Study report

PREVALENCE, PATTERN AND DISEASE COURSE OF ARTHRITIS AND ENTHESITIS IN PATIENTS WITH PSORIASIS, AND EFFECT OF APREMILAST IN SUBCLINICAL US-DEFINED PSORIATIC ARTHRITIS

– A POPULATION-BASED STUDY APPLYING CLINICAL, ULTRASONIC, MRI AND PATIENT-REPORTED OUTCOMES

An investigator-initiated study

Short English title: Danish Population-based Assessment of Psoriasis and Psoriatic arthritis (DANPAPP)

Danish title: Prævalens, sygdomsmønster og -forløb af artrit og entesit hos patienter med psoriasis, samt effekten af apremilast behandling ved subklinisk, ultralydsdefineret psoriasisartrit - et populationsbaseret studie med kliniske, ultrasoniske og patient-rapporterede effektmål.

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Publications

Part 1: *Musculoskeletal Pain in Patients with Psoriasis and its Influence on Health-related Quality of Life: Results from a Danish Population-based Survey.* Acta Derm Venereol. 2021 (1)

Part 2: *Musculoskeletal pain in psoriasis - relation to inflammation and additional value of ultrasound in psoriatic arthritis classification.* Rheumatology (Oxford). 2021. (2)

1 INTRODUCTION

1.1 Background

Psoriasis (PsO) is a common chronic immune-mediated skin disease that affects approximately 2-5% of the population (3, 4). Psoriatic arthritis (PsA) occurs in a considerable fraction (10-30% depending on the study population) of PsO patients (5, 6). PsA may present in different clinical forms, whose major features are various patterns of synovitis, enthesitis, dactylitis and/or axial inflammation. In most patients, but not all, PsO precedes the clinical onset of the joint inflammatory disease (7).

High-resolution ultrasonography (US) has been shown to be more sensitive than clinical assessment in detecting joint synovitis (8-10) and enthesitis (11-14) in inflammatory arthritis and in patients with PsO without clinical signs of arthritis or enthesitis (15). However, the occurrence of US detected pathologies in large population-based studies, nor is the impact of such findings on physical and psychological domains of health are not described. Further information may be obtained by magnetic resonance imaging (MRI) on inflammation and damage in inflamed joints and entheses, in particular, bone inflammation (bone marrow edema, osteitis), which can only be visualized by MRI (16, 17).

A large multinational population-based survey demonstrated that musculoskeletal pain is very frequent (44%) in patients with PsO without diagnosed PsA (18), suggesting a potential large pool of PsA patients, who would benefit from proper medical examination and early diagnosis, and thereby identifying those with an unmet need for therapy. However, the survey study did not include any clinical examinations or imaging measures to verify the symptoms reported by the patients.

The effect of therapy on early pathologies, as measured by US, MRI, clinical and PROs, is unknown. Knowledge on this would provide valuable information on the potential of introducing a standard measurable target of imaging remission (MRI and/or US-defined) in PsA. Furthermore, the effect of treatment of US-defined synovitis and enthesitis in patients without clinical signs of arthritis or enthesitis on clinical, US and patient-reported outcomes remains unknown.

Several questionnaires for screening for PsA in both PsO patients and the general population have been developed (19-23). They all showed good sensitivity and specificity in primary settings, but significantly lower in subsequent studies performed in other settings. (24-27). There has been no consensus on one screening tool.

In the present study, based on a large Danish population-based survey identifying individuals with self-reported, physician diagnosed PsO and/or PsA, we wished to investigate and compare the prevalence and pattern of clinical and US signs of inflammation in joints and entheses in three subsets of patients; a) patients with PsO without musculoskeletal pain, b) patients with PsO with musculoskeletal pain and c) patients with PsA, and to investigate the influence of such findings on important PROs on health related quality of life (HRQoL), functional level, depression, fatigue, sleep etc. Furthermore, in patients with US-documented joint or entheseal inflammation, we wished to investigate the effect of early intervention with apremilast on clinical, US and PROs. Patients with dactylitis or enthesitis in the ankle region (Achilles enthesitis or plantar fasciitis) was planned to be evaluated by MRI outcomes.

1.2 Hypothesis

We hypothesized that a large fraction of PsO patients with musculoskeletal pain had subclinical inflammation that could be detected by US, and that early intervention would improve these patients' quality of life.

1.3 Aim/Objective(s)

1.3.1 *Overall aim*

The overall aim of this study was to investigate and compare the prevalence and pattern of clinical and US signs of inflammation in joints and entheses in patients with psoriasis with/without musculoskeletal pain and patients with PsA, and to investigate the influence of these findings on important PROs.

1.3.2 *Objectives*

1. To quantify and describe a PsO patient population with regards to musculoskeletal pain and its impact on different PROs
2. To quantify and describe the prevalence and pattern of clinical and US signs of inflammation in joints and entheses in a PsO patient population, and their impact on patient's lives.
3. To identify patients within this PsO population, who have PsA by clinical and/or US criteria, which were undiagnosed prior to the study, and to describe the burden of disease and its impact on patient's lives by clinical, US and PROs.
4. To determine the effect of treating PsA patients identified in Objective 3 with apremilast, with respect to decreases in US detected inflammation scores, clinical signs and symptoms and impact on patient's lives, and the relation between these.
5. To determine the effect of treating the subgroup of PsA patients identified in Objective 3, which have dactylitis and/or ankle region enthesitis, with apremilast, with respect to decreases in MRI detected inflammation scores, and clinical signs and symptoms and impact on patient's lives, and the relation between these.
6. To investigate if induction therapy with apremilast for 6 months would, also after discontinuation, cause sustained improvements in clinical, US and patient/reported outcomes, or if symptoms and clinical and US findings will reappear, documenting a need for continuous treatment in such patients.

2 METHODS

2.1 Overall study design

The study was designed in three parts:

Part 1:
A population-based survey of Danish inhabitants, identifying persons with physician diagnosed PsO with or without PsA answering an internet-based questionnaire regarding demographics, skin and joint complaints, diagnosed diseases, contact to health care providers, and different aspect of psychological and physical function and wellbeing.

Part 2:

Participants from Part 1, accepting to participate in a clinical study, were seen at a local rheumatology department for the following examination programme: Clinical examination with a focus on skin, joints and entheses, US examination of joints and entheses, radiography of hand and feet, PROs and blood sampling.

Part 3:
Patients with musculoskeletal pain and joint and/or entheseal inflammation documented by US were invited to participate in a 12 months' interventional study (part 3a), whereas patients without musculoskeletal pain but with US findings were invited to participate in a 12 months non-interventional follow-up study (part 3b). The interventional study (3a) consisted of 6-month induction therapy with apremilast (in addition to their usual therapy) followed by cessation of apremilast and 6 months of observation. Clinical examination, PRO's, blood sampling and US was performed at months 3, 6, 9 and 12. The non-interventional study (3b) consisted of same examinations and visits as above, with patients continuing their current therapy. In a substudy, patients with clinical dactylitis or enthesitis in the ankle region (Achilles enthesitis or plantar fasciitis) had MRI performed at inclusion and at 6 months follow-up.

2.2 Part 1

2.2.1 *Survey design*

The online questionnaire contained questions concerning skin (location and body surface area (BSA)) and musculoskeletal symptoms (location and degree), severity of disease, healthcare-contacts and treatment, and included standardized questionnaires on HRQoL (European Quality of life - 5 Dimensions (EQ5D(28)), Dermatology Life Quality Index (DLQI(29)) and Psoriatic Arthritis Impact of Disease (PsAID(30))) and disability (Health Assessment Questionnaire-Disability Index (HAQ(31)). A list of questions can be found in Appendix 1.

2.2.2 *Patient subgroups*

Based on presence of musculoskeletal pain and diagnosed PsA, patients were divided in four groups: 'PsA', 'PsO-pain-now', 'PsO-previous-pain' and 'PsO-no-pain-ever'.

2.2.3 *Statistical analyses*

The full population as well as subgroups were described using descriptive statistics with numbers (%) for binary variables and medians (interquartile ranges (IQR)) for continuous variables. The 'PsO-previous-pain' group was for analyses related to clinical PsO and PsA features added to 'PsO-no-pain-ever' (creating a 'PsO-pain-ever' group). For analyses related to quality of life and disability the 'PsO-previous-pain' group was added to the 'PsO-no-pain-ever' group (creating a 'PsO-no-pain-now' group) to evaluate the impact of current pain on these parameters. Differences between groups were compared with Chi-square test for binary data and Kruskal-Wallis test for continuous data (between multiple groups), and with Fisher's exact test for binary data and Mann-Whitney U test for continuous data (between two groups). Spearman's correlation coefficient were used for correlations, with Rho was defined as: negligible <0.2, weak 0.2–0.39, moderate 0.40–0.59, strong 0.60–0.79 or very strong ≥0.80. Statistical significance was set to $p<0.05$. Analyses were performed with R, version 3.6.1.

2.3 Part 2

2.3.1 *Study design and patients*

Part 2 of the study was a cross-sectional, multi-centre study, including patients with physician-diagnosed PsO from part 1, see **figure 2.1.** Patients completing the questionnaire were invited to a full rheumatological evaluation at one of four Danish rheumatology departments. At this visit, clinical examination, laboratory tests, US examination of joints and entheses and conventional radiography of hands and feet were performed, and medical history and various PROs on physical and mental health were obtained.

2.3.2 *Clinical and biochemical examination*

Data on past medical and surgical history, disease duration, family history of PsO/PsA, current and previous PsO/PsA medication were obtained. Anamnestic features of PsA/spondyloarthritis (joint swelling, joint stiffness, joint pain, enthesis pain, inflammatory back pain (ASAS criteria (32)), unspecific musculoskeletal pain, dactylitis, uveitis, inflammatory bowel disease (physician-diagnosed)) were registered as never/previously/currently present.

Clinical examination included evaluation of tenderness of 18 entheses (according to the Spondyloarthritis Research Consortium of Canada (SPARCC(33)) Enthesitis Index and the Leeds Enthesitis Index (LEI(34)), 66 joints for swelling (SJC66), 68 joint for tenderness (TJC68), a 18 fibromyalgia tender point count (TPC(35)), and presence and location of any dactylitic digits. Skin involvement was evaluated using Psoriasis Area Severity Index (PASI) and number and location of nails with psoriatic nail changes were registered. Physician-assessed overall PsA disease activity on a Visual Analogue Scale (Physician global VAS) was also registered.

Biochemical analyses included C-reactive protein (CRP), IgM rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPA) and serum-urate (s-urate).

