Psoriatic arthritis

Cardiovascular risk factors, health-related quality of life and effects of weight loss treatment

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ABSTRACT

Background: Psoriatic arthritis (PsA) is an inflammatory rheumatic disease, characterized by arthritis, dactylitis, enthesitis and sometimes axial disease. PsA is associated with several comorbidities and reduced health-related quality of life (HRQoL), although less is known in relation to other common chronic rheumatic diseases. The increased secretion of cytokines and adipokines seen in obesity may be important in PsA. Weight loss has been shown to reduce disease activity, but the effects on cytokines and adipokines in PsA are unknown.

Objectives: Objectives corresponding to papers I-IV, were: To study the occurrence of cardiovascular risk factors (CVRFs) in PsA in comparison with general population (GP) controls (I) and in comparison with other inflammatory joint diseases (IJDs) (II), to compare HRQoL in PsA and other IJDs (III) and study the effects of weight loss on serum cytokines and adipokines in obese patients with PsA (IV).

Methods: I. PsA patients (n=982), 25-75 years old, were identified through the register at the Department of Rheumatology at Sahlgrenska University Hospital and sent a questionnaire regarding presence of CVRFs. Individuals from the National Swedish Public Health Survey were used as GP controls.

II-III. Individuals with PsA (n=1200), rheumatoid arthritis (RA) (n=1246), ankylosing spondylitis (AS) (n=1095) and gout (n=1589) were identified at three rheumatology clinics and 12 primary care centres (for patients with gout) in Western Sweden and sent a questionnaire regarding CVRFs and HRQoL, measured by RAND-36.

IV. Patients with PsA and body mass index (BMI) $\geq$33 kg/m^2 (n=41) and controls matched by sex, age and weight were included in a weight loss study. Serum levels of cytokines and adipokines were measured at baseline and at six months and related to Disease Activity in PSoriatic Arthritis (DAPSA) and

the Disease Activity Score for 28 joints using C-reactive protein (DAS28CRP).
Results: I. Obesity (28.6% vs 16.3%, $p<0.001$), hypertension (40.3% vs 24.1%, $p<0.001$) and diabetes (10.5% vs 6.2%, $p<0.001$) were more prevalent in PsA patients compared to GP controls.
II. Gout patients reported significantly more hypertension, hyperlipidaemia, diabetes, obesity and multiple CVRFs than PsA, RA and AS. In women, hypertension, obesity and multiple CVRFs were more common in PsA compared with RA and AS.
III. Gout patients reported better HRQoL than PsA, RA and AS. HRQoL was similar in PsA, RA and AS, but worse in physical domains compared with mental domains for all IJDs. Women reported worse HRQoL compared with men.
IV. Weight loss was associated with lowered serum levels of interleukin (IL)-23, median (interquartile range) 0.40 (0.17-0.54) ng/mL at baseline to 0.18 (0.10-0.30) ng/mL and leptin (both $p<0.001$) at six months. ΔIL-23 positively correlated with ΔBMI ($r_S=0.671$, $p<0.001$) and ΔDAS28CRP ($r_S=0.460$, $p=0.005$).
Conclusions: PsA was associated with increased prevalence of CVRFs compared to the GP and in women with PsA compared to RA and AS. CVRFs were more common in gout compared with PsA, RA and AS. HRQoL was better in gout, whereas similar in PsA, RA and AS. Serum IL-23, an important cytokine in PsA, was significantly reduced after weight loss.
Keywords: cardiovascular, epidemiology, obesity, psoriatic arthritis

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Psoriasisartrit (PsA) är en inflammatorisk reumatisk sjukdom som karaktäriseras av inflammation i leder (artrit), fingrar eller tår (daktylit), senfästen (entesit) och ibland inflammation i ryggen (axial sjukdom). PsA är associerat med en ökad förekomst av samsjuklighet och försämrad hälsorelaterad livskvalitet (HRQoL). Mindre är känt avseende samsjuklighet i relation till andra vanliga, kroniska reumatiska sjukdomar. De ökade nivåerna av cytokiner och adipokiner, som man ser vid fetma, kan vara viktiga vid PsA. Viktminskning har visat sig minska sjukdomsaktiviteten, men effekterna på cytokiner och adipokiner hos patienter med PsA är okända.

Syfte: Syftena med studie I-IV var: Att studera förekomsten av kardiovaskulära riskfaktorer (KVRF) hos PsA patienter jämfört med kontroller från den allmänna befolkningen (I) och i jämförelse med andra inflammatoriska reumatiska sjukdomar (IRS) (II), att jämföra HRQoL hos patienter med PsA jämfört med andra IRS (III) och att studera effekterna av viktminskning på cytokiner och adipokiner i serum hos patienter med fetma och PsA (IV).

Metoder: I. PsA patienter (n=982), mellan 25 och 75 år, identifierades genom diagnosregistret på Reumatologkliniken Sahlgrenska Universitetssjukhuset och fick en enkät skickad till sig gällande förekomst av KVRF. Individer som besvarat nationella folkhälsoenkäten användes som kontroller.

II-III. Individer med PsA (n=1200), reumatoid artrit (RA) (n=1246), ankyloserande spondylit (AS) (n=1095) och gikt (n=1589) identifierades genom diagnosregister på tre reumatologkliniker och 12 vårdcentraler (för giktpatienter) i västra Sverige och fick en enkät gällande KVRF och HRQoL, mätt med enkäten RAND-36, skickad till sig.

IV. Patienter med PsA (n=41) och BMI ≥33 kg/m^2 och kontroller matchade för kön, ålder och vikt, inkluderades i en viktminskningsstudie där deltagarna fick lågenergipulver. Cytokiner och adipokiner mättes i serum vid studiestart och efter sex månader och relaterades till sjukdomsaktivitetsmåtten, Disease Activity in PSoriatic Arthritis (DAPSA) och Disease Activity Score for 28 joints using C-reactive protein (DAS28CRP).

Resultat: I. Fetma (BMI ≥30 kg/m^2) (28,6% jämfört med 16,3%, p<0,001), blodtryckssjukdom (40,3% jämfört med 24,1%, p<0,001) och diabetes (10,5% jämfört med 6,2%, p<0,001) var mer frekvent förekommande hos PsA patienter jämfört med hos kontroller.

II. Patienter med gikt rapporterade signifikant mer blodtryckssjukdom, höga blodfetter, diabetes, fetma och högre förekomst av flera samtidiga KVRF jämfört med patienter med PsA, RA och AS. Hos kvinnor var förekomsten av blodtryckssjukdom, fetma och flera samtidiga KVRF vanligare hos PsA jämfört med RA och AS.

III. Giktpatienter rapporterade bättre HRQoL jämfört med PsA, RA och AS. HRQoL var liknande vid PsA, RA och AS. HRQoL var sämre i fysiska domäner jämfört med mentala domäner för alla IRS. Kvinnor rapporterade sämre HRQoL jämfört med män.
IV. Viktminskning var hos PsA patienter associerad med minskade nivåer av interleukin (IL)-23, median (interkvartilavstånd) från 0,40 (0,17-0,54) ng/mL vid studiestart till 0,18 (0,10-0,30) ng/mL, samt minskat leptin efter sex månader (båda $p<0,001$). ΔIL-23 uppvisade en positiv korrelation med ΔBMI ($r_S=0,671$, $p<0,001$) och ΔDAS28CRP ($r_S=0,460$, $p=0,005$).
Slutsatser: KVRF var vanligare hos patienter med PsA jämfört med hos kontroller från den allmänna befolkningen. Hos kvinnor var KVRF vanligare hos PsA jämfört med RA och AS. KVRF var vanligare hos giktpatienter jämfört med hos andra IRS. HRQoL var bättre hos giktpatienter, men liknande hos PsA, RA och AS. Viktminskning var associerat med minskade nivåer av IL-23, som är en viktig cytokin vid PsA.

LIST OF PAPERS

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

I. Landgren AJ, Bilberg A, Eliasson B, Larsson I, Dehlin M, Jacobsson LTH, Klingberg E. Cardiovascular risk factors are highly overrepresented in Swedish patients with psoriatic arthritis compared with the general population. Scandinavian Journal of Rheumatology, 2019;00:1–5.

II. Landgren AJ, Dehlin M, Jacobsson L, Bergsten U, Klingberg E. Cardiovascular risk factors in gout, psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis: a cross-sectional survey of patients in Western Sweden. RMD Open, 2021;7:e001568.

III. Landgren AJ, Klingberg E, Jacobsson LTH, Bergsten U, Dehlin M. Health-related quality of life in gout, psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis, results from a cross-sectional survey in Western Sweden. Scandinavian Journal of Rheumatology, 2023 Feb 6;1-13.

IV. Landgren AJ, Jonsson CA, Bilberg A, Eliasson B, Torres L, Dehlin M, Jacobsson LTH, Gjertsson I, Larsson I, Klingberg E. Serum IL-23 significantly decreased in obese patients with psoriatic arthritis six months after a structured weight loss intervention. Submitted.

CONTENT

ABBREVIATIONS

AS	Ankylosing spondylitis
Ax	Axial
B	Biologic
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BL	Baseline
BMI	Body mass index
CASPAR	ClASsification criteria for Psoriatic ARthritis
CRP	C-reactive protein
Cs	Conventional synthetic
CVD	Cardiovascular disease
CVRF	Cardiovascular risk factor
DAPSA	Disease Activity Index in PSoriatic Arthritis
DAS28	Disease Activity Score for 28 joints
DIP	Distal interphalangeal
DLQI	Dermatology Life Quality Index
DMARD	Disease modifying anti-rheumatic drug
EQ-5D	EuroQol-5-dimensions
ESC	European Society of Cardiology
ESR	Erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
GP	General population
HAQ	Health Assessment Questionnaire
HLA	Human leukocyte antigen
HMW	High molecular weight
HRQoL	Health-related quality of life
HT	Hypertension
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
IFN	Interferon
IJD	Inflammatory joint disease
IL	Interleukin
IQR	Interquartile range
LED	Low energy diet
LMW	Low molecular weight
M6	Month 6
MCS	Mental component summary
MDA	Minimal disease activity
MHC	Major histocompatibility complex
MI	Myocardial infarction

NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratios
PA	Physical activity
PASI	Psoriasis Area Severity Index
PCS	Physical component summary
PsA	Psoriatic arthritis
PsO	Psoriasis
RA	Rheumatoid arthritis
RAND-36	RAND 36-Item Health Survey
RF	Rheumatoid factor
SCORE	Systematic Coronary Risk Evaluation
SD	Standard deviation
SF-36	36-item short-form health survey
SpA	Spondyloarthritis
Th	T-helper
TNF	Tumour necrosis factor
Tot	Total
Ts	Targeted synthetic
UK	United Kingdom
US	Ultrasound
USA	United States of America
uSpA	Undifferentiated spondyloarthritis
VAS	Visual analogue scale
VLED	Very low energy diet
WAT	White adipose tissue

1 BACKGROUND

1.1 INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory rheumatic disease characterized by psoriasis (PsO), enthesitis (inflammation at the insertion site of tendon or ligament to bone), often peripheral arthritis, dactylitis (a swelling of the entire finger or toe) and sometimes involvement of the axial skeleton, sacroiliitis and spondylarthritis (1). Unlike rheumatoid arthritis (RA) where symmetric polyarticular synovitis, systemic inflammation and often autoantibodies are detected (2), PsA has a more asymmetric joint involvement, is often seronegative to rheumatoid factor (RF) and inflammatory markers such as elevated c-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) are absent in around 50% of patients. There is currently no laboratory test available to determine the diagnosis. PsA is associated with pain and stiffness and can cause significant joint damage, disability and reductions in health-related quality of life (HRQoL) (1). The disease course is variable, in some patients severe and the importance of early identification and management to improve the prognosis has been highlighted (3), although it is difficult to know when the disease starts and a preclinical phase of many years may exist (4). PsO comes before PsA in most cases, whereas in around 10-15% the opposite applies (5). Up to 30% of PsO patients progress to PsA (1). Several comorbidities are more common in PsA compared to the general population (GP), such as obesity, hypertension (HT), hyperlipidaemia, diabetes, anxiety, depression and "extraarticular" manifestations such as uveitis and inflammatory bowel disease (IBD) (6).

