity is a concern. However, there is some evidence of less immunogenicity observed as improved drug survival if TNF inhibitors are combined with methotrexate, mainly regarding infliximab.[53 69] Combining TNF inhibitors with methotrexate is shown to intensify efficacy in RA.[70] However, in a recent randomized controlled trial (RCT), etanercept was combined with methotrexate and compared to etanercept as monotherapy in PsA patients,

and the combination therapy was not superior to monotherapy assessed by different disease activity measures.[60]

Ustekinumab is a monoclonal antibody that inhibits IL-12 and -23. It is efficacious for the treatment of peripheral arthritis, including enthesitis and dactylitis in PsA.[71 72] Secukinumab and ixekizumab are both monoclonal antibodies targeting IL-17A. These antibodies are efficacious for treating both musculoskeletal manifestations (arthritis, enthesitis, dactylitis and spondylitis), skin and nail manifestations in PsA.[73-77]

Abatacept works by inhibiting CTLA-4, which in turn causes down regulation of T cells.[56] Some studies reported a modest improvement in PsA patients treated with abatacept compared with placebo.[78]

1.3.3 Targeted synthetic disease-modifying anti-rheumatic drugs

The targeted synthetic (ts) DMARDs include phosphodiesterase inhibitors and Janus kinase (JAK) inhibitors.

Apremilast is an oral agent, which acts as an inhibitor of the enzyme phosphodiesterase 4, that in turn leads to elevated levels of cyclic adenosine monophosphate (cAMP). This results in down regulation of pro-inflammatory cytokines.[56] Trials have demonstrated that apremilast is effective in PsA compared with placebo.[56] However, the effect on joint and skin symptoms are not within the range of the responses achieved by inhibitors of TNF and IL-17A.[79] Tofacitinib is an oral JAK inhibitor that is efficacious in both PsA patients naïve to and with inadequate responses to TNF inhibitors.[80-82]

1.4 Disease activity

Disease activity is monitored to optimize treatment in arthritis. In inflammatory arthritis several measures of disease activity are used both in clinical care and clinical trials including objective measures, patient reported outcomes (PROs), physician's global assessment, and composite scores. Disease activity in PsA has traditionally been assessed according to measures used in the assessment of RA and AS.[83] However, during the last years more specific measures for PsA have been developed as will be described further below. The assessment of disease activity in PsA is challenging due to the heterogeneous nature of the disorder with manifestations such as skin psoriasis, arthritis (mono-, oligo- and polyarticular), enthesitis, dactylitis and spondylitis.[82] In addition, there are several subjective aspects of the disease such as quality of life, functionality and work ability, that is not easily included in the

scores of disease activity. Thus, the total burden of the disease is difficult to assess in one single measure. Some of the most common used measures, including those used in this thesis, will be described in the following. However, specific measures of functionality and work ability are beyond the scope of this thesis and will not be described.

1.4.1 Objective and clinical measures

C-reactive protein (CRP) is a measure of systemic inflammation and is an obligate measurement in arthritis. The inflammatory process of arthritis, enthesitis and dactylitis can be assessed using e.g. MRI and ultrasound, and spondylitis by using MRI.

All measures of peripheral arthritis are traditionally based on the tender and swollen joint counts.[84] Swollen joint count assesses objective signs of active inflammation in affected joints. This is supported by a recent study reporting that synovitis as detected by ultrasound is only associated with swollen joint count and not tender joints.[85] In PsA the 68 tender joint/66 swollen joint count is preferred because it captures the broad specter of joint involvements in the disease.[86]

Assessment of enthesitis activity is challenging. Two clinical indices have been validated for the use in PsA, the Leeds Enthesitis Index (LEI)[87] and the Spondyloarthritis Research Consortium of Canada (SPARCC)-Enthesitis Index. The LEI includes three sites bilaterally (lateral epicondyles, medial condyles of the femur, and Achilles tendons),[84] and the SPARCC-Enthesitis Index of 18 entheseal sites that are examined for the presence or absence of tenderness and provides a score ranging from 0-16.[88 89] However, clinical assessment of pain at entheseal insertions has a poor correlation with ultrasound evidence of enthesitis.[90 91]

1.4.2 Patient reported outcomes (PROs)

Using PROs is a way to integrate patient input which is complementary to physician assessments and laboratory measures. PROs are measures of self- reported health status used to evaluate the patient's perception of symptoms, function and other aspects of their life potentially impacted by disease.[92] Thus, PROs may provide additional valuable information and has become a more accepted outcome measure in clinical trials in order to attend the patient`s perception.[92]

The GRAPPA has recommended three distinct patient global assessments which include separate skin and joint global assessments and a dual skin and joint global assessment, the patient global assessment (PGA).[93] The PGA question is phrased "In all the ways in which

your PSORIASIS and ARTHRITIS, as a whole, affects you, how would you rate the way you felt over the past week?" and responses are recorded on a 100 mm visual analog scale (VAS) with anchors "Excellent" (left) and "Poor" (right). In addition, the PGA is used in several composite scores.

Fatigue is a major problem in PsA, and patients have ranked fatigue as the second most important domain after pain.[94] The term fatigue is defined by the Oxford Dictionaries as "extreme tiredness resulting from mental or physical exertion or illness".[95] Thus, fatigue is not specific to inflammatory diseases and it is a well-known phenomenon in other chronic diseases.[96] In clinical care the Fatigue 100 mm VAS is in common use.[97]

Pain is a prevalent and debilitating symptom in PsA.[94] It is generally measured using a 100 mm VAS with anchors "no pain" (0) to "pain as bad as it could be" (100) with a recall period of seven day. The pain assessment is collected either uniformly or as implemented in composite scores in trials.[97]

The Psoriatic Arthritis Impact of Disease (PsAID) is a measure developed by the EULAR and is composed of domains selected by an international group of patients with PsA.[98] It is intended for use as a patient-reported measure of disease impact on life in general. There are two versions of PsAID, one for use in clinical care (12 domains) and another for use in RCTs (9 domains). It is a relatively new measure and was not developed at the onset of our study.[97]

1.4.3 Composite scores

A variety of composite scores have been developed for PsA to assess the different aspects of disease activity due to the heterogeneity of the disease.[82] The available composite scores incorporate different types of assessment, including clinical, laboratory and PRO endpoints. Different approaches have been discussed and applied regarding the composite scores. The two principal directions are the unidimensional approach that uses composite scores mainly related to joint assessments and PROs, and the multidimensional approach that includes assessment of disease activity related to several domains of the disease (e.g. enthesitis, dactylitis, spondylitis, and skin).[99]

The unidimensional approach is represented e.g. by using scores such as the disease activity score of 28 joints (DAS28) and the Disease Activity index for Psoriatic Arthritis (DAPSA). The most common measure used is the DAS28, which consists of the tender and swollen joint count of 28 joints, the patient global health assessment and the CRP.[100] However, the DAS28 does not capture activity in all joints affected in PsA,[101] especially not

in the oligo-articular state.[86] Consequently, the disease activity of 44 joints (DAS44) are sometimes used as it includes ankles and feet.[102] The DAPSA score, includes a 68/66 joint count summed with a patient global, patient pain score, and CRP level and has recently been validated for use in PsA trials.[103-105] However, it may not be representative in oligoarthritis.[84]

The multidimensional approach is used in scores such as the Psoriatic Arthritis Disease Activity Score (PASDAS) and the Minimal Disease Activity (MDA). The PASDAS is a weighted index that includes seven components identified on principle component analysis (arthritis, enthesitis, dactylitis, CRP, and PROs) and it performs well in clinical trials.[106 107] However, it was not validated for use at the onset of our study. The MDA score was developed specifically to be a target of therapy.[108] The MDA criteria encompass seven different items that are assessed individually. A state of MDA is achieved if five of the seven criteria are fulfilled: tender joint count ≤ 1, swollen joint count ≤ 1, enthesitis count ≤ 1, PASI ≤ 1 or BSA ≤ 3, PGA VAS ≤ 20 mm, patient pain VAS ≤ 15 mm and health assessment questionnaire (HAQ) ≤ 0.5. The MDA criteria have been recommended as a target of therapy in PsA by the international treat-to-target taskforce[99] and the GRAPPA- Outcome Measures in Rheumatology Act (OMERACT) group.[109]

Axial inflammation has been assessed using the score from AS, the AS Disease Activity Score (ASDAS). This score includes several questions from the Bath AS Disease Activity Index (BASDAI) combined with the CRP result. It has been validated for use in axial SpA including patients with axial PsA.[110 111] However, it is likely to be affected by peripheral disease activity as well.[84]

1.4.4 Recent recommended outcome measures in clinical trials with PsA

Choosing a suitable score for a clinical trial is challenging due to the described heterogeneity and the discordance between PROs and healthcare professionals' opinion on health-status.[104] A study has found residual disease activity measured by the MDA despite optimal medication.[112] In a physical activity intervention trial, PGA can be a valuable outcome measure as it may contain information on both disease activity, patient satisfaction and adverse events.

Recently the GRAPPA- OMERACT has developed a core domain set for PsA which highlights the domains relevant to this disease. The ''inner circle'' of the core set is recommended to be measured in all clinical trials (Figure 2).[101] However, it was not an available tool when our study was designed.

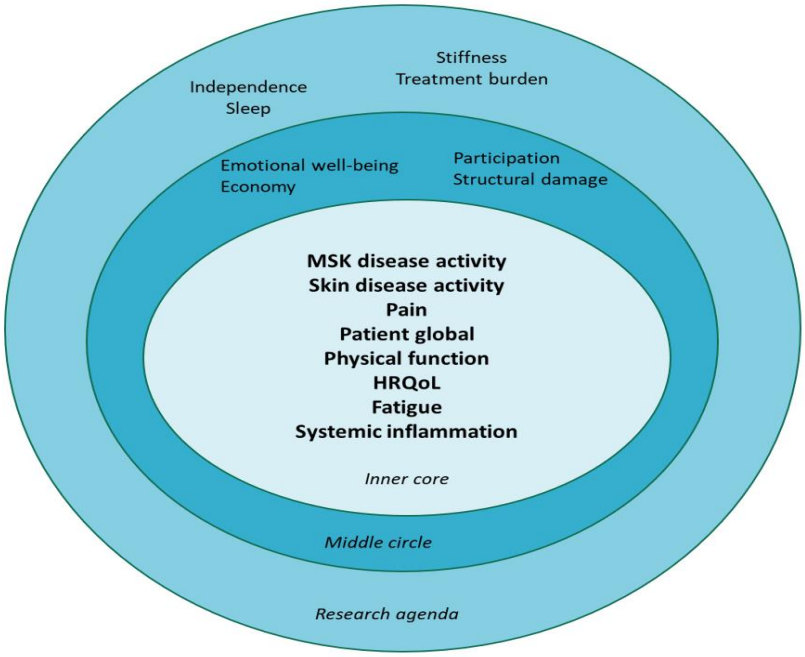

Figure 2 The GRAPPA psoriatic arthritis core domain set. MSK disease activity includes peripheral joints, enthesitis, dactylitis and spine symptoms; skin activity includes skin and nails; patient global is defined as patient-reported disease-related health status. The ‘‘inner circle’’ of the core set is recommended to be measured in all clinical trials. The middle circle includes domains that are important but may not be feasible to assess in all trials and studies. The outer circle or research agenda includes domains that may be important but need further study.[101]

Abbreviations: GRAPPA; Group for Research and Assessment of Psoriasis and Psoriatic Arthritis. MSK; Musculoskeletal: HRQoL; Health Related Quality of Life

1.5 Metabolic syndrome and cardiovascular morbidity in PsA

1.5.1 Metabolic syndrome

The metabolic syndrome is a constellation of risk factors for diabetes mellitus (DM) and cardiovascular diseases (CVD). The criteria of the metabolic syndrome, as defined by the National Cholesterol Education Program Adult Treatment Panel III, consists of 5 risk factors: waist circumference, triglycerides, HDL, blood pressure, and fasting glucose.[113] With the presence of pathological values in 3 of 5 risk factors, the metabolic syndrome is present.[113] Individuals with the metabolic syndrome have a doubled risk of CVD and five-fold risk of DM type II. Worldwide, the prevalence of metabolic syndrome is estimated to 20-25 % in the adult population.[114]

There is a body of evidence suggesting that obesity, dyslipidemia and insulin resistance, which are all part of the metabolic syndrome, are associated with PsA.[7 44 115-118] However, the temporal direction of the association is still uncertain. The prevalence of obesity

and metabolic syndrome in PsA patients is high compared to the general population.[119] One study found that PsA was associated with overweight, smoking and hypertension.[120] Further, the prevalence of DM II is higher in PsA than in RA.[121] Another study has reported a frequency of 44 % with metabolic syndrome in a PsA cohort.[122] In that cohort, the condition was associated with severity of PsA disease. Conversely, several studies indicate that obesity and metabolic syndrome may be a cause rather than a consequence of PsA.[27 29 41 123] Recently, a study, based on genotyping of biobank samples by using the method of mendelian randomization, reported evidence of a causal relationship between BMI and the development of psoriasis.[124]

In particular, obesity[125] may complicate the choice of treatment since the tolerance may be lower and clinical outcomes tend to be poorer.[126-128] In addition, glucocorticoids may increase weight further and increase the risk of DM II.[129] Weight loss can increase the probability of achieving MDA in PsA.[130-132]

Metabolic syndrome and psoriatic diseases have common inflammatory pathways with inflammation mediated by Th-1 and Th-17.[133] Further, the adipokines produced in adipose tissue play important roles in development of CVD[134] and may be a link between psoriatic disease and CVD.[135]

1.5.2 Cardiovascular morbidity

Globally, CVD is considered as the number one cause of death[136] and is a source for reduced quality of life and increased health care expenses.

