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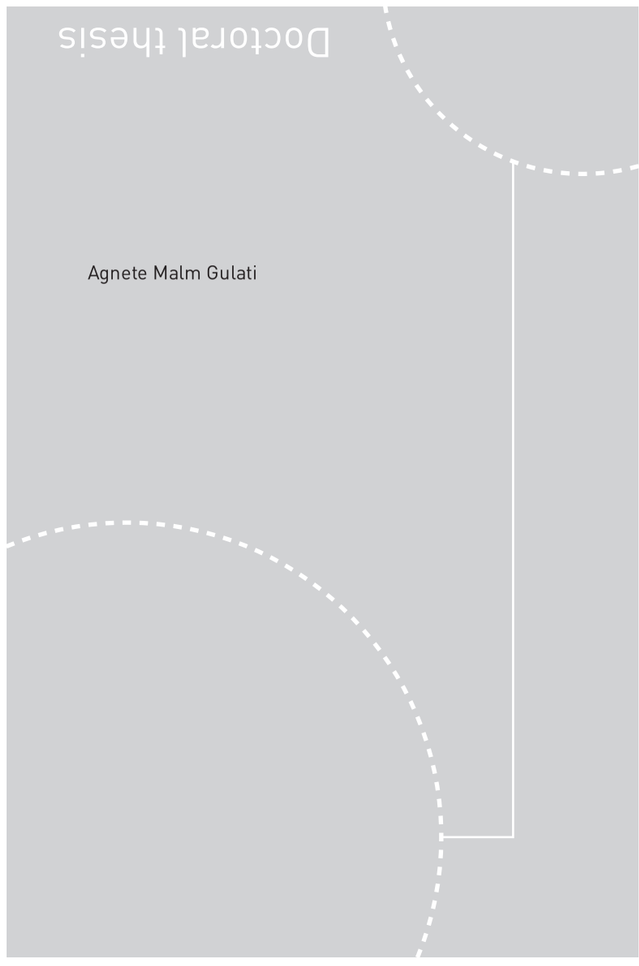
Agnete Malm Gulati

Cardiovascular Disease and Osteoporosis in Psoriatic Arthritis



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Trondheim, April 2018

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Risiko for hjerte - kar sykdom og osteoporose ved psoriasis artritt

Psoriasis artritt (PsA) er en kronisk inflammatorisk leddsykdom hvor hud og ledd er involvert. I tillegg til betennelse i ledd (artritt) og hud (psoriasis), kan også senefester (enteser) og negler være involvert. Ingen enkel test eller blodprøver kan bekrefte sykdommen, men klinisk anvendelige kriterier foreligger. Hyppigst brukt i dag er *ClASsification of Psoriatic ARthritis* (CASPAR) kriteriene. PsA kan være assosiert med flere andre sykdommer (komorbiditeter), blant annet hjerte - karsykdom, osteoporose, inflammatorisk tarmsykdom og depresjon.

I denne avhandlingen har vi undersøkt forekomsten av hjerte - karsykdom og osteoporose hos pasienter med PsA, for blant annet å kunne si noe om risikoen for disse tilstandene er økt hos pasienter som har PsA. Hittil har forekomst av disse komorbiditetene først og fremst blitt undersøkt hos pasienter med revmatoid artritt (RA). Til tross for at PsA og RA begge er inflammatoriske leddsykdommer, har de mange ulikheter, både når det gjelder klinisk presentasjon, patofysiologi og bildediagnostiske funn. Resultater fra studier på RA pasienter kan derfor ikke automatisk overføres til pasienter med PsA.

I tre av artiklene i denne avhandlingen er data hentet fra Helseundersøkelsen i Nord-Trøndelag (HUNT), en omfattende populasjonsstudie som inkluderer spørreskjema, klinisk undersøkelse og blodprøver, gjennomført i 1986-88 (HUNT1), 1995-97 (HUNT2) og 2006-08 (HUNT3). I den fjerde artikkelen brukte vi data fra Revmatologisk avdeling ved Sørlandet Sykehus.

Flere studier har vist at pasienter med PsA har økt risiko for hjerte - karsykdom. En del av denne økte risikoen synes å være relatert til økt forekomst av kjente risikofaktorer for hjerte - karsykdom, som f.eks røyking, overvekt og ugunstig kolesterolfordeling i blodet. Den første studien med data fra HUNT3 viste at pasienter med PsA hadde en økt forekomst av flere uheldige risikofaktorer for hjerte - karsykdom, blant annet overvekt, røyking, hypertensjon, CRP og økt triglyserid-nivå i blodet. Likevel observerte vi kun en økt forekomst av angina pectoris (brystsmerter), men ikke annen etablert hjerte - karsykdom hos pasienter med PsA. Estimert 10 års risiko for et dødelig hjerteinfarkt beregnet ved SCORE (Systematic Coronary Risk Evaluation) var sammenlignbar for PsA pasienter og kontrollene i denne studien.

Det er usikkert om byrden av kardiovaskulære risikofaktorer er økt allerede før pasientene får PsA diagnosen eller oppstår som et resultat av den immunologiske sykdommen. Resultater fra HUNT2 og HUNT3 viste at flere uheldige risikofaktorer for hjerte - karsykdom var tilstede før pasientene fikk PsA diagnosen. En mulig årsak til dette kan være at de fleste PsA pasientene allerede hadde psoriasis i huden før artrittsykdommen oppstod, en tilstand som også er assosiert med økt risiko for hjerte - karsykdom. Disse resultatene underbygger viktigheten av å evaluere PsA pasientene for livsstilsrelaterte og modifiserbare kardiovaskulære risikofaktorer. Intervensjon mot slike risikofaktorer kan trolig redusere PsA pasienters risiko for fremtidig hjerte - karsykdom.

Studier viser motstridene resultat når det gjelder risiko for osteoporose hos pasienter med PsA. Dette kan blant annet skyldes ulikheter i pasientgruppene som undersøkes, samt en mangel på store populasjonsstudier. Forekomsten av osteoporose ble undersøkt både hos PsA pasienter som deltok i HUNT3 studien og pasienter fra Revmatologisk avdeling ved Sørlandet Sykehus. Ved bruk av Verdens Helseorganisasjons kriterier for osteoporose, fant vi at forekomsten av osteoporose hos PsA pasientene var lav og sammenlignbar med kontrollgruppen. Våre funn understøtter at PsA pasienter kan følge de samme retningslinjer for undersøkelse av osteoporose som den generelle befolkningen. I tillegg må pasienter med vedvarende høy sykdomsaktivitet og pasienter som bruker glukokortikoider vurderes særlig med tanke på osteoporose.

Både hjerte - karsykdom og osteoporose kan være tilstede uten at pasienten selv er klar over det. Det er derfor viktig å kjenne til risikoen for disse tilstandene hos pasienter med PsA, slik at man kan identifisere de pasientene som trenger ekstra oppfølging fra helsevesenet.

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First and foremost I would like to express my sincere gratitude to Mari Hoff, my main supervisor, for her generosity in sharing the material from the HUNT study with me. Her experience in rheumatology research helped me through my work, and she was always available for questions and discussions.

My other co-supervisors have each in their own way contributed greatly to this thesis. Glenn Haugeberg recruited me into research during my very first year as a resident at the Rheumatology department. His generosity and humorous attitude made him a pleasure to work with. Anne Grete Semb introduced me to the interesting and important field of cardiovascular disease in rheumatology, and her vast experience in cardiovascular research made major contributions to the thesis.

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I would like to thank all of my colleagues at the Department of Rheumatology, and especially the head of department Erik Rødevand, for giving me the opportunity to achieve my PhD degree and feel welcome at the department despite a long absence from clinical work.

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"*The aim of science is not to open the door to infinite wisdom, but to set a limit to infinite error."*

Bertolt Brecht

ACRONYMS AND ABBREVIATIONS

ACPA	Anti-Citrullinated Peptide Antibody
AS	Ankylosing spondylitis
BMD	Bone mineral density
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
DAS28	Disease activity score for 28 joints
DMARD	Disease modifying anti-rheumatic drug
DXA	Dual energy x-ray absorptiometry
ESC	European Society of Cardiology
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HDL-c	High-density lipoprotein cholesterol
HLA	Human leukocyte antigen
HUNT	Helseundersøkelsen i Nord-Trøndelag/The Nord Trøndelag Health Study
IJD	Inflammatory joint diseases
IL	Interleukin
LDL-c	Low-density lipoprotein cholesterol
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drugs
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
SCORE	Systematic Coronary Risk Evaluation
SD	Standard deviation
SPSS	Statistical package for the Social Sciences
TNF	Tumor necrosis factor
WHO	World Health Organization

LIST OF PUBLICATIONS

The present PhD thesis is based on the following papers, which will be referred to in the text as Paper 1, Paper 2, Paper 3 and Paper 4.

Paper 1

On the HUNT for cardiovascular risk factors and disease in patients with psoriatic arthritis: population- based data from the Nord-Trøndelag health study. **Gulati AM, Semb AG, Rollefstad A, Romundstad PR, Kavanaugh A, Gulati S, Haugeberg G, Hoff M;**
Annals of the rheumatic diseases, 2016

Paper 2

Change in cardiovascular risk factors in patients who develop psoriatic arthritis: longitudinal data from the Nord-Trøndelag Health Study (HUNT) **Gulati AM, Salvesen Ø, Thomsen RS, Kavanaugh A, Semb AG, Rollefstad S, Haugeberg G, Hoff M; RMD Open, 2018**

Paper 3

Bone mineral density in patients with psoriatic arthritis – data from the Nord- Trøndelag Health Study 3. **Gulati AM, Hoff M, Salvesen Ø, Dhainaut A, Semb AG, Kavanaugh A, Haugeberg G; RMD Open, 2017**

Paper 4

Osteoporosis in psoriatic arthritis - A cross-sectional study of an outpatient clinic population. **Gulati AM, Michelsen B, Diamantopoulos A, Grandaunet B, Salvesen Ø, Kavanaugh A, Hoff M, Haugeberg G; Submitted, 2017**

SUMMARY

Psoriatic arthritis (PsA) is an inflammatory joint disease (IJD) associated with psoriasis. The clinical presentation is heterogeneous and may involve the peripheral joints, the axial skeleton and the entheses, as well as skin and nails. The diagnosis is based on clinical manifestations, and the *ClASsification of Psoriatic ARthritis* (CASPAR) criteria can be used. PsA has been associated with several comorbid conditions, such as cardiovascular (CV) disease (CVD), osteoporosis, inflammatory bowel disease and depression.

This thesis focuses on two important comorbidities in rheumatic diseases, namely CVD and osteoporosis. Until now, patients with rheumatoid arthritis (RA), the most prevalent IJD, have been most extensively examined concerning both CVD and osteoporosis. However, PsA is a disease distinct from RA, clinically, radiologically and pathologically. Research findings from RA on disease course, comorbidity, treatment and outcome cannot be automatically translated to PsA patients.

In three of the papers included in this thesis we used data from the Health study in Nord - Trøndelag (HUNT). The HUNT studies are population-based cohorts established in the 1980ies, HUNT1 (1984-86), HUNT2 (1995-97) and HUNT3 (2006-08). In Paper 4 we used data from the Department of Rheumatology, Hospital of Southern Norway Trust.

Increased CV burden has been documented in PsA patients, however the exact risk increase or causal relationship with inflammation is documented to a lesser degree. Paper 1 in this thesis showed that patients with PsA in the HUNT3 study had an increased burden of several CV risk factors, such as obesity, smoking, hypertension, CRP and high triglyceride levels. However, when it comes to established CVD, we observed only an increased risk of angina pectoris. Also, the estimated 10-years risk of a fatal CV event calculated with the Systematic Coronary Risk Evaluation (SCORE) was comparable to the background population. Whether CV risk factors are increased prior to diagnosis of PsA, co-existing or are a result of PsA itself has not been clarified. Longitudinal data from HUNT2 and HUNT3 in Paper 2 indicate that the unfavourable CV risk factors in PsA patients were present before the PsA diagnosis was established, which may be related to the patients already having psoriasis.

Because modifiable CV risk factors are often present in PsA patients, it is important to educate doctors and patients on how to manage their CV risk factors, to decrease their risk of CVD in the future.

Data from HUNT3 and the Rheumatology department of Hospital of Southern Norway Trust indicate that PsA patients did not have lower bone mineral density than the background population. The prevalence of osteoporosis according to the World Health Organization definition was low. This indicates that PsA patients may follow guidelines for osteoporosis assessment developed for the general population, in line with the current recommendations. However, extra vigilance for patients with long-standing high disease activity or on high doses of glucocorticoids is probably needed.

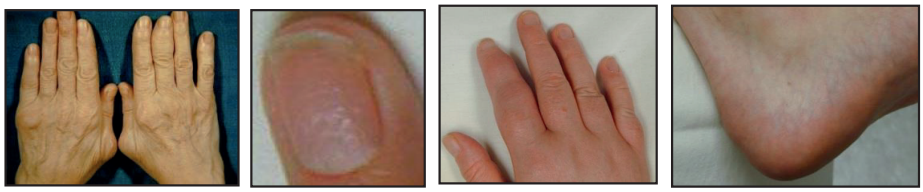
Both osteoporosis and CVD may be silent conditions that the patients are unaware of. Therefore, to wisely target the use our health resources, it is important to know the risk of these conditions, so that we can identify the patients who need extra surveillance. Hopefully, the knowledge from this thesis may guide both doctors who care for patients with PsA, and the patients themselves, on how to manage important comorbid conditions.

1 BACKGROUND

1.1 Epidemiology and classification of psoriatic arthritis

Psoriatic arthritis (PsA) is defined as an inflammatory arthritis associated with psoriasis, estimated to occur in about 15-30% of patients with psoriasis.[1] [2] Previous studies have reported a prevalence of PsA at 1.0 - 1.9 per 1000 inhabitants.[3] [4] However, recently a prevalence of 6.7 per 1000 inhabitants > 20 years of age has been reported in Norway.[5] PsA is classified as a spondyloarthropathy (SpA), a disease group that also includes ankylosing spondylitis (AS), reactive arthritis and arthritis related to inflammatory bowel disease.[6] The disease gained recognition as a separate entity in the 1960s.[7] The clinical presentation of PsA is heterogeneous and may involve the peripheral joints, the axial skeleton, the enthuses and other periarticular tissues.[8] (Figure 1) Distinctive features of PsA are dactylitis (sausage digits) and enthesitis, as well as absence of rheumatoid factor and anti-citrullinated peptide antigen (ACPA).[9] In patients with axial involvement, PsA is often associated with the genetic marker HLA-B27. The bone lesions in PsA are complex, including erosions and structural damage, but also new bone formation, especially of the axial skeleton.

Figure 1. Clinical manifestations of psoriatic arthritis: peripheral arthritis, nail disease with pitting, dactylitis and enthesitis. Printed with permission from Dr. Philip Helliwell and *Group for Research and Assessment of Psoriatic Arthritis* (GRAPPA).



Great variability exists in the severity and activity of the manifestations of PsA, and the pattern of involvement may also alter during the progression of the disease. Some patients have self-limiting disease and go spontaneously into remission,[10] but up to 47% of the patients have radiological damage after 2 years.[11] The variability in clinical presentation of PsA is reflected in the classical description by Moll and Wright from 1973.[12] In 2006 new classification criteria for PsA were developed, the CASPAR criteria (*ClASsification criteria for Psoriatic ARthritis*).[13] (Table 1) The polyarticular joint involvement is the most common type, affecting approximately 60% of PsA patients.[14] [15]

Table 1: The CASPAR criteria. Current psoriasis 2 points, other features 1 point.

The CASPAR criteria	
Inflammatory articular disease (joint, axial or enthesitis) and ≥ 3 points of the following:	
1. Evidence of psoriasis	- Current psoriasis - Personal history of psoriasis - Family history of psoriasis
2. Psoriatic nail disease	
3. A negative test for rheumatoid factor	
4. Dactylitis (sausage digit)	- Current -History
5. Radiological evidence of juxtaarticular new bone formation	

Severe skin psoriasis, psoriatic nail disease and obesity have all been identified as risk factors for developing PsA among patients who suffer from psoriasis. Nail disease, however, may actually be a sign of early phase of PsA.[16 17] In addition to ocular inflammation and bowel inflammation, which is considered part of the clinical picture of SpA, the risk of other comorbidities such as metabolic syndrome, cardiovascular disease (CVD), osteoporosis and depression is suspected to be increased in patients with PsA. PsA is now recognized as a disease clinically and radiographically distinct from rheumatoid arthritis (RA).[18-21] Therefore, research findings related to patients with RA on disease course, comorbidity, treatment and outcome cannot automatically be translated to PsA patients.[22]

1.2 Pathogenesis of psoriatic arthritis

Although the exact pathogenesis of PsA is not known, genetic, immunologic and environmental factors are believed to play a role.[2] PsA is a hereditable condition.[9] Among genetic factors, the HLA-B27, HLA-B38, HLA-B39 and HLA-C06 have been associated with PsA.[23] It is believed that CD8 T cells, by binding to self- peptides trough major histocompatibility complex (MHC) class I molecules, trigger an inflammatory cascade in PsA. T lymphocytes are the most common inflammatory cells in the skin and joints, and CD8 T cells are more common than CD4 T cells in the synovial fluid of PsA patients.[18] There is also increased expression of cytokines, including tumor necrosis factor (TNF), interleukin (IL)-1 and IL-6, which stimulates further proliferation of inflammatory cells as well as osteoclast maturation and activation, leading to cartilage loss and bone erosion.

