A rheumatologist undercover

Research of psoriatic arthritis at the dermatology clinic

Tamara van Hal

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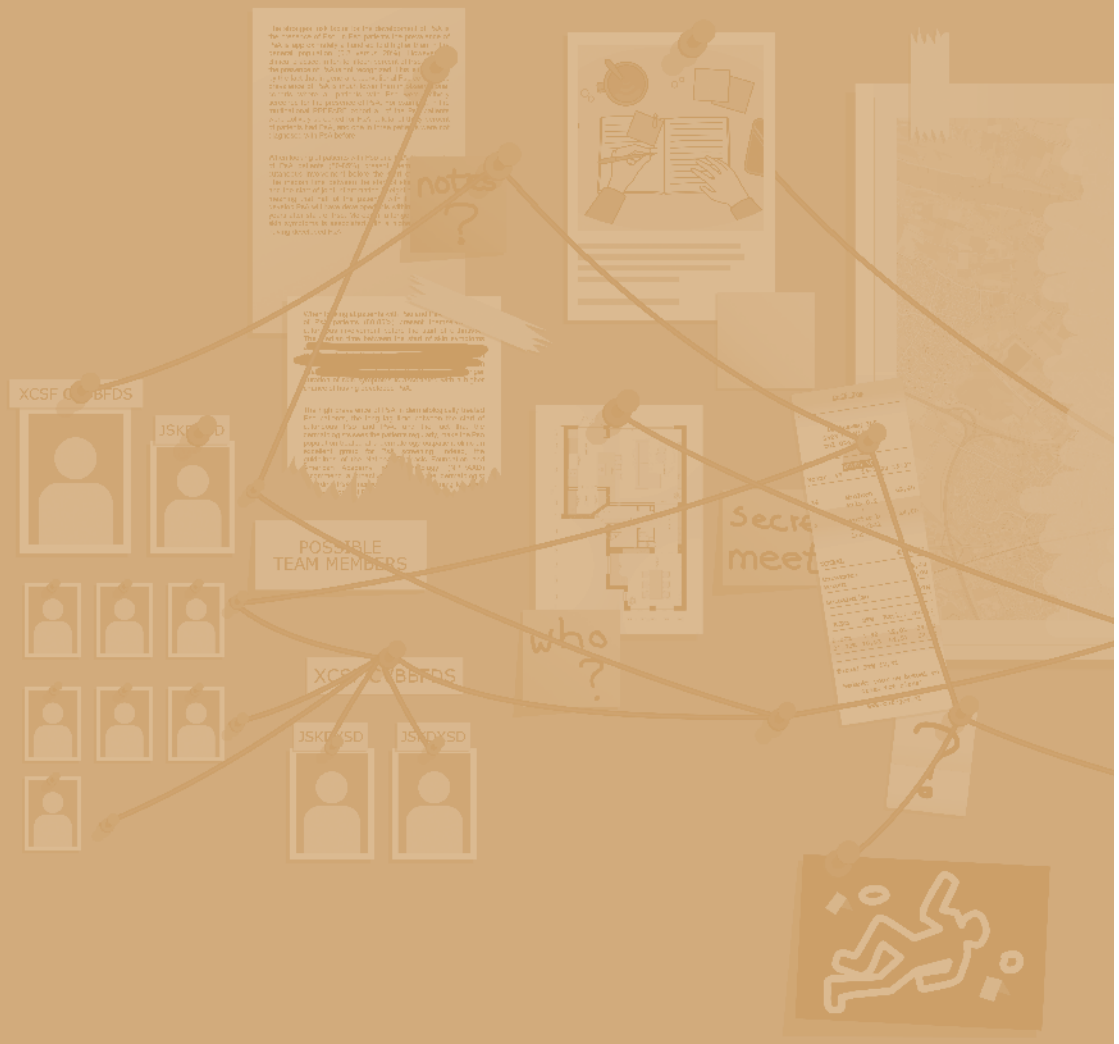
Chapter 1

General introduction and thesis outline



General introduction

Psoriasis

Psoriasis (Pso) is an immune-mediated inflammatory disease of skin and nails, which occurs in approximately two percent of people in Western countries[1]. Pso can present itself at any age, but shows two peaks in incidence: young adulthood and middle age[2,3]. It affects men as often as it affects women. Pso is characterized by thickened, red, inflamed plaques of skin, which can be covered in white, silvery scales. These lesions can cause an itching or burning sensation in the skin, and can bleed or lose scales[4]. Also, patients can experience stigma or psychological burden because of the visibility of the disease[5]. Psoriasis is a chronic disease, that can be treated to lessen symptoms, but currently cannot be cured[6]. Typical for Pso is its tendency to (re)occur at sites of trauma or injury (Koebner phenomenon)[7].

The best-known form of Pso is plaque psoriasis, which is characterized by the presence of erythrosquamous inflamed plaques on the skin (figure 1). Typically, these plaques are present on the extensor sides of the large joints (i.e., elbows and knees), the lumbosacral region, and the scalp. Next to plaque psoriasis, Pso can present itself as psoriasis guttate (drop-like small areas in a centripetal pattern) and psoriasis pustulosa (sterile pustules on an erythematous background, most often on palms and soles)[3,7]. Moreover, it can affect specific areas, such as the flexures (psoriasis inversa) and nails (psoriasis unguium).

Pso is a clinical diagnosis, based on the presence of characteristic skin lesions in typical locations. However, atypical presentations may occur, in which a skin biopsy may be helpful[8]. Most patients in the Netherlands with Pso are treated by the general practitioner (GP). However, when there is uncertainty about the diagnosis, or when systemic therapy is needed, patients are referred to the dermatologist. This is the case for about twenty percent of the patients[9]. Pso is closely related to psoriatic arthritis (PsA).

Psoriatic arthritis

PsA is a chronic immune-mediated inflammatory disease of joints and entheses, belonging to the rheumatological disease group of spondyloarthritis (SpA). Clinical characteristics of this group of diseases are asymmetric oligoarthritis of both large and small joints, axial spondyloarthritis, dactylitis, enthesitis, and (in contrast to rheumatoid arthritis - RA) the involvement of the distal interphalangeal joints (DIPs)[10]. It affects approximately two per thousand persons worldwide[11-13]. However, this prevalence is expected to rise due to an increase in new cases: a study in Denmark showed an incidence of 7.3 per 100 000 in 1997, increasing to 27.3 per 100 000 in 2010[14]. This increase in incidence is probably due to better recognition of PsA as a consequence of a combination of factors: a new set of classification criteria published in 2006[15], several screening questionnaires to identify PsA in high-risk populations[16-18], and the improved therapeutic arsenal after the introduction of biologicals (making it worthwhile to identify patients)[19].

PsA is a heterogenous disease, with considerable intra- and interindividual variability[20]. The multitude of possible musculoskeletal presentations is reflected well in the classifications made by Moll & Wright, who divided possible PsA presentations into five categories: predominant DIP-arthritis, predominant asymmetric oligoarthritis, predominant symmetric (RA-like) polyarthritis, predominant arthritis mutilans, and predominant spondylitis[21].

Moreover, the SpA diseases are closely related to manifestations in other organ systems, such as the skin (psoriasis - Pso), the eye (acute uveitis anterior - AUA), and the intestines (inflammatory bowel disease - IBD).

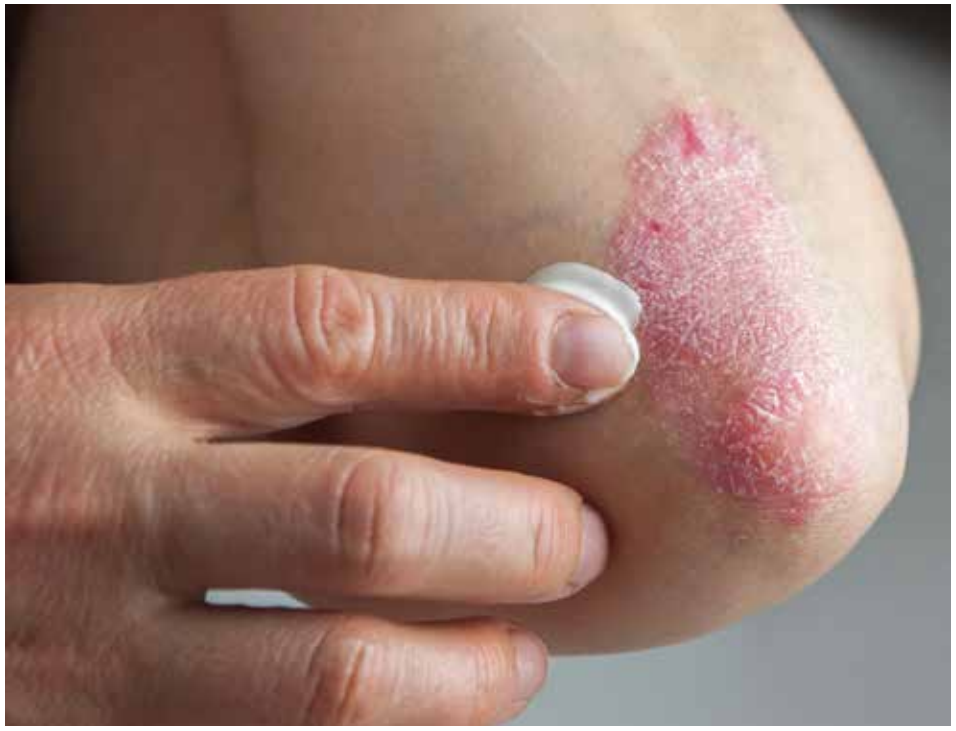


Figure 1: A typical erythrosquamous psoriasis plaque at the extensor side of the elbow

If left untreated, most patients with PsA will experience a deterioration of their disease, with a larger number of joints being involved over time[22]. Moreover, prolonged inflammation in a joint can lead to joint damage, deformity, and loss of function[23]. This is reflected in the fact that a prolonged time between the start of joint complaints and referral to the rheumatologist is associated with more joint damage[24]. This joint damage is associated with less strength, more pain in the damaged joint, and worse physical functioning in general[25-27]. Moreover, the number of damaged joints and the amount of functional impairment increases over time[28,29]. This makes it particularly important to recognize and treat PsA as soon as possible.

Diagnosis of PsA

The diagnosis of PsA is based on clinical features, while laboratory and imaging findings may support the diagnostic process[30]. In the absence of diagnostic criteria, the golden standard for PsA diagnosis is still expert physician diagnosis (i.e. diagnosis by a rheumatologist)[15]. However, classification criteria have been developed for use in clinical trials. The currently most used classification criteria are the CASPAR criteria (box 1), which recognize the presence of Pso (either in the index patient, or in first- or second-degree relatives), dactylitis, and nail involvement (onycholysis, pitting, and hyperkeratosis) as key clinical features for the diagnosis of PsA[15].

The entry criterion for the CASPAR criteria is the presence of inflammatory musculoskeletal disease, either in peripheral joints, spine, or entheses. This means it is still essential that a trained specialist is employed to diagnose a patient. Moreover, these classification criteria are designed to select a homogenous group of PsA patients for inclusion in clinical trials and are not meant for diagnosing an individual patient in clinical practice. This is reflected by the fact that in early PsA, the sensitivity of the CASPAR criteria is under ninety percent, while their specificity is almost hundred percent[31-33]. In other words, fulfilling the CASPAR criteria makes the diagnosis PsA almost certain. However, not fulfilling the CASPAR criteria does not makes the diagnosis PsA impossible. In conclusion, the diagnosis of PsA remains "in the eyes of the beholder" of the rheumatologist, rather than fulfilling a predefined checklist.

Box 1: Classification criteria for psoriatic arthritis (CASPAR)[15]
To meet the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis. Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.
2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.
3. A negative test for the presence of rheumatoid factor by any method except latex.
4. Either current dactylitis, or a history of dactylitis recorded by a rheumatologist.
5. Radiographic evidence of juxta-articular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

PsA in patients with Pso

The strongest risk factor for the development of PsA is the presence of Pso. In Pso patients the prevalence of PsA is approximately a hundred fold higher than in the general population (0.2 versus 20%)[34]. However, in clinical practice, in ten to fifteen percent of Pso patients the presence of PsA is not recognized[35]. This is illustrated by the fact that in general observational Pso cohorts the prevalence of PsA is much lower than in observational cohorts where all patients with Pso were actively screened for the presence of PsA[34]. For example, in the multinational PREPARE cohort all of the Pso patients were actively screened for PsA: a total of thirty percent of patients had PsA, and one in three patients were not diagnosed with PsA before[36].

When looking at patients with Pso and PsA, the majority of PsA patients (80-85%) present themselves with cutaneous involvement before the start of arthritis[30]. The median time between the start of skin symptoms and the start of joint inflammation is eight to ten years, meaning that half of the patients with Pso who will develop PsA will have developed this within eight to ten years after start of Pso[37,38]. Moreover, a longer duration of skin symptoms is associated with a higher chance of having developed PsA[39].

	NO	YES
Have you ever had a swollen joint (or joints)?		
Has a doctor ever told you that you have arthritis?		
Do your finger nails or toe nails have holes or pits?		
Have you had pain in your heel?		
Have you had a finger or toe that was completely swollen and painful for no apparent reason?		

In the drawing below, please tick the joints that have caused you discomfort (i.e., stiff, swollen, or painful joints).

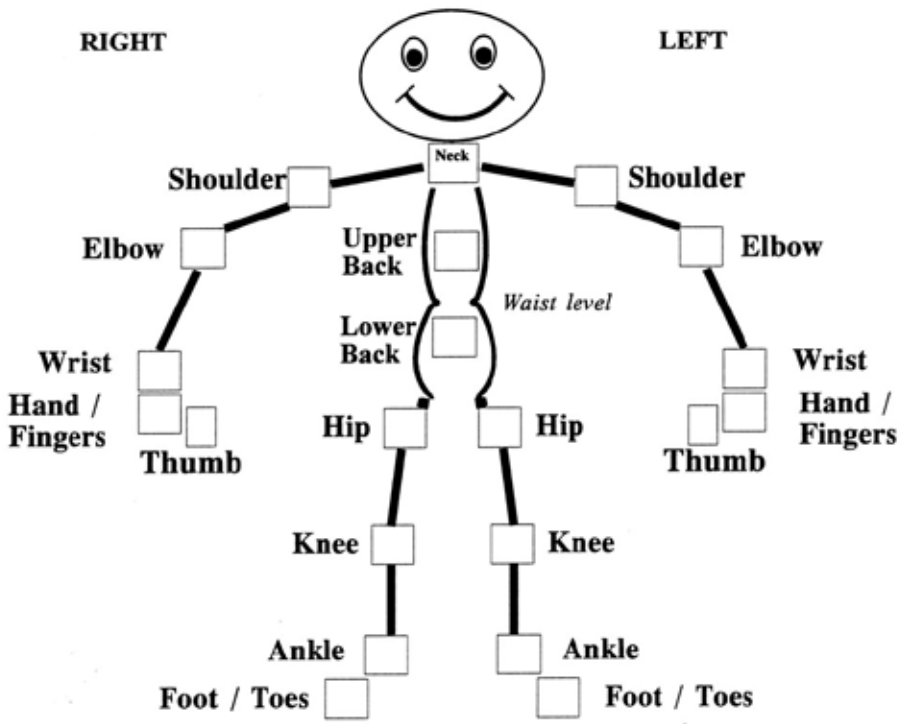


Figure 2: Psoriasis Epidemiology Screening Tool [16], one of the screening questionnaires used to identify Pso patients with concomitant PsA. Three or more questions with a positive answer warrants screening by a rheumatologist.

Screening for PsA in Pso patients

The high prevalence of PsA in dermatologically treated Pso patients, the long lag time between the start of cutaneous Pso and PsA, and the fact that the dermatologist sees the patients regularly, make the Pso population treated at a dermatology outpatient clinic an excellent group for PsA screening. Indeed, the guidelines of the National Psoriasis Foundation and American Academy of Dermatology (NPF/AAD) recommend a proactive attitude of the dermatologist regarding PsA, mentioning "routine screening for signs and symptoms of PsA"[40]. However, merely the presence of joint complaints is insufficient to identify PsA in Pso patients, since most Pso patients with musculoskeletal complaints do not have PsA[41]. To aid the dermatologist in the recognition of PsA, several patient-reported questionnaires have been developed. These questionnaires are for the largest part based on questions about symptoms, complemented with questions about previous doctor's visits and family history. The common mechanism of these questionnaires is that an end score is calculated based on the answers, and that referral to a rheumatologist is advised when a certain pre-specified cut-off score is reached[42].

Unfortunately, the diagnostic performance of these screening questionnaires leaves room for improvement, with a mean sensitivity of 66 to 85 per cent, and a mean specificity of 72 to 85 per cent[43]. Indeed, even with these screening tools, about one in three Pso patients with concomitant PsA remain undetected[44,45]. Despite these shortcomings, the implementation of routine screening has been calculated to be cost-effective[46]. However, implementation of PsA screening is not yet routine daily practice in dermatology clinics. Hurdles to the implementation of screening could be a lack of time in high-volume dermatology clinics, a lack of knowledge about (screening tools for) PsA, and limitations in the performance of the screening tools[42,47].

Pathogenesis of psoriasis and PsA

The pathogenesis of Pso and PsA show considerable overlap, which is reflected in the use of the 'psoriatic disease' nomenclature. Psoriatic disease is considered an immune-mediated disease, with a complex interplay between genetic susceptibility and aberrant immunologic responses. The interplay between genetic susceptibility and immunological aberrations is best demonstrated by the fact the best-known risk genes for Pso and SpA/PsA are located in the human leukocyte antigen (HLA) region of the genome: *HLA-Cw*06* for Pso, and *HLA-B27* for SpA/PsA[30,48].

Another way in which genetics crosses paths with immunology, is highlighted in the importance of the interleukin (IL) 23-IL17 pathway in psoriatic disease. Single nucleotide polymorphisms (SNP) in the IL23 receptor gene *(IL23R)* have been shown to be associated with a higher risk for both Pso and PsA[49-52]. Stimulation of the IL23R by IL23 results in the production of IL17 by Th17 T cells and type 3 innate lymphoid cells (ILC3)[3]. IL17 is, among other things, responsible for a self-perpetuating positive feedback loop by excreting CCL20, a chemokine attracting more Th17 cells[53]. Moreover, IL17 stimulates further inflammation by inducing, among others, keratinocytes, synoviocytes, and innate immune cells to produce tumour necrosis factor (TNF) alpha, IL1 beta and IL6[30,54,55]. Furthermore, the pro-proliferative effect of IL17 on keratinocytes and the stimulation of osteoclasts via receptor activator of NF-κb (RANK) ligand (RANKL) produced by synoviocytes upon stimulation by IL17 underlie the typical hyperkeratosis of the skin and the joint erosions of arthritis, respectively[3,30].

Treatment options and strategies in psoriatic disease

The overlap in pathogenetic mechanisms is also reflected in an overlap in the therapeutic arsenal. In brief, the therapeutics in psoriatic disease can be divided (in order of intensity) into non-systemic, conventional systemic and biologicals/small molecule inhibitor drugs (smi). In both diseases, current Dutch pharmacological guidelines recommend starting with a conventional systemic drug, before a biological or small molecule inhibitor is prescribed[56,57]. However, very high disease activity, an unfavourable prognosis, or therapeutic failure of the conventional systemic drug can be reasons to start a biological or smi. Therapeutic failure can be either due to ineffectiveness, side effects, or contra-indications.

Table 1: overview of systemic therapeutic options for Pso and PsA, as per July 2023.

	Indicated for Pso	Indicated for PsA	Indicated for Pso and PsA
Conventional systemic drugs			
	Acitretin Ciclosporin A Fumarates	Leflunomide Sulfasalazine	Methotrexate
Biologicals			
TNF-alpha inhibitors		Golimumab	Adalimumab Certolizumab pegol Etanercept Infliximab
Il12/IL23 inhibitors			Ustekinumab
IL17 inhibitors	Bimekizumab Brodalumab		Ixekizumab Secukinumab
IL23 inhibitors	Tildrakizumab		Guselkumab Risankizumab
Small molecule inhibitors			
PDE4 inhibitors			Apremilast
JAK inhibitors		Tofacitinib Upadacitinib	

Non-systemic therapies include the topical use of corticosteroid or vitamin D analogue creams on the skin, or local intra-articular corticosteroid injections. Conventional systemic drugs include classical immunosuppressive drugs, such as methotrexate[58]. They modulate the immune response in a non-specific way, and are usually used orally. Biologicals are antibodies or decoy receptors directed against certain specific proteins involved in the inflammatory process, such as TNF alpha, IL17 or IL23. They are administered either subcutaneously or intravenously. Small molecule inhibitors also target specific proteins, such as the Janus kinases (JAK) or phosphodiesterase (PDE) 4, and are administered orally. An overview of the different systemic therapies used in Pso and PsA is given in table 1.

An important difference in the treatment of Pso versus PsA lies in the fact that some therapeutic options are only available for one disease. This may be because of the mode of delivery (i.e. topical application of creams for Pso or local injections of corticosteroids for PsA), or because of a difference in efficacy in controlling either joint or skin disease (i.e. retinoids for Pso and leflunomide for PsA). Another difference lies in the treatment strategies. Current PsA guidelines advise physicians to intensify treatment until a predefined disease status (remission or low disease activity) is reached[59,60]. This treatment strategy is known among rheumatologist as treat-to-target (T2T), and its benefits in PsA have been shown in the ground-breaking TICOPA trial[61]. In this trial, a T2T strategy resulted in less active disease, and fewer cases of permanent joint damage, at a cost of more intensive treatment in the T2T group[61,62]. In Pso, treatment goals are not defined as a disease status, but a goal is set in shared decision making with the patient[56]. Moreover, certain biologicals can be prescribed as first line therapy in severe Pso, while in PsA disease severity is not an argument to forego a trial of conventional systemic drugs.

Impact of psoriatic disease on patients' daily life

Patients with psoriatic skin or joint disease can experience significant impact of their disease on their daily life. Patients report that their disease disrupts both their professional as well as personal life, and that this work/leisure domain is the most important life domain affected by the disease[63,64]. Regarding impact on professional life, patients with psoriatic disease report that psoriatic disease has an influence on their career choices[65], their ability to work at all[66-68], and their job performance[69-72]. In both Pso and PsA, a greater overall work impairment is associated with a higher disease activity[69,72-75], and adequate treatment diminishes the impact of disease on work performance[76-79]. In PsA specifically, starting five years before diagnosis, patients have a lower yearly income than the general population[67]. A longer disease duration[64,66] and a longer time to receive an adequate disease control[80] are associated with more work impairment in these patients with arthritis.

Regarding the impact of psoriatic disease on personal life, patients with psoriasis frequently report they feel stigmatized and excluded from social environments[6]. There is a strong connection between the ability to be able to participate in social events and the general satisfaction in life[81]. Unfortunately, one in four patients with psoriatic disease report that they are limited in their ability to participate in social roles and activities, and that they need to adapt their daily routine due to their disease[82,83]. In a cohort of PsA patients, up to half of patients report that they are impaired in their ability to perform activities of daily life (ADL), and one in five patients requires help to perform ADL[84]. Moreover, patients with psoriatic disease report that the disease disrupts family roles. Physical pain due to joint disease or genital inverse psoriasis, as well as embarrassment about physical appearance, can cause problems with intimacy[65]. Moreover, if help with daily life activities is necessary, this causes stress in the family role as partner or parent[65]. However, it is hopeful that in trials with biologicals, treatment results in a significant improvement in ADL impairment[76].

Aims and outline of this thesis

In this thesis, we aimed to research how to diminish the burden of disease for patients with Pso and PsA, by determining the following aims for our studies:

1. To determine (clinical) characteristics useful to predict future PsA in Pso patients treated at a dermatology outpatient clinic
2. To determine (clinical) characteristics useful to identify concomitant, current PsA in Pso patients treated at the dermatology outpatient clinic
3. To determine the impact of Pso and PsA on patients' work and activities of daily life

The first aim is investigated in chapter 2 and 3.
First, in chapter 2 we provide an overview of the literature describing previously discovered risk factors for the development or presence of PsA in Pso patients. In chapter 3, we proceed to investigate predicting factors for the development of PsA in Pso patients.

The second aim is investigated in chapters 4 to 6.
These chapters describe the findings of a monocenter cohort study of Pso patients, who were actively screened for the presence of PsA by a rheumatologist: the Discovery of Arthritis in Psoriasis Patients for Early Rheumatological referral (DAPPER). Chapter 4 describes the methodology and study protocol of the DAPPER study. In chapter 5 we present the primary results of this study: the prevalence of PsA in Pso patients treated at the dermatology outpatient clinic. In chapter 6, we describe the development of a prediction tool for the presence of concomitant, prevalent PsA in these Pso patients.

The third aim is investigated in chapter 7 and 8.
Chapter 7 describes the work and activity impairment in a dermatological cohort of psoriasis patients using biologicals, while chapter 8 looks at impairment in a rheumatological cohort of PsA patients. Moreover, in these studies we investigate factors associated with work and activity impairment.

Finally, chapter 9 summarizes the outcomes of the studies in this thesis. Furthermore, the implications of these outcomes are discussed in terms of limitations of the research, directions for further research and recommendations for clinical practice.

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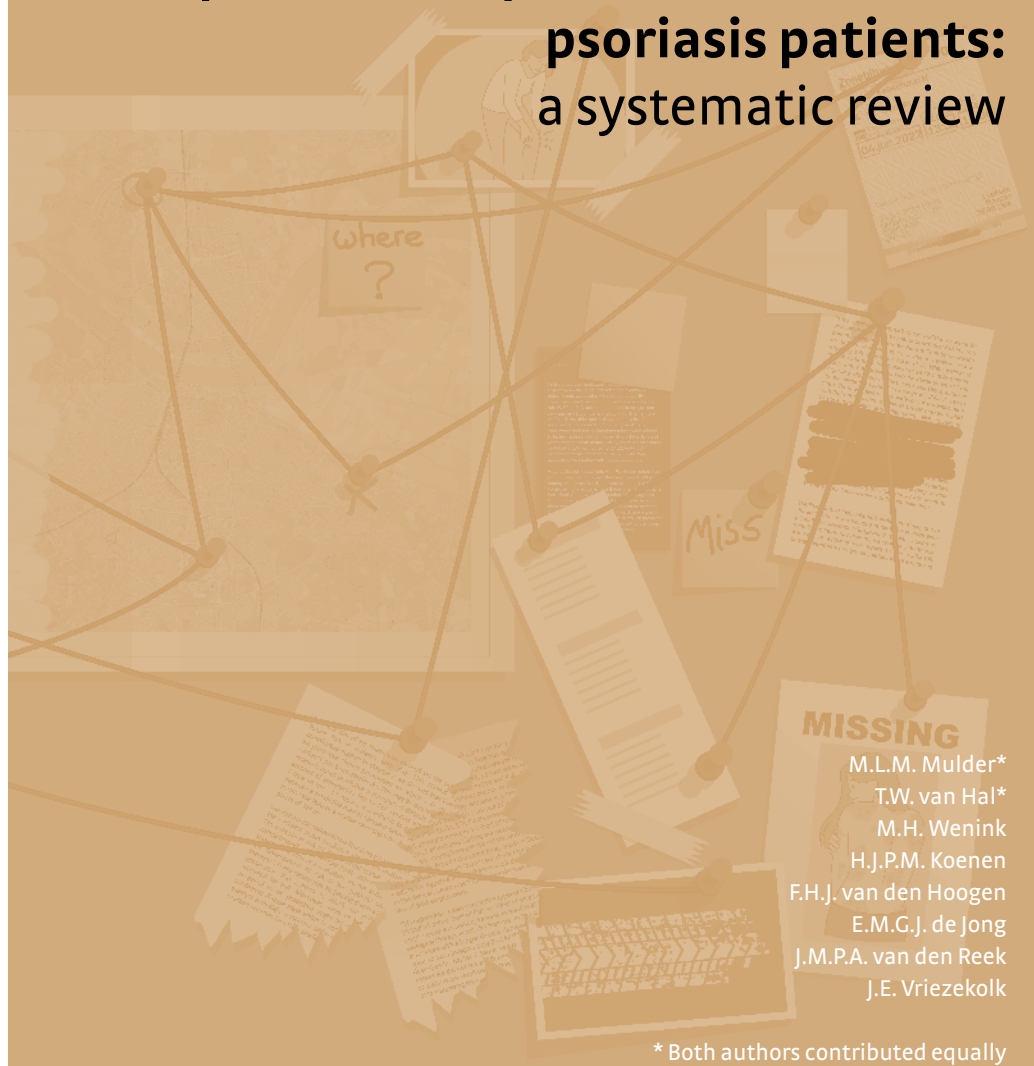
Chapter 2

Clinical, laboratory, and genetic markers for the development or presence of psoriatic arthritis in psoriasis patients: a systematic review



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Abstract

Twenty to thirty percent of psoriasis (Pso) patients will develop psoriatic arthritis (PsA). Detection of Pso patients that are (at risk for) developing PsA is essential to prevent structural damage. We conducted a systematic search of five bibliographic databases, up to May 2020. We searched for studies assessing markers (clinical, laboratory, genetic) associated with the development or presence of PsA in Pso patients. Study selection and quality assessment of the included studies was performed, followed by a qualitative best evidence synthesis to determine the level of evidence for a marker and its association with concomitant/developing PsA in Pso. Overall, 259 possible markers were identified in 119 studies that met the inclusion criteria. Laboratory markers related to inflammation and bone metabolism reached a strong level of evidence for the association (not prediction) of PsA in Pso. Only CXCL10 showed strong evidence for a positive predictive value for PsA in Pso. The importance of timely detecting PsA in a Pso population, and finding more (bio)markers contributing to early detection, remains high.

Introduction

Psoriatic arthritis (PsA) is an immune-mediated inflammatory disease affecting joints and entheses, and is strongly associated with psoriasis (Pso). Twenty to thirty percent of Pso patients will develop PsA, with an average lag time between Pso and PsA of 10 years[1,2]. This lag time creates a unique opportunity to identify patients with an increased risk for (developing) PsA. The (timely) recognition of concomitant PsA, or ideally early prediction, is important, because untreated PsA can lead to irreversible joint damage[3,4]. Treatment of arthritis leads to an improvement of both function and quality of life[5]. However, patients with Pso are mostly seen by physicians (e.g. dermatologists) who are not trained in recognizing early signs of arthritis. Identifying markers for PsA in patients with Pso can optimize screening to detect the onset of PsA as early as possible.

Current screening strategies mostly use questionnaires based on clinical characteristics to detect PsA[6,7]. Both characteristics of Pso as well as environmental factors may be relevant variables for PsA screening[8-10]. Next to clinical characteristics, extensive research has been done on genetic markers, in both HLA- (human leukocyte antigen) and non-HLA-regions[10-12]. Likewise, there are laboratory markers involved in inflammation pathways that might be able to help detect PsA in Pso patients[12,13]. However, most research focuses on the differentiation between Pso and/or PsA on one side, and healthy controls on the other side. To our knowledge, no comprehensive overview has been made to summarize the evidence for these clinical, genetic, and laboratory markers.

Therefore we conducted a systematic review to identify possible markers for the onset of PsA in a Pso population, with the purpose of providing a comprehensive summary of the available markers for PsA in Pso.

Material and methods

Protocol

The protocol was designed according to the Preferred Reporting Items for Systematic review and Meta-Analysis and registered in Prospero (CRD42018093982)[14].

Search strategy

Five bibliographic databases (PubMed, EMBASE, Web of Science, Medline, and Cochrane) were searched for studies from January 1st, 1990 up to April 29th, 2020. Search terms compromised keywords involving study population, study design, and etiology (supplementary table 1). In addition, reference lists of included articles were used for cross-reference checking.

Study selection

Studies were screened for eligibility based on title and abstract by two independent reviewers (MM, JV for laboratory and genetic studies; MM and TH for clinical studies). Potentially relevant papers were assessed in full text (MM, TH). Any disagreement was resolved by consensus or by discussion with a third reviewer (JR, MW, JV). Studies were excluded based on the following criteria: 1) <10 patients per group (Pso and PsA, respectively), 2) age of patients <18 years, 3) no statistical comparison between Pso and PsA, 4) languages other than English, German or

Dutch. We primarily focused on studies with a longitudinal design, meaning that the marker was present before the presentation of PsA. A very low number of longitudinal studies was available for laboratory studies (n=2), and none for genetic studies. To not miss potential relevant markers in these two categories, we also included genetic and laboratory studies with a cross-sectional design (i.e., marker was present at the same time as PsA) as a "second best" option. While these might not be useful to identify predictors for the development of PsA, they could provide information about possible markers for concomitant PsA.

Data extraction

Data extracted included study design, patient characteristics, markers, and outcome. Extraction was performed by two reviewers, with 10% overlap to check extraction quality (MM, TH).

Assessment of risk bias

Risk bias was assessed using the Newcastle Ottawa Scale for case-control and cohort studies [15]. This tool comprises three domains: selection, comparability, and outcome/exposure. A study was considered of "good" quality when it had a minimum of 3 stars in the selection domain, 1 star in the comparability domain, and 2 stars in the outcome/exposure domain. "Fair" quality was given when a study had a minimum of 2 stars in the selection, 1 star in the compatibility, and 2 stars in the outcome/exposure domain[16]. If a study failed to meet these standards, it was considered to be of "poor" quality. Risk of bias assessment was performed by two reviewers (MM, TH) independently. Any disagreement was resolved by consensus or by discussion with a third reviewer (JR, MW, JV).

Best evidence synthesis

For the best evidence synthesis (BES), we included markers that either showed a significant difference between Pso and PsA in at least one study, or markers that showed no significant results in at least two studies (i.e. we excluded markers that were only investigated once and showed no association). Markers were grouped into overarching categories (see Table 1-3). In addition, for markers presented as a categorical variable, we used the data of the most extreme level. For example, In the study from Love et al, body mass index (BMI) was categorized into four levels : < 25 (normal), 25-30, 30-35, >35 kg/m^2 [17]. For the best evidence synthesis, we looked at the highest level (i.e. BMI > 35 kg/m^2) compared to the reference level (i.e. BMI <25 kg/m^2) .

We then assessed the consistency of the results within and across studies. If within a study, a marker was represented in multiple non-hierarchical conceptually similar constructs, we considered the result consistent if ≥ 75% of the constructs pointed in the same direction. Otherwise, we considered the result for that marker "mixed". For example, one study looked at fracture, any trauma, and trauma leading to medical care[18]. Because two of these were not predictive of PsA, and one was, we considered this study to have "mixed results" with respect to the marker 'trauma'.

If across multiple studies, <75% of studies were in agreement with each other, we considered this "conflicting evidence". If ≥75% of studies were in agreement, we applied the evidence grading according to Sackett[16].

Because only a small minority of the included studies were of "good" quality, we adapted the Sackett best evidence synthesis as follows: strong evidence in case of two or more studies with good or fair quality, moderate evidence in case of two or more studies with low quality or one study of good or fair quality, and limited evidence in case of one study with low quality. In case of two or more good/fair quality studies, the results of the poor quality studies were not taken into account for the BES. The heterogeneity of the markers and statistics precluded a quantitative meta-analysis.

Results

Study selection

The search yielded 5517 non-duplicate articles and, in addition, 14 studies were included via cross-reference checking. After screening on title and abstract, 221 articles were assessed in full text. A total of 119 studies met the selection criteria and were included. Of these, 19 studied clinical markers[17-35], 69 studied laboratory markers[19,36-103], and 32 studied genetic markers[104-135]. One study described both clinical and laboratory markers[19]. A flow chart of the selection process is shown in figure 1.

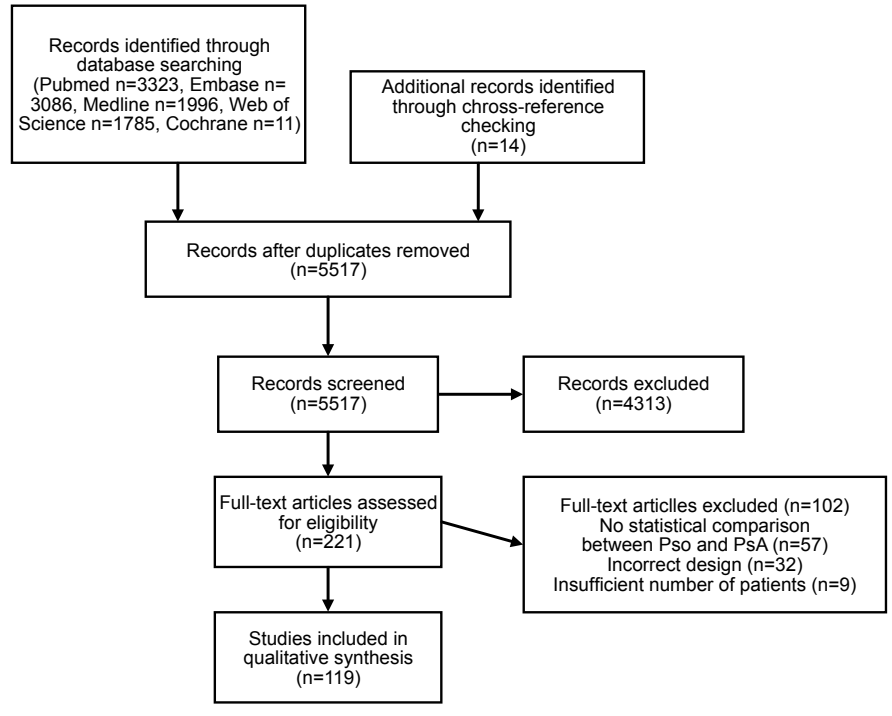

Figure 1: PRISMA flowchart of included studies.
PRISMA, preferred reporting items for systematic reviews and meta-analysis; PsA, psoriatic arthritis; Pso, psoriasis

Study characteristics

The characteristics of the included studies are listed in supplementary table 2. All clinical studies had a longitudinal design. Two laboratory studies had a longitudinal design and 67 had a cross-sectional design. All of the genetic studies had a cross-sectional design. Based on the criteria described in the best evidence synthesis, 259 markers were selected for further description (clinical: 51, laboratory: 137, genetic: 71), of which 104 were described in multiple studies (clinical: 32, laboratory: 36, genetic: 36). All markers are shown in supplementary table 3-5.

Quality assessment

Of the included studies, 19 studies were qualified as good quality, 11 studies were qualified as fair quality, and 89 studies were qualified as poor quality. Quality assessment of the included studies is shown in supplementary table 6 and 7.

Best evidence synthesis

Qualitative best evidence synthesis is depicted separately for clinical, laboratory, and genetic studies in tables 1-3. With respect to predictive markers for PsA in Pso, we report the markers for which there was at least a moderate level of evidence, or which were investigated in more than one study. With respect to markers associated with the presence of PsA in Pso, we report only the markers which were investigated in more than one study. An overview of the most promising findings are also shown in figure 2.

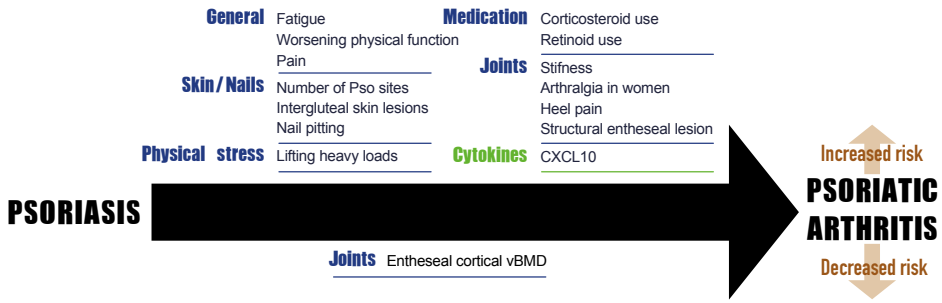

Figure 2: Overview of most promising predictors for the development of psoriatic arthritis in psoriasis patients.
Clinical parameters are depicted in blue, laboratory parameters are depicted in green. The strongest evidence is available for the predictive value of CXCL10, this is depicted in bold.
CXCL = C-X-C motif ligand

Clinical markers

Strong level of evidence

Strong evidence was available for 13 of the 51 investigated clinical markers. All these markers showed no association with the development of PsA in Pso patients. These markers included:

Table 1: Best evidence synthesis of clinical markers.

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
Comorbidities	Diabetes mellitus	2x no association [18, 22]		Strong evidence of no association
	Diarrhea	2x no association [20, 22]	1x no association [30]	Strong evidence of no association
	Infection requiring antibiotics	1x positive association [20] 1x no association [22]		Conflicting evidence
	Uveitis	1x positive association [22]		Moderate evidence of positive association
Disease characteristics (general)	(Worsening) Fatigue	1x positive association [23]		Moderate evidence of positive association
	Worsening function	1x positive association [23]		Moderate evidence of positive association
Disease characteristics (joints)	Arthralgia in women (not men)	1x positive association [23]		Moderate evidence of positive association
	Cortical vBMD entheseal	1x negative association [31]		Moderate evidence of negative association
	Heel pain	1x positive association [23]		Moderate evidence of positive association
	(Worsening) Stiffness	1x positive association [23]		Moderate evidence of positive association
	Structural entheseal lesion	1x positive association [31]		Moderate evidence of positive association
	Worsening pain	1x positive association [23]		Moderate evidence of positive association
Disease characteristics (skin/nails)	Duration of Pso	1x no association [19]	1x positive association [21]	Conflicting evidence
	Intergluteal lesions	1x positive association [34]		Moderate evidence of positive association

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
Disease characteristics (skin/nails)	Nail pitting	1x positive association [22]		Moderate evidence of positive association
	Psoriatic nail lesion	1x positive association [34] 3x no association [18, 19, 22]		Strong evidence of no association
	Scalp lesions	1x positive association [34] 1x no association [19]		Conflicting evidence
	Severity of Pso	3x positive association [22, 23, 34] 2x no association [19, 20]	1x positive association [21]	Conflicting evidence
	Younger age at Pso onset	2x positive association [24, 32] 1x no association [34]		Conflicting evidence
Fertility	Fertility treatment	1x no association [20]	1x no association [30]	Moderate evidence of no association
	Hormone replacement therapy	1x no association [20]	1x no association [30]	Moderate evidence of no association
	Menopause	3x no association [18, 20, 22]		Strong evidence of no association
	Oral contraceptives	2x no association [18, 20]	1x no association [30]	Strong evidence of no association
	Pregnancy	1x negative association [18] 1x no association [20]	1x no association [30]	Conflicting evidence
Intoxication	Alcohol consumption	1x mixed results [25] 3x no association [18, 20, 22]	3x no association [21, 30, 35]	Strong evidence of no association
	Current smoking	2x negative association [20, 29] 2x no association [22, 25]	1x negative association [21] 1x no association [27]	Conflicting evidence
	Past smoking	1x negative association [20] 3x no association [22, 25, 29]	2x no association [21, 27]	Strong evidence of no association
	Smoking intensity		1x positive association [27]	Limited evidence of positive association
Medication	Corticosteroids use	1x positive association [18]		Moderate evidence of positive association

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
Medication	Influenza vaccination	1x no association [20]	1x no association [30]	Moderate evidence of no association
	Methotrexate use	2x no association [18, 22]		Strong evidence of no association
	Retinoid use	1x positive association [22]		Moderate evidence of positive association
	Rubella vaccination	1x no association [20]	1x positive association [30]	Conflicting evidence
	Tetanus vaccination	1x no association [20]	1x no association [30]	Moderate evidence of no association
Patient characteristics	Age	4x no association [19, 20, 23, 34]		Strong evidence of no association
	BMI	2x positive association [17, 25] 3x no association [19, 22, 23]	1x positive association [28]	Conflicting evidence
	BMI at 18 years	1x positive association [32]	1x no association [28]	Conflicting evidence
	Patient reported family history of PsA	3x no association [19, 20, 22]		Strong evidence of no association
	Female sex	3x no association [19, 20, 23]	1x no association [21]	Strong evidence of no association
	Hip circumference		1x positive association [28]	Limited evidence of positive association
	University or high school	1x negative association [22]		Conflicting evidence
	level of education	1x no association [20]		
	Waist circumference		1x positive association [28]	Limited evidence of positive association
	Waist-hip ratio		1x positive association [28]	Limited evidence of positive association
	Weight increase from 18 years		1x positive association [28]	Limited evidence of positive association
Physical stress	Lifting heavy loads	1x positive association [20]		Moderate evidence of positive association

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
Physical stress	Trauma	2x no association [18, 20]	1x positive association [33] 1x mixed results [30]	Strong evidence of no association
Psychological distress	Anxiety/depression	1x positive association [26] 2x no association [20, 22]	1x no association [30]	Conflicting evidence
	Change in work status	1x no association [20]	1x no association [30]	Moderate evidence of no association
	Death of a family member	1x no association [20]	1x no association [30]	Moderate evidence of no association
	Move to a new house	1x no association [20]	1x positive association [30]	Conflicting evidence
	Psychological distress	2x no association [18, 23]		Strong evidence of no association

A positive association is defined as a higher risk of PsA when the marker is present/increased/higher. A negative association is defined as a lower risk of PsA when the marker is present/increased/higher.
BMI = body mass index; PsA = psoriatic arthritis; Pso = psoriasis; vBMD = volumetric bone mineral density.

diabetes[18,22], diarrhea[20,22], psoriatic nail lesion[18,19,22,34], menopause[18,20,22], oral contraceptives[18,20], alcohol consumption[18,20-22,25,30,35], past smoking[20-22,25,27,29], methotrexate use[18,22], age[19,20,23,25], a patient reported family history of PsA[19,20,22], female sex[19-21,23], trauma[18,20,30,33], and psychological distress[23,24]. There was no strong evidence available for clinical markers that had a positive or negative (i.e. protective) association with the development of PsA.