1.2 EPIDEMIOLOGY

PsA is similarly prevalent in women and men (7, 8), and often diagnosed around 30-50 years of age, although it may occur at any time. Varying prevalence estimates have been reported, perhaps reflecting differences in criteria for determining if the patient has PsA, study methodologies and actual differences between populations. Swedish registry/population-based studies have estimated the prevalence of PsA between 0.21 and 0.35% (8-10), similar to the 0.19% prevalence of PsA reported in a study from the United Kingdom (UK) (11), but substantially lower compared to the prevalence of 0.67% reported in a Norwegian study (12). In line with this, a survey study conducted in the Nordic countries reported the highest prevalence of PsO and PsA in Norway (13). The incidence of PsA has been reported as around 20 per 100 000 person-years in 2014-2016 in a Swedish registry study, highest in ages

50-59 years old (14). A Danish registry study reported that the mean age at PsA diagnosis was around 50 years of age (15). In a recent meta-analysis, a greater prevalence of PsA was reported in PsO patients with more severe skin disease, where the prevalence was around one in four, highest in Nordic countries and lowest in Asian countries (16). A Swedish population-based registry study reported a PsA prevalence of 17.3% in PsO patients (9), whereas a study from the UK reported a prevalence of 8.6% (11). The incidence of PsA in PsO patients has been estimated between 0.27 to 2.7 per 100 person-years (16). Given the diagnostic challenges of PsA, a number of PsA patients within the PsO group are likely to be undiagnosed. A study from Northern Sweden in a mixed community/hospital based setting found that among 202 patients with PsO (diagnosed by a dermatologist or primary care physician), one third currently had or have had peripheral arthritis or axial disease judged by a rheumatologist upon clinical examination (17).

1.3 PSORIASIS

PsO is a multifactorial inflammatory skin disease (18). The prevalence around the world varies greatly. Compared to many other parts of the world, the prevalence is high in Western Europe where a prevalence of around 2% has been reported (19). PsO typically presents in sharply demarcated plaques, where chronic plaque PsO (psoriasis vulgaris) is the most common form. Other presentations include, but are not limited to, erythroderm, guttate, invers, nail disease (hyperkeratosis, pitting, onycholysis) and scalp PsO (18). Several comorbidities, such as HT, hyperlipidaemia and obesity are more common in PsO patients compared to patients without PsO, further described in chapter two.

1.4 CLINICAL PRESENTATION OF PSORIATIC ARTHRITIS

The clinical presentation of PsA is heterogenous and in most patients include PsO. Disease manifestations may include dactylitis, arthritis, enthesitis, axial disease, and extraarticular manifestations such as IBD and uveitis (6). Arthritis mutilans is a severe, rare and destructive form of PsA (20). In a Swedish study of early PsA, around half of the patients had mono/oligoarticular disease, and the other half had polyarticular disease at two years follow-up (21). A more polyarthritic disease, higher disease activity and worse clinical outcomes have been reported in women compared to men, whereas men more frequently had mono/oligoarthritis and/or axial disease (22). From the same Swedish early PsA cohort, a greater radiographic progression was reported in men, where 86% had radiographic changes on hands or feet at five-years follow-up (23).

In a Spanish study of early PsA, 32/71 (45%) of PsA patients developed erosive disease at ten years follow-up, most commonly seen in those with polyarticular onset (24). Differences in disease presentation comparing men and women with PsA have been discussed in a recent review, where the worse patient-reported outcomes regarding pain, fatigue, HRQoL as well as the typically later diagnosis in women calls for further investigations (25).

PsA often presents diagnostic challenges, especially early in the disease. Differential diagnoses include gout, osteoarthritis and RA (1). In addition, pain syndromes such as fibromyalgia are more common in PsA and in other inflammatory joint diseases (IJDs) compared to in the GP (26). Nail disease, distal interphalangeal (DIP)-joint arthritis, dactylitis and enthesitis are more common in PsA than in RA or osteoarthritis (6). In several IJDs, PsA included, there is a significant delay from the patient experiencing symptoms to seeking primary care (27). Diagnostic delay has been reported as a negative prognostic factor (3, 22), where a delay of ≥6 months from symptom onset until diagnosis of PsA has been associated with more radiographic progression and worse function (3). Other negative prognostic factors at disease presentation include polyarthritic disease (22, 24), increased levels of CRP or ESR (28) and smoking (29). Dactylitis is frequently associated with a more severe form of PsA (30) and obesity has been reported to impair treatment response (31, 32).

1.5 SPONDYLOARTHRITIS

Spondyloarthritis (SpA) is a term encompassing inflammatory rheumatic diseases that commonly engage the entheses, ligaments, tendons, spine and sacroiliac joints (33). A considerable common genetic base exists in patients within the SpA group (33). Ankylosing spondylitis (AS), PsA, reactive arthritis, IBD-associated arthritis, juvenile SpA and undifferentiated SpA (uSpA), are all part of the group, where AS is most studied. AS is more common in men and has a prevalence that is higher in Human Leukocyte Antigen (HLA-B27) positive populations (34). HLA-B27 positivity is more common in Northern (35) compared to Southern Sweden (36). AS is characterized by inflammatory back pain (IBP) along with stiffness and reduced mobility (37), which according to expert opinion from the Assessment of SpondyloArthritis international Society is characterized by; “age at onset <40 years of age, insidious onset, improvement with exercise, no improvement with rest, pain at night (with improvement upon getting up)” (38). In a Swedish study, around 95% of patients with AS have had symptoms that began before the age of 45 years (39). Axial involvement is less common in PsA patients compared with axial (ax)-SpA and has in PsA a tendency towards an older age at onset, a more equal sex distribution, less typical IBP,

more asymmetric and less severe sacroiliitis and radiographically more asymmetric syndesmophytes (calcifications or ossifications) are seen compared with axSpA (40). Estimating axial involvement in PsA is difficult due to lack of a common definition, but few patients (five percent or less) have been reported to have exclusively axial involvement (40).

1.6 RHEUMATOID ARTHRITIS

RA is characterized by systemic inflammation, symmetric polyarticular involvement typically in the hands and feet and often presence of autoantibodies (2). RA is around two to three times more common in women than in men and usually diagnosed around 60 years of age, although it can occur at any age (41). RA can also present with extraarticular manifestations, such as interstitial lung disease, pericarditis, pleuritis, amyloidosis, vasculitis and rheumatic noduli. Comorbidities include but are not limited to myocardial infarction (MI), stroke and osteoporosis (42).

1.7 GOUT

Gout is characterized by acute attacks/flares of arthritis, typically in the first metatarsophalangeal joint (43), but other joints can also be affected. Gout is most often a mono- or oligoarthritis, but can also manifest as a polyarthritis. With a world-wide prevalence of <1% to 6.8%, gout is the most prevalent inflammatory rheumatic joint disease, more commonly seen in men than in women and often diagnosed between 60 and 70 years of age (43). An increasing incidence around the world has been reported and the incidence increases with increasing age (43). Significant comorbidity with higher prevalence of HT, diabetes and obesity in women and men compared to GP controls already at first gout diagnosis have been reported (44). In Western Sweden a gout prevalence of 1.8% in 2012 was found (45).

1.8 CLASSIFICATION OF PSORIATIC ARTHRITIS

PsA belongs to the seronegative (frequently negative for RF) SpA group and was by Moll and Wright in 1973 described as an inflammatory arthritis with PsO and usual absence of RF (20). The previously used Moll and Wright classification criteria for PsA comprised five subgroups: DIP-joint involvement, mainly axial/spondylitis, asymmetric mono- or oligoarthritis, symmetric/asymmetric polyarthritis and arthritis mutilans. A number of limitations for the Moll and Wright criteria for PsA have been raised, such as

difficulties in discriminating between seronegative RA and PsA (46). Other classification criteria have been suggested, including Vasey and Espinoza and the modified European Spondyloarthropathy Study Group criteria for PsA (46, 47). In 2006, the ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria (table 1) were developed (48). The CASPAR criteria have showed better sensitivity, with equal specificity, in early PsA compared to the Moll and Wright criteria (49) and may be used in patients with inflammatory articular disease (entheseal, joint or spine). To fulfil the criteria ≥3 points are required.

Table 1, Classification criteria for Psoriatic Arthritis (CASPAR)

Range of points	Applicable in patients with inflammatory articular disease, involving joint, spine or enthesis
0-2	Active skin psoriasis (2p), own history of psoriasis (PsO) or history of PsO in a first/second degree relative psoriasis (1p)
0-1	Typical psoriatic nail changes; onycholysis, hyperkeratosis or pitting
0-1	Negative test for rheumatoid factor (RF), latex method not included (1p)
0-1	Current dactylitis/a history of dactylitis documented by a rheumatologist (1p)
0-1	Radiographic juxta articular formation of new bone, ill-defined ossification near joint margins (osteophyte formation excluded) on plain radiographs of hand or foot (1p)

1.9 RISK FACTORS FOR PSORIATIC ARTHRITIS IN PSORIASIS PATIENTS

Risk factors for developing PsA in PsO patients include nail/invers/scalp PsO (50), severe skin PsO, uveitis and low education (51), subclinical enthesitis identified with ultrasound (US) (52), diffuse musculoskeletal symptoms and arthralgia (53) and obesity (both in patients with and without PsO) (54-56).

1.10 PATHOGENESIS OF PSORIATIC ARTHRITIS

There is a considerable heritability in PsO and PsA (57). An Icelandic study found a 39 times increased risk of PsA in individuals with a first-degree relative with PsA (58). Whereas RA is associated with class II Major Histocompatibility Complex (MHC)II, PsA and PsO are associated with

MHCI (1). Certain human leukocyte antigens (HLA)-variants are associated with different disease phenotypes, HLA*B08, HLA*B2 and HLA*B38 being more strongly associated with PsA compared with PsO (59), whereas HLA-C*06:02 is strongly associated with PsO (60). HLA*B27 has been associated with developing symmetric sacroiliitis, enthesitis and dactylitis (61). Genes associated with PsA include polymorphisms in the interleukin (IL)-23 receptor (IL23R) coding gene, genes that regulate the expression and signalling of nuclear factor κβ (NF-κβ), expression of tumor necrosis factor (TNF), IL-12A and IL-12B (1).

Although earlier reports have recognized the important role of T-cells in PsA (1), the enthesitis-driven hypothesis of psoriatic disease as autoinflammatory is increasingly recognized (62). Cytokines (proteins that are involved in communication between cells), mainly TNF-α, IL-23, IL-22 and IL-17, are of importance in PsA as well as in SpA (62). Diverse subsets of T-cells are capable of secreting different cytokines. T-helper (Th)1 cells, mainly implicated in cell-mediated immunity, produce interferon gamma (IFN-γ). Th2 cells are capable of IL-4, IL-5 and IL-13 production, which are vital in allergies and humoral immunity. Th17 cells can secrete IL-17A, IL-17F, IL-21 and IL-22. Th17 cells are crucial in PsA, contributing to autoimmune inflammation, mainly through production of IL-17A (63), that increases the production of inflammatory cytokines including TNF-α, IL-6 and IL-1. IL-17 can be produced by innate lymphoid cells, γδ T-cells and natural killer cells (64). IL-23 (comprising subunit p19 (unique for IL-23) and p40 (shared with IL-12)) promotes IL-17 production (64). IL-23 is produced by several immune cells, including monocytes, macrophages and dendritic cells (64), but also by cells within the enthesis that can produce IL-23 and IL-17 (62). IL-17, IL-22 and IL-23 have roles in keratinocyte proliferation (PsO) (65) and enthesitis, arthritis, new-bone formation and bone loss (PsA) (64). Inhibiting TNF-α, IL-17 and IL-23 is effective in PsO and PsA (65-67).