Inflammatory joint diseases as an entity has been recognized as an independent risk factor for CVD. In the European Society of Cardiology guidelines for CVD prevention, immunological diseases are mentioned as being a high-risk factor for CVD.[137] The Systematic Coronary Risk Evaluation (SCORE) is an algorithm that calculates CVD risk and is validated for use in the general population.[138] However, the SCORE does not contain obesity and inflammation measured by CRP both which contribute to CVD.[116 139] Thus, the risk of CVD according to the SCORE algorithm may be underestimated in inflammatory joint diseases such as PsA.[115]

Low cardiorespiratory fitness as measured by the maximum oxygen uptake is an independent risk factor for CVD.[140-142] As patients with PsA seem to have a more sedentary lifestyle,[143] a possible low cardiorespiratory fitness may add to their burden of CVD risk factors.

PsA has been linked to an increased prevalence of CVD comorbidities[20] and CVD risk factors due to prevalent elements of the metabolic syndrome.[117] Compared to patients with RA and AS, PsA patients have the highest frequency of at least one traditional CVD risk factor (due to hypertension and obesity).[44] Smoking is another risk factor for CVD, and among PsA patients the habit of smoking is more prevalent compared to the background population.[44 115 120]

Two decades ago it was reported that overall mortality was increased and CVD accounted for up to 36 % of the mortality in PsA subjects from a Canadian out-patient clinic.[144] However, despite an increased risk of CVD, a recent study based on a large cohort from UK found that PsA patients neither have a higher overall mortality risk, nor an increased risk for cause-specific mortality, unlike RA patients, who have a higher cardiovascular mortality.[145] Further, a Norwegian observational study found that the increased CVD risk seemed to be present even before an established PsA diagnosis, and it did not translate into a higher 10-year risk of a fatal cardiovascular event.[42 118] This could support the hypothesis that obesity and metabolic disease followed by increased CVD risk and the development of PsA may share pathogenetic pathways.

In summary, risk of CVD in PsA patients may be associated with traditional risk factors, disease activity and low cardiorespiratory fitness. However, it is suggested that the entire CVD risk mainly can be explained by the high prevalence of metabolic abnormalities and that the extent of inflammatory burden has an independent effect on CVD risk.[116] The association between inflammation and vascular abnormalities have been discussed in several studies.[146-148]

1.6 Physical exercise

1.6.1 Definitions

Physical activity is defined as 'any bodily movement produced by skeletal muscles that results in energy expenditure above resting (basal) levels.[149] Physical activity broadly encompasses exercise, sports and physical activities done as part of daily living, occupation, leisure and active transportation'.[149 150] Exercise is a subcategory of physical activity 'that is planned, structured and repetitive and has, as a final or intermediate objective, the improvement or maintenance of one or more dimensions of physical fitness'.[149 150]

Cardiorespiratory fitness is a health-related component of physical fitness defined as the ability of the circulatory, respiratory, and muscular systems to supply oxygen during

sustained physical activity. Cardiorespiratory fitness is usually expressed in metabolic equivalents (METs) or maximal oxygen uptake (VO_{2max}) measured by exercise tests such as treadmill or cycle ergometer.[151] Aerobic exercise is a physical activity that increases the heart rate and improves the body's utilization of oxygen, and it can improve a person's physical fitness, i.e. cardiorespiratory fitness.[152] Examples of aerobic exercises are jogging, rowing, swimming, or cycling, which all can be performed with different intensities from low to high. Especially physical exercise with high intensity is beneficial for cardiorespiratory fitness.[153] By increasing cardiorespiratory fitness, CVD risk factors such as obesity and metabolic syndrome can be modified.[140 154]

The method of high intensity interval training (HIIT), is defined as a way of organizing cardiorespiratory training with repeated bouts of short duration, high-intensity exercise intervals at 80-95 % of maximum heartrate (HR_{max}) interrupted by periods of active recovery (Figure 3).[155] Since the HIIT method is monitored according to the individual HR_{max}, it is possible to perform a standardized training with a group of participants with different levels of baseline cardiorespiratory fitness. HIIT is more effective in improving cardiovascular health compared to moderate intensity continuous training.[153 156]

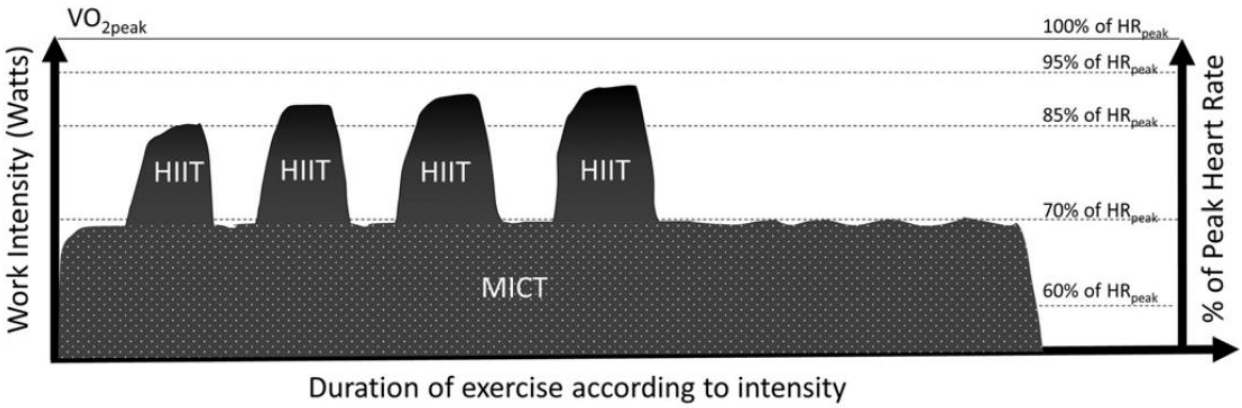

Figure 3 The principle of high intensity interval training, which facilitates the execution of repeated high intensity aerobic work. The work-bouts are interspersed by active pauses of lower intensity exercise that allow for recovery.[155]

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Abbreviations: HIIT = high intensity interval training. MICT = Moderate intensity continuous training. VO_{2peak} = maximal oxygen uptake. HR_{peak} = maximum heartrate.

The World Health Organization (WHO) recommendations on physical activity state that adults should perform ≥150 min/week of moderate intensity aerobic physical activity, or ≥75 min/week of vigorous intensity aerobic physical activity, or an equivalent weekly combination of both.[157]

Generally, physical activity as a treatment modality is gaining attention in patients with chronic diseases, mainly due to the protective benefits in CVD and metabolic diseases[141 142 158-160] but also in a disease such as dementia.[161]

1.6.2 Physical exercise in PsA

Individuals with rheumatic and musculoskeletal diseases in general have a more sedentary lifestyle compared with healthy controls.[162-164] Less activity could be due to fear of flare and joint damage both among patients and health care givers.[165] This fear might be caused by lack of knowledge, which is historically based. Patients with arthritis were two decades ago advised to rest and to avoid exercise involving the affected joints.[166-168] Empirically, before the era of available sufficient medical treatment, physical exercises with high intensity and/or high resistance was associated with a deterioration of arthritis.[167] In addition, a higher disease activity has been associated with lower self-reported physical activity levels in patients with arthritis.[169 170]

Currently, physical exercise is recommended as a supplement to medical therapy for all patients with arthritis, although there has been little evidence for its utility in PsA.[171 172] The last published EULAR recommendations on physical activity for patients with arthritis claim that physical activity should be an integral part of standard care.[173] However, the amount, intensity, and modality of physical activity is not specified. Nevertheless, previous studies concerning patients with arthritis did not reveal increased disease activity or joint destruction as a consequence of physical exercise.[171 174]

Traditionally, PsA patients have been observed in larger cohorts of patients with inflammatory arthritis including RA and AS when evaluating the benefits of physical activity and rehabilitation.[175-177] Thus, recommendations for physical activity, physical therapy and rehabilitation are obtained from recommendations reserved mainly for RA and AS.[171 178]

There are several studies presenting effect measures of different physical activity modalities in patients with arthritis, some of which include PsA (Table 2, Appendix). Within the last four decades, patients with inflammatory joint diseases in the Nordic countries have been admitted to rehabilitation in a warm climate.[179] Efficacy is usually described in terms of improved body functions and activity performance as well as better health-related quality of life. However, most of the studies describing the effect were evaluated to be of low to moderate quality.[179] One study consisting of patients with RA and PsA found an improvement of health related quality of life (HRQoL) after physical therapy at the Igalo Institute and good climate conditions.[175] Supervised group physiotherapy significantly improved Global Health,

function, pain and stiffness compared with individual home-based training in AS. Spa-exercise-therapy had an additional effect on physical therapy regarding pain, physical function and patient global in AS.[180] Dynamic strength training in patients with recent-onset arthritis (RA and PsA) lead to considerable increases in maximal strength of all major muscle groups without detrimental effects on disease activity or joint damage. The functional capacity also improved measured by health assessment questionnaire.[174] Combining behavioral education with physiotherapy-guided training has proven efficacy in reducing pain and improving psychological status and self-management in RA and PsA.[181] A better hand function in RA was a result of occupational therapy and strength exercises.[182 183]

A meta-analysis reported beneficial effects of cardiorespiratory and strength exercises on both inflammation and symptoms in patients with inflammatory rheumatic diseases.[184] However, PsA was not represented in that study. One study has evaluated the effect of resistance exercises in PsA and found an improvement in functional capacity, disease activity, and quality of life. However, the effect was not associated with improvement in muscle strength.[185]

Studying the effect of physical exercise is difficult since objective measures for physical activity often are lacking, especially concerning the amount and intensity of the activity.[169] Historically, an exposure such as physical exercise in observational studies has been monitored based on self-reported questionnaires, which are obviously lacking objectivity and the ability of standardization. In addition, trials using physical exercise as an intervention often include homebased trainings, which lack the ability of measuring intensity of the exercise and the adherence to the assigned training program. However, within the last decade it has become more common to use objective measurement tools such as accelerometers or armbands to monitor the volume and intensity of physical exercise.[169] Thus, the intensity as well as the adherence to an intervention is easier to monitor, and the estimated measures of effect can approach a true effect of the assigned training program.