2.3.3 *Ultrasonography*

US was performed according to EULAR standardized procedures (36) of 48 joints (bilateral metacarpophalangeal (MCP) joints 1-5, proximal and distal interphalangeal (PIP and DIP) joints 1-5, interphalangeal joints, metatarsophalangeal (MTP) joints 1-5, wrists, elbows, shoulders (glenohumeral), knees, and ankles (tibiotalar)) and 12 entheses (bilateral insertions of: the common extensor tendon at the lateral humeral epicondyle, quadriceps tendon at the superior pole of the patella, patellar tendon at the inferior pole of the patella, patellar tendon at the tibial tuberosity, Achilles tendon at the calcaneus, plantar aponeuroses at the calcaneus). The US examinations were performed by experienced sonographers blinded to the clinical examination. Examination time was max. 90 minutes. Examinations were performed with General Electric (GE) Logiq E9 or E10 US machines with 6-15 MHz linear transducers, or with Hitachi HI VISION Preirus scanner, with 5-13 MHz linear transducer, using greyscale (GS) and colour Doppler (CD) US. For CD, settings were optimized for slow flow according to published guidelines (37)(gain adjusted just below the noise level, the threshold set for 100%, pulse repetition frequency: GE Logiq E9 and E10 =0.4 kHz, Hitachi Preirus=0.35 kHz, Doppler frequency: GE Logiq E9=8.3 MHz, GE Logiq E10=7.3 MHz, Hitachi Preirus=10 MHz). Prior to the study, detailed agreement on scanning protocol and scoring was obtained and compiled in a standard operating procedure, including image examples.

Synovitis was assessed using the EULAR-OMERACT US scoring system, scoring separately GS synovial hypertrophy and synovial CD activity, semiquantitatively 0-3 (38). "US synovitis" was defined as present if GS grade ≥2 independent of the presence of CD OR GS grade ≥1 with CD grade ≥1. "CD+ synovitis" was defined as GS grade ≥1 with CD grade ≥1.

Entheses were evaluated for presence/absence of thickening, hypoechogenicity/loss of fibrillary structure, bone erosions, calcifications/enthesophytes and semiquantitatively 0-3 for CD signal near the enthesis (≤2 mm from the bony cortex) according to OMERACT definitions for larger entheses (39). "US enthesitis" was defined as thickening and/or hypoechogenicity of the enthesis with CD grade ≥1 (39).

A "US inflammation sum-score" and "CD+ inflammation sum-score" was calculated, adding number of entheses with "US enthesitis" and joints with "US synovitis" or "CD+ synovitis", respectively.

Other lesions, including tenosynovitis of the digital flexor tendons (GS 0-3, CD 0-3) (39) or paratenonitis (hypoechogenicity and CD activity of the paratenon) of the digital extensor tendons were registered if present.

2.3.4 *Conventional radiography*

Conventional radiography of hands and feet was performed and evaluated for presence and location of juxta-articular new bone formation (excluding osteophytes) and erosions by an experienced musculoskeletal radiologist blinded to clinical data.

2.3.5 *Patient-reported measures and definition of musculoskeletal pain*

All patients completed four different screening-questionnaires for PsA (Early psoriatic arthritis screening questionnaire (EARP (23)), Toronto Psoriatic Arthritis Screen Version 2 (ToPAS 2 (22)), Psoriasis Epidemiology Screening Tool (PEST (21)) and Psoriatic Arthritis Screening and Evaluation (PASE (40))) prior to clinical and US examinations. Following PROs were completed: Dermatology Life Quality Index (DLQI (29)), Health Assessment Questionnaire Disability Index (HAQ-DI (31)), patients' global assessment of arthritis disease activity, pain and fatigue on a VAS (Global VAS, Pain VAS, Fatigue VAS), Psoriatic Arthritis Impact of Disease (PsAID (30)), European quality of life 5-dimensions (EQ5D (28)), 36-Item Short Form survey (SF-36 (41)), Functional Assessment Chronic Illness Therapy – Fatigue (FACIT-Fatigue (42)), Pittsburgh Sleep Quality Index (PSQI (43)) and Center for Epidemiologic Studies Depression Scale (CES-D (44)). Furthermore, patients reported presence/absence of any current musculoskeletal pain.

Based on the presence/absence of current self-reported pain or pre-diagnosed PsA, patients were placed in 'PsO pain', 'PsO no pain' or 'PsA' group.

2.3.6 *Classification of PsA*

Classification of PsA was made by: 1) conventional CASPAR criteria (45); 2) US-modified CASPAR criteria where either "US synovitis" and "US enthesitis" ("US CASPAR") or "CD+ synovitis" and "US enthesitis" ("CD+ CASPAR") were accepted as CASPAR entry criterion, and; 3) US -only criteria defined as either presence of ≥2 sites with "US synovitis" or "US enthesitis" ("US defined PsA") or ≥2 sites with "CD+ synovitis" or "US enthesitis" ("CD+ defined PsA").

2.3.7 *Statistical methods*

For all patients and above defined subgroups demographic, anamnestic, clinical, PROs and US characteristics were described using numbers(%) for binary variables, and median(IQR) for continuous variables. Subgroups were compared using Fisher's exact test or Mann-Whitney U test, as appropriate. Correlations between clinical and imaging parameters and PROs were calculated as Spearman's correlation coefficient, with Rho defined as: negligible <0.2, weak 0.2–0.39, moderate 0.40–0.59, strong 0.60–0.79 and very strong ≥0.8. To investigate the association between anamnestic and clinical variables and "US defined PsA"/"CD+ defined PsA" univariable and multivariable logistic regression analyses were performed with Odds ratios (OR) adjusted for sex and age. The predictive ability of screening-questionnaires for subsequent classification of PsA (by CASPAR, "US CASPAR"/"CD+ CASPAR" and "US defined PsA"/"CD+ defined PsA") was evaluated using the area under the curve (AUC) of receiver operating characteristic (ROC) curves, and the screening-questionnaires' sensitivities, specificities, negative and positive predictive values at recommended cut-off values were determined. The statistical significance level was set to $p<0.05$. Analyses were performed with statistical software R, version 3.6.1.

2.4 Part 3

2.4.1 *Study design and patients*

Patients with joint and/or entheseal inflammation documented by US in part 2 were invited to participate in a 12 months' follow up study. Patients reporting pain in the area of the US findings were included in an interventional part of the study (part 3a), whereas patients without musculoskeletal pain but with US findings were included in a non-interventional part of the study (part 3b). The interventional study (3a) consisted of 6-month induction therapy with apremilast (in addition to their usual therapy) followed by cessation of apremilast and 6 months of observation. Clinical examination, PROs, blood sampling and US examinations were performed at months 3, 6, 9 and 12. The non-interventional study (3b) consisted of same examinations and visits as above, with patients continuing their current therapy. In a substudy, patients with clinical dactylitis or enthesitis in the ankle region (Achilles enthesitis or plantar fasciitis) had MRI performed at inclusion and at 6 months follow-up.

Patients with pre-diagnosed PsA that by US had active inflammation, was also invited to participate in the interventional study according to above criteria if in non/stable synthetic DMARD treatment and not currently in biologic DMARD treatment, otherwise they were invited to participate in non-interventional study. PsO patients fulfilling inclusion criteria for part 3a, but who could not be included due to exclusion criteria were also included in part 3b.

Important exclusion criteria included known inflammatory rheumatic disease other than PsA and current treatment with biological DMARDs for both part 3a and 3b, and for part 3a additionally contraindications for apremilast treatment.

2.4.2 *Definition of ultrasound inflammation*

The primary inclusion criteria for part 3, US inflammation, was defined as "CD+ defined PsA" as described in part 2, i.e. (in the presence of PsO) presence of ≥2 joints with "CD+ synovitis" OR presence of ≥1 joint with "CD+ synovitis" plus ≥1 enthesis with "US enthesitis", OR presence of ≥2 entheses with "US enthesitis". "CD+ synovitis" was defined as GS synovial hypertrophy grade ≥2

plus CD grade ≥1, whereas "US enthesitis" was defined as presence of CD grade ≥1 plus hypoechogenicity and/or thickening of the enthesis.

2.4.3 *Examinations*

Clinical examinations of 66/68 joints for swelling/tenderness and 18 entheses for tenderness as well as count of dactylitic digits, skin and nail evaluation and US examination was performed at all visits (3, 6, 9, and 12 months) for both part 3a and 3b as described under part 2. PROs included DLQI, HAQ-DI, Global VAS, Pain VAS, Fatigue VAS, PsAID, EQ5D, SF-36, FACIT-Fatigue, PSQI and CES-D at all visits. Blood samples for analyses of CRP were drawn at all visits. Conventional radiography of hands and feet was repeated at 12 months visit.

In a substudy, MRI of a dactylitic digit or a tender enthesis at the ankle/heel region was performed at baseline and the 6 months visit. Target area was selected at baseline. MRI included pre- and post-contrast T1-weighted images in 2 planes plus a short tau inversion recovery (STIR) sequence in 2 planes.

2.4.4 *Treatment*

In the interventional part of the study (part 3a) apremilast was dosed according to the prescription information, as approved by the Danish health authorities for psoriatic arthritis with titration according to a schedule from day 1 to 6 up to 30mg x 2 daily from day 7 up to the end of month 6. For the non-interventional part (3b), any changes in medication were registered.

2.4.5 *Statistical methods*

Within part 3, changes from baseline in clinical, biochemical, US, MRI, and PROs were to be assessed by paired tests (paired t-test if normal distribution, Wilcoxon-Pratt test if not normally distributed). A multiple regression analysis was to be performed to investigate predictors of response.

3 RESULTS

3.1 Part 1

A total of 561 patients who reported physician-diagnosed PsO and completed the full questionnaire were included in the study (**Figure 1.1**).

3.1.1 *Prevalence of musculoskeletal pain*

The prevalence of self-reported pain in joints or tendons (musculoskeletal pain) in patients with PsO without diagnosed PsA (n=453) were: 130 (29%) with current pain and 104 (23%) with previous but not current pain (16% within the past 12 months). In total, 45% of patients with PsO without diagnosed PsA reported pain now or within the past 12 months.