The enthesis was previously regarded as an avascular structure which function was limited to serve as a link between bone and joint or joint and muscle, however in recent years, it´s role in PsA has been highlighted (68). Repetitive loading of an enthesis, exacerbated by high body weight, leading to microtrauma and subsequent microdamage along with increased vascularity and influx of inflammatory cells into the enthesis are suggested to be important in SpA (69). The term synovio-entheseal complex has been used to describe the intimate anatomical link between synovium and enthesis (69). In a recent review by Girolimetto et al, the close link between flexor tenosynovitis and dactylitis as shown by US and magnetic resonance imaging is discussed (70). In early dactylitis, tenosynovitis and soft tissue oedema is more prominent than synovitis whereas in long-standing dactylitis, the

opposite is seen, perhaps signalling that the origin of the inflammation in dactylitis is outside rather than inside the synovium (70). The DIP joint is linked to the nail root and nail matrix through the extension tendon of the DIP joint and with the nail also being anchored to the bone, providing an intimate link between DIP joint involvement, enthesitis and psoriatic nail disease (71). The importance of mechanical stress in SpA is supported by the similarity between the enthesis and other junction points that are subject to repetitive mechanical stress, such as the aortic root, terminal ileum and ciliary body of the eye (62, 72) that are sites of extraarticular involvement in SpA. Mechanical stress, bone and joint trauma along with other factors such as certain infections (73-75), changes in gut microbiota and subclinical gut inflammation may also play a role in PsA (76). In PsO, keratinocytes (producing and responding to cytokines and chemokines (chemotactic cytokines), neutrophils, dendritic cells, T-cells and antimicrobial peptides present in psoriatic skin are central in PsO development (77).

1.11 TREATMENT OF PSORIATIC ARTHRITIS

Treatment guidelines for PsA are available from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (78), American College of Rheumatology/National Psoriasis Foundation (79), European Alliance of Associations for Rheumatology (EULAR) (80) and in Sweden from the Swedish rheumatologic society. The Swedish treatment guidelines for spondyloarthritis and PsA are updated yearly https://riktlinjer.svenskreumatologi.se/

The treatment of PsA is influenced by several factors: the presentation of the disease (mono/oligo/polyarticular, peripheral/axial), presence of negative prognostic factors including dactylitis, erosive disease, increased ESR or CRP, enthesitis, skin/nail PsO, musculoskeletal/articular manifestations, extra-articular manifestations such as IBD or uveitis as well as comorbidities. According to the Swedish guidelines, intra-articular injections with corticosteroids, along with oral non-steroidal anti-inflammatory drugs (NSAIDs), having a symptom relieving effect, can be used in mono/oligoarticular disease without negative prognostic factors. In mono/oligoarticular disease with negative prognostic factors, or if inadequate effect of intra-articular corticosteroids or NSAIDs, or in polyarticular disease, conventional synthetic (cs) disease modifying anti-rheumatic drug (DMARD)s (mainly methotrexate) is the first line of therapy. Leflunomide and sulfasalazine can also be used in mono/oligoarticular disease. Biologic (b)-DMARDs or targeted synthetic (ts)-DMARDs should be considered in patients with inadequate or no effect after ≥3 months treatment with cs-

DMARD and in patients presenting with very high disease activity. TNF-inhibitors are the currently preferred b-DMARD, due to their lower price. If presence of skin PsO and failing a TNF-inhibitor, an IL-17-inhibitor can be used (contraindicated if presence of IBD). Janus kinase-inhibitors, IL-12/IL-23 inhibitors, IL-23 p19 inhibitors, CTLA4-Ig fusion protein abatacept and phosphodieserase-4-inhibitors are other available options if failing a TNF-inhibitor. Physical therapy and increased physical activity (PA) are important parts of the non-pharmacological management. PsA is frequently associated with comorbidities, necessitating multidisciplinary efforts (for example between rheumatologist and dermatologist if severe PsO, gastroenterologist if concomitant IBD, or primary care physician or cardiologist if presence of cardiovascular risk factors (CVRFs).

1.12 DISEASE ASSESSMENT

Different instruments are available to assess PsO. Using the Body Surface Area , a grading of the severity of PsO (mild/moderate/severe) is done based on how large proportion of the skin that is affected (81). In Psoriasis Area Severity Index (PASI), scores between (0=no involvement and 4=severe involvement) are attributed to the head, arms, trunk and legs depending on the area of skin involved, erythema, induration or desquamation (82). The Dermatology Life Quality Index (DLQI) is an instrument used in various skin diseases to assess symptoms and impact of skin disease on daily life (83).

Disease Activity Score for 28 joints (DAS28), consists of 28 joint counts of tender/swollen joints (hands, elbows, shoulders and knees), along with the patient´s global health assessment, measured with a visual analogue (VAS) scale ranging 0-100 mm (84). DAS28 scores range from 0 to 9.4, where a score of <2.6 is defined as clinical remission, whereas scores from 2.6 to <3.2, 3.2-5.1 and >5.1 are considered low, medium, or high disease activity. DAS28 was originally developed for RA (85), but is frequently used in PsA although not including DIP-joints and joints of the feet. Disease Activity Index in PSoriatic Arthritis (DAPSA) (86, 87) has the advantage of including the 68 tender/66 swollen joints count, together with the patient´s assessment of disease activity, pain during the last week and CRP. High DAPSA scores have been associated with radiologic changes as well as changes in function in PsA (88). DAPSA scores of <4 indicates disease remission, low (4.1-14), average (14.1-27.9) and high (>28) disease activity. An improvement of DAPSA score of >50% is considered low, >75% average, and >85% considerable.

The Health Assessment Questionnaire (HAQ) is a 20-item questionnaire measuring activity limitations. Total scores range from zero to three where zero indicates no impairment and three total impairment (89). The Bath

Ankylosing Spondylitis Disease Activity Index (BASDAI) (90) comprises six questions assessing spinal pain, joint pain and swelling, enthesitis, fatigue and morning stiffness (duration, severity), during the last week. The Bath Ankylosing Spondylitis Functional Index (BASFI), is an instrument consisting of ten questions, used to assess functional limitations (91). BASDAI and BASFI are traditionally used in AS but can also be used in PsA to assess the axial component of the disease. The Leeds Enthesitis Index, specifically developed for PsA, is frequently used to assess enthesitis, by evaluating tenderness of the bilateral locations of the insertion of the achilles tendon, lateral elbow epicondyle and medial femoral condyle (92).

When treating PsA, Minimal Disease Activity (MDA) (93) is often strived for, defined as meeting five out of seven domains. The domains concern joints (tender joint count ≤1, swollen joint count ≤1), entheses (enthesitis count ≤1), PsO (PASI ≤1 or Body Surface Area ≤3%), physical function (HAQ) ≤0.5), global assessment (patient´s global VAS (0-100) ≤20) and patient´s pain VAS (0-100) ≤15). If meeting all seven criteria, the patient is considered to have very low disease activity (94). Instruments for assessing HRQoL are described in chapter four.

2 CARDIOVASCULAR RISK FACTORS IN INFLAMMATORY JOINT DISEASE

2.1 INTRODUCTION

More than 90% of the population attributable risk of MI in the GP has been ascribed to a number of CVRFs, there among smoking, HT, increased lipids, diabetes, obesity and low PA (95). Patients with IJDs are subject to a higher risk of cardiovascular disease (CVD), due to chronic inflammation and an increased number of CVRFs (96). In RA, an increased risk of MI, comparable to the risk in diabetes mellitus has been reported (97-99). Inflammation is likely to be important in atherosclerosis (100) and high disease activity has been associated with increased CVD risk in PsA (101), RA (102) and AS (103). In gout, a recent flare (characterized by acute inflammation abundant with neutrophils) has been associated with increased risk of subsequent MI or stroke (104). Some CVRFs are implicated in the pathogenesis of IJD, for example smoking in Anti-Citrullinated Protein Antibody positive RA (105) and obesity in PsA (55) and gout (106). Increased prevalence of CVRFs compared to the GP have been reported in RA (107, 108), as well as in gout (44) and AS (108, 109). Accumulation of CVRFs in patients with RA, axSpA and PsA have been shown in a Norwegian study where HT and elevated cholesterol were the most frequently occurring CVRFs and higher occurrence of obesity and HT were seen in PsA than in RA and axSpA (110). Prevalence of CVRFs and risk of CVD have been more extensively researched in RA compared with SpA.

The importance of controlling disease activity in RA, PsA and AS in order to lower CVD risk has been emphasized in EULAR recommendations (96). Earlier EULAR recommendations recommended a 1.5 multiplication of Systematic Coronary Risk Evaluation (SCORE) (111) in RA patients with certain disease characteristics (112) now applies to all RA patients (96). To date there is no recommendation for a multiplicative SCORE approach in other IJDs. CVD risk assessments are recommended at least once every five years in IJD patients with low to moderate risk, more often in those with higher risk and should also be considered after major changes in anti-rheumatic treatment (96). Due to the paradoxical lowering effect of inflammation on lipid components, lipids should be measured in stable disease activity, or in disease remission (96). CVD risk estimation through validated instruments are recommended in the guidelines from the European Society of Cardiology (ESC) (113). Different CVD risk calculation tools are available,

such as the Framingham risk score (114), Reynolds risk score (115), and the more recent SCORE2 (116).

2.2 PSORIATIC ARTHRITIS

The American Heart Association and American College of Cardiology recognizes PsO as a risk enhancing factor for CVD (117). Increased risk of MI, stroke and venous thromboembolism have been showed in PsA, uSpA and AS compared to the GP in a Swedish registry study (118). The burden of atherosclerosis has been reported as higher in PsA compared with PsO and to correlate with increased inflammation (119). In a study of 235 patients with PsA, higher disease activity was associated with more atherosclerotic plaque (120). Disease activity, as shown by high DAPSA scores, has been reported as an independent CVRF in patients with PsA (101), whereas treatment with biologics resulted in a reduction of coronary plaque burden in patients with moderate to severe PsO (121). Treatment with TNF-α inhibitors have demonstrated reductions in serum leptin, resistin and lipids in patients with PsO (122). An overrepresentation of CVRFs, such as obesity, HT, diabetes, hyperlipidaemia and smoking has been reported in PsO (123-125) and PsA (107, 126-129) compared to patients without PsO or PsA. In a multicentre study comprising 2254 patients with PsO or PsA from Canada, the United States of America (USA) and Israel, a substantial proportion of patients had dyslipidaemia or HT (130).

In PsA, higher prevalence of obesity, HT, diabetes and hyperlipidaemia, compared with PsO (126, 131, 132) and RA (126, 132) and more diabetes, elevated lipids and obesity compared with RA (133) and more obesity compared with other IJDs have been reported (134). An underestimation of CVD risk by different CVD risk calculators have been shown in early RA (135) as well as in PsA (136, 137). In the 2021 guidelines on CVD prevention, the ESC recognizes carotid plaque as an important CVRF (138). To assess CVD risk in IJD patients, a study combined US on carotid arteries with different CVD risk calculators in patients with PsA, RA and AS, resulting in a significant proportion of patients being reclassified into a higher CVD risk category upon adding information about presence of carotid plaque (136). Prevalence of asymptomatic carotid plaque were similar across IJDs, present in as many as 40.1% of the 49 PsA patients with a median age of 55, similar to another study that reported comparable degree of arterial stiffness in PsA, RA and AS (139).