Moderate level of evidence

Moderate evidence was available for 20 of 51 clinical markers. Only six of them were investigated in more than one study. All of these markers showed no association with the development of PsA in Pso. These markers included: fertility treatment[20,30], hormone replacement therapy[20,30], influenza vaccination[20,30], tetanus vaccination[20,30], change in work status[20,30] and death of a family member[20,30].

Moderate evidence of a positive association was available for 13 clinical markers. These included: uveitis[22], (worsening) fatigue[23], (worsening) function[23], (worsening) pain[23], (worsening) stiffness[23], arthralgia in women[23], heel pain[23], structural entheseal lesions[31], intergluteal skin lesions[34], nail pitting[22], corticosteroid use[18], retinoid use[22], and lifting heavy loads[20].

Moderate evidence of a negative association was available for 1 marker: entheseal cortical volumetric bone mineral density (vBMD)[31].

Conflicting evidence

Conflicting evidence was available for 13 of 51 clinical markers. These markers included several disease characteristics: younger age at Pso onset[24,32,34], longer duration of Pso[19,21], presence of scalp lesions[19,34], more severe Pso[19-23,34] and higher BMI[17,19,22,23,25,28]. Conflicting evidence was also found for: infection requiring antibiotics[20,22], pregnancy[18,20,30], current smoking[20-22,25,27,29], rubella vaccination[20,30], university or high school level of education[20,22], anxiety/depression[20,22,26,30], and moving to a new home[20,30].

Laboratory markers

Strong level of evidence

Strong evidence was available for nine of 137 investigated laboratory markers. CXCL10 (C-X-C motif ligand 10) was the only laboratory marker which showed a positive association with the development of PsA in Pso patients[19,39]. It was also the only laboratory marker studied in a longitudinal design.

Four markers showed a strong level of evidence for a positive association with the presence of PsA in Pso: a higher level of matrix metalloproteinase 3 (MMP3)[56,58,61,75], a higher level of osteoprotegerin (OPG)[44,47,56,59,61,75], a higher level of interleukin 6 (IL-6)[41,77,95,100], and a higher level of C-reactive protein (CRP)[19,45,50,56,58,59,64,66,72,74,77,79,80,82,83,98].

Five markers showed a strong level of evidence for no association with PsA in Pso: vitamin D[66,69,90,91,98], serum glucose[64,90-92,94,95], serum triglycerides[64,74,89,91,92,94,95], serum high density lipoprotein (HDL)[64,74,91,92,95], and serum low density lipoprotein (LDL)[44,47,59,61,64,74,90,91,94,95].

Moderate level of evidence

Moderate evidence was available for 56 of 137 investigated laboratory markers. Fourteen of

Table 2: Best evidence synthesis of laboratory markers.

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
ACPA	Anti-CCP		3x positive association [37, 40, 54] 1x no association [99]	Moderate evidence of positive association
	Anti-MCV		1x positive association [60]	Limited evidence of positive association
Bone metabolism	25(OH) Vitamin D	2x no association [91, 98]	3x no association [66, 69, 89]	Strong evidence of no association
	Alkalic Phosphate	1x no association [98]	2x no association [50, 70]	Moderate evidence of no association
	Calcium		2x no association [50, 70]	Moderate evidence of no association
	COMP	1x no association [56]	1x no association [47]	Moderate evidence of no association
	CPII:C2C	1x positive association [56]		Moderate evidence of positive association
	CTX		2x no association [50, 61]	Moderate evidence of no association
	DKK-1	1x no association [75]	1x positive association [59]	Conflicting evidence
	MMP3	3x positive association [56, 58, 75]	1x no association [61]	Strong evidence of positive association
	OPG	2x positive association [56, 75]	4x no association [44, 47, 59, 61]	Strong evidence of positive association
	OPG/RANKL ratio		2x negative association [47, 82]	Moderate evidence of negative association
	Osteoclast precursors		1x positive association [82]	Limited evidence of positive association

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
Bone metabolism	Phosphate	1x no association [98]	1x no association [50]	Moderate evidence of no association
	RANKL	1x no association [56]	2x positive association [42, 82] 3x no association [47, 59, 61]	Conflicting evidence
	Urine Hp		1x negative association [70]	Limited evidence of negative association
Cell culture	IL-2 secretion		1x positive association [51]	Limited evidence of positive association
	IL-17 secretion		1x positive association [49] 1x no association [51]	Conflicting evidence
Cytokines	(Change in) CXCL10	2x positive association [19, 39]		Strong evidence of positive association
	IL-6	2x positive association [95, 100]	1x positive association [41] 1x no association [77]	Strong evidence of positive association
	IL-12/23 p40	1x no association [56]	1x positive association [82]	Conflicting evidence
	IL-23		1x positive association [96]	Limited evidence of positive association
	IL-33		1x positive association [82]	Limited evidence of positive association
	IL-34	1x positive association [45]	1x positive association [82]	Moderate evidence of positive association
	IL-35		1x positive association [82]	Limited evidence of positive association
	IL-36a		1x negative association [82]	Limited evidence of negative association
	IL-38		1x positive association [82]	Limited evidence of positive association
	M-CSF	1x negative association [75]	1x positive association [59]	Conflicting evidence

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
Cytokines	TNFα		2x positive association [77, 82]	Moderate evidence of positive association
Cytologic phenotype	CD3+ CD71+ count		1x positive association [51]	Limited evidence of positive association
	CD4+CD45RA-CXCR3+CCR4-		1x negative association [62]	Limited evidence of negative association
	CD4+CD45RA-CXCR3+CCR6-		1x negative association [62]	Limited evidence of negative association
	CD4+CD45RA-IFNγ+		1x negative association [62]	Limited evidence of negative association
	CD4+CD45RA-IL17+		1x positive association [62]	Limited evidence of positive association
	CD4+T_{EM}CXCR3+CCR4-		1x negative association [62]	Limited evidence of negative association
	CD4+T_{EM}IL17A+		1x negative association [62]	Limited evidence of negative association
	CD8+CD45RA-CCR6+CXCR3-CD69+		1x positive association [62]	Limited evidence of positive association
	CD8+CD45RA-IL17+		1x positive association [62]	Limited evidence of positive association
	CD8+T_{CM}CD69+		1x positive association [62]	Limited evidence of positive association
	CD8+T_{EM}IL17A+		1x positive association [62]	Limited evidence of positive association
	CD8+T_{EMRA}CCR6+CXCR3-CD69-		1x positive association [62]	Limited evidence of positive association
	CD8+T_{EMRA}CXCR3+CCR4-		1x negative association [62]	Limited evidence of negative association
	CD8+T_{EMRA}CXCR3+CCR6-CD69+		1x positive association [62]	Limited evidence of positive association

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
Cytologic phenotype	Mean platelet volume		2x positive association [55, 78]	Moderate evidence of positive association
	Monocyte count		1x positive association [79]	Limited evidence of positive association
	Neutrophil count		1x positive association [79]	Limited evidence of positive association
	Neutrophil:lymphocyte ratio		1x positive association [79]	Limited evidence of positive association
	Platelet count		1x positive association [79] 1x no association [55]	Conflicting evidence
	Platelet:lymphocyte ratio		1x positive association [79]	Limited evidence of positive association
	White blood count		1x positive association [79] 1x no association [89]	Conflicting evidence
Inflammation marker	CRP	5x positive association [45, 56, 58, 64, 98] 1x no association [19]	8x positive association [50, 59, 66, 74, 79, 80, 82, 83] 4x no association [51, 72, 77, 89]	Strong evidence of positive association
	ESR	1x positive association [45] 1x no association [98]	5x positive association [50, 66, 79, 80, 82] 2x no association [72, 95]	Conflicting evidence
Lipid metabolism	Adiponectin	1x positive association [64]	1x negative association [77]	Conflicting evidence
	ApoA:ApoB ratio		1x positive association [94]	Limited evidence of positive association
	ApoB		1x positive association [94]	Limited evidence of positive association
	CER		1x positive association [89]	Limited evidence of positive association
	Glucose	2x no association [64, 91]	4x no association [89, 92, 94, 95]	Strong evidence of no association

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
Lipid metabolism	HDL	2x no association [64, 91]	3x no association [74, 92, 95]	Strong evidence of no association
	Insulin		1x negative association [92]	Limited evidence of negative association
	LDL	2x no association [64, 91]	3x no associated [74, 89, 94] 1x positive association [95]	Strong evidence of no association
	LDL:HDL ratio		2x positive association [94, 95]	Moderate evidence of positive association
	Leptin	1x positive association [64]	1x no association [77]	Conflicting evidence
	Total cholesterol	1x negative association [91] 1x no association [64]	2x no association [92, 94] 1x positive association [95]	Conflicting evidence
	Total cholesterol/HDL	1x no association [91]	1x positive association [94]	Conflicting evidence
	Triglycerides	2x no association [64, 91]	3x no association [89, 92, 94] 2x positive association [74, 95]	Strong evidence of no association
	VLDL		2x no association [94, 95]	Moderate evidence of no association
miRNA expression	let-7b-3p	1x negative association [93]		Moderate evidence of negative association
	let-7b-5p	1x negative association [93]		Moderate evidence of negative association
	let-7e-5p	1x positive association [93]		Moderate evidence of positive association
	miR-26a-5p	1x positive association [93]		Moderate evidence of positive association
	miR-27a-3p	1x positive association [93]		Moderate evidence of positive association
	miR-27b-3p	1x positive association [93]		Moderate evidence of positive association

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
miRNA expression	miR-29a-3p	1x positive association [93]		Moderate evidence of positive association
	miR-30e-5p	1x positive association [93]		Moderate evidence of positive association
	miR-92a-3p	1x negative association [93]		Moderate evidence of negative association
	miR-92b-3p	1x negative association [93]		Moderate evidence of negative association
	miR-98-5p	1x positive association [93]		Moderate evidence of positive association
	miR-139-3p	1x negative association [93]		Moderate evidence of negative association
	miR-146a-5p	1x positive association [93]	1x positive association [84]	Moderate evidence of positive association
	miR-203a	1x negative association [93]		Moderate evidence of negative association
	miR-486-5p	1x negative association [93]		Moderate evidence of negative association
	miR-1180-3p	1x negative association [93]		Moderate evidence of negative association
	miR-2379-5p	1x positive association [93]		Moderate evidence of positive association
	miR-3158-3p	1x negative association [93]		Moderate evidence of negative association
	miR-4732-3p	1x negative association [93]		Moderate evidence of negative association
mRNA expression whole blood	CCL1	1x negative association [38]		Moderate evidence of negative association
	CCL7	1x negative association [38]		Moderate evidence of negative association

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
mRNA expression whole blood	CCL20	1x negative association [38]		Moderate evidence of negative association
	CX3CL1	1x negative association [38]		Moderate evidence of negative association
	CXCL2	1x negative association [38]		Moderate evidence of negative association
	CXCL5	1x negative association [38]		Moderate evidence of negative association
	HAT1		1x positive association [97]	Limited evidence of positive association
	IL-3	1x negative association [38]		Moderate evidence of negative association
	IL-6	1x negative association [38]		Moderate evidence of negative association
	IL-8	1x negative association [38]		Moderate evidence of negative association
	IL-17C	1x negative association [38]		Moderate evidence of negative association
	IL-17F	1x negative association [38]		Moderate evidence of negative association
	ISG20	1x negative association [38]		Moderate evidence of negative association
	MMP-3	1x negative association [38]		Moderate evidence of negative association
	NOTCH2NL		1x negative association [97]	Limited evidence of negative association
	SET2D		1x negative association [97]	Limited evidence of negative association
	STAT3	1x negative association [38]		Moderate evidence of negative association

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
mRNA expression whole blood	STAT6	1x negative association [38]		Moderate evidence of negative association
	SYK	1x negative association [38]		Moderate evidence of negative association
	TBX21	1x negative association [38]		Moderate evidence of negative association
Serum	CD5L	1x positive association [58]		Moderate evidence of positive association
	Creatinine	1x no association [98]	1x no association [59]	Moderate evidence of no association
	Complement C9		1x negative association [68]	Limited evidence of negative association
	IFI16	1x negative association [43]		Moderate evidence of negative association
	sIL2R	1x positive association [100]		Moderate evidence of positive association
	ITGB5	1x positive association [58]		Moderate evidence of positive association
	Gelsolin		1x negative association [66]	Limited association of negative association
	K17		1x positive association [85]	Limited evidence of positive association
	M2BP	1x positive association [58]		Moderate evidence of positive association
	MPO	1x positive association [58]		Moderate evidence of positive association
	PRL		1x positive association [73]	Limited evidence of positive association
	STIP1		1x positive association [85]	Limited evidence of positive association

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
Serum	Uric acid	1x positive association [101] 1x no association [46]	1x no association [102] 1x negative association [92]	Conflicting evidence
	VCP		1x positive association [86]	Limited evidence of positive association
	VEGFR-3		1x positive association [71]	Limited e evidence of positive association
	YKL-40		1x positive association [76]	Limited evidence of positive association
Skin	C16ORF61		1x positive association [57]	Limited evidence of positive association
	CPN2		1x positive association [57]	Limited evidence of positive association
	CXCL12		1x positive association [36]	Limited evidence of positive association
	FHL1		1x positive association [57]	Limited evidence of positive association
	GPS1		1x positive association [57]	Limited evidence of positive association
	IL23R		1x positive association [81]	Limited evidence of positive association
	ITGB5		1x positive association [57]	Limited evidence of positive association
	POSTN		1x positive association [57]	Limited evidence of positive association
	PP2R4		1x positive association [57]	Limited evidence of positive association
	SNCA		1x positive association [57]	Limited evidence of positive association
	SRP14		1x positive association [57]	Limited evidence of positive association
Skin	SRPX		1x positive association [57]	Limited evidence of positive association
Miscellaneous	Anti-ADAMTS-L5 IgG antibodies		1x positive association [103]	Limited association of positive association
	Anti-LL37 antibodies		1x positive association [103] 1x mixed results [68]	Conflicting evidence
	Arylesterase activity		1x positive association [74]	Limited evidence of positive association
	Hemoglobin		1x negative association [79]	Limited evidence of negative association
	IgG response to C region of rM12 protein		1x positive association [88]	Limited evidence of positive association

A positive association is defined as a higher risk of PsA when the marker is present/increased/higher. A negative association is defined as a lower risk of PsA when the marker is present/increased/higher.

ACPA = anti citrullinated protein antibodies; ADAMTS = a disentegrin and metalloproteinase with thrombospondin motifs; anti-CCP = anti-cyclic citrullinated protein; Apo = apolipoprotein; C16ORF61 = endosomal protein sorting factor like (VSP35L); C2C = collagen fragment neoepitopes Col2-3/4 (long mono); CCL = C-C chemokine ligand; CCR = C-C chemokine receptor; CD = cluster of differentiation; CD5L = CD5 ligand; CER = ceramide; CM = central memory; COMP = cartilage oligometric matrix protein; CPII = C-propeptide of type II collagen; CPN2 = carboxypeptidase N subunit 2; CRP = C-reactive protein; CTX = collagen type I C-telopeptide; CX3CL = C-X3-C motif ligand; CXCL = C-X-C motif ligand; CXCR = C-X-C motif receptor; DKK = dickkopf; EM = effector memory; ESR = erythrocyte sedimentation rate; FHL1 = four and a half LIM domains; GPS = G protein pathway suppressor; HAT = human airway trypsin-like protein; HDL = high density lipoprotein; Hp = hydroxyproline ; IFI = interferon-inducible protein; IFN = interferon; IgG = immunoglobulin G; IL = interleukin; IL23R = IL23 receptor; ISG = interferon stimulated gene; ITGB = integrin beta ; K17 = keratin 17; LDL = low density lipoprotein; M2BP = Mac-2-binding protein; M-CSF = macrophage colony stimulating factor; MCV = mutated citrullinated vimentin; miRNA = micro RNA; MMP = matrix metalloproteinase; MPO = myeloperoxidase; mRNA = messenger RNA; OPG = osteoprotegerin; POSTN = periostin ; PPP2R4 = protein phosphatase 2 phosphatase activator (PTPA); PRL = prolactin ; RANKL = receptor activator of nuclear factor kappa-B ligand; RNA = ribonucleic acid; SETD = SET domain protein; sIL-2R = soluble IL-2 receptor; SNCA = synuclein alpha; SRP = signal recognition particle; SRPX = sushi repeat containing protein X-linked; STAT = signal transducer and activator of transcription; STIP = stress-inducible phosphoprotein ; SYK = spleen associated tyrosine kinase; TBX = T-box; TNF = tumor necrosis factor; VCP = valosin containing protein; VEGFR = vascular endothelial growth factor receptor; VLDL = very low density lipoprotein

these 56 have been investigated in more than one study.

Of those 14 markers, six showed a positive association with the presence of PsA in Pso: the presence of anti-citrullinated protein antibodies (ACPA)[37,54,80,99], a higher level of IL-34[45,82], a higher level of tumor necrosis factor alpha (TNFα)[77,82], a higher mean platelet volume (MPV)[55-78], a higher LDL:HDL ratio [63,77,94,95], and the presence of microRNA miR-146a-5p[84,93].

Only one of the 14 markers which were investigated more than once, showed moderate evidence of a negative association with the presence of PsA in Pso: a lower ratio of OPG to receptor activator of nuclear factor kappa-B ligand (RANKL) was associated with the presence of PsA in Pso[47,82].

There was moderate evidence for no association for seven laboratory markers: serum alkalic phosphate[50,70,98], serum calcium[50,70], serum cartilage oligometric matrix protein (COMP)[47,56], serum phosphate[50,98], serum collagen type I C-telopeptide (CTx)[50,61], serum very low density lipoprotein (VLDL)[94,95], and serum creatinine[59,98].

Conflicting evidence

Conflicting evidence was available for 14 of 137 laboratory markers: markers of bone metabolism (dickkopf (DKK1)[59,75], RANKL)[42,47,56,59,61,82], markers of lipid metabolism (serum leptin[64,77], total serum cholesterol[64,91,92,94,95], total cholesterol : HDL ratio[91-94], serum triglycerides[64,74,90-92,94]), inflammation markers (erythrocyte sedimentation rate (ESR))[45,50,65,72,79,80,82,95,98], cell numbers (platelet count[55-79], white blood cell count[79,89]), cell phenotype (IL-17 secretion[49,51]), cytokine levels (IL-12/23 p40[56,82], macrophage colony stimulating factor (M-CSF)[59-75]), uric acid[46,92,101,102], and antibodies against LL-37[68,103].

Genetic markers

Strong level of evidence

There were no genetic markers which reached a strong level of evidence for a positive, negative or no association with the presence of PsA.

Moderate level of evidence

Moderate evidence was available for 30 of 71 investigated genetic markers. Twenty-two of those 31 have been investigated in more than one study.

Of these 22 markers six showed a positive association with the presence of PsA in Pso: the presence of haplotype B*27-C*01[112,132], haplotype B*27-C*02[112,113,132], haplotype B*38-C*12[112,113,132], haplotype B*39:01-C*12[113,132], the presence of HLA-B*27[104,108,111,113,121,126,132], and the presence of the single nucleotide polymorphism (SNP) rs1800925 in the IL13 gene[106,111].

Moderate evidence of a negative association was available for three markers: the presence of haplotype B*57-C*06[112,132], the presence of HLA-C*06[104,108-110,112,113,115,116,121,126,132], and the presence of the SNP rs2082412 in the IL12B gene[123,134].

There was moderate evidence for no association for 13 genetic markers: the presence of HLA-B*57[104,112,113,126], HLA-C*01[104,113,132], HLA-DRB1*03[104,115], the presence of the SNP rs397211 of IL1RN[123,134], the presence of the SNP's rs3212227[109,122] and rs6887695 in the IL12B gene[109,122], the

Table 3: Best evidence synthesis of genetic markers

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
HLA	Haplotype B*08:01-C*07		1x positive association [132]	Limited evidence of positive association
	Haplotype B*08-C*07-MICA*00801	1x positive association [125]		Moderate evidence of positive association
	Haplotype B*18-C*07		1x positive association [112]	Limited evidence of positive association
	Haplotype B*27-C*01		2x positive association [112, 132]	Moderate evidence of positive association
	Haplotype B*27-C*02		3x positive association [112, 113, 132]	Moderate evidence of positive association
	Haplotype B*27-C*02-MICA*00701/026	1x positive association [125]		Moderate evidence of positive association
	Haplotype B*35-C*04-MICA*0201/020	1x negative association [125]		Moderate evidence of negative association
	Haplotype B*37-C*06		1x negative association [132]	Limited evidence of negative association
	Haplotype B*38-C*12		3x positive association [112, 113, 132]	Moderate evidence of positive association
	Haplotype B*39:01-C*12		2x positive association [113, 132]	Moderate evidence of positive association
	Haplotype B*57-C*06		2x negative association [112, 132]	Moderate evidence of negative association
	Haplotype B*57-C*06-MICA*017		1x negative association [112]	Limited evidence of .negative association
	HLA-A*03		1x mixed results [115]	Conflicting evidence
	HLA-B*08		2x positive association [112, 132] 3x no association [104, 108, 113]	Conflicting evidence

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
HLA	HLA-B*13		1x mixed results [115] 2x no association [104, 126]	Conflicting evidence
	HLA-B*18		1x positive association [132] 1x no association [113]	Conflicting evidence
	HLA-B*27		6x positive association [108, 112, 113, 121, 126, 132] 1x no association [104]	Moderate evidence of positive association
	HLA-B*37		1x negative association [132] 1x no association [104]	Conflicting evidence
	HLA-B*38		3x positive association [112, 113, 132] 1x no association [126] 1x mixed results [115]	Conflicting evidence
	HLA-B*39		1x positive association [113] 1x mixed results [132]	Conflicting evidence
	HLA-B*40		1x negative association [132]	Limited evidence of negative association
	HLA-B*44		1x negative association [132]	Limited evidence of negative association
	HLA-B*57		1x negative association [112] 3x no association [104, 113, 126]	Moderate evidence of no association
	HLA-B*70		1x mixed results [115]	Conflicting evidence
	HLA-B amino acid position 45 Glu		1x positive association [124] 2x no association [104, 108]	Conflicting evidence
	HLA-B amino acid position 95 Leu		1x positive association [104]	Limited evidence of positive association
	HLA-B amino acid position 97 Arg		1x mixed results [108] 1x no association [104]	Conflicting evidence
	HLA-C*01		1x positive association [112] 3x no association [104, 113, 132]	Moderate evidence of no association

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
HLA	HLA-C*02		2x positive association [112, 132] 2x no association [104, 113]	Conflicting evidence
	HLA-C*06	1x negative association [110]	7x negative association [104, 108, 112, 116, 121, 126, 132] 2x no association [109, 113] 1x mixed results [115]	Moderate evidence of negative association
	HLA-C*07		1x positive association [112] 2x no association [104, 113]	Conflicting evidence
	HLA-C*08		1x negative association [121]	Limited evidence of negative association
	HLA-C*12		1x positive association [113] 1x no association [112]	Conflicting evidence
	HLA-C amino acid position 305 Ala		1x positive association [104]	Limited evidence of positive association
	HLA-C rs10484554		1x positive association [119]	Limited evidence of positive association
	HLA-C rs12191877		1x negative association [123]	Limited evidence of negative association
	HLA-DQB1*02		1x mixed results [115] 1x no association [104]	Conflicting evidence
	HLA-DRB1*03		2x no association [104, 115]	Moderate evidence of no association
	HLA-DR*04		1x positive association [115]	Limited evidence of positive association
	HLA-DR*07		1x negative association [121]	Limited evidence of negative association
	HLA-DR*11		1x mixed results [115]	Conflicting evidence
Non-HLA	ADAMTS9-MAG1 deletion		1x positive association [120]	Limited evidence of positive association

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
Non-HLA	CCR2 rs1799864	1x positive association [128]		Limited evidence of positive association
	IL1RN rs397211		2x no association [123, 134]	Moderate evidence of no association
	IL12B rs2082412		2x negative association [123, 134]	Moderate evidence of negative association
	IL12B rs3212227	1x no association [122]	1x no association [109]	Moderate evidence of no association
	IL12B rs6887695	1x no association [122]	1x no association [109]	Moderate evidence of no association
	IL13 rs1800925	1x positive association [111]	1x positive association [106]	Moderate evidence of positive association
	IL13 rs20541		2x positive association [106, 134] 1x not associated [123]	Conflicting evidence
	IL13 rs848	1x positive association [111]		Moderate evidence of positive association
	IL17E rs79877597		1x positive association [105]	Limited evidence of positive association
	IL23A rs2066807		2x not associated [123, 134]	Moderate evidence of no association
	IL23R rs11209026	1x no association [122]	1x no association [109]	Moderate evidence of no association
	IL23R rs2201841		1x negative association [123] 1x not associated [134]	Conflicting evidence
	KIR2DS1 pos / C2 neg		1x positive association [131]	Limited evidence of positive association
	LOC100505817 rs4891505		1x positive association [129]	Limited evidence of positive association
	MICA*00701/026	1x positive association [125]		Moderate evidence of positive association

Category	Marker	Good/Fair Quality Studies	Poor Quality Studies	Evidence
Non-HLA	MICA*00801	1x positive association [125]		Moderate evidence of positive association
	MICA*016	1x negative association [125]		Moderate evidence of negative association
	NFKBIA rs7152376	1x positive association [110]		Moderate evidence of positive association
	PTPN22 rs2476601		1x positive association [107]	Limited evidence of positive association
	TNFa-238		2x not associated [109, 118]	Moderate evidence of no association
	TNFa-308		2x not associated [109, 118]	Moderate evidence of no association
	TNFa-857		1x positive association [109]	Limited evidence of positive association
	TNFacd haplotype a6c1d3		1x positive association [117]	Limited evidence of positive association
	TNFAIP3 rs610604		2x not associated [123, 134]	Moderate evidence of no association
	TNIP rs17728338		2x not associated [123, 134]	Moderate evidence of no association
	TRAF3IP2 rs240993		1x not associated [134]	Limited evidence of no association
	TRAF3IP2 rs458017		1x not associated [119]	Limited evidence of no association
	TSC1 rs1076160		2x not associated [123, 134]	Moderate evidence of no association
	ZNF816A		1x negative association [134]	Limited evidence of negative association

A positive association is defined as a higher risk of PsA when the marker is present/increased/higher. A negative association is defined as a lower risk of PsA when the marker is present/increased/higher.
ADAMTS = a disentegrin and metalloproteinase with thrombospondin motifs; Arg = arginine; CCR = C-C motif receptor; Glu = glutamic acid; HLA = human leukocyte antigen; IL = interleukin; IL1RN = IL-1 receptor antagonist; IL23R = IL-23 receptor; KIR = killer-cell immunoglobulin-like receptor; MAGI = membrane-associated guanylate kinase; MICA = MHC class I polypeptide-related sequence A; PTPN22 = protein tyrosine phosphatase non-receptor type 22; TNF = tumor necrosis factor; TNFAIP = TNF alpha-induced protein; TNIP = TNFAIP3 interacting protein; TRAF = TNF receptor associated factor; TRAF3IP = TRAF3 interacting protein; TSC1 = tuberous sclerosis 1; ZNF = zinc finger protein

presence of the SNP rs2066807 in IL23A[123,134], the presence of the SNP rs11209026 in IL23R[109,122], the presence of the SNP rs610604 in TNFAIP3 (TNF alpha-induced protein 3)[123,134], the presence of the SNP rs17728338 in TNIP (TNFAIP3 interacting protein)[123,134], the presence of the SNP rs1076160 in TSC1 (tuberous sclerosis 1)[123,134], and the presence of TNFa-238[109,118] and TNFa-308[109,118].

Conflicting evidence

Conflicting evidence was found for 17 of 71 genetic markers, of which 14 were investigated in more than one study. These were: the presence of HLA-B*08[104,108,112,113,132], HLA-B*13[104,115,126], HLA-B*18[113,132], HLA-B*37[104,132], HLA-B*38[112,113,115,126,132], HLA-B*39[113,132], HLA-C*02[104,112,113,132], HLA-C*07[104,112,113], HLA-C*12[112,113], HLA-DQB1*02[104,115], the presence of glutamic acid (Glu) at HLA-B amino acid position 45[104,108,124], the presence of Arginine (Arg) at HLA-B amino position 97[104,108], the presence of SNP rs20541 in the IL13 gene[106,123,134], and the presence of SNP rs2201841 in the IL23R gene[106,134].

Discussion

In this review, we summarized the available evidence for possible markers for the onset or presence of PsA in a Pso patient population in a systematic way. Thereby we provide an update and addition to a recent narrative review regarding this subject by Scher et al[10]. When looking at clinical markers, we found only strong evidence for markers which were not associated with the development of PsA. Regarding laboratory markers, there was strong evidence for the predictive value of (a change in) CXCL10 serum titers[19,39]. There was also strong evidence for the association with (but not prediction of) PsA of several markers related to bone metabolism[44,47,56,58,59,61,75], and inflammation[19,45,50,51,56,58,59,64,66,72,74,77,79,80,82,83,89,95,98]. With respect to genetic markers, we found no markers which reached a strong level of evidence for the association with PsA.

In line with previous beliefs on possible clinical risk factors[10,136], we found moderate evidence for a positive association of gluteal fold lesions[34] and nail pitting for the onset of PsA[22]. However, for nail involvement in general (e.g. distal onycholysis, oil drop phenomenon and crumbling) there was strong evidence of no association[18,19,22,34]. Therefore, this relationship seemed to be restricted to this specific nail feature.

Notably, we found conflicting evidence for the predictive value of obesity[17,19,20,22,23,25,28] and psoriasis severity[19-23,34] for the development of PsA in Pso patients. These studies may also be prone to bias because patients with severe Pso differ from patients with mild Pso in several aspects. For instance, when looking at Pso severity in particular, one can argue that more severe skin involvement is treated more intensively, thereby possibly suppressing concomitant arthritis. These kinds of bias may be the reason why these frequently reported markers reach conflicting evidence when all the studies are taking into account in a systematic way.

When looking at BMI at one unspecified timepoint, this marker shows conflicting evidence for a relationship with the development of PsA. In three out of five high/fair quality studies there was no association[19,22,23], while two out of five showed a positive association[17,25]. Even when taking into account that the beforementioned three studies are performed in a partially

overlapping cohort, this marker doesn't reach the 75% agreement level we consider necessary for a conclusive result. Therefore, BMI at any unspecified timepoint may not be specific enough for prediction of PsA. Interestingly, more specified markers of weight and body composure (e.g. recent weight gain, BMI at younger age, or abdominal adipositas) showed a positive association with the development of PsA in Pso, but were only investigated in one study of poor quality[28]. Increasing the evidence in a more detailed way may be more valid and relevant.

The association of trauma and psoriatic arthritis was theorized to be due to a deep Koebner phenomenon[136]. This phenomenon is comparable to the well-known Koebner phenomenon in the skin, where trauma can cause the appearance of new skin lesions. The theory on the deep Koebner phenomenon is based on a study of Thorarensen et al, who used diagnostic codes to establish two comparable cohorts (Pso with and without PsA)[33]. However, when forming cohorts in this way, there is a higher risk of misclassification in either cohort. This study is in disagreement with two other papers with higher diagnostic certainty[18,20]. Therefore we concluded that there is currently strong evidence that physical trauma is not associated with a higher rate of PsA in Pso patients.

The relationship between smoking and PsA development has been described previously as the "smoking paradox"[29]. This entails the fact that smoking appears to be a risk factor for PsA when looking at the general population, but this association disappears when only looking at psoriasis patients. This paradox may be explained by collider bias: bias resulting from correcting for a variable which is a common effect of the exposure and outcome[10]. In our review, we found conflicting evidence for an effect of (current) smoking[20,21,23,25,27,29]. However, due to this collider bias, it is hard to determine if smoking leads to additional risk for the development of PsA in a Pso population, unrelated to its effect on the development of Pso. Studies focusing on a change in smoking status after the development of Pso may shed a light on this enigma, as suggested by Nguyen[29].

With regard to laboratory markers, only CXCL10 was studied longitudinally. This cytokine was described in two good/fair quality studies, both found an association between CXCL10 and PsA. Pso patients who developed PsA had a higher CXCL10 serum level at baseline[19]. It was also shown that during the evolution to arthritis the serum level of CXCL10 diminished: a larger negative change was associated with a higher risk of PsA[39]. The reason why CXCL10 levels decreased towards the development of PsA is still unknown. One hypothesis could be that the psoriasis patient group with a high level of CXCL10 is more prone to develop arthritis due to its chemoattractant properties on CXCR3+ CD4+ and CD8+ T-cells[137]. In the evolution towards clinical manifest PsA, locally produced CXCL10 might get depleted by these infiltrating and locally expanding inflammatory cells, subsequently lowering circulating CXCL10 levels over time. However, since these two studies were published by the same research group, results may be based on (partially) overlapping patient groups. Therefore, the predicting value of CXCL10 should be interpreted cautiously.

With regard to cross-sectional studies, and markers that may indicate the presence of PsA in Pso patients, we found strong evidence for a positive association with PsA in Pso for markers of inflammation and bone metabolism. CRP is a well-known, widely used inflammatory marker. We found strong evidence that the CRP level in PsA patients was higher than in patients with Pso only[19,45,50,51,56,58,59,64,66,72,74,77,79,80,82,83,89,98]. We argue that the co-appearance of joint

inflammation is responsible for this observation. However, we found no articles which studied the level of CRP before the start of PsA in Pso. Therefore, it is unknown whether it can be used as a predictive marker. Also, a clear CRP cut-off value for the presence of PsA (and therefore, specificity and sensitivity) is lacking.

Other markers for which strong evidence of a positive association with the development of PsA in Pso exist, were IL-6, MMP3, and OPG. IL-6 is widely regarded as a marker for systematic inflammation and an important contributor to the production of CRP by the liver. MMP3 and OPG are associated with bone metabolism; one of the hallmark signs of PsA is new bone formation[136]. Also, untreated arthritis can lead to irreversible erosions[4]. Therefore, it is not surprising that MMP and OPG showed an association with the presence of PsA in our review. In line with CRP, the predictive value of these markers is unknown, because longitudinal studies are not performed yet.

Laboratory markers for cardiovascular disease are studied extensively in psoriatic disease[64,74,77,89-92,94,95]. From these findings, we can conclude with strong evidence that these levels do not differ between psoriasis patients with and without arthritis. This is in contrast to a recent review which showed that the prevalence of cardiovascular comorbidities is higher in patients with PsA when compared to Pso[138]. This suggests that there are additional factors (e.g. systemic inflammation) that play a role in cardiovascular morbidity in PsA.

With respect to genetic markers, we focus here on the most important HLA-markers for Pso and PsA, and the IL-12 – IL-23 – IL-17 axis. The most important genetic marker for psoriasis is HLA-C*06, also known as PSOR1[139]. This marker is responsible for up to 50% of Pso heritability in the healthy population. It is associated with type-I (early onset) psoriasis, as well as a guttate phenotype[140]. Interestingly, our review shows that, when looking within the population of Pso patients, patients with the HLA-C*06 marker were less likely to also have PsA. Despite multiple studies investigating this marker, high quality studies are needed to confirm the robustness of the negative relationship between HLA-C*06 and the onset of PsA.

We found a moderate level of evidence for the presence of concomitant PsA in Pso for HLA-B*27, known for its high prevalence (90%) in ankylosing spondylitis (AS)[141]. In other diseases of the spondyloarthritis spectrum, the presence of HLA-B*27 is still higher than in the general population, but less than in AS. Our review showed that the presence of HLA-B*27 was higher in the Pso patients who developed arthritis than in the Pso patients who did not. This could indicate that HLA-B*27 may be able to differentiate between Pso patients who do or do not have PsA, which is also considered a part of the spondyloarthritis spectrum.

When looking at the IL-17/IL-23 axis from a genetic viewpoint, there was moderate evidence that there are no SNPs in the IL23 or IL23R gene for which the presence differs significantly between PsA and Pso patients[109,122,123,134]. We found limited evidence that the presence of rs79877597 in the IL17 gene was more common in PsA versus Pso patients[105]. With regard to the common IL-12/IL-23 pathway, there was moderate evidence regarding several SNPs in the IL12 gene. We found that the presence of one SNP in IL12 (rs2082412) was lower in PsA versus Pso patients, while other SNPs in this gene showed no difference[109,122,123,134]. While the IL-17/IL-23 axis may be important for the development of psoriatic disease in the general population, these results may indicate that it is of limited importance in the development of PsA in Pso.

The strengths of this study include the extensiveness and systematic way of the search with respect to markers for PsA in patient cohorts with Pso, subsequentially providing a comprehensive overview of the available evidence. Also, the intertwining of clinical, laboratory, and genetic markers in a systematic way is unique. By conducting a best evidence synthesis, taking the study quality into account, we made a qualitative overview of the extensive data.

The limitations of this systematic review are mostly due to the limitations of the included studies. Since there were (almost) no prospective/longitudinal studies looking at genetic and laboratory markers, we could only summarize the level of evidence with regard to the relationship between laboratory and genetic markers with the presence of PsA in patients with Pso (i.e. only one predictive factor could be identified). The level of evidence was limited by a paucity of high or fair quality studies. Mostly, this was because of a lack of appropriate definition of patient and control groups, in addition to not adjusting for possible confounders.

Conclusion

This comprehensive systematic review on clinical, laboratory and genetic markers for PsA in patients with Pso revealed that a useful set of markers is not established yet. There were no clinical or genetic markers with strong evidence which could predict the development of PsA in Pso cohorts. There was strong evidence that laboratory markers related to bone metabolism and inflammation were associated with the presence of PsA. Promising is CXCL10, which reached a strong level of evidence for predicting development of PsA in a Pso population[19,39]. The importance of timely detecting PsA in a Pso population, and finding more (bio)markers contributing to early detection, remains high.