3.1.2 *Characteristics and pain pattern of patients with psoriasis and musculoskeletal pain*

Demography and characteristics of the subgroups are shown in **Table 1.1**. Patients with PsO and current or previous pain were more frequently female, were younger, had a higher body mass index (BMI) and a higher frequency of patients not currently working/studying or retired, compared to patients with PsO without pain. While skin and nail involvement did not differ between PsO patients with and without pain, symptoms suggestive of PsA, i.e. dactylitis and enthesitis, were

more frequent in patients with pain. The pattern of skin lesions showed a higher frequency of especially genital/skinfold- and nail-involvement in patients with PsA compared to the other groups (**Figure 1.2a**). The pattern of pain was similar in patients with PsA and PsO with pain, with the exception that wrists, fingers, ankles, and toes were more frequently involved in PsA patients (**Figure 1.2b**).

Contact to specialists in dermatology and rheumatology, time from symptom onset to diagnosis, and treatment are shown in **Table 1.1** (healthcare contact and treatment). Most respondents had been examined by a dermatologist at some point, while it varied for examinations by a rheumatologist. Contacts to specialist in dermatology and rheumatology are shown in **Figure 1.3**, where it is seen that 72% of patients in 'PsO-pain-ever' had never been examined by a rheumatologist. Diagnostic delay (time from symptom debut to diagnosis) was 1.5 (1-3) years for PsO and 7.5 (1.5-12.5) for PsA. Treatment with both methotrexate and biological DMARDs were more common in patients in the 'PsA' group compared to the other groups, and the 'PsO-pain-ever' group had significantly higher use of bDMARDs than the 'PsO-no-pain-ever' group.

Patients' perception of severity of PsO and PsA and satisfaction with current treatment was reported on a five-level scale (**figure 1.4**). Severity of PsO (**figure 4a**) was perceived highest in patients in the 'PsA' group, followed by 'PsO-pain-ever' and 'PsO-no-pain-ever'. Severity of PsA was reported higher than for PsO. Satisfaction with treatment of PsO (**figure 1.4c**) was relatively high in all groups, although lower in 'PsO-pain-ever' compared to 'PsO-no-pain-ever'. Satisfaction with PsA treatment was lower than for PsO (**figure 1.4d**).

3.1.3 *Relation between musculoskeletal pain and patient-reported outcomes*

HRQoL measures (DLQI score and EQ5D index) were worse in patients with PsO and current pain than in patients without current pain, and at the level of patients with PsA (**Table 1.1**). PsAID and HAQ were only obtained in patients with pain and patients with PsA. Both scores were better in patients with PsO and pain, compared to patients with PsA. The correlation between level of pain (EQ5D pain/discomfort) and PROs (**Table 1.2**) were strongest for EQ5D index (Spearman's rho = -0.81, all patients), followed by HAQ (rho=0.65) and PsAID (rho=0.54), and weaker for DLQI (rho=0.26). Both HAQ an PsAID showed stronger correlation with pain level in patients with PsA compared to patients with PsO and pain.

3.2 Part 2

In total, 126 patients with physician-diagnosed PsO from the survey (part 1) were included in the clinical study (part 2) (**Figure 2.1**). Presence of musculoskeletal pain was reported by 79 patients (63%), while 36 patients (29%) reported no pain, and physician-diagnosed PsA was reported by 11 patients (9%).

3.2.1 *Prevalence and pattern of clinical and ultrasound signs of inflammation*

Clinical scores of inflammation. i.e. tender/swollen joint counts, tender entheses counts, dactylitis scores etc. were overall low (**Table 2.1**). Parameters dependent on tenderness (i.e. TJC, entheses indices, fibromyalgia TPC and composite scores) were higher in patients with self-reported pain than patients without pain, while parameters not dependent on tenderness (SJC, dactylitis, and CRP) were not found different between these two groups. Erosions on radiographs were found in 14% of

patients with PsO and pain, which was numerically different from patients without pain (8%) and patients with PsA (36%). US signs of inflammation were more frequent in PsO patients with pain than patients without pain, with differences most pronounced for GS lesions. Synovitis including CD ("CD+ synovitis") was found in 35% of patients with musculoskeletal pain, compared to 19% of PsO patients without pain, and corresponding numbers for the more inclusive "US synovitis" was 71% compared to 44%. In contrast, "US enthesitis" was found with similar frequencies in all groups (16% of the total population). Pattern of synovitis and enthesitis are shown in **Figure 2.2**.

3.2.2 *Association between musculoskeletal pain and patient-reported outcomes*

Overall, PROs in patients with PsO and pain were found worse than in patients with PsO without pain, and comparable to patients with PsA. Sleep disturbances (PSQI score) were worse in patients with PsO and pain compared to PsA, and the same tendency was found for fatigue (Pt fatigue VAS and FACIT-fatigue) and depression (CES-D) (**Table 2.1**).

3.2.3 *Correlations between clinical and ultrasound signs of inflammation and patient-reported outcomes*

PROs were negligibly-moderately correlated with tenderness-related clinical scores, i.e. TJC, SPARCC, LEI and TPC (**Table 2.2**) (Spearman's rho=0.11-0.59, all patients), SJC was weakly correlated to HAQ-DI (rho=0.19), and negligibly to Pt pain VAS (rho=0.24), while PASI was moderately correlated to DLQI (rho=0.5) and inversely to SF36-MCS (rho=0.18). PROs were negligibly-weakly correlated with US sum-scores (rho=0.01-0.34), and stronger correlated with "US synovitis" than "CD+ synovitis" and not correlated with "US enthesitis". FACIT-fatigue, PSQI and CES-D showed no significant correlations with US sum-scores.

3.2.4 *Ultrasound in classification of psoriatic arthritis*

When US synovitis/enthesitis was included in in addition to clinical evaluation in the CASPAR entry criterion, more patients could be classified with PsA ("US CASPAR" criteria, 66% of all patients, "CD+ CASPAR" criteria 54%) compared to conventional CASPAR criteria (35%)(**Table 2.1**). Higher numbers were seen in patients with PsO and pain than patients with PsO without pain.

PsA classification based only on US, requiring PsO and minimum two US inflamed sites, classified less patients than criteria combining CASPAR and US ("US defined PsA", 52%, "CD+ defined PsA", 17%) (**Table 2.1**). Associations between anamnestic and clinical parameters and "US defined PsA" in patients with PsO was explored in univariate logistic regression analysis (**Table 2.3**). Associated anamnestic parameters were the presence of joint pain, joint swelling and unspecific musculoskeletal pain. Associated clinical variables were higher TJC and Physician VAS. For "CD+ defined PsA", no anamnestic parameters were significantly associated, and the only associated clinical variables were higher SJC and Physician global VAS. Multivariable analyses found Physician global VAS to be the only independent variable significantly associated with both US definitions (OR(95%CI) 1.3(1.1-1.6) and 1.1(1.0-1.3), for "US defined PsA" and "CD+ defined PsA", respectively).

3.2.5 *The ability of screening questionnaires in identifying patients with psoriatic arthritis*

The sensitivities of the various screening-questionnaires for identifying PsA were low for conventional CASPAR classification-criteria (0.23-0.66), US-modified CASPAR (0.17-0.57) and US-only (0.20-0.57) criteria (**Table 2.3**). Specificities were relatively low (<0.70), except for PEST (≥0.90).

3.3 Part 3

A total of 7 patients were included in this multi-center follow-up study. In the interventional part (part 3a) 2 patients were included. One patient had dactylitis and was additionally included in the MRI substudy. None of the two patients completed the study. Reasons for withdrawal in part 3a were severe worsening of the inflammatory joint disease in one of the patients, the other patient was withdrawn due to termination of the study.

In the non-interventional part (part 3b) 5 patients were included; all completed.

As a consequence of the low number of participants, the study was prematurely terminated. No analyses of the follow-up data have been made as the numbers are too small to evaluate the protocolled outcomes.

4 DISCUSSION

4.1 Part 1

In this population-based survey of Danish patients with PsO, patterns of pain, skin symptoms, health-care contacts, treatment, disability and HRQoL were described. musculoskeletal pain was frequent in patients with PsO without diagnosed PsA, and patients with PsO with musculoskeletal pain had lower HRQoL than patients with PsO without musculoskeletal pain. A high proportion of PsO patients with musculoskeletal pain had never been examined by a rheumatologist.

Patients with PsO were in our study found to have a prevalence of 45% for self-reported musculoskeletal pain within the past 12 months (Paper I), which is very similar to that found in a large multinational survey (44%)(46) and in a Scandinavian study (42%)(47).

We found that the patients with PsO and musculoskeletal pain had a higher proportion of self-reported ‘clinical’ features suggestive of dactylitis and enthesitis as compared to patients with PsO without musculoskeletal pain, while skin and nail involvement were similar in the two groups. It has previously been shown that PsO patients with psoriatic lesions in the scalp, skinfolds and nails are at risk of developing PsA (48). Though the psoriatic lesions in these locations did not differ between patients with PsO with and without musculoskeletal pain in our cohort, patients with diagnosed PsA as expected had more nail psoriasis, as well as genital and skinfold involvement. The degree of pain (EQ5D pain/discomfort score) was not significantly different between patients with PsA and PsO with musculoskeletal pain. When looking at the location of pain, patients with PsA in our study reported a higher frequency of pain in wrists, fingers, ankles and toes as compared to patients with PsO and musculoskeletal pain who most frequently reported of pain in knees and fingers. In the general Danish population, where musculoskeletal complaints (discomfort/pain) are also frequent (40%) (49), complaints are most frequently reported in low back, neck, shoulders and knees (49).

We found that patients who reported physician-diagnosed PsA had a long diagnostic delay, that more than half of these patients did not see a rheumatologist regularly and that treatment rates for both conventional synthetic and biological disease-modifying anti-rheumatic drugs (DMARDs) were low compared to findings in other Scandinavian countries (47). Furthermore, we found that three out of four patients with PsO and musculoskeletal pain had never been examined by a rheumatologist. Our findings support previous statements of underdiagnosis and undertreatment of PsA patients (5, 25, 50, 51), and raises the question of the prevalence of undiagnosed PsA in patients with PsO, and especially in patients with musculoskeletal pain as this have been found to be a predictor for PsA (52, 53).

PsA is known to have a worse impact on HRQoL (6, 46, 54) and work productivity (50, 55) than PsO alone, but the group of patients with PsO and musculoskeletal pain has in larger studies only been studied separately regarding specific outcomes such as disability (46). We therefore investigated HRQoL and other related PROs in this subgroup of PsO patients and found that patients with PsO and musculoskeletal pain had worse HRQoL, lower occupational attachment, lower PsO treatment satisfaction and higher perception of PsO severity compared to patients with PsO without pain, and comparable to scores of patients with PsA, despite comparable BSA. Disability was still reported higher in PsA patients than in patients with PsO and pain, which is in line with results of the international population-based survey (46).