2.3 UNDERDIAGNOSED AND UNDERTREATED CARDIOVASCULAR RISK FACTORS

CVRFs are often underdiagnosed and undertreated in IJDs. Suboptimal identification and management of obesity, HT and hyperlipidaemia in RA patients compared to patients with diabetes or the GP has been reported in a retrospective cohort study from the USA, where patient records were reviewed for 251 patients with RA, diabetes and from the GP that were matched for age, gender and ethnicity (140). In contrast, another study from the USA, showed that RA patients were more likely to receive anti-HT or anti-diabetic medications, but not statins, compared to matched GP controls (141). Yet another study from the USA reported that among 3298 RA patients, ≥65 years of age, without diabetes mellitus, hyperlipidaemia or CVD, only 45% had undergone lipid screening during the years 2004-2006 (142). In an English study from 2011, where a questionnaire was sent to 376 general practitioners, RA was identified as an independent CVRF by only 32% of the general practitioners (143). In a Norwegian multicentre study assessing RA, axSpA and PsA patients, undertreatment of hyperlipidaemia and HT were reported in all IJDs (144). RA patients were more often undertreated regarding lipids, whereas undertreatment of HT was more common in PsA patients (144). In another multicentre study, published in 2018, comprising over 2000 patients with PsO or PsA from eight centres in Canada, USA or Israel, a significant undertreatment of HT and dyslipidaemia was reported, more frequently in those with PsO instead of PsA, ≤50 years of age and in men (130). In RA, The management of CVRFs by a multidisciplinary approach, involving rheumatologists and cardiologists have been suggested (145) and successful treatment of hyperlipidaemia has been reported in RA, PsA and AS patients in a Norwegian preventive combined cardio-rheuma clinic, where lipid target levels were reached in around 90% of patients (146). From the same clinic, Rollefstad et al showed that the degree of inflammation at baseline (BL) did not affect the doses of lipid-lowering drugs needed to reach lipid target levels in IJDs (147).

3 OBESITY AND AUTOIMMUNITY

3.1 INTRODUCTION

In obesity, the white adipose tissue (WAT) secretes a number of cytokines that increase inflammation through increased influx of macrophages and other immune cells and a shift from an anti-inflammatory M2 type of macrophage to inflammatory M1 macrophages (148). Adipocytes themselves are capable of cytokine and adipokine secretion (149) and together with Th17 cells, macrophages and other immune cells that infiltrate the WAT in obesity, an inflammatory milieu is created (150).

3.2 OBESITY IN PSORIATIC ARTHRITIS

Several studies have reported an overrepresentation of obesity in PsA compared to the GP (126-128), PsO (126) and RA (126, 133). Obesity increases the risk of developing PsA (54, 55, 151), increases disease activity (152) and negatively affects treatment outcomes (32, 152-154). Mendelian randomization studies have found associations between BMI and PsO (155) and between genetically predicted body size during childhood and PsA (156). Several cytokines and adipokines, including TNF-α, IL-1, IL-6, IL-17, IL-23, leptin, resistin and adiponectin, are influenced by obesity (148, 157, 158). Cytokines and adipokines may be produced by the WAT, as well as in fat pads in joints, and can influence the development of enthesitis and PsA (159). A meta-analysis found elevated serum levels of TNF-α, IFN-γ, IL-2, IL-6, IL-8, IL-18, IL-22 and resistin in PsO, but no significant difference in IL-17 and IL-23 levels compared to controls (160). Cells that produce IL-17 have however been reported as increased comparing PsO skin to non-PsO skin (161) and in synovial fluid in joints of PsA patients compared with RA patients (162). Higher adiponectin levels have been reported in patients with PsA compared to PsO, along with positive but weak correlations with active and damaged joints in PsA (163).

3.2.1 EFFECTS OF WEIGHT LOSS IN PSORIATIC ARTHRITIS

Bariatric surgery has been shown to decrease the risk of developing PsO in patients without PsO at BL in a Swedish long-term follow-up study, where however no significantly reduced risk for PsA was seen (164). In a Danish nationwide study, gastric bypass but not gastric banding lowered the risk of PsO and PsA (165). In 41 patients with PsA with a BL BMI ≥33 kg/m^2, reduced weight through Very Low Energy Diet (VLED) has been associated

with lowered disease activity measured by Disease Activity Score for 28 joints using CRP (DAS28CRP) and DAPSA after six months follow-up (166), which remained lowered at two years follow-up (167). In a dietary weight loss study where 60 overweight patients were randomized to either Low Energy Diet (LED) or to a control group without LED, greater reductions in body weight, PASI and DLQI were seen in the LED-group both at 16 weeks (168) and remained improved at 64 weeks follow-up (169). In a study where overweight/obese PsA patients were started on treatment with TNF-α inhibitors and a hypocaloric diet, a significant and dose-dependent effect of weight loss on the chance of reaching MDA after six months was reported (153). A meta-analysis from 2019 indicates that weight loss can improve PsO and PsA and prevent PsO in obese individuals, but that less data exists for PsA (170).

3.3 OBESITY IN OTHER INFLAMMATORY JOINT DISEASES

Conflicting results regarding obesity and RA have been reported. Some have reported obesity to be associated with a higher risk of developing RA (171-173), whereas others have found a reduced risk of RA in overweight/obese men but not in women (174) and less radiographic progression in overweight RA patients (175). A long-term follow-up study, where patients without RA at BL were followed up to 29 years after bariatric surgery, did not detect any significant effect on the risk of developing RA (176). Gout is linked with the metabolic syndrome (43) and bariatric surgery was associated with a lowered risk for gout in a long-term follow-up study of individuals without gout at BL (177). In a Swedish study of 166 patients with AS, obesity at BL was associated to a higher risk of syndesmophyte progression in the spine at five-years follow-up (178). In a study assessing risk factors for AS, RA, PsO and PsA, obesity was a risk factor for PsO and PsA (179). In a recent systematic review and meta-analysis, obesity resulted in poorer response to TNF-α inhibition in RA and SpA including PsA (180).

3.4 CYTOKINES AND ADIPOKINES IN OBESITY IN INFLAMMATORY JOINT DISEASES

TNF-α, IL-1, IL-6 and CRP is frequently elevated in obesity (181). TNF-α has been reported to be secreted by WAT (149) and is important in PsA and in other SpA. In a small cross-sectional study of non-IJD patients, higher plasma levels of IL-17 and IL-23 were noted in obese (n=26) compared to non-obese

(n=20) women (182). In a study comprising 32 obese patients undergoing bariatric surgery, significantly reduced IL-1β, IFN-γ, IL-6, TNF-α, IL-23 but not IL-17 levels were seen comparing preoperative values and values six months after bariatric surgery (183). Others have reported altered cytokine secretion in follicular helper T-cells after bariatric surgery, including lowered IFN-γ, IL-2, IL-4 and IL-17 secretion (184).

Leptin is an adipokine with a central function communicating the size of the adipose tissue and regulating appetite. It is mainly produced in WAT and positively correlates with amount of body fat (149, 185). Leptin´s inflammatory properties include increasing the number of Th17 cells and levels of several cytokines, there among TNF-α, IL-1β, IL-6, IL-12, and IL-17 (186). Resistin, also inflammatory and secreted by WAT, is higher in obesity than in the lean state (149). In a meta-analysis comprising studies with information on leptin (n=26), adiponectin (n=25) and resistin levels (n=15) in patients with PsO and controls, higher serum leptin and resistin but lower adiponectin levels were reported in patients with PsO (187). Adiponectin, produced by adipocytes, but inversely related to the degree of obesity (149), circulates in the blood in different isoforms with different molecular weight and has been ascribed inflammatory as well as anti-inflammatory properties depending on it´s isoform, binding receptor and effector site (188, 189). In a recent review study, although not including patients with PsO or PsA, contrasting findings regarding adiponectin levels (increased as well as unchanged) along with reductions in several inflammatory cytokines and adipokines, there among leptin, CRP, IL-6 and TNF-α, were reported after weight loss by diet or bariatric surgery (190).

4 HEALTH-RELATED QUALITY OF LIFE IN INFLAMMATORY JOINT DISEASE

4.1 INTRODUCTION

HRQoL is often used to describe an individual´s function, physical and mental well-being (191). Lowered HRQoL has been reported in PsA (192), RA (192-194), AS (193, 195, 196) and gout (197), compared with controls. The IJD as well as comorbidities may affect HRQoL. A number of instruments can be used to measure HRQoL, there among the often used EuroQol-5-dimensions (EQ-5D), consisting of five questions (198). Another frequently used instrument is the Medical Outcomes Study 36-item short-form health survey (SF-36), comprising eight domains: physical functioning (PF), role physical (RP), social functioning (SF), role emotional (RE), mental health (MH), vitality (VT), bodily pain (BP), and general health (GH) (199). Summary scores for physical (Physical Component Summary (PCS)) and mental (Mental Component Summary (MCS) HRQoL, with scores 0-100 respectively based on values from a reference population, can be calculated. Scores higher than 50 represent better health status compared to the reference population. The RAND 36-Item Health Survey (RAND-36) is a newer, but similar alternative to SF-36 that has been reported as reliable in a study assessing the Swedish version of RAND-36 (200). Similar results for the summary scores have been reported for SF-36 and RAND-36 (201) and the SF-36 has been reported as valid in PsA (202), RA (194, 203), AS (195) and gout (204). Studies comparing physical HRQoL (PCS) and mental HRQoL (MCS) in different IJDs have shown conflicting results. Some studies have reported higher PCS in AS compared with RA (193, 205), whereas a review study stated similar reductions in HRQoL among patients with AS and RA (196).

4.2 HEALTH-RELATED QUALITY OF LIFE IN PSORIATIC ARTHRITIS

In a study of 405 patients with PsA, HRQoL was reduced compared to the GP already at PsA diagnosis (206). In a study comparing HRQoL in 201 PsA and 201 PsO patients, HRQoL was worse in PsA (207), in accordance with a newer review study (208). Similarly to in other IJDs, a lower PCS score compared to MCS score has been reported in PsA (192), nevertheless PsA has been shown to substantially impact mental well-being and participation in social activities (208). The prevalence of anxiety and depression have been reported as higher in PsA compared to PsO (209). Worse PCS scores have

however been reported in RA compared with PsA and AS, in non age-matched analysis (192), similarly to a study by Husted et al from 2001 that reported worse PCS but similar MCS in 43 RA patients compared with 107 PsA patients (210). In contrast, a small study of 47 PsA and 47 RA patients, showed no difference in HRQoL, using EQ-5D, in PsA compared to RA (211).

5 AIMS

The general aim of this thesis was to study CVRFs, HRQoL and effects of weight loss on serum cytokines and adipokines in PsA. Specific aims and corresponding studies were as follows.

I. Assess the prevalence of CVRFs in patients with PsA, compare the prevalence between sexes and with the GP (overall and by sex).
II. Assess and compare the prevalence of single and multiple CVRFs in PsA, gout, RA and AS, overall and stratified by sex.
III. Compare HRQoL, measured by RAND-36 between patients with PsA, gout, RA and AS, overall, divided by sex and between women and men for respective IJD diagnosis.
IV. Evaluate the effects of VLED on serum cytokines and adipokines six months after BL in a weight loss intervention in obese patients with PsA and controls matched for sex, age and weight.

6 SUMMARY OF METHODS

6.1 STUDY I

6.1.1 SETTING

This cross-sectional questionnaire study was performed in Western Sweden, where PsA patients were retrieved and compared to a national sample from the GP.

6.1.2 PATIENTS AND CONTROLS

PsA patients (n=982) in the ages 25-75 years old with International Classification of Diseases (ICD)-10 codes L40.5, M07.2, and M07.3 and ≥1 visit to the Rheumatology Clinic at Sahlgrenska University Hospital, Gothenburg, between 1 January 2014 and 1 March 2016, were identified through the clinic´s patient register.

As controls, individuals replying to the 2016 Swedish National Public Health Survey was used. The survey is administered by the Public Health Agency of Sweden and was in 2016 sent to 20 000 randomly selected Swedish citizens. The GP controls (n=7559) were matched for sex and age to the PsA patients. Data from the Swedish National Public Health Survey can be retrieved from the National Board of Health and Welfare upon request.

6.1.3 QUESTIONNAIRE

A postal questionnaire including questions about weight, height, smoking habits, HT, diabetes and hyperlipidaemia was sent to PsA patients. They were also asked if interested in participation in a weight loss study (study IV), if BMI ≥33 kg/m^2. A reminder questionnaire was sent to those not replying to the first one. Based on the answers in the questionnaire, variables were defined as following: Normal weight (BMI <25.0 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), obesity (BMI ≥30.0 kg/m^2). Occurrence of diabetes (self-reported treatment), hypertension, hyperlipidaemia and smoking status was assessed.