It seems obvious to argue that physical exercise should be an integral part of the treatment strategy in PsA due to comorbidities such as overweight, CVD and DM type II.[115-117 186 187] In addition, PsA is associated with poor physical function and HRQoL.[188] Overweight in PsA could partially be a consequence of physical inactivity.[189 190] Further, studies have demonstrated that patients with arthritis, including PsA, have a reduced cardiorespiratory fitness, likely due to factors such as a more sedentary lifestyle.[143 191 192]

However, recommending physical exercise as a therapeutic option in PsA could be complicated due to the concern that vigorous physical exercise may cause increased disease

activity by generating more enthesitis.[193 194] This relates to the notion that mechanical strain can drive entheseal inflammation.[195 196]

When motivating patients with arthritis to perform physical exercise or to participate in research evaluating the effect of physical exercise, health care providers and researchers have to consider several social and psychological factors in the patient.[197 198] Individual behaviors determined by antecedents in the patient's life must be taken into account.[199 200] Behavioral theories could be useful for that purpose.[199] Further, sustaining exercise is often a challenge.[201] A team based rehabilitation, with a team comprising professionals with sufficient knowledge about physical exercise, is a possible method of stimulating adherence to the exercise.[191] In addition, patients respond to a continuous motivation to perform physical exercise, and a positive relation with the therapist matters.[201 202]

1.6.3 Physical exercise as prophylactic measure

Evidence has demonstrated that physical activity can modify the detrimental effects of adiposity and metabolic diseases on risk of CVD.[203-207] Aiming for a reduction of body fat and an increase in cardiorespiratory fitness can reduce the risk of CVD. [140] Further, high physical activity level can reduce body fat,[207] and increase cardiorespiratory fitness,[153] and possibly also has an impact on inflammation.[206] Since there may be a link between the development of PsA, adiposity and CVD[42 118 135] it could be hypothesized that high level physical activity also has the ability to modify the risk of PsA. At least, by reducing body fat, high level physical activity may be prophylactic against the development of PsA.[135 207]

Contrary, it is unknown whether physical activity can cause the evolvement of PsA in susceptible individuals, e.g. patients with psoriasis. As described previously, mechanical stress could potentially trigger an inflammatory response, which again might lead to the onset of PsA.[14 195 196]

2 Aims

2.1 General aims

The first aim of this study was to evaluate the impact of high intensity interval training (HIIT) on disease activity and patient disease perception as well as CVD risk factors such as cardiorespiratory fitness and body composition in patients with PsA in a randomized controlled trial (RCT). The second aim of this study was to examine whether physical activity and adiposity, separately and combined, are associated with the risk of developing PsA in an observational study.

2.2 Specific aims

- Does HIIT have an impact on patient disease perception in PsA measured by PGA, fatigue and pain? (Paper I)
- Does HIIT have an impact on disease activity in PsA measured by DAS44 and SPARCC-Enthesitis Index? (Paper I)
- Can HIIT increase cardiorespiratory fitness in PsA? (Paper II)
- Can HIIT reduce total – and truncal fat % in patients with PsA? (Paper II)
- Is the effect of HIIT on disease activity and patient disease perception sustainable beyond the study period? (Paper I)
- Is the effect of HIIT on cardiorespiratory fitness and body composition sustainable beyond the study period? (Paper II)
- Is adiposity measured by BMI associated with the risk of developing PsA? (Paper III)
- Is a high waist circumference associated with the risk of developing PsA? (Paper III)
- Does physical activity have an impact on risk of developing PsA? (Paper III)
- Can high physical activity level modify the possible adverse effect of adiposity on the risk of incident PsA? (Paper III)

3 Participants and methods

3.1 Study design and study population

This thesis is based on a RCT (Paper I and II) and a longitudinal observational study (Paper III).

The RCT was conducted with two parallel groups, comparing an intervention group performing HIIT three times per week for 11 weeks to a control group with no change in pre-study physical exercise habits. Follow up was exhibited at three and nine months. The observational study was based on longitudinal data from the Nord-Trøndelag Health study (HUNT).

3.1.1 The RCT cohort (Paper I and II)

A total of 102 patients were assessed for eligibility of whom 35 were excluded due to exclusion criteria or withdrawal (Figure 4). This left 67 eligible patients for randomization. Inclusion criteria were an established PsA diagnosis fulfilling the CASPAR criteria and age ranging from 18 to 65 years. Exclusion criteria included: patients with inability to exercise; patients with unstable ischemic cardio vascular disease or severe pulmonary disease; an anticipated need for a change in synthetic or biologic DMARDs during the intervention period (However, a change of DMARDs was possible during the follow-up period from three to nine months. A change in corticosteroid doses and intra-articular corticosteroid injections were allowed until four weeks before any follow-up); pregnancy, breastfeeding; and drug or alcohol addictions. In addition, the investigator interviewed the participants about physical exercise habits. Those who reported vigorous endurance training like running, bicycling etc once or more a week for the last three months were excluded. Participants were recruited through local advertisement at the Department of Rheumatology, St. Olavs hospital; The Psoriasis and Eczema Association of Norway; and The Norwegian Rheumatism Association. The study was conducted at St. Olavs hospital and NTNU - Norwegian University of Science and Technology, Trondheim, Norway from 2013 to 2015.

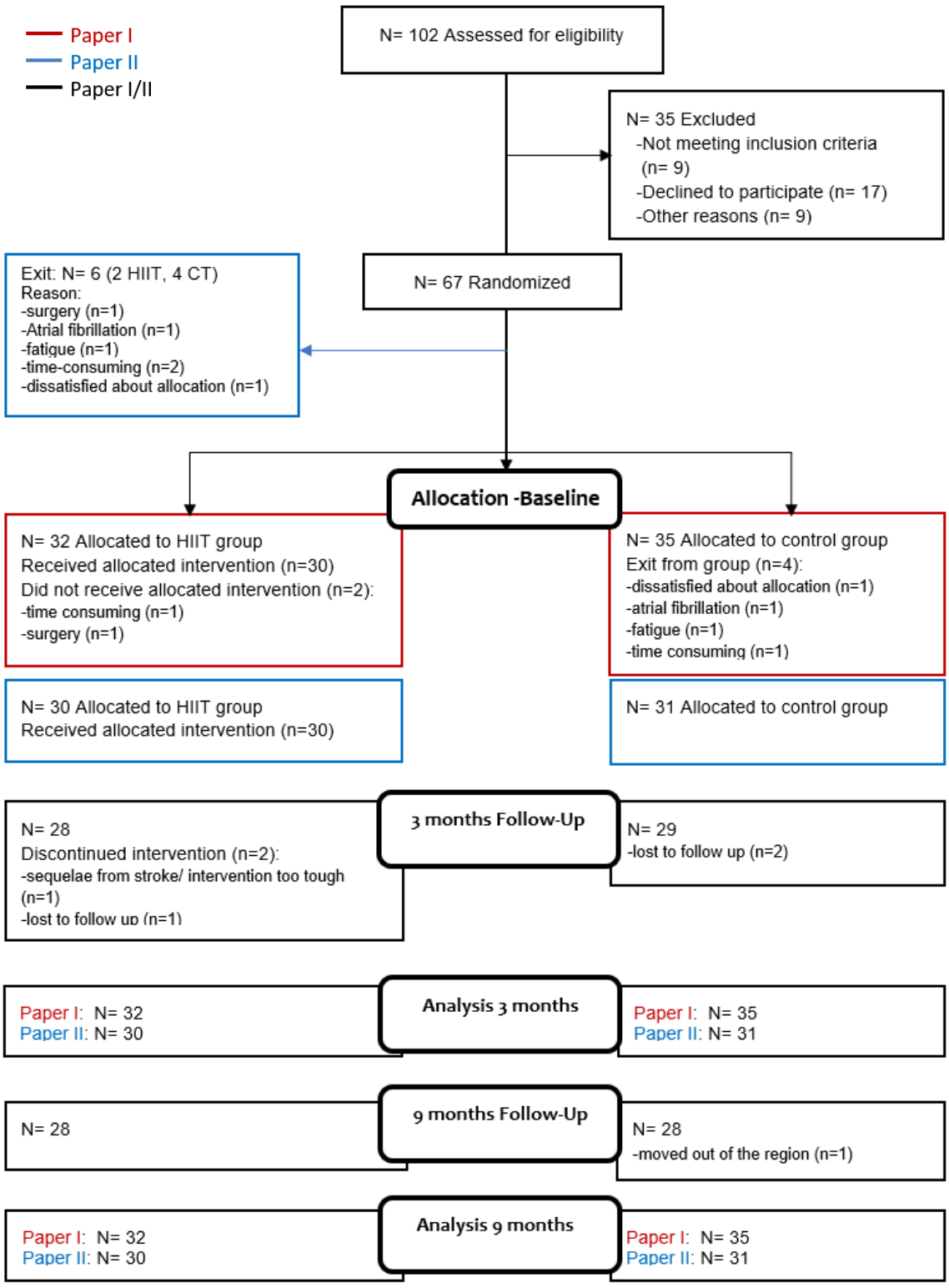

Figure 4 Flowchart Paper I and II
N/n; numbers
HIIT; high intensity interval training
CT; controls

3.1.2 The HUNT cohort (Paper III)

The HUNT study is a large population-based health study conducted within the county of Nord-Trøndelag, Norway and consists of four consecutive surveys; HUNT1 (1986-88), HUNT2 (1995-1997), HUNT3 (2006-2008) and HUNT4 (2017-2019). All individuals 20 years and older were invited to participate. For HUNT2, an invitation letter and first questionnaire were mailed to all adult inhabitants two weeks before the screening date. Those who responded underwent a clinical examination. Out of 93,898 invited individuals in HUNT2, 65,237 (70 %) responded. In HUNT3, 50,806 (54 %) of 93,860 invited individuals participated.[208]

Out of 116,043 participants, 37,070 individuals participated in both HUNT2 and HUNT3 and were selected for this study (Figure 5). Further, all participants in HUNT3 answered questions about psoriasis, RA and AS. Participants who reported psoriasis received more detailed questions about the disease, including PsA. In total, 1238 participants reported that they were suffering from either PsA, RA and psoriasis, or AS and psoriasis. These possible cases of PsA were then validated by a rheumatologist (MH), who evaluated the hospital medical records. This evaluation was conducted in 2012. The positive predictive value for reporting PsA was 68 %. In addition to cases of PsA occurring between baseline (HUNT2) and follow-up in HUNT3, new cases of PsA diagnosed according to the hospital records between the follow-up survey in 2006-08 and 2012 were also included. All PsA diagnoses were classified as such by applying the CASPAR criteria. Additional details of the validation study have been previously presented.[6]

We excluded 151 with missing information on BMI, as well as 200 participants with a BMI <18.5 kg/m^2. The latter group was excluded due to possible comorbidity related to low weight. In addition, 94 participants with onset of PsA before participation in HUNT2 were excluded. This left 36,626 participants available for analyses of BMI; analyses of waist circumference and physical activity included 36,595 and 34,834 persons, due to some missing data on these respective factors.