In conclusion, we found that almost half of patients with PsO without diagnosed PsA have musculoskeletal pain and that this subgroup of patients has significantly worse HRQoL compared to patients with PsO without musculoskeletal pain (at a level comparable to patients with PsA). Three out of four have never been examined by a rheumatologist. This demonstrates an unmet need for adequate evaluation of the cause of pain in these patients, as early diagnosis and treatment of possible PsA could improve quality of life and prevent further deterioration in physical function in these patients.

4.2 Part 2

In the cross-sectional clinical study of patients with PsO sampled from the population-based survey, we found that musculoskeletal pain was related to US findings of inflammation in patients with PsO. US-modified CASPAR criteria were able to classify almost twice as many patients with PsA than conventional CASPAR criteria, while screening questionnaires had limited value in correctly identifying patients with PsA.

Patients with PsO and musculoskeletal pain had higher scores of clinical parameters indicative of PsA, compared to patients without pain. In line with the perception of a possible preclinical phase in PsA (56) where pain precedes more ‘objective’ signs of disease, the most prominent differences were seen in tenderness-dependent scores (TJC, enthesis indices, TPC), including composite scores, whereas other clinical examinations (SJC, dactylitis, CRP) did not differ. Similarly, PROs were closer related to tenderness-dependent clinical scores than those that did not include tenderness.

Regarding US findings, especially GS changes were more frequently found in patients with PsO and pain than in those without pain, while such differences were less pronounced for CD activity. In contrast, “US enthesitis” was equally frequent in PsO with and without pain and in PsA - concurring with the high frequency of subclinical enthesitis, and low agreement with clinical tenderness, seen in PsO patients in other studies (57-59). A recent US study of PsO patients with

joint pain (60) similarly found higher frequencies of US synovitis in patients with compared to without joint pain, but in contrast to us also found higher frequencies of active enthesitis. Their exclusion of patients with osteoarthritis and fibromyalgia may explain this difference. Another recent study of patients with PsO and musculoskeletal pain (61) found a slightly higher number of patients with US inflammation with power Doppler activity (59.1%) compared to our study (48% with "CD+ inflammation"). The inclusion of tenosynovitis or peri/paratenonitis in their definition may explain this discrepancy. In all, data indicate that musculoskeletal pain in PsO is related to objectively verifiable inflammation.

When classifying patients according to conventional CASPAR criteria, the overall frequency of PsA was high (35%) compared to other studies (4-34%) (62, 63). However, our population was not restricted to primary care and included a high number of patients with pain and some with PsA. When allowing US synovitis and enthesitis as a CASPAR entry criterion in line with clinically evaluated arthritis/enthesitis/axial arthritis, we found that twice as many patients (66%) could be diagnosed with PsA. Subclinical US inflammation in PsO and PsA have previously been seen in several studies (15, 57, 64), but the added value of this in classification of PsA has, to our knowledge, not been investigated.

Screening-questionnaires had low values for prediction of PsA classification, and sensitivities for CASPAR were lower than those found in other studies (24-27, 65). A recent meta-analysis (65) found EARP to have the highest sensitivity and specificity, whereas we found all questionnaires to be comparable apart from PEST that stood out as being less sensitive but more specific. Overall, our data do not support the utility of the questionnaires for identifying patients with PsA.

In conclusion, we found that self-reported pain in PsO is related to inflammation verifiable by US. Adding US inflammation to CASPAR criteria identified almost twice as many patients as conventional CASPAR criteria (66% compared to 35%), while screening-questionnaires had limited value. Our data suggest that US would improve the process of identifying patients with PsA, which could potentially lead to earlier treatment of pain caused by inflammation. This, however, needs validation in future studies.

4.3 Part 3

The number of patients available for inclusion in the follow-up study was much smaller than expected. The number of eligible patients was marginally increased by making inclusion criteria somewhat less strict and additionally by recruiting patients from a department of dermatology, but this did not have sufficient effect.

The main aim of this part of the study was to evaluate the effect of treatment on US defined PsA on clinical, imaging and patient-reported outcome measures. This is still of high interest, especially in the light of the conclusion of part 2 of the study. Efforts are therefore being made to evaluate possible explanations for the low number of patients available for inclusion.

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6 TABLES AND FIGURES

Table 1.1. Demographics, clinical features of psoriasis/psoriatic arthritis, health-care contacts, treatment, quality of life and disability of all patients and for defined subgroups, Study Part 1. *SK Felbo et al, Acta Derm Venereol. 2021*

DEMOGRAPHICS								
	All	**PsO no pain ever**	**PsO previous pain[¤]**	**PsO pain now**	**PsA**	p-value*		
No. of patients	561	178	104	130	108			
Sex (male)	212 (38%)	79 (44%)	34 (33%)	36 (28%)	40 (37%)	0.02		
Age (y)	58 (43-68)	58 (43-68)	55.5 (42-63)	53 (43-63)	58 (48-68)	0.05		
BMI	27 (24-32)	26 (23-30)	28 (24-32)	29 (25-33)	28 (24 -33)	0.01		
Smoking status (current smoker)	142 (25%)	44 (25%)	31 (30%)	33 (26%)	26 (24%)	0.77		
Excessive alcohol use [a]	73 (13%)	22 (13%)	10 (10%)	21 (16%)	13 (12%)	0.50		
Occupational status (not working/studying/retired)	119 (21%)	20 (11%)	23 (22%)	34 (26%)	35 (32%)	<0.001		
PsO/PsA FEATURES								
	All	**1. PsO no pain ever**	**2. PsO pain ever**	**3. PsA**	**1 vs. 2**	**1 vs. 3**	**2 vs. 3**	
No. of patients	561	178	234	108				
BSA (%)[b]	1 (1-2)	1 (1-2)	1 (1-2)	2 (1-2)	0.10	<0.001	0.01	
Nail psoriasis [c1]	134 (24%)	27 (15%)	50 (21%)	46 (48%)	0.13	<0.001	<0.001	
'Dactylitis' [c2]	80 (14%)	2 (1%)	34 (15%)	40 (42%)	<0.001	<0.001	<0.001	
'Enthesitis' [c3]	74 (13%)	4 (2%)	30 (13%)	39 (41%)	<0.001	<0.001	<0.001	
HEALTHCARE CONTACT AND TREATMENT								
Examined by dermatologist	462 (82%)	148 (83%)	192 (82%)	85 (90%)	0.80	0.20	0.10	
Examined by rheumatologist	163 (29 %)	14 (8%)	65 (28%)	79 (73%)	<0.001	<0.001	<0.001	
Time from symptom onset to diagnosis – PsO (y)	1.5 (1-3)	1.5 (1-7.5)	1.5 (1-3)	1.5 (1-7.5)	0.19	0.74	0.17	

Time from symptom onset to diagnosis – PsA (y)	-	-	-	7.5 (1.5-12.5)	-	-	-
Methotrexate (current)	51 (9%)	6 (4%)	14 (6%)	30 (29%)	0.25	<0.001	<0.001
Biological DMARDs (current)	31 (6%)	2 (1%)	12 (5%)	17 (16%)	0.03	<0.001	0.003
QUALITY OF LIFE AND DISABILITY							
	All	**1. PsO no pain now**	**2. PsO pain now**	**3. PsA**	**1 vs. 2**	**1 vs. 3**	**2 vs. 3**
No. of patients	561	282	130	108			
DLQI score (0-30)	2 (1-5)	1 (1-4)	2 (1-5)	2 (1-6)	0.001	0.04	0.52
EQ5D index (0-1)	0.797 (0.691-0.859)	0.859 (0.768-1)	0.732 (0.679-0.859)	0.702 (0.598-0.802)	<0.001	<0.001	0.53
EQ5D global VAS (0-100)	78 (60-90)	82 (70-91)	70 (50-81)	67 (42-81)	<0.001	<0.001	0.45
HAQ score[d] (0-3)	0.625 (0-1.25)	-	0.5 (0-0.875)	0.875 (0.125-1.375)	-	-	0.03
PsAID score[d] (0-10)	3.7 (1.7-5.9)	-	2.9 (1.0-5.1)	4.6 (2.4-6.8)	-	-	<0.001

Numbers are numbers (%) for binary variables and median (interquartile range) for continuous variables.

BMI: Body Mass Index, BSA: Body Surface Area covered with psoriasis, DLQI: Dermatology Life Quality Index, DMARDs: Disease-modifying antirheumatic drugs, EQ5D: European Quality of life-5 Dimensions, HAQ: Health assessment questionnaire Disability Index, PsA: Psoriatic arthritis, PsAID: Psoriatic Arthritis Impact of Disease, PsO: Psoriasis, VAS: Visual analogue scale, y: years.

*p-value: Demographics: test between multiple groups (Chi-square test for binary data, Kruskal-Wallis test for continuous data). PsO/PsA features, Healthcare contact and treatment, Quality of life and disability: Pairwise testing (Fishers exact test for binary data, Mann-Whitney U test for continuous data)

¤PsO previous pain: Patients with psoriasis with pain in the past, but not now.

a. Excessive use defined as more than maximum recommended use by Danish authorities (>14 standard drinks(12g)/week for men, >7 standard drinks/week for women)

b. Derived from self- reported sum of palm-sized areas of psoriasis

c. "Which symptoms or problems have you had in the past 12 months due to your psoriasis?" 1. Nail psoriasis 2. Swollen entire finger or toe (sausage digit) 3. Tender or swollen tendon (e.g. at heel or elbow).

d. Answered by patients with PsO with pain now and patients with PsA.