Neovascularisation of the synovium takes place because of up-regulation of vascular endothelial growth factor, as seen in the skin.[24] [25] Another possible mechanism for inflammation in PsA, called the microtrauma theory, has proposed that ligament and tendon insertion points subjected to repeated microtrauma lead to the release of inflammatory cytokines.[26] [27] SpAs, including PsA, are currently rather viewed as predominantly autoinflammatory diseases, not associated with disease specific auto-antibodies.[28]

Another factor recently suspected to contribute to the pathogenesis of PsA, is the alteration in gut microbe diversity.[9] [29] Obesity is also identified as a risk factor for PsA both in patients already suffering from psoriasis and in the general population.[30] Interestingly, smoking has been shown to increase the risk of PsA in the general population, but to reduce the risk of PsA in psoriasis patients.[31-33]

1.3 Treatment of psoriatic arthritis

Early intervention against arthritis in PsA patients is important, as the longer the disease duration prior to treatment, the higher the risk of developing joint destruction.[34] According to the recommendations from the *European League Against Rheumatism* (EULAR) and *Group for Research and Assessment of Psoriatic Arthritis* (GRAPPA) for the management of PsA, non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line therapy.[35] [36] Intra-articular steroid injections are important additional therapy in PsA.[37] Systemic glucocorticoids are not typically recommended due to the potential risk of psoriasis flare after cessation of use, however may be used for short time periods in selected patients.[38]

Several disease modifying anti rheumatic drugs (DMARDs) have become available for patients with PsA. These now include conventional synthetic DMARDs (sDMARDs), targeted synthetic DMARDs (tsDMARDs), biological DMARDs (bDMARDs), including biological originator DMARDs (boDMARDs) and biosimilar DMARDs (bsDMARDs).[39] For patients with active disease, a sDMARD, such as methotrexate (MTX), should be started to prevent joint damage.[35] The immunopathophysiologic effects of MTX are largely unknown.[40] There is limited data on the effects of MTX in PsA from randomised controlled trials (RCTs),[41] however it is widely used in clinical practice and effect has been shown in observational studies.[42] [43] MTX has no documented effect against axial inflammation or psoriatic nail disease.[41] [44] [45] Leflunomide and sulfasalazin are also used, and some documented effect exist on peripheral arthritis, pain and skin symptoms.[37] [42] [46]

At the beginning of this millennium, the bDMARDs became available, proving to be a much more potent treatment for patients with PsA.[44] Several TNF-inhibitors are now available for patients with PsA (etanercept, adalimumab, certolizumab pegol, golimumab, and infliximab) and they are effective for the treatment of joint inflammation including axial symptoms, enthesitis, dactylitis as well as psoriatic skin and nail disease.[37 38 47] boDMARDs have also shown effect on radiographic progression.[42] For the TNF-inhibitors, bsDMARDs at a lower cost have also become available. Recently, antibodies to IL-12/23 (ustekinumab) and IL-17 (secukinumab) have emerged as effective treatments in PsA.[44] Somewhat lower efficacy is shown for the tsDMARD phosphodiesterase-4 inhibitor apremilast.[48] Another tsDMARD, the JAK inhibitor tofacitinib, has recently showed some effect in PsA.[49] For patients with peripheral arthritis and inadequate response to synthetic DMARDs, bDMARDs are recommended.[35 36] According to the EULAR and GRAPPA guidelines, patients with predominantly axial disease, enthesitis or dactylitis not responding to NSAIDs, should also be considered for bDMARDs.[35 36] MTX can improve drug survival of biologics, especially infliximab, and is often used concurrently with TNF-inhibitors.[37 50] tsDMARDs, e.g apremilast, are suitable for patients who do not respond to bDMARDs or in whom this treatment is not recommended.

1.4 Cardiovascular disease

1.4.1 Overview

CVD is defined by the World Health Organization (WHO) as "a disorder of the heart and blood vessels, and includes coronary heart disease, cerebrovascular disease, raised blood pressure (hypertension), peripheral artery disease, rheumatic heart disease, congenital heart disease and deep vein thrombosis."[51] However, in this thesis the CVD considered is mostly acquired coronary heart disease, cerebrovascular stroke and hypertension. CVD is the number one cause of death globally and contributes to reduced quality of life, earlier death and increased health care expenses.[52] In Norway, 335 064 patients were registered with a CV event in 2015.[53] Norway was considered a high-risk country with regard to CVD in the 1970, however a subsequent drop in CV mortality has reclassified Norway as being a country of low CVD mortality.[54] In recent years inflammatory joint diseases (IJD) have been recognized as an important risk factor for CVD. In the European Society of Cardiology (ESC) guidelines for

CVD prevention from 2016, immunological diseases are mentioned as a high risk factor for CVD.[55] An elevated risk of CVD and increased prevalence of CV risk factors in patients with PsA compared to the general population has been reported.[56-66] However, the underlying causes for increased CV risk in patients with PsA are not entirely understood.

1.4.2 Inflammation and atherosclerosis

The major cause of CVD is atherosclerosis. Atherosclerosis is a process that results in thickening of the intima of the vessel wall, with an accumulation of LDL-c in the intima followed by an increase in smooth muscle cells and extracellular matrix.[67] The atherosclerotic lesions consist of cells, lipids, connective tissue and debris. Established risk factors for atherosclerosis, such as smoking, hyperglycaemia, obesity or dyslipidaemia, enable the process by triggering the expression of adhesions molecules by endothelial cells, thus allowing the attachment of leucocytes to the arterial wall.[68] The inflammatory process is increasingly recognized as crucial in the pathogenesis of atherosclerosis.[69 70] Both innate and acquired immunity play key roles in the formation of the atheroma, including inflammatory cell adhesion to the endothelium, fatty streak formation and smooth muscles migration.[70] Inflammatory cells are also involved in the destabilization and rupture of an atherosclerotic plaque, which may lead to acute thrombosis and ischemia.[71] The inflammatory marker C-reactive protein (CRP), although not established as a causal factor for atherosclerosis, is associated with increased risk of CVD in the general population.[70]

The recognition of the pivotal role of inflammation in the atherosclerotic process highlighted the potential relationship between systemic inflammatory diseases and atherosclerosis. From extensive studies on RA during the last 50 years, it is recognized that the excess mortality in this group of patients is mostly due to CVD.[72] In RA the key feature explaining the increased CV risk seems to be systemic inflammation, in addition to immune dysregulation, plaque instability and some anti-rheumatic medications (glucocorticoids and NSAIDs).[73-75] In addition to RA, other autoimmune or chronic systemic inflammatory diseases have also been associated with increased CV risk, including systemic lupus erythematosus, large vessel vasculitis, AS and PsA.

1.4.3 Cardiovascular disease prevention in inflammatory joint disease

According to the WHO, 80% of coronary heart disease and cerebrovascular disease are due to behavioural risk factors, such as an unhealthy diet, physical inactivity and smoking.[51] Although the exact increase in CV risk in PsA is not established, the CV morbidity in RA is increased by 1.5 to two-fold, and comparable to patients with type 2 diabetes mellitus.[72 76-78] However, still many patients with IJD do not receive optimal CV risk management.[79 77 80] Although the evidence in PsA regarding CVD is less extensive than in RA, EULAR published joint recommendations for CV risk management in RA, PsA and AS in 2010, and provided an updated in 2016.[81 82] The latest recommendations state that CV risk assessment using national guidelines is recommended once every 5 year for patients with active PsA, and should be repeated if anti-rheumatic treatment is changed.[82] In Europe the Systematic Coronary Risk Evaluation (SCORE) algorithm for CV risk assessment is most widely used, and exists in separate versions for high and low risk countries. For patients with RA it is recommended to multiply the calculated risk for future CVD with a multiplication factor of 1.5.[81] This, however, has not been validated for PsA patients.

The Norwegian collaboration on atherosclerosis in patients with rheumatic joint diseases (NOCAR) project has implemented CV risk assessment by using the SCORE as a risk evaluation tool in rheumatology clinics throughout the country.[83] This can easily be incorporated in clinical practice, by measuring blood pressure (BP), non-fasting total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-c). Patients with a calculated risk $\geq$ 5 % for a fatal myocardial infarction coming 10 years will be referred to the primary care physician for interventions or follow up regarding CV risk factors.

For CVD risk reduction, intervention with lifestyle changes, anti-hypertensive treatment, lipid lowering drugs (statins) for cholesterol reduction and acetylsalicylic acid in case of very high risk of CVD, should be considered.[54] Statins are the most widely used lipid lowering agents worldwide today. Statins may obtain a risk reduction for future CVD of 20-24% pr 1 mmol/L reduction in LDL-c.[84] Their effect is on both reducing the atheroma volume and also importantly to stabilize the vulnerable plaque to prevent rupture.[85] This may in particular be due to the anti-inflammatory properties of lipid lowering drugs.[68] The JUPITER trial demonstrated that statin therapy reduced the risk of myocardial infarction and stroke in individuals from the general population with low levels of LDL-c, but who were at increased risk of CVD because of elevated CRP levels. [86 87] In PsA there is still a lack of reports on

effect of cardio-protective agents on CV endpoints. Is has been shown that the lipid lowering effect in PsA patients was comparable to patients with RA and AS. [88] Furthermore, post hoc analyses in 2 large secondary prevention randomized controlled statin trials, showed comparable lipid lowering effect and risk reduction for CVD in both non-IJD and IJD individuals, including PsA patients.[89]

1.4.4 Effect of anti-rheumatic medications on cardiovascular outcome

Epidemiologic data are currently insufficient to reach definitive conclusions on the effects of synthetic and biologic DMARDs on CV outcomes in PsA patients. In RA patients, data suggest that the use of MTX is associated with a decreased risk of CVD and mortality.[90 91 92] MTX reduces several inflammatory biomarkers including CRP, IL-6 and TNF in patients with IJDs, without affecting the lipid levels or BP. Two meta-analyses have sought to evaluate the relationship between DMARDs and CVD in PsA, but the available evidence was insufficient to draw a firm conclusion.[92 93] bDMARDs and tsDMARDS, with tofacitinib in particular, have been associated with increased lipid levels.[94 95] However, data also suggest that TNF-inhibitors may reduce the CV risk in patients with RA.[96] Whether this is effect is mediated by lowering the rheumatic disease activity or by direct effect on the inflammatory pathways of the atherosclerotic process, is not established. Data have shown that RA patients labelled as "good" responders to TNF-inhibitors had lower risk of myocardial infarction than "non"- or "moderate" responders.[97] Data from the CORRONA registry showed that RA patients using a TNF-inhibitor had reduced risk of CVD compared to users of non-biologic DMARDs.[98] The increase in lipids observed after initiation of TNF-inhibitors have been assumed to reflect a normalisation of the lipids to the level the patients had before the onset of the inflammatory disease. In addition, there seems to be a greater increase in HDL-c level compared to TC accompanying treatment with TNF-inhibitors, resulting in improved TC/HDL-c ratio, leading to a more favourable lipid-profile.[82] How bDMARDS affect the risk of CVD in PsA specifically is still largely unknown. However some evidence suggests a reduced CV risk also in PsA patients.[92] Interestingly, large phase III studies are currently being conducted in the general population to explore the effect of MTX (the CIRT trial) on CVD endpoints for secondary prophylaxis after heart attack.[99]

The use of NSAIDs is reported to increase the risk of CVD in the general population.[100] However, strict avoidance in patients with IJD is difficult and it is recommended that NSAIDs

should be used in the lowest effective dosage for the shortest possible time.[101] EULAR recommends cautious use in patients with established CVD or in the presence of CV risk factors.[82] However, in RA the risk for CVD in NSAIDs users were lower than the risk in non-RA individuals, suggesting that NSAIDs may also lead to benefits in patients with IJD, such as increased mobility and decreased pain and inflammation.[102]

The effect of glucocorticoids on CV risk in IJD is somewhat contradictory.[103] In general, glucocorticoids increase the risk of CVD in diverse diagnosis groups, and the effect seems to be dose-dependent.[104-106] Glucocorticoids use is associated with decreased insulin sensitivity, elevated lipid levels and hypertension.[107] In RA the use of glucocorticoids has been associated with increased mortality, independent of disease activity.[108] However, glucocorticoids may also have cardio-protective effect mediated by their anti-inflammatory properties.[109] According to the latest EULAR recommendations for CV risk management in patients with IJD, glucocorticoids should be used in the lowest effective dose.[82] The recommendations conclude that low dose glucocorticoids treatment does not seem to contribute significantly to the enhanced CV risk, in contrast to high-dose glucocorticoids.[82]

1.5 Osteoporosis

1.5.1 Overview

Osteoporosis is a systemic skeletal disorder characterized by low bone mineral density (BMD) and micro-architectural deterioration that can lead to bone fragility and increased susceptibility to fractures.[110] Hip fractures account for most of the cost and deaths related to osteoporosis, however vertebral fractures also cause pain and disability.[111-113] BMD measured by Dual Energy X ray absorptiometry (DXA) is the current gold standard for diagnosis of osteoporosis.[114] Osteoporosis is defined by the WHO as T score $\leq$ -2.5 SD.[115] [114] Data on systemic bone loss in patients with PsA are conflicting.[116] An association between PsA and low BMD has been reported by some,[117-119] whereas others find comparable BMD in PsA patients and the background population.[120-125] Slightly increased fracture risk compared to the general population has been reported, however significantly lower than in RA.[123] [124] [126]

1.5.2 Bone remodelling in inflammatory joint diseases

Remodelling of the skeletal bones is regulated by a dynamic interplay between osteoblast and osteoclast function, maintaining bone mass and the integrity of bone architecture. Osteoclasts, derived from hematopoetic progenitor cells in the bone marrow, resorb bone, and osteoblasts, derived from mesenchymal (stromal) lineage, produce bone matrix. In normal bone the bone resorption is followed by replacement of the resorbed bone by osteoblasts. In inflammatory conditions, this balance is altered, resulting in excess bone resorption, new bone deposition, or both.[127] RANK ligand (RANKL), a member of the TNF family, plays a key role in in osteoclastogenesis, by acting directly on osteoclast formation and activity. RANKL is produced by osteocytes and osteoblasts in normal bone remodelling, but also by lymphocytes and fibroblasts in conditions such as inflammation and oestrogen deficiency.[128] Proinflammatory cytokines such as TNF alpha, IL-6, IL-17 and IL-1 stimulate RANKL, demonstrating a link between inflammation and bone loss.[129 130]

In the SpAs the skeletal damage is a consequence of both bone destruction and bone formation, which may occur simultaneously.[131] As a consequence, patients with active PsA may show signs of both erosions and osteophyte formation.[21 132] This enhanced bone formation at sites of inflammation, is a unique feature of the SpAs in comparison to RA, where osteoclast activation is dominating, causing mainly erosions and osteoporosis.[133] Typical for SpA is the widespread axial involvement, leading to formation of syndesmophytes in the spine, but limited erosive damage to the vertebra.[134]

1.5.3 Measurement of bone mineral density

Although osteoporosis is characterized by both low bone mass and micro-architectural deterioration, only quantitative measures reflecting bone mass are available for assessment in clinical care. The WHO clinical operational definition of osteoporosis from 1994 is based on BMD measurements at the axial skeleton (hip or lumbar spine) assessed by DXA.[114] BMD is defined as the average concentration of mineral per unit area expressed as g/cm^2 (also referred to as areal BMD).[135] BMD is considered a surrogate marker for fracture risk. The relationship between BMD and fracture risk is a gradient without any definitive fracture threshold. The lower the BMD the higher the risk of fracture.[135] The distribution of BMD in the population is normally distributed. Because of this, the BMD values of an individual may be expressed in relation to a normal reference population, in standard deviation (SD) units.[136]

The T score is defined as the number of SD away from the mean of the BMD in the reference population of individuals with peak bone mass (age 20-40 years).

According to the WHO osteoporosis is defined as T score < -2.5 SD or below, osteopenia as T score between -2.5 SD and -1 SD, and normal BMD as ≥-1 SD. [115] [136] The Z score compares the BMD with a reference population of the same age and sex, however an age, sex and weight matched reference population can also be used.[137] Because BMD declines with age, T scores are consistently lower than Z scores after about 40 years, and the difference increases with age. The WHO definition of osteoporosis is meant to be applied on adult individuals. However, some advocate that Z score should be used in premenopausal women and men younger than 50 years of age.[137] The NHANES III, (National Health and Nutrition Examination) from the US has been suggested as a reference population.[138] [136]

For a measurement tool it is important that the measures are accurate and precise. Accuracy refers to the ability of the instrument to produce a measure close to the standard or known value, and precision refers to the ability of the instrument to produce the same results in several measurements. For DXA both accuracy and precision is considered to be good.[110] The precision error for DXA is usually expressed as coefficient of variation (CV), which is the ratio of the SD to the mean of the measurements.[139] Even though DXA is the "gold standard" for the measurement of BMD and diagnosis of osteoporosis it has some limitations.[136] Arthritis of the hip and spine, sclerosis of the aorta, and previous fracture may contribute to increased BMD value, but not necessarily to bone strength.

1.5.4 Fracture risk assessment

Apart from BMD several other risk factors for osteoporosis and fragility fracture have been identified.[140] One of the risk assessment tools available is the FRAX, based on age, sex, weight and height, as well as personal or family history of fracture, smoking habits, alcohol consumption, use of glucocorticoids, diagnosis of RA or presence of secondary osteoporosis.[141] The FRAX calculation can be performed with or without BMD of the femoral neck. It is available online (https://www.sheffield.ac.uk/FRAX/) and gives an estimate of the 10-year risk of a hip or major osteoporotic fracture (clinical spine, wrist, humerus or hip) among men and women aged 40-90 years.[137] Neither PsA nor other SpAs are included in the FRAX as a risk factor for fractures. Use of glucocorticoids and previous fracture increase the

fracture risk beyond the fracture risk according to the BMD level alone.[142] [143] Further, the absolute fracture risk for any given BMD is much higher in older postmenopausal women than in younger individuals, indicating that age is an important independent risk factor.[137]

1.5.5 Prevention and treatment of osteoporosis

To prevent fracture it is important to identity and treat patients at high risk of fractures. Patients with osteoporosis can either be identified by a case finding strategy based on clinical risk factors, or by a screening strategy. Guidelines to identify individuals with high risk of fractures exist. In Norway the recommended case-finding strategy suggests individuals with one or more risk factors for osteoporosis to be assessed with DXA.[144] Guidelines from the *International Osteoporosis Foundation* and the *British National Osteoporosis Guideline Group* suggest the use of FRAX risk score to determine the need for DXA and treatment.[110] [145] However, the role of screening, selecting patients for treatment, and which type of medications that should be recommended, are controversial issues in the management of osteoporosis.[140] [146] According to recommendations from the *US Preventive Services Task Force,* women aged 65 years or older should be screened for osteoporosis by BMD measurements using DXA.[147] The prevalence of osteoporosis in this population is nearly 25%.[137] Osteoporosis is much less common in men, with a prevalence of 5% for men 65 years or older.[137]

Life style measures for fracture prevention include maintaining a healthy body weight (BMI > 20 kg/m^2), adequate dietary protein, vitamin D and calcium intake, and weight-bearing physical activity, as well as avoidance of cigarette smoking, excessive alcohol intake and falls.[148] Effect of additional Vitamin D and calcium supplements on facture risk appear to be small, but some effect in seen in population groups with a low dietary intake of vitamin D or calcium.[149] [150] The primary goal of osteoporosis treatment is to reduce the risk for fracture. Bisphosphonates are the first line agent for treatment of osteoporosis. They inhibit bone resorption by inducing apoptosis of osteoclasts. Among postmenopausal women with osteoporosis treatment with alendronate, risendronate, and zoledronic acid reduces risk of clinical fracture including hip and vertebra.[146] [151] [152] Denosumab is the first biologic drug to treat osteoporosis.[153] Raloxifen, a selective oestrogen receptor modulator, only reduces the risk of vertebral fractures in postmenopausal women, and is not recommended, because of the potential harms.[154] The data on the efficacy of pharmacotherapy on fracture risk in men is

limited.[137] Whether to recommend drug treatment in adults with osteopenia is highly debated.[137] Systematic reviews of bisphosphonate trials in postmenopausal women without osteoporosis or existing fracture have not reported reduced risk for non-vertebral fractures.[151]

1.6 Epidemiological challenges when studying risk factors

Risk factors are variables that are associated with the development of a disease or an outcome. When it comes to CVD or osteoporosis, we are interested to know if PsA can be considered a risk factor for these comorbidities. However, a long latency between exposure to the risk factor and development of the disease can make it difficult to reveal the true relationship.[16] Also, risk factors are often related to one another, for instance the relationship between PsA and obesity, or PsA and the use of NSAIDS or corticosteroids.[30] [155] Further, the difference between causation (the risk factor directly causes the disease) and association (a relationship between risk factor and disease) must be kept in mind. To establish a causal relationship, the Bradford Hill criteria can be applied: the strength of the association, consistency, specificity, temporality, biological gradient (or dose-effect), plausibility, coherence and preferably interventional evidence.[156] The different observational study designs all have inherent pros and cons to consider when studying risk factors. Cross-sectional studies measure risk factors and disease at the same point in time, therefore a causal relationship cannot be established. However these studies may offer important clues on which potential risk factors to investigate further in other studies.