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Supplementary table 1: Search strategy

PubMed search strategy	
Psoriasis	Psoriasis [MESH] Psorias* [tiab] Psoriat* AND patients [tiab]
AND	
Risk factors (general)	Predict*[tiab] Risk factors [MESH] Risk AND factor* [tiab] Risk* [tiab] Etiology [tiab] Aetiology [tiab] Aetiology [tiab]
OR	
Risk Factors (detailed: phenotypic, laboratory and genetic)	Biological Markers [Mesh] Biomarker* [tiab] Biologic* AND marker* [tiab] Marker* [tiab] Phenotype [MESH] Phenotyp* [tiab] Genetic marker [MESH] Genetic* AND Marker [tiab]
AND	
Psoriatic arthritis	Psoriatic arthritis [MESH] arthri* AND psoria* [tiab] arthrop* AND psoria* [tiab] enthes* AND psoria* [tiab] Spondylarthritis [Mesh major topic] spondyloarthr* AND psoria* [tiab]
AND	
Limits	Dutch[lang] OR English[lang] OR German[lang]

Embase search strategy	
Psoriasis	exp psoriasis/ psorias$.ti,ab. (psoriat$ adj patients).ti,ab.
AND	
Risk factors (general)	Predict$.ti,ab. exp risk factors/ (risk adj factor$) ti,ab. Risk$. ti,ab. *etiology/ etiology.ti,ab. aetiology.ti,ab. Determinant$.ti,ab.
OR	
Risk Factors (detailed: phenotypic, laboratory and genetic)	exp biological marker/ biomarker$.ti,ab. (biologic$ adj1 marker$) Marker$.ti,ab. exp phenotype/ phenotyp$.ti,ab. exp genetic marker/ (genetic$ adj1 marker).ti,ab.
AND	
Psoriatic arthritis	exp psoriatic arthritis/ (arthr$ adj1 psoria$).ti,ab. (arthrop$ adj1 psoria$).ti,ab. (enthes$ adj1 psoria$).ti,ab. Spondylarthritis/ (spondyloarthr$ adj1 psoria$).ti,ab
AND	
Limits	2: limit 1 to (conference abstract or conference paper or conference proceeding or "conference review") 1 not 2 limit .. to (dutch or english or german)

Medline search strategy	
Psoriasis	exp psoriasis/ psorias$.ti,ab. (psoriat$ adj patients).ti,ab.
AND	
Risk factors (general)	Predict$.ti,ab. exp risk factors/ (risk adj factor*).ti,ab. Risk$.ti,ab. etiology.ti,ab. aetiology.ti,ab. determinant*.ti,ab.
OR	
Risk Factors (detailed: phenotypic, laboratory and genetic)	exp biological marker/ biomarker$.ti,ab. (biologic$ adj1 marker$).ti,ab. Marker$.ti,ab. exp phenotype/ phenotyp$.ti,ab. exp genetic marker/ (genetic$ adj1 marker).ti,ab.
AND	
Psoriatic arthritis	exp psoriatic arthritis/ (arthri$ adj1 psoria$).ti,ab. (arthrop$ adj1 psoria$).ti,ab. (enthes$ adj1 psoria$).ti,ab. Spondylarthritis/ (spondyloarthr$ adj1 psoria$).ti,ab.
AND	
Limits	limit … to (dutch or english or german)

Web of science search strategy	
Psoriasis	Psorias* Psoriat* NEAR/1 patients
AND	
Risk factors (general)	Predict* Risk NEAR/1 factor* Risk* Etiology Aetiology Determinant*
OR	
Risk Factors (detailed: phenotypic, laboratory and genetic)	Biologic* NEAR/1 marker* Biomarker* Phenotyp* Genetic* NEAR/1 marker
AND	
Psoriatic arthritis	arthri* NEAR/1 Psoria* arthrop* NEAR/1 psoria* enthes* NEAR/1 psoria* spondylarthritis spondyloarthr* NEAR/1 psoria
AND	
Limits	Refined by: [excluding] DOCUMENT TYPES: (MEETING ABSTRACT) AND LANGUAGES: (ENGLISH OR GERMAN)

Cochrane search strategy	
Psoriasis	MeSH descriptor: [Psoriasis] explode all trees psorias*:ti,ab,kw psoriat* near/1 patients:ti,ab,kw
AND	
Risk factors (general)	predict*:ti,ab,kw MeSH descriptor: [Risk Factors] explode all trees risk factor*:ti,ab,kw risk*:ti,ab,kw etiology:ti,ab,kw aetiology:ti,ab,kw determinant:ti,ab,kw
OR	
Risk Factors (detailed: phenotypic, laboratory and genetic)	MeSH descriptor: [Biomarkers] explode all trees biomarker*:ti,ab,kw biologic* marker*:ti,ab,kw marker:ti,ab,kw MeSH descriptor: [Phenotype] explode all trees phenotyp*:ti,ab,kw MeSH descriptor: [Genetic Markers] explode all trees genetic* marker:ti,ab,kw
AND	
Psoriatic arthritis	MeSH descriptor: [Arthritis, Psoriatic] explode all trees arthri* near/1 psoria*:ti,ab,kw arthrop* near/1 psoria*:ti,ab,kw enthes* near/1 psori*:ti,ab,kw MeSH descriptor: [Spondylarthritis] this term only spondyloarthr* near/1 psoria*:ti,ab,kw

Supplementary table 2: Characteristics of included studies (n=119)

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Abdelaal, 2018 [36] **Egypt** **Cross-sectional**	Diagnosis: by clinical and histopathological criteria N = 10 Age (median): 38 years Sex: 40% male Exclusion PsA: no	Diagnosis: by CASPAR criteria N = 10 Age (median): 39 years Sex: 30% male	Cytologic phenotype (3)	A higher mRNA-expression of CXCL12 in keratinocytes, dermal cells and blood vessels was associated with PsA.
Abdel Fattah, 2009 [37] **Egypt** **Cross-sectional**	Diagnosis: basis not reported N = 40 Age (mean): 43 years Sex: 65% male Exclusion PsA: no	Diagnosis: by Moll & Wright criteria N = 40 Age (mean): 43 years Sex: 45% male	ACPA (1)	Anti-CCP levels were not associated with PsA.
Abji, 2016 [19] **Canada** **Cohort** **Follow-up: 1-5 years**	Diagnosis: by dermatologist N = 45 Age (mean): 46 years Sex: 44% male Exclusion PsA: yes	Diagnosis: by rheumatologist and CASPAR N = 46 Age (mean): 47 years Sex: 54% male	Cytokines (1) Inflammation marker (1) Disease activity (4) Patient characteristics (4)	Baseline patient characteristics and disease activity were not associated with an increased risk of PsA. CXCL10 was associated with PsA.
Abji, 2017 [38] **Canada** **Cross-sectional**	Diagnosis: by dermatologist N = 20 Age (mean): 44 years Sex: 50% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 20 Age (mean): 48 years Sex: 45% male	mRNA expression, peripheral blood (25)	A lower mRNA-expression of 15 genes was associated of PsA.*
Abji, 2020 [39] **Canada** **Cohort** **Follow-up: 1-10 years**	Diagnosis: by dermatologist N = 583 Age (mean): 50 years Sex: 46% male PsA exclusion: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 61 Age (mean): 50 years Sex: 52% male	Cytokines (1)	A larger decline in CXCL10 over time was associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Alenius, 2005 [40] Sweden Cross-sectional	Diagnosis: basis not reported N = 146 Age: not reported Sex: 53% male Exclusion PsA: uncertain	Diagnosis: basis not reported N = 160 Age: not reported Sex: 45% male	ACPA (1)	A higher anti-CCP level was associated with an increased risk of PsA.
Alenius, 2009 [41] Sweden Cross-sectional	Diagnosis: basis not reported N = 85 Age (mean): 51 years Sex: 51% male** Exclusion PsA: yes	Diagnosis: by Moll and Wright criteria N = 134 Age (mean): 48 years Sex: 51% male**	Cytokines (1) Other serum markers (1)	A higher IL-6 level was associated with an increased risk of PsA.
Amin, 2015 [42] Egypt Cross-sectional	Diagnosis: basis not reported N = 40 Age (mean): 58 years Sex: 60% male Exclusion PsA: yes	Diagnosis: by CASPAR criteria N = 20 Age (mean): 46 years Sex: 40% male	Bone metabolism (1)	A higher serum RANKL level was associated with PsA.
De Andrea, 2019 [43] Italy Cross-sectional	Diagnosis: basis not reported N = 44 Age: not reported Sex: not reported Exclusion PsA: no	Diagnosis: by CASPAR criteria N = 158 Age (median): 50 years Sex: 50% male	Serum markers (1)	A lower level of IFI16 was associated with PsA.
Aterido, 2019 [104] Spain Cross-sectional	Diagnosis: by dermatologist N= 614 Age (mean): 50 years Sex: 60% male Exclusion PsA: yes, not by rheumatologist	Diagnosis: by rheumatologist, CASPAR criteria N = 2265 Age (mean): 53 years Sex: 56% male	HLA (1)	The presence of Leu at amino acid position 95 of HLA-C was positively associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Attia, 2011 [44] Egypt Cross-sectional	Diagnosis: by characteristic lesions N = 34 Age (mean): 37 years Sex: 65% male Exclusion PsA: no	Diagnosis: by CASPAR criteria N = 16 Age (mean): 35 years Sex: 63% male	Bone metabolism (1)	Serum OPG was not associated with PsA.
Ausavarungnirun, 2017 [45] Thailand Cross-sectional	Diagnosis: by dermatologist N = 55 Age (mean): 52 years Sex: 42% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 55 years Age (mean): 53 Sex: 42% male	Bone metabolism (1) Inflammation markers (2)	A higher (level of) ESR and hs-CRP were associated with PsA.
Barbarroja, 2019 [46] Spain Cross-sectional	Diagnosis: by dermatologist N = 1001 Age (mean): 48 years Sex: 51% male Exclusion PsA: yes	Diagnosis: by rheumatologist N = 100 Age (mean): 50 years Sex: 49% male	Uric acid (1)	Hyperuricemia was not associated with PsA.
Bartosinska, 2015 [47] Poland Cross-sectional	Diagnosis: by dermatologist N = 39 Age (mean): 46 years Sex: 39% male Exclusion PsA: yes	Diagnosis: by CASPAR criteria N = 22 Age (mean): 48 years Sex: 22% male	Bone metabolism (4) Cytokines (1)	A lower OPG/sRANKL ratio was associated with PsA.
Bartosinka, 2018 [48] Poland Cross-sectional	Diagnosis: by dermatologist N = 51 Age (mean): 47 years ** Sex: not reported Exclusion PsA: no	Diagnosis: basis not reported N = 21 Age (mean): 47 years ** Sex: not reported	mRNA expression, peripheral blood (3)	mRNA expression of PDCD1, NRP1 and HLA-G was not associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Batalla, 2015 [105] Spain Cross-sectional	Diagnosis: by 2 independent dermatologists N = 410 Age (mean): 47 years Sex: 54% male** Exclusion PsA: yes	Diagnosis: by Moll & Wright and CASPAR criteria N = 170 Age (mean): 47 years Sex: 54% male**	Non-HLA (6)	The presence of IL17E rs79877597 CC genotype was positively associated with PsA.
Benham, 2013 [49] UK Cross-sectional	Diagnosis: by dermatologist N = 12 Age (mean): 51 years Sex: 50% male Exclusion PsA: no	Diagnosis: by CASPAR criteria N = 11 Age (mean): 52 years Sex: 46% male	Cell culture (1) Cytologic phenotype (2)	A higher IL-22 secretion by PBMC's was associated with PsA.
Borman, 2008 [50] Turkey Cross-sectional	Diagnosis: by histopathology N = 29 Age (mean): 39 years Sex: 52% male Exclusion PsA: yes	Diagnosis: by inflammatory arthritis N = 18 Age (mean): 41 years Sex: 44% male	Bone metabolism (4) Inflammation markers (2)	A higher (level of) of ESR and CRP were associated with PsA.
Bose, 2014 [51] Italy Cross-sectional	Diagnosis: basis not reported N = 21 Age (mean): 54 years Sex: 90% male Exclusion PsA: no	Diagnosis by: CASPAR criteria N = 30 Age (mean): 54 years Sex: 67% male	Cell culture (7) Cytologic phenotype (1)	A higher IL-2 secretion by anti-CD3-stimulated T-cells and a higher percentage of CD3+CD71+ cells were associated with PsA.
Bostoen, 2014 [52] Belgium Cross-sectional	Diagnosis: by dermatologist N = 49 Age (mean): 49 years Sex: 59% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 55 Age (mean): 50 years Sex: 69% male	Inflammation marker (1)	CRP was not associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Bowes, 2011 [106] UK, Ireland Cross-sectional	Diagnosis: by dermatologist N = 743 Age: not reported Sex: not reported Exclusion PsA: yes	Diagnosis: by rheumatologist based on psoriasis and peripheral arthritis N = 937 Age: not reported Sex: 42% male	Non-HLA (2)	The presence of IL-13 rs1800925 and rs20541 major allele were positively associated with PsA.
Bowes, 2015 [107] Multiple countries (WTCCC2-cohort) Cross-sectional	Diagnosis: basis not reported N = 1784 Age: not reported Sex: not reported Exclusion PsA: yes	Diagnosis: basis not reported N = 1962 Age: not reported Sex: not reported	Non-HLA (1)	The presence of PTPN22 rs2476601 was positively associated with PsA.
Bowes, 2017 [108] Multiple countries (WTCCC2-cohort) Cross-sectional	Diagnosis: not reported basis N = 2808 Age: not reported Sex: not reported Exclusion PsA: yes	Diagnosis: by rheumatologist based on psoriasis and peripheral arthritis N = 1945 Age: not reported Sex: not reported	HLA (10)	The presence of Asp or Ser at amino acid position 97 of HLA-B was positively associated with PsA. HLA-C*0602 was negatively associated with PsA.
Cabaleiro, 2013 [109] Spain Cross-sectional	Diagnosis: basis not reported N = 109 Age: not reported Sex: not reported Exclusion of PsA: yes	Diagnosis: basis not reported N = 33 Age: not reported Sex: not reported	HLA (1) Non-HLA (8)	The presence of TNF-857 CC phenotype was positively associated with PsA.
Calzavara, 1998 [53] Italy Cross-sectional	Diagnosis: basis not reported N = 38 Age (mean): 50 years Sex: 63% male Exclusion PsA: no	Diagnosis: by Moll and Wright, Ruzicka criteria N = 76 Age (mean): 49 years Sex: 46% male	ACPA (1)	Presence of APF was not associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Candia, 2006 [54] USA, Columbia Cross-sectional	Diagnosis: by dermatologist N = 106 Age (mean): 43 years Sex: 48% male Exclusion PsA: no	Diagnosis: by Moll and Wright criteria N = 72 Age (mean): 48 years Sex: 43% male	ACPA (1)	A higher level of anti-CCP was associated with PsA.
Canpolat, 2010 [55] Turkey Cross-sectional	Diagnosis: basis not reported N = 58 Age (mean): 41 years ** Sex: 53% male Exclusion PsA: yes	Diagnosis: by Moll and Wright criteria N = 48 Age (mean): 41 years ** Sex: 58% male	Cytologic phenotype (2)	A higher MPV was associated with PsA.
Chandran, 2010 [56] Canada Cross-sectional	Diagnosis: by dermatologist N = 26 Age (mean): 45 years Sex: 46% male Exclusion PsA: yes	Diagnosis: by CASPAR criteria N = 26 Age (mean): 47 years Sex: 46% male	Bone metabolism (6) Cytokines (2) Inflammation markers (1)	Higher level of hs-CRP, OPG, MMP-3 and the CPII:C2C ratio were associated with PsA.
Coto-Segura, 2019 [110] Spain Cross-sectional	Diagnosis: by dermatologist N = 309 Age: not reported Sex: 59% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 187 Age: not reported Sex: 48% male	HLA (1) Non-HLA (3)	The presence of HLA-Cw6 was negatively associated with PsA. The presence of NFKB1A rs7152376 was positively associated with PsA.
Cretu, 2015 [57] Canada Cross-sectional	Diagnosis: basis not reported N = 10 Age: not reported Sex: 60% male Exclusion PsA: yes	Diagnosis: by CASPAR criteria N = 10 Age: not reported Sex: 60% male	Skin (36) Serum markers (2)	12/36 proteins were higher expressed in PsA lesional skin.*** A higher level of serum ITGB5 was associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Cretu, 2017 [58] Canada Cross-sectional	Diagnosis: basis not reported N = 100 Age (mean): 50 years Sex: 55% male Exclusion PsA: yes	Diagnosis: by CASPAR criteria N = 100 Age (mean): 51 years Sex: 49% male	Bone metabolism (1) Inflammation markers (1) Serum markers (4)	Higher levels of ITGB5, M2BP and CRP were associated with PsA.
Dalbeth, 2010 [59] Australia Cross-sectional	Diagnosis: by dermatologist N = 10 Age (median): 50 years Sex: 60% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 38 Age (median): 44 years Sex: 58% male	Bone metabolism (3) Cytokines (1) Inflammation marker (1) Serum markers (1)	Higher levels of CRP, DKK-1 and M-CSF were associated with PsA.
Dalmady, 2013 [60] Hungary Cross-sectional	Diagnosis: basis not reported N = 42 Age (mean): 46 years Sex: 74% male Exclusion PsA: yes	Diagnosis: by CASPAR criteria N = 46 Age (mean): 45 years Sex: 52% male	ACPA (1)	A higher level of anti-MCV titers was associated with PsA.
Diani, 2019 [61] Italy Cross-sectional	Diagnosis: by dermatologist N = 28 Age (mean): 45 years Sex: 69% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 15 Age (mean): 51 years Sex: 78% male	Bone metabolism (21)	None of the markers of bone metabolism were associated with PsA.
Diani, 2019 [62] Italy Cross-sectional	Diagnosis: by dermatologist N = 50 Age (median): 48 years Sex: 66% male Exclusion PsA: no	Diagnosis: basis not reported N = 50 Age (median): 48 years Sex: 78% male	Cytologic phenotype (27)	A higher percentage of 7$ and a lower percentage of 5¥ cell subsets were associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Eder, 2011 [20] Canada Case-control Follow-up: 10 years	Diagnosis: by dermatologist N = 159 Age (mean): 48 years Sex: 54% male Exclusion PsA: yes	Diagnosis: by CASPAR N = 159 Age (mean): 45 years Sex: 56% male	Comorbidities (4) Disease activity (2) Fertility (5) Intoxication (4) Medication (6) Patient characteristics (3) Physical stress (13) Psychological distress (6)	Lifting heavy loads and infections that required antibiotics were associated with an increased risk of PsA. Smoking was associated with a decreased risk of PsA.
Eder, 2011 [111] Canada Cross-sectional	Diagnosis: by dermatologist N = 342 Age: not reported Sex: 57% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 555 Age: not reported Sex: 59% male	Non-HLA (2)	The presence of IL-13 rs848 and rs1800925 major alleles were positively associated with PsA.
Eder, 2012 [21] Canada Case-control Follow-up: not reported	Diagnosis: by dermatologist N = 404 Age (mean): 46 years Sex: 56% male Exclusion PsA: yes	Diagnosis: by psoriasis and arthritis or CASPAR N = 728 Age (mean): 37 years Sex: 59% male	Disease activity (9) Intoxication (4) Patient characteristics (1)	Smoking was associated with a decreased risk of PsA.
Eder, 2012 [112] Canada Cross-sectional	Diagnosis: by dermatologist N = 335 Age (mean): 46 years Sex: 56% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 712 Age (mean): 42 years Sex: 58% male	HLA (18)	The presence of HLA-B*27, HLA-C*01, HLA-C*02 genotypes and HLA-B*18-C*07, HLA-B*27-C*01, HLA-B*27-C*02, HLA-B*38-C*12, HLA-B*08-C*07, and HLA-B*57-C*06 haplotypes are positively associated with PsA. HLA-C*06 and HLA-DRB1*07 were negatively associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Eder, 2012 [113] Canada Cross-sectional	Diagnosis: by dermatologist N = 30 Age: not reported Sex: not reported Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 178 Age: not reported Sex: not reported	HLA (14)	The presence of HLA-B*27, HLA-B*38, HLA-B*39 , HLA-C*12 genotypes and HLA-B*38-C*12, HLA-B*39-C*12 and HLA-B*37-C*02 haplotypes were positively associated with PsA.
Eder, 2013 [63] Canada Cross-sectional	Diagnosis: by dermatologist N = 114 Age (mean): 52 years Sex: 58% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 125 Age (mean): 54 years Sex: 52% male	Inflammation marker (1) Lipid metabolism (5) Uric acid (1)	A lower serum uric acid and a higher hsCRP were associated with PsA.
Eder, 2013 [64] Canada Cross-sectional	Diagnosis: by dermatologist N = 155 Age (median): 50 years Sex: 54% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 203 Age (median): 51 years Sex: 61% male	Inflammation marker (1) Lipid metabolism (6) Serum markers (1)	Higher levels of hsCRP, adiponectin and leptin were associated with PsA.
Eder, 2016 [22] USA Cohort Follow-up: 8 years	Diagnosis: by dermatologist N = 464 Age (mean): 47 years Sex: 56% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR N = 51 Age (mean): 47 years Sex: 55% male	Comorbidities (5) Disease activity (5) Fertility (1) Intoxication (4) Medication (3) Patient characteristics (6) Psychological distress (1)	More severe psoriasis, low level of education and the use of systemic retinoid medications were associated with an increased risk of PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Eder, 2017 [23] USA Cohort Follow-up: 8 years	Diagnosis: by dermatologist N = 410 Age (mean): 47 years Sex: 56% male Exclusion PsA: yes	Diagnosis: by rheumatologist N = 57 Age (mean): 49 years Sex: 54% male	Disease activity (17) Patient characteristics (3) Psychological distress (2)	Arthralgia in women, heel pain, fatigue and stiffness were associated with an increased risk of PsA. An increase in pain, stiffness, fatigue and functional disability were associated with an increased risk of PsA.
Egeberg, 2018 [24] Denmark Cohort Follow-up: 18 years	Diagnosis: dermatologist N = 8742 Age (mean): 52 years Sex: 51% male Exclusion PsA: no	Diagnosis: rheumatologist N = 1269 Age (mean): 52 years Sex: 51% male	Disease activity (4)	A longer duration of cutaneous symptoms was associated with an increased risk of PsA.
Eiris, 2014 [114] Spain Cross-sectional	Diagnosis: by dermatologist N = 314 Age (mean): 46 years** Sex: 55% male ** Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 91 Age (mean): 46 years** Sex: 55% male**	Non-HLA (4)	The presence of IL23R rs2201841 AA genotype and IL23R rs11209026 GG genotype was positively associated with PsA.
Elkayam, 2004 [115] Israel Cross-sectional	Diagnosis: basis not reported N = 32 Age: not reported Sex: not reported Exclusion PsA: no	Diagnosis: by rheumatologist N = 50 Age: 58 years Sex: 60% male	HLA (30)	The presence of HLA-A*03, -B*13 and -B*38 was negatively associated with PsA.
Engin, 2020 [65] Turkey Cross-sectional	Diagnosis: by dermatologist N = 89 Age (mean): 41 years Sex: 66% male Exclusion PsA: yes	Diagnosis: basis not reported N = 14 Age (mean): 43 years Sex: 57% male	Serum markers (1)	Serum TWEAK levels are not associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Esawy, 2019 [66] Egypt Cross-sectional	Diagnosis: by rheumatologist, characteristic lesions N = 40 Age (mean): 74 years Sex: 50% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR and Moll & Wright criteria N = 76 Age (mean): 45 years Sex: 55% male	ACPA (1) Inflammation markers (1) Serum markers (1)	A lower level of gelsolin was associated with PsA. Higher levels of hsCRP and BSE are associated with PsA.
Farrag, 2017 [67] Egypt Cross-sectional	Diagnosis: by characteristic lesions N = 21 Age (mean): 43 years Sex: 58% male Exclusion PsA: yes	Diagnosis: by CASPAR criteria N = 24 Age (mean): 47 years Sex: 52% male	Cytokines (1)	A higher level of serum IL-34 was associated with PsA.
Frasca, 2018 [68] Italy Cross-sectional	Diagnosis: basis not reported N = 24 Age (mean): 51 years Sex: 46% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 32 Age (mean): 54 years Sex: 59% male	Cytokines (1) Serum markers (4)	A lower level of plasma C9 is associated with PsA.
Gisondi, 2011 [69] Italy Cross-sectional	Diagnosis: by rheumatologist N = 86 Age (mean): 52 years ** Sex: 63% male** Exclusion PsA: no	Diagnosis: basis not reported N = 59 Age (mean): 52 years ** Sex: 63% male**	Bone metabolism (1)	25(OH) Vitamin D is not associated with PsA.
Green, 2020 [25] UK Cohort Follow-up: 17 years	Diagnosis: by code# N = 88780 Age (mean): 49 years Sex: 48% Exclusion PsA: no	Diagnosis: by code# N = 1409 Age (mean): 45 years Sex: 53%	Intoxication (5) Patient characteristics (3)	Higher BMI and moderate drinking were associated with an increased risk of PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Hein, 1991 [70] Germany Cross-sectional	Diagnosis: basis not reported N = 24 Age (mean): 34 years Sex: 50% male PsA exclusion: no	Diagnosis: basis not reported N = 24 Age (mean): 40 years Sex: 40% male	Bone metabolism (3)	A lower urine Hp excretion was associated with PsA.
Ho, 2008 [116] United Kingdom Cross-sectional	Diagnosis: by dermatologist N = 611 Age: not reported Sex: 54% male Exclusion PsA: subset	Diagnosis: by rheumatologist N = 480 Age: not reported Sex: 57% male	HLA (1)	The presence of HLA-C*06 was not associated with PsA.
Hohler, 2002 [117] Belgium, Germany Cross-sectional	Diagnosis: basis not reported N = 65 Age (mean): 44 years Sex: 66 % male PsA exclusion: no	Diagnosis: by rheumatologist, seronegative inflammatory arthritis Age (mean): 48 years Sex: 53% male	HLA (1) Non-HLA (4)	The presence of HLA-B*27 and haplotype TNFa6c1d3 were positively associated with PsA.
Hong, 2018 [71] USA Cross-sectional	Diagnosis: by code# N = 16 Age (mean): 47 years ** Sex: 58% male** Exclusion PsA: no	Diagnosis: basis not reported N= 16 Age (mean): 47 years ** Sex: 58% male**	Serum markers (1)	A higher level of VEGFR-3 was associated with PsA.
Hur, 2020 [72] South Korea Cross-sectional	Diagnosis: by clinical and histopathological criteria N = 281 Age (mean): 40 years ** Sex: 59% male** Exclusion PsA: no	Diagnosis: CASPAR criteria N = 19 Age (mean): 40 years** Sex: 59% male**	Inflammation markers (2)	ESR and CRP were not associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Husakova, 2015 [73] Country not reported Cross-sectional	Diagnosis: basis not reported N = 70 Age (mean): 46 years Sex: 54% male Exclusion PsA: yes	Diagnosis: by seronegative arthritis N = 40 Age (mean): 49 years Sex: 50% male	Serum markers (1)	A higher level of serum PRL was associated with PsA.
Husni, 2018 [74] USA Cross-sectional	Diagnosis: by dermatologist N = 145 Age (mean): 46 years Sex: 50% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 198 Age (mean): 50 years Sex: 51% male	Inflammation marker (1) Lipid metabolism (4) Serum markers (1)	A higher level of CRP and triglycerides, and a higher arylesterase activity were associated with PsA.
Isik, 2016 [118] Turkey Cross-sectional	Diagnosis: by dermatologist N = 71 Age: 41 years Sex: 42% male Exclusion PsA: no	Diagnosis: by CASPAR criteria N = 58 Age: 49 years Sex: 40% male	Non-HLA (2)	The presence of TNFa-238A and -308A was not associated with PsA.
Jadon, 2017 [75] UK, USA Cross-sectional	Diagnosis: by dermatologist N = 200 Age (median): 54 years Sex: 51% male Exclusion PsA: nee	Diagnosis: by CASPAR criteria N = 200 Age (median): 58 years Sex: 52% male	Bone metabolism (3) Cytokines (1)	A lower level of M-CSF was associated with PsA. A higher level of MMP-3 was associated with PsA.
Jensen, 2013 [76] Denmark Cross-sectional	Diagnosis: by dermatologist N = 48 Age (mean): 50 years Sex: 54% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 42 Age (mean): 52 years Sex: 43% male	Serum markers (1)	A higher level of YKL-40 was associated with PsA.
Johnson, 2019 [77] USA Cross-sectional	Diagnosis: by dermatologist N = 180 Age (median): 51 years Sex: 50% male Exclusion PsA: no	Diagnosis: basis not reported N = 143 Age (median): 51 years Sex: 56% male	Cytokines (3) Inflammation marker (1) Lipid metabolism (4)	A higher level of TNFα, and a lower level of adiponectin, were associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Julia, 2012 [119] Spain Cross-sectional	Diagnosis: by dermatologist N = 1050 Age: not reported Sex: 59% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 955 Age: not reported Sex: 54% male	HLA (1) Non-HLA (3)	The presence of HLA-C rs10484554 was positively associated with PsA.
Julia, 2015 [120] Spain Cross-sectional	Diagnosis: by dermatologist N = 822 Age: not reported Sex: not reported Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 1131 Age: 54 years Sex: 51% male	Non-HLA (1)	A deletion at ADAMTS-MAGI1 was positively associated with PsA.
Kilic, 2017 [78] Turkey Cross-sectional	Diagnosis: basis not reported N = 41 Age (mean): 38 years Sex: 54% Exclusion PsA: no	Diagnosis: basis not reported N = 116 Age (mean): 48 years Sex: 41% male	Cytologic phenotype (1)	A higher MPV was associated with PsA.
Kim, 2016 [79] South Korea Cross-sectional	Diagnosis: by dermatologist N = 111 Age (mean): 38 years Sex: 56% male Exclusion PsA: no	Diagnosis: by CASPAR criteria N = 25 Age (mean): 42 years Sex: 52% male	Cytologic phenotype (8) Inflammation markers (2)	A higher NLR, PLR and ESR were associated with PsA.
Krajewska, 2019 [80] Poland Cross-sectional	Diagnosis: by dermatologist N = 41 Age (mean): 48 years Sex: 54% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 31 Age (mean): 50 years Sex: 48% male	Inflammation marker (2)	A higher (level of) CRP and BSE were associated with PsA.
Lewinson, 2017 [26] UK Cohort Follow-up: 0-25 years	Diagnosis: by code# N = 73447 Age (mean): not reported Sex: not reported Exclusion PsA: no	Diagnosis: by code# N = 1466 Age (mean): not reported Sex: not reported	Psychological distress (1)	Major depressive disorder was associated with an increased risk of PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
El-Leithy, 2020 [81] Egypt Cross-sectional	Diagnosis: by dermatologist N = 20 Age (mean): 45 years Sex: 60% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 20 Age (mean): 50 years Sex: 60% male	Skin (2)	Higher expression of IL23R in dermis and epidermis were associated with PsA.
Li, 2012 [27] USA Cohort Follow-up: 0-14 years	Diagnosis: self-report N = 581 Age (mean): not reported Sex: 0% male Exclusion PsA: no	Diagnosis: self-report N = 157 Age (mean): not reported Sex: 0% male	Intoxication (7)	Smoking intensity and duration were associated with an increased risk of PsA.
Li, 2012 [28] USA Cohort Follow-up: 0-14 years	Diagnosis: self-report N = 556 Age (mean): not reported Sex: 0% male Exclusion PsA: no	Diagnosis: self-report N = 146 Age (mean): not reported Sex: 0% male	Patient characteristics (16)	A higher BMI, weight change since early adulthood, and a higher waist and hip circumference and waist-hip-ratio were associated with an increased risk of PsA.
Li, 2016 [82] China Cross-sectional	Diagnosis: basis not reported N = 20 Age (median): 52 years Sex: 70% male Exclusion PsA: not reported	Diagnosis: basis not reported N = 40 Age (median): 41 years Sex: 65% male	Bone metabolism (3) Cytokines (8) Cytologic phenotype (1) Inflammation marker (2)	A higher (level of) CRP, BSE, IL-12/23 p40, IL-33, IL-34, IL-35, IL-38, TNFα, RANKL and OCP were associated with PsA. A lower (level of) IL-36a and OPG/RANKL-ratio were associated with PsA.
Liao, 2008 [121] Taiwan Cross-sectional	Diagnosis: by dermatologist N = 80 Age: not reported Sex: 61% male Exclusion PsA: no	Diagnosis: by rheumatologist, Moll & Wright criteria N = 91 Age: not reported Sex: 55% male	HLA (5)	The presence of HLA-B*27 or HLA–C*12 was associated positively with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Lin, 2014 [83] USA Cross-sectional	Diagnosis: by dermatologist N = 145 Age (mean): 46 years Sex: 51% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 198 Age (mean): 50 years Sex: 50% male	Inflammation marker (1)	A higher level of CRP was associated with PsA.
Lin, 2019 [84] Taiwan Cross-sectional	Diagnosis: by dermatologist N= 34 Age (mean): 43 years Sex: 71% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 17 Age (mean): 48 years Sex: 73% male	miRNA (1)	A higher expression of miR-146a-5p in monocytes was associated with PsA.
Loft, 2018 [122] Denmark Cross-sectional	Diagnosis: by dermatologist N = 151 Age (mean): 45 years Sex: 66% male Exclusion PsA: no	Diagnosis: by rheumatologist N = 549 Age (mean): 46 years Sex: 46% male	Non-HLA (52)	The presence of TNF rs361525 was positively associated with PsA.
Love, 2012 [17] UK Cohort Follow-up: 0-15 years	Diagnosis: by code# N = 74419 Age (mean): 52 years ** Sex: 43% male** Exclusion PsA: no	Diagnosis: by code# N = 976 Age (mean): 52 years ** Sex: 43% male**	Patient characteristics (3)	A higher BMI was associated with an increased risk of PsA.
Maejima, 2014 [85] Japan Cross-sectional	Diagnosis: basis not reported N = 31 Age (mean): 56 years Sex: 84% male Exclusion PsA: no	Diagnosis: by CASPAR criteria N = 12 Age (mean): 45 years Sex: 67% male	Serum markers (2)	A higher level of STIP1 and K17 levels were associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Maejima, 2017 [86] Japan Cross-sectional	Diagnosis: basis not reported N = 23 Age (mean): 52 years Sex: 70% male Exclusion PsA: no	Diagnosis: by CASPAR criteria N = 11 Age (mean): 48 years Sex: 73% male	Inflammation markers (2)	ESR and CRP were not associated with PsA.
Mavropoulos, 2017 [87] Greece Cross-sectional	Diagnosis: by dermatologist N = 50 Age (mean): 53 years Sex: 43% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 60 Age (mean): 51 years Sex: 66% male	Cytologic phenotype (5)	Amount of regulatory B-cells was not associated with PsA.
Muto, 1996 [88] Japan Cross-sectional	Diagnosis: basis not reported N = 88 Age: not reported Sex: 71% male Exclusion PsA: no	Diagnosis: by Moll and Wright criteria N = 31 Age: not reported Sex: 57% male	Miscellaneous (2)	A higher level of IgG antibody against the C region was associated with PsA.
Mysliwiec, 2017 [89] Poland Cross-sectional	Diagnosis: basis not reported N = 72 Age (median): 53 years** Sex: 67% male** Exclusion PsA: no	Diagnosis: basis not reported N = 13 Age (median): 53 years** Sex: 67% male**	Lipid metabolism (2)	A higher level of CER was associated with PsA.
Mysliwiec, 2019 [90] Poland Cross-sectional	Diagnosis: basis not reported N = 40 Age (mean): 49 years Sex: 78% male** Exclusion PsA: no	Diagnosis: basis not reported N = 14 Age (mean): 55 years Sex: 78% male**	Bone metabolism (1) Cytologic phenotype (1) Inflammation marker (1) Lipid metabolism (25)	A higher SFA/UFA ratio is associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Nair, 2009 [123] Multiple Cross-sectional	Diagnosis: basis not reported N = 3523 Age: not reported Sex: not reported Exclusion PsA: not reported	Diagnosis: basis not reported N = 1755 Age: not reported Sex: not reported	HLA (1) Non-HLA (9)	The presence of HLA-C rs12191877, IL12B rs2082412 and IL23R rs2201841 were positively associated with PsA
Nguyen, 2017 [29] UK Cohort Follow-up: 0-20 years	Diagnosis: by code# N = 218156 Age (mean): 45 years ** Sex: 48% male** Exclusion PsA: no	Diagnosis: by code# N = 7057 Age (mean): 45 years ** Sex: 48% male**	Intoxication (2)	Current smoking was associated with a decreased risk of PsA.
Okada, 2014 [124] Multiple Cross-sectional	Diagnosis: by dermatologist N = 3098 Age: not reported Sex: not reported Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 3038 Age: not reported Sex: not reported	HLA (1)	The presence of Glu at amino acid position 45 of HLA-B*27 was positively associated with PsA.
Orgaz-Molina, 2013 [91] Spain Cross-sectional	Diagnosis: by dermatologist N = 70 Age (mean): 46 years Sex: 54% male Exclusion PsA: no	Diagnosis: by rheumatologist N=79 Age (mean): 45 years Sex: 54% male	Bone metabolism (1) Lipid metabolism (6)	A lower level of total cholesterol was associated with PsA.
Ortolan, 2019 [92] Italy Cross-sectional	Diagnosis: by dermatologist N = 33 Age (mean): 55 years Sex: 64% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 43 Age (mean): 60 years Sex: 74% male	Lipid metabolism (7) Serum marker (1)	A lower level of insulin and uric acid were associated with PsA.
Pasquali, 2020 [93] Sweden Cross-sectional	Diagnosis: by dermatologist N = 29 Age (mean): 40 years Sex: 59% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 28 Age (mean): 49 years Sex: 43% male	miRNA (20)	A lower level of 10 extravesicular miRNA§ and a higher level of 9 extravesicular miRNA¶ were associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Pattison, 2007 [30] USA Case-control Follow-up: 10 years	Diagnosis: by not reported N = 163 Age (mean): 46 years Sex: 44% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR N = 98 Age (mean): 54 years Sex: 54% male	Comorbidities (4) Fertility (6) Intoxication (2) Medication (6) Physical stress (5) Psychological distress (6)	A traumatic event, oral ulcerations, infectious diarrhea and vaccinations were associated with an increased risk of PsA.
Pietrzak, 2019 [94] Poland Cross-sectional	Diagnosis: by dermatologist N = 62 Age (mean): 41 years Sex: not reported Exclusion PsA: no	Diagnosis: by CASPAR criteria N = 31 Age (mean): 41 years Sex: not reported	Lipid metabolism (14)	Higher levels of apoB and oxLDL, and a higher ratio apoA:apoB, TC:HDL and LDL: HDL were associated with PsA. A lower level of HDL-C was associated with PsA.
Pietrzak, 2020 [95] Poland Cross-sectional	Diagnosis: by dermatologist N = 62 Age (mean): 41 years Sex: not reported Exclusion PsA: no	Diagnosis: by CASPAR criteria N = 31 Age (mean): 41 years Sex: not reported	Cytokines (1) Inflammation marker (1) Lipid metabolism (8)	Higher levels of cholesterol, LDL, triglycerides and hsIL6, and a higher ratio LDL:HDL, were associated with PsA.
Pirowska, 2018 [96] Poland Cross-sectional	Diagnosis: by dermatologist N = 26 Age: not reported Sex: 60% male** Exclusion PsA: no	Diagnosis: by CASPAR criteria N = 34 Age: not reported Sex: 60% male**	Cytokines (2)	A higher level of IL-23 was associated with PsA.
Pollock, 2011 [125] Canada Cross-sectional	Diagnosis: by dermatologist N = 243 Age: not reported Sex: 59% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 249 Age: not reported Sex: 61% male	HLA (4) Non-HLA (4)	The presence of MICA*00801 was positively associated with.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Pollock, 2013 [126] Canada Cross-sectional	Diagnosis: by dermatologist N = 240 Age: not reported Sex: 56% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 745 Age: not reported Sex: 57% male	HLA (n=5) Non-HLA (n=3)	The presence of MICA-129 was not positively associated with PsA.
Pollock, 2015 [97] Canada Cross-sectional	Diagnosis: basis not reported N = 48 Age (mean): 46 years Sex: 52% male Exclusion PsA: no	Diagnosis: basis not reported N = 48 Age (mean): 46 years Sex: 52% male	mRNA expression, whole blood (18)	A lower expression of NOTCH2NL and SETD2 was associated with PsA. A higher expression of HAT1 and P2RY5 was associated with PsA.
Pollock, 2019 [127] Canada Cross-sectional	Diagnosis: by dermatologist N =23 Age (mean): 51 years Sex: 100% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 13 Age (mean): 52 years Sex: 100% male	Non-HLA (10)	Hypermethylation of LOC391322, ERICH1-AS1, PPP2R2D and PTPRN2 were negatively associated with PsA. Hypermethylation of ELF5, SORCS2, EGFL8, NTF3, IL22 and PIP5K1C were positively associated with PsA.
Sag, 2018 [98] Turkey Cross-sectional	Diagnosis: by dermatologist N = 48 Age (mean): 43 years Sex: 64% male Exclusion PsA: no	Diagnosis: by rheumatologist, CASPAR criteria N = 43 Age (mean): 46 years Sex: 67% male	Bone metabolism (8) Inflammation marker (2) Serum markers (2)	A higher level of CRP was associated with PsA.
Shibata, 2009 [99] Japan Cross-sectional	Diagnosis: by histopathology N = 15 Age (mean): 50 years Sex: 73% male Exclusion PsA: no	Diagnosis: by Bennet criteria N = 16 Age (mean): 52 years Sex: 69% male	ACPA (1)	Presence of anti-CCP was not associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Simon, 2020 [31] Germany Cohort Follow-up: 7 years	Diagnosis: by dermatologist N = 90 Age (mean): 45 years Sex: 66% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR N = 24 Age (mean): 47 years Sex: 54% male	Disease activity (7)	Structural entheseal lesions and low cortical vBMD were associated with an increased risk of PsA.
Soltani-Arabshahi, 2010 [32] USA Cohort Follow-up: 6 years	Diagnosis: by dermatologist N = 693 Age (mean): not reported Sex: 38% male Exclusion PsA: yes	Diagnosis: by patient report N = 250 Age (mean): not reported Sex: not reported	Disease activity (2) Patient characteristics (1)	Younger age at psoriasis onset, higher worst ever BSA and higher BMI at age 18 years were associated with an increased risk of PsA.
Soto-Sanchez, 2010 [128] Spain Cross-sectional	Diagnosis: basis not reported N = 301 Age: not reported Sex: not reported Exclusion PsA: yes	Diagnosis: by rheumatologist N = 81 Age: not reported Sex: not reported	Non-HLA (3)	The presence of CCR2-64 rs1799864 was positively associated with PsA.
Spadaro, 1996 [100] Italy Cross-sectional	Diagnosis: basis not reported N = 15 Age: not reported Sex: not reported Exclusion PsA: no	Diagnosis: by rheumatoid factor negative polyarthritis N = 47 Age (mean): 52 years Sex: 64% male	Cytokines (2)	A higher level of IL-6 and sIL2R was associated with PsA.
Stuart, 2015 [129] Canada, Estonia, Germany, Sweden, USA Cross-sectional	Diagnosis: by dermatologist N = 3110 Age: not reported Sex: not reported Exclusion PsA: subset	Diagnosis: basis not reported N = 1631 Age: not reported Sex: not reported	HLA (1) Non-HLA (1)	The presence of rs1050414 (near HLA-C and –B) and rs48991505 (near LOC100505817) were positively associated with PsA.
Thorarensen, 2017 [33] UK Cohort Follow-up: 19 years	Diagnosis: by code# N = 70646 Age (mean): 48 years ** Sex: 50% male** Exclusion PsA: yes	Diagnosis: by code# N = 1010 Age (mean): 48 years ** Sex: 50% male**	Physical stress (5)	Bone and joint trauma were associated with an increased risk of PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Thumboo, 2002 [18] USA Case-control Follow-up: 2 years	Diagnosis: by dermatologist N = 58 Age (mean): not reported Sex: 49% male Exclusion PsA: yes	Diagnosis: inflammatory arthritis in Pso patients N = 40 Age (mean): not reported Sex: 48% male	Comorbidities (4) Disease activity (6) Fertility (3) Intoxication (1) Medication (7) Patient characteristics (1) Physical stress (2) Psychological distress (1)	Corticosteroid use was associated with an increased risk of PsA. Pregnancy was associated with a decreased risk of pregnancy.
Tsuruta, 2017 [101] Japan Cross-sectional	Diagnosis: by histopathology N = 276 Age (mean): 57 years Sex: 72% male Exclusion PsA: no	Diagnosis: by CASPAR criteria N = 55 Age (mean): 57 years Sex: 71% male	Uric acid (1)	The presence of hyperuricemia was associated with PsA.
Voiculescu, 2018 [130] Hungary Cross-sectional	Diagnosis: by dermatologist N = 69 Age (mean): 50 years** Sex: 56% male** Exclusion PsA: no	Diagnosis: basis not reported N = 13 Age (mean): 50 years** Sex: 56% male**	Non-HLA (5)	The presence of MC4R 17782313 was positively associated with PsA.
Williams, 2005 [131] USA Cross-sectional	Diagnosis: by dermatologist N = 145 Age: not reported Sex: not reported Exclusion PsA: no	Diagnosis: basis not reported N = 75 Age: not reported Sex: not reported	Non-HLA (1)	The presence of KIR2DS1 was positively associated with PsA.
Wilson, 2009 [34] USA Cohort Follow-up: 30 years	Diagnosis: self-report N = 1508 Age (mean): 43 years** Sex: 50% male** Exclusion PsA: yes	Diagnosis: self-report N = 57 Age (mean): 43 years** Sex: 50% male**	Disease activity (14) Patient characteristics (1)	Scalp lesions, nail dystrophy, involvement of intergluteal/perianal regions and a higher number of affected sites were associated with an increased risk of PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Winchester, 2012 [132] Ireland Cross-sectional	Diagnosis: by dermatologist N = 214 Age: not reported Sex: not reported Exclusion PsA: yes	Diagnosis: by rheumatologist based on psoriasis, negative RF and arthritis N = 359 Age: not reported Sex: not reported	HLA (27)	The presence of HLA-C*06 was negatively associated with PsA.
Wu, 2015 [35] USA Cohort Follow-up: 16 years	Diagnosis: by code# N = 573 Age (mean): not reported Sex: 0% male Exclusion PsA: yes	Diagnosis: by code# N = 141 Age (mean): not reported Sex: 0% male	Intoxication (5)	Regular beer consumption and heavier alcohol use were associated with an increased risk of PsA.
Yan, 2018 [133] USA Cross-sectional	Diagnosis: by dermatologist N = 479 Age (mean): 45 years Sex: 58% male Exclusion PsA: yes, not by rheumatologist	Diagnosis: by rheumatologist or dermatologist N = 175 Age (mean): 48 years Sex: 51% male	HLA (2)	The presence of HLA-C*06:02 was negatively associated with PsA.
Yang, 2012 [134] China Cross-sectional	Diagnosis: by dermatologist N = 379 Age: 39 years Sex: 55% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 595 Age: 43 years Sex: 60% male	Non-HLA (20)	The presence of IL12B rs2082412 was negatively associated with PsA.
Yilmaz, 2017 [102] Turkey Cross-sectional	Diagnosis: basis not reported N = 47 Age (mean): 45 years ** Sex: 44% male** Exclusion PsA: no	Diagnosis: by CASPAR criteria N = 23 Age (mean): 45 years ** Sex: 44% male**	Uric acid (1)	Serum uric level was not associated with PsA.

Study, design	Patient characteristics Psoriasis	Patient characteristics Psoriatic Arthritis	Predictors (n)	Main results
Yuan, 2019 [103] **USA** **Cross-sectional**	Diagnosis: by clinical and histopathological criteria N = 73 Age (mean): 47 years Sex: 58% male Exclusion PsA: no	Diagnosis: basis not reported N = 22 Age: not reported Sex: not reported	Serum marker (2)	A higher level of anti-ADAMTS-L5 and anti-LL-37 antibodies were associated with PsA.
Zhao, 2019 [135] **China** **Cross-sectional**	Diagnosis: by dermatologist N = 376 Age (mean): 41 years Sex: 47% male Exclusion PsA: yes	Diagnosis: by rheumatologist, CASPAR criteria N = 379 Age (mean): 43 years Sex: 60% male	Non-HLA (12)	The presence of IL12B rs4921485 was negatively associated with PsA. The presence of IL23R rs4655683 and NFKBIA rs12883343 were positively associated with PsA.