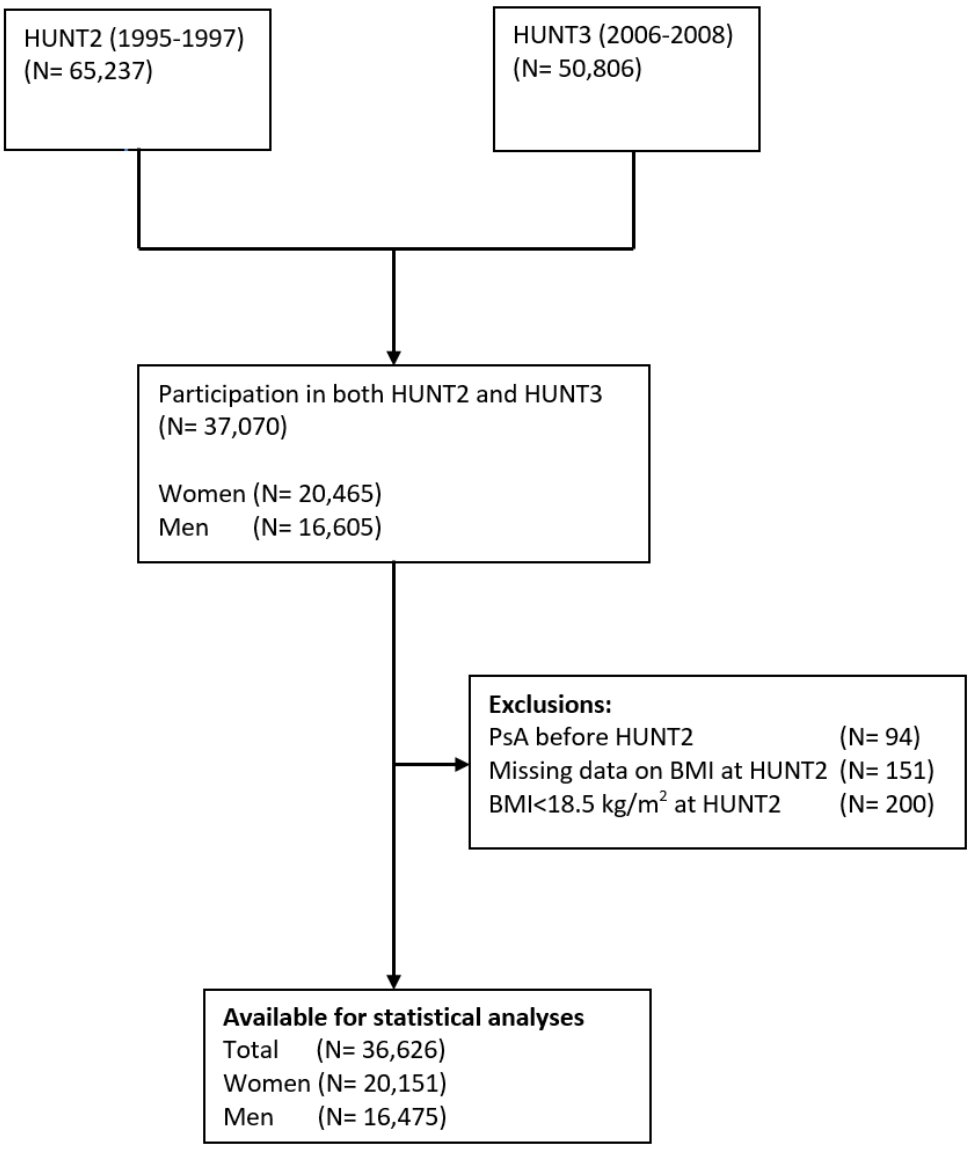

Figure 5 Flowchart Paper III. Selection of study participants.
HUNT; Nord-Trøndelag Health Study
N; numbers
PsA; psoriatic arthritis
BMI; body mass index

3.2 Cardiorespiratory fitness and level of physical activity

Cardiorespiratory fitness measured by VO_{2max} was assessed at baseline in the RCT for all participants (Paper I and II) and was the main outcome after intervention in Paper II. In Paper III, level of physical activity was used as an exposure for the risk of developing PsA.

3.2.1 Cardiorespiratory fitness testing (Paper I and II)

After randomization all the participants did a baseline cardiorespiratory fitness test. VO_{2max} was assessed with a maximal bicycling test on an ergometer bike (Monark 839 Medical) using a portable metabolic measurement system for measurements of gas exchange and ventilation (MetaMax® II).[209] The test was initiated by a warm up and proceeded by an increase in resistance and speed until subjects reached VO_{2max}. Levelling-off of oxygen uptake despite an increase in workload and respiratory-exchange-ratio (RER) >1.10 were used as a criteria for reaching VO_{2max}. The highest heart rate was recorded during the VO_{2max} test and HR_{max} was then calculated by adding five beats to that value.[210] HR_{max} was used to calculate the required individual heart rate during the exercise intervention. All tests were performed at the Cardiac Exercise Research Group (CERG) by professionals with educational backgrounds in physiology and bioengineering, who were certified to do cardiorespiratory fitness testing by the CERG or NeXtMove facilities, NTNU.

3.2.2 Level of physical activity (Paper III)

Leisure-time physical activity in HUNT2 was assessed by the following question: 'How much of your leisure time have you been physically active during the last year? (Think of a weekly average for the year. Your commute to work counts as leisure time)'. The participants were then asked to specify number of hours per week of light (no sweating or heavy breathing) and/or hard (sweating and heavy breathing) physical activity with the response options: 'none', 'less than 1 hour', '1–2 hours' and '3 or more hours' for both light and hard activity.[211] Based on this information, a new variable with four categories was constructed combining information on light and hard activity: inactive (no light or no hard activity), low activity (<3 h light and no hard activity), moderate activity (≥3 h light and/or <1 h hard activity) and high activity (any light and ≥1 h hard activity).[212]

3.3 The RCT Intervention

The exercise intervention was performed as a supervised HIIT program starting with a 10 minutes warm up, followed by four times four minutes exercise at 85-95 % of HR_{max} interspersed by three minutes exercise at 70 % of the HR_{max}..[153] The supervised HIIT was performed on a stationary bicycle at CERG twice a week with an intermitting day of rest. The supervisors were experienced in guiding a HIIT, and one supervisor guided a maximum of six participants at a time. Additionally, the participants did one self-guided HIIT a week. They were instructed in using the HIIT concept by e.g. running, bicycling or walking uphill. All exercises were supported by a heart rate monitor. During the period of follow-up from three to nine months, the participants in the HIIT group were encouraged to keep on exercising, but without guidance.

Participants in the control group were instructed to not change their pre-study physical exercise habits during the study period from baseline to three months. However, in the period from three to nine months they were encouraged to start exercising although they were not given any specific instructions in how to perform HIIT.

At the nine months follow-up the investigator interviewed all participants. If they were reporting vigorous endurance training once or more a week, they were classified as “doing endurance exercise”.

3.4 Assessment of adherence to the RCT

Assessment of adherence to the training program was achieved by asking the HIIT group to deliver diaries every week during the intervention period from baseline to three months. The diaries included information on the type of exercise, time, location, and with whom it was performed. Moreover, the intensity was rated by the registered heart rate and by the 15-point Borg scale (from 6-20), the latter being a method of rating perceived exertion.[213 214] However, during follow-up from three to nine months, they did not fill in diaries or collect data such as heart rates. The control group did not register heart rate or deliver diaries at any time during the study.

3.5 Data collection

In the RCT patients were evaluated at baseline, three and nine months of follow-up. Assessment included questionnaires, clinical examinations and laboratory measurements.

Blood samples were taken fasting in the morning at the Department of Research and Development, St. Olavs hospital. An experienced rheumatologist (RST) performed the clinical examinations including joint and enthesis assessment. Demographics, disease measures, comorbidities and medication were obtained from the medical journal system and the GoTreatIT® Rheuma computer tool,[215] the latter developed for use in daily clinical care and for research purposes (www.diagraphit.com).

In the observational study, data on demographics and exposures such as anthropometric measurements and level of physical activity were obtained from questionnaires and clinical examinations in HUNT2.

3.5.1 Assessment of disease activity (Paper I)

The main outcome was PGA in Paper I. It was an accessible tool used in daily clinical practice at our clinic at study start. PGA has been found to be a reliable tool in the assessment of both joint and skin disease[93] and a PGA ≤20 is defined as low disease activity.[216]

Fatigue and intensity of pain was reported on a 100 mm VAS. Fatigue was based on the question "To what degree has unusual tiredness or exhaustion been a problem for you the last week?" and pain on the question "How much pain did you experience during the last week?" A change in VAS of ≥10 mm is considered as the minimal clinically important difference.[217]

Peripheral joint inflammation was assessed by the DAS44.[102 218] It was chosen to include the joints in the ankles and feet. In addition, the 68/66 joint count was done. Axial inflammation was evaluated by the ASDAS-CRP,[219] and the burden of enthesitis was defined by the SPARCC-Enthesitis Index.[88 89]

3.5.2 Anthropometric measurements (Paper I, II and III)

In Paper I and II, BMI (kg/m^2) was calculated based on measurements of height and weight assessed fasting in the morning at the Department of Research and Development, St. Olavs hospital. Body composition measuring the proportion of fat and lean mass in the whole body was assessed using Dual energy X-ray Absorptiometry (DXA)(GE Healthcare Lunar©) registering total fat (%), truncal fat (%) and lean muscle mass (g) at the Department of Rheumatology, St. Olavs hospital.[220 221]

In Paper III, standardized measures of body height (to the nearest centimeter) and weight (to the nearest half-kilogram) were obtained at the clinical examination at HUNT2.[222]

BMI was calculated as weight divided by the squared value of height (kg/m^2) and then classified into one of three BMI categories according to the cutoff points suggested by the WHO: normal weight (BMI: 18.5–24.9 kg/m^2), overweight (BMI: 25.0–29.9 kg/m^2) or obese (BMI: ≥30.0 kg/m^2).[223] Waist circumference was measured with a steel band to the nearest centimeter at the level of the umbilicus.[222] Based on the distribution of the measures, participants were classified into four categories using the sex-specific quartiles as cut-offs (<74, 74-79, 80-87 and >87 cm in women; <87, 87-90, 91-96 and >96 cm in men). Participants were also classified into two categories of waist circumference according to the sex-specific cutoff points suggested by the WHO: 1=Low (<81cm in women, <95 cm in men) and 2=High (≥81 cm in women, ≥ 95 cm in men).[139]

3.5.3 Assessments associated with CVD risk (Paper II)

Assessment of resting heart rate (HR), blood pressure and blood samples were performed at the Department of Research and Development, St. Olavs hospital. HR, measured as beats/minute, was assessed repeatedly three times, registering the lowest value. Furthermore, systolic and diastolic blood pressures were measured at rest as mmHg and were assessed repeatedly three times. The mean value of the second and third measurements was registered. Lipid status including cholesterol (mmol/L), triglyceride (mmol/L) and LDL (mmol/L) were assessed fasting.

3.6 Sample size calculations for the RCT

In Paper I, a difference in the main outcome measure (PGA) of 10 mm in VAS (0-100 mm) was considered clinically important,[217] and based on a standard deviation of 15 and a correlation of 0.4 between repeated measures[224] we estimated that 30 patients were required in each group to achieve a power of 90 % at an alpha level of 0.05. In Paper II the main outcome measure was ($VO_{2\ max}$) and a difference of 3 ml/kg/min was considered clinically important. Based on a standard deviation of 5[225] and a correlation of 0.4 between repeated measures we estimated that 30 patients were required in each group to achieve a power of 90 at an alpha level of 0.05.

3.7 Randomization and blinding in the RCT

Patients were randomized to either a HIIT group or control group according to a 1:1 allocation in permuted blocks after the signed consent and clinical investigation using a

computer random-number-generator (Unit for Applied Clinical Research, St. Olavs hospital). Participants were stratified according to sex. The block randomization did not allow the investigator to reveal the next allocation. The rheumatologist (i.e., one of the researchers) was blinded to the group allocation at baseline evaluations, but not at three- and nine-months follow-up. The assessors at the laboratory (blood samples), at CERG, at the Department of Research and Development, and the Department of Rheumatology, St. Olavs hospital were blinded for allocation and through all follow-ups.

3.8 Statistical analyses

The statistical analyses were conducted using Stata for Windows (Version 14.2, StataCorp, College Station, TX).

3.8.1 Descriptive statistics (Paper I, II and III)

Descriptive statistics are presented as means and standard deviation (SD) for continuous variables, as numbers and percentages for categorical variables and as median and interquartile range for non-normally distributed variables.

3.8.2 Linear mixed model for repeated measures (Paper I and II)

The main analyses of both primary and secondary outcomes were conducted according to an intention to treat (ITT) strategy using all available data from all time points. We used a linear mixed model for repeated measures to estimate mean difference with 95 % confidence interval (CI) in outcome variables between the HIIT group and the control group at three and nine months after randomization. Changes from baseline to three and nine months were calculated using a joint baseline level of the outcome measure, assuming that any baseline differences between groups are due to chance. From these models, we also estimated mean change in outcome variables within each group. All measures of effect were adjusted for sex (men, women) and age (continuous) to control for possible bias due to baseline imbalances in these factors.