Also, in attempt to examine the true occurrence of a disease, it is important that the patient sample is representative for the background disease population. For example, in a hospital population the patients are more likely to have more active disease, overestimating a comorbidity or disease when extrapolating results to the whole population with the same diagnosis.

2 AIMS

The general aim of this PhD thesis was to study the comorbidity of CVD and osteoporosis in patients with PsA.

The specific aims were addressed in the following research questions:

- Do PsA patients have increased prevalence of CV risk factors and CVD compared to the background population? (Paper 1)
- Is there a difference in the estimated 10-year risk of a fatal CV event, using the SCORE algorithm, between PsA patients and controls? (Paper 1)
- Do CV risk factors change over time in patients who are diagnosed with PsA compared to the background population? (Paper 2)
- Do patients with PsA from a population cohort have lower BMD than background population? Are the odds of having osteoporosis or osteopenia higher in PsA patients than controls? (Paper 3)
- Do patients with PsA from a hospital cohort have lower BMD than the background population? (Paper 4)
- Are disease duration and activity associated with BMD in PsA? (Paper 4)

3 PATIENTS AND METHODS

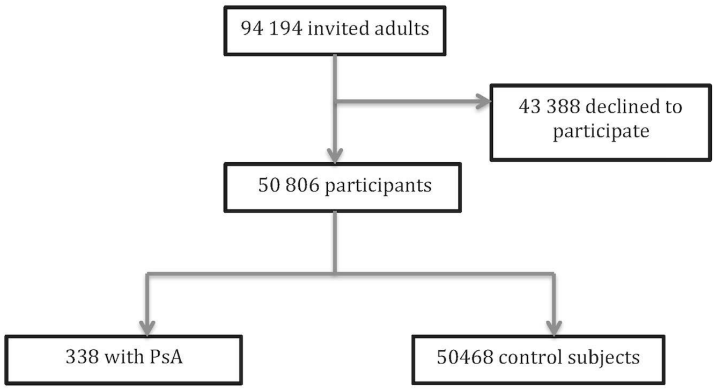
3.1 Study population and study design

3.1.1 The HUNT studies

In Papers 1, 2 and 3 we used data from the Nord -Trøndelag Health study (HUNT). Nord-Trøndelag is one of 19 Norwegian counties and is located in the middle part of the country.
In total, approximately 120000 Norwegians have participated in the three population studies that have been carried out so far: HUNT1 (1984-86), HUNT2 (1995-97) and HUNT3 (2006-08).[157] In HUNT2, an invitation letter and first questionnaire (Q1) was mailed to all adult inhabitants 2 weeks before the screening date. 64560 out of 92566 (70%) individuals responded to Q1 and then participated in a brief medical examination. A total of 93680 adults were eligible for participation in HUNT3, and out of these 50806 participated (54%).

Data presented in Papers 1 and 3 were retrieved from HUNT3, and data from Paper 2 were retrieved from both HUNT2 and 3. In HUNT3, 338 persons (0.67%) were validated to have PsA according to the CASPAR criteria.[5] In Paper 1 all 338 patients with a validated PsA diagnosis were included, and controls were all other participants in HUNT3 (Figure 2). In Paper 2 we included 151 patients diagnosed with PsA between HUNT2 and HUNT3 (1998 through 2008). Patients diagnosed with PsA before HUNT2 were excluded.

Figure 2: Flow chart for Paper 1: HUNT3



The DXA study in HUNT3 was initially designed as part of a study on pulmonary disease patients. An invitation to DXA measurement was sent to 14247 persons in the HUNT3 population born after January 1st 1921 and living in one of the five largest municipalities in the Nord-Trøndelag county. 11772 persons participated (82.6%), 7570 women and 4202 men. Of these 6,887 were invited based on a random sample of the total HUNT3 cohort, and 4885 were invited based on reporting a wide spectrum of lung symptoms (asthma and chronic obstructive pulmonary disease (COPD)). This included 69 patients with PsA (36 invited by random selection and 33 because of self-reported pulmonary symptoms). Controls were all other participants in the HUNT3 study.

3.1.2 Study cohort from the Hospital of Southern Norway Trust

Among 581 patients with a diagnosis of PsA registered at the Department of Rheumatology outpatient clinic of the Hospital of Southern Norway Trust, Kristiansand, during the study period from January 2013 to May 2014, 471 fulfilled the CASPAR criteria.[14] Among these, 141 patients were consecutively recruited at routine visits for more extensive investigations, and 140 patients underwent DXA scanning of lumbar spine and hip.[158] All the included patients had peripheral inflammatory involvement clinically, as patients with only axial manifestations were excluded.

3.2 Data collection

3.2.1 Data collection in the HUNT study

Self-administered questionnaires, clinical measurements and blood samples are the basis for data collection in the HUNT studies. In Paper 1 total CVD was defined as one or more of angina pectoris, myocardial infarction, cerebrovascular stroke, coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). Information on CABG or PCI were only available for 3919 and 3911 participant, respectively, as these questions were part of a questionnaire only distributed to people answering "yes" to having CVD in Q1. In Paper 1 and 2 we calculated LDL-c using the Friedewald formula (TC minus HDL-c minus [triglycerides/2.2]), excluding those with triglyceride concentrations ≥ 4.5 mmol/l.[159] The disease characteristics of the PsA patients in the HUNT study, including use of anti-rheumatic medication, were obtained from reviewing patient hospital medical records through year 2008, as part of the validation of PsA diagnosis in HUNT3.[5]

3.2.2 The SCORE model

To calculate the 10-year risk of a fatal cardiovascular event with the SCORE, age, sex, systolic BP, cholesterol values (TC/ HDL-c ratio) and smoking are incorporated into the algorithm. According to the current guidelines, we stratified into four levels; low risk<1 %; moderate risk 1-4 %; high risk 5-9% and very high risk ≥ 10 %.[160] [161] Patients with established CDV, diabetes mellitus type 2 or type 1 with end organ damage, chronic kidney disease with glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 are in the latest ESC guidelines for CVD prevention automatically classified as having a very high risk of CVD, and a CVD risk calculation by SCORE calculation is not necessary.[162] In Paper 1 we included patients with myocardial infarction, stroke, CABG, PCI and diabetes mellitus in the "very high risk" group without calculation of SCORE. However, we did not have information on GFR, type of diabetes mellitus or end organ damage and peripheral vascular disease, thus we could not follow the recommendations on these characteristics.

3.2.3 Bone mineral density in the HUNT study

In Paper 3 BMD (as g/cm^2) was measured at lumbar spine (L1-L4), and hip (femoral neck and total hip) by DXA, (Lunar Prodigy, GE Healthcare). We preferably used measurements from the left hip. Lumbar spine BMD was calculated as the mean of the BMD score in L1-L4. In Paper 3 T score calculations were based on data from a European / US reference population provided by Lunar. Previous studies have shown that this European/US reference population database supplied by the manufacturer corresponds well with the Norwegian normal population across all adult age groups.[163]

For male T score estimation the following mean BMD (SD) for young male adults (age 20-39) were used: femoral neck 1.07 (0.13), total hip 1.09 (0.13) and spine L1-L4 1.24 (0.12). For female T score estimation the following mean BMD (SD) for young female adults (age 20-39) were used: Femoral neck 0.98 (0.12), total hip 1.00 (0.12) and spine L1-L4 1.20 (0.12).

$$\text{T score calculation: } \frac{\text{measured BMD} - \text{mean BMD (peak bone mass from reference population)}}{\text{SD (peak bone mass from reference population)}}$$

Regular phantom calibration of the densitometer was performed according to the existing densitometry procedures and quality assessment guidelines at HUNT.

3.2.4 Bone mineral density in the study from Hospital of Southern Norway Trust

In Paper 4 the T score (compared with peak bone mass of the same sex) and Z score (comparison with age, sex and weight matched controls) were based on the reference values in the DXA machine provided by the manufacturer (NHANES reference population).

3.3 Statistics

Statistical analyses were mainly performed using Statistical package for the social sciences (SPSS) for Mac version 20-23 (Chicago, IL). Mixed model analyses in Paper 2 were performed in R for Windows. Statistical significance level was defined as $p < 0.05$ on the basis of two-sided test, with no adjustments made for multiple comparisons. For missing data patients were excluded only if they were missing data required for the specific analysis. They were still included in the analyses for which they had the necessary information. Demographical characteristics in PsA patients and controls were compared with Chi-square test for counts and Student‘s t-test for continuous variables, or Fishers Exact test when small numbers.

In Paper 1 Student‘s t-test, Pearson‘s Chi-square test and logistic regression analyses were performed for group comparison. Multivariable analyses adjusting for age and sex were performed for group comparison of CV risk factors and CVD by multivariable logistic regression (dichotomous outcome variables) or linear regression (continuous outcome variables). For comparison of hypertension between groups we added BMI to the logistic regression model.

In Paper 2 PsA patients were matched in a 1:5 ratio to controls with the same sex and age at both HUNT2 and 3. Difference in mean change with 95%CIs of CV risk factors from HUNT2 to HUNT3 between PsA and controls were calculated by mixed linear models. This type of statistical model can manage missing data that may occur in repeated measurements, and also account for dependence introduced by the matching, by including group identity as a random effect. Both crude p-values and p-values with adjustments for BMI, smoking and use of anti-hypertensive medication were calculated for cholesterol values and BP values.

In Paper 3 mean difference in BMD between PsA and controls with 95%CIs were calculated using Student's t-test. Crude p-values were presented as well as p-value with adjustments made for age, sex, BMI, physical activity, smoking, asthma/ COPD and reason for invitation to DXA. Since the selection of patients for DXA in the HUNT3 study was not completely random we added both the diagnosis of asthma / COPD and reason for invitation to DXA to the multivariable linear regression model. To assess the association between PsA and the outcome with 3 ordinal categories (normal bone density, osteopenia or osteoporosis) we used ordinal logistic regression, after assessment for parallel lines. Here we also presented crude p-value and a p-value with adjustments made for the same variables as listed above.

In paper 4 CIs were used to assess the difference between the mean Z score at each anatomical site and the general population data from the DXA machine provider. Assuming a normal distribution of the Z score, the risk is 68% of being within ± 1 SD of the mean, thus, the expected proportion of Z scores ≤–1.0 SD is 16% by default. The 95% CI range for proportions of patients having a Z score of ≤–1.0 SD was calculated using the equation for binomial distribution. Association between clinical and demographical factors and BMD was analysed using multivariable linear regression. Variables from the univariable analyses with a p-value <0.10 was included in a multivariable model, which also included sex and age regardless of the significance in the univariable analyses.

4 SUMMARY OF PAPERS

Paper 1

On the HUNT for cardiovascular risk factors and disease in patients with psoriatic arthritis: population-based data from the Nord-Trøndelag Health Study

The aim of this study was to investigate the prevalence of CV risk factors and CVD in patients with PsA. The 338 PsA patients identified according to the CASPAR criteria were compared to the 50468 controls from the background population in HUNT3. The self-reported prevalence of CVD (myocardial infarction, angina pectoris, cerebrovascular stroke, CAGB and PCI) and CV risk factors (smoking, BMI, cholesterol, BP) were compared between groups, adjusting for age and sex. Further, we compared the 10-year risk of a fatal CV event calculated by the SCORE algorithm.

There was an increased prevalence of angina pectoris (5.0% vs 3.6%, p=0.01), history of PCI (2.4% vs 1.4%, p=0.04), hypertension (45.3% vs 39.3%, p=0.01), obesity (32.0% vs 22.4 %) and tobacco smoking (21.3% vs 16.4 %, p= 0.02) in PsA patients compared to controls. PsA patients had elevated levels of CRP (p<0.001), BMI (p<0.001) and triglycerides (p=0.01) compared to controls. The median calculated CV risk by SCORE in PsA patients was low and comparable to controls (0.87 vs 0.83, p=0.24). The distribution across CV risk classes was similar amongst PsA patients and controls. The associations between PsA and hypertension, PsA and history of PCI and PsA and triglyceride level were attenuated when adjusting for BMI in addition to age and sex.

This population-based study supports that PsA patients have a greater burden of CV risk factors. There was no difference between groups in 10-year risk of a fatal CV event estimated by SCORE, which may be explained by the fact that the patients had elevated CV risk factors not included in the SCORE algorithm. The PsA patients had increased prevalence of angina pectoris, hypertension and history of PCI, but not myocardial infarction, cerebrovascular stroke or CABG compared to the background population. Higher BMI seemed to be contributing to the higher prevalence of hypertension, history of PCI, and elevated triglyceride level found in the PsA patients.

Paper 2

Change in cardiovascular risk factors in patients who develop psoriatic arthritis: longitudinal data from the Nord-Trøndelag Health Study (HUNT)

Whether increased CV risk factors are present prior to diagnosis of PsA or a result of the disease itself, has not been clarified. The aim of this population-based study was to compare changes in CV risk factors over a decade-long period in patients who develop PsA and the background population. Patients diagnosed with PsA (N=151) between 1998 and 2008 and matched controls (N=755) who participated in both the HUNT2 (1995-97) and HUNT3 (2006-08) were included. Mixed linear and logistic models were used to analyse the difference in mean change between HUNT2 and HUNT3 in patients and controls for weight, BMI, TC, triglycerides, LDL-c, HDL-c, and BP.

At baseline persons who developed PsA had significantly higher mean BMI (27.2 vs 25.9 kg/m^2, $p< 0.001$), lower HDL-cholesterol (1.32 vs 1.40 mmol/L, $p = 0.03$) and more were smokers (41.1 vs 28.5%, $p< 0.01$) compared to those who did not develop PsA. Of the PsA patients, 77% had psoriasis symptoms at HUNT2, and 90% reported psoriasis symptoms before PsA diagnosis. The mean time (SD) from PsA diagnosis to HUNT3 was 4.8 (3.0) years. The PsA patients gained less weight compared to the control group (2.1 vs 3.9 kg), difference in mean change -1.8 kg (95% CI -3.9 to -0.5, $p<0.01$). TC, triglycerides, LDL-c or HDL-c values, and BP declined in both groups, with no significant differences between groups (adjusted for BMI).

Longitudinal ten-year data did not show an increase in CV risk factors in patients who developed PsA compared to controls. The PsA patients even experienced a smaller increase in weight than the controls. This study implies that unfavourable CV risk factors in PsA patietns were present before the PsA diagnosis was established.

Paper 3

Bone mineral density in patients with psoriatic arthritis – data from the Nord-Trøndelag Health Study 3.

The aim of this study was to compare BMD measured by DXA in PsA patients and controls. We recruited PsA patients and controls from the HUNT3 study. PsA patients (n=69) and controls (n=11703) were comparable in terms of age (56.8 vs 55.3 years, p=0.32), gender distribution (females 65.2% vs 64.3%, p=0.87), and postmenopausal status (75.6% vs 62.8%, p=0.08). BMI was higher in PsA patients compared to controls (28.5 vs 27.2 kg/m^2, p=0.01). After adjusting for potential confounding factors (including BMI), BMD was higher in PsA patients compared to controls at lumbar spine 1-4 (1.213 vs. 1.147 g/cm^2, p=0.003) and femoral neck (0.960 vs 0.926 g/cm^2, p=0.02), but not at total hip (1.013 vs. 0.982 g/cm^2, p=0.11). Controls had significantly higher odds of having osteopenia or osteoporosis based on measurements of BMD in femoral neck (p = 0.001), total hip (p=0.033) and lumbar spine (p=0.033).

Data from this population-based study shows that BMD in PsA patients were higher than in controls. This supports that the PsA population is not at increased risk of osteoporosis.

Paper 4

Osteoporosis in psoriatic arthritis - A cross-sectional study of an outpatient clinic population

The object of this study was to investigate BMD at the hip and lumbar spine measured by DXA in PsA patients. From an outpatient clinic in southern Norway, 140 patients with PsA were consecutively recruited and assessed for osteoporosis with DXA as part of a prospective study from January 2013 to May 2014. An extensive data collection was performed including demographic data and measures reflecting disease activity, health status and treatment.

Mean age was 52.4 years and 71 (50.7%) were females. Median disease duration was 7.8 years. Mean ± SD BMD of the PsA patients was 0.967 ± 0.141 g/cm^2 at femoral neck, 1.017 ± 0.148 g/cm^2 at total hip and 1.208 ± 0.170 g/cm^2 at lumbar spine. The proportion of patients with low BMD (defined as Z score ≤ -1.0 SD) was comparable to the expected value of 16%, according to the normal distribution of the Z score in the population. Osteoporosis based on WHO criteria (T score ≤-2.5) was only found in 6.4% (95% CI 3-11%) of the patients. No significant association was found between BMD and disease measures except for total hip and lumbar spine BMD and erythrocyte sedimentation rate (ESR) for males only (N=69).

The prevalence of PsA patients with osteoporosis was low and the proportion with Z score ≤ -1.0 SD was in the range seen in the reference population. This supports that PsA patients are not at high risk for osteoporosis compared with the general population. Therefore, clinicians may follow the general population guidelines for monitoring of osteoporosis for PsA patients.

5 DISCUSSION

The methodological strengths and limitations of this thesis are discussed in the first part of the discussion. The second part addresses the interpretations of the main results.

5. 1 Methodology

5.1.1 Study design

Because of the cross-sectional design of Papers 1, 3 and 4, a causal association between PsA and outcome cannot be established, as this design lack a temporal association as described by the Bradford Hill criteria.[164] The control group in the HUNT papers consisted of all other participants in the HUNT study, regardless of whether they had another rheumatic condition, i.e RA or AS, however this group is estimated to compose only 1-2% of the HUNT population.[165] This was mainly because of the lack of validation of these diagnoses, a work that later has been undertaken.[165] The number of included PsA patients was relatively low, especially in Paper 3, providing wide CIs and increasing the risk of a type 2 error (a false negative finding), however the high number of controls increases the power of the statistical tests used to compare groups.

Paper 4 was conducted without a control group. Instead CIs were used to assess the difference between the mean Z score of the PsA patients and the reference population data from the DXA machine provider. Data indicate that the reference population provided by the DXA manufacturer reflects the bone density of the background Norwegian population. A study from Western Norway found comparable BMD in the investigated population and the reference data provided by the DXA manufacturer, except for lower BMD for males at total hip in the examined population.[163] Further, a study from Oslo, Norway also found comparable BMD in a reference population compared to Lunar DXA European/US reference population.[166]

5.1.2 Selection bias

Selection of participant in the HUNT studies

Selection bias is a distortion that results from procedures used to select subjects, and factors that influence study participation.[167] The participation rate in HUNT2 was 71%, and in

HUNT3 54%. In both HUNT studies more women than men participated, and the highest participation was in the middle aged and the elderly (50-79 years old) with lower participation in the age group >80 years and <40 years.[157] Non-participants in HUNT 3 have been shown to have more CVD than participants, which can represent a potential selection bias in Paper 1, although this should be expected to affect both PsA patients and controls equally.[168]

Selection of participants for DXA in the HUNT study

Since the selection of patients for DXA scanning was based on a study on lung diseases conducted as part of the HUNT3 study, the total inclusion of individuals for DXA was not completely random. Participants were invited to DXA based on a random sample from participants in HUNT3 (N=6887), and persons who answered "yes" to the following questions about pulmonary symptoms, diagnosis and medication in HUNT3 (N= 4885):
1) Have you ever had asthma? 2) Have you ever had COPD, emphysema or chronic bronchitis? 3) Have you at any time during the last 5 years used medicine for asthma, chronic bronchitis, emphysema or COPD? 4) Have you ever had episodes of dyspnoea in the last year?