* CCL1, CCL20, CCL7, CX3CL1, CXCL2, IL-17C, IL-17F, IL-3, IL-6, IL-8, ISG20, MMP-3, STAT3, STAT6, SYK
** Data only known for entire cohort, not reported for Pso and PsA separately.
*** C16ORF62, CPN2, FHL1, GPS1, ITGB5, LZIC, PAFAH1B2, PPP2R4, POSTN, SNCA, SRP14, SRPX
$ CD8+TEMRACCR6+CXCR3-CD69+, CD8+TEMRACCR6-CXCR3+CD69-, CD8+TEMCD69+, CD8+CD45RA+CXCR3-CCR6-CD69+, CD4+CD45RA-IL17+, CD8+CD45RA-IL17+, CD8+TEMIL17A+
¥ CD4+CD45RA-IFNγ+, CD8+TEMRACXCR3+CCR4-, CD4+CD45RA-CXCR3+CCR4-, CD4+TEMCXCR3+CCR4-, CD4+CD45RA-CXCR3+CCR6-
Diagnosis by code includes record linkage, international classification of diseases (ICD)-9 codes and (THIN) read codes.
§ hsa-miR-92a-3p, hsa-miR-139-3p, hsa-let-7b-5p, hsa-miR-92b-3p, hsa-let-7b-3p, hsa-miR-486-5p, hsa-miR-1180-3p, hsa-miR-3158-3p, hsa-miR- 4732-3p, hsa-miR-203a
¶ hsa-miR-23a-3p, hsa-miR-379-5p, hsa-miR-98-5p, has-let-7e-5p, hsa-miR-29a-3p, hsa-miR-27b-3p, hsa-miR-26a-5p, hsa-miR-146a-5p
ACPA = anti citrullinated protein antibodies; ADAMTS = a desintegrin and metalloproteinase with thrombospondin motifs; anti-CCP = anti-cyclic citrullinated peptide; APF = antiperinuclear factor; Apo = apolipoprotein; Asp = aspartic acid; BMI = body mass index; BSA = body surface area; C16ORF61 = endosomal protein sorting factor like (VSP35L); C2C = collagen fragment neoepitopes Col2-3/4 (long mono); CASPAR = classification criteria for psoriatic arthritis; CCL = C-C chemokine ligand; CD = cluster of differentiation; CER = ceramide; CCR = chemokine receptor; CPII = C-propeptide of type II collagen; CPN2 = carboxypeptidase N subunit 2; CRP = C-reactive protein; CTNNBIP = catenin beta interacting protein; CX3CL = C-X3-C motif ligand; CXCL = C-X-C motif ligand; CXCR = C-X-C motif chemokine receptor; DKK = dikkop; ESR = erythrocyte sedimentation rate; FHL1 = four and a half LIM domains; Glu = glutamic acid; GPS = G protein pathway suppressor; HDL = high-density lipoprotein; HLA = human leukocyte antigen; Hp = hydroxyproline; hs = high sensitivity; IFI = interferon-inducible protein; IFN = interferon; IgG = immunoglobulin G; IL = interleukin; IL23R = interleukin 23 receptor; ISG = interferon stimulated gene; ITGB = integrin beta; K17 = keratin 17; KIR = killer-cell immunoglobulin-like receptor; LDL = low-density lipoprotein; LZIC = leucine zipper and CTNNBIP1 domain containing; M2BP = Mac-2-binding protein; MAGI = membrane-associated guanylate kinase; M-CSF = macrophage colony stimulating factor; MCV = mutated citrullinated vimentin; MICA = MHC class I polypeptide-related sequence; MMP = matrix metalloproteinase; MPV = mean platelet volume; mRNA = messenger RNA; NLR = neutrophile:lymphocyte ratio; NRP = neuropilin; OCP = osteoclast precursors; OPG = osteoprotegerin; oxLDL = oxidated LDL; PAFAH1B2 = platelet activating factor acetylhydrolase 1b catalytic subunit 2; PBMC = peripheral blood mononuclear Cells; PDCD = programmed cell death 1; PLR = platelet:lymphocyte ratio; POSTN = periostin; PPP2R4 = protein phosphatase 2 phosphatase activator (PTPA); PRL = prolactin; PsA = psoriatic arthritis; Pso = psoriasis; PTPN22 = protein tyrosine phosphatase non-receptor type 22; RANKL = receptor activator of nuclear factor kappa-B ligand; RF = rheumatoid factor; RNA = ribonucleic acid; Ser = serine; SFA = saturated fatty acids; sIL-2R = soluble IL-2 receptor; SNCA = synuclein alpha; sRANKL = soluble RANKL; SRP = signal recognition particle; SRPX = sushi repeat containing protein X-linked; STAT = signal transducer and activator of transcription; STIP = stress-inducible phosphoprotein; SYK = spleen associated tyrosine kinase; TC = total cholesterol; TEM = effector memory T cell; TEMRA = TEM re-expressing CD45RA; TNF = tumor necrosis factor; TWEAK = TNF-like weak inducer of apoptosis; UFA = unsaturated fatty acids; UK = United Kingdom; USA = United States of America; vBMD = volumetric bone mineral density; VEGFR = vascular endothelial growth factor receptor; WTCCC = Welcome Trust Case Control Consortium

Supplementary table 3: Statistical significance and effect sizes of clinical markers

Category	Marker	Study	Significance	Effect Size
Comorbidities	Diabetes	[18]	P = 0.403	OR = 0.40 (0.05-3.42)
		[22]	P = 0.32	HR = 0.53 (0.15-1.84)
	Diarrhoea	[20]	P = 0.19	OR = 1.7 (0.76-3.79)
		[22]	P = 0.08	HR = 3.18 (0.88-11.4)
		[30]	P = Not reported	OR = 0.23 (0.05-1.06)
	Infections requiring antibiotics	[20]	P = 0.046	OR = 1.72 (1.01-2.95)
		[22]	P = 0.72	HR = 1.15 (0.53-2.49)
	Uveitis	[22]	P = 0.0002	RR = 31.5 (5.06 –195.8)
Disease characteristics (general)	Fatigue (MFSS > 5)	[23]	P = 0.007	OR = 2.36 (1.27-4.39)
	Worsening fatigue	[23]	P = 0.001	OR= 1.27 (1.09-1.57)
	Worsening function	[23]	P = 0.04	RR = 0.96 (0.92-0.99)
Disease characteristics (joints)	Arthralgia	[23]	P = 0.02	Not reported
	Arthralgia men	[23]	P = Not reported	RR = 0.52 (0.12-2.22)
	Arthralgia women	[23]	P = Not reported	RR = 2.59 (1.15-5.88)
	Cortical vBMD entheseal	[31]	P = Not reported	HR = 0.64 (0.42-0.98)
	Heel pain	[23]	P = 0.02	OR = 4.18 (1.26-13.8)

Category	Marker	Study	Significance	Effect Size
Disease characteristics (joints)	Stiffness (VAS>2)	[23]	P = 0.045	OR = 2.03 (1.02-4.06)
	Structural entheseal lesion	[31]	P = 0.008	HR = 5.10 (1.53-16.99)
	Worsening pain	[23]	P = < 0.001	RR = 1.34 (1.14-1.57)
	Worsening stiffness	[23]	P = 0.03	RR = 1.21 (1.02-1.42)
Disease characteristics (skin/nails)	Age at Pso onset	[32]	P = < 0.001	OR = 0.98 (0.96-0.98)
		[34]	P = 0.25	RR = 0.91 (0.77-1.07)
	Duration of Pso	[19]	P = 0.99	OR = 1 (1.0-1.0)
	Duration of Pso, 6-10 years	[28]	P = 0.09	OR = 0.70 (0.47-1.06)
	Duration of Pso, 11-15 years	[28]	P = 0.003	OR = 0.49 (0.31-0.79)
	Duration of Pso, 16-20 years	[28]	P = 0.002	OR = 0.46 (0.28-0.74)
	Duration of Pso, 21 years and more	[28]	P = <0.0001	OR = 0.37 (0.26-0.53)
	Early (<20 years) vs late onset pso (cutaneous symptoms)	[31]	P = 0.777	OR = 1.03 (0.84-1.27)
	Early (<30 years) vs late onset pso (cutaneous symptoms)	[31]	P = 0.018	OR = 1.22 (1.03-1.45)
	Early (<20 years) vs late onset pso (dermatologist)	[31]	P = <0.001	OR = 0.52 (0.39-0.69)
	Early (<30 years) vs late onset pso (dermatologist)	[31]	P = 0.051	OR = 0.84 (0.71-1.0)
	Intergluteal lesions	[34]	P = Not reported	RR = 1.95 (1.07-3.56)
	Nail pitting	[17]	P = 0.0007	HR = 2.21 (1.24-3.92)
	Number of Pso sites 2	[34]	P = Not reported	RR = 0.77 (0.37-1.64)

Category	Marker	Study	Significance	Effect Size
Disease characteristics (skin/nails)	Number of Pso sites = > 3	[34]	P = Not reported	RR = 2.24 (1.23-4.08)
	PASI	[19]	P = 0.57	OR = 1.0 (0.9-1.1)
		[23]	P = 0.03	OR = 1.05 (1.01-1.09)
	PASI 10-20 vs <10	[22]	P = 0.73	HR = 1.16 (0.50-2.64)
	PASI >20 vs <20	[22]	P = 0.0006	HR = 5.39 (1.64-17.7)
	Psoriatic nail lesion	[18]	P = 0.752	OR = 1.16 (0.46-2.92)
		[19]	P = 0.68	OR = 1.2 (0.5-3.2)
		[22]	P = 0.31	HR = 1.36 (0.76-2.45)
		[34]	P = Not reported	RR = 2.24 (1.26-3.98)
	Scalp lesions	[19]	P = 0.98	OR = 1.0 (0.4-3.0)
		[34]	P = Not reported	RR = 3.75 (2.09-6.71)
	Severe Pso	[20]	P = 0.89	OR = 0.89 (0.49-1.61)
		[21]	P = < 0.0001	OR = 2.07 (1.47-2.97)
Fertility	Fertility treatment	[20]	P =0.83	OR = 0.9 (0.26-2.98)
		[30]	P = Not reported	OR = 0.17 (0.04-0.79)
	Hormone replacement therapy	[20]	P = 0.83	OR = 1.1 (0.5-2.39)
		[30]	P = Not reported	OR = 1.38 (0.53-3.6)

Category	Marker	Study	Significance	Effect Size
Fertility	Menopause	[18]	P = 0.86	OR = 0.89 (0.26-3.10)
		[20]	P = 0.50	OR = 1.8 (0.31-11.49)
		[22]	P = 0.75	OR = 1.19 (0.40-3.53)
	Oral contraceptives	[18]	P = 0.15	OR = 2.9 (0.68-12.28)
		[20]	P = 0.23	OR = 1.7 (0.71-4.23)
		[30]	P = Not reported	OR = 1.4 (0.55-3.5)
	Pregnancy	[18]	P = 0.04	OR = 0.19 (0.04-0.95)
		[20]	P = 0.73	OR = 1.2 (0.47-2.09)
		[30]	P = Not reported	OR = 1.06 (0.44-2.55)
Intoxication	Alcohol: 0-15 vs 15-30 g/day	[35]	P = Not reported	RR = 1.45 (0.67-3.16)
	Alcohol: 0-15 vs >30 g/day	[35]	P = Not reported	RR = 2.79 (1.24-6.26)
	Alcohol: >35 units/week	[30]	P = Not reported	OR = 0.57 (0.27-1.20)
	Alcohol: daily (= 1 or more per day vs none)	[19]	P = 0.97	HR = 1.02 (0.40-2.59)
		[20]	P = 0.96	OR = 1.0 (0.42-2.51)
		[21]	P = 0.05	OR = 1.65 (0.99-2.67)
	Alcohol: heavy drinker (=>3 units/day) vs none	[25]	P = 0.82	OR = 0.94 (0.56-1.58)
	Alcohol: moderate drinker (=0.1-3 units/day) vs none	[25]	P = 0.0033	OR = 1.57 (1.16-2.11)

Category	Marker	Study	Significance	Effect Size
Intoxication	Alcohol: none vs 0-15 g/day	[35]	P = Not reported	RR = 0.75 (0.50-1.12)
	Alcohol: none vs 15-30 g/day	[35]	P = Not reported	RR = 1.09 (0.48-2.47)
	Alcohol: none vs >30 g/day	[35]	P = Not reported	RR = 2.09 (0.90-4.84)
	Alcohol: social (= 1 or more per week vs none)	[20]	P = 0.73	OR = 0.9 (0.56-1.50)
		[21]	P = 0.67	OR = 0.94 (0.68-1.28)
		[22]	P = 0.92	HR = 1.02 (0.40-2.59)
	Alcohol: weekly alcohol use	[18]	P = 0.57	OR = 0.77 (0.32-1.89)
	Smoking: at or before arthritis	[30]	P = Not reported	OR = 0.68 (0.39-1.17)
	Smoking: current smoking	[20]	P = 0.038	OR = 0.54 (0.31-0.96)
		[21]	P = 0.002	OR = 0.57 (0.41-0.81)
		[22]	P = 0.38	HR = 1.36 (0.68-2.73)
		[25]	P = 0.54	OR = 0.94 (0.76-1.16)
		[27]	P = Not reported	OR = 1.62 (1.00-2.63)
		[29]	P = Not reported	HR = 0.91 (0.84-0.99)
	Smoking: current smokers 1-14 cig/day	[27]	P = Not reported	OR = 1.22 (0.58-2.56)
	Smoking: current smokers =/> 15 cig/day	[27]	P = Not reported	OR = 1.93 (1.09-3.4)
	Smoking: duration < 25 years	[27]	P = Not reported	OR = 1.35 (0.9-2.04)

Category	Marker	Study	Significance	Effect Size
Intoxication	Smoking: duration =/>25 years	[27]	P = Not reported	OR = 1.9 (1.09-3.33)
	Smoking: ex-smokers	[20]	P = 0.015	OR = 0.52 (0.31-0.88)
		[21]	P = 0.21	OR = 0.81 (0.56-1.12)
		[22]	P = 0.87	OR = 1.05 (0.56-1.99)
		[25]	P = 0.073	OR = 0.83 (0.69-1.02)
		[27]	P = Not reported	OR = 1.39 (0.89-2.16)
		[29]	P = Not reported	HR = 1.07 (0.97-1.18)
	Smoking: pack-years <20	[27]	P = Not reported	OR = 1.22 (0.79-1.89)
	Smoking: pack-years =/>20	[27]	P = Not reported	OR = 2.02 (1.24-3.29)
Medication	Corticosteroids use	[18]	P = 0.015	OR = 4.33 (1.34-14.02)
	Influenza vaccination	[20]	P = 0.87	OR = 1.0 (0.58-1.57)
		[30]	P = Not reported	OR = 0.40 (0.14-1.14)
	Methotrexate use	[18]	P = Not reported	Not reported
		[22]	P = Not reported	Not reported
	Retinoid use (ever)	[22]	P = 0.02	HR = 3.42 (1.24-9.44)
	Rubella vaccination	[20]	P = 0.81	OR = 0.8 (0.22-3.32)
		[30]	P = Not reported	OR = 12.4 (1.20-122.14)

Category	Marker	Study	Significance	Effect Size
Medication	Tetanus vaccination	[20]	P = 0.87	OR = 1.1 (0.29-4.24)
		[30]	P = Not reported	OR = 1.91 (1.0-3.7)
Patient characteristics	Age	[19]	P = 0.38	OR = 1.0 (0.9-1.0)
		[20]	P = 0.29	OR = 0.99 (0.97-1.01)
		[23]	P = 0.61	RR = 0.99 (0.96-1.02)
		[34]	P = 0.15	RR = 0.76 (0.54-1.08)
	BMI	[23]	P = 0.11	RR = 1.05 (0.99-1.13)
	BMI 25-30 vs <25	[17]	P = <0.001	RR = 1.09 (0.93-1.28)
		[25]	P = <0.001	OR = 1.76 (1.41-2.19)
		[28]	P = Not reported	OR = 1.81 (1.23-2.93)
	BMI 30-35 vs <25	[17]	P = <0.001	RR = 1.22 (1.02-1.47)
		[25]	P = <0.001	OR = 2.04 (1.60-2.60)
		[28]	P = Not reported	OR = 1.90 (1.13-3.18)
	BMI >30	[19]	P = 0.39	OR = 1.5 (0.6-4.2)
	BMI >35 vs <25	[17]	P = <0.001	RR = 1.48 (1.2-1.81)
		[25]	P = <0.001	OR = 2.42 (1.85-3.16)
		[28]	P = Not reported	OR = 2.98 (1.86-4.78)

Category	Marker	Study	Significance	Effect Size
Patient characteristics	BMI at age 18	[32]	P = < 0.01	OR = 1.06 (1.02-1.10)
	BMI at age 18, <21	[28]	P = Not reported	OR = 1.28 (0.79-2.06)
	BMI at age 18, 23.0-24.9 vs <21	[28]	P = Not reported	OR = 1.73 (0.96-3.13)
	BMI at age 18, 25.0-29.9 vs <21	[28]	P = Not reported	OR = 1.69 (0.88-3.26)
	BMI at age 18, = or > 30 vs <21	[28]	P = Not reported	OR = 1.53 (0.71-3.29)
	Female sex	[20]	P = 0.86	OR = 0.86 (0.53-1.42)
		[21]	P = 0.85	OR = 1.03 (0.78-1.36)
	High school graduate	[22]	P = 0.049	HR = 0.30 (0.09-0.99)
	Hip circumference (38.0-40.9 inch vs < 38.0 inch)	[28]	P = Not reported	OR = 1.24 (0.51-3.0)
	Hip circumference (>41.0 inch vs < 38.0 inch)	[28]	P = Not reported	OR = 2.59 (1.18-5.69)
	Male sex	[19]	P = 0.75	OR = 1.2 (0.5-2.9)
		[23]	P = 0.41	RR = 1.46 (0.59-3.63)
	Obese vs normal	[22]	P = 0.1	HR = 1.76 (0.89-3.47)
	Overweight vs normal	[22]	P = 0.95	HR = 1.02 (0.50-2.10)
	Patient reported family history of PsA	[19]	P = 0.85	OR = 1.2 (0.1-10.5)
		[22]	P = 0.29	HR = 1.96 (0.57-6.71)
	University level of education	[20]	P = 0.56	OR = 1.18 (0.66-2.13)

Category	Marker	Study	Significance	Effect Size
Patient characteristics	University vs high school incomplete	[22]	P = 0.005	HR = 0.22 (0.08-0.62)
	Waist circumference (28.0-31.9 inch vs < 28.0 inch)	[28]	P = Not reported	OR = 1.46 (0.54-3.99)
	Waist circumference (> 32.0 vs < 28.0 inch)	[28]	P = Not reported	OR = 3.02 (1.21-7.56)
	Waist-hip ratio (0.744-0.800 vs < 0.744)	[28]	P = Not reported	OR = 1.41 (0.63-3.15)
	Waist-hip ratio (>0.800 vs <07.44)	[28]	P = Not reported	OR = 2.48 (1.20-5.15)
	Weight change from 18 years (increase 20-49.9lb vs < 20lb)	[28]	P = Not reported	OR = 1.34 (0.82-2.17)
	Weight change from 18 years (increase 50-99.9lb vs < 20lb)	[28]	P = Not reported	OR = 2.42 (1.49-3.91)
	Weight change from 18 years (increase 100 lb vs < 20 lb)	[28]	P = Not reported	OR = 3.84 (1.93-7.63)
Physical stress	Any trauma	[20]	P = 0.054	OR = 1.97 (0.99-3.96)
		[30]	P = Not reported	OR = 1.10 (0.65-1.86)
		[33]	P = Not reported	RR = 1.32 (1.13-1.54)
	Fracture	[18]	P = 0.41	OR = 1.50 (0.58-3.91)
		[20]	P = 0.69	OR = 1.2 (0.54-2.51)
		[30]	P = Not reported	OR = 1.0 (0.34-2.96)
		[33]	P = Not reported	RR = 1.46 (1.04-2.04)
	Joint trauma	[33]	P = Not reported	RR = 1.50 (1.19-1.90)

Category	Marker	Study	Significance	Effect Size
Physical stress	Lifting heavy loads (>100 pounds/hour)	[20]	P = 0.0008	OR = 2.92 (1.56-5.46)
	Trauma leading to medical care	[30]	P = Not reported	OR = 2.53 (1.1-6.0)
Psychological distress	Becoming employed	[20]	P = 0.85	OR = 1.0 (0.54-1.66)
	Becoming unemployed	[30]	P = Not reported	OR = 1.92 (0.6-6.0)
	Changed job	[20]	P = 0.44	OR = 1.2 (0.73-2.07)
		[30]	P = Not reported	OR = 1.72 (0.85-3.5)
	Death of family member	[20]	P = 0.82	OR = 1.1 (0.63-1.79)
		[30]	P = Not reported	OR = 1.1 (0.6-2.0)
	Depression	[22]	P = 0.85	HR = 0.92 (0.35-2.34)
		[26]	P = 0.021	HR = 1.37 (1.05-1.80)
	Move to a new home	[20]	P = 0.68	OR = 1.1 (0.67-1.82)
		[30]	P = Not reported	OR = 2.29 (1.21-4.4)
	Psychological distress	[18]	P = 0.87	OR = 0.93 (0.36-2.36)
		[23]	P = 0.11	RR = 1.17 (0.89-3.35)
	Treated for anxiety/depression	[20]	P = 0.41	OR = 0.8 (0.39-1.45)
		[30]	P = Not reported	OR = 0.67 (0.27-1.7)

BMI = Body mass index; Cig = cigarettes; HR= hazard ratio; Ib = international pound; OR = odds ratio; PASI = Psoriasis Area and Severity Index; Pso = psoriasis; PsA = psoriatic arthritis; RR = relative risk; vBMD = volumetric bone mineral density.

Supplementary table 4: Statistical significance and effect sizes of laboratory markers

Category	Marker	Study	Significance	Effect Size
ACPA	Anti-CCP	[37]	P = 0.012	Not reported
		[40]	P = 0.006	Not reported
		[54]	P = < 0.001	Not reported
		[99]	Not significant	Not reported
Bone metabolism	25(OH) Vitamin D	[69]	P = 0.4	Not reported
		[90]	Not significant	Not reported
		[91]	P = 0.083	Not reported
		[98]	P = 0.685	Not reported
	25(OH) Vitamin D < 20 mg/L	[98]	P = 0.090	Not reported
	25(OH) Vitamin D 20-30 mg/L	[98]	P = 0.795	Not reported
	25(OH) Vitamin D > 30 mg/L	[98]	P = 0.876	Not reported
	Alkalic Phospate	[50]	P = 0.231	Not reported
		[70]	Not significant	Not reported
		[98]	P = 0.234	Not reported
	Calcium	[50]	P = 0.47	Not reported
		[70]	Not significant	Not reported
		[98]	P = 0.207	Not reported
	COMP	[47]	P = 0.145	Not reported
		[56]	P = 0.35	OR = 1.000
	CPII:C2C	[56]	P = 0.01	OR = 12.031
	CTX	[50]	P = 0.169	Not reported
	CTx-I	[61]	Not significant	Not reported
	CTx-II	[61]	Not significant	Not reported
	DKK-1	[59]	P = < 0.001	Not reported
		[61]	Not significant	Not reported
		[75]	P = 0.07	OR = 1.14
	MMP3	[56]	P = 0.04	OR = 1.323
		[58]	P = 1.00 E-03	OR = 1.59
		[61]	Not significant	Not reported
		[75]	P = 0.0004	OR = 1.02

Category	Marker	Study	Significance	Effect Size
Bone metabolism	OPG	[44]	P = 0.77	Not reported
		[47]	P = 0.986	Not reported
		[56]	P = 0.04	OR = 1.323
		[59]	Not significant	Not reported
		[61]	Not significant	Not reported
		[75]	P = 0.17	OR = 2.51
	OPG/RANKL ratio	[47]	P = 0.049	OR = 0.92
		[82]	P = < 0.001	Not reported
	Osteoclast precursor	[82]	P = < 0.001	Not reported
	Phosphate	[50]	P = 0.456	Not reported
		[98]	P = 0.541	Not reported
	RANKL	[42]	P = < 0.001	Not reported
		[47]	P = 0.221	Not reported
		[56]	P = 0.77	OR = 0.999
		[59]	Not significant	Not reported
		[61]	Not significant	Not reported
		[82]	P = < 0.001	Not reported
	Urine Hp	[70]	P = < 0.05	Not reported
Cell culture	PBMC's: IL-17 secretion	[49]	P = < 0.05	Not reported
	T-cells: IFNy secretion	[51]	P = 0.367	Not reported
	T-cells: IL-2 secretion	[51]	P = 0.023	Not reported
	T-cells: IL-4 secretion	[51]	P = 0.27	Not reported
	T-cells: IL-5 secretion	[51]	P = 0.695	Not reported
	T-cells: IL-10 secretion	[51]	P = 0.285	Not reported
	T-cells: IL-17 secretion	[51]	P = 0.16	Not reported
	T-cells: TNFa secretion	[51]	P = 0.64	Not reported
Cytokines	CXCL10	[19]	P = 0.004	OR = 1.3
	CXCL10 decline over time	[39]	P = < 0.001	Not reported
	IL-6	[40]	P = 0.002	Not reported
		[100]	P = 0.05	Not reported
	IL-6 (high)	[77]	Not significant	OR = 1.28
	IL-6 (hs)	[95]	P = <0.01	Not reported
	IL-12p40	[56]	P = 0.12	OR = 1.014
		[82]	P = < 0.05	Not reported

Category	Marker	Study	Significance	Effect Size
Cytokines	IL-23	[96]	P = 0.0038	Not reported
	IL-33	[82]	P = < 0.05	Not reported
	IL-34	[45]	P = 0.001	Not reported
		[82]	P = < 0.001	Not reported
	IL-35	[82]	P = < 0.01	Not reported
	IL-36a	[82]	P = < 0.001	Not reported
	IL-38	[82]	P = < 0.001	Not reported
	M-CSF	[75]	P = 0.01	OR = 0.44
		[59]	P = < 0.01	Not reported
	TNF-a	[77]	P = < 0.001	Not reported
		[82]	P = < 0.001	Not reported
	TNF-a (high)	[77]	P = > 0.05	OR = 2.25
Cytologic phenotype	CD3+CD71+ count	[51]	P = 0.034	Not reported
	CD4+CD45RA-CXCR3+CCR4-	[62]	P = 0.001	Not reported
	CD4+CD45RA-CXCR3+CCR6-	[62]	P = 0.025	Not reported
	CD4+CD45RA-IFNy+	[62]	P = 0.015	Not reported
	CD4+CD45RA-IL17+	[62]	P = 0.034	Not reported
	CD4+T_{EM}CXCR3+CCR4-	[62]	P = 0.037	Not reported
	CD4+T_{EM}IL17A+	[62]	P = 0.029	Not reported
	CD8+CD45RA-CCR6+CXCR3-CD69+	[62]	P = 0.026	Not reported
	CD8+CD45RA-IL17+	[62]	P = 0.005	Not reported
	CD8+T_{CM}CD69+	[62]	P = 0.035	Not reported
	CD8+T_{EM}IL17A+	[62]	P = 0.034	Not reported
	CD8+T_{EMRA}CCR6+CXCR3-CD69-	[62]	P = 0.0001	Not reported
	CD8+T_{EMRA}CXCR3+CCR4-	[62]	P = 0.018	Not reported
	CD8+T_{EMRA}CXCR3+CCR6-CD69+	[62]	P = 0.01	Not reported
	Mean platelet volume	[55]	P = < 0.001	Not reported
		[78]	P = 0.072	Not reported
	Monocyte count	[79]	P = 0.0172	Not reported
	Neutrophil count	[79]	P = < 0.0001	Not reported
	Neutrophil:lymphocyte ratio	[79]	P = 0.0002	Not reported
	Platelet count	[79]	P = 0.001	Not reported
		[55]	P = 0.09	Not reported
	Platelet:lymphocyte ratio	[79]	P = 0.0227	OR = 1.012

Category	Marker	Study	Significance	Effect Size
Cytologic phenotype	White blood count	[79]	P = < 0.0001	Not reported
		[90]	Not significant	Not reported
mRNA expression whole blood	CX3CL1	[38]	p = 0.046	Not reported
	CXCL2	[38]	P = 0.002	Not reported
	CXCL5	[38]	P = 0.042	Not reported
	CXCL10	[97]	P = 0.23	Not reported
	HAT1	[97]	P = 0.02	Not reported
	IL3	[38]	P = 0.021	Not reported
	IL6	[38]	P = 0.044	Not reported
	IL8	[38]	P = 0.001	Not reported
	IL17C	[38]	P = 0.009	Not reported
	IL17F	[38]	P = 0.014	Not reported
	ISG20	[38]	P = 0.008	Not reported
	MMP3	[38]	P = 0.001	Not reported
	NFKB1	[38]	P = 0.581	Not reported
	NOTCH2NL	[97]	P = < 0.001	Not reported
	SETD2	[97]	P = 0.03	Not reported
	STAT3	[38]	P = 0.022	Not reported
	STAT6	[38]	P = 0.035	Not reported
	SYK	[38]	P = 0.004	Not reported
	TBX21	[38]	P = 0.004	Not reported
Inflammation marker	CRP	[19]	P = 0.147	Not reported
		[50]	P = < 0.05	Not reported
		[51]	Not significant	Not reported
		[58]	P = 2.55 E-07	OR = 1.96
		[59]	P = < 0.05	Not reported
		[72]	P = 0.487	OR = 0.398
		[74]	P = 0 .001	Not reported
		[79]	P = < 0.0001	Not reported
		[80]	P = < 0.001	Not reported
		[82]	P = <0.05	Not reported
		[83]	P = 0.001	Not reported
		[90]	Not significant	Not reported
		[98]	P = < 0.001	Not reported

Category	Marker	Study	Significance	Effect Size
Inflammation marker	CRP (high)	[77]	Not significant	OR = 1.24
	hs-CRP	[45]	P = 0.01	Not reported
		[56]	P = 0.03	OR = 2.402
		[64]	P = < 0.001	Not reported
		[66]	P = 0.008	Not reported
	ESR	[45]	P = < 0.001	Not reported
		[50]	P = < 0.05	Not reported
		[66]	P = < 0.0001	Not reported
		[72]	P = 0.600	OR = 0.984
		[74]	P = 0.017	Not reported
		[79]	P = < 0.0001	OR = 1.036
		[82]	P = <0.05	Not reported
		[95]	P = 0.57	Not reported
		[98]	P = 0.066	Not reported
Lipid metabolism	Adiponectin	[64]	P = 0.005	Not reported
		[77]	P = 0.12	Not reported
	Adiponection (high)	[77]	P = < 0.05	OR = 0.61
	ApoA:ApoB	[94]	P = < 0.05	Not reported
	ApoB	[94]	P = < 0.05	Not reported
	CER	[89]	P = 0.003	Not reported
	Glucose	[64]	P = 0.12	Not reported
		[90]	Not significant	Not reported
		[91]	P = 0.068	Not reported
		[94]	P = 0.0519	Not reported
		[95]	P = 0.08	Not reported
	Glucose (fasting)	[92]	P = 0.49	Not reported
	HDL	[64]	P = 0.69	Not reported
		[74]	P = 0.627	Not reported
		[91]	P = 0.196	Not reported
		[92]	P = 0.1	Not reported
		[95]	P = 0.25	Not reported
	Insulin	[92]	P = 0.02	Not reported
	LDL	[64]	P = 0.52	Not reported

Category	Marker	Study	Significance	Effect Size
Lipid metabolism	LDL:HDL	[74]	P = 0.192	Not reported
		[90]	P = 0.36	Not reported
		[91]	P = 0.087	Not reported
		[94]	P = 0.0798	Not reported
		[95]	P = < 0.05	Not reported
		[94]	P = < 0.01	Not reported
		[95]	P = < 0.05	Not reported
	Leptin	[64]	P = 0.04	Not reported
	Leptin (high)	[77]	Not significant	OR = 1.21
	Total cholesterol	[64]	P = 0.45	Not reported
		[91]	P = 0.042	Not reported
		[92]	P = 0.13	Not reported
		[94]	P = 0.0637	Not reported
		[95]	P = < 0.05	Not reported
	Total cholesterol/HDL	[91]	P = 0.606	Not reported
		[94]	P = < 0.05	Not reported
	Triglycerides	[64]	P = 0.55	Not reported
		[74]	P = 0.037	Not reported
		[90]	Not significant	Not reported
		[91]	P = 0.189	Not reported
		[92]	P = 0.32	Not reported
		[94]	P = 0.4156	Not reported
		[95]	P = <0.05	Not reported
	VLDL	[94]	P = 0.1268	Not reported
		[95]	P = 0.16	Not reported
miRNA expression	hsa-let-7b-3p (extracellular vesicle)	[93]	P = 0.015	Not reported
	hsa-let-7b-5p (extracellular vesicle)	[93]	P = 0.018	Not reported
	hsa-let-7e-5p (extracellular vesicle)	[93]	P = 0.024	Not reported
	hsa-miR-26a-5p (extracellular vesicle)	[93]	P = 0.032	Not reported
	hsa-miR-27a-3p (extracellular vesicle)	[93]	P = 0.045	Not reported
	hsa-miR-27b-3p (extracellular vesicle)	[93]	P = 0.032	Not reported
	hsa-miR-29a-3p (extracellular vesicle)	[93]	P = 0.045	Not reported
	hsa-miR-30e-5p (extracellular vesicle)	[93]	P = < 0.05	Not reported
	hsa-miR-92a-3p (extracellular vesicle)	[93]	P = 0.04	Not reported

Category	Marker	Study	Significance	Effect Size
miRNA expression	hsa-miR-92b-3p (extracellular vesicle)	[93]	P = 0.02	Not reported
	hsa-miR-98-5p (extracellular vesicle)	[93]	P = 0.033	Not reported
	hsa-miR-139-3p (extracellular vesicle)	[93]	P = 0.022	Not reported
	hsa-miR-146a-5p (extracellular vesicle)	[93]	P = 0.007	Not reported
	miR-146a-5p in CD14+ monocytes	[84]	P = < 0.05	Not reported
	hsa-miR-203a (extracellular vesicle)	[93]	P = 0.01	Not reported
	hsa-miR-486-5p (extracellular vesicle)	[93]	P = 0.042	Not reported
	hsa-miR-1180-3p (extracellular vesicle)	[93]	P = 0.017	Not reported
	hsa-miR-2379-5p (extracellular vesicle)	[93]	P = 0.039	Not reported
	hsa-miR-3158-3p (extracellular vesicle)	[93]	P = 0.022	Not reported
	hsa-miR-4732-3p (extracellular vesicle)	[93]	P = 0.018	Not reported
Serum	Anti-ADAMTS-L5 IgG	[103]	P = < 0.001	Not reported
	Anti-LL37 IgG	[103]	P = < 0.001	Not reported
	Anti-LL37 citrinullated	[68]	Not significant	Not reported
	Anti-LL37 carbamylated	[68]	P = 0.02	Not reported
	C9	[68]	P = 0.02	Not reported
	CD5L	[58]	P = 3.63 E-01	OR = 1.08
	Creatinin	[59]	P = > 0.05	Not reported
		[98]	P 0.145	Not reported
	Gelsolin	[66]	P = < 0.0001	Not reported
	IFI16	[43]	P = 0.0006	Not reported
	IL2R	[100]	P = 0.05	Not reported
	ITGB5	[58]	P = 3.05 E-06	OR = 3.82
	K17	[85]	P = 0.0264	Not reported
	M2BP	[58]	P = 3.07 E-04	OR = 32.32
	PRL	[73]	P = 0.0003	Not reported
	STIP1	[85]	P = 0.050	Not reported
	Uric acid	[92]	P = 0.001	Not reported
		[101]	P = 0.01	OR = 4.28
		[102]	Not significant	Not reported

Category	Marker	Study	Significance	Effect Size
Serum	Hyperuricemia	[46]	P = 0.302	Not reported
	VCP	[86]	P = 0.0098	Not reported
	VEGFR-3	[71]	P = 0.026	Not reported
	YKL-40	[76]	P = < 0.0001	Not reported
Skin	C16ORF61, laesional 1	[57]	P = < 0.001	Not reported
	C16ORF61, laesional 2	[57]	P = 0.667	Not reported
	C16ORF61, non-laesional	[57]	P = 0.007	Not reported
	CPN2, laesional 1	[57]	P = < 0.001	Not reported
	CPN2, laesional 2	[57]	P = 0.032	Not reported
	CPN2, non-laesional	[57]	P = 0.03	Not reported
	CXCL12 in blood vessels	[36]	P = 0.000	Not reported
	CXCL12 in dermal cells	[36]	P = 0.000	Not reported
	CXCL12 in keratinocytes	[36]	P = 0.000	Not reported
	FHL1, laesional 1	[57]	P = <0.001	Not reported
	FHL1, laesional 2	[57]	P = 0.016	Not reported
	FHL1, non-laesional	[57]	P = 0.021	Not reported
	GPS1, laesional 1	[57]	P = 0.014	Not reported
	GPS1, laesional 2	[57]	P = 0.008	Not reported
	GPS1, non-laesional	[57]	P = 0.385	Not reported
	IL23R, epidermal	[81]	P = 0.001	Not reported
	IL23R, dermal	[81]	P = 0.018	Not reported
	ITGB5, laesional 1	[57]	P = 0.006	Not reported
	ITGB5, laesional 2	[57]	P = 0.032	Not reported
	ITGB5, non-laesional	[57]	P = 0.017	Not reported
	POSTN, laesional 1	[57]	P = > 0.05	Not reported
	POSTN, laesional 2	[57]	P = 0.001	Not reported
	POSTN, non-laesional	[57]	P = 0.013	Not reported
	PPP2R4, laesional 1	[57]	P = 0.043	Not reported
	PPP2R4, laesional 2	[57]	P = 0.008	Not reported
	PPP2R4, non-laesional	[57]	P = 0.678	Not reported
	SNCA, laesional 1	[57]	P = < 0.001	Not reported
	SNCA, laesional 2	[57]	P = < 0.001	Not reported
	SNCA, non-laesional	[57]	P = 0.089	Not reported
	SRP14, laesional 1	[57]	P = 0.019	Not reported

Category	Marker	Study	Significance	Effect Size
Skin	SRP14, laesional 2	[57]	P = 0.016	Not reported
	SRP14, non-laesional	[57]	P = 0.57	Not reported
	SRPX, laesional 1	[57]	P = 0.043	Not reported
	SRPX, laesional 2	[57]	P = 0.08	Not reported
	SRPX, non-laesional	[57]	P = 0.014	Not reported
Miscellaneous	Arylesterase activity	[74]	P = 0.003	Not reported
	Hemoglobin	[79]	P = 0.0011	OR = 0.685
	IgG response to C region of rM12 protein	[88]	P = < 0.001	Not reported

ACPA = anti citrullinated protein antibodies; ADAMTS = a disintegrin and metalloproteinase with thrombospondin motifs; anti-CCP = anti-cyclic citrullinated protein; Apo = apolipoprotein; C16ORF61 = endosomal protein sorting factor like (VSP35L); C2C = collagen fragment neoepitopes Col2-3/4 (long mono); C9 = complement factor 9; CCR = C-C chemokine receptor; CD = cluster of differentiation; CD5L = CD5 ligand; CER = ceramide; CM = central memory; COMP = cartilage oligometric matrix protein; CPII = C-propeptide of type II collagen; CP2N = carboxypeptidase N subunit 2; CRP = C-reactive protein; CTX = collagen type I C-telopeptide; CXCL = C-X-C motif ligand; CXCR = C-X-C motif receptor; DKK = dickkopf; EM = effector memory; ESR = erythrocyte sedimentation rate; FHL1 = four and a half LIM domains; GPS = G protein pathway suppressor; HAT = human airway trypsin-like protein; HDL = high density lipoprotein; hs = high sensitivity; IFI = interferon-inducible protein; IFN = interferon; Ig = immunoglobulin; IL = interleukin; IL2R = IL2 receptor; IL23R = interleukin 23 receptor; ISG = interferon stimulated gene; ITGB = integrin beta; K17 = keratin 17; L = liter; LDL = low density lipoprotein; M2BP = Mac-2-binding protein; M-CSF = macrophage colony stimulating factor; mg = milligram; miRNA = micro RNA; MMP = matrix metalloproteinase; mRNA = messenger RNA; NFKB = nuclear factor kappa-B; OPG = osteoprotegerin; OR = odds ratio; PBMC = peripheral blood mononuclear cells; POSTN = periostin; PPP2R4 = protein phosphatase 2 phosphatase activator (PTPA); RANKL = receptor activator of NFKB ligand; RNA = ribonucleic acid; SETD = SET domain protein; SNCA = synuclein alpha; SRP = signal recognition particle; SRPX = sushi repeat containing protein X-linked; STAT = signal transducer and activator of transcription; STIP = stress-inducible phosphoprotein; SYK = spleen associated tyrosine kinase; TBX = T-box; TNF = tumor necrosis factor; VCP = valosin containing protein; VEGFR = vascular endothelial growth factor receptor; VLDL = very low density lipoprotein

Supplementary table 5: Statistical significance and effect sizes of genetic markers

Category	Marker	Study	Significance	Effect Size
HLA	Haplotype B*08:01-C*07	[132]	P = 0.0020	OR = 1.81
	Haplotype B*08-C*07-MICA*00801	[125]	P = 0.021	OR = 1.730
	Haplotype B*18-C*07	[112]	P = 0.004	OR = 10.1
	Haplotype B*27-C*01	[112]	P = < 0.0001	OR = 41.1
		[132]	P = 0.0020	OR = 4.61
	Haplotype B*27-C*02	[112]	P = < 0.0001	OR = 19.9
		[113]	P = 0.04	Not reported
		[132]	P = 0.0333	OR = 2.59
	Haplotype B*27-C*02-MICA*00701/026	[125]	P = 0.000	OR = 12.923
	Haplotype B*35-C*04-MICA*0201/020	[125]	P = 0.047	OR = 0.490
	Haplotype B*37-C*06	[132]	P = 0.0424	OR = 0.54
	Haplotype B*38-C*12	[112]	P = 0.01	OR = 2.9
		[113]	P = 0.02	Not reported
		[132]	P = 0.3865	OR = 1.66
	Haplotype B*39:01-C*12	[113]	P = 0.005	Not reported
		[132]	P = 0.0190	OR = 3.93
	Haplotype B*57-C*06	[112]	P = 0.03	OR = 0.5
		[132]	P = 0.0004	OR = 0.49
	Haplotype B*57-C*06-MICA*017	[112]	P = 0.020	OR = 0.577
	HLA-A3 Ashkenazi	[115]	P = < 0.05	Not reported
	HLA-A3 Sephardic	[115]	Not significant	Not reported
	HLA-B*08	[104]	P = $1.76x10^{E}$-3*	Not reported
		[108]	P = > 0.05	Not reported
		[112]	P = 0.009	OR = 1.61
		[113]	P = 0.12	Not reported
	HLA-B*08:01	[104]	P = $1.76x10^{E}$-3*	Not reported
		[132]	P = 0.0019	OR = 1.81
	HLA-B*13 Ashkenazi	[115]	P = < 0.05	Not reported
	HLA-B*13 Sephardic	[115]	Not significant	Not reported
	HLA-B*13	[104]	P = $1.72x10^{E}$-3*	Not reported
		[126]	Not significant	Not reported
	HLA-B*18	[113]	P = 0.52	Not reported
	HLA-B*18:01:01	[132]	P = 0.0037	OR = 6.59
	HLA-B*27	[104]	P=$7.96x10^{E}$-7*	Unclear
		[112]	P = < 0.0001	OR = 5.17
		[113]	P = 0.002	Not reported
		[121]	P = 0.0007	Not reported
		[126]	P = < 0.001	OR = 4.2
	HLA-B*27:05	[108]	P = 3.53 x 10^{E}-7	OR = 2.34
	HLA-B*27:05:02	[132]	P = 0.0001	OR = 3.77
	HLA-B*37	[104]	P = $1.05x10^{E}$-2*	Not reported
	HLA*B37:01	[104]	P = $1.05x10^{E}$-2*	Not reported
	HLA-B*37:01:01	[132]	P = 0.0424	OR = 0.54
	HLA-B*38	[112]	P = 0.026	OR = 1.65
		[113]	P = 0.04	Not reported
		[126]	Not significant	Not reported
	HLA-B*38 Ashkenazi	[115]	Not significant	Not reported
	HLA-B*38 Sephardic	[115]	P = < 0.05	Not reported
	HLA-B*38:01:01	[132]	P = 0.3865	OR = 1.66
	HLA-B*39	[113]	P = 0.03	Not reported
	HLA-B*39:01:01:01	[132]	P = 0.0288	OR = 2.86
	HLA-B*39:06:01	[132]	P = 1	OR = 1.20
	HLA-B*44:02:01:01	[132]	P = 0.0198	OR = 0.60
	HLA-B*57	[104]	P = $2.64x10^{E}$-2*	Not reported
		[112]	P = 0.001	OR = 0.58
		[113]	P = 0.47	Not reported
		[126]	Not significant	Not reported
	HLA-B57*01	[104]	P = 1.98 x 10^{E}-2*	Not reported
	HLA-B*57:01:01	[132]	P = 0.0002	OR = 0.48
	HLA-B*70 Ashkenazi	[115]	P = < 0.05	Not reported
	HLA-B*70 Sephardic	[115]	Not significant	Not reported
	HLA-B amino acid position 45 Glu	[104]	P = 1.46 x 10^{E}-4*	Not reported
	HLA-B amino acid position 45 Glu/Gly	[104]	P = 2.02 x 10^{E}-4*	Not reported
	HLA-B amino acid position 45 Glu/Lys	[104]	P = $7.89x10^{E}$-3*	Not reported
	HLA-B amino acid position 45 Glu/Thr	[104]	P = 2.24 x 10^{E}-3*	Not reported