Table 1.2. Correlations between self-assessed severity of psoriasis and psoriatic arthritis, and level of pain/discomfort and different patient-reported outcomes, Study Part 1. *SK Felbo et al, Acta Derm Venereol. 2021*

	All	PsO no pain now	PsO pain now	PsA
No. of patients	561	282	130	108
Self-assessed severity of psoriasis (1-5)				
BSA (0-100)	0.57***	0.55***	0.55***	0.53***
DLQI score (0-30)	0.65***	0.60***	0.66***	0.65***
EQ5D index (0-1)	-0.29***	-0.29***	-0.24**	-0.17
EQ5D VAS (0-100)	-0.28***	-0.21***	-0.29***	-0.18
PsAID score (0-10)	0.39***	-	0.40***	0.32**
HAQ score (0-3)	0.16**	-	0.23*	0.09
Self-assessed severity of psoriatic arthritis (1-5)				
BSA (0-100)	-	-	-	0.17
DLQI score (0-30)	-	-	-	0.13
EQ5D index (0-1)	-	-	-	-0.29***
EQ5D VAS (0-100)	-	-	-	-0.50***
PsAID score (0-10)	-	-	-	0.39***
HAQ score (0-3)	-	-	-	0.16**
EQ5D pain/discomfort (1-5)				
BSA (0-100)	0.21***	0.19**	0.15	0.21*
DLQI score (0-30)	0.26***	0.25***	0.15	0.16
EQ5D index (0-1)	-0.81***	-0.78***	-0.69***	-0.85***
EQ5D VAS (0-100)	-0.62***	-0.50***	-0.59***	-0.66***
PsAID score (0-10)	0.54***	-	0.40***	0.69***
HAQ score (0-3)	0.65***	-	0.59***	0.71***

Numbers are Spearman's correlation coefficient (rho). Statistical significance shown as: *p<0.05, **p<0.01, ***p<0.001.
BSA: body surface area, DLQI: dermatology life quality index, EQ5D: EuroQol-5 Domain, HAQ: Health assessment questionnaire, VAS: visual analogue scale. PsAID: Psoriatic Arthritis Impact of Disease.

Figure 1.1. Patient disposition Study Part 1. *SK Felbo et al, Acta Derm Venereol. 2021*

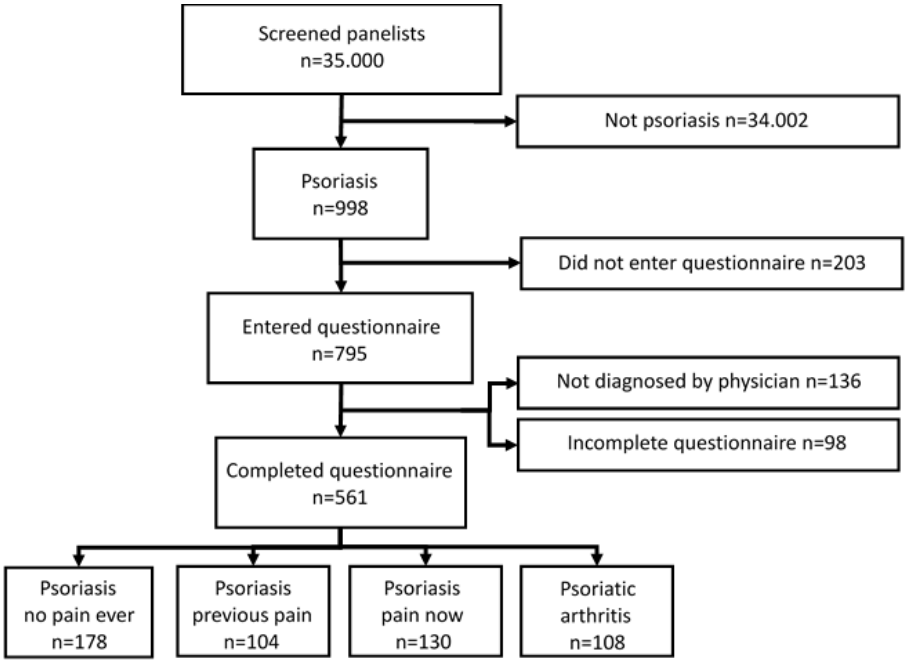

Figure 1.2. Location of (a) psoriasis (past 12 months) and (b) musculoskeletal pain in participants in the defined subgroups, Study Part 1. Statistical significance of pairwise test between the groups (by Fishers exact test) displayed as: *<0.05, **<0.01, ***<0.001. PsO: psoriasis, PsA: psoriatic arthritis. *SK Felbo et al, Acta Derm Venereol. 2021*

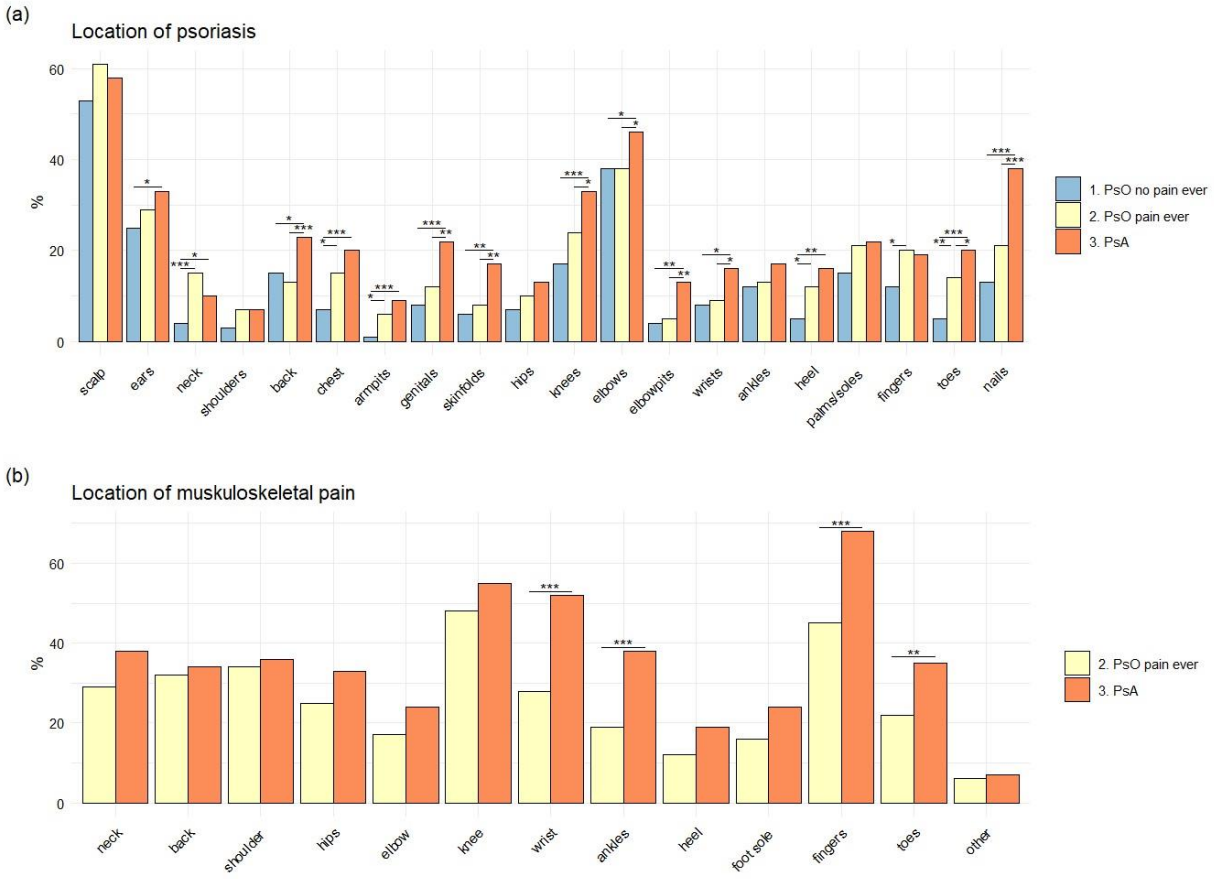

Figure 1.3. Contacts to (a) dermatologist and (b) rheumatologist for participants in the three subgroups, Study Part 1. PsO: psoriasis, PsA: psoriatic arthritis. *SK Felbo et al, Acta Derm Venereol. 2021*

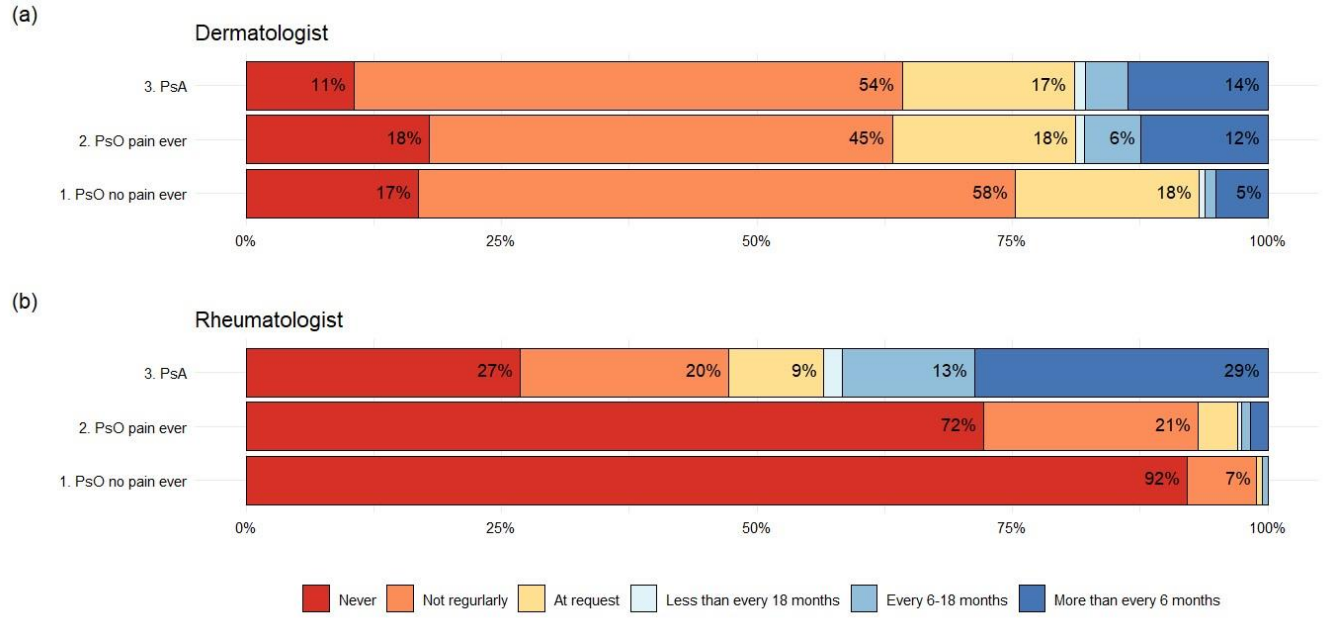

Figure 1.4. Self-assessed severity of (a) psoriasis and (b) psoriatic arthritis, and satisfaction with treatment of (c) psoriasis and (d) psoriatic arthritis in the defined subgroups, Study Part 1. PsO: psoriasis, PsA: psoriatic arthritis. *SK Felbo et al, Acta Derm Venereol. 2021*