The DXA selection included 69 patients with PsA (36 invited by random selection and 33 because of self-reported pulmonary symptoms) with age between 20 to 95 years, and 11703 controls. As the selection of patients for DXA from the HUNT population was not completely random, we adjusted for inclusion criteria (random or based on reported lung symptoms) in the multivariable analysis. However, applying probability weights in the statistical analyses to weight participants with BMD measurements to the total HUNT3 study population has been done in another study, to obtain estimates representative for the total HUNT3 population.[169] This study showed no association between psoriasis and reduced T score or osteoporosis.

Selection of patients from the Hospital of Southern Norway Trust, Kristiansand

Among the 471 CASPAR verified PsA patients registered at the outpatients clinic, 141 were recruited for more extensive examinations, including DXA.[158] The demographical and clinical characteristics of the 141 study participants has been compared with the remaining 330 PsA patients not included in the study. The included patients were younger than the non-included. They also had higher median 28 tender joint count, DAS28 and CDAI. More included than non - included patients were currently using leflunomide, but less were currently on

glucocorticoids.[158] This information was collected at the patients' last visit during the study period.

5.1.3 Diagnostic bias

Diagnostic bias refers to error in the collection of information. It is also referred to as misclassification when dealing with categorical data. The diagnoses of PsA in HUNT3 have previously been validated from hospital records by an experienced rheumatologist, according to the CASPAR criteria.[5] Questionnaire 1 in HUNT3 included questions about psoriasis, RA, and AS. Persons who answered that they had psoriasis also received a more detailed questionnaire including a question if they had PsA. In total, 1238 persons reported that they had or may have either PsA; RA and psoriasis; or AS and psoriasis. The positive predictive value for reporting PA in the questionnaire was 68%. The identification of PsA patients from HUNT3 has been published in detail, and laid the base for further research on the PsA patients in the HUNT studies.[5]

As most of the data in the HUNT study are questionnaire-based, including information on CVD, there is a potential problem of misclassification. Although self- reported risk factors may be prone to systematic report errors, self-reported tobacco use has previously been shown to be a valid marker for tobacco exposure.[170] Also self-reported use of anti-hypertensive medication has been shown to agree with pharmacy records.[171] We consider the diagnosis of angina pectoris to be the most susceptible to misclassification, as chest pain may not always lead to examination by a specialist, and also may origin from joint inflammation in PsA patients. On the other hand, myocardial infarction and cerebrovascular stroke would in most cases have led to hospitalization and follow up from specialists that would make the patient aware of their diagnosis. Validation of CVD reported in the HUNT study would require linking data from several sources (i.e. hospitals, general practitioners and health registers), and ethical and legal approval procedures for such studies are complicated. The lack of validation of the CVD diagnoses may be a potential limitation of Paper 1.

5.1.4 Confounding bias

Confounding is alteration of the association between the outcome and exposure by that of a third factor. For the exposure to be a confounder it has to be associated with both the exposure and the outcome, and should not be on the causal pathway between factor of interest

and the outcome. A confounding factor can over - or underestimate the true effect. Multivariable analysis is a statistical model that can be used to estimate independent relationships while adjusting for potential confounders.[172] Identification of possible confounding factors may come from previous studies on the topic or associations found in univariable analyses.

When investigating comorbidity in PsA patients, one must keep in mind that the patients may differ in several aspects compared to the controls. The unadjusted (crude) estimate for CVD or osteoporosis can indicate if this group of patients have increased risk of these comorbidities. However, if we want to know the isolated effect of PsA on the risk of an outcome, all other variables must be kept similar between the groups, by controlling for potential confounding factors in the analysis. Nevertheless, in observational studies there might always be confounding factors that are not considered, and which may influence the results. The main goal in Paper 1 was to assess the risk of CVD in PsA patients rather than to attribute the risk to inflammation only, therefore we only adjusted for age and sex in the analyses. However, the risk of having hypertension was attenuated after also adjusting for BMI. To further investigate the effect of BMI on the risk of CVD, we later added BMI to the regression model (Table 2, see page 44). Adjusting for BMI also attenuated the associations between PsA and high triglyceride level, and PsA and low HDL-c level. Therefore, our results suggest that the increased BMI of the PsA patients may explain some of the increased CV risk. We did not explore other potential confounding factors on the association between PsA and CVD, such as smoking or medications, and the results therefore cannot describe the isolated effect of the inflammatory condition on CVD.

In Paper 3 we presented the adjusted p-value for the association between PsA and BMD, adjusted for several potential confounding factors (sex, age, BMI, smoking, physical activity level, asthma/COPD and if the patients were included randomly or based on reported lung symptoms). We choose these variables based on previous knowledge related to factors influencing BMD, and also because of the non-random inclusion of patients for DXA in the HUNT study. Further, regarding Paper 3 and 4 we did not control for other potential confounders, including radiographic evidence of existing fractures or syndesmophytes of the hip or spine, and calcifications of the aorta, which may lead to increased BMD value. However, with a low number of cases included, it is recommended to restrict the number of variables in a multivariable regression model.

5.1.5 Representativeness and validity of the results

A central question is if the results from our studies are valid for PsA patients outside our study population. In Papers 1, 2 and 3 the PsA patients were identified from the population-based HUNT study, where health status of the participants is considered to be fairly representative of the general Norwegian population.[173] However, they probably represent a healthier population of PsA patients than if recruited from a hospital cohort. Further, the PsA patients in the HUNT study were relatively young with respect to having established CVD, and the low number of events for some of the CVD may have weakened the statistical power to detect a difference between PsA patients and controls. The risk of osteoporosis was also investigated in a hospital cohort, with similar findings regarding PsA and low BMD as seen in the population cohort. However, the PsA patients from Hospital of Southern Norway Trust in Paper 4 had low disease activity, as is to be expected in patients treated in a contemporary rheumatology outpatient clinic, with publically funded healthcare, and a liberal use of biologic medication. Therefore, since high disease activity in PsA may be associated with CVD and osteoporosis, our results may underestimate the actual risk of these comorbidities in PsA patients with high disease activity.

5.2 Interpretation of findings and comparison with other studies

5.2.1 Cardiovascular risk factors and disease in psoriatic arthritis patients

The PsA patients in the HUNT3 cohort had increased prevalence of several traditional CV risk factors: obesity, smoking, high triglyceride level, low HDL-c level, and hypertension. As expected, the inflammation marker CRP, considered a novel CV risk factor, was elevated in the PsA group. Regarding risk of established CVD, the results in Paper 1 showed an increased age and sex adjusted risk for angina pectoris and PCI in PsA patients, but not for myocardial infarction, cerebrovascular stroke, CABG and CVD in total. Further, the association between PsA and PCI and PsA and hypertension was attenuated when also adjusting for BMI in the statistical model (Table 2).

Table 2: Risk of cardiovascular disease in psoriatic arthritis patients, analysed with logistic regression.

	Adjusted for age and sex		Adjusted for age, sex and BMI	
	OR (95%CI)	P	OR (95%CI)	P
Angina pectoris	2.06 (1.24-3.40)	0.01	2.02 (1.20-3.40)	0.01
Myocardial infarction	1.39 (0.75-2.60)	0.30	1.35 (0.72-2.54)	0.33
Stroke	1.12 (0.55-2.28)	0.75	1.12 (0.55-2.28)	0.75
PCI	2.11 (1.03-4.30)	0.04	2.03 (0.99-4.14)	0.05
CABG	1.74 (0.80-3.98)	0.19	1.66 (0.72-3.82)	0.23
Hypertension	1.39 (1.09-1.75)	0.01	1.23 (0.96-1.56)	0.09

OR: Odds ratio, CI: confidence interval, BMI: body mass index, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft.

Others have found higher prevalence of established CVD in PsA patients compared to the general population.[56 59 65 174] A review from 2013 concluded with increased risk of ischemic heart disease, cerebrovascular stroke, peripheral vascular disease and congestive heart failure in PsA.[62]

The relative CV risk across distinctive IJDs is debated.[175] Several studies have also demonstrated a higher CV risk in psoriasis patients.[176 177] In summary, it seems that there are slight differences in risk of CVD between RA, PsA and psoriasis.[60 65] In a study comparing CV risk in these three inflammatory conditions RA patients had the highest risk.[65] Others have reported comparable CV risk in patients with severe psoriasis and PsA.[176] In line with our results in Paper 1 and 2, a higher prevalence of traditional CV risk factors in PsA patients compared to the general population is consistently reported.[59-61 63 178-182] This is in contrast to RA patients, where CV risk factors such as hyperlipidemia, hypertension, high BMI and diabetes mellitus do not consistently seem to be increased.[183 184] Compared to RA, higher prevalence of hypertension, diabetes mellitus, dyslipidaemia and obesity in PsA patients has been reported.[185] A Norwegian study found PsA patients to have the highest frequency of at

least one traditional CV risk factor compared to RA and AS.[182] Why increased prevalence of traditional CV risk factors in PsA compared to RA does not also lead to higher risk of CVD, is not fully understood.[175]

In Paper 1 we also found a higher prevalence of smokers (21.3%) among the PsA patients compared to controls. According to the Norwegian Institute of Health data for 2017, 18% of adults in Norway were smokers (both daily and occasional).[186] Limited data exist on smoking in PsA compared to the general population, with conflicting results.[61 64 178 181] Comparable prevalences between RA and PsA patients have been reported.[63 66 182 187 188]

5.2.2 Body weight

The increased BMI of the PsA patients in the HUNT population is consistent with several other studies, [63 64 178] and obesity is a greater problem in PsA patients compared to both RA and AS.[63 182] In Paper 1, BMI was found to be a positive confounder in the association between PsA and hypertension, triglycerides, and history of PCI. It therefore seems that the increased body weight in PsA patients is highly important to address, as it probably contributes to the increased CV risk in PsA patients. The strong association between obesity and psoriatic disease is well recognized.[179 180 189 190] Increased body weight in early adulthood is suspected to be a predictor of PsA.[191] Likewise, it has been shown that in patients with psoriasis, the PsA incidence rate increases with increasing BMI.[30] However, it has also been hypothesized that the PsA diagnosis leads to increased body weight because of less physical activity due to pain and disease activity. Our results presented in Paper 2 support that the increased body weight in patients with PsA compared to controls is present *before* the patient is diagnosed with PsA. This is in line with another study that showed a mean BMI of 30 kg/m^2 and 44% classified as obese (BMI ≥ 30) already at the time of PsA diagnosis.[187]

The relationship between obesity, psoriatic disease and CVD has become clearer in the recent years. Adipose tissue is now considered an endocrine organ, and a source of several different adipokines and pro-inflammatory cytokines, (such as TNF-alpha) that drive inflammation in psoriatic disease.[192] These adipokines are also important in the development of metabolic syndrome and CVD and may be an important link between psoriatic disease and CVD.[193] An additional link between overweight and PsA has been proposed, saying that elevated body

mass leads to increased mechanical stress on the entheses in particular, resulting in microtrauma that subsequently triggers inflammation.[27]

5.2.3 Hypertension

In Paper 1 we found an increased prevalence of hypertension in the PsA group (45.3%), in the higher end of the range previously reported.[60 179 181] A meta-analysis of 28 studies on CVD in PsA reported hypertension in approximately 30 % of PsA patients.[61] The age and sex-adjusted OR for having hypertension in PsA patients compared to controls in Paper 1 was 1.39 (95%CI 1.10-1.75). However, this was attenuated after adjusting for BMI, indicating that body weight is a confounder that contributes to the increased BP in PsA patients. This is in contrast to other studies reporting a higher prevalence of hypertension in PsA patients even after adjusting for BMI.[179 181] In Paper 1 hypertension was the most prevalent CV comorbidity in PsA patients, which has also been reported by others.[179] A recent Norwegian study comparing CV risk factors in PsA, RA and SpA reported hypertension to be the most prevalent among PsA patients.[182]

5.2.4 Lipids

The PsA patients in Paper 1 had higher triglycerides levels and lower HDL-c levels compared to the control group. However the association between PsA and lipids were weakened when also adjusting for BMI. The relationship between PsA and lipids has been reported earlier with conflicting results.[61] Studies have shown a higher prevalence of combined dyslipidaemia (low HDL-c, high LDL-c and triglyceride level) in PsA patients compared to RA and AS.[60 63] However, lower levels of TC and LDL-c, and higher levels of HDL-c in PsA patients have also been reported.[181]

The relationship between lipids and risk of CVD is complex. A U-shaped relationship between lipids (TC and LDL-c) and the risk of CVD has been observes both in RA and non-RA cohorts, as both high and very low levels of TC and LDL-c are strongly associated with increased risk of CVD.[194 195] The increased risk of CVD in RA patients with low TC and LDL-c is believed to be related to systemic inflammation, as an increase in inflammation leads to a decline in lipid levels.[194 196] The increased risk of CVD in RA patients with low levels of lipid have been termed the “lipid paradox.”[194] This paradoxical relationship between low lipids and CVD observed in RA patients has not been reported in patients with PsA. In

Paper 1 and 2 we did not have information on fasting status for the lipids values, however no significant variation between fasting and non-fasting levels of TC and LDL-c has been demonstrated.[197]

5.2.5 Change over time in cardiovascular risk factors in psoriatic arthritis patients

Whether CV risk factors are increased prior to the diagnosis of PsA, co-existing or a result of having PsA has not been clarified.[191] Unlike RA, where a decrease in BMI and lipids over the disease course is well recognized, there is a lack of studies exploring changes in CV risk factors in patients who develop PsA.[198 199] Longitudinal data from Paper 2 did not show an increase in CV risk factors in patients who developed PsA compared to non-PsA controls. In fact, the PsA group experienced a smaller increase in weight and a greater reduction in TC during the 10 years from HUNT2 to HUNT3 compared to controls. All the PsA patients included in this study had skin psoriasis, and 90% reported skin psoriasis symptoms before the diagnosis of PsA. The results from Paper 2 imply that further increase in weight in psoriasis patients who develop arthritis does not happen. Thus, we can assume that the increased weight of these patients before the diagnosis of PsA may be associated with the skin condition, as high BMI is also associated with psoriasis.[192] However, time of clinical diagnosis of PsA is probably preceded by a "pre-clinical phase", that we as yet have little knowledge about.[200] It is believed that this phase may already be associated with comorbidities and physiological changes, as proved in RA.[200 201] This can make interpretation of comorbidities related to PsA before and after clinical diagnosis difficult, especially in the setting of already having psoriasis, another systemic inflammatory disease. To address the pre-clinical phase in epidemiological studies it has been suggested that sensitivity analyses with data for instance 3 years prior to diagnosis of PsA could be done.[200]

The patients being heavier at baseline may perhaps explain the smaller weight gain in PsA patients compared to controls. Further, the medical attention the patients receive as a consequence of the PsA diagnosis may include lifestyle interventions for weight loss. Triglycerides, TC and LDL-c levels declined from HUNT2 to HUNT3, with no difference in mean change between PsA patients and controls. This is in line with other population studies.[202-204] We did not have information on use of lipid lowering drugs in our study, however a study from 2016 estimated that between 21-28 % of the drop in TC could be explained by treatment with lipid lowering drugs.[204] Also systolic BP showed a decline from

HUNT2 to HUNT3, with no difference between the PsA and the control group. This is in line with other reports, although the reason for this decline in BP in the population is not certain.[205]

5.2.6 Cardiovascular risk evaluation in psoriatic arthritis patients

In Paper 1 we found no difference in the overall median 10-year risk of a fatal myocardial infarction between PsA patients and controls, although several CV risk factors were increased in the PsA population. This may partially be explained by the fact that CRP, BMI and triglycerides, important CV risk factors elevated in the PsA patients, are not included in the SCORE risk algorithm.[160] The distribution of CV risk groups according to SCORE was comparable between PsA patients and controls, in line with other studies.[206] [207] However, SCORE has also been found to be comparable in PsA, RA and AS patients.[88] [182] A recent population based study showed no increased risk of CVD related death in PsA versus the general population, supporting our finding of a comparable CV risk by SCORE in PsA and controls.[208] The reason for the comparable mortality risk despite of increased CV risk factors in PsA is not clear.

Although inflammation seems to play a pivotal role in the increased risk of CVD in patients with IJD, it is only included in the Reynolds risk assessment tool.[209] It has been shown that both the Framingham risk sore and the Reynolds risk score underestimate risk in patients with RA.[209] For RA patients, a modified SCORE (mSCORE), using a 1,5 multiplication factor, is advocated by the EULAR 2016 recommendations.[82] A Study from Denmark found comparable age- and sex adjusted CV risk by SCORE in PsA and RA patients. However, when comparing the mSCORE for RA patients with SCORE from PsA and AS patients the RA patients had significantly higher estimated risk.[64] We did not use the mSCORE in our PsA patients, in line with the EULAR recommendations.

5.2.7 Risk of osteoporosis in psoriatic arthritis – is there any?

Our findings in Papers 3 and 4 are in line with other publications that report comparable BMD in PsA patients and the general population.[120-124] [210] However, comparing results across studies is difficult, as outcomes and comparison group differ (Table 3, Appendix).[211] The PsA patients in Paper 3 were recruited from a population cohort, which may imply lower disease activity than expected in a hospital cohort. The disease activity of the patients in Paper 4 was also low, and there was no association between BMD and disease duration, disease activity or

outcome measures, except for subgroup analyses of males that showed an association between BMD and erythrocyte sedimentation rate (ESR).