6.1.4 STATISTICS

Utilizing data from the 2016 Swedish National Public Health Survey, comparisons of PsA patients with the GP were done for the entire groups as well as by sex and age groups (27-44, 45-60, 61-75, years of age). Descriptive statistics (percentages, mean and standard deviation (SD)) were calculated. Composite variables of prevalence of 0-4 CVRFs (obesity, ever smoking,

hypertension, diabetes) were computed. PsA and controls were compared by independent samples t-test, chi-square or Fischer´s exact test. Odds ratios (OR) were calculated by logistic regression. SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

6.1.5 ETHICS

The study was approved by the Regional Ethics Committee in Gothenburg (reference number 901-15). Replying to the questionnaire was considered informed consent.

6.2 STUDY II-III

6.2.1 SETTING

In the cross-sectional questionnaire studies II-III that were set in Western Sweden, patients with PsA, gout, RA and AS, were retrieved from local patient registries and sent a postal questionnaire (a different questionnaire compared to the one used in study I).

6.2.2 PATIENTS

Individuals ≥18 years of age and with ≥1 ICD-10 diagnosis of PsA, gout, RA or AS, documented at a healthcare visit to a doctor at a rheumatology clinic (for all patients) or at any of twelve randomly selected primary care centres (patients with gout), during January 2015 through February 2017, were identified. The rheumatology clinics of Sahlgrenska University Hospital (gout, PsA, RA, AS), Uddevalla hospital (RA, AS) and Skövde hospital (PsA, RA, AS) were used to retrieve patients. Randomly selected patients with RA (n=1246) and PsA (n=1200), with a pre-decided equal distribution of women and men, were included and sent a questionnaire. All patients with AS (n=1095) and gout (n=1589) were sent a questionnaire. The questionnaires were sent in 2017.

6.2.3 QUESTIONNAIRE

The postal questionnaire sent to the patients with PsA, RA, AS and gout included questions about height, weight, education, CVRFs (HT, diabetes, hyperlipidaemia, low PA, sedentary lifestyle, smoking), HRQoL (RAND-36), numeric rating scales (NRS) for global health, pain, fatigue and current medication. CVRFs (study II) were defined as: Obesity (BMI ≥30.0 kg/m^2), low PA (≤3 hours per week), a sedentary lifestyle (total daily sitting time, excluding time spent sleeping ≥7 hours + ≤3 hours of PA per week), smoking (‘current’, ‘ever’ smoker), hypertension (yes), hyperlipidaemia (yes) or

diabetes (yes). Composite variables assessing occurrence of ‘minimum one to four CVRFs‘ (hypertension, obesity, hyperlipidaemia, diabetes, current smoking and a sedentary lifestyle) were created. In study III, a comorbidity score ranged from zero to six was created by attributing one point per each self-reported diagnosis of: diabetes, MI, stroke, cancer, kidney disease, lung disease.

6.2.4 STATISTICS

Descriptives (absolute counts and percentages) were calculated for categorical variables and means (SD) for continuous variables. For comparing categorical variables and age-standardised rates/prevalence across IJDs (study II), chi-square tests were used. Age standardisation was done to enable comparisons of CVRFs across IJDs with different age distributions. The Swedish population from 2018, retrieved from Statistics Sweden and divided in five-year age intervals, was used as the standard population for age standardisation. For comparing mean values for continuous variables, independent samples t-tests or analysis of variance were used. In study III, age- and sex-matching on +/-2 years were done across the four IJDs. The RAND-36 summary scores (PCS and MCS) were calculated using the Swedish normative population.

6.2.5 ETHICS

Ethical approval was granted by the Regional Ethical Review Board in Gothenburg, Sweden (approval number 519-16). Returning the questionnaire was considered informed consent, and participants received written information that the data would be published on a group level.

6.3 STUDY IV

6.3.1 SETTING

This open intervention study was set at the Department of Rheumatology at Sahlgrenska University hospital, Gothenburg, Western Sweden. Data from the six months (M6) follow-up visit was used and compared to the baseline (BL) visit.

6.3.2 PATIENTS AND CONTROLS

Patients between 25-75 years of age with PsA (ICD-10 codes L40.5, M07.2, and M07.3) were recruited from the Sahlgrenska University Hospital and the rheumatology clinics in Alingsås and Borås, Patients that fulfilled the CASPAR criteria (48) and had a BMI $\geq$33 kg/m^2 were included. Exclusion criteria were: binge eating disorders, epilepsy, mental imbalance affecting

participation, pregnancy, porphyria, severe heart, kidney or catabolic disease and type 1 diabetes. In addition, those treated with warfarin, lithionin or phenantoin, having had a MI, stroke, major surgery or trauma during the last three months or treated for cancer the last five years were not eligible for the study. Controls with obesity already planned for weight loss treatment were recruited from the Regional Obesity Centre at Sahlgrenska University Hospital and matched for age, sex and weight to the PsA patients. In controls, the same exclusion criteria as in PsA patients, with the addition of PsO or any rheumatic disease, were applied.

6.3.3 INTERVENTION

PsA patients and controls were given VLED, containing 640 kcal per day, for 12 or 16 weeks, depending on BMI <40 or ≥40 kg/m^2 at BL. Subsequently, food was gradually reintroduced during 12 weeks along with personal energy-restricted dietary advice. Patients and controls were followed during 12 months at the Regional Obesity Centre at Sahlgrenska University Hospital compliant with the routine for structured weight loss treatment. Patients and controls were seen by a physiotherapist at the rheumatology department at BL and after six, 12 and 24 months and were encouraged to do PA ≥150 min per week throughout the study period.

6.3.4 ASSESSMENTS

The PsA patients were examined at the Department of Rheumatology at Sahlgrenska University hospital at BL, three, six, 12 and 24 months. The controls were followed in a similar manner until 12 months. In study IV, data from BL and M6 was utilized. PsA patients were assessed with joint and skin examinations, measurements of weight and height and answered questionnaires (HAQ, VAS scales for pain, fatigue and patients´ global disease activity) at BL and M6, whereas controls were assessed with body weight and height measurements. Serum levels of CRP, cytokines (TNF-α, IL-1β, IL-6, IL-8, IL-12/IL-23 p40, IL-13, IL-17, IL-23, interferon (IFN)-γ) and adipokines (leptin, resistin, total (tot)-adiponectin and High Molecular Weight (HMW) adiponectin were measured at BL and at M6. CRP was analysed by standard laboratory techniques. Cytokines and adipokines were measured using Human Magnetic Luminex® Assays (R&D-systems), according to instructions by the manufacturers, at the Department of Rheumatology and Inflammation research, University of Gothenburg.

6.3.5 STATISTICS

Descriptive statistics (numbers, percentages, median and interquartile range (IQR)) were calculated. Group comparisons were made using the Mann-

Whitney U and chi-square test, for continuous and categorical unrelated variables respectively. For continuous related samples, Wilcoxon Signed Rank Test was performed. Spearman's correlation (r_S) was performed to assess correlations between delta values (change between BL and M6) of selected variables.

6.3.6 ETHICS

Study approval was granted by the Regional Ethics Committee in Gothenburg (approval number 901-15) and the study participants provided written informed consent.

7 SUMMARY OF RESULTS

7.1 STUDY I

In this cross-sectional study, a questionnaire was sent to 982 PsA patients, of which 692 (70.6%) replied. The mean (SD) age of the respondents were 55.6 (11.4) years, with a similar sex ratio, 360 (52%) women and 332 (48%) men. From the GP, 7559 individuals were matched for sex and age to the PsA patients. Self-reported CVRFs comprised: Overweight/obesity, HT, diabetes, smoking status (current/former/ever/non) smokers and hyperlipidaemia (available in PsA but not in the GP). Obesity, ever smoking, HT, diabetes and two, three and four CVRFs were more prevalent in PsA patients compared to the GP controls (table 2).

Table 2, Comparison of patients with PsA and matched GP controls

	PsA (n=692)	Controls (n=7559)	p-value
Obesity	198 (28.6)	1231 (16.3)	<0.001
Ever smoking	354 (51.1)	3121 (41.3)	<0.001
Hypertension	279 (40.3)	1801 (24.1)	<0.001
Diabetes	73 (10.5)	468 (6.2)	<0.001
1 CVRF	251 (36.3)	2828 (37.4)	0.553
2 CVRFs	151 (21.8)	1182 (15.6)	<0.001
3 CVRFs	96 (13.9)	375 (5.0)	<0.001
4 CVRFs	17 (2.4)	76 (1.0)	<0.001

Data are n (%), CVRFs (obesity, ever smoking, hypertension, diabetes)
CVRFs Cardiovascular risk factors
PSA Psoriatic arthritis

Comparing women and men with PsA, overweight was less common in women (31.1% vs 41.6%, p=0.004), whereas current (13.6% vs 7.5%, p=0.008), former (48.3% vs 37.7%, p=0.001) and ever-smoking (58.6% vs 43.1%, p<0.001) were more common in women. Stratifying by age-group, obesity was more common in women and men with PsA, all age-groups, except in men 45-60 years of age, compared with the GP. In women (in addition to obesity), HT, diabetes (age groups 45-60 and 61-75 years), and ever smoking (age groups 27-44 and 45-60 years), were more prevalent in PsA, compared with the GP. In men (in addition to obesity in all age-groups except 45-60 years of age), only HT was more prevalent in PsA compared to the GP. Occurrence of multiple CVRFs were significantly more common in women (two and three CVRFs (21.7% vs 14.7%, p<0.001 and 18.9% vs 4.1%,

p<0.001) respectively and in men with PsA (two and four CVRFs (22.0% vs 16.7%, p=0.014 and 3.0% vs 1.1%, p=0.003) respectively compared with the GP.

7.2 STUDY II

In this cross-sectional study, the response frequencies were 699/1200 (58.3%) for PsA, 868/1589 (54.6%) for gout, 742/1246 (59.6%) for RA and 587/1095 (53.6%) for AS. The sex distributions (% men) were: PsA (46.9%), gout (79.6%), RA (47.8%) and AS (56.4%). HT was the most commonly reported CVRF (gout 64.6%, RA 43.4%, PsA 40.5% and AS 29.3%). The occurrence of obesity was: gout 24.7%, PsA 23.0%, AS 17.0% and RA 15.2%. Hyperlipidaemia was reported in 32.1% of gout patients, followed by RA (18.9%), PsA (17.3%) and AS (10.9%). Multiple CVRFs were more common in gout, followed by PsA, RA and AS.

In women (table 3), age-standardized prevalence of obesity, diabetes, hyperlipidaemia, sedentary lifestyle and multiple CVRFs were higher in gout than in PsA, RA and AS. In addition, a higher prevalence of HT in gout compared with RA and AS was found along with no significant difference between gout and PsA. In PsA, prevalence of obesity and HT were higher than in RA or AS. Diabetes and hyperlipidaemia were more common in PsA compared with AS. Occurrence of ≥2 and ≥3 CVRFs were higher in PsA than in RA and AS.

Table 3, Age-standardized prevalence of CVRFs in women, 45-89 years

	PsA n=291	RA n=347	AS n=163	Gout n=159	p-value PsA vs RA	p-value PsA vs AS	p-value PsA vs gout	p-value RA vs AS	p-value RA vs gout	p-value AS vs gout
Obesity	28.8	17.9	17.5	38.7	<0.001	0.009	0.028	0.983	<0.001	<0.001
Hypertension	46.9	40.6	36.0	52.9	<0.001	0.030	0.216	0.338	<0.001	0.003
Diabetes	11.5	7.4	5.4	18.1	0.095	0.040	0.042	0.412	<0.001	<0.001
Hyperlipidemia	21.2	16.6	12.4	30.6	0.139	0.016	0.025	0.193	<0.001	<0.001
PA≤3 hours/week	50.4	59.1	47.3	60.9	0.030	0.503	0.033	0.012	0.681	0.013
Sedentary	19.0	23.4	21.0	34.7	0.172	0.614	<0.001	0.531	0.008	0.006
Current smoking	13.9	13.3	5.5	12.8	0.857	0.007	0.728	0.009	0.834	0.027
Minimum 1 CVRF	72.2	68.4	60.7	76.3	0.288	0.012	0.366	0.093	0.073	0.003
Minimum 2 CVRF	43.6	33.8	26.1	58.3	0.010	<0.001	0.003	0.096	<0.001	<0.001
Minimum 3 CVRF	19.7	13.1	7.8	36.4	0.023	0.001	<0.001	0.098	<0.001	<0.001
Minimum 4 CVRF	5.0	3.6	2.6	15.4	0.289	0.168	<0.001	0.544	<0.001	<0.001

AS Ankylosing spondylitis
CVRF Cardiovascular risk factor
PA Physical activity
PsA Psoriatic arthritis
RA Rheumatoid arthritis

In men (table 4), higher age-standardized prevalence of obesity was found in gout compared with RA and PsA, along with more HT and hyperlipidaemia compared with PsA, RA and AS. Diabetes and having a sedentary lifestyle were also more common in gout compared with PsA and AS. Multiple CVRFs (≥1, ≥2 and ≥3 CVRFs) were more prevalent in gout compared with PsA, RA and AS. The occurrence of obesity, diabetes, HT, hyperlipidaemia, sedentary lifestyle and multiple CVRFs were comparable across RA, PsA, AS. Current smoking was more common in RA than in PsA.