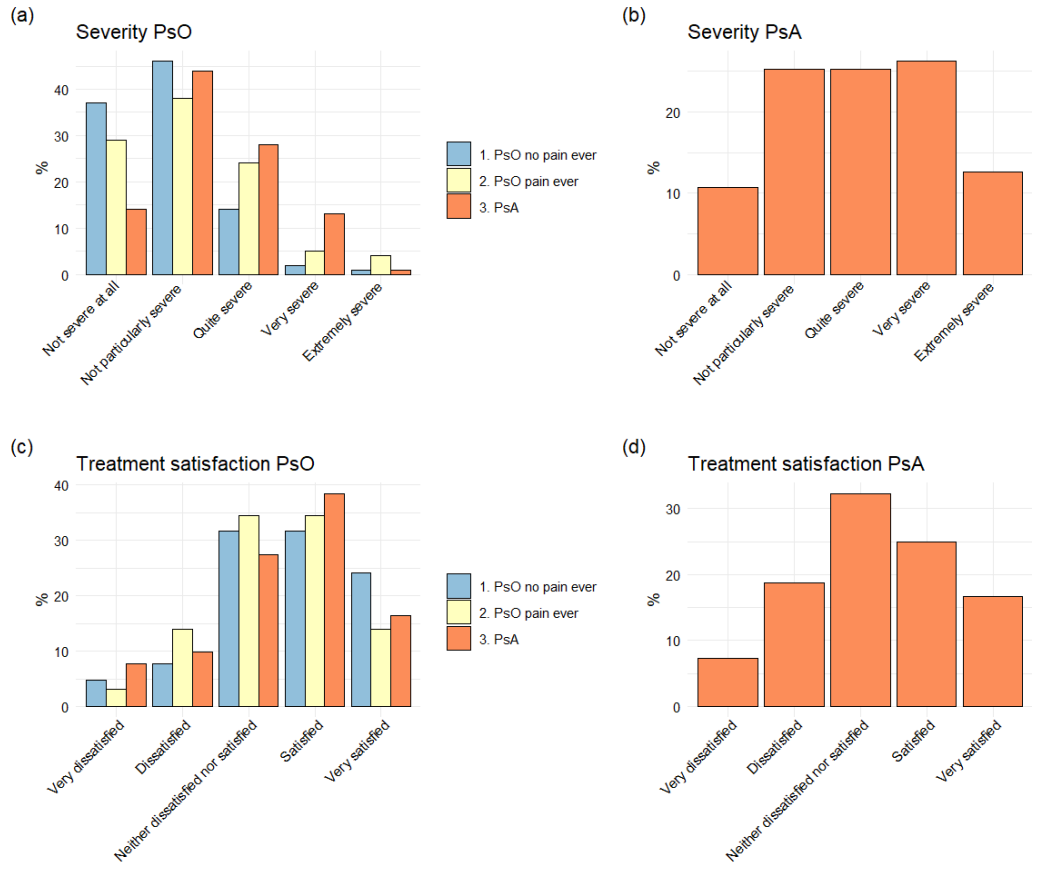

Table 2.1. Characteristics of all patients and subgroups (based on patients' reports of musculoskeletal pain) and estimates of the differences between patients with PsO and pain and patients with PsO without pain and with PsA, respectively, Study Part 2. *Numbers from table by SK Felbo et al Rheumatology (Oxford), 2021.*

	All (n=126)	**PsO no pain** (n=36)	**PsO pain** (n=79)	**PsA** (n=11)	**PsO no pain vs PsO pain**	**PsO pain vs PsA**
	median (IQR)/ no. (%)				difference in medians (95% CI) /OR (95% CI)	
DEMOGRAPHY						
Sex (female)	68 (54)	17 (47)	33 (42)	6 (55)	0.6 (0.3-1.5)	1.8 (0.4-7.9)
Age (years)	57 (47-66)	59 (47-67)	57 (47-66)	55 (51-71)	1 (-4-6)	-3 (-12-6)
Body Mass Index, kg/m²	27.8 (24.6-34.4)	26.8 (24.2-32.0)	28.4 (24.8-34.8)	27.1 (21.9-29.9)	-1.7 (-4-0.8)	3.3 (-1.3-7.3)
Smoking (current)	25 (20)	7 (19)	16 (20)	2 (18)	1.1 (0.4-3.7)	0.9 (0.1-4.9)
Disease duration PsO (years)	26 (12-39)	23 (11-34)	25 (11-39)	36 (30-40)	-0.9 (-8-5.7)	-9.3 (-20.2-0.6)
Disease duration PsA (years)	NR	NR	NR	16 (11-26)	NR	NR
Methotrexate	11 (9)	2 (6)	4 (5)	5 (46)	1.1 (0.1-8.1)	0.1 (0.0-0.4)**
Biological DMARDs	5 (4)	0 (0)	1 (1)	4 (36)	0.0 (0-85.5)	0.0 (0-0.3) **
NSAID	23 (18)	5 (14)	14 (18)	4 (36)	0.8 (0.2-2.5)	0.4 (0.1-2.0)
CLINICAL SCORES						
SJC (0-66)	0 (0-0.8)	0 (0-0)	0 (0-1)	1 (0-2)	0 (0-0)	0 (-1-0)*
TJC (0-68)	1 (0-3)	0 (0-1)	2 (0-5)	1 (0-8)	-1 (-2-0)***	0 (-2-2)
SPARCC (0-16)	0 (0-2)	0 (0-0)	1 (0-2)	1 (0-3)	0 (-1-0)**	0 (-1-1)
TPC (0-18)	0 (0-2)	0 (0-0)	1 (0-5)	2 (0-6)	-1 (-2-0)***	0 (-2-1)
No. of pts with dactylitis ≥1	3 (2)	0 (0)	2 (3)	1 (9)	0 (0-11.7)	0.3 (0.0- 16.8)
PASI (0-72)	1.5 (0.4-3.6)	1.7 (0.5-3.3)	1.5 (0.2-4.2)	0.6 (0.2-1.6)	0.1 (-0.7-0.8)	0.6 (-0.2-2.1)
Nail psoriasis, no. of pts	55 (44)	21 (58)	26 (33)	8 (73)	2.8 (1.2-7.0)*	0.2 (0.0-0.9)*
Physician VAS (0-100)	2 (0-5)	0 (0-1)	3 (1-6)	9 (5-17)	-3 (-4--2)***	-5 (-10--1)*
CRP (mmol/l)	2.1 (0.5-4)	2.5 (0.4-4)	2.1 (0.5-4.1)	1.5 (0.8-5.2)	0 (-0.6-0.6)	-0.2 (-1.4-1.9)
PATIENT-REPORTED OUTCOMES						

	All (n=126)	**PsO no pain** (n=36)	**PsO pain** (n=79)	**PsA** (n=11)	**PsO no pain vs PsO pain**	**PsO pain vs PsA**
Global VAS (0-100)	9 (0-34)	0 (0-1)	16 (4-45)	26 (16-46)	-16 (-31--10)***	-6 (-22-10)
Pain VAS (0-100)	11 (0-33)	0 (0-1)	20 (5-39)	28 (9-55)	-18 (-26--12)***	-5 (-25-9)
Fatigue VAS (0-100)	27 (11-56)	10 (0-25)	48 (21-59)	20 (9-63)	-24 (-38--14)***	6 (-12-28)
HAQ-DI (0-3)	0.13 (0.00 -0.50)	0.00 (0.00-0.00)	0.25 (0.00-0.69)	0.38 (0.06-1.25)	-0.13 (-0.38- -0.12)***	-0.12 (-0.50-0.13)
DLQI (0-30)	1 (1-3)	1 (0-2)	2 (1-4)	1 (0-3)	-1 (-1-0)*	1 (-1-2)
PsAID (0-10)	1.0 (0.2-2.9)	0.2 (0.0-0.7)	1.4 (0.6-4.0)	2.3 (1.3-4.4)	-1.0 (-2.1--0.6)***	-0.6 (-2.0-0.6)
EQ5D index (0-1)	0.81 (0.73-1.0)	1.0 (0.86-1.0)	0.79 (0.69-0.86)	0.80 (0.67-0.84)	0.19 (0.14-0.21)***	0.00 (-0.07-0.10)
SF36-PCS (0-100)	50 (37-55)	56 (54-58)	42 (34-53)	46 (31-48)	11.8 (7.0-16.8)***	2.9 (-5.5-10.7)
SF36-MCS (0-100)	56 (46-60)	59 (48-61)	53 (39-58)	59 (54-60)	3.1 (0.2-6.6)*	-3.1 (-10.0-0.9)
FACIT fatigue (0-52)	9 (3-19)	2 (1-7)	13 (6-22)	11 (6-20)	-8 (-12--5)***	2 (-5-8)
PSQI (0-21)	6 (4-10)	4 (2-7)	8 (5-12)	5 (5-6)	-3 (-5--2)***	2 (0-5)*
CES-D (0-60)	6.5 (2-13.8)	3.5 (1-9.3)	8 (4-16)	6 (4-9)	-4 (-7--1)**	2 (-2-7)
COMPOSITE SCORES						
DAS28-CRP (0-10)	1.8 (1.4-2.4)	1.5 (1.1-1.6)	1.6 (1.5-2.6)	2.2 (1.7-2.8)	-0.6 (-0.8--0.3)***	-0.2 (-0.8-0.3)
DAPSA (0-164)	6.9 (3.3-15.4)	4 (1.2-5.2)	5.2 (4.1-20.7)	11.5 (6.8-17.8)	-6.3 (-10--2.9)***	-1.9 (-7.5-5.3)
mCPDAI (0-12)	2 (1-3.75)	1 (1-2)	3 (1-4)	3 (2-4)	-1 (-2-0)***	0 (-1-1)
RADIOGRAPHY						
Erosions, no of pts	18 (14)	3 (8)	11 (14)	4 (36)	0.5 (0.1-2.3)	0.3 (0.1-1.6)
Proliferations, no of pts	10 (8)	2 (5)	7 (9)	1 (9)	0.6 (0.1-3.3)	1.0 (0.1-48.1)
ULTRASOUND CHANGES						
GS sum-score (0-144)	11 (4-18)	6 (1-13)	11 (4-19)	16 (12-35)	-4 (-8-0)*	-8 (-17--1)*
CD sum-score (0-144)	0 (0-1)	0 (0-0)	0 (0-1)	0 (0-2)	0 (0-0)*	0 (-1-0)
US synovitis, sum-score (GS≥2 OR CD≥1) (0-48)	1.5 (0-4)	0 (0-2)	2 (0-4)	6 (2-9)	-1 (-2-0)*	-2 (-6-0)*
US synovitis, no. of pts	82 (65)	16 (44)	56 (71)	10 (91)	0.3 (0.1-0.8)*	0.2 (0.0-1.9)
CD+ synovitis, sum-score (GS≥1 & CD≥1) (0-48)	0 (0-1)	0 (0-0)	0 (0-1)	0 (0-2)	0 (0-0)	0 (-2-0)