There is great diversity in the reported proportion of osteoporosis in PsA, ranging from 1.4% to 68.8%. [117 120 122 212] The findings from Paper 3 and 4, of 7.2% and 6.4% respectively, lie in the lower range of the results reported, in line with a Croatian study by Grazio et al.[122] Freidani et al reported in 2001 a prevalence of osteoporosis in Italian PsA patients of 30%, however this was before the biologic therapy era.[117] The results in Paper 3 are also in line with a study on the psoriasis population in HUNT3 that showed similar T score, prevalence of osteoporosis and risk of forearm or hip fracture compared to the general population.[169]

The relationship between RA, low BMD and increased fracture risk has been established in several studies.[133 213] The difference in pathophysiological mechanisms between SpA and RA may explain the difference in bone density reported.[133] Further, SpA, including PsA, is not associated with disease specific auto-antibodies.[28] ACPAs, a hallmark of RA, has been shown to increase osteoclast numbers and activity.[214] A comparable BMD in PsA and ACPA negative RA patients, and a reduced BMD in ACPA positive RA patients has been reported.[215] Clinical differences such as age of onset, the potential for more intermittent inflammation, and less use of glucocorticoids in PsA compared with RA may also influence the difference in risk of systemic bone loss. In Paper 3, 25% of PsA patients had previously used glucocorticoids, and in Paper 4 only 11% were currently using glucocorticoids. While the negative effect of long-term glucocorticoids use on bone density in the general population has been established, use in patients with chronic inflammation has been shown to have an ambiguous effect.[216 217] Controlling inflammation may lower the risk of inflammatory bone loss, due to its harmful effect on bone remodelling.[218]

In AS, another IJD in the SpA disease group, increased prevalence of osteoporosis and fractures has been established, with prevalence of osteoporosis between 14-25%.[217 219] The risk of vertebral fractures is especially increased, with reported OR as high as 7.[220 221] AS is typically a disease of young men, and glucocorticoids are not used in the treatment of the disease, so it is believed that osteoporosis is the result of systemic inflammation, as well as decrease in physical activity level and subclinical gut involvement.[133] However the risk of non-vertebral fractures does not seem to be elevated in AS, pointing towards the vertebral deformities of the spine as a contributing factor.[130] In PsA the radiographic changes of the

spine tends to be less severe than in AS, perhaps explaining the difference in vertebral fracture risk between the two diseases.[222]

5.2.8 New bone formation and bone mineral density in psoriatic arthritis

Of the PsA patients in Paper 3, 14 patients (20.3%) had axial involvement based on clinical and radiological findings. In this paper, spine BMD was significantly higher in PsA patients compared to controls. We did not examine radiologic images of the PsA patients to control for syndesmophytes in the spine, thus new bone formation may be an explanation for this finding. However, the PsA patients in Paper 3 also had significantly higher femoral neck BMD compared to controls, but not higher total hip BMD. The hip may be a better mean of detecting osteoporosis in PsA, as the BMD measurements of the hip is mostly unaffected by new bone formation and degenerative processes.[134 135] However, spine BMD, measuring the largely trabecular vertebral bodies, is more prone to changes from for instance glucocorticoid excess, and may therefore also be important to evaluate in patients with IJDs.

In Paper 3 and 4, 7% and 32% of the PsA patients were currently using TNF- inhibitors, respectively. Despite the strong anti-inflammatory effect of TNF-inhibitors it is yet to be proven that these agents have effect on the new bone formation that occur in SpA.[223-225] Some studies even suggest that treatment with TNF-inhibitors *increases* the formation of new bone following the resolution of inflammation.[226] The reason for this effect on new bone formation is not fully understood, but is partially explained because TNF acts as a "brake" on new bone formation by regulating Dickkopf-related protein 1, which further stimulates the osteoblasts. It has been hypothesized that very early inflammatory lesions may resolves without new bone formation.[227] Another theory is that new bone formation is an independent feature uncoupled from inflammation.[228] Some animal studies of arthritis support this theory, by showing new bone formation despite minimal inflammation.[229 230] There is a lack of studies on the effect of TNF-inhibitors on BMD in PsA, however TNF-inhibitors have been shown to increase BMD in both lumbar spine and hip in other SpAs.[224 231-233] This may be related to the new bone formation, which can increase BMD in the spine, however similar results were found in a study that adjusted for radiographic progression.[224] This suggests that TNF-inhibitors may improve bone metabolism.[218] However, it is still unclear if this increase in BMD leads to reduction in fractures in PsA and other SpAs.

5.2.9 Bone strength and risk of fracture

In this thesis we have analysed BMD, as a surrogate marker for fracture risk. High correlation between BMD measurements and bone strength of the hip and spine has been demonstrated in in vitro studies, and a strong association between BMD and risk of fracture exists.[234] However, besides BMD there are several other risk factors for fracture, as bone strength also includes other characteristics of bone. Therefore, our conclusion from this thesis is based on the WHO definition of osteoporosis, as the actual risk of fracture has not been examined in our studies.

The concept of bone strength is now known to be more complex and also include several characteristics of bone that indicate "quality". The bone quality determines how well the bones of the skeleton can resist fracturing. The microarchitecture, including microscopic damage, the quality of the collagen and the rate of bone turnover determines the bone quality.[235] To make the matter even more complex, denser bone does not always mean stronger bone. For instance, the use of sodium fluoride to treat osteoporosis showed that a large increase in bone mass (and bone density) made bone more brittle, because it changed the quality of the bone.[236] Older bone is weaker than younger bone in strength, even with similar bone density, as shown by the increased fracture risk in older individuals across all levels of T score.

If the higher BMD found in the PsA patients compared to controls in Paper 3 necessary leads to stronger bone, is unknown. Higher cortical porosity and lower cortical bone density of the distal radius on high resolution CT in PsA patients, despite a normal BMD, has been reported.[125] This may affect the cortical bone quality and predispose the bone to fractures, and is not investigated in this thesis. It is therefore obviously also important to look at the risk of evident fracture, in addition to BMD. In a recent population based study a small but significantly increased risk of all fractures was reported in PsA and psoriasis patients.[126] In Paper 4 we only reported a prevalence of self-reported fragility fractures, which was low (6.4%). Some studies have reported higher frequency of fractures in PsA, despite comparable BMD.[123] [124] On the other hand, a study on the psoriasis population in HUNT3 showed no association between psoriasis and increased risk of forearm or hip fracture.[169]

6 CONCLUSIONS AND CLINICAL IMPLICATIONS

6.1 Main conclusions

The results presented in this thesis will hopefully contribute to useful insight in the management of patients with PsA. The following knowledge can be drawn from the work in this thesis:

- PsA patients had higher BMI and were more often obese than the background population (Paper 1). PsA patients were more often smokers, had higher triglyceride levels and lower HDL-c levels than controls (Paper 1).
- PsA patients had increased prevalence of angina pectoris, hypertension and history of PCI compared to controls (Paper 1).
- There was no difference between PsA patients and controls in 10-year risk of a fatal CV event estimated by SCORE. However, PsA patients had elevated levels of CV risk factors not included in the SCORE algorithm, such as BMI, triglycerides, and CRP (Paper 1).
- Already before the time of diagnosis, the PsA patients had higher BMI and lower HDL-c, and were more often smokers compared to the control group. However, CV risk factors (BMI, lipids and BP) did not increase in patients who developed PsA compared to controls over a ten-year period (1995-97 to 2006-08). The PsA patients experienced a smaller increase in weight and a greater reduction in TC levels during the decade-long observation period.
- PsA patients from a population cohort did not have lower BMD compared to controls. After adjusting for potential confounding factors, BMD was higher in PsA patients compared to controls at lumbar spine and femoral neck, but not at total hip. Of the PsA patients, 7.2% had osteoporosis. Controls had higher odds of having osteopenia or osteoporosis based on measurements of BMD (Paper 3).
- In PsA patients from an outpatient clinic the proportion of patients with low Z score was comparable to the reference material from the DXA machine provider. The proportion of PsA patients with osteoporosis was 6.4% (Paper 4).
- There was no association between disease duration of PsA and BMD (Paper 3).
- No correlation was found between BMD and PsA disease activity measures. (Paper 4)

6.2 Clinical implications

- Our finding support that focus on risk factors for CVD in the PsA patient group should be increased.
- Modifiable behavioural CV risk factors, in particular BMI, may contribute to the increased CV risk in PsA patients. Therefore physical exercise and a healthy BMI should be encouraged.
- CV risk assessment should be done according to local guidelines. Interventions or follow up regarding CV risk factors or CVD may be warranted.
- Since CV risk factors are present before the diagnosis of PsA, interventions on a population level to counteract the high rise in obesity in the western world is necessary, both to reduce the incidence of PsA and CVD. Also, intervention to encourage a healthy BMI in the psoriasis patient group is important, since increased BMI is often present before PsA, both to reduce CV risk and risk of developing PsA.
- Data from this thesis suggest that osteoporosis is not a significant clinical problem in PsA, supporting the recommendation that PsA patients may follow guidelines for osteoporosis assessment developed for the general population.
- This may not apply to patients with long-standing high disease activity and patients who use high doses of oral glucocorticoids.

7 ERRATA

- Paper 1: Correct p-value adjusted for age and sex for difference in HDL-c between PsA and controls is not 0.11 but 0.01. Adding BMI as a covariate in the linear regression model, p-value is 0.30.
- Paper 1: N for CABG and PCI are not presented in the paper. Correct N for CABG is 35 for PsA, 3884 for controls. N for PCI is 35 for PsA, 3876 for controls. The reason for this reduction in number, is that these questions were part of another questionnaire (Q3) only presented to those answering "yes" to having CVD in Q1. However, we can assume that the patients who have not been presented with Q3 have answered "no" to having CVD, and do probably not have PCI or CABG in their medical history. The persons answering "yes" have therefore been compared to the whole cohort in the logistic regression model.

8 APPENDIX

Table 3: Papers exploring bone mineral density in psoriatic arthritis (PsA) patients

Authors	Cohort	Finding
Nolla 1999 Spain	52 PsA patients and healthy controls	No difference in BMD Low BMD not a problem in PsA
Freidani 2001 Italy	186 patients with PSA, 100 healthy controls	BMD lower in PsA patients regardless of sex, age or menopausal status. 30% osteoporosis (pre-menopausal 11%, postmenopausal 47%, men 29%). BMD no correlation with ESR, CRP or disease duration. BMI and HAQ predictors of BMD.
Grisar 2002 Austria	30 AS, 23 PsA, 10 reactive arthritis, 41 healthy controls	Normal BMD in PsA patients at spine and hip, reduced BMD at femoral neck in AS. PsA: increased levels of ALP and OPG, but not OC
Borman 2008 Turkey	47 patients with skin psoriasis, 18 with PsA	No difference in BMD between PsA and skin psoriasis. 5 % Osteoporosis in PsA 50 % osteopenia. Reduced BMD at femoral neck and lumbar spine compared to age matched controls (Z score).
Reddy 2010 USA	530 PsA and 7166 RA (CORRONA)	RA lower T score than PsA, however same BMD in RA and PsA when adjusted for BMI and smoking.
Pedreira 2011 Brazil	45 PsA, 52 skin psoriasis, 98 controls	No difference in BMD or osteoporosis, matched for age and BMI. More fragility fractures in PsA and skin psoriasis vs controls.
Anandarajah 2011 US	2212 PsA patients	PsA patients with erosions lower lumbar spine T score than PsA without erosions, adjusted for glucocorticoid use.
Grazio 2011 Croatia	69 PsA	Low BMD not a problem in PsA. Spine osteoporosis 7,2 %, femoral neck osteoporosis 2,9%, total hip osteoporosis 1.4%. Higher HAQ was associated with lower total hip BMD.
Kocijian 2014 Germany	60 RA and 50 PsA	RA and PsA comparable BMD. RA ACPA positive lower BMD than RA ACPA negative and PsA. Conclusion: ACPA leads to low BMD.
Busuets 2014 Spain	155 PsA, 65 males, 65 post-menopausale females	Low BMD not a problem in PsA. Osteoporosis in 16% (post – menopausal women 28%, pre-menopausal women 4% men 9%.)

Del Puente 2015 **Italy**	92 postmenopausal PsA women and matched controls	No difference in BMD No difference in fragility vertebral fractures (36 % in both groups), however very high in both groups.
Zhu 2015 **China**	53 PsA (24 males, 29 females), age 53, age and gender matched controls	No difference in BMD, except for higher BMD in PsA patients at lumbar spine. Microstructural deficits in PsA; lower cortical vBMD and inferior cortical microstructure. More asymptomatic vertebral fractures in PsA vs controls (23.8 vs 3.8%). Higher cortical porosity in PsA.
Chandaran 2016 **Canada**	21 peer reviewed studies 2001-2014	13 studies: low BMD a problem in PSA. 8 studies: low BMD not a problem in PsA. Prevalence of osteoporosis: 1.5-68% Osteopenia 20-60%. Prevalence of low BMD inconsistent. Risk factors for low BMD: disease duration, swollen joint count, erosions, enthesitis, PASI.
Ogdie 2017 **US**	9788 PsA 158323 psoriasis 821834 controls	Risk of all fracture in PsA: aHR1.16 (1.06-1.27). Hip fracture: 1.17 (0.80-1.59) Vertebral fracture: 1.07 (0.66 – 1.72) Patients with only skin psoriasis had higher risk of fracture than PsA.

BMD: bone mineral density, PsA: psoriatic arthritis, RA: rheumatoid arthritis, AS: ankylosing spondylitis, ALP: alkaline phosphatase, OPG: osteoprotegrin, OC: osteocalcin, ESR: erythrocyte sedimentation rate, CRP: c-reactive protein, ACPA: anti citrullinated protein antigen, CTX: crosslinked telopeptide of collagen-1, OPG: osteoprotegerin, PASI: psoriasis area severity index. HR: hazard ratio.

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PAPER I

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PAPER II

RMD Open
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ORIGINAL ARTICLE

Change in cardiovascular risk factors in patients who develop psoriatic arthritis: longitudinal data from the Nord-Trøndelag Health Study (HUNT)

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ABSTRACT

Objectives The aim of this population-based study was to compare changes in cardiovascular (CV) risk factors over a decade-long period in patients who developed psoriatic arthritis (PsA) and the background population.

Methods Patients diagnosed with PsA (n=151) between 1998 and 2008 and matched controls (n=755) who participated in both the Nord-Trøndelag Health Study (HUNT) 2 (1995–1997) and HUNT3 (2006–2008) were included. Mixed linear and logistic models were used to analyse the difference in mean change between HUNT2 and HUNT3 in patients and controls for body mass index (BMI), total cholesterol (TC), triglycerides, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and blood pressure (BP).

Results At baseline (HUNT2), the patients who developed PsA compared with controls had higher BMI (27.2 vs 25.9 kg/m^2, p<0.001) and lower HDL-c (1.32 vs 1.40 mmol/L, p<0.03) and more were smokers (41.1 vs 28.5%, p<0.01). Seventy-eight per cent had skin psoriasis. The mean PsA disease duration at HUNT3 was 4.8 (+/–3.0) years. The patients who developed PsA gained less weight from HUNT2 to HUNT3 compared with the control group (2.1 vs 3.9 kg, difference in mean change −1.8 kg, 95% CI −3.9 to −0.5, p<0.01). TC, triglycerides, LDL-c or HDL-c values and BP declined in both groups, with no significant differences between groups.

Conclusion Longitudinal 10-year data did not show an increase in CV risk factors in patients who developed PsA compared with controls. This study implies that unfavourable CV risk factors in PsA were present before the diagnosis was established.

Key messages

What is already known about this subject?

- The increased risk of cardiovascular (CV) disease in patients with psoriatic arthritis (PsA) can to some extent be explained by increased prevalence of traditional CV risk factors and the presence of skin psoriasis.
- Data on changes in CV risk factors over time in patients with PsA are lacking.

What does this study add?

- This population-based study investigated the course of body weight, cholesterol, blood pressure (BP) and smoking habits, from 1995 to 2008 in patients who were diagnosed with PsA during this period.
- This study implies that unfavourable CV risk factors in PsA were present before the diagnosis was established, perhaps as a result of pre-existing skin psoriasis.

How might this impact on clinical practice?

- As unfavourable CV risk factors in patients with PsA were present before the diagnosis was established, the focus on CV disease prevention must begin when the patient presents with psoriasis.

BACKGROUND

Psoriatic arthritis (PsA) is an inflammatory joint and musculoskeletal disease characterised by synovial and enthesal inflammation. Several studies have demonstrated an increased prevalence of cardiovascular (CV) risk factors in patients with PsA.[1–5] A systematic review concluded with increased CV morbidity in patients with PsA, including myocardial infarction, cerebrovascular and peripheral vascular disease.[4] We have previously reported increased prevalence of obesity, hypertension, triglyceride level and angina pectoris in patients with PsA from the Nord-Trøndelag Health Study (HUNT) 3.[3] Whether increased CV risk factors are present prior to diagnosis of PsA or a result of the disease itself has not been clarified.[6] Unlike rheumatoid arthritis (RA), where a decrease in body mass index (BMI) and lipids over the disease course is well recognised, there is a paucity of studies exploring changes in

Table 1A Demographics of the patients developing PsA and controls at HUNT2 (observed values)

	Patients who develop PsA (n=151)	Matched controls (n=755)	P values*	Non-matched controls (n=36 812)	P values†
Female sex, n (%)	87 (57.6)	435 (57.6)	NA	20 314 (55.2)	0.55
Age, years (SD)	43.8 (10.1)	43.8 (10.1)	NA	47.1 (13.4)	<0.001
Married or partner, n (%)	102 (67.5)	521 (69.0)	0.61	24 839 (67.5)	0.98
Skin psoriasis, n (%)	100/128 (78.1)	NA	NA	NA	NA
Weight, kg (SD)	80.4 (15.5)	76.0 (13.5)	<0.001	76.4 (13.6)	<0.001
Height, cm (SD)	170.0 (8.6)	170.8 (9.1)	0.19	170.7 (9.0)	0.30
Body mass index, kg/m^2 (SD)	27.2 (4.5)	25.9 (3.7)	<0.001	26.2 (3.9)	<0.01
Current smoking, n (%)	62 (41.1)	215 (28.5)	<0.01	9341 (26.6)	<0.001
Total cholesterol, mmol/L (SD)	5.85 (1.16)	5.77 (1.16)	0.47	5.83 (1.2)	0.87
HDL cholesterol, mmol/L (SD)	1.32 (0.35)	1.40 (0.39)	0.03	1.39 (0.38)	0.01
LDL cholesterol, mmol/L (SD)	4.83 (1.04) (n=146)	4.81 (1.05) (n=735)	0.87	3.68 (1.08) (n=35 774)	0.83
Triglycerides, mmol/L, median (IQR)	1.87 (1.23)	1.69 (1.10)	0.08	1.7 (1.09)	0.05
Systolic blood pressure, mm Hg (SD)	132.7 (15.0)	131.5 (16.6)	0.40	132.7 (15.0)	0.35
Diastolic blood pressure, mm Hg (SD)	79.9 (10.1)	79.1 (10.7)	0.41	79.5 (11.3)	0.68

P values for difference between PsA and matched controls analysed with mixed linear and logistic analysis.
Unless stated, continuous values are mean (SD), categorical values are number (%).
*Comparing patients with PsA and matched controls.
†Comparing patients with PsA and all non-matched controls.
HDL, high-density lipoprotein; HUNT, Nord-Trøndelag Health Study; LDL, low-density lipoprotein; PsA, psoriatic arthritis.

CV risk factors in patients with PsA.[7 8] The aim of this study was to compare changes in CV risk factors between HUNT2 (1995–1997) and HUNT3 (2006–2008) in patients who are diagnosed with PsA in this time period and the background population.

RESEARCH DESIGN AND METHODS

Study population

Patients were recruited from the population-based HUNT studies, which have been performed three times: HUNT1 (1986–1988), HUNT2 (1995–1997) and HUNT3 (2006–2008). Nord-Trøndelag is one of 19 Norwegian counties and is located in the middle part of the country. Description of the HUNT studies has been published in detail.[9] A total of 93 680 adults were eligible for participation in HUNT3, and out of these 50 807 participated (54%). In HUNT3, 338 persons (0.67%) were validated to have PsA according to the ClASsification of Psoriatic ARthritis (CASPAR) criteria.[10] All the patients had a diagnosis of psoriasis verified by a dermatologist or a rheumatologist as well as arthritis at peripheral joints and/or at spine verified by a rheumatologist. The diagnosis of spinal involvement was based on inflammatory back pain (IBP) and limitation of motion of the lumbar spine. IBP was defined as chronic low back pain that improves with exercise and is not relieved with rest; insidious onset; onset before the age of 40 years and pain at night. This study includes 37 070 persons who participated in both HUNT2 and HUNT3. Of 338 PsA cases identified in HUNT3, 151 were diagnosed between HUNT2 and HUNT3 (through 2008) and included in this study. Patients diagnosed with PsA before HUNT2 were excluded. The persons who developed PsA were compared with non-PsA controls matched in a 1:5 ratio for age and sex (n=755).