Category	Marker	Study	Significance	Effect Size
HLA	HLA-B amino acid position 45	[108]	P = 0.16	Not reported
	Glu vs Thr/Lys/Met	[124]	P = 2.9 x 10^{E}-12	OR = 1.46
	HLA-B amino acid position 45 Gly/Met	[104]	P = 3.57x 10^{E}-3*	Not reported
	HLA-B amino acid position 45 Lys/Met	[104]	P = 2.62x10^{E}-3*	Not reported
	HLA-B amino acid position 45 Lys/Thr	[104]	P = 1.74x10^{E}-2*	Not reported
	HLA-B amino acid position 95 Leu	[104]	P = 3.50 x 10^{E}-8	OR = 1.595
	HLA-B amino acid position 95 Trp	[104]	P = 3.18 x 10^{E}-3*	Not reported
	HLA-B amino acid position 97 Arg/Asn/Ser	[104]	P = 1.47 x 10^{E}-6*	Not reported
	HLA-B amino acid position 97 Arg/Thr	[104]	P = 1.20 x 10^{E}-2*	Not reported
	HLA-B amino acid position 97 Asn	[104]	P = 4.73 x 10E-6*	Not reported
	HLA-B amino acid position 97 Asn/Ser	[104]	P =1.31 x 10^{E}-6*	Not reported
	HLA-B amino acid position 97 Asn/Ser/Thr	[104]	P = 1.62 x 10^{E}-3*	Not reported
	HLA-B amino acid position 97 Asn/Ser/Trp	[104]	P = 9.47 x 10^{E}5*	Not reported
	HLA-B amino acid position 97 Asn/Trp	[104]	P = 3.92 x 10^{E}-2*	Not reported
	HLA-B amino acid position 97 Asn/Ser/Val	[104]	P = 2.12 x 10^{E}-3*	Not reported
	HLA-B amino acid position 97 Asp vs Arg	[108]	P = 5.76 x 10^{E}-8	OR = 2.46
	HLA-B amino acid position 97 Ser	[104]	P = 1.37 x 10^{E}-2*	Not reported
	HLA-B amino acid position 97 Ser/Trp	[104]	P = 4.82 x 10^{E}-2*	Not reported
	HLA-B amino acid position 97 Ser vs Arg	[108]	P = 3.58 x 10^{E}-5	OR = 1.45
	HLA-B amino acid position 97	[104]	P = 2.74 x 10^{E}-2*	Not reported
	HLA-B amino acid position 97 Thr/Trp	[104]	P = 1.33 x 10^{E}-2	Not reported
	HLA-B amino acid position 97 Thr/Val	[104]	P = 2.49 x 10^{E}-3*	Not reported
	HLA-B amino acid position 97 Thr vs Arg	[108]	P = 0.716	OR = 0.959
	HLA-B amino acid position 97 Try vs Arg	[108]	P = 0.283	OR = 0.795
	HLA-B amino acid position 97 Trp/Val	[104]	P = 2.35 x 10^{E}-2*	Not reported
	HLA-B amino acid position 97 Val	[104]	P = 3.89 x 10^{E}-2*	Not reported
	HLA-B amino acid position 97 Val vs Arg	[108]	P = 0.913	OR = 0.988
	HLA-C*01	[104]	P = 3.43 x 10^{E}-3*	Not reported
		[112]	P = 0.001	OR = 2.54
		[113]	P = 0.21	Not reported
	HLA-C*01:02	[104]	P = 3.43 x10^{E}-3*	Not reported
	HLA-C*01:02:01	[132]	P = 0.0828	OR = 1.78

Category	Marker	Study	Significance	Effect Size
HLA	HLA-C*02	[104]	P = 2.40 x 10^{E}-2*	Not reported
		[112]	P = 0.0008	OR = 2.42
		[113]	P = 0.27	Not reported
	HLA-C*02:02	[104]	P = 2.40 x 10^{E}-2*	Not reported
	HLA-C*02:02:02	[132]	P = 0.0316	OR = 2.35
	HLA-C*06	[104]	P = 6.96 x 10^{E}-11	OR = 0.5275
		[110]	P = < 0.001	Not reported
		[112]	P = 0.0002	OR = 0.58
		[113]	P = 0.69	Not reported
		[116]	P = 0.02	OR = 0.72
		[121]	P = 0.014	OR = 0.41
		[126]	P = < 0.001	OR = 0.5
	HLA-C*06 Ashkenazi	[115]	P = < 0.05	Not reported
	HLA-C*06 Sephardic	[115]	Not significant	Not reported
	HLA-C*06:02	[104]	P = 6.96 x10^{E}-11	OR = 0.5275
		[108]	P = 9.57 x 10^{E}-66	OR = 0.37
		[109]	p = 0.491	Not reported
	HLA-C*06:02:01:01	[132]	P = 9.94 x 10^{E}-12	OR = 0.30
	HLA-C*07	[104]	P = 2.21 x 10^{E}-4*	Not reported
		[112]	P = 0.027	OR = 1.35
		[113]	P = 0.32	Not reported
	HLA-C*07:01	[104]	P = 8.27 x 10^{E}-3*	Not reported
	HLA-C*07:01:01:01	[132]	P = 0.0023	OR = 1.76
	HLA-C*07:02	[104]	P = 3.05 x 10^{E}-2*	Not reported
	HLA-C*08	[121]	P = 0.021	OR = 0.35
	HLA-C*12	[112]	P = 0.13	OR = 1.29
		[113]	P = 0.005	Not reported
	HLA-C*12:03:01:01	[132]	P = 0.0668	OR = 1.83
	HLA-C amino acid position 305 Ala	[104]	P = 4.47 x 10^{E}-8	OR = 1.582
	HLA-C amino acid position 305 Thr	[104]	P = 2.21 x 10^{E}-4*	Not reported
	HLA-C rs10484554	[119]	P = 1.69 x 10^{E}-6	Not reported
	HLA-C rs12191877	[123]	P = 0.006	Not reported
	HLA-DQB1*02:01	[104]	P= 3.25 x 10^{E}-3*	Not reported
	HLA-DQB1*02:01 Ashkenazi	[115]	P = < 0.05	Not reported

Category	Marker	Study	Significance	Effect Size
HLA	HLA-DQB1*02:01 Sephardic	[115]	Not significant	Not reported
	HLA-DRB1*03	[104]	P = 4.03 x $10^{E}3^{*}$	Not reported
	HLA-DRB1*03:01	[104]	P = 3.06 x $10^{E}3^{*}$	Not reported
	HLA-DRB1*03:01 Ashkenazi	[115]	Not significant	Not reported
	HLA-DRB1*03:01 Sephardic	[115]	Not significant	Not reported
	HLA-DRB1*04:02 Ashkenazi	[115]	P = < 0.05	Not reported
	HLA-DRB1*04:02 Sephardic	[115]	Not significant	Not reported
	HLA-DRB1*04:05 Ashkenazi	[115]	P = < 0.05	Not reported
	HLA-DRB1*04:05 Sephardic	[115]	P = < 0.05	Not reported
	HLA-DRB1*04:06 Ashkenazi	[115]	P = < 0.05	Not reported
	HLA-DRB1*04:06 Sephardic	[115]	P = < 0.05	Not reported
	HLA-DRB1*07	[121]	P = < 0.001	OR = 0.12
	HLA-DRB1*14:01 Ashenazi	[115]	P = < 0.05	Not reported
	HLA-DRB1*14:01 Sephardic	[115]	Not significant	Not reported
	rs1050414 (near HLA-C and HLA-B)	[129]	P = 7.4 x 10^{E}-11	OR = 1.53
Non-HLA	5q31 rs715285	[134]	P = 7.05 x 10^{E}-7	Not reported
	ADAMTS9-MAG1 deletion	[120]	P = 0.0088	Not reported
	CCR2 rs1799864	[128]	P = 0.0007	Not reported
	IL1RN rs397211	[123]	P = 0.79	Not reported
		[134]	P = 0.74	Not reported
	IL12B rs2082412	[123]	P = 0.01	Not reported
		[134]	P = 0.04	Not reported
	IL12B rs3212227	[109]	P = 0.549	Not reported
		[122]	P = 0.55	OR = 1.13
	IL12B rs6887695	[109]	P = 0.522	Not reported
		[122]	P = 0.33	OR = 1.20
	IL13 rs1800925	[106]	P = 0.015	Not reported
		[111]	P = 0.045	OR = 1.28
	IL13 rs20541	[106]	P = 0.004	Not reported
		[123]	P = 0.11	Not reported
		[134]	P = 0.48	Not reported
	IL13 rs848	[111]	P = 0.047	RR = 1.30
	IL17E rs79877597	[105]	P = 0.032	OR = 1.50

Category	Marker	Study	Significance	Effect Size
Non-HLA	*IL23A* rs2066807	[123]	P = 0.23	Not reported
		[134]	P = 0.96	Not reported
	IL23R rs11209026	[109]	P = 0.459	Not reported
		[122]	P = 0.11	OR = 1.96
	IL23R rs2201841	[123]	P = 0.02	Not reported
		[134]	P = 0.08	Not reported
	IL23R rs7530511	[109]	P = 0.994	Not reported
	KIR2DS1 pos / C2 neg	[131]	P = 0.0046	Not reported
	MICA*00701/026 (presence)	[125]	P = < 0.001	OR = 4.402
	MICA*00801 (presence)	[125]	P = 0.110	OR = 1.339
	MICA*00801 (homozygosity)	[125]	P = 0.009	OR = 2.260
	MICA*016 (presence)	[125]	P = 0.034	OR = 0.418
	NFKBIA rs696	[122]	P = 0.1	OR = 1.36
	NFKBIA rs7152376	[110]	P = < 0.001	Not reported
	NFKBIA rs8016957	[134]	P = 0.06	Not reported
	PTPN22 rs2476601	[107]	P = 4.4 x 10^{E}-4	Not reported
		[122]	P = 0.41	OR = 1.21
	rs4891505 (near LOC100505817)	[129]	p = 6.7 x 10^{E}-9	OR = 1.63
	TNFa-238	[109]	P = 0.577	Not reported
		[118]	P = 0.99	OR = 1.002
	TNFa-308	[109]	P = 0.673	Not reported
		[118]	P = 0.93	OR = 1.04
	TNFa-857	[109]	p = 0.038	Not reported
	TNFa-1031	[109]	P = 0.657	Not reported
	TNFacd haplotype a2c2d4	[117]	Not significant	Not reported
	TNFacd haplotype a6c1d3	[117]	P = 0.008	RR = 5.3
	TNFacd haplotype a10c1d3	[117]	Not significant	Not reported
	TNFacd haplotype a11c1d3	[117]	Not significant	Not reported
	TNFAIP3 rs610604	[123]	P = 0.67	Not reported
		[134]	P = 0.58	Not reported
	TNIP1 rs17728338	[123]	P = 0.07	Not reported
		[134]	P = 0.07	Not reported

Category	Marker	Study	Significance	Effect Size
Non-HLA	*TSC1* rs1076160	[123]	P = 0.52	Not reported
		[134]	P = 0.42	Not reported
	ZNF816A	[134]	P = 0.01	Not reported

* no correction for multiple testing, not genome-wide significant

ADAMTS = a disentegrin and metalloproteinase with thrombospondin motifs; Ala = alanine; Arg = Arganine; Asn = Asparagine; CCR = C-C motif receptor; DNA = deoxyribonuclease acid; Glu = glutamic acid; Gly = glycine; HLA = human leukocyte antigen; IL = interleukin; IL1RN = IL-1 receptor antagonist; IL23R = IL-23 receptor; KIR = killer-cell immunoglobuline-like receptor; Leu = leucine; Lys = lysine; MAGI = membrane-associated guanylate kinase; Met = methionine; MHC = major histocompatibility complex; MICA = MHC class I polypeptide-related sequence A; NFKB = nuclear factor kappa B; NFKBIA = NFKB inhibitor alpha; OR = odds ratio; PTPN22 = protein tyrosine phosphatase non-receptor type 22; Ser = Serine; Thr = threonine; TNF = tumor necrosis factor; TNFAIP = TNF alpha-induced protein; TNIP = TNFAIP3 interacting protein; Trp = tryptophan; TSC1 = tuberous sclerosis 1; Val = valine; ZNF = zinc finger protein

Supplementary table 6: Quality assessment of cohort studies

Article	Selection				Comparability		Outcome			Conclusion
	Represen-tativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Controls for age	Controls for additional factor	Assessment of outcome	Sufficient follow-up	Adequacy of follow-up	Quality
Abji, 2016 [19]	A	A	A	A	yes	yes	A	A	C	Fair
Abji, 2020 [39]	A	A	A	A	no	yes	A	A	C	Fair
Eder, 2016 [22]	A	A	B	A	no	yes	A	A	B	Good
Eder, 2017 [23]	A	A	B	A	yes	yes	A	A	B	Good
Egeberg, 2018 [24]	A	A	A	B	no	yes	B	A	A	Good
Green, 2020 [25]	A	A	A	B	yes	yes	B	A	A	Good
Lewinson, 2017 [26]	A	A	A	B	yes	yes	B	A	C	Fair
Li, 2012 [27]	C	A	C	B	yes	yes	C	A	C	Poor
Li, 2012 [28]	C	A	C	B	yes	yes	C	A	B	Poor
Love, 2012 [17]	A	A	A	B	yes	yes	B	A	A	Good
Nguyen, 2018 [29]	C	A	A	B	yes	yes	B	A	A	Fair
Simon, 2020 [31]	A	A	A	A	yes	yes	A	A	A	Good
Soltani, 2010 [32]	B	B	A	B	no	yes	D	A	A	Fair
Thorarensen, 2017 [33]	A	A	A	B	no	no	B	A	D	Poor
Wilson, 2009 [34]	A	B	A	B	yes	yes	B	A	A	Fair
Wu, 2015 [35]	C	A	C	B	yes	no	C	A	B	Poor

Risk of bias was assessed using the Newcastle-Ottawa scale and for further explanation of the exact answer options, we refer to the original paper [15]. A study was considered of "good" quality when it had a minimum of 3 stars in the selection domain, 1 star in the comparability domain and 2 stars in the outcome/exposure domain. "Fair" quality was given when a study had a minimum of 2 stars in the selection, 1 star in the compatibility and 2 stars in the outcome/exposure domain [16] .

Supplementary table 7: Quality assessment of case control studies

Article	Selection				Comparability		Exposure			Conclusion
	Adequate case definition	Representative-ness of cases	Selection of controls	Definition of controls	Controls for age	Controls for additional factor	Ascertainment of exposure	Method of ascertainment	Non response rate	Quality
Abdelaal, 2018 [36]	C	B	C	B	yes	yes	C	A	A	Poor
Abdel Fattah, 2009 [37]	A	A	A	B	no	no	A	A	A	Poor
Abji, 2017 [38]	A	B	A	A	yes	yes	A	A	A	Good
Alenius, 2005 [40]	C	A	A	B	no	no	A	A	A	Poor
Alenius, 2009 [41]	A	B	A	A	no	no	A	A	A	Poor
Amin, 2015 [42]	A	A	A	B	no	no	A	A	A	Good
De Andrea, 2019 [43]	A	A	C	B	yes	yes	A	A	A	Fair
Aterido, 2019 [104]	A	A	C	B	no	no	A	B	C	Poor
Attia, 2011 [44]	A	A	A	A	no	no	A	A	A	Poor
Ausavarungnirun, 2017 [45]	A	B	A	B	yes	yes	A	A	A	Fair
Barbarroja, 2019 [46]	A	A	A	A	yes	yes	A	A	A	Good
Bartosinka, 2015 [47]	C	B	A	B	no	no	A	A	C	Poor
Bartosinka, 2018 [48]	C	B	A	B	yes	yes	A	A	A	Poor
Batalla, 2015 [105]	A	B	A	A	no	no	A	A	A	Poor
Benham, 2013 [49]	C	B	C	B	no	no	C	A	A	Poor

Article	Selection				Comparability		Exposure			Conclusion
	Adequate case definition	Representative-ness of cases	Selection of controls	Definition of controls	Controls for age	Controls for additional factor	Ascertainment of exposure	Method of ascertainment	Non response rate	Quality
Borman, 2008 [50]	B	A	A	B	no	no	A	A	A	Poor
Bose, 2014 [51]	A	B	A	B	no	no	C	A	C	Poor
Bostoen, 2014 [52]	A	A	A	B	no	no	A	A	A	Good
Bowes, 2011 [106]	A	B	C	B	no	no	A	A	C	Poor
Bowes, 2015 [107]	B	B	C	B	no	yes	A	B	A	Fair
Bowes, 2017 [108]	A	A	C	B	no	yes	A	B	B	Poor
Cabaleiro, 2013 [109]	C	B	A	B	no	yes	A	A	A	Poor
Calzavara, 1998 [53]	A	B	C	B	no	no	B	A	A	Poor
Candia, 2006 [54]	A	B	C	A	no	no	A	A	A	Poor
Canpolat, 2010 [55]	C	B	A	B	no	no	A	A	A	Poor
Chandran, 2010 [56]	A	B	C	A	yes	yes	A	A	A	Fair
Coto-Segura, 2019 [110]	A	B	A	B	no	yes	A	A	A	Fair
Cretu, 2015 [57]	C	B	C	A	yes	yes	A	A	A	Poor
Cretu, 2017 [58]	A	B	C	A	yes	yes	A	A	A	Fair
Dalbeth, 2010 [59]	A	B	B	B	no	no	A	A	A	Poor
Dalmady, 2013 [60]	A	B	C	A	no	no	A	A	A	Poor
Diani, 2019 [61]	A	B	A	B	no	no	A	A	A	Poor

Article	Selection				Comparability		Exposure			Conclusion
	Adequate case definition	Representative-ness of cases	Selection of controls	Definition of controls	Controls for age	Controls for additional factor	Ascertainment of exposure	Method of ascertainment	Non response rate	Quality
Diani, 2019 [62]	C	B	A	B	no	no	C	A	A	Poor
Eder, 2011 [20]	A	B	A	A	yes	yes	D	A	A	Good
Eder, 2011 [111]	A	B	B	A	no	yes	A	A	C	Fair
Eder, 2012 [21]	A	B	A	A	yes	yes	C	A	B	Poor
Eder, 2012 [63]	A	A	A	A	no	no	A	A	A	Poor
Eder, 2012 [112]	A	A	C	A	no	no	A	A	A	Poor
Eder, 2012 [113]	A	A	A	A	no	no	A	A	A	Poor
Eder, 2013 [64]	A	A	A	A	yes	yes	A	A	A	Good
Eiris, 2014 [114]	A	B	A	B	no	no	A	A	A	Poor
Elkayam, 2004 [115]	A	A	C	B	no	no	A	A	A	Poor
Engin, 2020 [65]	C	B	A	B	no	no	A	A	A	Poor
Esawy, 2019 [66]	A	B	A	B	no	no	A	A	A	Poor
Farrag, 2017 [67]	A	A	A	A	no	no	A	A	A	Poor
Frasca, 2018 [68]	A	B	A	B	no	no	A	A	C	Poor
Gisondi, 2011 [69]	C	A	A	B	no	no	A	A	A	Poor
Hein, 1991 [70]	C	B	A	B	no	no	A	A	A	Poor
Ho, 2008 [116]	A	A	C	B	no	no	A	A	C	Poor

Article	Selection				Comparability		Exposure			Conclusion
	Adequate case definition	Representative-ness of cases	Selection of controls	Definition of controls	Controls for age	Controls for additional factor	Ascertainment of exposure	Method of ascertainment	Non response rate	Quality
Hohler, 2002 [117]	A	B	C	B	no	no	A	A	C	Poor
Hong, 2018 [71]	C	B	C	B	no	no	A	A	C	Poor
Hur, 2020 [72]	C	B	A	B	no	no	A	A	A	Poor
Husakova, 2015 [73]	A	B	C	A	no	no	A	A	A	Poor
Husni, 2018 [74]	A	A	A	B	no	no	A	A	C	Poor
Isik, 2016 [118]	C	B	A	B	no	no	A	A	A	Poor
Jadon, 2017 [75]	A	A	C	B	yes	yes	A	A	B	Fair
Jensen, 2013 [76]	A	B	C	B	no	no	A	A	A	Poor
Johnson, 2019 [77]	B	B	A	B	yes	yes	A	A	A	Poor
Julia, 2012 [119]	A	B	C	B	no	yes	A	A	A	Poor
Julia, 2015 [120]	A	A	C	B	no	no	A	A	C	Poor
Kilic, 2017 [78]	B	B	A	B	no	no	D	A	A	Poor
Kim, 2016 [79]	B	B	A	B	no	no	A	A	A	Poor
Krajewska, 2019 [80]	A	B	C	B	no	no	A	A	A	Poor
El-Leithy, 2020 [81]	A	B	A	B	no	no	C	A	A	Poor
Li, 2017 [82]	A	B	C	B	no	no	A	A	A	Poor
Liao, 2008 [121]	A	A	A	A	no	no	A	A	A	Poor

Article	Selection				Comparability		Exposure			Conclusion
	Adequate case definition	Representative-ness of cases	Selection of controls	Definition of controls	Controls for age	Controls for additional factor	Ascertainment of exposure	Method of ascertainment	Non response rate	Quality
Lin, 2014 [83]	A	B	A	A	no	no	A	A	A	Poor
Lin, 2019 [84]	A	B	C	A	no	no	A	A	A	Poor
Loft, 2018 [122]	A	A	C	B	yes	yes	A	A	A	Fair
Maejima, 2014 [85]	C	B	C	B	no	no	C	A	A	Poor
Maejima, 2017 [86]	B	B	C	B	no	no	C	A	A	Poor
Mavropoulos, 2017 [87]	A	A	A	B	no	no	C	A	A	Poor
Muto, 1996 [88]	B	B	C	B	no	no	A	A	A	Poor
Mysliwiec, 2017 [89]	B	B	A	B	no	no	A	A	A	Poor
Mysliwiec, 2019 [90]	C	B	A	B	no	no	A	A	A	Poor
Nair, 2009 [123]	C	A	A	B	no	no	A	A	A	Poor
Okada, 2014 [124]	A	A	C	B	no	no	A	A	C	Poor
Orgaz-Molina, 2013 [91]	A	B	A	B	yes	yes	A	A	A	Poor
Ortolan, 2019 [92]	A	A	A	B	no	no	A	A	A	Poor
Pasquali, 2020 [93]	A	B	A	A	yes	yes	A	A	A	Good
Pattison, 2008 [30]	A	B	C	B	yes	yes	D	A	C	Poor
Pietrzak, 2018 [94]	C	B	A	B	no	no	A	A	A	Poor
Pietrzak, 2020 [95]	C	B	A	B	no	no	A	A	A	Poor

Article	Selection				Comparability		Exposure			Conclusion
	Adequate case definition	Representative-ness of cases	Selection of controls	Definition of controls	Controls for age	Controls for additional factor	Ascertainment of exposure	Method of ascertainment	Non response rate	Quality
Pirowska, 2018 [96]	C	B	A	B	no	no	A	A	A	Poor
Pollock, 2011 [125]	A	B	B	A	no	yes	A	A	C	Fair
Pollock, 2013 [126]	A	B	A	A	no	no	A	A	A	Poor
Pollock, 2015 [97]	C	B	C	B	no	yes	A	A	A	Poor
Pollock, 2019 [127]	A	B	A	A	no	no	A	A	A	Poor
Sag, 2018 [98]	A	A	A	B	yes	yes	A	A	A	Good
Shibata, 2009 [99]	B	B	A	B	yes	yes	A	A	A	Poor
Soto-Sanchez, 2010 [128]	A	B	A	A	yes	yes	A	A	A	Good
Spadaro, 1996 [100]	A	A	C	B	no	yes	A	A	A	Fair
Stuart, 2015 [129]	C	A	C	B	no	no	A	A	C	Poor
Thumboo, 2018 [18]	B	A	A	B	yes	yes	D	A	A	Good
Tsuruta, 2017 [101]	B	A	A	B	yes	yes	D	A	A	Fair
Voiculescu, 2018 [130]	C	B	A	B	no	no	A	A	A	Poor
Williams, 2005 [131]	C	B	C	B	no	no	A	A	A	Poor
Winchester, 2012 [132]	A	B	C	A	no	no	A	A	A	Poor
Yan, 2018 [133]	B	B	A	B	yes	yes	A	A	A	Fair
Yang, 2012 [134]	A	B	A	A	no	no	A	A	A	Poor
Yilmaz, 2017 [102]	C	B	A	B	no	no	A	A	A	Poor
Yuan, 2019 [103]	C	B	C	B	no	no	A	A	C	Poor
Zhao, 2019 [135]	A	B	A	A	no	yes	A	A	A	Good

Risk of bias was assessed using the Newcastle-Ottawa scale and for further explanation of the exact answer options, we refer to the original paper [15]. A study was considered of "good" quality when it had a minimum of 3 stars in the selection domain, 1 star in the comparability domain and 2 stars in the outcome/exposure domain. "Fair" quality was given when a study had a minimum of 2 stars in the selection, 1 star in the compatibility and 2 stars in the outcome/exposure domain [16] .

Chapter 3

The Skin may Clear but the Arthritis Won't Disappear: Focusing on Concomitant and New-Onset Psoriatic Arthritis in a Daily Practice Cohort of Psoriasis Patients on Biologic Therapy

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Abstract

Background
Previously identified risk factors for psoriatic arthritis (PsA); nail dystrophy and scalp lesions are highly prevalent in patients with moderate-to-severe psoriasis. Therefore, these variables may not be useful as predictors for PsA in this population.

Objective
We assessed the predictive value of demographic and clinical characteristics for development of PsA in a cohort of patients with moderate-to-severe psoriasis, currently treated with biologics. Furthermore, we reported the incidence of new-onset PsA in this population and described the characteristics of patients that developed PsA during biologic treatment.

Methods
Demographics and treatment characteristics of psoriasis patients currently using biologic therapy were extracted from the BioCAPTURE database (n=427). Poisson regression was used to calculate incidence rates. Multivariable logistic regression was performed to identify factors independently associated with PsA onset. Patient and treatment characteristics of patients that developed PsA during biologic treatment were described.

Results
The incidence of PsA was 1.0 (95% CI 0.8– 1.2) per 100 psoriasis-years. Except for a lower risk for PsA in male gender (OR 0.58, 95% CI 0.34– 0.98, p-value 0.04), no clinical factors were significantly associated with an altered risk of developing PsA. During biologic therapy, 32 patients (9.4%) newly developed PsA. In this group, 53.8% had PASI <5 at PsA diagnosis. The incidence rate of PsA was 1.6 (95% CI 1.1– 2.2) per 100 years on biologic therapy.

Conclusion
Clinical risk factors might be inaccurate to predict PsA onset in patients with moderate-to-severe psoriasis on biologics. Even with low disease activity, psoriasis patients on biologics are still prone to develop PsA.

Introduction

Psoriatic arthritis (PsA) is strongly associated with cutaneous psoriasis; about 25% of the patients with moderate-to-severe psoriasis will eventually develop PsA compared to 16% of the patients with mild disease[1]. It is of clinical importance to diagnose PsA as early as possible, to prevent irreversible damage to the joints and loss of function[2]. Dermatologists play a key role in the detection of joint involvement, and in order to facilitate the screening for PsA, various studies have identified clinical factors such as nail dystrophy and scalp lesions to be associated with PsA onset[3]. However, since nail psoriasis is also associated with higher psoriasis disease severity[4], nail psoriasis may not be suitable as a predictor for PsA in a population of patients with severe psoriasis.

Systemic therapies may reduce the occurrence of PsA in psoriasis patients[5]. Especially biologic therapies could theoretically mask or delay PsA onset. However, despite receiving biologic therapy, psoriasis patients are still prone to develop PsA[6-8]. Currently, there is a lack of data regarding the demographics and treatment characteristics of patients that develop PsA while receiving biologic therapy in the treatment of psoriasis. Knowledge of these factors might prove useful in future research in this specific population.

In this study, we assessed the predictive value of demographic and clinical factors for the onset of PsA in a daily practice cohort of patients with moderate-to-severe psoriasis, currently receiving biologic therapy. Furthermore, we tried to provide insight into the characteristics of psoriasis patients that developed PsA during biologic treatment as well as report the incidence rate of new-onset PsA in our cohort of psoriasis patients on biologic therapy.

Methods

The BioCAPTURE Registry

In this prospective cohort study, all adult patients with a history of plaque psoriasis that were enrolled in the prospective BioCAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry with Biologics) registry[9,10] and had been treated with biologic therapy at the Radboud university medical center (Radboudumc) before May 1, 2018 were included. All patients had one or more treatment episodes with TNF-α inhibitors (adalimumab, etanercept, infliximab), an IL-12/IL-23 inhibitor (ustekinumab), IL-17 inhibitors (brodalumab, ixekizumab, secukinumab) or an IL-23 inhibitor (guselkumab). Some patients underwent treatment with the currently withdrawn drugs alefacept (T-cell CD2 receptor blocker) or efalizumab (monoclonal IgG1 antibody against CD11a) in their medical history. A total of 427 patients were included.

Data Collection

Data were collected from the BioCAPTURE database from May 1, 2005 until May 1, 2018. Baseline characteristics extracted from the registry were sex, age, dates of psoriasis onset and start of biologic therapy, PsA diagnosis (as confirmed by a rheumatologist), family history of psoriasis (both first and second degree), first PASI (Psoriasis Area and Severity Index) score that was measured in the Radboudumc, Body Mass Index (BMI), and historic psoriasis phenotypes and localizations. For all patients, data on psoriasis phenotypes and localizations were collected until either data lock or loss to follow-up occurred. Psoriasis phenotypes

were subdivided into plaque, guttate, pustular and erythrodermic psoriasis. The presence of these phenotypes was noted if they appeared at some point during follow-up, not exclusively presenting as the main phenotype. Specific psoriasis localizations and types were recorded: scalp lesions, nail psoriasis, inverse psoriasis (including intergluteal and perianal lesions, and lesions in the axilla, groin and inframammary folds), and palmoplantar psoriasis.

In patients with a rheumatologist-confirmed diagnosis of PsA, the following additional data were collected: date of PsA diagnosis, type of articular involvement at diagnosis (first presentation), PASI score at PsA diagnosis (allowing a timeframe of 3 months prior to 6 weeks after PsA diagnosis), and prior and current use of biologics. Additionally, a distinction was made between psoriasis phenotypes and localizations that presented either prior, or subsequent to PsA onset. Types of articular involvement at PsA diagnosis were classified by a resident rheumatologist using the classification by Moll and Wright, into the following subgroups: distal interphalangeal (DIP) arthritis, arthritis mutilans, polyarthritis, asymmetrical oligoarthritis and spondylitis[11]. In patients with a history of biologic therapy prior to PsA onset, the exact number of patient-years "on drug" was calculated, accepting a treatment interruption with a maximum of 90 days.

Statistical Analysis

Descriptive statistics using standard parameters were used to display patient and treatment characteristics. The incidence rate of PsA expressed as new cases per 100 psoriasis-years was calculated using Poisson regression. Since the onset of cutaneous and musculoskeletal symptoms could be overlapping in patients that were diagnosed with psoriasis and PsA within the same year, the determination of the chronological course of events would most likely be arbitrary. Therefore, this group was excluded from calculating percentages/incidence rates of new-onset PsA in psoriasis patients at risk.

Part 1: Assessing the Predictive Value of Psoriasis Phenotype and Localizations For PsA in Patients with Moderate-To-Severe Psoriasis from the BioCAPTURE Cohort

Based on the absence or presence of PsA, patients were divided into two groups: patients with cutaneous psoriasis only (Pso-group) or with concomitant PsA (PsoPsA-group). In the PsoPsA-group in our primary analysis, only the patients with data available on psoriasis phenotype and localization that presented prior to PsA onset were included. For comparisons, Pearson X2 tests or Fisher's exact tests were performed for categorical variables. Continuous variables were first checked for normality, after which independent sample t-tests were performed for parametric, and Mann–Whitney U-tests for nonparametric data, respectively. Only the variables of interest with a *P*-value <0.20 were selected to be incorporated in a logistic regression analysis using the enter method, in order to identify factors associated with PsA onset.

In order to detect possible bias due to missing values or selection, two sensitivity analyses were performed by repeating the abovementioned procedures. For the first sensitivity analysis, all patients with PsA, even if psoriasis phenotypes or localizations presenting prior to PsA diagnosis were unknown, were included in the PsoPsA-group. Furthermore, all psoriasis phenotypes and localizations that had ever presented prior to data lock were included, instead of only including the characteristics that manifested prior to PsA onset only. For the second sensitivity analysis, patients with musculoskeletal complaints suspected of PsA were also included in the PsoPsA-group, as well as all psoriasis phenotypes and localizations that had ever presented prior to data lock.

Part 2: Focusing on the Patients with PsA Onset During Biologic Therapy

The incidence rate of PsA expressed as new cases per 100 patient-years on biologic therapy was calculated using Poisson regression, in which the time on biologic therapy was calculated from the administration of the first biologic until data lock or end of follow-up (not corrected for temporary interruptions of biologic therapies).

The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS (Version 25.0, Armonk, NY: IBM Corp).

Results

In our daily practice cohort of psoriasis patients on biologic therapy, 117 patients (27.4%) had rheumatologist-confirmed PsA. In this group, 4 (3.4%) patients had developed PsA prior to the onset of cutaneous symptoms, and 13 (11.1%) patients were diagnosed with both disease entities within the same year. For the entire cohort, the incidence of PsA was 1.0 case (95% CI 0.8–1.2) per 100 psoriasis-years.

Part 1: Association between Psoriasis Phenotype and Localization and PsA in Patients with Moderate-to-Severe Psoriasis

Figure 1 depicts the inclusion and exclusion of patients with psoriasis and, if applicable, PsA. Out of all 427 psoriasis patients that were treated at the Radboudumc and included in BioCAPTURE, 70 patients with PsA (PsoPsA-group A) and 288 patients with cutaneous psoriasis only (Pso-group) were included in our primary analysis. Baseline patient characteristics are presented in table 1. Of the 69 patients that were initially excluded, 47 patients had PsA, but data on psoriasis phenotype or localization prior to PsA onset were not available, or PsA developed prior to or simultaneously with psoriasis. (PsoPsA-group B). Twenty-two patients were excluded due to a clinically suspected yet not rheumatologist-confirmed diagnosis of PsA (PsoPsA-group C). PsoPsA-group B and C were excluded from the primary analysis, but included in the sensitivity analyses.

Male gender was more prevalent in the Pso group (63.9%), compared to PsoPsA-group A (51.4%) with a nearly statistically significant difference (p=0.06). Mean age at psoriasis onset and age at the initiation of biologic therapy were comparable. The distribution of phenotypes and psoriasis localizations was similar in both groups, with only inverse psoriasis showing a trend towards an inversed relationship with the onset of PsA (p=0.06). Scalp and nail psoriasis had a high prevalence in both Pso (97.2% and 81.9%, respectively) and PsA groups (95.7% and 78.6%, respectively). The prevalence of scalp and nail psoriasis was not significantly different between both groups.

Gender and inverse psoriasis were incorporated in a multivariable logistic regression model. Male gender was the only factor that showed a significant, *negative* association with the

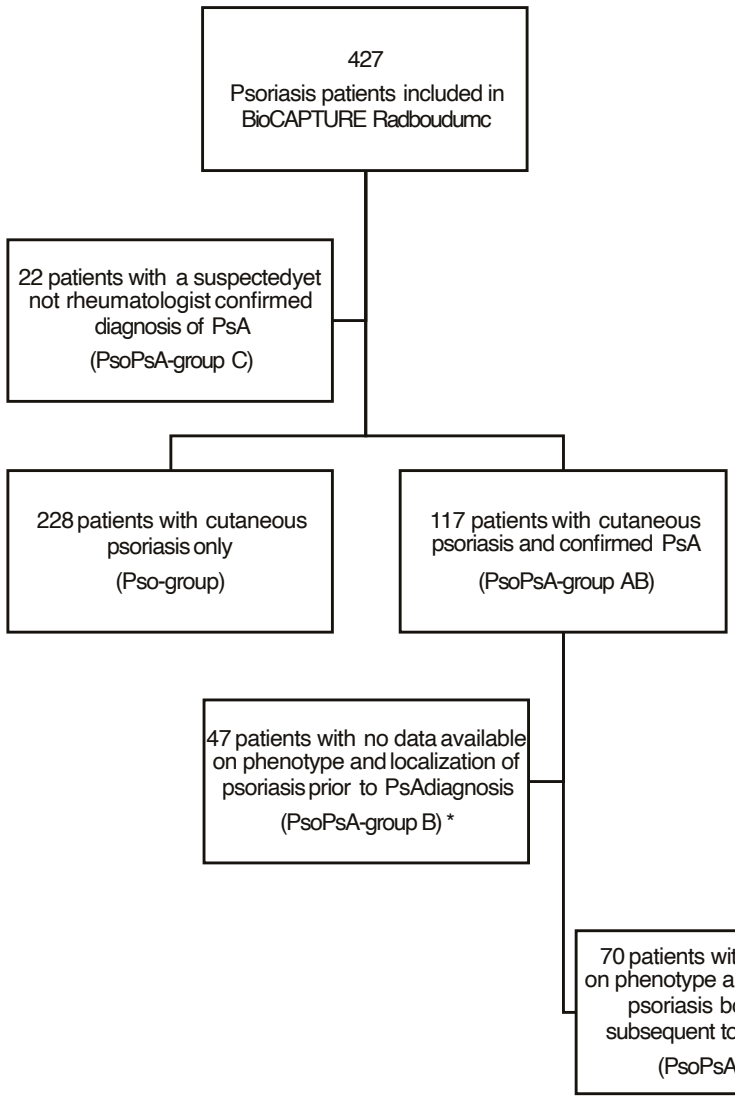

Figure 1: Flow chart of the inclusion and exclusion for primary and sub-analysis in part 1 of the study, of patients with psoriasis and, if applicable, PsA.
* PsoPsA-group B also includes patients who developed PsA prior to or simultaneously with psoriasis.

onset of PsA (Odds ratio (OR) 0.58, 95%CI 0.34–0.98, *p*=0.04). Inverse psoriasis (OR 0.61, 95% CI 0.36–1.05, *p*=0.07) proved nearly significant.

In sensitivity analyses, all phenotypes and localizations of psoriasis that had ever presented prior to data lock or end of follow-up were included. In the first sensitivity analysis, all 117 patients with PsA were included (PsoPsA-group AB). Univariable and multivariable analyses for the Pso-group vs PsoPsA-group AB were repeated. Gender, BMI and inverse psoriasis

Table 1: Socio-demographic and clinical characteristics in patients with only psoriasis (Pso-group) and psoriasis with confirmed psoriatic arthritis (PsoPsA group A)

	Pso-group (n=288)	PsoPsA-group A (n=70)	P-value
Gender (male)	184 (63.9%)	36 (51.4%)	0.06[a]
Age (years)	53.1 ± 13.8	56.5 ± 14.0	0.06[b]
Average duration of psoriasis (years)	28.6 ± 13.3	31.3 12.0	0.05[c]
Mean age at psoriasis diagnosis (years)	24.5 ± 13.0	25.2 ± 14.5	0.95[c]
Mean age at PsA diagnosis (years)	n/a	45.9 ± 13.7	n/a
Mean age at start biologic therapy (years)	45.1 ± 13.0	47.0 ± 12.9	0.27[b]
Mean Pso duration at start biologic therapy (years)	20.6 ± 12.5	21.9 ± 10.7	0.21[c]
Family history of psoriasis (yes)	145 (50.3%)	39 (55.7%)	0.42[a]
First PASI score in Radboudumc	12.8 ± 7.1	14.2 ± 8.3	0.19[c]
BMI (kg/m^2)	28.4 ± 6.2[d]	28.6 (4.7)[e]	0.33[c]
Psoriasis phenotypes (multiple options)			
Plaque	288 (100%)	70 (100%)	
Guttate	136 (47.2%)	29 (41.4%)	0.38[a]
Pustular	19 (6.6%)	4 (5.7%)	> 0.99[a]
Erythrodermic	14 (4.9%)	6 (8.6%)	0.25[a]
Topographic psoriasis localizations (multiple options)			
Scalp lesions	280 (97.2%)	67 (95.7%)	0.51[a]
Inverse	191 (66.3%)	39 (55.7%)	0.10[a]
Palmoplantar	54 (18.8%)	11 (15.7%)	0.56[a]
Psoriatic nail changes	236 (81.9%)	55 (78.6%)	0.52[a]

Data are in N (%) or mean ± SD
PASI = Psoriasis Area and Severity Index; BMI = Body Mass Index
a = Pearson Chi-square test/Fisher's exact test; b = Independent sample T-Test, c = Mann-Whitney U-test; d = 2 missing values; e = 1 missing value

were included in the multivariable model. Male gender (OR 0.65, 95%CI 0.41–1.01, *p*=0.06) and inverse psoriasis (OR 0.67, 95%CI 0.43–1.06, *p*=0.09) proved nearly significant in logistic regression. In the second sensitivity analysis, the 22 patients with an unknown PsA status were also included in the PsA group (N= 139, PsoPsA-group AB + PsoPsA-group C). Gender, age at psoriasis diagnosis, BMI, and inverse psoriasis were included in the multivariable model. Male gender (OR 0.64, 95% CI 0.42–0.97, *p*=0.04) and inverse psoriasis (OR 0.64, 95% CI 0.42-0.98, *p*=0.04) proved a significant, negative association with having a diagnosis of PsA.

Part 2: Development of New-Onset PsA During Biologic Therapy

Thirty-two patients (27.4%) developed PsA during biologic therapy. Patient and treatment characteristics of this group are depicted in table 2. Of all psoriasis patients without PsA when starting biologics, 9.4% developed PsA during biologic therapy. We found an incidence rate of 1.6 new cases of PsA (95% CI 1.1–2.2) per 100 years on biologic therapy.

In patients that developed PsA despite biologic therapy, the mean PASI score around the time of PsA diagnosis was 6.6 ± 6.6. Fourteen patients (53.8%) had a PASI score <5 around PsA diagnosis, and 8 patients (30.8%) had a PASI score <3. Most patients (67.9%) presented with asymmetrical oligoarthritis at the time of diagnosis, and had one or more treatment episodes with adalimumab or etanercept prior to diagnosis. Fourteen patients (44%) were on adalimumab therapy when PsA was diagnosed, which is in line with the proportion of patients that had been treated with adalimumab (59%). The total number of patient-years "on drug" per patient ranged from 0.21 to 9.74 years, with a median of 2.64 years. Year of PsA diagnosis ranged from 2004 to 2018.

Discussion

In this observational study on a daily practice cohort of patients with moderate-to-severe psoriasis treated with biologic therapy, the incidence rate of PsA was 1.0 (95% CI 0.8–1.2) per 100 psoriasis-years. Male gender was associated with a lower risk of developing PsA when compared to female gender. Inverse psoriasis showed a trend towards significance for a lower risk of PsA onset, and was significantly associated with a lower risk of having PsA in one sensitivity analysis. None of the other psoriasis phenotypes and localizations, regardless whether they presented prior to PsA onset or not, were significantly associated with an altered risk of PsA in the multivariable analyses. Furthermore, in our cohort of psoriasis patients on biologic therapy, 9.4% of the patients at risk (without a prior history of PsA) developed PsA during biologic treatment. The incidence rate of PsA was 1.6 (95% CI 1.1–2.2) per 100 years on biologic therapy. In this group, PsA even developed in psoriasis patients with low psoriasis activity on biologic therapy; 53.8% had a PASI < 5 around the time of PsA diagnosis.

In our study population, due to the high prevalence of psoriatic nail changes and scalp lesions in both patient groups with and without PsA, these factors could not discriminate between patients at risk. It must be noted that these results are only generalizable in cohorts of patients with moderate-to-severe psoriasis that are treated with biological therapy. This is probably the reason why in contrast to our results, in a population-based prospective study by Wilson et al, scalp lesions (HR 3.89; 95% CI 2.18–6.94), nail dystrophy (HR 2.93; 95% CI 1.68–5.12) and intergluteal/perianal lesions (HR 2.35; 95% CI 1.32–4.19) were significantly associated with an increased risk of developing PsA[3]. In looking for associations rather than predictors for PsA, several other studies performed in populations of psoriasis patients with a mean BSA>10% or PASI>10 also found a positive association or a higher prevalence of nail involvement in concomitant PsA[12-17]. These findings are supported by the growing evidence for an anatomical correlation between nail psoriasis and enthesitis of the DIP joints, as a manifestation of PsA[18,19]. Besides a higher psoriasis severity[4], a longer duration of psoriatic skin lesions is also associated with a higher frequency of nail changes[20]. The relatively long duration of disease could partly account for the high prevalence of nail changes in our population[20]. Likewise, this could also be the reason for the high prevalence of scalp lesions. Although scalp lesions are sometimes reported as more prevalent in patients with PsA[14,21], there is no consensus regarding the association between scalp lesions and PsA in literature, since both positive[3], negative[17] and no associations[13,22] have been reported.