	All (n=126)	PsO no pain (n=36)	PsO pain (n=79)	PsA (n=11)	PsO no pain vs PsO pain	PsO pain vs PsA
CD+ synovitis, no. of pts	40 (32)	7 (19)	28 (35)	5 (46)	0.4 (0.1-1.2)	0.7 (0.2-3.0)
Enthesitis GS inflam. Sum[1]	0 (0-2)	0 (0-1)	1 (0–2)	1 (0-1)	0 (-1-0)*	0 (-1-1)
Enthesitis GS struc. sum[2]	4 (0-6)	4 (1-6)	3 (0-7)	4 (1-5)	0 (-1-2)	0 (-2-2)
Enthesitis CD sum	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
US enthesitis sum-score (0-12)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
US enthesitis, no. of pts	20 (16)	5 (14)	13 (17)	2 (18)	0.8 (0.2-2.7)	0.9 (0.2-9.4)
US inflammation sum-score (0-60)	2 (0-4)	1 (0-2)	2 (0-4)	6 (2-9)	-1 (-2-0)*	-2 (-6--1)*
US inflammation, no. of pts	87 (69)	18 (49)	58 (73)	11 (100)	0.4 (0.2- 0.8)*	0 (0-1.2)
CD+ inflammation sum-score (0-60)	0 (0-1)	0 (0-1)	0 (0-1)	1 (0-3)	0 (0-0)	0 (-2-0)
CD+ inflammation, no. of pts	54 (43)	10 (27)	38 (48)	6 (55)	0.4 (0.2-1.0)*	0.8 (0.2-3.3)
Paratenonitis, no. of pts	6 (5)	1 (3)	3 (4)	2 (18)	0.7 (0.0-9.1)	0.2 (0.0-2.5)
Tenosynovitis, no. of pts	15(12)	3 (8)	11 (14)[3]	1 (9)	0.5 (0.1-2.3)	1.6 (0.2-76.5)
PsA classification						
CASPAR criteria	45 (35)	5 (14)	31 (39)	9 (82)	0.3 (0.1-0.7)**	0.1 (0.0-0.8)**
US CASPAR[4]	84 (66)	18 (49)	55 (70)	11 (100)	0.4 (0.2-1.0)*	0.0 (0.0-1.0)*
CD+ CASPAR[4]	68 (54)	12 (32)	45 (57)	11 (100)	0.4 (0.1-0.9)*	0.0 (0.0-0.6)**
US defined PsA[5]	65 (52)	12 (33)	44 (56)	9 (82)	0.4 (0.2-1.0)*	0.3 (0.0-1.5)
CD+ defined PsA[5]	21 (17)	4 (11)	12 (15)	5 (46)	0.7 (0.2-2.6)	0.2 (0.0-1.1)*

Numbers are numbers (%) for binary variables and median (interquartile range) for continuous variables. Differences estimated by Fishers exact test for binary variables (Odds Ratio (95% confidence interval)) and Mann Whitney U test for continuous variables (median of the differences (95% confidence interval)). Statistical significance shown as: *: p<0.05, **: p<0.01, ***: p<0.001. PsO: psoriasis; PsA: psoriatic arthritis; IQR: interquartile range; 95% CI: 95% confidence interval; DMARDs: disease modifying antirheumatic drugs; NSAID: nonsteroidal anti-inflammatory drug; SJC: swollen joint count; TJC: tender joint count; SPARCC: Spondyloarthritis Research Consortium of Canada; LEI: Leeds Enthesitis Index; TPC: tender point count; PASI: Psoriasis Area and Severity Index; VAS: visual analog scale; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire disability index; DLQI: Dermatology Life Quality Index; PsAID: Psoriatic Arthritis Impact of Disease questionnaire; EQ5D: European quality of life 5-dimensions; SF-36: 36-Item Short Form survey; MCS: mental component summary; PCS: physical component summary; FACIT: Functional Assessment of Chronic Illness Therapy; PSQI: Pittsburgh Sleep Quality Index; CES-D: Center for Epidemiological

	All (n=126)	**PsO no pain** (n=36)	**PsO pain** (n=79)	**PsA** (n=11)	**PsO no pain vs PsO pain**	**PsO pain vs PsA**

Studies Depression; DAS28-CRP: Disease Activity Score in 28 joints using C- reactive protein; DAPSA: Disease Activity in Psoriatic Arthritis; mCPDAI: modified Composite Psoriatic Disease Activity Index; CASPAR: Classification for Psoriatic Arthritis; GS: grey scale; CD: Color Doppler; US: ultrasound

1. hypoechogenicity, thickening
2. calcifications/enthesophytes, erosions
3. All GS grade 1, CD grade 0
4. US/CD+ CASPAR: Inflammatory disease defined clinically or by ultrasound (US CASPAR: US synovitis/US enthesitis, CD+ CASPAR: CD+ synovitis/US enthesitis).
5. Defined as ≥2 sites with US synovitis/enthesitis

Table 2.2. Correlations between clinical/ultrasound sum-scores and patient-reported outcomes, Study Part 2. *Numbers from table by SK Felbo et al Rheumatology (Oxford), 2021.*

	Clinical parameters						**Ultrasound sum-scores**				
	SJC (0-66)	**TJC** (0-68)	**SPARCC** (0-16)	**LEI** (0-6)	**TPC** (0-18)	**PASI** (0-72)	**US synovitis sum-score**	**CD+ synovitis sum-score**	**US enthesitis sum-score**	**US inflammation sum-score**	**CD+ inflammation sum-score**
Global VAS (0-100)	0.17	0.51***	0.41***	0.37***	0.47***	-0.07	0.30**	0.17	0.10	0.33***	0.25**
Pain VAS (0-100)	0.24**	0.51***	0.39***	0.37***	0.45***	-0.09	0.30**	0.20*	0.10	0.33***	0.27**
HAQ-DI (0-3)	0.19**	0.40***	0.35***	0.25**	0.40 ***	-0.08	0.22*	0.18*	-0.04	0.22*	0.16
DLQI (0-30)	0.14	0.15	0.11	0.12	0.18*	0.50***	0.02	0.02	0.01	0.03	0.04
PsAID (0-10)	0.09	0.45***	0.41***	0.35***	0.48***	0.14	0.20*	0.09	0.04	0.21*	0.12
EQ5D index (0-1)	-0.16	-0.39***	-0.38***	-0.33***	-0.36***	0.06	-0.17	-0.15	0.01	-0.17	-0.16
SF36 MCS (0-100)	-0.04	-0.19*	-0.22*	-0.24**	-0.44***	0.18*	0.16	0.18*	0.11	0.17	0.19*
SF36 PCS (0-100)	-0.17	-0.46***	-0.37***	-0.31**	-0.48***	0.07	-0.33***	-0.25**	-0.02	-0.34***	-0.28**
FACIT-fatigue (0-52)	0.11	0.47***	0.44***	0.42***	0.48***	0.02	0.07	0.05	-0.05	0.08	0.05
PSQI (0-21)	0.01	0.32***	0.34***	0.31***	0.59***	-0.11	0.15	0.07	0.01	0.15	0.12
CES-D (0-60)	0.09	0.31***	0.32***	0.34***	0.44***	-0.03	0.01	-0.03	-0.01	0.03	0.00

Numbers are Spearman's rho. Rho defined as negligible when <0.2, weak 0.2–0.39, moderate 0.40–0.59, strong 0.60–0.79 or very strong ≥0.8. Statistical significance indicated as: *: p<0.05, **: p<0.01, ***: p<0.001. TJC: tender joint count; SJC: swollen joint count; SPARCC: Spondyloarthritis Research Consortium of Canada; LEI: Leeds Enthesitis Index; TPC: tender point count; PASI: Psoriasis Area and Severity Index; US: Ultrasound; CD+: Colour Doppler positive; VAS: Visual Analogue Scale; HAQ-DI: Health Assessment Questionnaire disability index; DLQI: Dermatology Life Quality Index; PsAID: Psoriatic Arthritis Impact of Disease questionnaire; EQ5D: European quality of life 5-dimensions; SF-36: 36-Item Short Form survey; MCS: mental component summary; PCS: physical component summary; FACIT: Functional Assessment of Chronic Illness Therapy; PSQI: Pittsburgh Sleep Quality Index; CES-D: Center for Epidemiological Studies Depression.
NB. EQ5D index and SF-36 scores show worse health related quality of life with lower scores, i.e. negative correlations are expected.

Table 2.3. Results from logistic regression analyses of selected parameters association with "US defined PsA" (≥2 sites with "US synovitis"/"US enthesitis") and "CD+ defined PsA" (≥2 sites with "CD+ synovitis"/"US enthesitis") in psoriasis (PsO) patients without diagnosed psoriatic arthritis (PsA), Study Part 2.