Table 4, Age-standardized prevalence of CVRFs, in men, 30-89 years

	PsA n=320	RA n=349	AS n=300	Gout n=674	p-value PsA vs RA	p-value PsA vs AS	p-value PsA vs gout	p-value RA vs AS	p-value RA vs gout	p-value AS vs gout
Obesity	11.8	10.6	14.2	18.9	0.602	0.364	0.006	0.149	<0.001	0.087
Hypertension	38.2	31.5	33.5	48.2	0.083	0.260	0.002	0.581	<0.001	<0.001
Diabetes	9.0	10.0	6.1	14.1	0.706	0.153	0.024	0.070	0.055	<0.001
Hyperlipidemia	14.1	14.5	13.8	24.0	0.885	0.899	<0.001	0.786	<0.001	<0.001
PA≤3 hours/week	33.1	35.9	29.6	39.9	0.465	0.354	0.039	0.097	0.202	0.002
Sedentary	28.2	32.7	26.7	37.5	0.203	0.684	0.004	0.096	0.123	<0.001
Current smoking	7.1	15.3	12.5	10.7	<0.001	0.021	0.074	0.343	0.035	0.375
Minimum 1 CVRF	56.3	56.9	53.7	63.7	0.841	0.518	0.025	0.391	0.039	0.003
Minimum 2 CVRF	27.6	30.6	28.0	42.9	0.369	0.889	<0.001	0.459	<0.001	<0.001
Minimum 3 CVRF	12.0	13.3	13.1	20.7	0.611	0.671	<0.001	0.946	0.003	0.004
Minimum 4 CVRF	4.4	4.7	3.7	7.4	0.896	0.654	0.068	0.559	0.083	0.026

AS Ankylosing spondylitis
CVRF Cardiovascular risk factor
PA Physical activity
PsA Psoriatic arthritis
RA Rheumatoid arthritis

7.3 STUDY III

This cross-sectional questionnaire study was based on the same questionnaire and responders as study II. Overall, physical HRQoL, represented by PCS scores, were poorer compared with mental HRQoL, represented by MCS scores, across IJDs and with a similar pattern in all IJDs. Gout patients reported better PCS and somewhat better MCS scores than the other IJDs (table 5). The rating of NRS for global health, pain and fatigue and HAQ scores were also more favourable in gout compared with the other IJDs both overall and stratified by sex. RA patients reported the worst PCS scores in both women and men compared to PsA and AS (except in women where the scores for PsA and RA were comparable), but after age-matching PCS and MCS scores were similar in PsA, RA and AS.

Table 5, Comparison of PCS and MCS across IJD diagnoses, overall and stratified by sex

Overall

	PsA n=699	RA n=742	AS n=587	Gout n=868	p-value PsA vs RA	p-value PsA vs AS	p-value PsA vs gout	p-value RA vs AS	p-value RA vs gout	p-value AS vs gout
PCS	38.3 (12.2)	36.1 (12.5)	39.7 (11.4)	41.2 (12.3)	<0.001	0.035	<0.001	<0.001	<0.001	0.022
MCS	45.3 (12.8)	47.4 (12.2)	43.7 (13.0)	48.9 (11.1)	0.003	0.025	<0.001	<0.001	0.012	<0.001

Women

	PsA n=371	RA n=387	AS n=256	Gout n=177	p-value PsA vs RA	p-value PsA vs AS	p-value PsA vs gout	p-value RA vs AS	p-value RA vs gout	p-value AS vs gout
PCS	34.5 (11.6)	34.7 (12.7)	37.4 (11.6)	36.4 (13.9)	0.827	0.003	0.151	0.007	0.188	0.481
MCS	44.0 (13.4)	46.1 (12.5)	42.6 (12.8)	47.9 (12.1)	0.030	0.220	0.002	0.001	0.144	<0.001

Men

	PsA n=328	RA n=355	AS n=331	Gout n=691	p-value PsA vs RA	p-value PsA vs AS	p-value PsA vs gout	p-value RA vs AS	p-value RA vs gout	p-value AS vs gout
PCS	42.5 (11.4)	37.5 (12.2)	41.5 (10.9)	42.3 (11.7)	<0.001	0.282	0.799	<0.001	<0.001	0.340
MCS	46.8 (11.9)	48.7 (11.8)	44.5 (13.1)	49.1 (10.9)	0.044	0.019	0.004	<0.001	0.607	<0.001

Values are mean (SD)
AS Ankylosing spondylitis
MCS Mental component summary
PsA Psoriatic arthritis
PCS Physical component summary
RA Rheumatoid arthritis

Comparing women and men with the same IJD, a similar pattern with worse PCS scores, HAQ, NRS scores (global health, pain and fatigue) in women compared with men was seen in all IJDs, except for pain in RA. In table 6, comparisons between women and men with PsA are shown.

Table 6, Comparisons between women and men with PsA

Variables	Women n=371	Men n=328	p-value
Age	56.9 (14.0)	56.3 (12.2)	0.549
NRS global	4.6 (2.4)	3.3 (2.3)	<0.001
NRS pain	4.8 (2.5)	3.4 (2.3)	<0.001
NRS fatigue	5.7 (2.6)	4.3 (2.5)	<0.001
HAQ	0.73 (0.59)	0.34 (0.46)	<0.001
PCS	34.5 (11.6)	42.5 (11.4)	<0.001
MCS	44.0 (13.4)	46.8 (11.9)	0.004

Values are mean (SD)
HAQ Health assessment questionnaire
MCS Mental component summary

NRS Numeric rating scale
PCS Physical component summary

7.4 STUDY IV

In study IV, 41 PsA patients (median (interquartile range (IQR)) 54 (49-62) years, 26 (63%) women)) and 39 matched controls (55 (46-60) years, 29 (74%) women)) were followed from BL to M6. At BL, body weight was median (IQR) 106 (96-114) kg in PsA patients and 105 (97-120) kg in controls, p=0.690. The DAPSA score at BL in PsA patients was 15.3 (6.6-29.1), indicating moderate disease activity. At M6, PsA patients and controls had a median (IQR) weight loss of 19 (15-27) kg and 23 (15-29) kg respectively. Serum levels of IL-23 and leptin decreased in patients and controls, comparing BL and M6, whereas HMW adiponectin and tot-adiponectin increased (Table 7).

Table 7, Comparisons of serum levels of selected cytokines and adipokines at baseline and after six months

Analytes	PsA BL	PsA M6	PsA p-value BL vs M6	Controls BL	Controls M6	Controls p-value BL vs M6
TNF-α, pg/mL	12.9 (10.0-17.2)	12.5 (9.1-17.1)	0.234	11.7 (8.5-13.5)	9.6 (7.8-13.0	0.003
IL-13, pg/mL	906.6 (680.0-1131.6)	885.1 (561.5-1171.1)	0.377	885.1 (650.5-1103.9)	778.0 (551.4-1023.6)	0.053
IL-23, ng/mL	0.4 (0.2-0.5)	0.2 (0.1-0.3)	<0.001	0.5 (0.3-0.7)	0.2 (0.1-0.3)	<0.001
Leptin, ng/mL	26.3 (14.4-48.7)	9.3 (4.4-16.2)	<0.001	38.8 (20.5-59.9)	14.0 (10.1-26.9)	<0.001
HMW adiponectin, µg/mL	3.4 (2.1-5.1)	6.0 (3.8-8.5)	<0.001	4.3 (2.1-6.5)	5.8 (4.5-7.9)	<0.001
Tot-adiponectin, µg/mL	4.0 (3.2-6.1)	5.9 (4.0-7.9)	<0.001	4.2 (3.3-5.1)	5.7 (4.3-6.7)	<0.001

HMW High molecular weight
IL Interleukin
M6 Month 6 after baseline
BL Baseline
PsA Psoriatic arthritis
TNF tumor necrosis factor
Tot total

In PsA patients, ΔBMI correlated positively with ΔIL-23 (table 8) and ΔDAS28-CRP (r_S=0.450, p=0.003). ΔBMI also correlated positively with ΔTNF-α, ΔIL-13, Δleptin and negatively with Δtot-adiponectin (table 8). In addition, ΔIL23 correlated positively with Δleptin (r_S=0.818, p<0.001) and negatively with Δtot-adiponectin (-0.355, p=0.036).

Table 8, Spearman correlations between baseline and month 6 values for selected analytes and BMI and DAS28CRP in PsA

Changes in analytes	ΔBMI	p-value	ΔDAS28CRP	p-value
ΔTNF-α	0.342	0.028	0.303	0.054
ΔIL-13	0.401	0.010	0.232	0.150
ΔIL-23	0.671	<0.001	0.460	0.005
ΔLeptin	0.554	<0.001	0.368	0.019
ΔHMW adiponectin	-0.251	0.113	-0.113	0.481
ΔTot-adiponectin	-0.318	0.043	-0.189	0.237

BMI Body mass index
DAS28CRP Disease Activity Score for 28 joints using CRP
HMW High molecular weight
IL interleukin
TNF Tumor necrosis factor
Tot total

8 DISCUSSION

8.1 MAIN FINDINGS

8.1.1 STUDY I

In study I, assessing CVRFs in PsA patients compared with GP controls, obesity, HT and diabetes were more prevalent in PsA. In women, obesity, HT, diabetes, ever smoking and multiple CVRFs were more common in PsA. In men, obesity, HT and multiple CVRFs were more prevalent in PsA. The higher prevalence of CVRFs in PsA compared with the GP is in accordance with other studies (107, 126-129). We found that 64.7% of PsA patients were overweight or obese, somewhat lower compared with the 75.3% of overweight/obese patients with PsO or PsA reported by Eder et al in a multi-centre study of 2254 patients with PsO or PsA (41.1% and 58.9% respectively) with a mean age of 52 and 47% women, from USA, Canada or Israel. The age and sex distribution was similar to our study, but BMI was by Eder et al calculated using physical examination of height and weight at a healthcare visit (130), rather than the self-reported data that we used. Self-reported height and weight may overestimate actual height and underestimate actual weight (212, 213), which may account for some of the differences between our study and other studies. Also, as reported in a Lancet Global Burden of Disease Study from 2014, the prevalence of obesity is higher in North America compared with Sweden (214). In a Canadian study by Bhole et al, comparing PsA, PsO, RA and GP controls, 37% of PsA patients were obese, significantly higher than for PsO, RA and GP (126). Similarly, as in the study be Eder et al, measurements of height and weight were done. In our study, 74.4% of patients with PsA had ≥1 CVRF. Eder et al reported that the majority (87.6%) of patients with PsO or PsA had ≥1 modifiable CVRF (130) and in a Norwegian study by Wibetoe et al, comparing 3517 patients with PsA, RA, or axSpA, the proportion of patients with ≥1 CVRF and HT and obesity was highest in PsA (110). The accumulated number of CVRFs are difficult to compare between studies, due to the inclusion of different CVRFs as well as varying numbers of CVRFs assessed in different studies.