OUTCOME MEASURES

Changes in the following CV risk factors were the outcomes of interest: weight, BMI, blood pressure (BP),

Table 1B Disease characteristics of the patients with PsA at HUNT3 (2008)

Disease characteristics	All (n=151)	Male (n=64)	Female (n=87)
PsA disease duration, years (SD)	4.8 (3.0)	5.3 (3.2)	4.5 (2.8)
Skin psoriasis disease duration, years, median (IQR) (n=78)	9.0 (12.3)	9.0 (12.3)	8.5 (12.8)
Skin psoriasis symptom duration, years, median (IQR) (n=130)	20 (24.4)	18.9 (21.5)	21.2 (28.4)
Peripheral joint involvement, n (%)	146 (96.7)	62 (96.9)	84 (96.6)
Axial involvement, n (%)	43 (28.5)	20 (31.3)	23 (26.4)
Enthesitis, n (%)	101 (66.9)	43 (67.2)	58 (66.7)
CRP value, median (IQR)	4.0 (4) (n=143)	4.0 (4) (n=59)	4.0 (6) (n=84)
ESR value, median (IQR)	9.0 (14) (n=139)	6.0 (9) (n=57)	10.0 (15) (n=82)
Ever use of peroral steroids, n (%)			
Previous	66 (43.7)	22 (34.4)	44 (50.6)
Current	6 (4.0)	3 (4.7)	3 (3.4)
Ever users of anti-TNF therapy, n (%)			
Previous	10 (6.6)	1 (1.6)	9 (10.3)
Current	15 (9.9)	6 (9.4)	9 (10.3)
Ever use of methotrexate, n (%)			
Previous	29 (19.2)	10 (15.6)	19 (21.8)
Current	45 (29.8)	21 (32.8)	24 (27.6)
Ever use of synthetic DMARDs other than methotrexate, n (%)			
Leflunomide	37 (24.5)	12 (18.8)	25 (28.7)
Sulfasalazin	8 (5.3)	2 (3.1)	6 (6.9)

Unless stated, continuous values are mean (SD), categorical values are number (%).
CRP, C reactive protein; DMARD, disease modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HUNT3: Health Study in Nord-Trøndelag 3; PsA, psoriatic arthritis; TNF, tumour necrosis factor.

cholesterol, triglycerides and smoking. The disease characteristics of the 151 patients with PsA, including use of synthetic and biological disease modifying antirheumatic drugs (DMARDs) were obtained from reviewing patient hospital medical records through 2008. The only biological DMARDs available in Norway at the time of the study were tumour necrosis factor inhibitors, and the hospital is the exclusive prescriber of this medication to all patients. C reactive protein and erythrocyte sedimentation rate values were only available in the HUNT3 study. BP was measured with Dinamap 845XT Criticon apparatus. The

Table 2 Changes in cardiovascular risk factors in patients with PsA and matched controls (values obtained from the mixed linear model)

	PsA (n=151)			Matched controls (n=755)			Difference in mean change between groups (95% CI)	P crude	P value
	HUNT2 (1995–1997)	HUNT3 (2006–2008)	Mean change	HUNT2 (1995–1997)	HUNT3 (2006–2008)	Mean change			
Weight, kg	80.4 (78.2 to 82.7)	82.5 (80.2 to 84.7)	2.06 (0.90 to 3.22)	75.9 (74.5 to 77.3)	79.8 (78.4 to 81.2)	3.88 (3.36 to 4.40)	−1.82 (−3.98 to −0.55)	<0.01	NA
BMI, kg/m^2	27.3 (26.6 to 27.9)	28.2 (27.6 to 28.9)	0.97 (0.57 to 1.37)	25.9 (25.6 to 26.3)	27.5 (25.2 to 27.8)	1.53 (1.35 to 1.70)	−0.65 (−1.00 to −0.12)	0.01	NA
Triglycerides	1.87 (1.70 to 2.04)	1.80 (1.62 to 1.97)	−0.07 (−0.25 to 0.11)	1.69 (1.60 to 1.77)	1.69 (1.60 to 1.77)	0.00 (−0.08 to 0.08)	−0.07 (−0.27 to 0.12)	0.46	0.99*
Total cholesterol	5.85 (5.68 to 6.03)	5.57 (5.39 to 5.74)	−0.29 (−0.48 to −0.10)	5.78 (5.69 to 5.90)	5.71 (5.62 to 5.81)	−0.06 (−0.15 to 0.02)	−0.22 (−0.43 to −0.02)	0.04	0.08*
LDL cholesterol	4.82 (4.66 to 4.10)	3.44 (3.28 to 3.60)	−1.39 (−1.56 to −1.21)	4.81 (4.73 to 4.89)	3.60 (3.52 to 3.70)	−1.2 (−1.28 to −1.13)	−0.18 (−0.38 to 0.01)	0.06	0.11*
HDL cholesterol	1.32 (1.26 to 1.37)	1.32 (1.26 to 1.38)	0.00 (−0.04 to 0.05)	1.39 (1.36 to 1.42)	1.36 (1.33 to 1.39)	−0.03 (−0.05 to −0.02)	0.04 (−0.01 to 0.09)	0.13	0.45*
Systolic blood pressure	132.8 (129.9 to 135.6)	132.1 (129.1 to 135.1)	−0.65 (−3.63 to 2.32)	131.5 (129.9 to 133.1)	131.6 (129.9 to 133.2)	0.02 (−1.31 to 1.35)	−0.67 (−3.93 to 2.59)	0.69	0.98†
Diastolic blood pressure	79.9 (78.2 to 81.6)	75.5 (73.7 to 77.3)	−4.42 (−9.22 to −2.62)	79.1 (78.1 to 79.9)	75.1 (74. 1 to 76.1)	−3.96 (−4.76 to −3.15)	−0.46 (−2.43 to 1.52)	0.65	0.90†

Values are mean (95% CI). Difference in mean change between groups with 95% CI is calculated with mixed models as mean of the patients with PsA minus mean of the matched controls.
*Adjusted for BMI and smoke at baseline.
†Adjusted for BMI, smoke and use of antihypertensive medication at baseline.
BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable; PsA, psoriatic arthritis.

average of the second and third measurement was used. Smoking was reported as daily smoking of cigarettes. Non-fasting blood samples were analysed in mmol/L for triglycerides, total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-c) by standardised methods at Levanger hospital. Low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald formula (TC – HDL-c – (triglycerides/2.2)) excluding those with triglyceride concentrations≥4.5 mmol/L.[11]

STATISTICAL ANALYSES

Statistical analyses were performed with SPSS for Mac V.21 (Chicago, Illinois, USA) and R for Windows. Statistical significance level was set at p<0.05. The demographical data were compared with mixed models to account for the matching design and also compared with the whole HUNT population. Diagnosis of PsA was registered as a dichotomous variable. Differences in mean change from HUNT2 to HUNT3 in weight, BMI, lipids and BP between the two groups with 95% CI were calculated with mixed linear models, to account for the correlations between repeated measurements within each patient, the matching design and missing values. For BP and lipids, possible confounding variables (BMI, smoking and use of antihypertensive medication at HUNT2 and HUNT3) were also added to the mixed model. The proportion of smokers in HUNT2 and HUNT3 were compared with Fisher's exact test because of small numbers.

RESULTS

As shown in table 1A, 57.6% were females, and mean age±SD was 43.8±10.1 years. At baseline (HUNT2), the patients who developed PsA compared with controls had higher BMI (27.2 vs 25.9 kg/m^2, p<0.001) and lower HDL-c (1.32 vs 1.40 mmol/L, p<0.03), and more were smokers (41.1 vs 28.5%, p<0.01). Seventy-eight per cent had skin psoriasis. The mean (±SD) PsA disease duration at HUNT3 was 4.8±3.0 years, and mean (±SD) disease duration of skin psoriasis at HUNT3 was 11.4±10.4 years (table 1B). The number of patients with PsA currently using methotrexate, leflunomide and biological DMARDs in 2008 was 45 (24.9%), 37 (24.2%) and 15 (9.9%), respectively.

Table 2 shows the difference in mean change in CV risk factors between HUNT2 and HUNT3 in patients with PsA and controls. The patients with PsA gained less weight compared with the control group (2.1 vs 3.9 kg), with a significant difference in mean change of −1.8 kg (95% CI −3.9 to −0.5, p<0.01). Patients with PsA had a greater reduction in TC values compared with the controls, with difference in mean change between groups of −0.22 mmol/L (p=0.04), however, adding BMI and smoking to the mixed linear model attenuated the association (p=0.08). Both groups showed a reduction in diastolic BP and stable systolic BP, without significant difference between groups. Of all the smokers in HUNT2, 56.5% of the patients with PsA still smoked in HUNT3 versus 54.0% of the controls (p=0.75). More patients with PsA started smoking during the decade compared with controls (8.5 vs 3.1%, p=0.03).

DISCUSSION

Longitudinal data from this observational study did not show an increase in CV risk factors in patients who develop PsA compared with controls. In fact, the PsA group experienced a smaller increase in weight during the decade from HUNT2 to HUNT3. However, at baseline, the patients who developed PsA had higher BMI, lower HDL-c and were more often smokers compared with the control group. This may be explained by the fact that 78% in this group had psoriasis symptoms at baseline, and psoriasis is associated with high BMI and other CV risk factors.[12]

To our knowledge, there is a paucity of studies exploring the development of CV risk factors over time in patients with PsA. In RA, it has been shown that there is no difference in development of CV risk factors compared with non-RA controls after disease onset for hypertension, high BMI or diabetes mellitus.[7] In fact, patients with RA are more likely to develop low BMI and less likely to develop dyslipidaemia over the course of their disease compared to non-RA patients, related to disease-activity.[7] However, increased body fat mass with loss of muscle mass is reported in patients with RA.[13]

The strong association between obesity and PsA is well recognised and reported in several studies.[3 4 14] Increased BMI in early adulthood is suspected to be a predictor of PsA.[6] Likewise, it has been shown that in patients with psoriasis, the PsA incidence rate increases with increasing BMI.[15] However, it has also been hypothesised that the PsA diagnosis leads to a further increase in BMI because of less physical activity from pain and disease activity. Result from this study favours that the increased BMI in patients with PsA is present before the diagnosis. The relationship between obesity, psoriatic disease and CV disease is recently starting to become clear. Adipose tissue is a source of several different adipokines that drive inflammation in psoriatic disease.[16] These adipokines are also important in the development of metabolic syndrome and CV disease and may be an important link between psoriatic disease and CV disease.

Of the patients with PsA included in this study, 78% had psoriasis symptoms at baseline in HUNT2, before the PsA diagnosis. Thus, we hypothesise that the increased weight before PsA diagnosis may be associated with psoriasis, as high BMI is also associated with this disease.[12 16] This study implies that further increase in weight in patients with psoriasis who develop arthritis does not happen. However, time of clinical diagnosis of PsA is probably preceded by a 'preclinical phase', that we as yet know little about. It is believed that this phase may already be associated with comorbidities and physiological changes, as proved in RA.[17–19] This can make interpretation of comorbidities related to PsA before and

after clinical diagnosis difficult, especially in the setting of already having the systemic inflammatory disease of psoriasis. The smaller weight gain in patients with PsA compared with controls may partially be explained by the patients with PsA being heavier at baseline. Further, the medical attention they receive as a consequence of the PsA diagnosis may include lifestyle interventions for weight loss.

Triglycerides, TC and LDL-c levels declined from HUNT2 to HUNT3, with no difference between patients with PsA and controls. This is in line with other studies demonstrating a decline in lipids in the general population.[20 21] We did not have information on use of statins; however, data from 2016 estimated that between 21% and 28% of the drop in TC could be explained by treatment with statins.[21] Also, systolic BP showed a decline from HUNT2 to HUNT3, with no difference between the PsA and the control group. This is in line with previous reports, but the reason for this decline in the population is uncertain.[22] The beneficial effect of reduced salt and increased fruit and vegetable intake has been opposed by reduced physical activity and increased BMI.[23]

There are some limitations to our study. We did not adjust for potential important PsA clinical factors, such as use of DMARDs and steroids, disease duration of PsA or psoriasis and disease activity. We did not have information on fasting status for the serum lipids values; however, no significant variation between fasting and non-fasting levels of TC and LDL-c has been reported.[24] In this study, a relatively small part of patients with PsA were on biological medication (9.9%) compared with present-day clinical experience. However, these data were registered up to 2008, at a point were the use of biological medications in Norway were more limited. Also, the patients with PsA were identified from a population survey, not a clinical hospital setting. However, almost 30% were currently using methotrexate, and in addition almost 20% had used this medication previously. Further, 25% had ever used leflunomide. We therefore believe that the patients with PsA from the HUNT study are comparable with the PsA population in Norway at the time of the study.

In summary, longitudinal 10-year data did not show an increase in CV risk factors in patients who developed PsA compared with the background population. However, at baseline, the patients who developed PsA had higher BMI, lower HDL-c and were more often smokers compared with the control group. This study indicates that unfavourable CV risk factors were present before the diagnosis of PsA was established, probably related to the fact that a majority of the patients with PsA already had psoriasis.

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Contributors AMG, MH: planning, interpretation of statistical analyses, writing. ØS: planning, statistical analyses, writing. RST, AK, AGS, SR, GH: interpretation of statistical analyses, writing.

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PAPER III

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ORIGINAL ARTICLE

Bone mineral density in patients with psoriatic arthritis: data from the Nord-Trøndelag Health Study 3

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ABSTRACT

Background The risk of osteoporosis in patients with psoriatic arthritis (PsA) remains unclear. The aim of this study was to compare bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) in patients with PsA and controls.

Patients and methods Patients with PsA and controls were recruited from the Nord-Trøndelag Health Study (HUNT) 3.

Results Patients with PsA (n=69) and controls (n=11 703) were comparable in terms of age (56.8 vs 55.3 years, p=0.32), gender distribution (females 65.2% vs 64.3%, p=0.87) and postmenopausal status (75.6% vs 62.8%, p=0.08). Body mass index (BMI) was higher in patients with PsA compared with controls (28.5 vs 27.2 kg/m^2, p=0.01). After adjusting for potential confounding factors (including BMI), BMD was higher in patients with PsA compared with controls at lumbar spine 1–4 (1.213 vs 1.147 g/cm^2, p=0.003) and femoral neck (0.960 vs 0.926 g/cm^2, p=0.02), but not at total hip (1.013 vs 0.982 g/cm^2, p=0.11). Controls had significantly higher odds of having osteopenia or osteoporosis based on measurements of BMD in both the femoral neck (p=0.001), total hip (p=0.033) and lumbar spine (p=0.033).

Conclusion Our population-based data showed comparable BMD in patients with PsA and controls. This supports that the PsA population is not at increased risk of osteoporosis.

Key messages

What is already known about this subject?
- The risk of osteoporosis in psoriatic arthritis (PsA) remains uncertain.

What does this study add?
- In this population-based study, the bone mineral density (BMD) of 69 patients with PsA, both male and female, was measured with dual-energy X -ray absorptiometry and compared with controls without PsA.
- BMD was higher in patients with PsA compared with controls at lumbar spine 1–4 and femoral neck, but not at total hip.

How might this impact on clinical practice?
- This study supports that patients with PsA are not at increased risk of osteoporosis and may follow guidelines for osteoporosis assessment developed for the general population.

BACKGROUND

Data on systemic bone loss in patients with psoriatic arthritis (PsA) are conflicting, and population-based data are lacking.[1–3] It is well documented that patients with rheumatoid arthritis (RA) are at increased risk for osteoporosis, presumably due to factors including systemic and local inflammation, inactivity related to arthritis and treatment with glucocorticoids.[4 5] Despite some similar features in clinical presentation and joint damage, substantial differences exist between RA and PsA concerning immunopathogenesis, clinical manifestations and radiographic features. In PsA, activation of both osteoclasts and osteoblasts can be involved, and as a consequence, patients may show signs of both bone destruction (erosions) and bone formation (periostitis, osteophyte formation).[6] This in contrast to RA where osteoclast activation is dominating, causing erosions and osteoporosis.[7]

The aim of this study was to compare bone mineral density (BMD) in patients with PsA and controls.

MATERIALS AND METHODS

Data were retrieved from the Nord-Trøndelag Health Study (HUNT) 3,[8] performed between 2006 and 2008. The study population and validation of diagnoses have been described in detail previously.[8 9] The study was approved by the Regional Committee for Medical Research Ethics, South-Eastern Norway (REK number 2010/2661).

Inclusion of patients and controls

An experienced rheumatologist reviewed the medical records of persons in HUNT 3 with self-reported PsA, plus self-reported ankylosing spondylitis and psoriasis or self-reported RA and psoriasis to validate PsA. In total, 338 persons in HUNT 3 were found to have PsA according to the Classification of Psoriatic Arthritis criteria. Details on patients with PsA and controls are previously described in details.[9]

An invitation to Dual-energy X-ray absorptiometry (DXA) measurement was sent to 14 247 persons in the HUNT 3 population born after 1 January 1921 and living in one of the five largest municipalities in the Nord-Trøndelag county. Eleven thousand seven hundred and seventy-two persons participated (82.6%)—7570 women and 4202 men. Of these, 6887 were invited based on a random sample of the total HUNT cohort, and 4885 were invited based on reporting a wide spectrum of lung symptoms (asthma and chronic obstructive pulmonary disease (COPD)), as the DXA study in HUNT 3 was also initially designed as part of a study on patients with pulmonary disease. This sample included 69 patients with PsA (36 invited by random selection and 33 because of self-reported pulmonary symptoms) with age between 20 to 95 years. Controls were all other participants in the HUNT 3 study.

Measurement of variables

Information about risk factors and disease was collected by self-administered questionnaires, clinical measurements and blood samples. Data on medication use, clinical and disease spesific charcateristics among the PsA patients were collected from the patient´s hospital journals. Measurements of height and weight were performed with lightweight clothing and no shoes. Females were asked about age at cessation of menstrual cycle.

DXA measurements were performed in the lumbar spine (L1–L4) and hip (femoral neck and total hip) using a Lunar/Prodigy (GE Healthcare) DXA machine. Lumbar spine BMD was calculated as the mean of the BMD score in L1–L4. We preferably used measurements from the left hip. Bone density was expressed as g/cm^2 and T-score (SD from the mean of a healthy young female population). The data for T-score estimation were provided by the manufacturer. Regular phantom calibration of the densitometer was performed according to the existing densitometry procedures and quality assessment guidelines at HUNT.