n=115	"US defined PsA"		"CD+ defined PsA"	
	Univariate	**Multivariable**	**Univariate**	Multivariable
Age and sex corrected	OR (95%CI), p	OR (95%CI), p	OR (95%CI), p	**OR (95%CI), p**
Demography, anamnestic variables				
Obesity (BMI≥30)	1.5 (0.7-3.4), p=0.29	-	1.6 (0.5-5.2), p=0.39	-
Smoking (current)	1.5 (0.6-4.0), p=0.39	-	2.3 (0.6-7.8), p=0.19	-
Alcohol (excessive use)	0.3 (0.1-1.1), p=0.08	0.5 (0.1-1.6), p=0.24	1.2 (0.2-9.6), p=0.85	-
Disease duration PsO (years)	1.0 (1.0-1.0), p=0.61	-	1.0 (0.9-1.0), p=0.13	-
Joint swelling, anamnestic	**2.4 (1.1-5.5), p=0.03**	1.8 (0.7- 4.4), p=0.21	1.6 (0.2-4.8), p=0.41	-
Joint stiffness, current	2.5 (0.8-8.7), p=0.13	-	2.0 (0.4-8.0), p=0.37	-
Joint pain, current	**3.1 (1.4-7.0), p=0.005**	2.2 (0.8-6.2), p=0.12	0.8 (0.3-2.5), p=0.73	-
Enthesis pain, anamnestic	1.3 (0.58-2.7), p=0.57	-	0.7 (0.2-2.0), p=0.49	-
Inflammatory back pain[1], current	0.8 (0.1-5.4), p=0.85	-	0 (NA-4.0e+70), p=0.99	-
Unspecified musculoskeletal pain, current	**2.5 (1.1-5.8), p=0.03**	1.5 (0.5-4.5), p=0.43	0.9 (0.3-2.7), p=0.85	-
Dactylitis, anamnestic	1.9 (0.5-9.8), p=0.39	-	1.6 (0.2-7.9), p=0.60	-
Inflammatory bowel disease	0 (NA-1.4e+70), p=0.99	-	0 (NA-4.6e+70), p=0.99	-
Uveitis	4898412.3 (0-NA), p=0.99	-	0 (NA-5.4e+122), p=1.00	-
Clinical variables				
SJC 66 joints	1.3 (0.9-1.8), p=0.19	-	**1.7 (1.2-2.8), p=0.01**	**1.4 (0.8-2.3), p=0.28**
TJC 68 joints	**1.1 (1.0-1.2), p=0.04**	1.0 (0.9-1.2), p=0.49	1.0 (1.0-1.1), p=0.19	-
SPARCC enthesitis index	1.2 (1.0-1.5), p=0.10	0.9 (0.6-1.4), p=0.61	1.2 (0.9-1.5), p=0.11	-
Dactylitis (patients with)	0.6 (0.0-15.5) , p=0.71	-	4.1 (0.1-115.7), p=0.35	-
Fibromyalgia TPC	1.1 (1.0-1.3), p=0.06	1.0 (0.8-1.3), p=0.94	1.0 (0.9-1.2), p=0.62	-
Nail psoriasis (patients with)	1.3 (0.6-2.8), p=0.53	-	1.9 (0.6-5.8), p=0.25	-
PASI	1.0 (0.8-1.1), p=0.47	-	1.0 (0.8- 1.1) p=0.67	-
Physician VAS	**1.3 (1.1-1.6), p=0.001**	**1.3 (1.1-1.6), p=0.004**	**1.2 (1.1-1.3), p=0.002**	1.1 (1.0-1.3), p=0.02
C-reactive protein	1.1 (1.0-1.2), p=0.07	1.1 (1.0-1.1), p=0.11	1.0 (0.9-1.1), p=0.49	-

Numbers are age and sex adjusted Odds Ratio (OR) (95% confidence interval). Statistically significant results (p<0.05) marked with bold. Multivariable analyses with variables from univariate with p≤0.1, for demographic/anamnestic variables and clinical variables separately. PsO: psoriasis; PsA: psoriatic arthritis; 95% CI: 95% confidence interval; SJC: swollen joint count; TJC: tender joint count; SPARCC: Spondyloarthritis Research Consortium of Canada; TPC: tender point count; PASI: Psoriasis Area and Severity Index; VAS: visual analog scale; CRP: C-reactive protein, US: ultrasound; CD: Color Doppler. 1. By Assessment of Spondyloarthritis international Society criteria: At least four out of five: Age onset <40; Insidious onset; Improvement with exercise; No improvement with rest; Pain at night

Table 2.4. Sensitivity/specificity and positive/negative predictive values of screening questionnaires at recommended cut-off values for PsA prediction. *Numbers from table by SK Felbo et al Rheumatology (Oxford), 2021*.

	Sensitivity	Specificity	PPV	NPV	AUC
CASPAR (44 pos/82 neg)					
EARP	0.61 (0.46-0.76)	0.60 (0.48-0.70)	0.45 (0.32-0.58)	0.74 (0.62-0.84)	0.67
PASE	0.52 (0.37-0.68)	0.67 (0.56-0.77)	0.46 (0.32-0.61)	0.72 (0.61-0.82)	0.65
PEST	0.23 (0.12-0.38)	0.92 (0.83-0.96)	0.59 (0.33-0.82)	0.69 (0.59-0.77)	0.66
ToPAS2	0.66 (0.50-0.80)	0.55 (0.44-0.66)	0.44 (0.32-0.57)	0.75 (0.62-0.85)	0.67
US CASPAR (84 pos/42 neg)					
EARP	0.50 (0.39-0.61)	0.57 (0.41-0.72)	0.70 (0.57-0.81)	0.36 (0.25-0.49)	0.57
PASE	0.44 (0.33-0.55)	0.69 (0.53-0.82)	0.74 (0.60-0.85)	0.38 (0.27-0.50)	0.63
PEST	0.17 (0.09-0.26)	0.93 (0.80-0.98)	0.82 (0.57-0.96)	0.36 (0.27-0.46)	0.63
ToPAS2	0.57 (0.46-0.68)	0.57 (0.41-0.72)	0.73 (0.60-0.83)	0.40 (0.28-0.54)	0.58
CD+ CASPAR (68 pos/58 neg)					
EARP	0.54 (0.42-0.66)	0.60 (0.47-0.73)	0.62 (0.48-0.74)	0.53 (0.40-0.65)	0.62
PASE	0.47 (0.35-0.60)	0.69 (0.56-0.80)	0.64 (0.49-0.77)	0.53 (0.41-0.64)	0.66
PEST	0.21 (0.12-0.32)	0.95 (0.86-0.99)	0.82 (0.57-0.96)	0.50 (0.41-0.60)	0.69
ToPAS2	0.63 (0.51-0.75)	0.60 (0.47-0.73)	0.65 (0.52-0.76)	0.58 (0.45-0.71)	0.63
US defined PsA (65 pos/61 neg)					
EARP	0.49 (0.37-0.62)	0.54 (0.41-0.67)	0.53 (0.40-0.66)	0.50 (0.37-0.63)	0.56
PASE	0.42 (0.29-0.54)	0.62 (0.49-0.74)	0.54 (0.39-0.68)	0.50 (0.38-0.62)	0.56
PEST	0.20 (0.11-0.32)	0.93 (0.84-0.98)	0.76 (0.50-0.93)	0.52 (0.42-0.62)	0.61
ToPAS2	0.57 (0.44-0.69)	0.52 (0.39-0.65)	0.56 (0.43-0.68)	0.53 (0.40-0.66)	0.56
CD+ defined PsA (21 pos/105 neg)					
EARP	0.48 (0.26-0.70)	0.52 (0.42-0.62)	0.17 (0.08-0.28)	0.83 (0.72-0.91)	0.50
PASE	0.38 (0.18-0.62)	0.60 (0.50-0.69)	0.16 (0.07-0.29)	0.83 (0.72-0.91)	0.53
PEST	0.29 (0.11-0.52)	0.90 (0.82-0.95)	0.35 (0.14-0.62)	0.86 (0.78-0.92)	0.56
ToPAS2	0.48 (0.26-0.70)	0.47 (0.37-0.57)	0.15 (0.08-0.26)	0.82 (0.70-0.90)	0.51

Numbers are sensitivity/specificity/ positive predictive value (PPV)/ negative predictive value (NPV) (95% confidence interval) and area under the curve (AUC). CASPAR: EARP: Early Psoriatic Arthritis Screening Questionnaire. PASE: Psoriatic Arthritis Screening and Evaluation; PEST: Psoriasis Epidemiology Screening Tool; ToPAS2: Toronto Psoriatic Arthritis Screening Tool 2.

Figure 2.1. Patient disposition, Study Part 2.

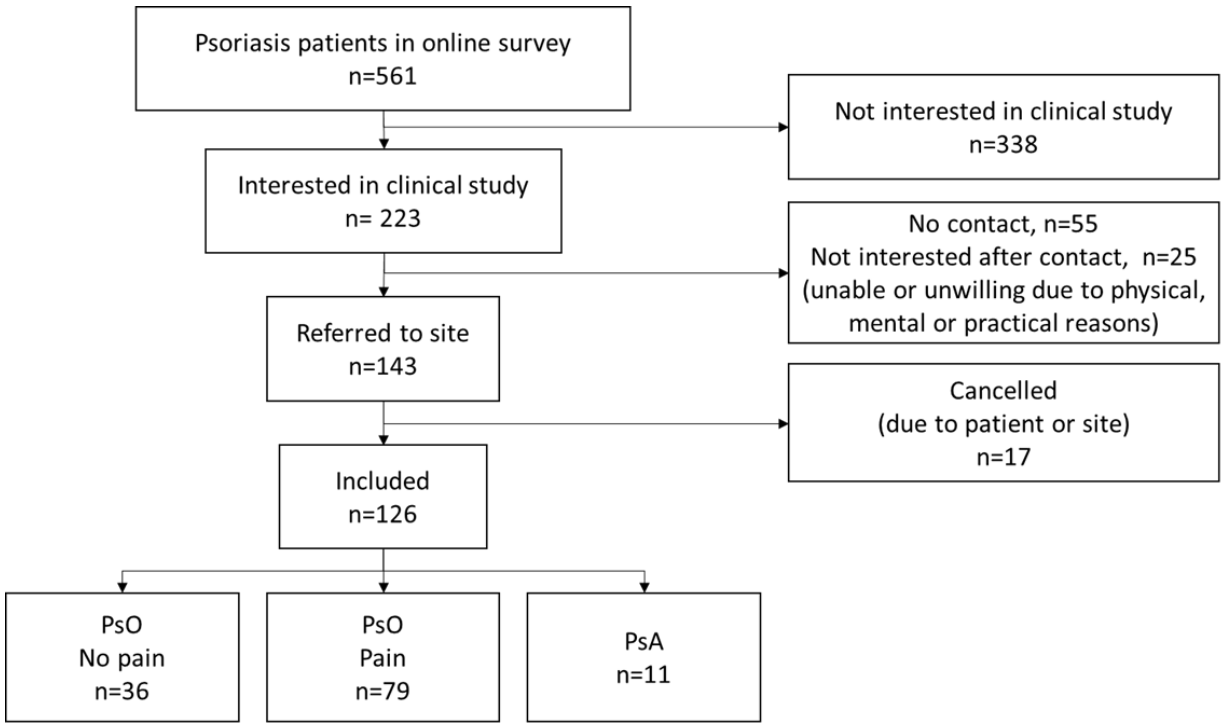

Figure 2.2. Frequencies of ultrasound findings. A) "US enthesitis" (GS≥1 (hypoechogenic/thickened) &CD≥1), B) "CD+ synovitis" (GS≥1 & CD≥1), and C) "US synovitis" (GS≥2 OR GS≥1&CD≥1), for all examined entheses/joints, Study Part 2. US: ultrasound. CD: Color Doppler.