The high occurrence of CVRFs in PsA raises the importance of increased awareness and CVRF assessments in PsA to prevent further morbidity. Although an increased CVD risk in IJD is recognized in the EULAR recommendations (96), less evidence exists in PsA compared to RA making additional data on CVRFs in PsA valuable. In contrast to in patients with RA, no risk adjustments are currently recommended when using SCORE in patients with PsA (96). Also, Swedish data on CVRFs in PsA is scarce. In a

Swedish registry study, a higher risk of stroke and acute coronary syndrome in PsA compared to GP and a comparable risk between PsA, AS and uSpA was reported (118). Preliminary Swedish data suggest increased mortality in patients with PsA compared to the GP (215). In a recent Norwegian nationwide registry-based cohort study, a small increase in all-cause and CVD mortality was seen in women but not in men with PsA compared to the GP (216). Similarly, a recent review and meta-analysis found an increased all-cause mortality in women but not in men with PsA compared to the GP, and overall an increased CVD mortality in PsA compared to the GP (217). Previous data on CVD mortality in PsA has been conflicting, as described in a review study from 2018 (218). Data on BMI is difficult to capture in registry studies and given the importance of obesity in PsA, our study can contribute with sex-stratified data. Knowledge about the high occurrence of obesity and other CVRFs in PsA may lead to recognizing weight loss treatment as an important adjuvant for these patients.

8.1.2 STUDY II

In study II, comparing age-standardized CVRFs in PsA, RA, AS and gout, CVRFs were most prevalent in gout patients. In women, PsA patients reported a higher occurrence of HT and obesity, compared with RA and AS, and more frequently obesity, HT, hyperlipidaemia and diabetes compared to AS. However, in men, the occurrence of CVRFs were comparable in PsA, RA, AS.

Similarly to our results, others have found greater occurrence of obesity in PsA than in RA (110, 126, 133) and in PsA compared with RA and AS (134). Sex-stratified results regarding CVRFs in IJDs are often not presented (108, 110, 126, 133). Although Bhole et al found increased risk of obesity in PsA women compared with PsA men (126) and Castaneda et al presented some sex-stratified results, but not for obesity in particular (134).

HT was the most commonly reported CVRF in all IJDs. Similarly, Wibetoe et al found that HT was the most common CVRF, overall prevalent in 49.8% of patients with PsA, RA or axSpA (110). The highest occurrence was found in PsA where 55.5% had hypertension, higher than the 40.5% reported by us, despite similar age and sex distribution. (110). Differences in blood pressure assessment (measured in the clinic by a nurse in the study by Wibetoe et al, whereas self-reported in our study) may account for some of the differences. In a cross-sectional study from the USA by Han et al where CVRFs were compared across PsA, RA and AS, similar prevalence ratios (prevalence in respective IJD compared with matched controls) for HT in PsA, RA and AS were reported (108). Differences in smoking status and obesity (not available

in the study by Han et al) across IJDs could influence the prevalence estimates of HT (108).

Diabetes was more frequent in women and men with gout compared with PsA, RA (although p=0.055 for gout vs RA in men) and AS. In women, diabetes was more common in PsA compared with AS, but similar in PsA and RA, whereas similar in PsA, RA and AS in men. Others have reported diabetes as more frequent in PsA than in RA (132, 133) and compared with RA and AS (134), as well as similarly prevalent (numerically higher estimates in PsA but no significant difference) in PsA, axSpA and RA (110) and in PsA, RA and AS (108). Obesity being more causally linked with PsA than with RA or AS might partly explain the overall higher prevalence of metabolically related diseases such as obesity and diabetes in PsA compared with other IJDs.

Hyperlipidaemia was most frequent in gout, least frequent in AS and in women more common in PsA compared to AS, whereas similar in PsA, RA and AS in men. Contrasting findings have been reported in other studies. Some reporting higher frequencies in PsA compared with RA and AS (134) and compared with RA (133) whereas others reported similar prevalence in IJDs (108, 110). Hyperlipidaemia is difficult to assess and compare across IJDs, since many factors can account for the observed differences, including differences in disease activity across IJDs, different definitions of hyperlipidaemia using self-reported data, ICD-codes or blood samples.

In our study, current smoking was in women less frequent in AS, but similarly common in PsA, gout, RA, however in men more common in RA. In line with the evidence for smoking in the pathogenesis of IJD being more solid in RA than in PsA or AS (219-222). In the Norwegian study by Wibetoe at al, the prevalence of current smoking was similar between PsA, RA and axSpA, except less frequent in older PsA patients (110). Across all IJDs the number of current smokers (around 20% in the Norwegian study) were higher compared to what we reported, which is surprisingly high given the prevalence of 13% of smokers in Norway in the GP at the time of the study, as reported by the authors. The prevalence of smoking in the GP is generally lower in Sweden (223). In our study, overall around ten percent in PsA, RA and AS were current smokers, numbers that were even lower in patients with gout.

Reflecting the different prevalence of individual CVRFs across IJDs, multiple CVRFs were more frequent in gout compared with PsA, RA and AS. In women, a higher prevalence of multiple CVRFs were found in PsA compared to RA and AS. In men the prevalence was comparable in PsA, RA and AS. Wibetoe et al reported a higher occurrence of multiple CVRFs in PsA than in RA and AS (110) and both Wibetoe et al (110) and Eder et al (130) found

higher occurrence of multiple CVRFs compared to what we reported. As previously mentioned, the prevalence of multiple CVRFs is difficult to compare across studies due to inclusion of different CVRFs.

Study II highlights the high occurrence of single and multiple CVRFs in gout, a disease that is frequently undertreated, associated with cardiovascular comorbidities, increased CVD mortality (224) and has an increasing prevalence and incidence worldwide (43). The comorbidity burden in especially women with PsA is also notable and future studies of CVRFs in women and men with PsA are important. In a Danish registry study from 2017 where PsA patients were compared with matched GP controls, comorbidities were more prevalent in PsA compared with GP controls already a few years before PsA diagnosis (225). Comorbidity patterns in IJDs may change over time and might be influenced by factors such as an increasing worldwide prevalence of obesity (226). Comorbidities can add to the complexity of treating IJDs by making response to treatment less effective (obesity in IJD), limiting treatment choices through contraindications to certain medications, along with changing how the IJD should be treated, sometimes requiring a multidisciplinary approach (for example specialized weight loss treatment in obesity). It is important to regularly assess and compare the occurrence of comorbidities in IJDs, as reference points for future studies, advances in treatment and healthcare allocation of resources. Also, since less data exist regarding CVD in PsA and AS compared to RA (96), a comparative study such as the current is valuable. In PsA, study II also replicates the findings of a high occurrence of CVRFs with similar estimates seen in a slightly different patient-group compared to study I.

8.1.3 STUDY III

In study III, greater reductions in physical HRQoL compared with mental HRQoL in PsA, gout, RA and AS, overall as well as stratified by sex was seen. Gout patients had better physical and mental HRQoL, HAQ and NRS scores for global health, pain and fatigue, compared with PsA, RA and AS. Similar HRQoL, HAQ and NRS scores were reported in PsA, RA and AS.

Conflicting results have been reported comparing HRQoL across IJDs, where some have found better physical HRQoL in AS compared with RA (193, 205), whereas in a review study from 2009, HRQoL was similarly reduced in AS and RA compared to the GP and worse in women compared with men in both AS and RA (196). Both Ovayolu et al (193), using a sample of 264 RA and 117 AS patients, divided in different age-strata and Chorus et al (205), using a sample of 1056 RA and 658 AS patients of working age (mean age 49 in RA and 43.5 in AS) used the SF-36 to measure HRQoL. In an Italian study by

Salaffi et al, worse physical HRQoL as measured by SF-36 in RA compared with PsA (divided into peripheral and axPsA) and AS was found, perhaps partly explained by a higher comorbidity score and higher proportion of women in RA (192). In a small study by Sokoll et al, using EQ-5D to assess HRQoL in 47 patients with RA and 47 patients with PsA, matched for disease duration, similar HRQoL in PsA and RA was found, despite more joint damage in RA (211). Husted et al reported better physical HRQoL and similar mental HRQoL comparing 107 patients with PsA and 43 patients with RA, in a study where patients with PsA were significantly younger and more often men (210). Overall, studies report lower HRQoL in IJD patients compared to the GP, but comparisons between IJDs are in many studies hampered by differences in sex, age, comorbidities and few patients. In line with our study, worse physical HRQoL compared to mental HRQoL has been reported in PsA (192), RA (192), AS (192, 227) and gout (228).

We reported worse physical HRQoL in women compared with men in all IJDs and worse mental HRQoL in women with PsA and RA compared with men. Others have found greater reductions in physical HRQoL in women with AS (229), whereas in a Swedish cross-sectional study from 2018, using SF-36, no significant differences were seen in PCS and MCS scores comparing women (n=89) and men (n=121) of similar age, despite higher VAS fatigue in women (227). In a sample from the general Swedish population (the Swedish normative SF-36 population, n=8930), women reported worse HRQoL compared with men (230), perhaps indicating a generally worse perceived health in women compared with men. In line with our findings, in PsA, women have reported worse clinical outcomes, more pain and fatigue, poorer function and worse HRQoL compared with men (25, 231-233). Comorbidities, such as obesity and depression may have additional impact on HRQoL in PsA as reported by Husted et al (234). As shown by Kavanaugh et al, in order to achieve the largest improvements in HRQoL in PsA patients, treatments need to be effective for both skin and joint disease (235). The reasons behind the worse HRQoL in women compared with men in the IJDs in the current study should be further explored in future studies.

HRQoL is an important measure in chronic diseases and the results from the current study may be used as references as treatment and occurrence of comorbidities in IJDs change over time. Despite improvement in treating IJDs, residual pain, fatigue and IJD-associated comorbidities may affect HRQoL. Even though patients with gout had more comorbidities, better HRQoL compared with the other IJDs was reported. Speculatively the intermittent nature of gout is not captured by RAND-36 or gout may in many cases be a less severe disease compared with other IJDs. Others have reported

that gout flares and tophi (228) as well as comorbidities negatively affect HRQoL in gout (197).

8.1.4 STUDY IV

In study IV, in the PsA patients, the levels of serum IL-23 and leptin decreased comparing BL and M6, whereas serum tot-adiponectin and HMW adiponectin increased. Also in PsA patients, changes in BMI correlated with DAS28CRP, IL-13, IL-17, IL-23, TNF-α, leptin and tot-adiponectin. In controls, reductions in IFN-γ, TNF-α, IL-1β, IL-6, IL 12/IL-23 p40, IL-23, and leptin serum levels were seen, and serum tot-adiponectin and HMW adiponectin increased.

Studies have shown that weight reduction in obese PsA patients is associated with reduced disease activity (166) and improved chance of reaching MDA (153). To my knowledge, no previous study has assessed cytokine and adipokines in PsA before/after weight reduction. Reductions in CRP and several inflammatory cytokines and adipokines, such as IL-6, TNF-α and leptin after weight loss have been described in a review study comprising bariatric surgery as well as dietary weight loss studies, although not in PsA patients (190). The reductions in IL-23 after weight loss in PsA patients and controls in the current study are in line with what Villarreal et al reported (although not in PsA patients), in a study where reductions in IL-23, IL-1β, IFN-γ, TNF-α, IL-6, IL-8, IL-10, IL-12 and IL-18 levels were found six months after bariatric surgery (183).