Table 2: Patient and treatment characteristics of psoriasis patients from the Radboudumc BioCAPTURE cohort that developed PsA during biologic therapy (n=32)

Gender (male)	15 (46.9%)
Age (years)	57.2 ± 14.1
Mean duration of psoriasis (years)	29.6 ± 12.1
Mean age at psoriasis diagnosis (years)	27.6 ± 14.6
Mean age at start biologic therapy (years)	47.3 ± 12.4
Mean age at PsA diagnosis (years)	50.6 ± 13.0
Mean psoriasis duration at start biologic therapy (years)	19.7 ± 10.5
Mean psoriasis duration at PsA onset (years)	23.0 ± 11.1
Mean time between first biologic use and PsA onset (years)	3.3 ± 2.2
Mean PASI score at PsA diagnosis	6.6 ± 6.6; *range* 0 - 31.6[a]
Type of articular involvement at PsA diagnosis [b]	
DIP arthritis	0 (0%)
Arthritis mutilans	0 (0%)
Polyarthritis	9 (32.1%)
Asymmetrical oligoarthritis	19 (67.9%)
Spondylitis	0 (0%)
Number of patients on biologic treatment at time of PsA diagnosis	
Adalimumab	14 (43.8%)
Etanercept	6 (18.8%)
Infliximab	3 (9.3%)
Ustekinumab	2 (6.3%)
Secukinumab	1 (3.1%)
Alefacept	1 (3.1%)
Efalizumab	1 (3.1%)
Biologic treatment temporarily interrupted (> 90 days)	4 (12.5%)
Total number of years on biologics prior to PsA diagnosis (sum)	89.75
Mean number of years on biologics prior to PsA diagnosis	2.80 ± 2.01
Median number of years on biologics prior to PsA diagnosis	2.64 [2.99]
Minimum number of years on biologics prior to PsA diagnosis	0.21
Maximum number of years on biologics prior to PsA diagnosis	9.74
Mean number of years on biologic prior to PsA diagnosis	
Adalimumab (n=19)	1.26 ± 1.10
Etanercept (n=16)	2.02 ± 1.49
Infliximab (n=5)	1.66 ± 0.62
Ustekinumab (n=6)	2.98 ± 2.53
Secukinumab (n=1)	0.33
Alefacept (n=3)	0.28 ± 0.12
Efalizumab (n=5)	1.21 ± 1.29

Data are in N (%), Mean ± SD, or Median [IQR] unless indicated otherwise
a = 6 missing values; b = 4 missing values

In our study, inverse psoriasis was significantly associated with a lower risk of PsA when patients with a "suspected yet not rheumatologist-confirmed" diagnosis of PsA were included. However, only a trend towards significance was shown in our primary analysis. Since we used the umbrella term 'inverse psoriasis' instead of one of its subsets, we could not directly compare our results to others who reported on the relationship between subgroups of inverse psoriasis and PsA[14,17,23]. No other psoriasis phenotypes were associated with PsA onset, which is in line with previous studies[24]. In our present study, male gender was the only variable that was associated with a lower risk of PsA in patients treated with biologics. Literature states that in the general population, the gender distribution in both psoriasis and psoriatic arthritis is balanced[25,26]. It could be possible that gender would have some association in other cohorts of psoriasis patients on biologic therapy, as it has been suggested that due to a higher psoriatic disease severity amongst males, the use of biologics is higher in men[27,28].

In this cohort of psoriasis patients on biologic therapy, 9.4% of the patients at risk developed PsA despite using biologic therapy. Similar results were reported by Napolitano et al, who reported that 22 out of 327 (6.7%) patients with plaque psoriasis developed PsA while on biologic therapy[6]. In the patients in our study that developed PsA despite being on biologic therapy, the mean duration of psoriasis prior to PsA onset was 23 years. This was relatively long, since most psoriasis patients that develop PsA do so within 10 years following their psoriasis diagnosis[29]. Oligoarthritis was the most common manifestation pattern of PsA at diagnosis (67.9%), followed by polyarthritis (32.1%).

In psoriasis patients not exclusively on biologic therapy, Eder et al reported similar results in a prospective cohort study in which they annually assessed symptoms of PsA (76.2% oligoarthritis vs 23.8% polyarthritis at PsA diagnosis [N=51]). In this study, patients were mainly recruited from phototherapy centers and through local advertisements. They reported an annual incidence rate of PsA of 2.7 per 100 psoriasis patients, which is relatively high compared to our findings in a hospital-based population[30].

In a cross-sectional study by Haroon et al, 29 psoriasis patients were newly diagnosed with PsA. Eleven of them (38%) were treated with biologic therapy at the moment of diagnosis. The percentages of patients with oligoarthritis and polyarthritis were both 31% at initial presentation. Contrary to our findings, seven patients (24%) had inflammatory axial disease[8]. The imbalance of PsA manifestation patterns between different cohorts may be a result of differences regarding systemic agents used to treat psoriasis or various screening methods for PsA (either repetitive or cross-sectional). Adequate psoriasis control does not guarantee adequate control of joint inflammation, as 53.8% of the patients in our study had a PASI <5, and 30.8% had a PASI <3 at the time of PsA diagnosis.
One of the main limitations of this study is the possible underestimation of the presence of psoriasis localization or phenotype. As data on phenotypes and psoriasis localization were derived from medical files, data could be lacking or not detailed enough to subtract localizations. Despite thorough screening procedures, some patients with early symptoms of PsA might have been left unnoticed.

Our study points out that the potential of a clinical predictor for the onset of PsA greatly depends on the population that is observed. Clinicians should keep this in mind when referral to a rheumatologist is considered, given the risk of both under- and overdiagnosis, and the

subsequent additional burden on the feasibility and costs of healthcare. On the other hand, we showed that patient characteristics in psoriasis patients that clinicians might associate with a lower risk of PsA, such as relatively long disease duration, low disease activity, and even treatment with biologic therapy, are not in fact that reassuring after all. Although self-administered screening tools for PsA seem to have moderate accuracy[31], implementation of questionnaire-based screening tools could increase the detection rate, and improve the recognition of PsA in dermatology clinics.

In conclusion, in this prospective cohort study on patients with moderate-to-severe psoriasis on biologic therapy, psoriasis phenotypes and localizations were not clearly associated with the onset of PsA, in contrast to studies on less-selected psoriasis patients. Male gender was associated with a lower risk of developing PsA. In this group of patients with moderate-to-severe psoriasis, other biomarkers are therefore needed for PsA prediction. In our cohort of psoriasis patients at risk, 9.4% developed PsA during biologic treatment. Even though biologic therapy can potentially mask or delay the onset of PsA, psoriasis patients on biologic therapy are still at risk, and should be carefully screened for signs and symptoms of musculoskeletal involvement.

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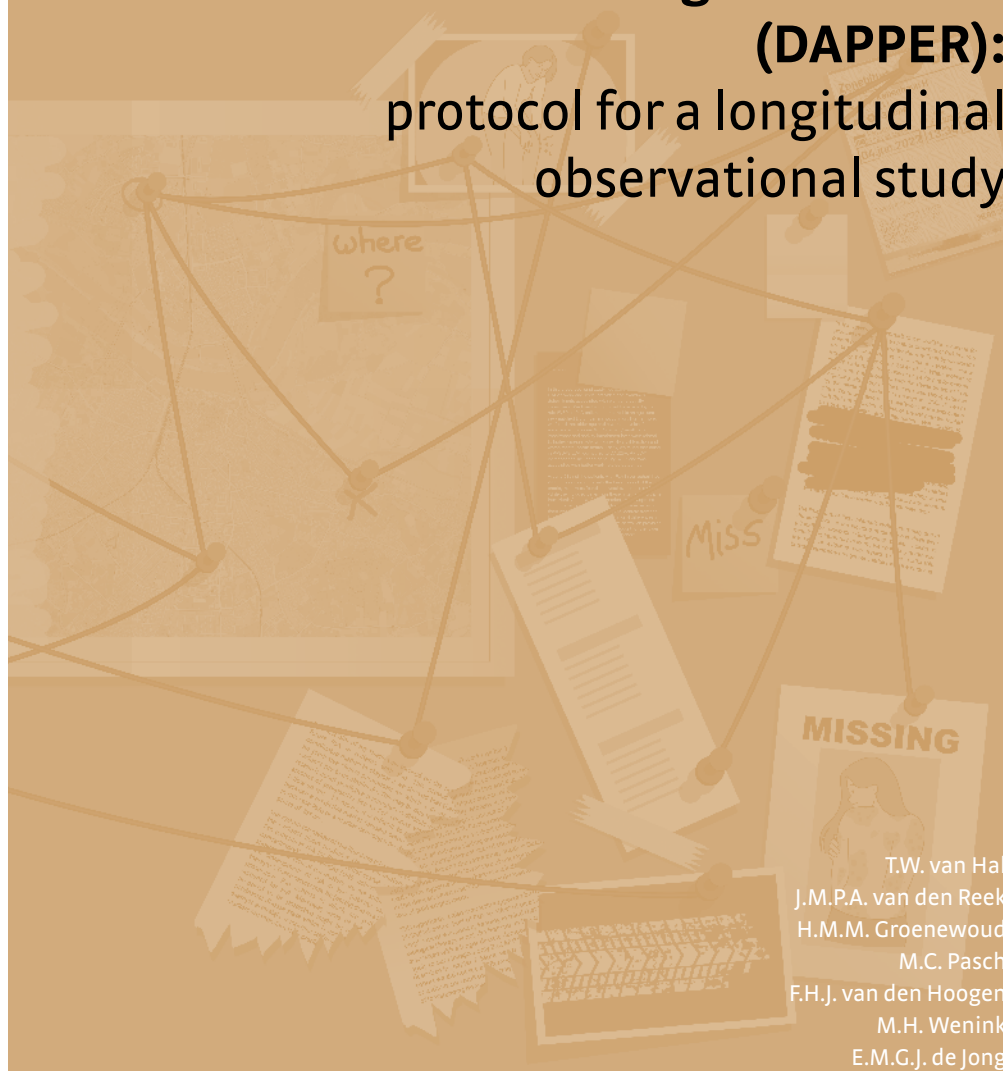
Chapter 4

Discovery of Arthritis in Psoriasis Patients for Early Rheumatological referral (DAPPER): protocol for a longitudinal observational study



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Abstract

Background

One in three patients with psoriasis (Pso) will develop psoriatic arthritis (PsA). If left untreated, this can lead to pain, impaired function, and irreversible joint damage. Timely recognition and referral to a rheumatologist are therefore key. However, current methods used to screen psoriasis patients for those who might benefit from referral to a rheumatologist, are not performing well enough.

Objectives

DAPPER is designed to determine the prevalence of PsA in a Pso population, and to find parameters that can be used to develop a new, or enhance an existing instrument for, rheumatological referral.

Methods

DAPPER is a longitudinal observational study with a one-year follow-up. Patients with psoriasis (n = 300) who are treated at an outpatient dermatological clinic will be screened extensively for signs and symptoms of PsA by a trained rheumatologist. If there is clinical suspicion of PsA, and the patient is not yet treated by a rheumatologist, referral to the department of rheumatology will follow for confirmation of the diagnosis and further care. After 1 year, data on changes in quality of life (QoL), and PsA and Pso disease activity will be collected of the referred patients. Screening visit will be used to gather demographical and medical data, which can later be used to develop the above-mentioned screening instrument.

Results

Inclusion started in June 2019, and finished in June 2021. Follow-up of newly-discovered PsA patients is ongoing.

Discussion

The DAPPER study is specifically designed to improve the detection of existing PsA in a dermatologic outpatient setting. While internal validity will be tested, external validity will have to be checked using a second validation cohort. To predict the development of PsA in the future, longitudinal/prospective data collection is required, and will be performed in a follow-up study (DAPPER-i).

Introduction

Psoriasis (Pso) is a common, immune-mediated skin disease. Besides skin and nails, psoriatic disease can also involve several other domains such as the entheses and the peripheral as well as the axial joints. This involvement of the musculoskeletal system defines psoriatic arthritis (PsA). PsA is an inflammatory rheumatic disease, related to other spondyloarthritides (SpA) such as reactive arthritis, ankylosing spondylitis, or inflammatory bowel disease associated arthritis. About one in three patients with Pso in the dermatological outpatient clinic will eventually develop PsA[1,2]. The order and amount of domains involved displays a large variation in different patients and at different time points[3]. However, the musculoskeletal symptoms often develop after the disease shows itself in skin or nails. On average, the lag time between skin and joint involvement is ten years[4].

When joints or entheses become inflamed, these can cause significant pain and have a large impact on the quality of life (QoL)[5]. Moreover, ongoing inflammation of joints can lead to irreversible joint damage and disability[6,7]. Early and adequate treatment of arthritis leads to an improvement of both joint function and quality of life[8,9]. Therefore, it is important to recognize and treat patients with concomitant arthritis as soon as possible.

The treatment strategies for Pso and PsA show considerable overlap[10,11]. Several pharmacological options are effective and recommended to treat both skin and joints. These encompass for example conventional systemic drugs such as methotrexate, as well as several biological drugs such as tumor necrosis factor alpha inhibitors (TNFi) and interleukin-17 (IL-17) inhibitors. However, some options are only available for one of these disease entities. This may be because of mode of delivery (for example topical application of creams for Pso or local injections of corticosteroids for PsA), or because of a difference in efficacy in controlling either joint or skin disease (for example retinoids for Pso and leflunomide for PsA). This could mean that the therapy a patient uses for their skin, can also be effective for their musculoskeletal complaints.

To ensure early adequate treatment and prevent (irreversible) morbidity, early recognition and early referral to a rheumatologist are key. The combined guidelines of the American Association of Dermatologist and the National Psoriasis Foundation calls screening of patients with Pso for PsA “essential at each visit”[12]. However, recognition of inflammatory joint complaints is not part of the dermatological scope. Also, due to a large prevalence of non-inflammatory joint complaints, referral of all patients with musculoskeletal pain is considered an unnecessary drain of resources. Therefore, about one in three PsA patients remain unrecognized in the dermatological clinic[1] and are at risk for irreversible damage.

To aid the recognition of PsA by dermatologists, several screening questionnaires have been developed[13-16]. Most of these are based on multiple patient-reported signs or symptoms, and result in a cumulative score. Referral to a rheumatologist is recommended when a certain score is reached. Unfortunately, testing of these questionnaires in new cohorts often had disappointing results[17,18]. The long average lag time between Pso and PsA also necessitates repeated use of a screening tool on a regular basis. However, none of the questionnaires were validated for re-use. These are all clues that current referral strategies are inadequate.

By screening a Pso population for the presence of concomitant PsA, we want to determine the prevalence of (undiscovered) PsA in this group. During this screening visit, we will gather data about several clinical characteristics. These will be used to ultimately develop a new, or enhance an existing, instrument for rheumatologic referral. This study is therefore called the Discovery of Arthritis in Psoriasis Patients for Early Rheumatology referral (DAPPER).

Methods

Aim

The aim of this study is to determine the number of patients with (untreated) PsA in a Pso patient group in a dermatological outpatient clinic. Furthermore, we want to optimize the detection of PsA in Pso patients in a dermatological outpatient clinic. For this purpose, we defined the following research questions:

Primary objective

To determine the prevalence of very early, newly-discovered, and known PsA, in a cohort of Pso patients treated at a dermatology outpatient clinic.

Secondary objectives

1. To determine if, in newly diagnosed PsA patients, psoriatic arthritis disease activity and quality of life differ before and one year after rheumatological referral in case of PsA.
2. To discover clinical parameters which are associated with the presence of PsA in a cohort of Pso patients.
3. To use above-mentioned parameters to develop a new or enhance an existing screening tool for concomitant PsA in Pso patients.

Design

The DAPPER study is a monocenter observational study with a follow-up of one year. We will examine three hundred patients, stratified 1:1:1 according to current dermatological treatment (topical and/or UV-therapy only, conventional systemic medication but no biologicals, biological therapy).

The initial screening at the dermatology department will include a 68 tender joint count (TJC), 66 swollen joint count (SJC), a dactylitis count (zero to twenty), and enthesitis scores (Leeds Enthesitis Index (LEI)[19] and the enthesitis score of the SPondyloArthritis Research Consortium of Canada (SPARCC)[20]). Inflammatory back pain will be assessed via the criteria of the Assessment of SpondyloArthritis International Society (ASAS)[21]. At this study visit, no laboratory tests or imaging will be performed for diagnostic purposes.

To investigate possible identifying characteristics and/or confounders for the detection of PsA, the study visit will also be used to gather demographical data (comorbidity, treatment data, and clinical characteristics of the skin). An example of the interview guide used is shown in supplemental file 1.

Referral and referral criteria

If there is a clinical suspicion of PsA in the study visit according to the study physician (trained rheumatologist), he or she will be referred to the department of rheumatology. Referral to a rheumatologist will be at the discretion of the investigator. A patient will be referred when not under current rheumatological care, and when meeting one of the following criteria: one or more swollen joints, clinical evidence of inflammatory enthesitis, and/or inflammatory back pain. Other reasons to suspect PsA can also give rise to referral (for example, restricted movement in a joint or prolonged morning stiffness). From there on, these patients will be investigated and treated as in regular PsA care. This will include confirmation of the diagnosis with additional laboratory tests and imaging, and treat-to-target via the Psoriatic ArthritiS Disease Activity Score (PASDAS)[22].

Follow-up

Only those patients with a newly-discovered PsA, as confirmed by a rheumatologist after referral, will be approached for follow-up after one year. At that moment, changes in treatment, disease activity, and health-related quality of life (HR-QoL) will be noted.

Study setting

This study will be carried out in the outpatient clinic of the department of dermatology in an academical center in the Netherlands (Radboud University Medical Center, Nijmegen). This department is a national psoriasis expertise center. Patients will initially be screened at the department of dermatology for signs or symptoms of enthesitis, dactylitis, arthritis, or inflammatory back pain by a trained rheumatologist. When additional rheumatological evaluation is required, patients are preferentially referred to the department of rheumatology of the Sint Maartenskliniek in Nijmegen. Here, the patient will be assessed by a rheumatologist with special expertise in PsA. When requested by the patient, a referral to another rheumatologic center is also possible.

Participants

All patients with a clinical diagnosis of psoriasis who are treated at the outpatient clinic are eligible for this study. Neither current nor previous treatment by a rheumatologist, nor a previous diagnosis of PsA, are exclusion criteria. Patients must be aged 18 years or older, and be able to give written informed consent.

Study size

For the logistic model, we aim to use five to ten independent variables. The number of independent variables used in the model will be restricted to one per ten events (i.e. one per ten PsA cases). Therefore, we aim to have fifty to one hundred PsA cases. Assuming a prevalence of PsA of twenty to thirty percent[1], this means we need 167 (prevalence thirty percent, five predictors) to five hundred (prevalence twenty percent, ten predictors) Pso patients. Using a total number of three hundred patients, we expect to find up to sixty to ninety PsA cases, ensuring we can incorporate six to nine independent variables.

Recruitment

All patients eligible for the study will be asked for study participation by their dermatologist. Written and oral information about the study will be given by the investigator. A study visit will be planned adjacent to a regular outpatient visit with the dermatologist. Before the study visit starts, written informed consent is obtained from the patients.

Outcome measures

Primary outcome measure will be the percentage of investigated patients with the diagnosis of PsA. This diagnosis will be accepted if it was confirmed by a rheumatologist in correspondence. Fulfillment of ClASsicification criteria for Psoriatic ARthritis (CASPAR) is not required[23]. After one year, patient files of the referred patients will be checked to confirm the diagnosis. If the suspicion of active PsA is confirmed, treatment changes and their effect on disease activity will be noted. Alternatively, the other rheumatological diagnosis will be noted.

In the referred patients with PsA, HR-QoL will be assessed via two disease-specific questionnaires at referral, and one year thereafter. Skin-related impact will be explored via the Dermatological Life Quality Index (DLQI)[24]. Joint-related impact will be explored via the Psoriatic Arthritis Impact of Disease (PsAID)[25].

Outcome variables

Prevalence of PsA

To ascertain the presence of PsA, we will ask the patient about joint and enthesis complaints (location, pattern and intensity), morning stiffness (duration), and whether or not they ever had a diagnosis of arthritis. For confirmation of arthritis, dactylitis, or enthesitis, we will perform joint counts (swollen, tender, and dactylitis) and enthesitis indices (LEI and SPARCC). After referral, the diagnosis of PsA and/or alternative diagnosis will be retrieved from (the correspondence gathered in) the electronic patient file.

Effect of referral

In referred patients with confirmed PsA, we will retrieve data at the time of referral as well as one year later. We will use the PASDAS as a disease activity score, which gives a full overview of the PsA disease spectrum. We will evaluate both the combined disease activity score, as well as the specific scores of tender and/or swollen joints, dactylitis, and enthesitis. Also, treatment changes (either instigated by rheumatologist or dermatologist) will be retrieved from the electronic patient file. Impact on HR-QoL will be assessed by questionnaires before referral, and after 1 year (DLQI, PsAID12[24,25]).

Possible identifying characteristics for the presence of PsA in Pso

We will gather information about demographic variables, comorbidity, intoxications, and family history. Family history and comorbidity will be targeted at diseases that are associated with spondyloarthritis, such as uveitis, psoriasis, and inflammatory bowel disease. Next to that, the Charlson Comorbidity index and Functional Comorbidity Index will be used to evaluate a total comorbidity burden[26,27]. Data about comorbidity specifically associated with either Pso or PsA (for example, hepatic, psychological, and cardiovascular diseases) will added[28-30]. Also, current and previous treatment for either PsA or Pso will be noted. Severity and location of Pso (via Psoriasis Area and Severity Index (PASI) and Body Surface Amount (BSA) will be noted[31]. Nail involvement will be assessed via Nail Psoriasis Severity Index (NAPSI) and Nijmegen Nail psoriasis Actitivity Index tooL (N-NAIL)[32,33]. Three of the currently used screening questionnaires (i.e. PEST, ToPAS, and PASE) will be used to collect clinical characteristics which have been previously discovered in their respective development[13-15].

Statistics

Prevalence

The primary outcome of this study will be the point prevalence (n per 100 patients) of PsA in established Pso patients. Sensitivity analyses will be performed by in- or excluding patients with an uncertain diagnosis after 1 year, patients who refuse referral, or patients who are otherwise lost to follow-up.

Effect of referral

The effect of referral on treatment changes, disease activity, and HR-QoL will be assessed qualitatively in an explorative, descriptive matter. No formal statistical analyses will be applied.

Possible identifying characteristics for the presence of PsA in Pso

The identifying value of various clinical markers for the presence of PsA in Pso will be processed as independent variables in a univariate logistic regression model. Diagnosis of PsA (yes/no) will be the dependent variable. Variables that are statistically related to the outcome ($P \leq .20$ in univariate modeling), and are clinically and methodologically feasible (based on a favorable balance between prevalence in the cohort, effect size, and ease of measurement) will be selected. The subsequent selection of variables will be tested in a multivariable logistic regression model with backward stepwise selection. Sensitivity analysis will be performed by reclassifying patients with an uncertain diagnosis as cases. Number of possible independent variables will be limited based on a minimum of ten events (PsA diagnoses) per variable. Bootstrapping will be used to assess the internal validity of the model in terms of over-optimism and shrinkage.

Data handling

The collected data will be entered in CASTOR, an electronic database set up for clinical trials. Data will be coded and kept by personnel trained in Good Clinical Practice. Handling of personal data will comply with the Data Protection Law.

During the informed consent procedure, patients will be asked if gathered data can be used for further research involving Pso or PsA. Only data from patients who gave consent for this can be re-used in accordance to FAIR principles (Findable, Accessible, Interoperable, Reusable).

Monitoring will be performed by certified personnel from the Radboud University Medical Center, according to the guidelines of the NFU (Dutch Federation of University Medical Centers).

Ethical considerations

DAPPER has been approved by the Ethical Committee of the region Arnhem-Nijmegen, Radboud University Medical Centre (NL68137.091.18). It has been registered in the Dutch Trial Register (NTR 7604). All study procedures will be performed in accordance with the ICH guidelines on Good Clinical Practice and the principles of the Declaration of Helsinki.

Results

Ethical approval was obtained by the Ethical Committee of the region Arnhem-Nijmegen, Radboud University Medical Centre (NL68137.091.18) in April 2019. Inclusion started in June 2019 and finished in June 2021. Follow-up will be finished in December 2022.

Discussion

PsA is an inflammatory disease of joints and entheses, which can cause pain, disability, and a diminished quality of life. Moreover, prolonged arthritis can lead to permanent, irreversible joint damage[6,7]. Early recognition, for example by screening populations at high risk for PsA, may be able to prevent joint damage by facilitating timely treatment. The high prevalence of PsA in Pso patients, as well as the fact that skin complaints mostly appear years before joint involvement, make this population very suitable for the implementation of screening. However, current screening questionnaires are not sufficient. Therefore, we wish to determine if current screening and referral strategies are satisfactory and to improve them if necessary.

In our study, we used three of the previously developed questionnaires: PASE, PEST, and ToPAS[13-15]. While their sensitivity and specificity could be improved, we feel that the possibly identifying variables used in these questionnaires warrant further evaluation[17,18]. Our study has several strengths which may overcome the suboptimal performance of the beforementioned questionnaires. First of all, the PASE and PEST development studies were hampered by a low amount of PsA cases (seventeen and twelve, respectively)[13,14]. Secondly, the setting of our study in the dermatology department ensures access to the target population, with minimal extra burden for the patient. While the ToPAS study included 164 PsA patients, most of these were recruited via the rheumatology department. Only 123 study participants were recruited via the dermatology department, giving rise to thirty PsA cases[15]. As stated in the study size, we expect to find sixty to ninety PsA cases in our cohort. Therefore, we expect our model to be more precise.

To develop a good referral tool, the patient population on which the development of the model is based is crucial. A limitation of our study could be the academic setting. However, to ensure a more representative case mix, we stratified for current treatment. By using treatment modality as a proxy for severity, and by limiting the amount of patients using third-line therapy (e.g. biological and targeted therapies), we aim to simulate a population representative of an average dermatological outpatient clinic. Noteworthy in this context is the fact that the current study does not provide a validation cohort. Internal validity will be checked by bootstrapping. Before implementing the referral tool, external validity has to be assessed via a second (validation) cohort. Ideally, this second cohort will be found at one or more other centers, both academic and non-academic.

A second important choice is the definition of the outcome. In this cohort, we choose not to use the CASPAR criteria[23]. These classification criteria are designed to ensure a homogenous PsA population at the start of the trial. However, these criteria are not meant to be used as diagnostic criteria. In clinical practice, the diagnosis made by the rheumatologist (expert opinion) remains the gold standard. However, since all referred patients in this cohort will

have clinical psoriasis, they only need 1 more point (i.e., nail psoriasis, negative rheumatoid factor, dactylitis, or PsA-specific laesions on imaging) to fulfill the criteria (assuming that there is an inflammatory joint or entheseal lesion). Therefore, we expect that (almost) all patients diagnosed with PsA from this cohort will fulfill CASPAR criteria.

The long lag time between skin and joint involvement (on average, ten years[4]) also has several consequences for a referral tool. When screening for current, concomitant PsA, a tool must be applied several times during follow-up. Ideally, every contact moment between the treating dermatologist and patient would be an opportunity to check for suspicion of PsA. This means that the investment to use the tool must be minimal, both in time and in money. Therefore, we choose to use only clinical parameters in our data collection. It will be easy for dermatologists to gather this data from a patient, without the necessity for further laboratory or imaging techniques.

A second consequence of the repeated use of the referral tool is that its validity in re-use must be evaluated. With the current study design, we cannot assess this validity in repeated use. Implementation of the developed tool in the follow-up of the current cohort can be a way to test this.

Ideally, one would want to predict the development of PsA before symptoms and/or damage arise. However, it is important to realize that the above-described design of the DAPPER is focused on detection rather than prediction. We strongly believe that prediction is a much-desired goal, and several studies have reported signs and symptoms that may present themselves at some time before the development of full-blown PsA[34,35]. However, the long lag time of PsA in Pso patients means that development and validation of a prediction tool takes a decade or longer. Therefore, we choose to focus on improving the detection of PsA, until such prediction tools are available.

In conclusion, the DAPPER study will help improve psoriasis care by providing us information about the extent of (un)diagnosed arthritis in this population. The gathered data about the patients with and without arthritis can then be used to develop an improved screening and referral tool, to ensure adequate and timely care for those patients who need it.

4

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Supplemental file 1: Interview guide

Demographic data:
1a. Year of birth
1b. Age
1c. Sex

Intoxications:
2. *Smoking:* currently / in the past / never
If applicable:
2a. Year of start smoking
2b. Year of stop smoking
2c. Number of cigarettes per day
3. Use of alcohol: currently / in the past / never
3a. If currently: amount per day

Family history for SpA-related diseases (to the second degree)
If yes, note the relationship to patient
4a. Psoriasis
4b. Psoriatic arthritis
4c. Inflammatory bowel disease
4d. Uveitis
4e. Axial spondyloarthritis

Comorbidity
Charlson Comordity Index, Functional Comorbidity Index[26,27]
Supplemented with:
5. Known diagnosis of PsA
If yes, note year of diagnosis
6. Diseases associated with PsA and/or Pso
If yes, note year of diagnosis:
6a. Hypertension
6b. Hypercholesterolemia
6c. Thyroid disease
6d. Cholelithiasis, cholangitis, or cholecystectomy
6e. Celiac disease
6f. Obesity
6g. Bariatric surgery
7. Other SpA-related diseases
7a. Uveitis
7b. Inflammatory bowel disease
7c. Axial spondyloarthritis
8. Diseases with impact on possible treatments
8a. Hepatitis B infection
8b. Hepatitis C infection
8c. Hepatic steatosis
8d. Tuberculosis

8e. Eczema/atopic dermatitis
8f. Hidradenitis suppurativa
9. Other rheumatologic disease with impact on possible symptoms
9a. Fibromyalgia
9b. Gout

Physical exposure during occupational or leisure activities
10a. Is the current occupation physical demanding?
10b. Sports injury in the past year?
10c. Fall or other accidental trauma in the past year?
10d. Fracture (which year)?

Topical medication for Pso:
Note first and last year of use, if known
11a. Corticosteroid ointment: currently/in the past/never
11b. Vitamin D creams: currently/in the past/never
11c. Calcineurin inhibitor creams: currently/in the past/never
Note first and last year of use and number of courses, if known
11d. Dithranol/cignolin creams
11e. UVB phototherapy
11f. (P)UVA phototherapy

Systemic medication for Pso or PsA:
For example, but not limited to: methotrexate, fumaric acid, leflunomide, biologicals.
12a. Name of medication
12b. Year of start
12c. Physician who started it (dermatologist/rheumatologist/other)
12d. Year of discontinuation
12e. Physician who discontinued medication
12f. Reason for discontinuation (e.g. primary or secondary ineffectiveness, pregnancy or pregnancy wish, side effects, contra-indication, other)
12g. Highest dose/shortest interval
12h. Currently used dose/interval

Other medication with a possible effect on Pso or PsA:
Note last known date of use
13a. NSAID
13b. Prednisone (plus route of administration, e.g. oral, intramuscular, intra-articular)
13c. Lithium
13d. Beta-blocker
13e. ACE-inhibitor
13f. Tetracycline
13g. Terbinafine
13h. Immunomodulators (e.g. cancer treatment)

Screening questionnaires for PsA in Pso
PEST, ToPAS, EARP[13,15,16]

4

Characteristics of skin involvement
14a. Year of psoriasis initiation
14b. Locations involved (at start, during disease, during last year; scalp, face, extremities, trunk, inversa, genital, palmoplantar, nails)
14c. Morphology involved (at start, during disease, during last year; plaque, guttate, pustulosa, erythroderma)
14d. VAS of skin involvement severity
14e. Koebner-phenomenon

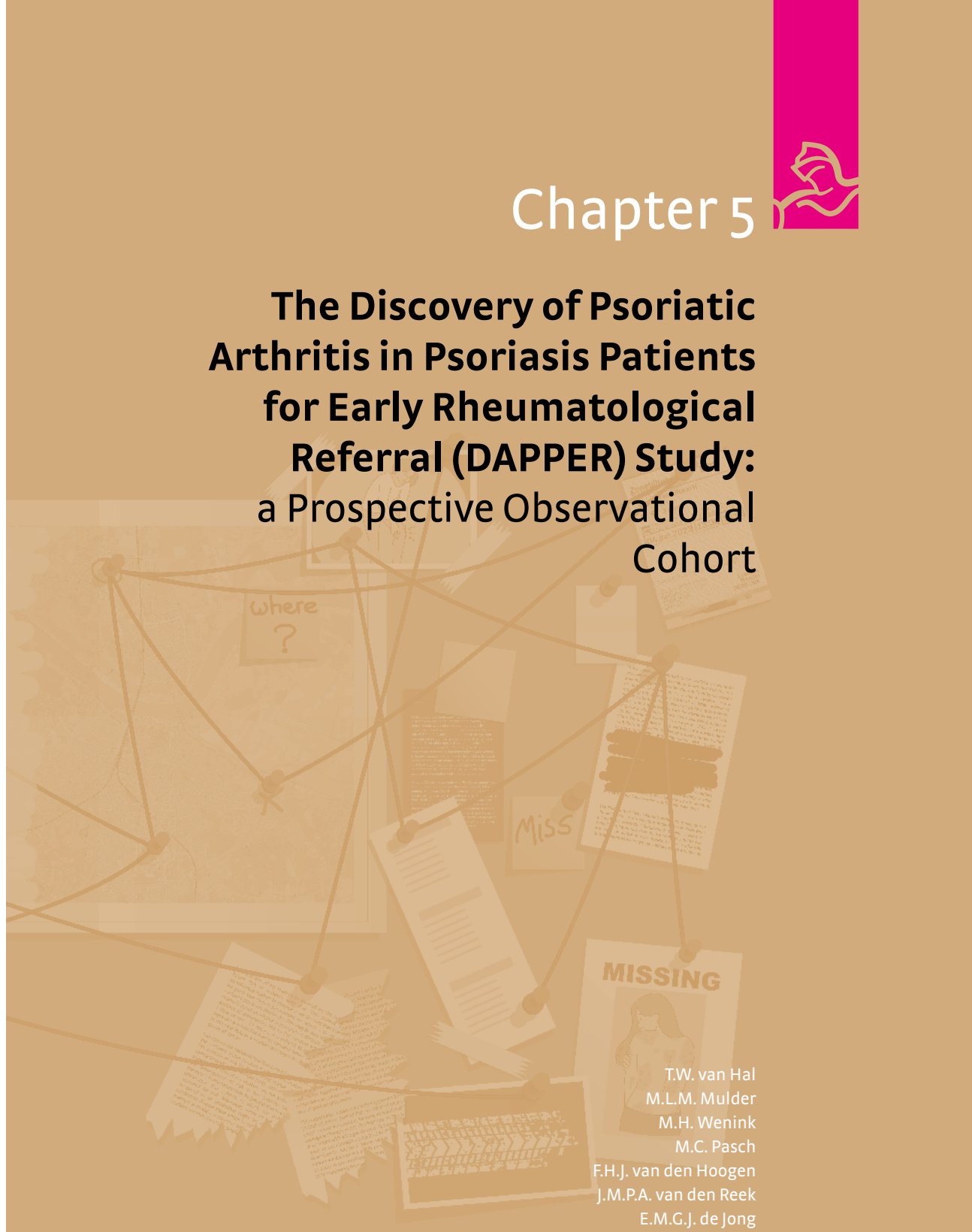
Characteristics of nail involvement
15a. Pitting (never, more than one year ago, last year, currently)
15b. Oil drop phenomenon (never, more than one year ago, last year, currently)
15c. Leukonychia (never, more than one year ago, last year, currently)
15d. Distal onycholysis (never, more than one year ago, last year, currently)
15e. Crumbling (never, more than one year ago, last year, currently)
15f. Red spots in lunula (never, more than one year ago, last year, currently)
15g. Splinter hemorrhages (never, more than one year ago, last year, currently)

Characteristics of joint involvement
16. Pain
16a. Joint pain and location
16b. Time of day with worst complaints (night, morning, afternoon, evening)
16c. Worsening or improvement on exertion
16d. VAS on joint involvement
17. Swelling
17a. Joint swelling and location of swelling
17b. Rubor, calor of joints
17c. Swelling of Achilles tendon
18. Back pain
Inflammatory back pain according to ASAS criteria[21]
19. Other
19a. Morning stiffness: how long, change in the last year
19b. Tiredness: VAS, change in the last year

ACE = angiotensin converting enzyme; ASAS = Assessment of SpondyloArthritis International Society; NSAID = non-steroidal anti-inflammatory drug; PsA = psoriatic arthritis; Pso = psoriasis; PUVA = psoralen-UVA; SpA = spondyloarthritis; VAS = visual analogue scale

Chapter 5

The Discovery of Psoriatic Arthritis in Psoriasis Patients for Early Rheumatological Referral (DAPPER) Study: a Prospective Observational Cohort



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Abstract

Patients with psoriasis are at risk for developing psoriatic arthritis (PsA), which can lead to irreversible joint damage. However, a part of psoriasis patients with concomitant PsA remains undiscovered in practice. The aims of this study were: to prospectively determine prevalence, characteristics, and disease burden of PsA in a Pso population; and to determine prevalence and characteristics of patients with active PsA, who were not under rheumatological care. Psoriasis patients were screened by a rheumatologist at the dermatology outpatient clinic for PsA. Patients with suspected active PsA not seeing a rheumatologist were referred to a rheumatologist for confirmation. The total prevalence of PsA in this observational, prospective cohort (n=303) was 24%. Psoriasis patients with concomitant PsA had longer skin disease duration and more often a treatment history with systemic therapies. In this academic, specialized setting, 2.3% of patients (n=7) were not receiving rheumatological care despite having active PsA. These patients were characterized by a combination of low (perceived) disease burden and low yield of screening questionnaires, making it hard for the dermatologist to discover PsA in these patients. Thus, screening for more subtle active arthritis in psoriasis patients in a dermatology setting could be improved.

Introduction

Psoriatic arthritis (PsA) is a debilitating immune-mediated inflammatory disease of joints and entheses, which can lead to permanent joint damage[1]. Adequate and early treatment of PsA improves joint function and quality of life (QoL)[2]. Therefore, it is crucial to discover and treat PsA patients as soon as possible. The population most at risk for PsA are patients with psoriasis (Pso): one in three Pso patients will develop PsA[3]. Because Pso usually presents itself before the onset of PsA, dermatologists are in a unique position to screen Pso patients for the presence of PsA[4].

Unfortunately, in Pso patients at the dermatology clinic, PsA is frequently undiscovered[5]. While this leads to undertreatment of joint complaints in the individual patients, it also leads to an underestimation of the prevalence of PsA in the Pso population. This is exemplified by a lower prevalence of PsA in Pso in population studies (where PsA was scored by looking at registered diagnoses in electronic health files) when compared to observational studies (where PsA was actively sought in Pso patients)[6]. To aid dermatologists in discovering PsA patients, several screening questionnaires have been developed[7-11]. However, when tested in external validation cohorts, the sensitivity of these questionnaires differed widely, ranging from 24 to 92 percent[12]. This means that even with the use of these validated questionnaires, PsA patients elude detection. Also, the predictive performance of the screening questionnaires is known to fare worse in patients who have undiscovered PsA when compared to patients with known PsA[13,14].

In designing the screening questionnaires, studies have been hampered by a scarce amount of Pso patients with newly discovered PsA[7,8]. To improve power, some groups have chosen to increase the group of PsA cases by adding patients with already known PsA from the rheumatology department[7,9]. However, patients with undiscovered PsA may differ from those who are already known and treated at the rheumatology department, which may lead to underperformance of the screening tools in this specific population. It is therefore important to increase our knowledge on the population of Pso patients with PsA, especially with regard to those who aren't actively treated by a rheumatologist.

The aim of our DAPPER study (Discovery of Arthritis in Psoriasis Patients for Early Rheumatological referral) was to identify and describe the Pso patients with concomitant PsA at the dermatology outpatient clinic. Firstly, we determined the prevalence, characteristics, and disease burden of PsA in a Pso population. Furthermore, we investigated the prevalence of patients with active PsA, who were not (yet) under current rheumatological care. We further characterized the medical history and joint complaints of these active PsA patients without current rheumatological care. Lastly, we examined whether the treatment, disease activity, or QoL of these active PsA patients without rheumatological care changed after referral to a rheumatologist.

Material and methods

DAPPER is a prospective observational study, conducted at the department of dermatology of the Radboud university medical center (Radboudumc) from June 1st, 2019 to February 17th, 2022 (recruitment and data collection June 2019-June 2021, follow-up until February 2022 for newly discovered PsA patients). The Radboudumc is a national expertise center for psoriasis. In line with this specialized setting, patients in certain study cohorts (e.g. patients using biologicals) are screened annually using the Psoriasis Epidemiology Screening Tool (PEST) questionnaire[7]. However, patients outside these study cohorts are not routinely screened for the presence of PsA. The study protocol of the DAPPER study has been published in detail elsewhere[15]. It was approved by the Ethical Committee of the region Arnhem-Nijmegen, Radboudumc (NL68137.091.18), and registered in the Dutch Trial Register (NTR 7604). The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice.

Participants

Patients with physician-diagnosed Pso, aged ≥18 years, currently treated by a dermatologist, were eligible for inclusion. Patients were stratified 1:1:1 for current treatment (topicals only, conventional systemics, biologicals/small molecule inhibitors (biol/smi)) to enable outcome assessment per treatment group. Current treatment may serve as a proxy for disease severity[16]. A concomitant diagnosis of PsA was not an exclusion criterium. All patients gave written informed consent before inclusion in the study.

Study procedure

After informed consent, a study visit was planned adjacent to a regular outpatient visit with the dermatologist. During the study visit, patients were screened for suspicion of active PsA by a trained rheumatologist using a structured interview and physical examination. For the full list of parameters, see supplementary file 1.

When there was a clinical suspicion of active PsA at the study visit, and the patient was not under current rheumatological care, the patient was referred to a rheumatologist. There, additional examinations were performed for confirmation or dismissal of diagnosis (i.e. laboratory tests, and/or imaging such as ultrasound, X-ray, or MRI). When there was a clinical suspicion of active PsA, and the patient was already under current rheumatological care, he/she was advised to contact their treating rheumatologist. Current rheumatological care was defined as patients who were still actively visiting a rheumatologist for their PsA care, i.e. who had a planned appointment with their rheumatologist in the following year.

Patients with a rheumatologist-confirmed active PsA after referral were followed for a year. After a year, data on changes in treatment, PsA disease activity, and QoL were collected.

Outcomes

The primary outcome was the prevalence of concomitant PsA in Pso patients. A patient was considered to have PsA if either he/she had received a previous diagnosis by a rheumatologist, or if he/she had a confirmed diagnosis of PsA after referral in this study. Active PsA was defined as having PsA, and at least one inflamed enthesis or joint (axial or peripheral) at the moment of study visit. For axial arthritis or enthesitis, imaging was required to affirm active inflammation. Groups were defined as either 'Pso' (cutaneous Pso only) or 'PsoPsA' (Pso with concomitant PsA).

Demographic data and disease characteristics of Pso and PsoPsA were compared. Secondary outcome was the prevalence of active PsA not under care of rheumatologist in Pso patients. Of these PsoPsA patients, medical history and joint complaints were described. Also, changes in treatment, disease activity, and QoL one year after referral of these patients were assessed by comparing scores on the Psoriatic Arthritis Disease Activity Score (PASDAS), Dermatology Life Quality Index (DLQI), and Psoriatic Arthritis Impact of Disease (PsAID) with measurements at the moment of referral[17-19].

Statistical analysis

Continuous data were described with means (with standard deviation, SD) or medians (with interquartile ranges, IQR), when appropriate. Categorical data were described as absolute frequencies with percentages.