The World Health Organization (WHO) definition was applied for osteoporosis (T-score ≤ −2.5 SD), osteopenia (T-score between −1.0 and −2.5 SD) and normal BMD (T-score ≥ −1.0 SD) (WHO, 1994). Details on the registration of variables have been published previously.[10]

Statistical analysis

All statistical analyses were performed using the SPSS V.21. A two-sided statistical significance level was defined as p<0.05. Continuous variables were analysed using an unpaired two-tailed t-test for normally distributed data. The χ^2 test, or Fisher exact test when small numbers, was used to examine the associations between categorical variables. A multivariable linear regression model was used to assess the relationship between PsA and BMD, controlling for potential confounders (age, sex, BMI, smoking status, physical activity, asthma/COPD and reason for invitation to DXA measurement). Ordinal logistic regression was used to compare the frequency of osteoporosis in patients with PsA and controls, after assessment of parallel lines.

RESULTS

As shown in table 1, there were no differences between patients with PsA and control subjects concerning age, sex, postmenopausal status, height, smoking, ever use of asthma or COPD medication and C-reactive protein (CRP).

A statistically significant difference between patients with PsA and controls was seen for weight (83.8 kg vs 77.9 kg, p<0.01), BMI (28.5 kg/m^2 vs 27.2 kg/m^2, p=0.01) and self-reported asthma (37.7% vs 26.8%, p=0.04) and COPD (14.5% vs 7.1%, p=0.02). Mean disease duration for patients with PsA was 8.3±6.8 years. Among patients with PsA, 14 (20.3%) had axial involvement in addition to peripheral joint disease. We excluded 60 persons in the control group with bilateral hip prostheses or invalid measurements from further analyses of BMD of the hip. BMD values and T-scores for patients with PsA and controls are presented in table 2.

When adjusting for potential confounding factors listed in table 2, BMD was significantly higher in patients with PsA compared with controls in spine L1–L4 (1.213 vs 1.147 g/cm^2, p=0.003) and femoral neck (0.960 vs 0.926 g/cm^2, p=0.02) but not in total hip (1.013 vs 0.982 g/cm^2, p=0.11). In females, the PsA group had significantly higher BMD in the lumbar spine (mean difference 0.056, 95% CI 0.003 to 1.109, p=0.04) but not in the hip. Postmenopausal patients with PsA (n=34) had significantly higher BMD than controls at femoral neck (mean difference 0.071, 95% CI 0.025 to 0.117, p=0.043) and spine (mean difference 0.106, 95% CI 0.045 to 0.166, p=0.009) when controlling for potential confounding factors (data not shown).

Neither univariable nor multivariable linear regression models (controlling for age, sex, BMI, smoke and asthma diagnosis) showed an association between disease duration and BMD (adjusted p values for femoral neck BMD 0.93, total hip BMD 0.98, spine L1–L4 0.09).

As shown in table 3, the odds of being classified as having osteopenia or osteoporosis was greater for the control subjects than the patients with PsA (ordinal logistic regression).

DISCUSSION

This population-based cohort study found a higher BMD in the lumbar spine and femoral neck in individuals with PsA compared with individuals without PsA. Our findings are in line with other publications that report comparable BMD in

Table 1 Demographic and clinical characteristics in patients with psoriatic arthritis and controls with bone density measurement in the HUNT 3 study. Results are mean (±SD) for continuous variables or absolute values (percentages) for categorical variables

Demographic variables	Psoriatic arthritis n=69	Controls n=11703	p Value*
Female	45 (65.2)	7525 (64.3)	0.87
Postmenopausal females	34 (75.6)	4722 (62.8)	0.08
Age, years	56.8 (12.5)	55.3 (16.5)	0.32
Weight, kg	83.8 (16.3)	77.9 (15.4)	<0.01
Height, m	1.70 (0.09)	1.69 (0.09)	0.09
BMI, kg/m^2	28.5 (4.3)	27.2 (4.5)	0.01
Daily smoking	18 (26.1)	2814 (24.0)	0.69
Physical activity ≥2 times per week	40 (58)	6848 (58.5)	0.93
Asthma ever	26 (37.7)	3138 (26.8)	0.04
COPD/emphysema ever	10 (14.5)	830 (7.1)	0.02
Ever use of asthma/COPD medication last 5 years	23 (33.3)	2800 (23.9)	0.07
C-reactive protein, mg/L	3.9 (4.9)	2.9 (5.8)	0.17
Self-reported fractures			
Forearm (PsA n=65)	11 (16.9)	1938 (17.3)	0.93
Hip (PsA n=65)	1 (1.5)	187 (1.7)	1.00†
Spine (PsA n=63)	3 (4.8)	649 (6.0)	1.00†
Self-reported osteoporosis (PsA n=64)	6 (9.4)	538 (4.8)	0.08
Ever use of hormone replacement therapy among females	16/30 (53.3%)	1541/3766 (40.9)	0.17
Disease duration, years	8.3 (6.8)	NA	
Peripheral joint involvement	69 (100)	NA	
Joint involvement			
Isolated DIP joint	1 (1.4)	NA	
Monoarthritis	1 (1.4)		
Oligoarthritis	44 (63.8)		
Polyarthritis	23 (33.3)		
Axial involvement	14 (20.3)	NA	
Entesitis	43 (62.3)	NA	
Ever use of peroral steroids			
Previous	25 (36.2)	NA	
Current	4 (5.8)		
Ever users of anti-TNF therapy			
Previous	2 (2.9)	NA	
Current	5 (7.2)		
Ever use of methotrexate			
Previous	11 (15.9)	NA	
Current	18 (26.1)		
Ever use of synthetic DMARDS other than methotrexate			
Leflunomide	15 (21.7)	NA	
Salazopyrin	7 (10.1)		
Ever use of NSAIDs			
previous	14 (20.3)	NA	
current	44 (63.8)		

*χ^2 test for counts and independent samples t-test for continuous variables,
†Fisher's exact test due to small numbers.
Anti-TNF therapy, antitumour necrosis factor therapy; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DIP, distal interphalangeal; DMARD, disease modifying antirheumatic drug; DXA, dual-energy X-ray absorptiometry; HUNT, Nord-Trøndelag Health Study; NSAIDs, non-steroidal anti-inflammatory drugs; NA, not applicable.

patients with PsA and the general population.[3 11–14] However, comparing results across studies is difficult, as outcomes and comparison groups differ.[2] A rather low proportion of patients with PsA in this study were currently using tumour necrosis factor (TNF)-inhibitors. This may be explained by the inclusion being performed between 2006 and 2008 when use of TNF-inhibitors was still low in PsA patients in Norway. As the patients with PsA in our study were identified from a population survey and had similar CRP as the control group, we also suspect a relatively low disease activity. The patients with PsA had higher BMI, which is associated with greater BMD in the general population.[15] However, controlling for BMI in a multivariable linear regression model did not influence the results on BMD in our study. Further, the spine may be affected by new bone formation in PsA, which should be taken into account when evaluating BMD data from the lumbar spine.[2]

Higher BMD in PsA compared with RA has been reported.[16 17] Further, it is well documented that patients with RA are at increased risk for osteoporosis and fracture.[5 18] The pathophysiological mechanisms that affect bone appear to be different in PsA and RA. In RA, the inflammatory process causes an increased stimulation of the osteoclasts, together with a downregulation of the osteoblasts, whereas in PsA both osteoclasts and osteoblasts are stimulated.[19] Autoantibodies such as anticyclic citrullinated peptide antibodies are known to represent a higher risk of developing bone erosions by directly stimulating the differentiation of

Table 2 Bone mineral density in patients with psoriatic arthritis and controls in the HUNT 3 study

DXA Females and males	PsA n=69	Controls n=11703	Mean difference (95% CI) (PsA vs controls)	p Value*	p Value†
Left femoral neck					
BMD	0.960 (0.134)	0.926 (0.157)	0.034 (-0.003 to 0.071)	0.07	0.02
T-score	−0.42 (0.99)	−0.70 (1.24)	0.30 (0.04 to 0.52)	0.02	0.02
Left total hip					
BMD	1.013 (0.141)	0.982 (0.158)	0.030 (-0.007 to 0.067)	0.11	0.11
T-score	−0.15 (1.04)	−0.41 (1.22)	0.26 (-0.03 to 0.54)	0.09	0.11
Spine L1–L4					
BMD	1.213 (0.177)	1.147 (0.183)	0.065 (0.021 to 0.108)	0.003	0.003
T-score	0.15 (1.43)	−0.39 (1.50)	0.55 (0.19 to 0.91)	0.003	0.003
Females	**PsA n=45**	**Controls n=7525**	**Mean difference (95% CI) (PsA vs controls)**	**p Value***	**p Value‡**
Left femoral neck					
BMD	0.921 (0.106)	0.897 (0.155)	0.024 (-0.008 to 0.056)	0.14	0.19
T-score	−0.487 (0.88)	−0.69 (1.29)	0.20 (-0.06 to 0.47)	0.14	0.19
Left total hip					
BMD	0.973 (0.115)	0.946 (0.153)	0.026 (-0.007 to 0.061)	0.13	0.30
T-score	−0.22 (0.96)	−0.45 (1.28)	0.22 (-0.065 to 0.51)	0.13	0.30
Spine L1–L4					
BMD	1.174 (0.148)	1.118 (0.181)	0.056 (0.003 to 0.109)	0.04	0.04
T-score	−0.05 (1.23)	−0.52 (1.51)	0.46 (0.02 to 0.91)	0.04	0.04

Mean (±SD).
*Independent samples t-test,
†Linear regression analysis with adjustments made for age, sex, BMI, physical activity, smoking, asthma/COPD and reason for invitation to DXA,
‡Linear regression analysis with adjustments made for age, BMI, physical activity, smoking, asthma/COPD and reason for invitation to DXA.
BMD, bone mineral density; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; COPD, chronic obstructive pulmonary disease; HUNT, Nord-Trøndelag Health Study; PsA, psoriatic arthritis.

osteoclasts and promoting bone resorption.[20] In PsA, there is an absence of recognised autoantibodies. The clinical implications of these pathophysiological differences are that osteoporosis and joint erosions are more prominent in RA, whereas PsA is also characterised by new bone formation.[19] This may explain the higher BMD seen in patients with PsA compared with patients without PsA in our population cohort, particularly in the spine where syndesmophytes are common in PsA. In our PsA cohort, 14 patients (20.3%) had axial involvement based on clinical and radiological

Table 3 Osteoporosis, osteopenia and normal bone mineral density (BMD) among patients with psoriatic arthritis and controls in the HUNT 3 study: Ordinal regression shows higher odds of being classified as having osteopenia or osteoporosis for the control group

Based on T-score femoral neck	PsAoriatic Arthritis	Controls	Overall p- vValue*	Overall p -vValue **†
Osteoporosis	1 (1.4)	739 (6.4)	0.002	0.001
Osteopenia	15 (21.7)	4065 (35.4)		
Normal BMD	53 (76.8)	6690 (58.2)		
Based on T-score total hip				
Osteoporosis	1 (1.4)	474 (4.1)	0.024	0.033
Osteopenia	12 (17.4)	3143 (27.5)		
Normal BMD	56 (81.2)	7824 (68.4)		
Based on T-score spine L1–L4				
Osteoporosis	3 (4.4)	903 (7.8)	0.021	0.033
Osteopenia	11 (16.2)	3065 (26.4)		
Normal BMD	54 (79.4)	7629 (65.8)		

Frequency (percentage).
*Ordinal regression with no adjustments made,
†Ordinal regression with adjustments made for age (continuous), BMI, physical activity, smoking, asthma/COPD and reason for invitation to DXA (randomly or based on self-reported pulmonary symptoms).
BMD, bone mineral density; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DXA, dual-energyX-ray absorptiometry; HUNT, Nord-Trøndelag Health Study; PsA, psoriatic arthritis.

findings, but we were unable to obtain X-ray of the spine for all patients with PsA to control for syndesmophytes or degeneration of the spine. New bone formation may also form at the hip, and may therefore in theory also affect the BMD value of both femoral neck and total hip.[21]

High correlation between BMD measurements and bone strength in hip and spine has been demonstrated in in vitro studies, and a strong association between BMD and risk of fracture exists.[22] However, besides BMD, there are several other risk factors for fracture. One study found higher cortical porosity and lower cortical bone density of the distal radius on high-resolution CT in patients with PsA despite a normal BMD.[23] This may affect the cortical bone quality and predispose the bone to fractures. Other studies have reported higher frequency of fractures in PsA despite comparable BMD.[13 14]

The strengths of this study include the population-based study design and the use of objective criteria for the PsA diagnoses. A limitation is the relatively small number of PsA cases. We did not have access to clinical data on disease activity of the patients with PsA, but CRP was similar in the two groups. Unfortunately, we had limited information about steroid use in the control group and could therefore not include this variable in our regression models. In addition, we did not examine radiological images of the patients with PsA to control for syndesmophytes in the spine or new bone formation of the hip area, or calcifications of the aorta, which may influence the BMD values at these sites.

CONCLUSION

Our population-based data showed similar BMD in patients with PsA and controls. Slightly higher BMD values at femoral neck and lumbar spine were observed in patients with PsA. A higher proportion of the PsA population had a normal BMD. Thus our findings support that patients with PsA do not seem to have a significantly increased risk of osteoporosis compared with the background population.

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PAPER IV

Osteoporosis in psoriatic arthritis - A cross-sectional study of an outpatient clinic population

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Key words: Psoriatic arthritis, bone mineral density, osteoporosis

Abstract

Background: The risk of osteoporosis in psoriatic arthritis (PsA) patients still remains unclear. The aim of this study was to investigate bone mineral density (BMD) at the hip and lumbar spine measured by dual energy X-ray absorptiometry (DXA) in PsA patients.
Methods: From an outpatient clinic in southern Norway, 140 patients with PsA were consecutively recruited and assessed for osteoporosis as part of a prospective study from January 2013 to May 2014. An extensive data collection was performed including demographic data and measures reflecting disease activity and health status.
Results: Mean age was 52.4 years and 71 (50.7%) were females. Median disease duration was 7.8 years. The proportion of patients with low BMD (defined as Z score ≤ -1.0 SD) was comparable to the expected value of 16%, according to the normal distribution of the Z score in the population. Osteoporosis was only found in 6.4% (95% CI 3-11%) of the patients. No significant association was found between BMD and disease activity measures.
Conclusion: The prevalence of PsA patients with osteoporosis or low BMD was low and in the range seen in the reference population. This supports that PsA patients are not at high risk for osteoporosis compared with the general population. Therefore, clinicians may follow the general population guidelines for monitoring of osteoporosis for PsA patients.

Background

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. The clinical presentation of PsA is heterogeneous and may involve both the peripheral joints and the axial skeleton (sacroiliitis or spondylitis) and also skin, nails and entheses. In PsA, activation of both osteoclasts and osteoblasts can be involved, and as a consequence patients may show signs of both bone destruction and new bone formation (1). In rheumatoid arthritis (RA), osteoclast activation is dominating, and the increased risk of generalised bone loss and the development of osteoporosis is well established (2-5).

Data on systemic bone loss in patients with PsA are conflicting and are likely highly dependent on patient selection (6). An association between PsA and osteoporosis has been reported (7, 8), whereas others find comparable bone mineral density (BMD) in PsA patients and the background population (9-13). The major advances in pharmacological treatment of PsA, particularly the arrival of biologic therapies, have led to an improvement in controlling disease activity and inflammation, that may impact the presence of low bone mass in PsA patients.

In this cross-sectional study from a Norwegian outpatient clinic we report the BMD measured with dual energy X-ray absorptiometry (DXA) at the hip and lumbar spine in 140 PsA patients. Further, we wanted to identify demographic, clinical and treatment factors that might be associated with BMD in PsA patients.

Methods

Study population

Of the 581 patients carrying a diagnosis of PsA registered at the Department of Rheumatology outpatient clinic of the Hospital of Southern Norway Trust, Kristiansand, during the study period from January 2013 to May 2014, 471 fulfilled the Classification of Psoriatic Arthritis criteria (CASPAR)(14). Of these, 141 patients were consecutively recruited at routine visits for more extensively investigation, and 140 patients, both male and female, had DXA scanning of lumbar spine and hip (15). All the included patients had peripheral inflammatory involvement clinically, as patients with only axial manifestations were excluded. The included and non – included patients were similar in disease activity, except for tender joint count (TJC) 28 and disease activity score for 28 joints with ESR (DAS 28), which was higher for the included patients. Also the included patients were younger than the non-included. A

comparison of the included and non-included patients from the PsA cohort at Hospital of Southern Norway Trust has previously been described in detail (16).
Informed consent was obtained according to the declaration of Helsinki. The study was approved by the Regional Committee for Medical Research Ethics in South-Eastern Norway (REK number: 2012/101).

Collection and measurement of data

Data collection included demographics, clinical and laboratory measures, treatments and previous fracture history. The following data were recorded: age, sex, postmenopausal status, weight, height, body mass index (BMI), duration of PsA, smoking status, alcohol consumption (more than 3 units pr day), erythrocyte sedimentation rate (ESR), (Westergren´s method), C- reactive protein (CRP), (lowest detectable value 1 mg/L), level of physical activity (> 1 time pr. week or < 1 time pr. week), DAS 28, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), cutaneous involvement (Psoriasis Area Severity Index, PASI), patient´s global assessment (PGA), investigator´s global assessment (IGA), tender joint count 68, swollen joint count 66, Modified Health Assessment Questionnaire (MHAQ), Nonsteroidal anti-inflammatory drug (NSAID) use, disease modifying anti-rheumatic drug (DMARD) use, tumor necrosis factor (TNF)- inhibitors, glucocorticoid treatment (current use or ever use of ≥ 5 mg > 3 months), Vitamin D and calcium supplements and anti-osteoporotic treatment. Fragility fracture was defined as vertebral or peripheral fracture occurring spontaneously or caused by low impact trauma at any time in the life of the subjects as reported by the patients. Blood samples were analysed by standard laboratory techniques at the participating hospital. Use of medications was self-reported by the patients.

Bone density measurements

BMD (as g/cm^2) was measured at the lumbar spine (L1-L4), and hip (femoral neck and total hip) by DXA, (Lunar Prodigy, GE Healthcare). We preferably used measurements from the left hip. Scans from the right hip were used in 5 (3.6%) patients because of missing values from the left hip. All participants had measurements of the lumbar spine. The DXA machine was stable during the whole study period and all DXA measurements were performed by experienced technicians. As a measure of BMD variability, the in-vitro long-term coefficient of variance (CV) for the spine phantom was 0.62%. The in-vivo CV was 0.91 % for L1-L4 measurements, 1.56% for left femoral neck and 0.88 % for left total hip.

The T score (comparison with normal, young subjects of same sex) and Z score (comparison with age, sex and weight matched normal controls) were based on the reference values in the DXA machine provided by the manufacturer (NHANES). Further we also calculated the percentage of patients with T score ≤ -2.5 standard deviations (SD) and Z score ≤ -1.0 SD. The World Health Organisation (WHO) definition was applied for osteoporosis (T score ≤ −2.5 SD) and normal BMD (T score ≥ −1.0 SD) (WHO, 1994).(17)

Statistical analyses

All statistical analyses were performed with SPSS for Mac version 21 (Chicago, IL). Statistical significance level was defined as $p < 0.05$. To test whether data was normally distributed we used Q-Q plots. Continuous data are presented as mean with SD when normally distributed, or median with Interquartile range (IQR) when non-normally distributed. Confidence intervals (CI) were used to assess the difference between the mean Z score at each anatomical site and the reference population data from the DXA machine provider. Assuming a normal distribution, the risk is 68% of being within ± 1 SD of the mean Z score, thus, the expected proportion of Z scores ≤−1.0 SD in the reference population is 16% by default. The proportions of patients having a Z score of ≤−1.0 SD was compared to the expected value of 16% by a binomial test and the 95% CIs for the proportions of patients with T score ≤ -2.5 and Z score ≤-1.0 were calculated.