We found a positive correlation between changes in BMI and TNF-α in PsA patients at M6, in accordance with other studies in patients without PsA (190). The observed reductions in serum leptin in PsA patients and controls are expected, since serum leptin levels correlates with body fat (185) and has frequently been reported to be reduced after weight loss (236, 237). We observed increased levels of tot-adiponectin and HMW adiponectin in PsA patients and controls after weight loss. Others have reported higher (237) as well as unaffected (238) levels of adiponectin after weight loss in studies not specifically including PsA patients. In a small progressive weight loss study of subjects with a BL BMI of around 38 kg/m^2, Magkos et al did not find a significant increase in adiponectin until 16% of BL weight was lost, although a decrease in leptin was seen already at 5% weight loss (239). Adiponectin has been reported to inhibit TNF-α and IFN-γ production in macrophages and to increase levels of the anti-inflammatory cytokine IL-10 (157). Inflammatory effects of adiponectin have been suggested in joints of RA patients (240) and a long-term follow-up study showed that high levels of serum tot-adiponectin at study start predicted RA development in obese subjects that were followed up to 29 years (241). In PsA, adiponectin has been

reported to positively correlate with active and damage joint count (163). However, the effects of elevated serum adiponectin after weight loss in patients with PsA remains unclear. By reducing leptin levels, its´ inflammatory role may be lowered, including a decreased number of Th17 cells and lowered levels of IL-1β, IL-6, IL-12 and IL-17 among other inflammatory cytokines (186).

8.2 LIMITATIONS

8.2.1 STUDY I

Study I is a cross-sectional study, where a survey was sent to PsA patients. The response rate of 70.6% and the underrepresentation of young men among the responders may affect the generalizability of the findings. In a questionnaire study from Southern Sweden of RA patients who had received treatment with biologics, those who did not respond to a postal questionnaire had more severe disease compared to responders (242). In the current study, the PsA patients were identified in specialized care, whereas the controls are a national random sample from the GP. This may not be a fair comparison since tertiary care populations may be more ill compared to the GP. Having a chronic disease like PsA might lead to more healthcare utilization and more screening for comorbidities, although a multicentre study of PsO and PsA patients showed significant underdiagnosis of HT and hyperlipidaemia, especially in those ≤50 years of age (130). There may be socioeconomic differences between different parts of the country, although Western Sweden is considered representative of Sweden as a whole regarding health status and demography (243). Self-reported data may be uncertain and subject to over- as well as underestimation. Validating the comorbidities used in the study through register linkage, telephone interview or a physical visit at the clinic (although some of the patients with PsA came to a physical visit in study IV) might have increased the reliability of the data. ICD-10 codes were used to identify PsA patients, and diagnostic misclassification is another limitation. However, after this study was conducted, a validation study of ICD-10 codes for PsA in the Swedish national patient register has been performed. Among the 400 PsA patients included from five Swedish rheumatology clinics, 80 patients were retrieved from the Sahlgrenska University Hospital. A good validity was reported, with positive predictive values between 69-82% for fulfilment of the CASPAR criteria and 86% for meeting any established PsA classification criteria (244).

8.2.2 STUDY II-III

Study II and III are based on the same cross-sectional survey, with a response rate of 58.3% for PsA and with non-responders that were younger (all IJD diagnoses) and more frequently men (some IJD diagnoses). Differences in age and sex between responders and non-responders may affect generalizability of results and the low response rates can also affect generalizability. The differences in age and sex between IJD diagnoses made comparisons difficult, therefor age-standardized (study II), age-matched (study III) and sex-stratified analyses were performed.

The high age, especially in gout patients, may hamper the generalizability to younger age groups. Many of the limitations of study I is applicable also to study II and III, although no GP controls were used for comparisons. Increased awareness of CVRFs in chronic diseases and more healthcare utilization in chronic diseases may lead to more screening and increased identification of CVRFs. However, this may be similar across IJDs, or influenced by the knowledge of CVD risk for the respective IJD in healthcare professionals meeting the patient for their IJD or for other reasons visiting healthcare. In a questionnaire study of general practitioners, around a third of the general practitioners recognized that RA conveys a higher CVD risk (143). The knowledge of risk for CVD in RA is speculatively greater than in PsA and AS, which may lead to increased screening and an overidentification of CVRFs in RA compared with other IJDs. As in study I diagnostic misclassification is another limitation, although validation studies of PsA (244), RA (245), AS (39) and gout (246, 247) have demonstrated acceptable validity of an ICD-10 code for respective IJD diagnosis. Although the study was set in a geographically similar setting (Western Sweden) for the different IJDs, gout patients were retrieved from primary care, whereas the other IJD diagnoses were retrieved from tertiary care. As previously mentioned, tertiary care may comprise patients with more severe disease and as reported by others, a significant proportion of patients with PsO may have undiagnosed PsA (17), speculatively consisting of less severe PsA disease not captured in the current studies. However, among patients diagnosed with PsA in specialized care during 2014-2016, around 70%, similarly in women and men, have been reported to be treated with a DMARD (14) and are therefor likely to be under rheumatologic care. Due to the comparisons across several groups, multiple statistical tests were performed and no correction for multiple testing was performed, increasing the risk of false positives.

8.2.3 STUDY IV

Study IV is a prospective open intervention study. A limitation is that the study is not randomized and that we did not include a control group with PsA that

did not undergo the same weight loss treatment. There were some difficulties in measuring cytokines, some analytes being expressed at low levels and concentrations were in some cases determined from an extrapolated part of the standard curve, making results less reliable. However, measurements were done in the same manner for PsA patients and controls. The cytokines and adipokines levels at M6 may be influenced by the temporary starvation, although the patients and controls had at M6 started to regain some weight compared with the three months visit. Inclusion of PsA patients with varying disease activity at BL, where 12 had MDA, increases the generalizability of the results to every-day practice PsA populations. Despite not limiting the inclusion to PsA patients with high disease activity, significant results were obtained. Few of the PsA patients were men (n=15/41), making sex-stratified analysis less reliable and hampering generalizability to other PsA populations with more equal sex distributions. The median disease duration was long (32 years for PsO and 17 years for PsA) making results less generalizable to patients with early disease. The impact of disease modifying treatment on cytokines and adipokines was not assessed in detail, although no significant differences in cytokines and adipokines in PsA patients with/without bDMARDS were noted. However, DMARD treatment was unchanged from three months before BL until M6 to minimize impact of treatment on cytokines and adipokines.

8.3 IMPLICATIONS AND FUTURE PERSPECTIVES

This thesis adds to the knowledge of an increased prevalence of CVRFs in PsA patients compared with the GP (no Swedish comparison had previously been done) and especially in women with PsA compared to RA and AS. Greater decrements were seen in physical HRQoL compared with mental HRQoL and more affected HRQoL in women compared with men. The thesis provides new insights on the effects of weight loss on important cytokines, mainly IL-23, and adipokines in PsA patients.

Despite the heavy burden of CVRFs in PsA, others have reported suboptimal management of CVRFs in PsA (130, 144). There is a need for increased awareness and treatment of CVRFs in PsA, due to the increased risk of CVD (96, 118), the poorer response to anti-rheumatic treatment and reduced likelihood of reaching MDA that obesity in PsA patients entails (153, 248). As previously mentioned, combined rheumatology/cardiology clinics have successfully treated hyperlipidaemia in several IJDs including PsA (146). In Sweden, primary CVD prevention is in the majority of cases managed in primary care and more cooperation between rheumatology and primary care

would enable primary care physicians and nurses to better management of CVRFs in IJD patients. In 2008, Ridker et al demonstrated a reduced risk of cardiovascular events along with reduced CRP in men and women with normal cholesterol levels, increased CRP, but no rheumatic disease, that were treated with statins (249). Currently no multiplication factor of CVD risk scores are recommended in PsA, in contrast to RA (96), despite the frequent underestimation of CVD risk in IJDs including PsA using current CVD risk estimation tools (135-137). The optimal target level, taking the effects of DMARD treatment and disease activity into account, when treating hyperlipidaemia in PsA needs to be further explored.

Worse clinical outcomes in women compared to men have previously been reported in PsA (22, 25) and includes more pain, fatigue and disability (25), worse HRQoL due to skin PsO, despite men having objectively worse skin PsO (25, 250) and poorer response and persistence to TNF-inhibitors (251) that calls for further investigations. As treatments for PsA and related comorbidities improve, additional studies on HRQoL in PsA patients are needed. In a recent Swedish study where patients with early PsA and RA were assessed at diagnosis and after five years, less improvement in HRQoL in PsA compared with RA was seen, perhaps indicating unmet treatment needs or consequences of a longer diagnostic delay in PsA (252). Pain has, by PsA patients been recognized as the most important domain having an impact on health, more important than fatigue and skin problems (208, 253) and treatment of pain in PsA is an important research area. Treatment strategies such as acceptance and commitment therapy or cognitive behavioral therapy aimed towards pain, anxiety or depression in selected PsA patients to improve the outcomes of pharmacological, non-pharmacological and lifestyle interventions are interesting ways to combat residual symptoms in PsA. In an ongoing project we will study the effects of weight loss by VLED on HRQoL, anxiety and depression in obese PsA patients with up to two years follow-up. Obesity is a national as well as a global health issue. Weight loss and maintaining weight loss is often difficult and specialized, individually tailored treatment is in Sweden only available to a minority of patients. Given the high prevalence of obesity in PsA and demonstrated positive effects, specialized weight loss treatment should be an integral part in clinical practice when treating obese PsA patients. In the 2018 American College of Rheumatology/National Psoriasis Foundation guidelines for the treatment of PsA, weight loss is recommended (although the evidence is graded as low) in adult overweight/obese patients with active PsA (79). It would be interesting to study the effects of weight maintenance after initial weight loss therapy by different medications such as orlistat, glucagon like peptide-1 analogues and sodium-glucose transport protein 2 inhibitors on the incidence of new onset PsA among PsO patients and the effects on disease activity, cytokines and

adipokines in patients with established PsO or PsA. In a small study where seven patients with PsO (of which non had PsA) and type 2 diabetes were treated with a glucagon like peptide-1 analogue for 12 weeks, significant reductions in BMI, hemoglobin A1c and PASI were reported after 12 weeks (254). In another publication from the previously described VLED-study in obese PsA patients (study IV) it was showed that despite weight loss, muscle strength did not deteriorate in PsA or controls (255). In a study where 67 PsA patients were randomized to either high intensity interval training for 11 weeks or to a control group, no significant effect at three months were seen on disease activity, but an improvement in fatigue in the physical training group was reported (256), perhaps signalling that high intensity training can be performed in PsA without risk of aggravating the disease activity. A further step would be to study the effects of a structured high-intensity physical training programme in combination with weight loss treatment in obese patients with PsA on disease activity, cytokines and adipokines.

Populations with musculoskeletal pain and Anti-Citrullinated Protein Antibody positivity without arthritis (257) represent, similarly to PsO patients, populations at risk for developing arthritis and PsA respectively. In a retrospective study of 464 PsO patients with moderate/severe plaque PsO where 234 were treated with bDMARDs and 230 were treated with phototherapy, Gisondi et al showed a lower incidence of PsA in the group treated with bDMARDs (258). A similarly protective effect of bDMARDs on PsA incidence was reported in a retrospective cohort study by Acosta et al (259), whereas Meer et al, in another retrospective study, reported a higher risk of PsA among PsO patients treated with biologics compared to oral/phototherapy (260). As discussed by the authors, confounding by indication may be an issue and prospective studies are warranted (260). The potential of aggressively treating PsO to prevent PsA development is intriguing and thorough characterization and selection of PsO patients at risk for developing PsA along with finding a possible window of opportunity for treatment are important areas of future research.

9 CONCLUSIONS

- Obesity, HT, diabetes and multiple CVRFs were overrepresented in PsA compared to the general Swedish population.
- HT was the most common CVRF in PsA, gout, RA and AS.
- CVRFs were overrepresented in gout compared to PsA, RA and AS. Women with PsA had more CVRFs compared to women with RA and AS.
- Worse physical HRQoL, compared with mental HRQoL was seen in PsA, gout, RA and AS, overall and in women and men separately.
- HRQoL was worse in women compared with men in PsA, gout, RA and AS.
- In obese PsA patients that went through weight loss treatment, serum levels of IL-23 decreased significantly and ΔIL-23 was positively correlated with ΔBMI and ΔDAS28CRP.
- Weight loss was accompanied by significant reductions in serum leptin and increased levels of serum tot-adiponectin and HMW-adiponectin in PsA and controls matched for sex, age and weight.
- The aggregated results of this thesis highlight the importance of identifying and treating CVRFs in PsA and the positive effect on disease-related variables that can be achieved through adding weight loss treatment to standard care in patients with PsA and obesity.

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