Due to non-normal distribution of HS-CRP we used a logarithmic transformation of the variable in the regression model before transforming back the estimates. The results for HS-CRP are thus expressed as geometric means.

3.8.3 Other statistical analyses in Paper I and II

Logistic regression analysis was performed to calculate the odds ratio (OR) with 95 % CI for worsening in SPARCC-Enthesitis Index between the HIIT group and the control group. The difference in SPARCC-Enthesitis Index between baseline and three months was used to classify patients as having worse or same/improved enthesitis burden.

The diaries were reviewed to find the number of accomplished supervised and self-guided exercises. The mean intensity referring to the Borg scale was calculated according to the values recorded in the diaries.

3.8.4 Cox regression to estimate relative risk (Paper III)

Cox regression was used to calculate hazard ratios as estimates of relative risk (RR) for incident PsA between categories of baseline BMI, waist circumference and physical activity. Further, estimates of RRs associated with continuous measures of BMI and waist circumference, using both the original scale and sex-specific normalized values (z-score), were calculated. Precision of the estimated associations was assessed by a 95 % CI. Potential confounders were selected a priori based on knowledge about factors that could be associated with both the outcome and the exposures. All estimates were adjusted for possible confounding by age (as the time scale in the model), sex (female, male), smoking (current, former, never, unknown (3.9 %)) and education (<10 years (elementary school), 10-12 years (high school), ≥13 years (college/university), and unknown (1.4 %)). Missing data on possible confounders were treated as a separate category. In addition, complete case analyzes were done (data not shown). Linear trend across categories of BMI and waist circumference was assessed by including the categories as an ordinary variable in the regression model. Due to uncertainty about the direction of possible confounding effects between BMI and physical activity, as well as waist circumference and physical activity, these factors were mutually adjusted in a supplementary analysis.

Similarly, the combined effects of BMI and physical activity; waist circumference and physical activity; as well as BMI and waist circumference on risk of PsA were estimated. In the first combined analysis, normal BMI and high physical activity level constituted the reference group. In the second analysis, low waist circumference according to the WHO and high physical activity level constituted the reference groups. In the third analysis, normal BMI and waist circumference below median was the reference group. The within category median value of BMI and/or waist circumference was calculated for all the combined analyzes.

3.8.5 Assessment of effect modification and interaction (Paper III)

Potential effect modification between the variables was assessed both as departure from additive effects calculating the relative excess risk due to interaction (RERI) and as departure from multiplicative effects in a likelihood ratio test of a product term in the regression model. RERI estimates were calculated with 95 % CIs from the following equation: RERI = RR_{11} – RR_{10} – RR_{01} + 1,[226] i.e. RERI > zero indicate a synergistic effect beyond an additive effect.

3.8.6 Other statistical analyses in Paper III

In a sensitivity analysis, participants with a new onset of PsA within the first three years after HUNT2 were excluded. The purpose was to reduce possible reverse causality due to existing undiagnosed disease at baseline.

Assuming that the estimated associations represent causal effects of high BMI and waist circumference on PsA risk, we estimated the population attributable fraction to quantify the proportion of PsA that potentially could be prevented by avoiding overweight and obesity.

Departure from the proportional hazard's assumption was evaluated by tests of Schoenfeld residuals and by graphical inspection in log-log plots.

4 Summary of papers

Paper I

The impact of high intensity interval training on disease activity and patient disease perception in patients with psoriatic arthritis: a randomized controlled trial.

The aim of this study was to evaluate the impact of high intensity interval training (HIIT) on disease activity and patient disease perception in patients with psoriatic arthritis (PsA), and to evaluate if a potential effect could be sustained for a longer period.

We randomly assigned 67 PsA patients (43 women and 24 men) to an intervention group performing HIIT for 11 weeks or a control group who were instructed to not change their physical exercise habits. Outcomes were assessed at three and nine months with the patient global assessment (PGA); fatigue and pain were measured with a 100 mm visual analog scale and the composite disease activity score of 44 joints (DAS44) was calculated. We used linear mixed models to calculate mean difference with 95 % (CI) between the groups according to the intention-to-treat principle.

At three months there was no clear difference in PGA (-0.49; 95 % CI -10.91 to 9.94), DAS44 (-0.08; 95 % CI -0.36 to 0.20) or pain intensity (5.45; 95 % CI -4.36 to 15.26) between the groups. However, the HIIT group reported less fatigue (-12.83; 95 % CI -25.88 to 0.23) than the control group. There was no evidence of long-term effects of HIIT on outcomes measured at nine months.

In conclusion, no evident effects on disease activity markers and pain were observed after HIIT in PsA patients. However, the exercise group reported meaningfully less fatigue after the intervention period. Thus, we concluded that HIIT was well tolerated in PsA patients evaluated both by measures of disease activity and patient disease perception. However, the benefit was not sustained without HIIT maintenance.

Paper II

The effect of high intensity interval training on cardiovascular disease risk factors and body composition in psoriatic arthritis. A randomized controlled trial.

Psoriatic arthritis (PsA) is associated with an accumulation of cardiovascular disease (CVD) risk factors. The aim of this study was to evaluate the effect of high intensity interval training (HIIT) on CVD risk factors such as cardiorespiratory fitness and body composition in patients with PsA. Furthermore, we aimed to see if any benefit was enduring beyond the study time.

We randomly assigned 61 PsA patients (41 women and 20 men) to an intervention group performing HIIT for 11 weeks or a control group with no change in pre-study physical exercise habits. Outcomes were assessed at three and nine months with measures on maximal oxygen uptake (VO_{2max}), fat percentage, and body mass index (BMI). We used linear mixed models to calculate mean difference with a 95 % confidence interval (CI) between the groups according to the intention-to-treat principle.

At three months, the HIIT group had a 3.72 ml/kg/min (95 % CI 2.38 to 5.06) higher VO_{2max} and a 1.28 (95 % CI -2.51 to -0.05) lower truncal fat % than controls. There was also some evidence that the HIIT group had lower total fat % (-0.80; 95 % CI -1.71 to 0.10) and slightly lower BMI (-0.31; 95 % CI -0.78 to 0.17) than the control group. At nine months, the HIIT group had still a higher VO_{2max} (3.08; 95 % CI 1.63 to 4.53) than the control group, whereas the difference in other factors were small.

In conclusion, in patients with PsA, three months with HIIT was associated with a substantial increase in VO_{2max} and a reduction in truncal fat percentage compared to controls. The beneficial effect on VO_{2max} was also sustained through nine months.

Paper III

Adiposity and physical activity as risk factors for developing psoriatic arthritis. Longitudinal data from the HUNT study.

Adiposity is prevalent among patients with psoriatic arthritis (PsA). However, the temporal relation is unclear. The aim of this longitudinal population-based study was to investigate the association of adiposity and body fat distribution with the risk of developing PsA. Further, we examined if a high physical activity level could modify the possible adverse effect of high BMI and waist circumference on the risk of incident PsA.

This study was based on data from the Norwegian HUNT Study. Out of 116,043 participants from HUNT2 and HUNT3, 37,070 individuals participated in both surveys and were selected for this study. We included 36,626 women and men from HUNT2 (1995-97) without diagnosed PsA at baseline. Cox regression was used to estimate adjusted relative risks (RRs) with 95 % confidence intervals (CIs) of incident PsA at follow-up in HUNT3 (2006-08).

During follow-up, 185 new cases of PsA were reported. One standard deviation increase in BMI and waist circumference was associated with RRs of 1.40 (95 % CI 1.24-1.58) and 1.48 (95 % CI 1.31-1.68), respectively. Obese individuals had a RR of 2.46 (95 % CI 1.65-3.68) compared to normal weight individuals. Comparing extreme quartiles of waist circumference was associated with a RR of 2.63 (95 % CI 1.73-3.99). In analyzes of combined effects using BMI <25 kg/m^2 and high physical activity as reference, BMI ≥25 kg/m^2 was associated with RRs of 2.06 (95 % CI 1.18-3.58) and 1.53 (95 % CI 0.80-2.91) among those with low and high physical activity levels, respectively. Corresponding RRs for high waist circumference and physical activity were 2.25 (95 % CI 1.40-1.63) and 1.85 (95 % CI 0.95-3.50).

In conclusion, the results from this population-based longitudinal study indicate a positive association between adiposity, and in particular central obesity, with the risk of incident PsA. Although there was no clear modifying effect of physical activity on adiposity, individuals performing high level physical activity had a reduced risk of PsA, regardless of BMI.

5 Discussion

The first part of the discussion covers methodological limitations related to possible sources of bias and confounding, whereas the second part addresses interpretations of the main results.

5.1 Methodological issues

In research studies it is a goal to present precise and valid estimates of effect. The main types of errors in research are random and systematic errors, which are linked to precision and validity, respectively.[227] Random error is affected by study size, whereas systematic errors are not. The main types of systematic errors are selection bias, information bias and confounding.[227]

5.1.1 Study design

The results of Paper I and II are based on a RCT, whereas the results of Paper III are based on a longitudinal observational study.

A RCT is considered the gold standard of medical research[228 229] and is the preferred study design to allow for inferences about cause and effect. The randomization procedure is the cornerstone of a well-conducted clinical trial because of the ability to allocate participants in an unpredictable way to the intervention strategy. The goal of randomization is mainly to create comparable groups and avoid confounding and selection bias. If the numbers of participants are large enough in a RCT, possible confounding factors should be evenly distributed between the intervention and control groups, and thus not influence the results.[227] In our study, the randomization was blinded and did not allow the investigator to reveal the allocations to either intervention or control.

Paper III is a longitudinal observational study based on the HUNT surveys. A strength of this design is the ability to investigate and to evaluate the temporal relationship between the exposure and the disease.[227] In our study, the observation period was 14 years. However, we do not know whether this is enough to evaluate the effect of lifestyle factors such as physical activity and overweight on the risk of PsA. The effect of overweight seems to be cumulative which implies an expected higher risk the longer the exposure.[40] There is a sparsity on data about physical activity as a risk factor for the development of PsA, and we

have no information about the amount of physical activity exhibited between baseline and follow-up.

An advantage of observational studies is that they are not restrained by strict inclusion criteria and no intervention is conducted such as in RCTs. That way, they are suitable for studying differences in exposures being present in daily life and making inference on long-term efficacy of an exposure.[191]

However, reverse causality is a potential problem in observational studies. In Paper III, those with low level physical activity at baseline had more pain. This could express early disease of PsA that was not yet diagnosed and consequently may give rise to reverse causality. Nevertheless, sensitivity analyzes excluding the cases with disease onset within the first three years after baseline in HUNT2 did not change the association of physical activity with risk of PsA.

5.1.2 Precision and sample size

Random error, or the role of chance, is inversely related to both sample size and the variability in the data.[227] A small sample size or a high variability increases the likelihood of chance findings, whereas increasing the sample size will reduce the role of random error and increase the precision of the associations under study. Confidence intervals (CIs) give information about both the precision and strength of the associations, where narrow CIs reflect high precision of the estimates.[227]

In Paper I and II, the sample size with 30 participants in each group was estimated to achieve a power of 90 % with the ability to reveal a difference of clinical relevance in the primary outcomes VO_{2max} and PGA. However, the number of participants was too limited to do sex-specific subgroup analyzes as it would result in imprecise estimates with wide CIs.

Despite randomization, there were some baseline differences between the groups with less women, younger age (approximately 5 years), higher VO_{2max} and less overweight in the control group compared with the intervention group. This imbalance might be due to a relatively small sample size. With a small sample size there is a risk that baseline differences may affect the estimated results erroneously. Further, using a linear mixed model for repeated measurements with joint baseline categories between the intervention and control groups, this baseline imbalance is a possible limitation when evaluating the observed effects. However, any baseline differences between the groups are considered as a result of chance and therefore no statistical significance testing was done to evaluate these differences.[227] Nevertheless, to compensate for the actual imbalance all analyses were adjusted for age and sex.