Association between clinical and demographic factors and BMD was analysed using linear regression. Variables from the univariable analyses with a p-value ≤ 0.10 were included in a multivariable model, which also included sex and age regardless of the significance in the univariable analyses. For missing data we excluded cases pairwise. This method excludes patients only if they have missing data required for the specific analysis. They are still included in any of the analyses for which they have the necessary information.

Results

Demographic characteristics are presented in table 1. Mean ± SD age was 52.4 ± 10.3 years and 71 (50.7%) were females. The age of the included patients ranged from 23 to 74 years, and 60.7% were over 50 years old. Median (IQR) disease duration was 7.8 (9.3) years. Bone density data are presented in table 2. Mean ± SD BMD of the PsA patients was 0.967 ± 0.141 g/cm^2 at femoral neck, 1.017± 0.148 g/cm^2 at total hip and 1.208± 0.170 g/cm^2 at lumbar

spine 1- 4. The percentage of PsA patients with Z score ≤−1.0 SD was comparable to the DXA reference population for the overall PsA patients and for females separately. For men, there was an increased proportion with low BMD at all three anatomical locations compared to the expected value of 16% in the reference population, however only statistically significant for femoral neck (26.1% (95% CI 16.3 – 38.1%), p = 0.02) (Figure 1). As shown in table 2, T score ≤ -2.5 was found in 6 (4.3%) patients at femoral neck, 2 (1.4%) at total hip and 3 (2.1%) at lumbar spine (table 2). At any site 9 (6.4%) patients had osteoporosis, 3 males and 6 females. A normal BMD both in the lumbar spine and hip (femoral neck and total hip) were found in 55.7% of patients. Patients with a normal BMD were younger (49.3 ± 9.2 vs 56.3 ±10.2 years, p< 0.001) and had higher BMI (28.8 ±4.6 vs 27.3 ±3.6 kg/m^2, p= 0.03), but were similar in terms of disease duration, disease activity and outcome measures. There was no difference in T score between users and non - users of glucocorticoids and biologic DMARDs for all three anatomical locations.

Multivariable linear regression showed an association between BMD and age, and BMD and BMI for the overall series, but not with ESR or swollen joint count 66 (Table 3, appendix). No association was found between BMD and use of medications (DMARDs, TNF- inhibitors, glucocorticoids, NSAIDs or anti-osteoporotic medication) or other disease activity measures (DAS28, MHAQ, BASDAI, MASES, PGA or IGA). For males ESR was associated with total hip BMD (p< 0.01) and lumbar spine BMD (p< 0.01). Swollen joint count 66 showed significant association with BMD in the univariable analysis, however the association was only significant for BMD at lumbar spine of females in the multivariable analyses (p=0.02).

Discussion

In this cross-sectional study we found a low prevalence of osteoporosis and low BMD in PsA outpatients. Thus according to our data osteoporosis does not seem to be a major co-morbidity in PsA patients. Our data showed that Norwegian outpatients with PsA had similar age, weight and gender adjusted BMD (Z score) compared to the normative reference population data. However, in the male group there was a slightly higher proportion of patients with low Z score compared to the expected reference population. Our findings support other publications reporting comparable BMD in PsA patients and the general population (9, 11-13, 18, 19). In a recent population based study from Norway, BMD in PsA patients was comparable to the background population (20).

There is great diversity in the reported proportion of osteoporosis in PsA, ranging from 1.4% to 68.8% (7, 9, 19, 21). The findings from this study, of 6.4 %, lie in the lower range of the results reported. Comparing results across studies is difficult, as outcomes, patient selections and control groups differ (6). A study from 2001 reported a prevalence of osteoporosis in Italian PsA patients of 30 %, however this was before the biologic therapy era (7). Disease activity of PsA patients is probably lower today than it was 17 year ago, with greater focus on early diagnosis and more effective treatment options. A frequency of osteoporosis of 16 % was reported in a study including pre-and postmenopausal female and male PsA patients from an outpatient clinic (9). Grazio et al reported a similar frequency of osteoporosis to our data, along with a negative correlation with MHAQ (19). In the present study we did not discover any association between BMD and disease duration, disease activity or outcome measures, except for subgroup analyses of males that showed an association between BMD and ESR. However, the disease activity of the patients in the present study was low, with a median 66 swollen joint count of 0, as well as low CRP and ESR. This is what would be expected in a contemporary clinic population, where healthcare is publically funded, as doctors adhere to the goal of getting patients to the lowest possible disease activity.

Based on the existing data, it seems that the risk of osteoporosis is lower in PsA than in RA. In normal bone the osteoclast mediated bone resorption is followed by a replacement of the resorbed bone by osteoblasts. In spondyloarthropaties, including PsA, the so called "coupling" of bone formation and resorption is de-regulated such that there is local loss of bone at the enthesal insertion sites, and excessive bone formation in periosteal sites adjacent to the sites of bone erosion. The characteristic skeletal changes that occur are results of this endochondral ossification, in which new bone is formed by replacement of cartilaginous matrix (22). This enhanced bone formation at sites of inflammation is a typical feature of PsA and the other spondyloarthropaties in comparison to RA. This difference in pathophysiological mechanism between the spondyloarthropaties and RA may explain the difference in bone density reported in the literature. Further, clinical differences such as age of onset, the potential for more intermittent inflammation, and less use of glucocorticoids in PsA compared with RA may also influence the difference in risk of systemic bone loss. In our outpatient clinic we have previously reported current prednisolone treatment in 13.7% of all the PsA patients, compared to 54.3% of all the RA patients (23). In the present study only 11% were currently using glucocorticoids.

TNF-inhibitors have been shown to increase BMD in both lumbar spine and hip in spondyloarthropaties (24-26). Some relate this to a possible increase in new bone formation after TNF- inhibitor treatment, which can increase BMD in the spine, however similar results were also found in a study that adjusted for radiographic progression (27). This suggests that TNF-inhibitors improve bone metabolism in spondyloarthropaties by relatively increasing the effect of osteoblasts and reducing the activity of osteoclasts (28). In our data, more than one third of the PsA patients were currently using TNF-inhibitors, and therefor may be protected from generalized bone loss. However, no difference in T score between users and non - users of biologic DMARDs was found in this study.

The concept of bone strength has expanded in the recent years to also include the *quality* of the bone, which includes factors such as microarchitecture, the quality of collagen and the speed of bone turnover (29). In PsA patients, a higher cortical porosity and lower cortical bone density of the distal radius on high resolution CT, despite a normal BMD, has been reported (30). This may affect the cortical bone quality and predispose the bone to fractures. Higher prevalence of fractures in PsA patients has been reported (13, 18, 31). In a recent population based study a small but significantly increased risk of all fractures was reported in PsA and psoriasis patients (31). In our study we did not find a high prevalence of self-reported fragility fractures (6.4%).

Over the last decade the rheumatology community has become more aware of the importance of comorbidities contributing to outcome in patients with chronic inflammatory rheumatic disorders, including PsA. This is addressed in the EULAR initiative aiming to improve the prevention of comorbidities in rheumatic disorders (32). A recent review article recommends that general screening for osteoporosis should be followed in PsA patients (33), except for patients on glucocorticoids, where the American College of Rheumatology (ACR) recommendations should be followed (34).

The main strength of this study is the use of objective criteria for PsA, and that the selection of patients seems to reflect the cohort of PsA outpatients in southern Norway. Furthermore, extensive clinical data on the study cohort is included. The main limitation is that we do not have a control group recruited from the background population. However, data indicate that the reference population provided by the DXA manufacturer reflects the bone density of the background Norwegian population. A study from western Norway found comparable BMD in

the investigated population and the reference data provided by the DXA manufacturer, except for lower BMD for males at total hip in the examined population (35). Further, a study from Oslo, Norway also found comparable BMD in a reference population compared to Lunar DXA European/US reference population (36).Another limitation of this study is that we did not examine radiologic images of the PsA patients to control for syndesmophytes in the spine or new bone formation of the hip area, or calcifications of the aorta, which may influence the BMD values at these sites. Also, for the subgroup analyses we had only 71women and 69 men, which may have lead to the higher proportion of low Z score observed in men failing to reach statistical significance (type 2 error).

Conclusion

Data from our study on PsA patients from an outpatient clinic suggest that low BMD is not a significant clinical problem in PsA. This therefor supports the recommendation that PsA patients may follow guidelines for osteoporosis assessment developed for the general population.

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Table 1: Demographical and clinical variables of the 140 psoriatic arthritis patients included*

	All psoriatic arthritis patients N=140	Females N=71	Males N=69
Age, years, mean (SD)	52.4 (10.3)	52.9 (10.3)	51.9 (10.3)
Female, n (%)	71 (50.7)	NA	NA
Postmenopausal, n (%)	34 (24.3)	34 (47.9)	NA
Weight, kg, mean (SD)	82.5 (14.7)	79.2 (13.6)	91.9 (13.0)
Height, cm, mean (SD)	174.0 (8.8)	168.2 (6.5)	180.0 (6.6)
BMI, kg/m2, mean (SD)	28.2 (4.2)	28.0 (4.8)	28.4 (3.6)
Disease duration, median (IQR)	7.8 (9.3)	7.6 (8.8)	7.8 (10.4)
Smoking, n (%) - **Current** - **Previous**	 23 (16.4) 72 (51.8)	 14 (19.7) 33 (46.5)	 9 (13.0) 39 (56.5)
Alcohol consumption (more than 3 units pr day), n (%)	1 (0.7)	0	1 (1.4)
CRP, mg/L, median (IQR)	2.0 (4.0)	2.0 (3.0)	3.0 (6.0)
ESR, mm/h, median (IQR)	13 (15)	16 (16)	10 (11)
Physical activity ≥ 1 time pr week, n (%)	62 (44.3)	33 (46.5)	29 (42.0)
HLA B 27, n (%)	34 (24.3)	14 (19.7)	20 (29.0)
DAS 28, mean (SD)	3.16 (1.14)	3.55 (1.08)	2.74 (1.05)
BASDAI, mean (SD)	3.35 (2.24)	3.84 (2.34)	2.84 (2.03)
MASES, mean (SD)	2.97 (3.19)	4.14 (3.39)	1.77 (2.45)
PASI, mean (SD)	2.56 (3.63)	1.88 (2.94)	3.24 (4.12)
Patient global assessment, mean (SD)	36.12 (24.32)	41.69 (25.15)	30.39 (22.18)
Investigator global assessment, mean (SD)	14.56 (12.11)	14.69 (11.69)	14.43 (11.00)

TJC 68, median (IQR)	6 (14)	8 (16)	4 (9)
SJC 66, median (IQR)	0 (1)	0 (1)	0 (1)
MHAQ, mean (SD)	0.43 (0.40)	0.50 (0.44)	0.35 (0.33)
Current use of NSAIDs, n (%)	45 (32.1)	24 (33.8)	21 (30.4)
Current use of synthetic DMARDs, n (%)	80 (57.1)	38 (53.5)	42 (60.9)
Current use of biologic DMARDs n (%)	45 (32.1)	18 (25.4)	27 (39.1)
Current use of glucocorticoids, n (%) **Ever use of glucocorticoids ≥ 5 mg ≥ 3mnd, n (%)**	15 (10.7) 37 (26.4)	10 (14.1) 19 (26.8)	5 (7.2) 18 (26.1)
Use of calcium or vitamin D supplements, n (%)	17 (12.1)	16 (22.5)	1 (1.4)
Osteoporosis medication, n (%)	3 (2.1)	3 (4.2)	0
Previous low energy fracture, n (%)	9 (6.4)	6 (8.5)	3 (4.3)

*Unless stated, results are mean (± standard deviation) for continuous variables or absolute values (percentages) for categorical variables.

BMI: body mass index, IQR: inter quartile range, CRP: C-reactive protein, ESR: erythorycte sedimentation rate, HLA B 27: human leukocyte antigen B 27, DAS-28: disease activity score for 28 joints with ESR, TJC 68: tender joint count 68 joints, SJC 66: swollen joint count 66 joints, MHAQ: Modified Health Assessment Questionnaire, NSAIDs: Non-steroidal anti inflammatory drugs, DMARD: disease modifying anti rheumatic drug, Anti-TNF therapy: anti tumor necrosis factor therapy, NA: not applicable.

Table 2: Bone mineral density of the psoriatic arthritis patients.

95% CIs for the proportion of patients with T score ≤ 2.5 and Z score ≤ 1.0 were calculated by using a binomial test.

	Femoral neck	Total hip	Lumbar spine 1-4	Any site
Overall PsA patients (N=140)				
BMD g/cm^2 (SD)	0.967 (0.141)	1.017 (0.148)	1.208 (0.170)	-
T score (95% CI)	-0.68 (-0.87 to -0.49)	-0.25 (-0.44 to -0.06)	0.10 (-0.15 to 0.33)	-
Z score (95% CI)	-0.11 (-0.26 to 0.06)	-0.05 (-0.22 to 0.12)	0.14 (-0.08 to 0.35)	-
T score ≤ -2.5 No (%, 95%CI)	6 (4.3%, 1.6-9.1%)	2 (1.4%, 0.2-5.1%)	3 (2.1%, 0.4-6.1%)	9 (6.4%, 3.0-11.9%)
Z score ≤ -1.0 No (%, 95%CI)	28 (20.0%, 13.7-27.6%)	25 (17.9%, 11.9-25.2%)	25 (17.9%, 11.9—25.2%)	43 (30.7%, 23.2-39.1%)
Females (N=71)				
BMD g/cm^2 (SD)	0.954 (0.151)	0.987 (0.161)	1.188 (0.184)	-
T score (95% CI)	-0.69 (-0.98 to -0.39)	-0.15 (-0.45 to 0.16)	0.11 (-0.26 to 0.47)	-
Z score (95% CI)	0.05 (-0.19 to 0.29)	0.12 (-0.15 to 0.40)	0.345 (0.02 to 0.66)	-
T score ≤ -2.5 No (%, 95%CI)	5 (7.0%, 2.3-15.7%)	2 (2.8%, 0.3-9.8%)	1 (1.4%, 0.0-7.6%)	6 (8.5%, 3.2-17.5%)
Z score ≤ -1.0 No (%, 95%CI)	10 (14.1%, 7.0-24.4%)	12 (16.9%, 9.0-27.7%)	10 (14.1%, 7.0-24.4%)	16 (22.5%, 13.5-34.0%)
Males (N=69)				
BMD g/cm^2 (SD)	0.981 (0.130)	1.047 (0.128)	1.229 (0.152)	-
T score (95% CI)	-0.67 (-0.91 to -0.43)	-0.36 (-0.58 to -0.15)	0.09 (-0.21 to 0.39)	-
Z score (95% CI)	-0.27 (-0.48 to -0.05)	-0.24 (-0.43 to -0.04)	-0.09 (-0.36 to 0.21)	-
T score ≤ -2.5 No (%, 95%CI)	1 (1.4%, 0.0-7.8%)	0 (0%, 0.0-5.2%)	2 (2.9%, 0.4-10.1%)	3 (4.3%, 0.9-12.2%)
Z score ≤ -1.0 No (%, 95%CI)	18 (26.1%, 16.3-38.1%)	13 (18.8%, 10.4-30.1%)	15 (21.7%, 12.7-33.3%)	27 (39.1%, 27.6-51.6%)

Appendix:

Table 3a: Results from multiple linear regression analyses with BMD as the outcome for all psoriatic arthritis patients included (N=140).

Demographic and disease -related variables that were significantly correlated with BMD in the univarible analyses were entered as covariates.

Demographic variables	Femoral neck BMD	Total hip BMD	Lumbar spine BMD
Age (years)	B = -0.006 (-0.008 to -0.004) p<0.01	B= -0.004 (-0.006 to -0.002) p<0.01	B = -0.002 (-0.005 to 0.001) p= 0.15
Sex (ref. male)	B= - 0.016 (-0.057 to 0.026) p= 0.45	B= - 0.047 (-0.090 to -0.003) p= 0.04	-0.025 (-0.082 to 0.031) p= 0.37
BMI (kg/m2)	B = 0.010 (0.005 to 0.015) p<0.01	B = 0.013 (0.008 to 0.018) p< 0.01	B = 0.009 (0.002 to 0.016) p= 0.01
ESR (mm/h)	B= -0.001 (-0.003 to 0.001) p=0.50	B = -0.001 (-0.003 to 0.001) p= 0.24	B= -0.002 (-0.005 to 0.001) p= 0.15
SJC 66 (0-66)	B = -0.018 (-0.038 to 0.003) p= 0.09	B = -0.02 (0.041 to 0.002) p= 0.06	B= -0.018 (-0.046 to 0.010) p= 0.20

Table 3b: Results from multiple linear regression analyses with BMD as the outcome for female psoriatic arthritis patients only (N = 71)

Demographic variables	Femoral neck BMD	Total hip BMD	Lumbar spine BMD
Age (years)	B = -0.008 (-0.011 to 0.005) p<0.01	B = -0.007 (-0.01 to -0.003) p<0.01	B =-0.006 (-0.01 to -0.002) p<0.01
BMI (kg/m2)	B = 0.006 (.0.001 to 0.013) p= 0.10	B = 0.009 (0.002 to 0.017) p= 0.02	B = 0.002 (-0.007 to 0.011) p= 0.69
ESR (mm/h)	B= 0.001 (-0.002 to 0.004) p= 0.43	B = 0.001 (-0.002 to 0.005) p= 0.36	B = (-0.002 to 0.006) p= 0.33
SJC 66 (0-66)	B = -0.026 (-0.063 to 0.011) p= 0.17	B = -0.036 (-0.077 to 0.005) p= 0.08	B = - 0.059 (-0.108 to -0.009) p= 0.0

Table 3c: Results from multiple linear regression analyses with BMD as the outcome for male psoriatic arthritis patients only (N = 69)

Demographic variables	Femoral neck BMD	Total hip BMD	Lumbar spine BMD
Age (years)	B = -0.003 (-0.006 to -0.001) p= 0.02	B = -0.001 (-0.004 to 0.001) p= 0.29	B=0.003 (-0.001 to 0.006) p= 0.11
BMI (kg/m2)	B = 0.017 (0.009 to 0.024) P<0.01	B = 0.018 (0.011 to 0.026) P< 0.01	B = 0.018 (0.008 to 0.028) P= 0.01
ESR	B = -0.002 (-0.005 to 0.00) p=0.07	B = -0.004 (-0.006 to -0.001) P< 0.01	B = -0.005 (-0.008 to -0.002) P< 0.01
SJC 66 (0-66)	B = -0.011 (-0.034 to 0.013) p= 0.36	B = -0.009 (-0.032 to 0.013) p= 0.42	B = 0.008 (-0.021 to 0.038) p= 0.58

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