Prevalence estimates were calculated as n per 100 Pso patients, with 95% confidence intervals (CI). Patients with unclear diagnoses were classified as not having PsA, but a sensitivity analysis was done in which patients with unclear diagnosis were classified as cases.

Differences between groups were tested with unpaired student t-test or Mann-Whitney U (continuous data), or Chi-square/Fisher exact (categorical data) when appropriate. Missing data were not imputed. Patients with suspected PsA after study visit, who were unable or unwilling to visit a rheumatologist for confirmation of diagnosis, were defined as 'unclear diagnosis'. Patients with unclear diagnoses were not included in the comparisons between Pso and PsoPsA groups.

Bonferroni correction for multiple testing was applied, with an alpha of 0.001 (0.05/58 tests) being considered significant. Data were analysed using SPSS Statistics software, version 25 (IBM).

Results

Participants

Figure 1A shows the flow chart of included patients. We approached 516 patients (consecutive per treatment group), of which 304 were willing to participate. Patients used topicals only (N=101), conventional systemics (N=102), or biol/SMI (N=101). One patient dropped out during study visit, because of the inability to undergo physical examination. Four patients had a clinical suspicion of PsA during the study visit, but refrained from visiting a rheumatologist (n=3 declined referral, n=1 intercurrent illness). Table I shows the characteristics of the included patients. Mean age at inclusion was 54 years; 36% of patients were female (109/304).

Prevalence of PsA

Figure 1B shows the diagnosis of all patients. After excluding the patients in whom no diagnosis could be made (n=5: 1 unfulfilled screening, 4 unfulfilled referral), the prevalence of PsA in this treatment-stratified cohort was 24.4% (74/304; 95% CI 21.9-26.8%). The prevalence of PsA was 11.9% (12/101; 95% CI 8.7-15.1%) in the topicals only group, 17.5% (18/103; 95% CI 13.7-21.2%)

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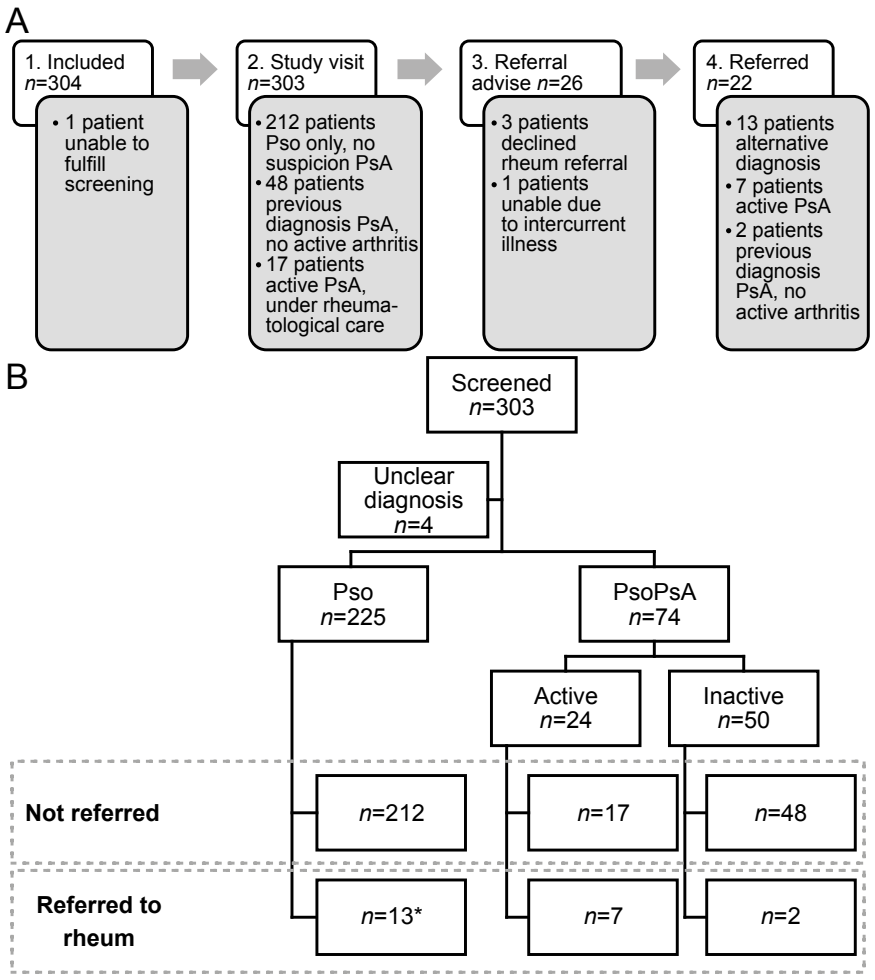

Figure 1: Flowchart of included patients

PsA = psoriatic arthritis; Pso = psoriasis; PsoPsA = psoriasis with concomitant PsA.

1A Study procedure. 304 patients were included, of which 303 could be screened. In 277, classification was clear after study visit (Pso only n = 212, Pso with inactive PsA n=48, Pso with active PsA under current rheumatological care n= 17; see also top dotted box figure 1B). In 26 patients classification was unclear after study visit: these were eligible for rheumatological referral, and 22 were actually referred.

1B Outcomes. Top dotted box represents patients for whom rheumatological referral wasn't deemed necessary (as also seen in box 2 of figure 1A). Bottom dotted box represents patients who were referred to a rheumatologist (as also seen in box 4 of figure 1A).

*Alternative diagnoses were: osteoarthritis n=6, degenerative discopathy n=2, shoulder cuff tendinopathy n=2, diffuse idiopathic skeletal hyperostosis n=2, mucoid cyst of distal interphalangeal joint n=1. In two patients, no definite diagnosis could be made, but there was no active arthritis and PsA was deemed unlikely.

Table 1: Patient characteristics at time of screening.

		All patients	Pso	PsoPsA	P
N - %		304 (100%)	225 (74%)	74 (24%)	
Age at study inclusion, years		53.6 (±16.1)	53.4 (±16.6)	54.5 (±15.0)	.62
Female sex		109 (36%)	80 (36%)	29 (39%)	.57
BMI		28.7 (±5.7)[a]	28.6 (±5.7)[b]	29.6 (±5.4)[c]	.20
Physically taxing job		59 (19%)	41 (18%)	15 (20%)	.15
Age at start Pso, years[#]		25 (16, 41)[d]	26.5 (16,44)[e]	23 (15,37)[f]	.11
Disease duration Pso, years[#]		24 (11,36)[g]	21 (10,35)[h]	27 (17, 39)	.02
Intoxications	Current smoking	68 (22%)	52 (23%)	12 (16%)	.21
	Current alcohol	204 (67%)	151 (67%)	49 (66%)	.89
Family history	Pso	176 (58%)	128 (57%)	44 (60%)	.70
	PsA	48 (16%)[i]	34 (15%)[i]	13 (18%)	.63
Comorbidity	FCI[#]	2 (1, 3)	2 (0, 3)	2 (1,4)	.02
	Cardiovascular	129 (42%)	95 (42%)	34 (46%)	.58
	Depression	36 (12%)	25 (11%)	10 (14%)	.58
	Osteoarthritis	119 (39%)	77 (34%)	42 (57%)	.001
Treatment history					
Topical	UV	252 (83%)	184 (82%)	63 (85%)	.51
	Dithranol	110 (36%)	77 (34%)	30 (41%)	.33
Conventional systemic drugs	All conv. drugs	241 (81%)	170 (76%)	71 (96%)	<.001
	Methotrexate	210 (69%)	140 (62%)	68 (92%)	<.001
	Acitretin	77 (25%)	50 (22%)	36 (35%)	.03
	Fumaric Acid	126 (41%)	92 (41%)	33 (45%)	.58
	Cyclosporin	56 (18%)	38 (17%)	17 (23%)	.24
Biological and small molecule inhibitors	All biol/SMI	120 (40%)	72 (32%)	48 (65%)	<.001
	TNFα-inhibitor	100 (33%)	56 (25%)	43 (58%)	<.001
	IL17-inhibitor	24 (8%)	10 (4%)	14 (19%)	<.001
	IL23-inhibitor	3 (1%)	1 (0.4%)	2 (3%)	.15
	Ustekinumab	51 (17%)	31 (14%)	20 (27%)	.01
	PDE4-inhibitor	8 (3%)	4 (2%)	4 (5%)	.11

		All patients	Pso	PsoPsA	P
Current therapy					
Conventional systemic drugs	All conventional	113 (38%)	88 (39%)	23 (34%)	.41
	Methotrexate	80 (26%)	63 (28%)	16 (22%)	.28
	Acitretin	11 (4%)	8 (4%)	3 (4%)	.74
	Fumaric Acid	17 (6%)	14 (6%)	3 (4%)	.58
	Cyclosporin	2 (0.7%)	2 (0.9%)	0 (0%)	
Biological and small molecule inhibitors	All biol/SMI	101 (33%)	57 (25%)	44 (60%)	<.001
	TNFα-inhibitor	47 (16%)	28 (12%)	19 (26%)	.01
	IL17-inhibitor	21 (7%)	9 (4%)	12 (16%)	.001
	IL23-inhibitor	2 (0.7%)	1 (0.4%)	1 (1%)	.43
	Ustekinumab	29 (10%)	19 (8%)	10 (14%)	.20
	PDE4-inhibitor	2 (0.7%)	0 (0%)	2 (3%)	.06
Screening questionnaires	EARP positive (≥3)	152 (50%)	93 (41%)	55 (74%)	<.001
	PEST positive (≥3)	98 (33%)[i]	43 (19%)[i]	53 (72%)[i]	<.001
	ToPAS2 positive (≥8)	129 (42%)	70 (31%)	58 (78%)	<.001

Continuous variables are in mean ± standard deviation, unless stated otherwise. Parameters with missing values are marked. Differences between Pso (cutaneous Pso only) and PsoPsA (Pso with concomitant PsA) were tested, P-values given.
Biol = biological; BMI = body mass index; PDE = phosphodiesterase; EARP = early arthritis for psoriatic patients questionnaire; FCI = functional comorbidity index; IL = interleukin; IQR = interquartile range; PEST = psoriasis epidemiology screening tool; PsA = psoriatic arthritis; Pso = psoriasisis; PsoPsA = psoriasis with concomitant PsA; SMI = small molecule inhibitor; TNF = tumour necrosis factor; ToPAS = Toronto psoriatic arthritis screen questionnaire; UV= ultraviolet
# = reported in median, IQR
a = missing in 25 patients; b = missing in 20 patients; c = missing in 6 patients; d = missing in 13 patients; e = missing in 9 patients; f = missing in 5 patients; g = missing in 12 patients; h = missing in 8 patients; i = missing in 1 patient; j = missing in 1 patient

in the conventional systemics group, and 44.0% (44/100; 95% CI 39.0-49.0%) in the biol/SMI group. A sensitivity analysis, where all patients with an unclear diagnosis were classified as cases, showed similar results (total prevalence 25.7%, 95% CI 23.2-28.2%; topicals only 14.9%; 95% CI 12.2-19.5%; conventional systemics 18.4, 95% CI 14.6-22.2%; biologicals unaltered).

Characteristics and disease burden of Pso and PsoPsA patients

Table 1 and 2 show the characteristics and disease burden of the cohort. When applying Bonferroni correction, Pso patients differed from PsoPsA patients with regard to: a previous diagnosis of osteoarthritis (Pso 77/225, 34%; PsoPsA 42/74, 57%; P = 0.001), ever use of conventional systemics (Pso 170/224, 76%; PsoPsA 71/74, 96%; P < 0.001), ever use of biol/SMI (Pso 72/225, 32%; PsoPsA 48/74, 65%; P < 0.001), current use of biol/SMI (Pso 57/225, 25%; PsoPsA 44/74, 60%; P < 0.001), patient-reported joint pain in proximal joints (Pso 92/225, 41%; PsoPsA 53/75, 72%; P < 0.001), and number of swollen joints at physical examination (P<0.001) . When applying an explorative cut-off of P< 0.05, we also found differences in psoriasis skin disease duration (Pso 21 years (10, 35); PsoPsA 27 years (17, 39); P = 0.02 (median, IQR)), current joint pain (Pso 159/225, 71%; PsoPsA 63/74, 85%; P = 0.01), morning stiffness with a duration of more than

Table 2: Disease burden at moment of screening.

			All patients	Pso	PsoPsA	P
N - %			304 (100%)	225 (74%)	74 (24%)	
Skin and nails	PASI		2.7 (1.4, 4.4)[a]	2.8 (1.6, 4.5)[b]	2.4 (1.1, 4.0)	.08
	BSA		1.9 (0.3, 4.5)[c]	1.6 (0.4, 4.6)[a]	2.0 (0.4, 3.8)	.73
	VAS skin		18 (5, 47)	18 (4, 47)	17 (7, 43)	.83
	NAPSI	Median, IQR	14 (6, 25)[d]	15 (6, 25)[e]	12 (5, 20)[f]	.18
	N-NAIL	Median, IQR	4 (1, 10)[d]	4 (1, 10)[e]	4 (0, 9)[f]	.30
		0	49 (16%)[d]	32 (18%)[e]	17 (25%)[f]	.34
		1-2	51 (17%)[d]	39 (21%)[e]	11 (16%)[f]	
		≥3	153 (50%)[d]	110 (61%)[e]	39 (58%)[f]	
	Current nail pitting		133 (53%)[d]	95 (53%)[e]	38 (54%)[f]	.88
Joints and entheses	Current joint pain		222 (74%)	159 (71%)	63 (85%)	.01
	Axial		99 (33%)	70 (31%)	27 (37%)	.39
	Proximal		149 (49%)	92 (41%)	53 (72%)	<0.001
	Distal		157 (52%)	116 (52%)	37 (50%)	.82
	VAS joints		22 (3, 52)	21 (2, 50)	28 (6, 58)	.14
	VAS fatigue		40 (9, 69)	34 (8,68)	46 (17, 73)	.13
	Morning stiffness ≥ 30m		45 (15%)	26 (12%)	19 (26%)	.003
	Heel pain		80 (27%)	55 (25%)	25 (34%)	.12
	Swollen joint count	0	271 (89%)	215 (86%)	55 (75%)	<0.001
		1	23 (8%)	9 (4%)	12 (16%)	
		2-4	9 (3%)	1 (0.4%)	7 (9%)	
	Tender joint count	0	222 (73%)	172 (76%)	46 (62%)	.02
		1	30 (10%)	22 (10%)	8 (11%)	
		2-4	32 (11%)	22 (10%)	10 (14%)	
		≥5	19 (6%)	9 (4%)	10 (14%)	
	Leeds enthesitis index	0	262 (87%)	197 (88%)	62 (84%)	.70
		1	25 (8%)	17 (8%)	7 (9%)	
		≥2	16 (5%)	11 (5%)	5 (7%)	
	Dactylitis		1 (0.3%)	0 (0%)	1 (1%)	.08

thirty minutes (Pso 26/225, 12%; PsoPsA 19/74, 26%; P = 0.003) and number of tender joints at physical examination (P = 0.02). Sensitivity of used screening questionnaires was 74%, 72%, and 78% for EARP, PEST, and Topas, respectively.

		All patients	No PsA	PsA, active	PsA, inactive
Demographics					
N		22 (100)	13 (59)	7 (32)	2 (9)
Age (mean, SD)		56 (± 13)	55 (± 15)	54 (± 11)	66 (1)
Female sex		6 (27)	4 (31)	2 (29)	0 (0)
BMI ≥ 30		7 (32)	5 (39)	1 (14)	1 (50)
Current medication	No systemic	7 (32)	5 (39)	2 (29)	0 (0)
	All conventional	7 (32)	6 (46)	1 (14)	0 (0)
	Methotrexate	5 (23)	5 (39)	0 (0)	0 (0)
	Acitretin	2 (9)	1 (8)	1 (14)	0 (0)
	All b/tsDMARD	8 (36)	2 (15)	4 (57)	2 (100)
	TNF-inhibitor	4 (18)	1 (8)	1 (14)	2 (100)
	IL17-inhibitor	2 (9)	0 (0)	2 (29)	0 (0)
	Ustekinumab	1 (5)	1 (8)	0 (0)	0 (0)
	Apremilast	1 (5)	0 (0)	1 (14)	0 (0)
Interview					
History of	Osteoarthritis	13 (59)	8 (62)	3 (43)	2 (100)
	Swollen joints	12 (55)	6 (46)	5 (71)	1 (5)
Current joint pain		20 (91)	12 (92)	7 (100)	1 (50)
VAS joints (median, IQR)		43 (12, 70)	49 (26, 66)	16 (5, 79)	48 (5, 90)
Painful joints	Axial	9 (41)	6 (46)	2 (29)	1 (50)
	Proximal joints	12 (55)	6 (46)	6 (86)	0 (0)
	Distal joints	14 (64)	10 (77)	3 (43)	1 (5)
Back pain	All back pain	14 (64)	9 (69)	3 (43)	2 (100)
	Inflammatory back pain	3 (14)	1 (8)	2 (29)	0 (0)
VAS skin (median, IQR)		31 (5, 72)	35 (5, 73)	51(17, 79)	8 (0, 16)
Screening	EARP positive (≥3)	13 (59)	7 (54)	5 (71)	1 (50)
	PEST positive (≥3)	10 (46)	5 (39)	4 (58)	1 (50)
	ToPAS positive (≥8)	11 (50)	7 (54)	3 (43)	1 (50)

Continuous variables are in median (interquartile range), unless stated otherwise. Parameters with missing values are marked. Differences between Pso (cutaneous Pso only) and PsoPsA (Pso with concomitant PsA) were tested, P-values given.
BSA = body surface area; IQR = interquartile range; NAPSI = nail psoriasis severity index; N-NAIL = Nijmegen nail psoriasis activity index; PASI = psoriasis area and severity index; PsA = psoriatic arthritis; Pso = psoriasisis; PsoPsA = psoriasis with concomitant PsA; VAS = visual analogue scale;
a = missing in 2 patients; b = missing in 1 patients; c = missing in 3 patients; d = missing in 51 patients; e = missing in 44 patients; f = missing in 7 patients

Suspicion of active PsA, in patients not under rheumatological care

Table 3 shows the characteristics of the patients who were referred to the department of rheumatology (N=26 suspected of active PsA, of which N=22 referred). In 9/22 patients with suspicion of active PsA not under rheumatological care, the diagnosis PsA was confirmed. In seven out of these nine patients the PsA was deemed active (32% of all referred patients), which accounted for 2.3% of the entire cohort. Of these patients, 5/7 did not have the diagnosis before; 2/7 were previously diagnosed with PsA but were not currently treated by

Table 3: characteristics of referred patients

		All patients	No PsA	PsA, active	PsA, inactive
Physical examination					
Skin	PASI (mean, IQR)	2.9	2.7	3.4	1.6
		(1.7, 5.3)	(1.8, 6.1)	(2.4, 6.2)	(1.3, 1.8)
	NAPSI (mean, IQR)	11 (4, 20)[a]	8 (4,20)[b]	15 (7, 35)[b]	9 (0, 17)
	N-NAIL (mean, IQR)	3.5 (0, 10)[a]	3 (0, 9)[b]	5 (2, 19)[b]	5 (0,10)
Swollen joint count	0	9 (41)	8 (62)	0 (0)	1 (50)
	1	10 (46)	4 (31)	5 (71)	1 (50)
	2-4	3 (14)	1 (8)	2 (29)	0 (0)
Tender joint count	0	11 (50)	7 (54)	3 (43)	1 (50)
	1	3 (14)	2 (15)	1 (14)	0 (0)
	2-4	3 (14)	3 (23)	0 (0)	0 (0)
	5 or more	5 (23)	1 (8)	3 (43)	1 (50)
Leeds enthesitis index	0	17 (77)	10 (77)	5 (71)	2 (100)
	1	3 (14)	2 (15)	1 (14)	0 (0)
	2 or more	2 (9)	1 (8)	1 (14)	0 (0)
Reason for referral					
Suspicion of	Peripheral arthritis	14 (64)	6 (46)	7 (100)	1 (50)
	Axial arthritis	8 (36)	5 (39)	2 (29)	1 (50)
	Enthesitis	3 (14)	2 (15)	1 (14)	0 (0)

All values are N (%), unless indicated otherwise. There were no patients with dactylitis. Inflammatory back pain was defined by a score of 4 or more on the ASAS inflammatory back pain criteria..
ASAS = assessment of spondyloarthritis international society; BMI = body mass index; EARP = early arthritis for psoriatic patients questionnaire; IL = interleukin; IQR = interquartile range; NAPSI = nail psoriasis severity index; N-NAIL = Nijmegen nail psoriasis activity index; PASI = psoriasis area and severity index; PEST = psoriasis epidemiology screening tool; PsA = psoriatic arthritis; SD = standard deviation; TNF = tumour necrosis factor; ToPAS = Toronto psoriatic arthritis screen questionnaire; VAS = visual analogue scale;
a = 2 missing; b = 1 missing

a rheumatologist. In 2/9 patients additional imaging did not reveal active musculoskeletal inflammation at the time of their visit to the rheumatology department. These two patients, who were in remission for PsA, both had a previous diagnosis of PsA but weren't under current care of a rheumatologist.

Baseline characteristics of patients with confirmed active PsA upon new referral to the rheumatology clinic

Table 4 and supplementary table 1 show the characteristics of the seven patients with confirmed active PsA, who were not under rheumatological care. All patients (7/7) fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR); 2/7 patients showed irreversible joint changes (i.e., erosions) on imaging. Five out of seven patients presented themselves in the study visit with a mono-arthritis. Only 2/7 patients indicated a significant burden of joint pain (VAS joints ≥ 50 mm) and impact on QoL (PsAID12 ≥ 4.0) at the study visit. All patients with complete clinical data (6/6) were in moderate disease activity according to PASDAS (range: 3.8 – 5.3). The screening questionnaires identified 2/5 patients with a new diagnosis, and 2/2 patients with previously known PsA.

Longitudinal follow-up of patients with confirmed active PsA upon new referral to the rheumatologist

Supplementary table 1 shows the follow-up data of the seven referred patients with confirmed active PsA. In 6/7 patients, rheumatological referral led to one or more treatment changes (intra-articular injections n=3, start conventional systemics n=3, switch in biol/SMI n=1; 1 patient started conventional systemic after intra-articular injections). In 1/7 patient, treatment was changed by the dermatologist already from a conventional systemic drug to a biological. During follow-up, 1/7 patients stopped all systemic medications after a Covid19-infection, and refused further systemic rheumatological or dermatological follow-up. Regarding disease activity, 5/6 patients showed improvement in the number of swollen joints after one year. Two out of four patients with complete PASDAS follow-up were in low disease activity (PASDAS ≤3.2). Regarding HR-QoL, before referral, 4/7 patients showed a large burden of Pso/PsA on their QoL as measured by DLQI or PsAID12 (DLQI ≥ 5 or PsAID12 ≥ 4, respectively). After one year, 3/7 patients showed a large burden of PsA (PsAID12 ≥ 4). Of these three patients, two still had active PsA despite treatment changes (PASDAS ≥ 5.4), while the other patient reported a large burden of skin disease (DLQI ≥ 5).

Discussion

In this prospective observational study, we identified Pso patients with concomitant PsA in the dermatology outpatient clinic via a structured interview and physical examination by a trained rheumatologist. We found a prevalence of PsA in Pso of 24% in the entire cohort. When separated by current treatment modality, the prevalence of PsA in Pso was 12% for topicals only, 18% for conventional systemics and 44% for biol/SMI. When comparing PsoPsA with Pso patients, PsoPsA patients were more often diagnosed with osteoarthritis, had a higher functional comorbidity index, had more often used conventional systemic medication and biologics, had a longer duration of skin disease, and more often reported joint pain and morning stiffness. With our extensive screening, we identified seven (2.3%) Pso patients with active PsA who were not under current rheumatological care. These patients were referred to

Table 4: Comorbidity, treatment history, skin and joint examination at moment of screening of referred patients with confirmed active PsA.

	Participant	A	B	C	D	E	F	G						
	Age, y	61-80	41-60	21-40	41-60	41-60	41-60	61-80						
	Sex	Male	Male	Female	Female	Male	Male	Male						
	BMI	21.9	25.1	27.9	29.3	28.2	35.2	26.5						
Comorbidity	FCI	2	1	1	1	3	5	1						
	Other		Steatosis OA	Asthma	Depression	Asthma OA	Steatosis Malignancy OA, HT							
Treatment	History	1 csD	1 csD 3 biol/smi	3 csD 4 biol/smi	Topical	1 csD 3 biol/smi	3 csD	1 csD						
	Current	topical	secukinumab	brodalumab	topical	adtretin	adalimumab	apremilast						
Skin disease	Age at start, y	60-80	20-40	0-20	40-60	20-40	0-20	40-60						
	Duration, y	5-10	20-25	25-30	10-15	26-30	30-35	10-15						
	PASI	6.2	3.3	0.8	3.9	10.4	3.4	2.4						
	BSA	3.0 %	2.4 %	0.3 %	5.0 %	7.5 %	0.5 %	2.3%						
	VAS skin	86	51	1	67	79	21	17						
	N-NAIL	5	5	N/A	0	47	10	3						
Screening questionnaires	EARP	2	2	7#	3#	4#	8#	3#						
	PEST	2	0	3#	1	3#	5#	3#						
	Topas	5	5	10#	6	10#	12#	7						
Joints, patient reported	Joint swelling	Yes	Never	Yes	Never	Yes	Yes	Yes						

# denotes questionnaire scores which would warrantee a rheumatological referral
BMI = body mass index; b/ts D = biological/targeted systemic drug; BSA = body surface area; csD = conventional systemic drug; EARP = early arthritis for psoriatic patients questionnaire; FCI = functional comorbidity index; HT = hypertension; LEI = Leeds enthesitis index; MI = myocardial infarction; N-NAIL = Nijmegen nail psoriasis activity index; OA = osteoarthritis; PASI = psoriasis area and severity index; PEST = psoriasis epidemiology screening tool; PsA = psoriatic arthritis; SJC = swollen joint count; TJC = tender joint count; ToPAS = Toronto psoriatic arthritis screen questionnaire; VAS = visual analogue scale

the rheumatologist: conventional systemic therapy was started in 3/7, biologic therapy was switched in 1/7 patients, local glucocorticoid joint injections were given to 3/7 patients. After one year, 5/6 patients showed improvement of arthritis.

One in four patients in our Pso cohort had concomitant PsA. These results are in line with those of the systematic review of Alinaghi et al, who found a pooled prevalence of 22.7% (95 CI 20.6%-25.0%) for PsA in Pso patients in Europe[6]. The increase of PsA prevalence parallel to an increase in treatment intensity is also comparable to previous studies[3,20]. A possible explanation for this phenomenon could be that the increase in treatment severity represents an increase in skin disease severity. For instance, Ogdie and all showed that a higher affected BSA is associated with a higher PsA incidence[16].

Characteristics differed between Pso and PsoPsA patients. It is known that Pso precedes PsA in the majority of patients. The PsoPsA group showed a longer disease duration compared to the Pso group, but their current age did not differ. Indeed, the age at start of Pso showed a numerical difference, indicating that psoriasis was diagnosed at an earlier age in the PsoPsA group. PsoPsA patients were more often diagnosed with osteoarthritis, which could be detection bias due to the fact that they visited a rheumatologist more often, or misclassification where PsA symptoms were interpreted as osteoarthritis. Although the patients more often used conventional systemic medication and biologics, part of the newly detected patients were on conventional systemic or biologic treatment, which is in line with previous studies[3,21,22].

Of interest, in our cohort still one-third of the patients (28/79, both known and unknown PsA patients) had active PsA when screened. However, our cohort contained only seven patients with active PsA not under current rheumatologic care, of which five were undiagnosed. This is lower than that 15.5% undiagnosed cases reported in the meta-analysis of Villani et al[5]. The setting and cohort composition might contribute to these differences. Our cohort consisted of 3 treatment groups (topical, conventional systemic and biol/SMI) and the setting was a psoriasis expertise center in which patients on biologics were already screened on a regular basis using the PEST questionnaire. In this specialized academic setting, dermatologists could have had more time during their consultations to ask for joint complaints, compared to dermatologists working in other settings. Because ideally all active PsA cases are discovered and treated, this relatively low number of newly discovered PsA patients in this cohort may be a hopeful sign that improved detection is feasible.

When further looking at these seven active PsA patients not under rheumatological care, three things are worth mentioning. First, in these patients, the disease burden of PsA was relatively low: 5/7 patients presented themselves with a mono-arthritis, and patients did not report a significant burden of joint pain, nor a significant impact of PsA complaints on their HR-QoL. Second, 2/7 patients were already known to have PsA, but were not under treatment of a rheumatologist anymore. Third, the yield of the screening PsA questionnaires (e.g. PEST) in these patients was low: only 2/5 previously undiscovered PsA patients would have been marked as being suspect for PsA. Previous research also showed a lower sensitivity of the screening questionnaires in patients without a previous PsA diagnosis[14]. This can be partially explained by the fact that both PEST and Topas ask whether a patient has been diagnosed with arthritis before, providing all previously diagnosed PsA patients with an extra point[7,9].

One of the aims of our research was to describe the changes in treatment, disease activity and QoL in the patients with active PsA who were referred to the rheumatologist. While the arthritis improved in the majority of the patients, it is humbling to see that 3/7 patients still experience a significant burden of PsA one year after referral. In 2/7 patients, this can be explained by the fact that there was still a high disease activity of PsA as reflected by PASDAS. Unfortunately, studies have shown that in clinical practice, a significant part of PsA patients still have active disease, despite treatment[23,24]. Even in the stringent treat-to-target TICOPA trial, only 62% of patients undergoing protocolized tight control showed a significant response in joint scores (ACR20)[2]. In this light, evaluation of the effect of PsA screening and referral on the disease burden as experienced by patients is a valuable addition to the Pso/PsA research agenda.

The strengths of this study are the thorough interview and physical examination of all patients by a trained rheumatologist, and the setting in the dermatology outpatient clinic. Instead of using questionnaires with known low sensitivity, we employed a rheumatologist to assess all patients[13,14]. As rheumatologist diagnosis is the gold standard, the risk of misclassification using this process was deemed very low[25]. By placing this rheumatologist at the location of dermatological care, we ensured maximal participation of the Pso patients. Thereby, we avoided “healthy participant” bias, where patients who are more interested in a healthy life(style) are more prone to join a study, as much as possible.

The limitations of this study are the setting in a tertiary hospital with special expertise in Pso care. This hampers the translation to non-academic cohorts, thereby abating the external validity. When comparing our academic cohort with a nation-wide cohort of patients approached via the Dutch Psoriasis Association, our cohort is more often treated with systemic medication (conventional systemic 38% versus 26%, biologicals/smi 33% versus 16%) and has a lower burden of skin disease (PASI 5.5 versus 2.7)[26]. Moreover, a part of the patients in our cohort has already been screened regularly for psoriatic arthritis in the past. The treatment guideline of the Dutch Society for Dermatology and Venereology does recommend alertness for the signs of PsA, the use of screening questionnaires is not formally recommended[27]. As a consequence of the increased use of systemic medication and increased use of screening as compared to non-academic dermatology clinics, our academic cohort showed a low amount of previously undetected PsA patients, making it hard to determine characteristics of these patients to aid detection in another setting.

In conclusion, the observational, prospective DAPPER study revealed that the prevalence of PsA in this tertiary center was 24%, comparable to literature. The PsoPsA patients were characterized by a longer disease duration of psoriasis and a different treatment history with more conventional systemic and biologic therapies compared to Pso patients. In this academic, specialized setting where patients are already screened with questionnaires, many PsA cases were already identified. While this yield was already higher than in literature[5], still an additional 2.3% of patients were identified with active PsA who were not receiving rheumatological care. These patients were characterized by a combination of low (perceived) disease burden and low yield when using screening questionnaires, making it hard for the dermatologist to discover PsA in these patients. While our results show that it is possible to identify the majority of PsA patients in regular care, improving current screening strategies for PsA in Pso is needed if we want to detect more subtle active arthritis in psoriasis patients in a dermatology setting.

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Supplemental file 1: full list of interview parameters

The screening included oral history taking about skin and joint complaints, as well as parameters that could possibly be used to identify patients with concomitant arthritis, such as family history. Comorbidity was assessed using the Functional Comorbidity Index (0-18)[28]. Current and previous treatment for Pso and/or PsA were recorded. Patient perceived burden of skin and joint involvement was measured with a visual analogue scale (VAS; 0-100 mm); a score of > 50 mm corresponds to an unacceptable symptom state, and was considered a high burden[29]. Also, we used three existing screening questionnaires (PEST, Toronto Psoriatic Arthritis Screen – ToPAS, Early Arthritis for Psoriatic Patients – EARP) to collect clinical characteristics that have previously been linked to a higher risk of concomitant arthritis[7,9,10].

Physical examination entailed a 68 tender joint count, 66 swollen joint count, dactylitis count, and Leeds enthesitis index (0-6)[30]. Skin disease was assessed using the Psoriasis Area and Severity Index (PASI; 0-72) and body surface amount (BSA; 0-100)[31]. Nail disease was assessed using the Nail Psoriasis Severity Index (NAPSI; 0-80) and the Nijmegen Nail Psoriasis Activity Index (N-NAIL; 0-150)[32,33].

Disease activity at the rheumatology department was assessed via the modified Psoriatic ArthritiS Disease Activity Score (PASDAS), a PsA-specific composite disease activity score, and its subscales[17]. A higher PASDAS equals higher disease activity, with predefined cut-offs of ≤ 3.2, > 3.2 - < 5.4 and ≥ 5.4 for low, moderate, and high disease activity, respectively[34]. HR-QoL were assessed via the Dermatological Life Quality Index (DLQI) and Psoriatic Arthritis Impact of Disease (PsAID)[18,19]. While DLQI measures only skin-related issues and is not specific for Pso, the PsAID is developed to assess the impact of both joint and skin issues as a consequence of PsA. In both questionnaires, a higher score indicates a heavier disease burden. A score of >4 on the PsAID, or a score of >5 on the DLQI, is considered a high impact on the QoL of the patient[18,29,35].

Supplementary table 1: First visit and follow-up of referred patients with confirmed active PsA at the department of rheumatology.

		Newly diagnosed PsA					Previously known, active Not under rheumatological care	
Participant		A	B	C	D	E	F	G
First visit rheumatology department								
Physical examination	68TJC	5	1	1	1	4	19	0
	66SJC	3	0	0	1	1	6	1
	LEI	1	0	1	0	0	3	0
	Dactylitis	0	0	0	0	0	0	0
	PASDAS	3.8	3.8	4.0	4.0	5.3	5.2	N/A[a]
Patient reported outcomes	DLQI	7	0	0	12	15	2	2
	PsAID12	3.2	0	0.7	0.6	5.7	5.6	0.5
	SF12 PCS	36.32	49.8	47.7	47.00	32.19	29.1	52.6[b]
	VAS Global	50	40	60	50	80	20	30
	HAQ	0.75	0	0.5	0.5	0.25	0.5	0[b]
Erosive disease		None	None	None	None	Yes	None	Yes
CASPAR criteria		Yes	Yes	Yes	Yes	Yes	Yes	Yes
Follow-up after one year								
Physical examination	68TJC	4	0	7	1	N/A[c]	32	1
	66SJC	1	0	4	0	N/A[c]	1	1
	LEI	0	0	2	N/A[c]	N/A[c]	2	N/A[d]
	Dactylitis	0	0	0	N/A[c]	N/A[c]	0	N/A[d]
	PASDAS	2.7	2.1	5.8	N/A[c]	N/A[c]	5.5	N/A[d]
Patient reported outcomes	DLQI	1	4	0	8	3	0	2
	PsAID12	0.6	0.8	6.0	4.3	1.1	4.6	1.0
	SF12 PCS	50.5	53.6	19.9	N/A[c]	59.1	28.2	N/A[d]
	VAS Global	25	10	85	N/A[c]	N/A[c]	60	N/A[d]

CASPAR = classificiation criteria for psoriatic arthritis; DLQI = dermatological life quality index; LEI = Leeds enthesitis index; N/A = not available; PASDAS = psoriatic arthritis disease activity score; PsAID = psoriatic arthritis impact of disease; SF12 PCS = short form 12 physical component summary score; SJC = swollen joint count; TJC = tender joint count; VAS = visual analogue scale

a = no PASDAS due to missing actual SF12 PCS; b = at start of systemic medication; c = not noted at follow-up by treating rheumatologist; d = partial rheumatological follow-up; patient declined further treatment

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Chapter 6

Development of a new referral tool identifying psoriasis patients with concomitant psoriatic arthritis: results of the prospective DAPPER cohort

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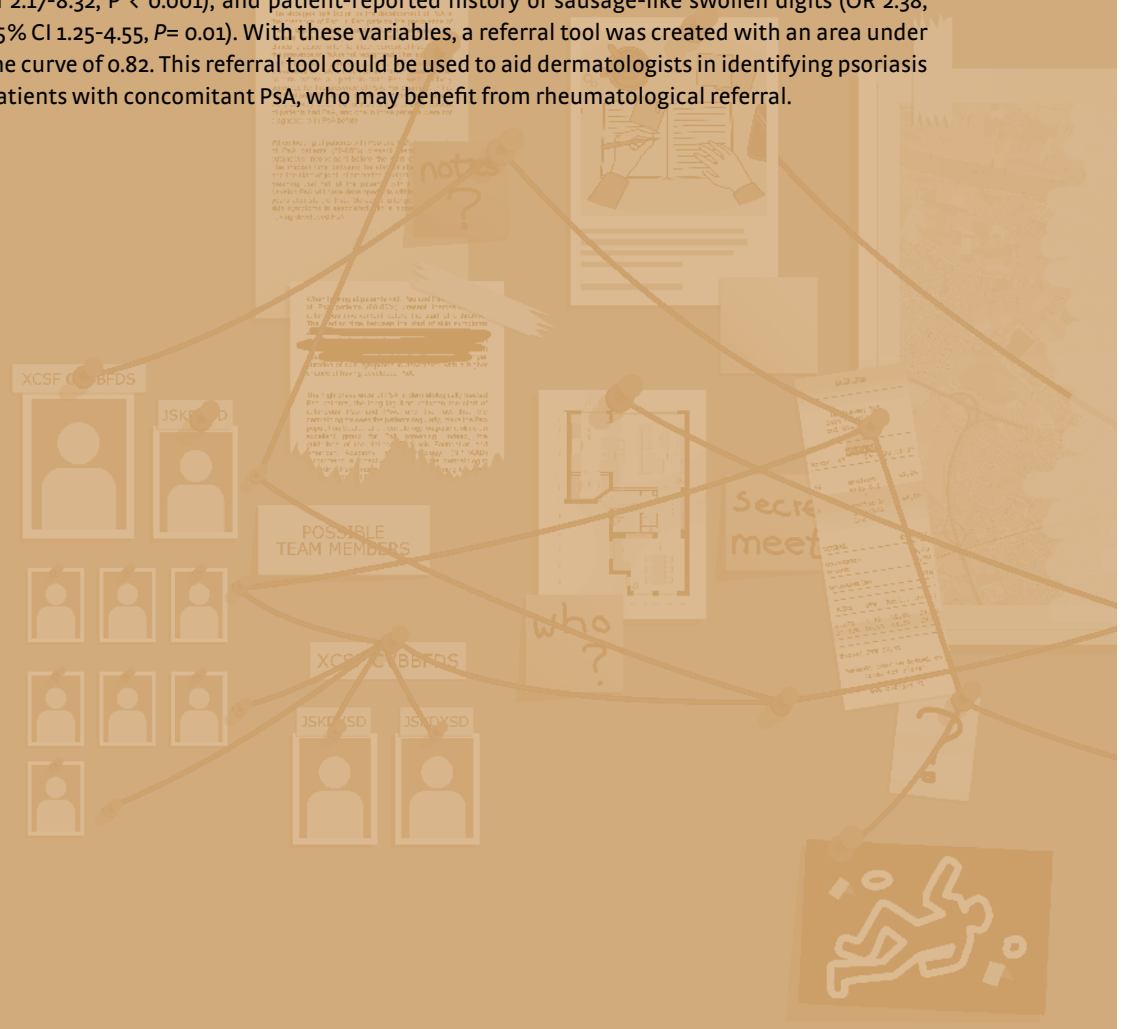
Abstract

Patients with psoriasis are at risk for developing psoriatic arthritis (PsA), which can lead to joint damage. While screening questionnaires have been developed, their performance varies. Objective of this study was to develop a referral tool for dermatologists to identify psoriasis patients with concomitant PsA for rheumatological referral. We used data from the DAPPER study, in which psoriasis patients were screened by a rheumatologist for the presence of concomitant PsA. Using multivariable regression analysis, predictive variables for the presence of concomitant PsA were identified: treatment history with conventional systemic drugs (OR 2.97, 95% CI 1.01-8.74, *P*= 0.04), treatment history with biologicals/small molecule inhibitors (OR 2.90, 95% CI 1.52-5.53, *P*=0.01), patient-reported history of joint pain not caused by trauma (OR 4.23, 95% CI 1.21-14.79, *P*=0.01), patient-reported history of swollen joints (OR 4.25, 95% CI 2.17-8.32, P < 0.001), and patient-reported history of sausage-like swollen digits (OR 2.38, 95% CI 1.25-4.55, *P*= 0.01). With these variables, a referral tool was created with an area under the curve of 0.82. This referral tool could be used to aid dermatologists in identifying psoriasis patients with concomitant PsA, who may benefit from rheumatological referral.



Introduction

One in three patients with psoriasis (Pso) at the dermatology clinic will develop psoriatic arthritis (PsA), which can lead to disability, discomfort, and irreversible joint damage[1,2]. In the majority of patients, Pso precedes the development of PsA[3]. Early treatment of arthritis is important to prevent joint damage, and to improve physical functioning and quality of life of affected patients[4,5]. Therefore, early recognition by dermatologists and rheumatological referral of Pso patients with arthritis is crucial. Unfortunately, a considerable amount of Pso patients with PsA are not diagnosed in clinical practice[6].

To aid dermatologists in selecting patients with a high risk of PsA, several screening questionnaires have been developed[7-15]. Nevertheless, diagnostic accuracy of these questionnaires varies widely between studies[16]. For the most studied questionnaires (Psoriatic Arthritis Screening and Evaluation tool – PASE[8], Psoriasis Epidemiology Screening Tool – PEST[7], Toronto Psoriatic Arthritis Screen – ToPAS[10]), sensitivities ranged from 24-100%, 28-92%, and 41-96%, while specificities ranged from 20-94%, 37-98%, and 30-97%, respectively[16].

Because of varying performance results, we developed a new cohort to overcome some of the problems encountered in the development of the beforementioned tools[17]. Specifically, by using an outpatient dermatology cohort with a sufficient amount of Pso patients with concomitant PsA relative to the number of possible predictive parameters, we aimed to avoid overfitting[7,14,15] and the need to enrich the sample with PsA patients from other sources (e.g., the rheumatology department)[7,10,14].

Aim of our study was to develop a new referral tool to aid dermatologists in identifying Pso patients with concomitant PsA. We selected patients with concomitant PsA in a cohort of three hundred Pso patients at a dermatology outpatient clinic. We identified parameters that distinguished Pso patients with and without concomitant PsA and used these to build a new referral tool. In addition, we explored the possibility to build a referral tool to identify PsA patients with active PsA, because these are most likely to benefit from rheumatological referral.

Material and methods

Study setting and participants

We used data from the prospective observational DAPPER study, conducted at the department of dermatology of the Radboud university medical center from June 2019 until April 2022. The study protocol and initial results have been published before[17,18].

Briefly, 304 adult patients with Pso visiting the dermatology outpatient clinic were included. Patients were stratified 1:1:1 for current treatment modality (topicals only, conventional systemics, biologicals/small molecule inhibitors (smi)). Patients with previously diagnosed, concomitant PsA were not excluded. Patients were screened by a rheumatologist at the dermatology outpatient clinic for signs and symptoms of PsA with a structured interview and physical examination (supplementary file 1). If PsA was suspected at study visit, and the patient was not currently treated by a rheumatologist, they were referred to a rheumatology

center for additional examinations and confirmation or PsA diagnosis.

The study was approved by the Medical Ethical Committee of the region Arnhem-Nijmegen, Radboudumc (NL68137.091.18), registered prospectively in the Dutch Trial Register (NTR 7604), and performed according to the Declaration of Helsinki and Good Clinical Practice. The current report was written according to Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidelines[19].