The study sample in Paper III is based on a large population from the HUNT study. Nevertheless, due to relatively few cases of PsA in some of the exposure categories, particularly when examining combined effects, the precision of the estimated associations for some of the categories was low.

5.1.3 Bias

Biases are systematic errors that may influence the results and reduces the validity of the findings.[230 231] There are several types of biases that must be considered in research, from outset of planning, through conducting and interpreting results of a study. The biases discussed in the following are: selection bias, information bias, and performance bias.

5.1.3.1 Selection bias

Selection biases are "Distortions that result from procedures used to select subjects and from factors that influence study participation."[230-232]

In RCTs the randomization and allocation process can cause selection bias if patients are recruited selectively based on what the next treatment allocation is likely to be.[232] However, we performed block randomization that did not allow the investigator to reveal the next allocation (Paper I and II) and thus, eliminating selection bias.

In a prospective cohort study, like the HUNT study, the process of enrollment was completed before choosing exposures, and the outcome, the diagnosis of PsA, was not yet established (Paper III). Thus, the exposures are expected to be equally distributed among cases and non-cases and should not cause selection bias.

Attrition bias is a type of selection bias and is a systematic error caused by the selective occurrence and biased handling of protocol deviations and losses to follow-up, which may lead to results that differ from a study's true values.[233] It could be caused by systematic differences in withdrawals between the trial groups and thereby create missing data. A way of modifying the effect of an imbalance in withdrawal and missing data is using ITT analyzes[227] as was done in our RCT instead of per protocol case analyzes (Paper I and II). In ITT all the randomized individuals are included in the analyzes. In the RCT the number of withdrawals were approximately the same in both groups (13% in the intervention group and 17% in the control group). Thus, with an almost equal and relatively low withdrawal rate, it minimizes missing data and make the estimates of effect from the ITT analyzes more valid. However, using ITT analyzes can underestimate the true effect of the intervention. As

conducted in our study, performing physical exercise in groups might reinforce both the individual adherence and effort.

5.1.3.2 Performance bias

Performance bias can occur in a clinical trial if systematic differences in care between the trial groups are exhibited.[234] In addition, when researcher and participants are not blinded for the intervention, this type of bias can occur, e.g. that knowledge of the intervention received will influence outcomes. In the RCT, the participants in both the intervention and control group had the same type and amount of planned follow-up. However, patients in the intervention group had better access to on-demand care as the researcher (the rheumatologist) was in close contact with those patients. Nevertheless, the total amount of intra-articular corticosteroid injections was the same in each group during the total study period. Since the intervention was physical exercise, it was not possible to blind neither the researcher nor the participants for the intervention.

Another potential cause of performance bias in a physical exercise intervention study, is that controls can seek guided physical exercise elsewhere. Since our controls did not deliver diaries, we have no exact information about their activity level during the intervention period. However, a slight improvement in VO_{2max} was observed in the control group.

5.1.3.3 Information bias

The main type of information bias is misclassification that can be differential (when misclassification is different in the groups to be compared, or between those who experience the outcome and not) or non-differential (when the misclassification is the same across the groups to be compared). Differential misclassification bias can occur when assessments of outcomes in follow up studies are done in an inappropriate way.[227 230] Avoiding this type of bias could be achieved by blinding the assessors. The outcomes in the RCT are a mixture of objective measures and PROs. Assessors at the laboratory (blood samples) were blinded through all follow-ups.

In Paper I the main outcome, PGA and two of the secondary outcomes (pain and fatigue) were PROs, which hamper blinded assessments since the participants are aware of their group allocation. The DAS44 is a composite score with elements from PRO, physician's global assessment and CRP. The ASDAS-CRP is another composite score consisting of PRO and CRP. The SPARCC-Enthesitis Index was assessed by the rheumatologist (one of the

researchers). The rheumatologist was blinded to the group allocation at baseline evaluations, but not at three- and nine-months follow-up. In Paper II the outcome measures such as VO_{2max} and measures of body composition were all objective measures and the assessors were all blinded. Nevertheless, non-differential misclassification could occur if the patients did not reach their maximum level. This would underestimate the observed results. We measured the truncal fat percentage with DXA, which provide results highly correlated to abdominal fat percentage.[221 235 236] However, others suggest that magnetic resonance imaging is a better method of measuring abdominal/visceral fat.[207 237]

Information bias and misclassification can arise during the collection of information, e.g. when validating the outcome.[230] The diagnoses of PsA in HUNT3 (Paper III) have previously been validated from hospital records by an experienced rheumatologist according to the CASPAR criteria.[6] Thus, the diagnosis of PsA is less prone to be misclassified. However, only the participants who reported symptoms suspicious of a diagnosis of arthritis were subject to the validation process. Thus, undiagnosed cases could exist, which would underestimate the observed results. Nevertheless, we assume this possible error to be negligible.

As most of the data in the HUNT study are based on questionnaires, there is a potential problem of misclassification. Questionnaires have a poor validated methodology for assessing physical activity.[238] Missing values when physical activity is used as a confounder and misinterpretation of own physical activity level can cause misclassification.[230] Yet, the misclassification is probably non-differential as it would be equally distributed between PsA-cases and non-cases. However, this can cause underestimation of the observed results. Further, the level of leisure time physical activity from the questionnaire in HUNT2 has been validated against measured maximum oxygen uptake, and the term "hard leisure time physical activity" was a moderately good measure of vigorous physical activity.[211] This suggests that our category of high level physical activity represents vigorous activity. However, the validation was performed in a group of younger men and thus, may not be representative for the remaining participants.

The Hawthorne effect is a potential information bias in clinical trials, which means that people change their behaviors when they are being observed.[239] This could explain the slight improvement in disease activity markers and cardiorespiratory fitness in controls (Paper I and II).

5.1.4 Confounding

Confounding is a condition where known and unknown factors bias the results of a study.[231 240] It is associated with both the exposure and the outcome. Simultaneously, the exposure and the outcome cannot affect confounding. Confounders are factors that from prerequisite subject knowledge can cause confounding. In addition, a confounder cannot be on the causal pathway between the exposure and the outcome.[240] To minimize confounding in research, RCT is the preferred study design since possible confounders are equally distributed among the study groups in the process of randomization.[241] Other methods of reducing confounding are the use of exclusions, matching, standardization and multivariate analyses. Observational studies are more prone to confounding. There may be confounder misclassification or residual confounding, which make adjustment insufficient. Residual confounding caused by unknown factors or measurement error, can disrupt causal inference and give biased results. Missing data in the covariates can result in measurement error and hence give rise to residual confounding.[242] To account for such missing data in the covariates, those with missing values were placed in a numbered category to not lose any cases and thus, avoiding loss of precision in the observed estimations of effect. In addition, complete case analyzes were done, which resulted in less cases (data not shown). However, the estimated effects did not change. Further, it is not possible to rule out that the exposures (BMI, waist circumference, and physical activity) are linked to hidden confounders such as other lifestyle habits and comorbidity. This can cause residual confounding. Physical activity is linked to socioeconomic status,[243] and we accommodated for that by adjusting for educational level.

In Paper I and II, confounding was dealt with by the randomization and by adjusting all measures of effect for sex and age. In Paper III all estimates were adjusted for possible confounding in the multivariable regression analysis. The potential confounders chosen by a priori knowledge were age, sex, smoking, and education.

5.1.5 Physical activity intervention and potential challenges

Using physical activity as an intervention (Paper I and II) or as an exposure (Paper III) is challenging in several ways.[244] Physical activity as an intervention is resource-intensive for the research team and time consuming for the participants.

Deciding how to assess an effect of the physical activity intervention is one challenge. Primarily, the concern is whether the chosen study design is feasible in this type of patient category.[244] Pilot studies using HIIT intervention in patients with RA and SpA have been executed and proven to be feasible in Norway.[225 245] Secondarily, to avoid detection bias,

assessors of outcome measures should be blinded especially since participants cannot be blinded.[230]

Standardization of the intervention can be difficult. However, the method of HIIT is well standardized with baseline testing of VO_{2max} and maximum heartrate.[153 210] Thus, the intervention can be individualized and performed at the relative same intensity. The use of guided exercise intervention is another way of fulfilling a standardized intervention. Hence, the duration and intensity of the exercise can be monitored. As described in Paper I and II, we had two guided trainings a week and one self-guided training. Furthermore, the supervisors were experienced in guiding a HIIT, and one supervisor guided a maximum of six participants at a time. Ideally all the HIIT sessions ought to be guided, but for practical reasons and time constraints for the participants, only two of three weekly exercises were supervised. This could have resulted in lower exercise intensities for the unsupervised sessions, and consequently a smaller observed effect of HIIT.

A potential problem is that controls are motivated for physical exercise as well and may find other ways of performing a similar mode of activity as the intervention. This may underestimate the effect of the intervention. A way of preventing that, is to have active controls by offering a kind of training that does not have an impact on the outcome. However, we did not plan for that. Nevertheless, controls were told that they could continue with activities as usual but avoid aerobic exercises during the first follow-up.

Assessment of intervention adherence is an important issue.[244] In our RCT (Paper I and II) patients in the intervention group were taught how to use heart rate monitors during exercises. In addition, they delivered diaries weekly to report all aerobic activities, including intensity of the activity measured either by the heart rate monitor or Borg scale. Even though such reporting is rather subjective, we apprehended the adherence as satisfactory. The intervention group delivered completed diaries for 95 % of all the weeks. The completion of the guided exercises was 78 % of sessions. However, they also did more self-guided endurance exercises than requested, i.e. 1.2 times a week. According to diaries, the mean intensity during guided exercise was 16.4 (SD 3.3) referring to the Borg scale which is considered ‘very hard’ effort. The intensity during self-guided exercise was 12.8 (SD 3.4) referring to the Borg scale which is considered ‘moderate‘ effort. Furthermore, performing physical exercise in groups might reinforce both the individual adherence and effort.

5.1.6 Validity and representativeness

Validity of a study can be interpreted by the internal validity that refers to conduction of the study with possible biases and confounding, and the external validity referring to whether the observations can be applied to individuals outside from the sample that is observed, i.e. representativeness.[227] Internal validity is a premise for external validity and factors associated with internal validity, such as biases and confounding, are already discussed.

The external validity in Paper I and II might be violated since patients volunteered to participate and might be more experienced with and more motivated for physical activity than non-participants. However, baseline VO_{2max} in our patients was similar to that of healthy inactive people in Norway, indicating recruitment of patients with a sedentary lifestyle.[140] Nevertheless, VO_{2max} was higher than in RA patients from UK[246] and AS patients from Dublin.[247] Chronic pain is more common among women and could reduce their willingness to participate.[248 249] In addition, women tend to be less willing to participate in clinical trials.[250] However, 65 % of the participants were women.

Further, the recruitment of patients was limited to those living close enough to the hospital to be able to attend the guided trainings, implying participants from a more urban area. Previous studies report that rural inhabitants are more likely to be physically inactive and to report poorer health related outcomes (e.g., higher prevalence of obesity and chronic disease).[160 251] However, recruitment was accomplished from both primary and secondary healthcare, and thus participants resemble PsA patients from other centers in Norway and Europe regarding disease activity and duration.[252 253] One could argue that with low disease activity at baseline the risk of worsening of disease as a response to HIIT would be less prone (Paper I). In addition, with a low disease activity at baseline, CVD risk factors could be less pronounced and thus underestimate the results on CVD risk factors after HIIT (Paper II).

The observed sample in Paper III had to participate in both HUNT2 and HUNT3 to be included, which could violate the external validity and thereby the representativeness if the relation between exposures and outcome were different for participants and non-participants in HUNT3. Non-participants in HUNT3 had more CVD and diabetes as well as a lower socioeconomic status than the participants.[254] These factors are associated with PsA. In addition, participants did more physical exercise than non-participants and they had a slightly higher BMI according to self-reports. However, the prevalence of self-reported psoriasis was higher among participants than diagnosed psoriasis among non-participants according to the general practitioner journal.

5.2 Interpretation of results and comparison with other studies

5.2.1 Disease activity and patient`s disease perception (Paper I)

We chose to use scores of disease activity and PROs that were accessible from the tools used in daily clinical practice at our clinic at study start. Further, some of the current recommended tools for assessing disease activity in PsA were not yet available when the study was designed.[84 98 106 255]

Physical training in patients with arthritis has not lead to increased disease activity or joint destruction according to previous studies.[171 174] However, HIIT has not previously been tested in PsA patients. In our data, there was no evidence of a deterioration in disease activity measured by both objective markers and PROs after the intervention with HIIT. It was either unchanged or slightly reduced in both groups regarding DAS44, ASDAS-CRP and PGA with no difference between the groups. Previous studies reported reduced disease activity in patients with RA and SpA due to HIIT performed two to three times a week over a period of 12 weeks.[225 245] I.e., the type of intervention was comparable to ours (Table 2, Appendix).

Further, measured by the SPARCC-Enthesitis Index the risk of an increased enthesitis activity was not higher in the intervention group compared to the control group. One study found increased Achilles enthesitis in PsA patients due to physical exercise, though, the type of exercise was not defined.[194] Another study reported an association of avoidance of physical activity with less enthesitis activity measured by ultrasound in PsA patients.[193] Enthesitis primarily affects the lower limbs, which are exposed to higher mechanical forces than the upper limbs.[256] One study found that obese and overweight PsA patients had a higher prevalence of Achilles and calcaneal spurs as well as pelvic enthesitis.[30] In our study, the patients used a stationary bicycle, which might reduce the mechanical overload on lower limbs. This might explain the lack of increased enthesitis activity after the intervention.

Patients in the intervention and control groups had equal treatment with methotrexate and TNF inhibitors at baseline. Further, objective measures of disease activity such as DAS44, CRP and joint counts were equal at baseline in both groups as well, and they were relatively low. However, patient disease perception as measured by PGA, the main outcome in Paper I, was higher than expected compared to the objective measures. It is a known phenomenon that patients' perception of disease activity is higher than judged by the physicians`.[112 257-259] Further, PGA could also be influenced by other factors than disease activity,[260 261] for instance experience of pain for other reasons than inflammatory disease activity. PGA was a little lower in the intervention group compared to controls at baseline

which make it less likely to find a reduced PGA due to the intervention. On the other hand, we do not know whether patients with low and stable disease activity are less prone to increased disease activity than patients with a higher disease activity when exposed to an intervention such as vigorous physical exercise. It has been hypothesized that the threshold for triggering entheseal inflammation is substantially lower in patients with PsA than in healthy individuals, which allows the development of enthesitis with little or no mechanical force.[14]

ASDAS-CRP as a measure of spinal inflammation was equal in both study groups at baseline with a medium level. After the intervention the ASDAS-CRP declined in both groups. However, the decline in the intervention group was not clinically relevant with a decrease of 0.31 (95 % CI -0.60-0.02). A clinical important improvement is believed to be at least a reduction of 1.1 on the ASDAS-CRP scale.[262] Other studies have reported effect on markers of spinal inflammation in axial SpA after physical exercise.[225 263] In contrary, a recent systematic review did not conclude with a convincing effect on disease activity of aerobic exercise in patients with axial SpA.[264] In PsA, the axial phenotype is associated with HLA-B27.[265 266] Further, among the PsA patients from the HUNT3 survey, 3.8 % only had axial affection, whereas 26.9 % had both axial and peripheral manifestations.[6] In our cohort, only 15 % were HLA-B27 positive which could indicate a lower degree of spondylitis and thereby explain the lack of improvement in marker of spinal inflammation.

One could consider whether a seasonal change might influence on disease activity and fatigue.[267] Especially in a country such as Norway with changing weather conditions between seasons, that might have implications for the results. In our study, two-thirds of the participants were included late winter with post-intervention follow up in May/June and 9 months of follow up in November/December. One third was included in September with post-intervention follow up in December and 9 months of follow up in May/June. We did not account for that during randomization. Nevertheless, the proportion of participants among controls and intervention group were equally distributed within seasons. Furthermore, a study from Toronto found no seasonal difference in PGA in patients with PsA.[268]

5.2.1.1 Fatigue

Fatigue improved to an extent that is clinically relevant after HIIT as described in Paper I. Previous studies in RA, SpA and Systemic Lupus Erythematosus (SLE) reported similar effects on measures of fatigue as a response to aerobic exercise.[198 269-273] In addition, studies

of aerobic exercise in chronic fatigue syndrome, fatigue in cancer as well as in depression report improvement in fatigue scores.[274-276] All the referred studies did analyses on estimated effects partially or totally based on aerobic exercises, which implies a type of exercise that increases the heart rate. Thus, possible explanations for the impact of aerobic exercise on fatigue could be an exercise induced endorphin response[277] or improvement in aerobic capacity.[278]

Although fatigue is a major problem in PsA,[279] its etiology is not well understood. Fatigue and depression often are associated factors in chronic diseases, and there seems to exist a link between these factors and immune activation.[280-282] Depression also plays a role in the burden of PsA and may be associated with fatigue.[283] However, we did not evaluate depression in our study. Partially, fatigue in PsA may be explained by inflammation,[284] as a higher degree of fatigue has been associated with a higher disease activity measured by enthesitis, joint count and skin disease.[279 285] However, medical therapy like TNF-inhibitors only have small effects on fatigue.[286] In a multicenter cross-sectional study it was found that fatigue among patients with PsA was associated with female gender; level of education; skin psoriasis; enthesitis; as well as tender and swollen joints.[279] Among our participants, the association to female gender was possible since two thirds were women but an association with disease activity was not apparent. The women in our study also had a higher baseline level of fatigue than the men (data not shown). Further, the baseline fatigue level was lower in the intervention group than control group (mean (SD) 43.5 (30.7) and 52.9 (28.2), respectively), which might underestimate the results of an effect on fatigue.

5.2.1.2 Pain

We observed a minor reduction in pain intensity in both groups after the intervention (Paper I). However, the estimated size of reduction was not of clinical significance.[217] In chronic pain such as fibromyalgia, aerobic exercise has some beneficial effect on pain.[287] Similarly, a reduction in pain scores are observed in axSpA and other inflammatory arthritides after aerobic exercises.[184 263] However, the baseline pain score among our patients was mild to moderately high,[288] and thus the potential for a reduction in pain was less probable. The level of pain in our cohort was comparable to pain level in another Norwegian PsA cohort[252] but lower than reported in a Turkish cohort,[289] both with the same disease duration as our cohort. Pain is in general, a considerable problem in PsA patients[259 283] and does not necessarily correlate with objective measures of disease activity.[259] The discordance between subjectively and objectively influenced measures of inflammation may reflect non-inflammatory factors

that impact pain.[290] Level of pain is found to be multifactorial and may be influenced by adverse life events and other personality traits.[291] Increased pain has been associated with enthesitis in PsA[292] and fatigue in RA.[261] Hence, the baseline pain level in our cohort correlates well with the low enthesitis activity. However, the pain level does not correlate with the level of fatigue, thus, the minor reduction in pain intensity cannot reflect the impact on fatigue in our data.

5.2.2 CVD risk factors (Paper II)

5.2.2.1 Cardiorespiratory fitness

In Paper II, we used VO_{2max} as a measure of cardiorespiratory fitness since it is known to be an important predictor of cardiovascular health.[142] We observed an increase of 13.5 % in VO_{2max} in the intervention group which corresponds to at least 13 % decrease in all-cause mortality.[141] The observed effect on VO_{2max} is in line with previous studies on HIIT in otherwise healthy people,[153 156] as well as in patients with heart disease[293] and arthritis.[225 245]

Higher levels of cardiorespiratory fitness are associated with protection against CVD and all-cause mortality.[154 294] Further, low cardiorespiratory fitness is found to be a more powerful predictor of mortality than traditional risk factors, such as hypertension, smoking, obesity, hyperlipidemia, and type 2 diabetes.[295 296]

In our study, patients were selected on a self-reported low cardiorespiratory fitness. Except for a mean BMI of 28.3 that corresponds to overweight, they had little other traditional CVD risk factors. Serious CVD was an exclusion criterion in our study. Thus, none of the PsA patients in our study had established CVD. Despite of increased BMI and truncal fat at baseline, the blood pressure in our patients was normal and only 13 % were on antihypertensive medication. That is in line with a demonstrated trend, that blood pressure is declining in the Norwegian population in general.[297] In addition, the baseline lipid profile was normal in both groups, and only 10 % were using statins. According to other studies a decline in total cholesterol has been demonstrated in the general population as well.[298 299] Daily smoking was reported in 20 % and 13 % in the HIIT and control groups, respectively. That is in line with results from a Norwegian study on CVD risk factors in patients with inflammatory arthritis as well as in the background population.[44 300]

5.2.2.2 Body composition

Measures of body composition such as BMI and abdominal fat were chosen as outcomes due to their detrimental effects on disease activity[128] and cardiovascular health[117] in established PsA (Paper II). Excess abdominal fat contributes to increased CVD risk,[301] and PsA is associated with obesity.[115-117 186 187] A recent study described that truncal fat is highly associated with CVD risk even with a normal BMI in postmenopausal women. The study found neither whole-body fat mass nor fat percentage to be associated with CVD risk.[302] We found a reduction of abdominal fat and a somewhat lower total fat mass and BMI after the HIIT intervention. The effect of aerobic exercise on abdominal fat is in line with other studies.[207 225 237 303] However, a meta-analysis evaluating the effect of physical exercise concluded that high-intensity training was more successful in reducing whole body adiposity, while lower intensities had a greater effect on changes in abdominal and visceral fat mass.[207] The studies with better estimated effects on abdominal fat were based on obese participants.[225 237] Our patients were not selected based on obesity and had a baseline BMI corresponding with overweight. Hence, the magnitude of the reduction was not as prominent and might not be of clinical relevance. However, the study was of short duration and with an extended duration of the intervention one might expect an effect of clinical relevance on the reduction in truncal fat. Otherwise, one could question whether the reduction in total fat and abdominal fat would equalize due to aerobic exercise of longer duration.

Some studies have illustrated the beneficial effect of weight reduction on disease activity in PsA.[128 132] A recent published intervention study, in which obese PsA patients were put on a diet (<800 kcal/day), described a clinical relevant reduction in disease activity related to weight loss.[132] Thus, advice about lifestyle interventions such as physical exercise and weight loss ought to be mandatory in the management of PsA.

5.2.3 Effects after nine months follow-up (Paper I and II)

After the intervention, during the second follow-up from 3-9 months, the trial was conducted as an observation period without any rules for either group. The purpose was to evaluate the long-term effect on physical activity behavior, and to evaluate whether the effects on disease activity, patient disease perception and VO_{2max} were sustainable. During this follow-up, none of the groups delivered diaries, and they were not offered guided exercises. Further, they were not supported by any extra attention. However, changes in medication were allowed, and both groups were encouraged to exercise. We observed few drop outs, but for different reasons

four and six in the HIIT and control groups, respectively, could not perform the VO_{2max} test at the nine months follow-up. At that follow-up, 12 (43 %) in the HIIT and 5 (18 %) in the control group reported that they were doing endurance exercise. Even with less effort in the HIIT group and increased physical activity in the control group, there was still a sustained effect on cardiorespiratory fitness in the HIIT group, which is in line with results from patients in cardiac rehabilitation.[304] The sustained effect may be explained by the fact that the intervention group could take advantage of the learned technique of HIIT, whereas the controls were never supervised in that specific technique. However, the effect on fatigue was not sustained. The other measures of disease activity and patient disease perception were mainly unchanged.

5.2.4 Risk factors for development of PsA (Paper III)

5.2.4.1 Body composition

Body composition measured by BMI and waist circumference was evaluated as an exposure for PsA risk in Paper III. We found that adiposity, and in particular central obesity, was associated with increased risk of PsA. Our results correspond to previous studies suggesting that overweight seems to be associated with the development of PsA.[27-30 41 42 123] Results from a longitudinal observation study also indicated that central obesity was strongly associated with the risk of PsA in non-obese individuals.[123] The mechanisms for the detrimental effect on risk of PsA is debated. It has been observed that obesity at young age is a predictor of PsA presence in adult psoriatic patients leading to the hypothesis that a cumulative effect of excess bodyweight might exist.[27 40] A high bodyweight results in an increased mechanical stress on musculoskeletal structures, especially in lower limbs.[305] This could trigger a local auto-inflammatory response and cause an inflammatory cascade reaction that leads to the onset of PsA.[195 196 306] Another theory is that the obesity-related chronic inflammatory state could cause the onset of PsA,[38] since the adipose tissue produces adipokines and pro-inflammatory cytokines, which influence the pathophysiology of inflammation in psoriatic diseases.[37] The metabolic disturbances caused by excessive fat seems to be associated with visceral fat.[307] Waist circumference may be a more accurate measure of visceral fat than BMI,[308] as the latter is influenced by lean muscle mass as well as fat mass. Hence, measure of waist circumference might be a better indicator of metabolic abnormalities and CVD risk.[139] Since we found a higher risk association with waist circumference than BMI, the visceral fat may also play an important role in the development of PsA.

A recent study has elucidated that the reduction in abdominal fat during vigorous exercise is regulated by IL-6. With higher intensity and longer exercise, more IL-6 is secreted from the muscles.[237] IL-6 is involved in the pathophysiological mechanisms in the development of RA[309] and to some degree in PsA.[310] The lesser importance of IL-6 in PsA pathophysiology is demonstrated by the difference in treatment effects of IL-6-inhibitors, which is efficacious in RA[309 311] but less efficacious in PsA.[311 312]

5.2.4.2 Physical activity

In Paper III we also investigated whether high level physical activity could modify the risk of developing PsA. We observed no evidence of a synergistic effect between a high BMI and low-level physical activity. In general, there was a tendency that lower levels of physical activity exhibited a little higher risk of PsA, regardless of BMI. There is little previous evidence about the impact of level of physical activity and risk of developing any of the inflammatory arthritides.

One study reported that low fitness is associated with abdominal adiposity and low-grade inflammation independent of BMI.[313] Further, physical exercise seems to be protective against diseases associated with low-grade systemic inflammation such as CVD, metabolic syndrome and diabetes mellitus.[314] Assuming that physical activity and obesity are often inversely related it is not obvious whether the anti-inflammatory health benefits of a physically active lifestyle are caused directly by the exercise or as a result from favorable changes in body composition. However, it is evident that regular physical activity induces favorable changes in the metabolic state.[314] Hence, high level physical activity may have the ability to reduce the risk of PsA.

In contrary, as discussed earlier, there is a concern that mechanical stress inflicted by physical exercise can cause inflammation and thus increase the risk of PsA.[16 195] Increased inflammatory activity has otherwise been described in association with high level physical activity such as marathon running.[315] However, this inflammation might only be present in the "acute phase" during or right after the activity,[315] and thus does not exhibit an increased risk of inflammatory diseases such as PsA. One study observed increased TNF-α 24 hours after marathon running whereas IL-6 increased in the acute phase and normalized after 24 hours.[316] Several studies have measured increased IL-6 activity in the "acute phase" after high intense physical activity.[225 237 245 316 317] However, two of those studies evaluated the effect of high intense physical activity in RA and AS and did not find increased disease activity.[225 245]

6 Conclusions and clinical implications

6.1 Main conclusions

The following interpretations can be deduced from the work of this thesis:

- After HIIT, PGA and pain were slightly reduced in both groups but without clinical significance and with no difference between the groups. Fatigue improved with clinical significance in the intervention group compared to controls. (Paper I)
- After HIIT, disease activity measured by DAS44 was slightly reduced in both groups with no difference between the groups. The risk of an increased enthesitis activity was not higher in the intervention group compared to the control group measured by SPARCC-Enthesitis Index. (Paper I)
- HIIT for three months resulted in a substantial increase in maximal oxygen uptake, i.e. the cardiorespiratory fitness improved. (Paper II)
- HIIT for three months resulted in reduced truncal fat mass but no reduction in total fat mass in patients with PsA. (Paper II)
- The effect of HIIT on disease activity and patient disease perception was not sustainable beyond the study period. (Paper I)
- The effect of HIIT on cardiorespiratory fitness was sustainable beyond the study period, whereas the effect on body composition was not. (Paper II)
- Adiposity, measured by BMI, was found to be associated with the risk of developing PsA. (Paper III)
- Central obesity, measured by waist circumference, was found to be associated with an increased risk of developing PsA and the association was stronger than with BMI. (Paper III)
- Individuals performing high level physical activity had a somewhat reduced risk of PsA, regardless of BMI. (Paper III)
- There was no clear modifying effect of physical activity on adiposity and risk of PsA in the combined analyzes. (Paper III)

6.2 Clinical implications

In this thesis we aimed to investigate whether physical activity level may have an impact on disease activity, patient disease perception and CVD risk factors in established PsA. In addition, we aimed to evaluate whether physical activity level and adiposity are associated with the development of PsA.

We found that HIIT in the short term was well tolerated without an increase in disease activity in patients with PsA. In addition, fatigue improved after HIIT. The findings from this study also indicate that HIIT could be beneficial in PsA patients in preventing CVD by increasing cardiorespiratory fitness and reducing abdominal fat.

Comorbidities such as cardiovascular disease, metabolic syndrome, and fatigue could all contribute to the global burden of disease in PsA. These factors are not eliminated by traditional disease modifying treatment.[115] Thus, it is important to introduce other methods of intervention, primarily to reduce the CVD risk factors. With this knowledge it seems reasonable to recommend HIIT as a relevant mode of physical exercise among PsA patients to improve cardiorespiratory fitness. However, it is challenging for health care providers to motivate and encourage the patients to initiate physical activity and to remain physical active. Informing the patients that HIIT is a method of physical exercise that is less time consuming but more beneficial in improving cardiorespiratory fitness with an additive effect on fat metabolism could be a possible approach. In addition, the patients should be informed that physical exercise does not cause increased disease activity. Further, it is important that the physician inform the patient about the beneficial effects of physical exercise and implement it as a treatment modality in addition to medical treatment. Cooperation with a physiotherapist may be advisable. Specific information and advice about lifestyle interventions such as weight loss should also be emphasized in the management of PsA in order to better control disease activity and to reduce the risk of CVD.

The results from our study also support evidence that central obesity is a major risk for PsA. In addition, high physical activity level was associated with a somewhat reduced risk of PsA. Further, the increased CVD risk in PsA patients may be prevalent before the onset of PsA according to a previous study,[42] and central obesity is modifiable by high level physical activity. In conclusion, our results support evidence that the risk of PsA is modifiable and highlight the importance of preventive work against obesity including encouragement to be physically active to reduce the incident of PsA.

7 Appendix

Table 2 Studies of physical exercise intervention in chronic arthritis disorders

Authors	Year	Cohort	Exercise intervention	Study design	Results
***Häkkinen**[174]	1994	43 RA and PsA patients from Finland	Dynamic strength training, 6 months	RCT	Increased maximal strength of all major muscle groups
***Van Tubergen**[180]	2001	120 AS patients from Netherland	Combined spa-exercise therapi[1], 3 weeks	RCT	Improved PIC
***Mustur**[175]	2007	69 RA patients and 40 PsA patients from Norway	Physical therapy/rehabilitation in warm climate, 4 weeks	Open uncontrolled trial	Improved HRQoL
***Baillet**[167]	2010	1,040 RA patients	Aerobic vs non-aerobic exercise, 2-104 weeks	Meta-analysis of 14 RCTs	Improved Quality of life, HAQ, pain
***Hagel**[191]	2010	174 patients (115 with peripheral arthritis (11 PsA), 59 with SpA (8 PsA)) from Sweden	Interdisciplinary rehabilitation, 18 days	Open uncontrolled trial	Improved aerobic capacity and HRQoL
Durcan[270]	2014	78 RA patients from Ireland	Home-based exercise Intervention (strength, stretch, walk) vs. usual care, 12 weeks	RCT	Improved sleep quality and fatigue
Chimenti[202]	2014	30 PsA patients from Italy	Home-based isokinetic strength exercises, 12 weeks	Open uncontrolled trial	No effect on pain, patient global and SF-36
Sveaas[225]	2014	28 axSpA patients from Norway	High intensity exercise and strength exercise, 12 weeks	RCT	No effect on ASDAS. BASDAI and VO_{2max} improved
Manning[182]	2014	108 RA patients from UK	Education, Self-Management, and Upper Extremity Exercise Training, 12 weeks	RCT	Improved upper extremity disability, function, handgrip strength
Rongen-van Dartel[273]**,**	2015	34-298 RA patients	Aerobic exercise, 4-104 weeks	Meta-analysis of 5 RCTs	Improved fatigue

Sandstad[245]	2015	7 RA and 11 JIA patients (all women) from Norway	High intensity interval training, 10 weeks	Cross-over	Increased VO_{2max} and decreased BMI, total body fat and waist circumference
Sveaas[271]	2017	28 axSpA patients from Norway	High intensity exercise and strength exercise, 12 weeks	Sub-analyses of RCT	Improved emotional distress and fatigue
Sveaas[184]	2017	1286 patients with inflammatory rheumatic diseases (none with PsA)	Cardiorespiratory and strength exercises	Meta-analysis of 26 trials	Beneficial effect on disease activity scores, pain and fatigue
Roger-Silva[185]	2018	41 PsA patients from Brazil	Resistance exercises for upper/lower limbs and trunk, 12 weeks	RCT	Improved BASDAI, HAQ-S, pain, general health
Katz[198]	2018	96 RA patients from California, US	Provision of pedometers +/- step targets vs. education, 21 weeks	RCT	Pedometers with or without step targets increased activity levels and decreased fatigue
Thomsen[318]	2018	67 PsA patients from Norway	High intensity interval training, 11 weeks	RCT	PGA, pain and DAS44 stable Improved fatigue
Thomsen[319]	2018	61 PsA patients from Norway	High intensity interval training, 11 weeks	RCT	Increased VO_{2max} Reduced abdominal fat
Sveaas[263]	2019	100 axSpA patients from Norway and Sweden	High intensity cardiorespiratory and muscular strength exercises, 12 weeks	Multicenter RCT	Improved ASDAS, BASDAI, patient global
Verhoeven[264]	2019	300 axSpA patients	Aerobic exercise vs. physiotherapy, 3-12 weeks	Meta-analysis of 6 trials (5 randomized and 6 controlled)	No beneficial effect on BASDAI compared to controls
Lange[320]	2019	74 RA patients (age 65-75 years) from Sweden	Moderate-to-high-intensity, aerobic and resistance exercise vs. active controls, 20 weeks	RCT	Improved VO_{2max}, endurance and strength
Kucharski[321]	2019	74 RA patients (age 65-75 years) from Sweden	Moderate-to-high-intensity, aerobic and resistance exercise vs. active controls, 20 weeks	Sub-analyses of RCT	Improved fatigue and symptoms of depression

Abbreviations: RA = rheumatoid arthritis, PsA = psoriatic arthritis, RCT = randomized controlled trial, AS = ankylosing spondylitis, PIC = pooled index of change (functional ability, patient's global well-being, pain, and duration of morning stiffness), HRQoL = health related quality of life, HAQ = Health Assessment Questionnaire, SpA = Spondyloarthritis, axSpA = axial SpA , ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, VO_{2max} = maximum oxygen uptake, JIA = juvenile idiopatic arthritis, BMI = body mass index, HAQ-S = Health Assessment Questionnaire for the Spondylarthropathies, PGA = Patient global assessment, DAS44 = Disease activity score of 44 joints.

[1] group physical exercises, walking, correction therapy (lying supine on a bed), hydrotherapy, sports, and visits to either the Gasteiner Heilstollen (Austria) or sauna (Netherlands)

***Published before our study was initiated**

8 References

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