Outcome

Outcome of the prediction model was presence of concomitant PsA. A patient was classified as "Pso with concomitant PsA" if either they had been previously diagnosed by a rheumatologist, or if a (new) diagnosis of PsA was made after study referral to the rheumatology department. Patients without a previous diagnosis of PsA, and patients without signs/symptoms of concomitant PsA, or with rejection of PsA diagnosis after referral, were classified as "Pso only". Patients with "Pso with concomitant active PsA" were Pso patients with concomitant PsA who in addition fulfilled the following criteria at study visit: ≥1 swollen joint and/or active enthesitis and/or active axial spondyloarthritis. In case of suspicion of active enthesitis and/or axial spondyloarthritis, affirmation by imaging was required. Patients with "Pso with concomitant inactive PsA" were Pso patients with a previous diagnosis of concomitant PsA who did not have swollen joints, active enthesitis, or active axial spondyloarthritis at study visit.

Variables

During the study visit, the following variables were collected via structured interviews and chart reviews: demographics, intoxications, family history of Pso and PsA, treatment history, comorbidity, (previous) disease activity of skin and nails (Psoriasis Area and Severity Index – PASI, range 0-72[20], Nail Psoriasis Severity Index – NAPSI, range 0-160[21]; Nijmegen Nail Psoriasis Activity Index Tool – N-NAIL, range 0-150[22]); (previous) signs and symptoms of joint disease, and questions from several screening questionnaires for PsA in Pso (Early Psoriatic Arthritis Screening Questionnaire - EARP, PEST, and ToPAS)[7,9,1].

Sample size

This study included patients from the DAPPER-study (n=304). For the prediction model, we aimed to use a maximum of ten parameters with a restriction of one parameter per ten events. Therefore, assuming a prevalence of PsA in Pso of thirty percent[23], we included three hundred Pso patients.

Statistical procedures

Data were described with mean (standard deviation, SD), median (interquartile range, IQR), or absolute frequencies (percentages), where appropriate.

Possible associations between disease or patient characteristics and presence of PsA were explored using logistic regression. Missing data were not imputed. All models presented are based on complete cases.

For possible predictors, dichotomous questions (yes/no, presence/absence) were included to ease use in clinical practice. Because we included patients with a known PsA diagnosis in the development cohort, questions referring to previous diagnosis of arthritis were not included (e.g. "Did a doctor ever tell you you have arthritis?").

Possible predictive variables were preselected in two steps for entry in the multivariable model. First, univariable logistic regression was used to select variables with a $P < 0.20$. Second, variables with overlapping concepts (based on biological plausibility and/or collinearity) were removed. We employed both forward and backward selection multivariable logistic regression models. $P < 0.05$ was considered significant in the multivariable regression models. The area under the receiver operating characteristics (ROC) curve (AUC) was used to assess the performance of the models.

Internal validity was assessed by estimating the optimism of the models using repeated K-fold cross-validation, with 10 splits and 20 repeats. A sensitivity analysis was done, where we created a scenario in which we reclassified patients with an uncertain diagnosis (n=4). These were classified as Pso with concomitant PsA in the original scenario, and in the sensitivity analysis they were classified as Pso only.

Based on the variables associated with concomitant PsA, we developed a referral tool for dermatologists. Goal of the referral tool was to alert the dermatologist when Pso patients have a high chance of concomitant PsA. If these patients are not under current rheumatological care, a referral to a rheumatologist could be considered. Test characteristics of the referral tool were tested using two-by-two tables to assess sensitivity and specificity.

Using the same methodology (i.e. logistic regression analysis followed by the construction of a referral tool), we explored the possibility of developing a referral tool for active PsA only. For this analysis, we compared the patient groups "Pso only" and "Pso with concomitant inactive PsA" versus "Pso with concomitant active PsA".

All analyses were performed in SPPS Statistics software version 25.0 (IBM) and R studio version 3.6.2 (Rstudio Inc.) using the caret package.

Results

Participants

In this study, 303 Pso patients of the DAPPER study were included (drop-out n=1) Mean age was 54±16 years, 109/303 patients (36%) were female. Seventy-four percent of patients (225/303) were classified as Pso only; seventeen percent as having concomitant inactive PsA (50/303); and nine percent as having active PsA (28/303). Clinical characteristics of the cohort are shown in table 1.

Identification of potential predictors for concomitant PsA in Pso patients

Using univariable logistic regression, we compared clinical characteristics of patients with Pso only and patients with Pso with concomitant PsA (supplementary tables 2 and 3). Using a cut-off of $P < 0.2$, 25 variables were deemed statistically relevant. By eliminating overlapping variables, 11 variables remained for input in the multivariable model.

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Table 1: Patient characteristics of Pso only and Pso with concomitant PsA patients

		Pso only n=225	Pso+PsA n=78
Age, years (mean, SD)		53 (17)	54 (15)
Female sex		80/225 (36%)	29/78 (37%)
BMI (mean, SD)		28.6 (5.7)	29.1 (5.8)
Smoking ever		159/225 (71%)	50/78 (64%)
Physically taxing job		41/225 (18%)	17/78 (22%)
Trauma past year		74/225 (33%)	28/78 (36%)
Family history	Pso	128/225 (57%)	47/78 (60%)
	PsA[a]	34/224 (15%)	14/78 (18%)
Comorbidity	MACE	24/225 (11%)	9/78 (12%)
	Depression	25/225 (11%)	11/78 (14%)
Current therapy	No systemic	85/225 (38%)	15/78 (19%)
Conventional systemic drugs	All	88/225 (39%)	26/778 (33%)
	Methotrexate	63/225 (28%)	17/78 (22%)
	Acitretin	8/225 (4%)	3/78 (4%)
	Fumaric Acid	14/225 (6%)	3/78 (4%)
	Cyclosporin	2/225 (1%)	0/78 (0%)
Biologicals/ small molecule inhibitors	All	57/225 (25%)	44/78 (56%)
	TNF-inhibitor	28/225 (12%)	19/78 (24%)
	IL17-inhibitor	9/225 (4%)	12/225 (15%)
	IL23-inhibitor	1/225 (1%)	1/78 (1%)
	IL12/IL23 p40 inh.	19/225 (8%)	10/78 (13%)
	PDE4-inhibitor	0/225 (0%)	2/78 (3%)
Skin disease, current	Age at start[b]	27 (16, 44)	23 (15, 32)
	Disease duration[b]	21 (10, 35)	2.7 (1.7, 3.9)
	PASI[a]	2.8 (1.6, 4.5)	2.4 (1.1, 4.0)
	NAPSI[c]	15 (6, 26)	12 (5, 20)
	N-NAIL[c]	4 (1, 10)	4 (1, 9)
Joint complaints, current	Joint pain	159/225 (71%)	67/78 (86%)
	Back pain	95/225 (42%)	41/78 (53%)
	Morning stiffness ≥ 30 min	26/225 (12%)	19/78 (24%)

Continuous variables are noted in median (IQR), categorical parameters in N (%), unless stated otherwise. Parameters with missing values are marked.
BMI = body mass index; IL = interleukin; MACE = major adverse cardiovascular event; NAPSI = nail psoriasis severity index; N-NAIL = Nijmegen nail psoriasis activity index; PASI = psoriasis area and severity index; PDE = phosphodiesterase; PsA = psoriatic arthritis; Pso = psoriasis; TNF = tumour necrosis factor; SD = standard deviation
a = missing in 1 patient with Pso only; b = missing in 9 patients with Pso only, and 4 patients with Pso+PsA; c = missing in 44 patients with Pso only, and 7 patients with Pso+PsA

Table 2 shows the results of multivariable logistic regression models using forward and backward selection. Both forward and backward selection showed independent association of presence of concomitant PsA with: treatment history with conventional systemics (OR 2.97, 95%CI 1.01-8.74, *P*=0.04), treatment history with biologicals/smi (OR 2.90, 95%CI 1.52-5.53, *P*=0.01), patient-reported history of joint pain not caused by trauma (OR 4.23, 95%CI 1.21-14.79, *P*=0.02), patient-reported history of swollen joints (OR 4.25, 95%CI 2.17-8.32, *P*<0.001), and patient-reported history of sausage-like swollen digits (OR 2.38, 95% CI 1.25-4.55, *P*=0.01). Overall fit of this multivariable logistic regression model as determined by AUC was 0.83.

Internal validation and sensitivity analyses

We estimated the optimism of the model using repeated K-fold validation. The AUC of the model was 0.83, the AUC of the internal validation model was 0.82, therefore giving an optimism of 0.01.

In the sensitivity analyses, we re-classified patients who were not referred to the rheumatologist but did have a suspicion of PsA at study visit (n=4) as Pso only instead of Pso with concomitant PsA. This analysis denoted the same five variables as independent predictors, as shown in supplementary table 4.

Development of referral tool for Pso patients with concomitant PsA

Based on the results of the above-mentioned analyses, we developed a referral tool for dermatologist to help them identify Pso patients with concomitant PsA. The following variables were included: treatment history with conventional systemics, treatment history with biologicals/smi, patient-reported history of joint pain not caused by trauma, patient-reported history of swollen joints, and patient-reported history of sausage-like swollen digits. Every variable was scored 1 point if present, and 0 points if absent. ROC curve of this five variable model showed an AUC of 0.82.

To increase ease of use, and to anticipate on the increased use of biologicals/smi without earlier treatment of conventional systemics (as is recommended in treatment guidelines for PsA[24]), we also made a version where we combined the variables “treatment history with conventional systemics” and “treatment history with biologicals/smi” to a single variable “treatment history with systemic medication”. ROC curve of this four variable model showed an AUC of 0.80. Table 3 shows the sensitivity and specificity of both versions of the referral tool at different cut-off points.

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Table 2: Results of multivariable logistic regression analysis, discriminating patients with Pso only from patients with Pso with concomitant PsA

	Univariable Odds ratio (95% CI)	Multivariable Odds ratio (95% CI)
Treatment history: All conventional systemic	4.72 (1.82 – 12.28)	2.97 (1.01 – 8.74)
Treatment history: All biological/small molecule inhibitor	3.80 (2.21 – 6.52)	2.90 (1.52 – 5.53)
Skin disease ever: Erythroderma	1.68 (0.77 – 3.69)	
Nail disease ever: Holes/pits	2.32 (1.35 – 3.99)	
Joint complaints ever: Non-trauma joint pain	9.30 (2.83 – 30.59)	4.23 (1.21 – 14.79)
Joint complaints ever: Swollen joints	6.62 (3.65 – 12.01)	4.25 (2.17 – 8.32)
Joint complaints ever: Swollen digits	4.53 (2.62 – 7.84)	2.38 (1.25 -4.55)
Joint complaints ever: Heel pain	1.54 (0.88 – 2.69)	
Joint complaints current: Joint pain	2.53 (1.26 – 5.09)	
Joint complaints current: Back pain	1.52 (0.90 – 2.54)	
Joint complaints current: Morning stiffness	2.47 (1.28 – 4.77)	
Intercept		- 4.89
Area under curve		0.83

Possible predictors for PsA in Pso patients were tested using multivariable logistic regression. After elimination of overlapping variables, predictors with a p-value ≤ 0.20 were inserted in the multivariable model. Odds ratios (Pso only versus Pso with concomitant PsA) are depicted with 95% confidence intervals. Complete regression formulas are shown in supplementary file 7.

Table 3: Test performance of referral tool for concomitant PsA in Pso patients at different cut-off points

	5 variable test	4 variable test
Cut-off ≥ 1	Sens: 99%	Sens: 99%
	Spec: 4%	Spec: 4%
Cut-off ≥ 2	Sens: 97%	Sens: 96%
	Spec: 23%	Spec: 32%
Cut-off ≥ 3	Sens: 88%	Sens: 79%
	Spec: 56%	Spec: 69%
Cut-off ≥ 4	Sens: 67%	Sens: 47%
	Spec: 85%	Spec: 92%
Cut-off ≥ 5	Sens: 35%	
	Spec: 96%	
Area under curve	0.82	0.80

The questions in the 5 variable test are:

1. *Have you ever used conventional systemic medication for your psoriasis? (i.e., methotrexate, acitretin, fumaric acid, cyclosporin)*
2. *Have you ever used biologicals or small molecule inhibitors for your psoriasis? (i.e. TNF-alpha-inhibitors, IL-17-inhibitors, IL-23-inhibitors, ustekinumab or apremilast)*
3. *Have you ever had joint pain that was not the result of injury?*
4. *Have you ever had a swollen joint (or joints)?*
5. *Have you had a finger or toe that was completely swollen and painful for no apparent reason?*

In the 4 variable test, question 1. and 2. were combined:
Have you ever used systemic medication (i.e., pills or injections) for your psoriasis?

Development of a referral tool for Pso patients with concomitant *active* PsA

Using the same methodology, we also explored the possibility to develop a referral tool to identify only Pso patients with concomitant *active* PsA. Supplementary table 5 shows the results of logistic regression analysis comparing the patient groups "Pso only" plus "Pso with concomitant inactive PsA" versus "Pso with concomitant active PsA". Backward selection multivariable logistic regression analysis showed independent associations of active PsA with: a treatment history with biologicals/smi (OR 3.33, 95%CI 1.44-7.71, *P*= 0.01) and current joint pain (OR 9.60, 95%CI 1.27-72.38, *P*= 0.03). Overall fit of the backward selection model as determined by AUC was 0.73. Forward selection multivariable logistics regression analysis also showed independent associations with a patient-reported presence of prolonged morning stiffness (OR 2.34, 95%CI 0.96-5.70, *P*= 0.06), in addition to a treatment history with biologicals/smi (OR 2.92, 95%CI 1.24-6.88, *P*= 0.01), and current joint pain (OR 7.80, 95%CI 1.02-59.72 *P*= 0.05). Overall fit of the forward selected model as determined by AUC was 0.75. Translation of these variables into a referral tool is shown in supplementary table 6.

6

Discussion

In the DAPPER study, patients with psoriasis at the dermatology outpatient clinic were investigated for the presence of PsA[17]. In this population, we identified five variables that were independent predictors for the presence of PsA: treatment history with conventional systemics, treatment history with biologicals/smi, patient-reported history of swollen joints, patient-reported history of sausage-like swollen digits, and patient-reported history of joint pain not caused by trauma. Using these variables, we developed a referral tool to aid dermatologists in identifying Pso patients with concomitant PsA.

Our referral tool included items about treatment history and musculoskeletal signs and symptoms, i.e. pain and swelling. Joint swelling is considered to be discriminating between inflammatory and non-inflammatory joint diseases, while sausage-like swelling of the digits (dactylitis) is considered a hallmark of PsA[25]. The item "history of joint pain not caused by trauma" is derived from the ToPAS questionnaire[10]. While several other questionnaires include items enquiring about joint pain in general[8,9,26] or joint pain combined with redness and/or swelling[11,13], a history of joint pain not caused by trauma is unique to ToPAS. Interestingly, in our cohort, a history of joint pain not caused by trauma was independently associated with concomitant PsA, while current joint pain was not. Presumably, the partial overlap of patients answering yes to both variables is the reason only one was selected using the backward/forward selection procedures.

The item "treatment history with systemic medication" has, to our knowledge, not been used before to identify Pso patients with concomitant PsA. The relationship between the use of systemic medication and the risk of PsA is still unclear. Since the biologicals/smi used for Pso are also effective for PsA, a protective effect is biologically plausible[27]. However, Pso patients who use biologicals/smi can still develop PsA[28]. A higher burden of skin involvement is associated with a higher prevalence of PsA, and patients with more severe skin involvement are more likely to receive systemic medication[29]. Moreover, patients with joint complaints are at a higher risk for PsA, and physicians might be more inclined to intensify treatment if joint complaints are present (protopathic bias)[30,31].
Remarkably, prevalence of nail disease ever and heel complaints, two items which are present in many other screening questionnaires, did not reach significance in our multivariable model[16]. Recently, Cui et al tested four different questionnaires in a Japanese Pso population, and extracted key questions which were discriminative between Pso only and Pso with concomitant PsA. Previous nail disease and heel complaints were also not found to contribute significantly to the distinction between both patient groups[32]. In contrast, in 2014 Coates et al found nail disease and heel complaints to be contributory[12]. We hypothesize that, while the prevalence of previous nail disease and heel complaints are indeed higher in Pso with concomitant PsA (as shown by the univariable models), this effect is overshadowed by the discriminative capabilities of the other items in our referral tool.

Ideally, any referral tool should have a balance between sensitivity and specificity. We believe that, based on the current data, the 4-variable-test (ever use of systemic medication, non-traumatic joint pain, swollen joints, and swollen fingers) with a cut-off of 3 or higher has the best characteristics for this goal. With a sensitivity of 79%, a specificity of 69% and a prevalence of 26%, this would mean that out of a hundred patients with Pso, half of the patients would be referred, of which again half would have PsA. However, one in five patients with PsA would be missed.

Comparison of the performance of our referral tool to previously designed screening questionnaires is difficult, because of the large variation of the reported performances in different studies and the different populations used to develop and evaluate these questionnaires[16]. In the DAPPER cohort, psoriasis patients with previously diagnosed PsA were not excluded. Because of inclusion of these patients with known PsA, we were unable to include predictors directly related to the PsA diagnosis such as a question enquiring about a previous arthritis diagnosis by a physician. Inclusion of predictors related to a previous diagnosis would bias the performance results of the tool, leading to an inaccurate high estimation of specificity and sensitivity. However, several previously developed screening questionnaires do contain a question enquiring about a previous arthritis diagnosis (e.g. PEST, ToPAS, PASE)[16]. In the DAPPER cohort, the sensitivity/specificity of PEST and ToPAS were 71/81% and 75/78%, respectively[17]. This is in the same range as the performance of our referral tool. However, due to the use of the "previous diagnosis" question, the performance of PEST and ToPAS in this cohort might be inaccurately high.

Because patients with currently active PsA are most likely to benefit from referral to, and thus cotreatment by, a rheumatologist, we also explored the option of a referral tool to identify patients with active PsA. However, our analysis was hampered by a low number of events (n=28 with active PsA), therefore our results must be interpreted with caution. Moreover, the performance of the model identifying active PsA only was low (AUC 0.75). Therefore, we must conclude that the data gathered in our cohort were insufficient to develop a useful tool to identify patients with active concomitant PsA.

Limitations of our study are the setting in an academic psoriasis expertise center, and the inclusion of patients with known PsA in our cohort. However, inclusion of these patients also made it possible to only use patients from the dermatology outpatient clinic, without the need to "supplement" cases from a rheumatology clinic. Moreover, the use of an "unfiltered" Pso population at the dermatology clinic (e.g. including patients with and without medication, in contrast to the EARP questionnaire[9]) improved the generalizability of our results. Another strength of our study is the study size, with enough events relative to the amount of possible predictive parameters, minimalizing the risk of overfitting. In the future, validation of the DAPPER referral tool in a second validation cohort should be performed, preferably in a multicenter setting involving both academic and non-academic centers.

In conclusion, with this prospective observational study we developed a referral tool to aid dermatologists in identifying Pso patients with concomitant PsA. We showed that a patient-reported history of swollen joints, sausage-like swollen digits, joint pain not caused by trauma, and a treatment history with systemic medication are independent risk factors for the presence of concomitant PsA in Pso patients. To improve the detection of Pso patients with concomitant PsA, future research could benefit from collaborations forming large, combined cohorts of screened Pso patients such as the Hippocrates consortium[33]. In addition, the use of only clinical parameters

may not be sufficient to adequately distinguish Pso patients with and without concomitant PsA. The combination of clinical parameters with laboratory and genetic markers could also be further explored as a means of screening[34]. In the meantime, use of screening questionnaires is considered a cost-effective approach to improve the care for Pso patients with (undiscovered) PsA[35].

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6

Supplementary file 1

Screening interview and physical examination

Screening was done using a structured interview.
Patients were asked about:
Joint pain and location
Time of day with worst complaints
Worsening or improvement on exertion
Joint swelling and location
Rubor and calor of joints
Swelling of Achilles tendon
Inflammatory back pain according to ASAS criteria[36]
Morning stiffness in minutes

Physical examination entailed:
68 tender joint count
66 swollen joint count
dactylitis count
SPARCC enthesitis index[37]
Leeds enthesitis index[38]

Supplementary table 2: possible predictors for concomitant PsA in Pso patients

		Pos only n=225	Pso+PsA n=78
Treatment history			
Non-systemic	UV-therapy	184/225 (82%)	67/78 (86%)
	Dithranol	77/148 (34%)	32/78 (41%)
Conventional Systemic drugs	All	170/225 (76%)	73/78 (94%)
	Methotrexate	140/225 (62%)	70/78 (90%)
	Acitretin	50/175 (22%)	27/78 (35%)
	Fumaric Acid	92/225 (41%)	34/78 (44%)
	Cyclosporin	38/225 (17%)	18/78 (23%)
Biologicals/small molecule inhibitors	All	72/225 (32%)	50/78 (64%)
	TNF-inhibitor	56/225 (25%)	44/78 (56%)
	IL17-inhibitor	10/225 (4%)	14/78 (18%)
	IL23-inhibitor	1/225 (1%)	2/78 (3%)
	IL12/IL23 p40 inh.	31/225 (14%)	20/78 (26%)
	PDE4-inhibitor	4/225 (2%)	4/78 (5%)
Skin disease			
At start	Scalp[a]	67/206 (33%)	23/71 (32%)
	Inverse[a]	9/206 (4%)	2/78 (3%)
Ever	Scalp	208/225 (93%)	75/78 (96%)
	Inverse	125/225 (56%)	43/78 (55%)
	Erythroderma	20/225 (9%)	11/78 (14%)
Current	Scalp[b]	102/224 (46%)	36/78 (46%)
	Inverse[b]	49/224 (22%)	14/78 (18%)
Nail disease			
Ever	All[b]	107/224 (48%)	53/78 (68%)
	Pitting	134/225 (60%)	56/78 (72%)
	Oil drop	64/225 (28%)	36/78 (46%)
	Onycholysis	108/225 (45%)	55/78 (71%)
	Crumbling	84/225 (37%)	44/78 (56%)
	Splinter haemorrhage	47/225 (21%)	15/78 (19%)
Current	Pitting[c]	95/181 (53%)	38/71 (54%)
	Oil drop[c]	89/181 (49%)	34/71 (48%)
	Onycholysis[c]	118/181 (65%)	48/71 (68%)
	Crumbling[c]	67/181 (37%)	23/71 (32%)
	Splinter haemorrhage[c]	146/181 (81%)	53/71 (75%)

		Pos only n=225	Pso+PsA n=78
Joint complaints			
Ever	Non-trauma joint pain	164/225 (73%)	75/78 (96%)
	Swollen joints[b]	75/224 (34%)	60/78 (77%)
	Swollen digit	48/225 (21%)	43/78 (55%)
	Heel pain[b]	55/224 (25%)	26/78 (33%)
	Heel swelling	22/225 (10%)	11/78 (14%)

PDE = phosphodiesterase; IL = interleukin; PsA = psoriatic arthritis; Pso = psoriasis; TNF = tumour necrosis factor; UV= ultraviolet.
a = missing in 19 patients with Pso only, and 7 patients with Pso+PsA; b = missing in 1 patient with Pso only; c = missing in 44 patients with Pso only, and 7 patients with Pso+PsA

Supplementary table 3: odds ratios of possible predictors for concomitant PsA in Pso patients, univariable logistic regression analysis

		Odds ratio	95% CI	P
Demography				
Female sex		1.07	0.63 – 1.83	0.80
Smoking ever		0.74	0.43 – 1.28	0.28
Physically taxing job		1.25	0.66 – 2.36	0.49
Trauma past year		1.14	0.67 – 1.96	0.63
Family history	Pso	1.15	0.68 – 1.94	0.60
	PsA[a]	1.22	0.62 – 2.42	0.57
Comorbidity	MACE	1.09	0.48 – 2.46	0.83
	Depression	1.31	0.61 – 2.81	0.48
Treatment history				
Non-systemic	UV-therapy	1.36	0.66 – 2.79	0.41
	Dithranol	1.34	0.79 – 2.27	0.28
Conventional Systemic drugs	All	4.72	1.82 – 12.28	0.01
	Methotrexate	5.31	2.44 - 11.58	<0.001
	Acitretin	1.85	1.06 – 3.25	0.03
	Fumaric Acid	1.12	0.66 – 1.88	0.68
	Cyclosporin	1.48	0.79 – 2.78	0.23
Biologicals/ small molecule inhibitors	All	3.80	2.21 – 6.52	<0.001
	TNF-inhibitor	3.91	2.28-6.70	<0.001
	IL17-inhibitor	4.70	1.99 – 11.09	<0.001
	IL23-inhibitor	5.90	0.53 – 65.93	0.15
	IL12/IL23 p40 inh.	2.16	1.15 – 4.07	0.02
	PDE4-inhibitor	2.99	0.73 – 12.24	0.13
Current therapy				
Conventional systemic drugs	No systemic	0.39	0.21 – 0.73	0.73
	All	0.78	0.45 -1.34	0.37
	Methotrexate	0.72	0.39 – 1.32	0.29
	Acitretin	1.09	0.28 – 4.20	0.91
	Fumaric Acid	0.60	0.17 – 2.16	0.44
Biologicals/small molecule inhibitors	All	3.81	2.23 – 6.54	<0.001
	TNF-inhibitor	2.27	1.18 – 4.35	0.01
	IL17-inhibitor	4.36	1.76 – 10.81	0.01
	IL12/IL23 p40 inh.	2.91	0.18 – 47.07	0.45

		Odds ratio	95% CI	P
Skin disease				
At start	Scalp[b]	0.99	0.56 – 1.77	0.98
	Inverse[b]	0.63	0.13 – 3.01	0.57
Ever	Scalp	2.04	0.58 – 7.17	0.27
	Inverse	0.98	0.59 – 1.65	0.95
	Erythroderma	1.68	0.77 – 3.69	0.19
Current	Scalp[a]	1.03	0.61 – 1.72	0.93
	Inverse[a]	0.78	0.40 – 1.51	0.46
Nail disease				
Ever	All[a]	2.32	1.35 – 3.99	0.01
	Pitting	1.73	0.99 – 3.03	0.06
	Oil drop	2.16	1.27 – 3.67	0.01
	Onycholysis	2.83	1.63 – 4.92	<0.001
	Crumbling	2.35	1.40 – 3.93	0.01
	Splinter haemorrhage	0.90	0.47 – 1.72	0.75
Current	Pitting[c]	1.04	0.60 – 1.81	0.88
	Oil drop[c]	0.95	0.55 -1.65	0.85
	Onycholysis[c]	1.11	0.62 – 2.00	0.72
	Crumbling[c]	0.82	0.46 – 1.46	0.49
	Splinter haemorrhage[c]	0.71	0.37 – 1.35	0.29
Joint complaints				
Ever	Non-trauma joint pain	9.30	2.83 – 30.59	<0.001
	Swollen joints[a]	6.62	3.65 – 12.01	<0.001
	Swollen digit	4.53	2.62 – 7.84	<0.001
	Heel pain[a]	1.54	0.88 – 2.69	0.13
	Heel swelling	1.52	0.70 – 3.29	0.29
Current	Joint pain	2.53	1.26 – 5.09	0.01
	Back pain	1.52	0.90 – 2.54	0.12
	Morning stiffness ≥ 30	2.47	1.28 – 4.77	0.01

Possible predictors for concomitant PsA were studied using univariable logistic regression. Groups consisted of patients with Pso only (N=225) and patients with Pso+PsA (N=78).
PDE = phosphodiesterase; IL = interleukin; MACE = major adverse cardiovascular event; PsA = psoriatic arthritis; Pso = psoriasis; TNF = tumour necrosis factor.
a = missing in 1 patient with Pso only; b = missing in 19 patients with Pso only, and 7 patients with Pso+PsA; c = missing in 44 patients with Pso only, and 7 patients with Pso+PsA.

Supplementary table 4: sensitivity analysis reclassifying suspected patients without referral

	Univariable	Multivariable
Therapy history: All conventional systemic	7.84 (2.38 – 25.87)	5.42 (1.48 – 19.89)
Therapy history: All biologicals/small molecule inhibitors	3.87 (2.23 – 6.71)	2.70 (1.40 – 5.19)
Current therapy: No systemic	0.31 (0.16 – 0.61)	
Current therapy: Methotrexate	0.71 (0.38 – 1.33)	
Nail disease ever: Pitting/holes	2.24 (1.29 – 3.88)	
Joint complaints ever: Non-trauma joint pain	13.37 (3.18 – 56.13)	5.83 (1.31 – 25.91)
Joint complaints ever: Swollen joints	7.11 (3.83 – 13.19)	4.44 (2.21 – 8.92)
Joint complaints ever: Swollen digits	4.82 (2.76 – 8.42)	2.56 (1.32 – 4.96)
Joint complaints ever: Heel pain	1.57 (0.89 – 2.77)	
Joint complaints current: Joint pain	2.32 (1.15 – 4.68)	
Joint complaints current: Back pain	1.52 (0.90 – 2.57)	
Joint complaints current: Morning stiffness	2.70 (1.39 – 5.23)	
Intercept		-5.87
AUC		0.92

Patients with suspicion of PsA, who were unable to visit a rheumatologist, were categorized as Pso only for this analysis. Parameters with P <0.20 in univariable logistic regression were entered in a multivariable model. Odds ratios (Pso only versus Pso+PsA) are depicted with 95% confidence intervals.

Supplementary table 5: results of multivariable logistic regression analysis, active PsA versus Pso only/ inactive PsA

	2 variable test	3 variable test
Cutoff ≥ 1	Sens: 95%	Sens: 96%
	Spec: 18%	Spec: 17%
Cutoff ≥ 2	Sens: 50%	Sens: 71%
	Spec: 72%	Spec: 67%
Cutoff ≥ 3		Sens: 32%
		Spec: 93%

Possible predictors for active PsA in Pso patients were tested using multivariable logistic regression. After elimination of overlapping variables, predictors with a p-value ≤ 0.20 were inserted in the multivariable model. Odds ratios (Pso only/ inactive PsA versus active PsA) are depicted with 95% confidence intervals.

Supplementary table 6: test performance of referral tool for *active* PsA at different cut-off points

	2 variable test	3 variable test
Cutoff ≥ 1	Sens: 95%	Sens: 96%
	Spec: 18%	Spec: 17%
Cutoff ≥ 2	Sens: 50%	Sens: 71%
	Spec: 72%	Spec: 67%
Cutoff ≥ 3		Sens: 32%
		Spec: 93%

The questions in the 2 variable test are:

1. Have you ever used biologicals or small molecule inhibitors for your psoriasis? (i.e. TNF-alpha-inhibitors, IL-17-inhibitors, IL-23-inhibitors, ustekinumab or apremilast)
2. Are you currently having pain in your joints?

In the 3 variable test, an extra question is added:

3. Are you currently experiencing stiffness in joints and muscles upon arising in the morning, that lasts for more than 30 minutes?

Supplementary file 7: regression formula

Logit(P) = -4.89 (intercept)
+ (1.09 * treatment history with conventional systemics)
+ (1.06 * treatment history with biologics/small molecule inhibitors)
+ (1.44 * patient-reported history of non-trauma joint pain)
+ (1.45 * patient-reported history of swollen joints)
+ (0.87 * patient-reported history of swollen digits)

Chapter 7

Impairment in work and activities of daily life in patients with psoriasis: results of the prospective BioCAPTURE registry

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Abstract

Background
Little is known about the extent of impairments in work and activities of daily life (ADL) in patients with psoriasis, and the influence of contextual factors such as disease-related characteristics and treatment. Therefore, this study aimed to assess these impairments in patients with psoriasis who started using biologicals/small molecule inhibitors.

Methods
Using data from the prospective BioCAPTURE registry, we collected patient, disease, and treatment parameters, as well as work/ADL impairments at baseline, 6 and 12 months. Changes in impairment parameters and correlations between impairment and patient/disease characteristics were assessed using generalized estimating equations.

Results
We included 194 patients in our analysis. After biological initiation, disease activity decreased significantly (PASI 11.2 at baseline versus 3.9 at 12 months, $p < 0.001$). Work-for-pay in this cohort was lower than in the Dutch general population (53% versus 67%, $p = 0.01$). In patients who had work-for-pay, presenteeism improved over time (5% at baseline versus 0% at 12 months, $p = 0.04$). Up to half of the patients reported impairments in ADL, which did not change over time. Associations between impairments and contextual factors varied, but all impairments were associated with worse mental/physical general functioning.

Conclusion
Patients with psoriasis using biologicals are less likely to have work-for-pay. Treatment improves the work productivity of employed patients, but we were unable to detect changes in ADL performance.

Introduction

Psoriasis is an immune-mediated inflammatory disease of skin and nails, which can impact a patient's life in several ways. Sensations of pain, burning, or itching can affect the physical well-being of a patient, while the stigma of (visible) skin lesions can have an impact on psychological well-being[1]. Moreover, treatment of psoriasis can be time-consuming (e.g. application of topicals multiple times a day, or multiple hospital visits for UV therapy) or have side effects (e.g. nausea or injection site reactions)[2]. All these burdens can culminate in impairments in a patient's personal and professional daily life.

Patients with psoriasis mention that pain and fatigue disrupt their normal family roles[3]. Moreover, patients experience a negative influence of the disease on work performance[4,5]. Sick leave has shown to be more common in psoriasis patients when compared to the US general population: during one year, 56% of psoriasis patients took sick leave, versus 42% of the general population[6]. Moreover, impairments in work and daily life activities increase with increased severity of psoriasis[4,7,8], and diminish after successful treatment[9-11].

While we know that the impact of psoriasis on work and activities of daily life (ADL) is an important theme for patients, we know little about the different areas of ADL affected by the disease[12,13]. Also, the influence of contextual factors such as sex, relationship status, educational level, and comorbidity on these impairments of ADL is unknown. Moreover, most data on treatment effects on work and ADL impairment are based upon (secondary outcomes of) randomized clinical trials, where real-world data is lacking[9,14-21].

Therefore, we assessed the extent of impairments in work and ADL in a daily practice cohort of patients with plaque psoriasis treated with biologicals/small molecule inhibitors (smi). In addition, we examined the effect of 6-12 months of treatment on these impairments and explored associations between impairment and contextual factors and treatment success.

Patients and methods

Study design and population
For this study, we used data from the Continuous Assessment of Psoriasis Treatment Use Registry with Biologics (BioCAPTURE registry – www.biocapture.nl). In short, this prospective, multicenter registry records data of adult patients with plaque psoriasis using biologicals/smi from 4 academic and 17 non-academic dermatology centers in the Netherlands. Under Dutch law, this non-interventional study is exempt from ethics review by the medical ethical committee. Informed consent was obtained from all patients before inclusion in the study, and it was performed in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki.

Data collection
We collected data from patients from inclusion in the BioCAPTURE registry from 2010-2021, with a per-patient follow-up time of one year. Patients were included for the present analysis from the start of their first biological therapy registered in BioCAPTURE on, and data were collected every three months up to one year after initiation (regardless of treatment

switch within this first year). For this analysis, we used all data of patients who completed questionnaires about work participation and/or ADL impairment at baseline assessment and at least one follow-up timepoint. Patients who discontinued their biological or switched to another biological, but continued to provide data, were also included. Patients who did not provide follow-up data were excluded from the analysis.

Data collected included information about contextual factors and disease-related characteristics. Contextual factors included were age, sex, relationship status, education, and comorbidity (using the Charlson Comorbidity Index (CCI))[22]. Comorbidity was further categorized into low (CCI 0 points), intermediate (CCI 1-2 points), and high (CCI 3 or more). Disease-related characteristics included were disease duration, presence of concomitant psoriatic arthritis -PsA-, current biological use, and disease activity assessed with the Psoriasis Area and Severity Index (PASI)[23]. Current biological use was categorized per mode of action: TNFα-inhibitors (i.e. etanercept, adalimumab, infliximab, certolizumab), IL-17 inhibitors (i.e. secukinumab, ixekizumab, brodalumab), IL23-inhibitors (i.e. guselkumab, risankizumab), IL12/23 p40 inhibitors (i.e. ustekinumab), and PDE4-inhibitors (apremilast).

Other patient-reported outcomes included skin-related quality of life assessed with the Dermatological Life Quality Index (DLQI)[24], and physical and mental wellbeing assessed with the component scores of the Short Form 36 (PCS/MCS)[25].

Primary outcomes were impairments in work participation and ADL. Data about work participation were collected using the PROductivity and DISease Questionnaire (PRODISQ)[26]. Work participation parameters were: having work-for-pay, absenteeism (percentage of time being away from work), and presenteeism (percentage of estimated "productivity loss" while at work). Absenteeism and presenteeism can be combined into overall work impairment as follows: Absenteeism + ((1-Absenteeism) * Presenteeism). All work parameters are reported in percentage of maximum work output as reported by patients, usually in median percentage reported and interquartile ranges (IQR).

Data about impairments in ADL were collected from the TIC-P questionnaire[27]. Patients were asked if they experienced any impairments in four ADL domains household chores (i.e. cooking, cleaning), grocery shopping (outside of the home), home maintenance and childcare. Answers were dichotomized into ADL impairment present or not for each domain.

Statistical analysis

Continuous data were described with mean (standard deviation, SD) or median (interquartile ranges, IQR). Categorical data were described as absolute frequencies (percentages).

We used generalized estimating equations (GEE) to explore differences in disease-related and patient-reported outcomes (i.e. PASI, DLQI, PCS, MCS, work and ADL impairment) at different timepoints, and to explore associations of work/ADL impairments with disease-related characteristics and contextual factors. GEE allows the estimation of the average effect of an independent variable on a specific outcome at the population level[28]. For example, we can estimate the average effect of a change in PASI on the likelihood of having work-for-pay. Since GEE makes use of all available data, missing data was not imputed.

First, differences in disease-related and patient-reported outcomes between different timepoints were tested. For continuous outcomes (e.g. PASI, DLQI, presenteeism) a linear GEE model was used, while for binary outcomes (e.g. work-for-pay, ADL impairment) a logistic GEE model was used. Timepoints (baseline, 6 months – M6, 12 months – M12) were entered as independent variables. Baseline values were regarded as the default state, and statistical significance of values at M6 and M12 were tested in comparison to baseline.

Second, we assessed the extent of work impairment in the study patients. Also, we compared the work-for-pay status (proportion with paid work) of the BioCAPTURE cohort with the Dutch general population by using an age- and sex-matched model based on data from the Central Bureau of Statistics (CBS) of the Netherlands[29]. The CBS provides yearly data on employment rates, stratified for sex and age groups per ten years of age. Data were available from 2013 onwards. BioCAPTURE patients included before 2013 were matched to the general population of 2013. Differences between the proportions of patients with work for pay in the BioCAPTURE cohort vs. the general population were tested by a Chi-square test.

Third, we used four separate logistic GEE models to test associations of work/ADL impairments with disease-related characteristics and contextual factors. Work-for-pay (yes/no), impairment in household chores (yes/no), impairment in grocery shopping (yes/no), and impairment in home maintenance (yes/no) were the dependent variable in each of the models. To explore the influence of disease-related characteristics and contextual factors on presenteeism, we used a linear GEE model. Independent variables entered in the models were: age, sex, relationship status, education (primary/secondary versus tertiary), presence of PsA, disease duration of psoriasis, PASI over-time, DLQI over-time, MCS over-time, PCS over-time, and whether the biological/smi used at baseline was still used after 6/12 months.

Last, to assess the association of work/ADL impairments with treatment success, we compared the parameters of work/ADL impairment (work-for-pay, presenteeism, and impairments in household chores, grocery shopping, and home maintenance) at different timepoints between patients who did and did not have treatment success. As a proxy for treatment success, we used PASI ≤ 1.0 at 6/12 months, PASI ≤ 3.0 at 6/12 months, or whether the biological/smi used at baseline was still used after 6/12 months. Proportions were compared using a Chi-square or Fisher's exact test where appropriate. Non-parametrical data were compared using a Mann-Whitney U test.

$P < 0.05$ was considered statistically significant. All analyses were performed in SPSS Statistics software, version 25.0 (IBM, Armonk, NY, USA).

Results

Table 1 shows the patient characteristics (n=194). Mean age of patients was 52 years (SD 13), and 79/189 were female (42%). A majority was in a relationship (132/186, 71%), and almost all had secondary or higher education (182/191, 95%). Mean disease duration was 19 years (IQR 11-35 years), and one in three patients had concomitant PsA (53/185, 29%). Most patients had low to intermediate comorbidity scores (low 84/197, 43%; intermediate 85/194, 44%; high 25/194, 13%). Dispersion of patient data throughout time points, including explanation of missing data, is shown in figure 1.

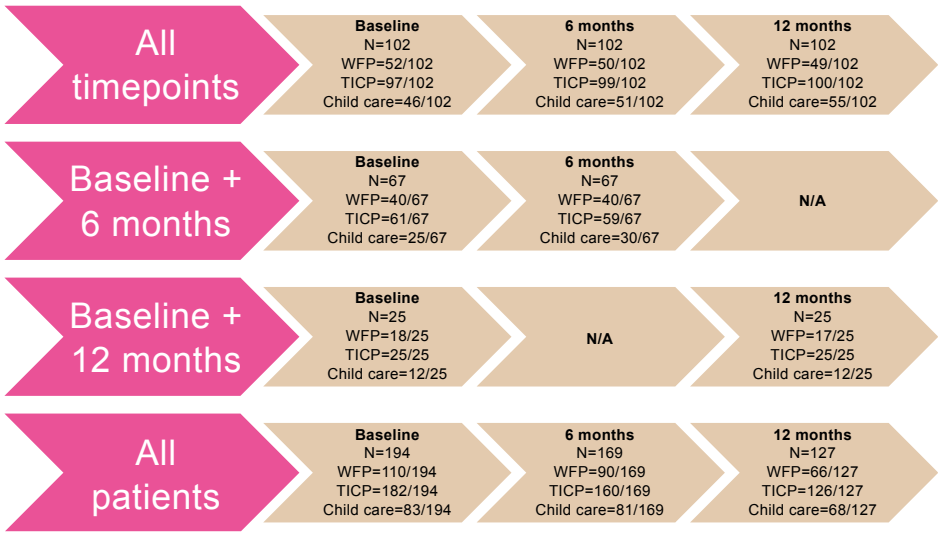


Figure 1: Inclusion of patients and explanation of missing data
Patients were included if they had filled out a PRODISQ questionnaire at baseline and at least 1 follow-up timepoint (i.e. 6 or 12 months). 102 patients provided data for all three timepoints, 67 patients provided data on baseline and 6 months only, and 25 patients provided data on baseline and 12 months only.
All patients provided data on their work-for-pay (WFP) status (inclusion criteria). Only patients with WFP could provide information on presenteeism and overall work impairment. Not all patients filled in the TIC-P questionnaire, and therefore not all patients provided data on impairment in activities of daily living (ADL). Only patients with a filled in TICP, who were taking care of underage children, could provide data about child care.
N/A = not applicable; WFP = work-for-pay

Table 1: Sample characteristics at baseline

N		194
Demographics		
Age	Mean, SD	52 (13)
Sex, female[a]	Mean, SD	79/189 (42%)
Relationship state[b]	Single	54/186 (28%)
	In a relationship	132/186 (71%)
Education level[c]	Primary	9/191 (5%)
	Secondary	127/191 (66%)
	Tertiary	55/191 (29%)
Charlson Comorbidity Index	Low (0)	84/194 (43%)
	Intermediate (1-2)	85/194 (44%)
	High (≥3)	23 (13%)
Disease characteristics		
Disease duration (years)[d]	Median, IQR	19 (11, 35)
Concomitant PsA[e]		53/185 (29%)
Current biological/smi	TNFa-inhibitors	110/194 (57%)
	IL17-inhibitors	21/194 (11%)
	IL23-inhibitors	13/194 (7%)
	IL12/IL23 p40 inhibitors	44/194 (23%)
	PDE4-inhibitors	6/194 (3%)

Parameters are expressed in number/percentages unless indicated otherwise.
Relationship status was dichotomized into having a partner, or being single, regardless of marital status. Education was categorized into primary, secondary and tertiary education. Primary education represents primary school only, tertiary education represents college or university, and secondary education represents high school or community college.
a = missing in 6 patients, b = missing in 8 patients; c = missing in 3 patients; d = missing in 17 patients; e = missing in 9 patients
IL = interleukin; IQR = interquartile range; PDE = phosphodiesterase; PsA = psoriatic arthritis; TNFa = tumour necrosis factor alpha; SD = standard deviation; smi = small molecule inhibitor

Disease characteristics and health status during 12 months follow-up

Table 2 shows the follow-up data of the cohort, where timepoint differences were tested using GEE with the different timepoints as independent variables. At M12, the number of patients using the same biological/smi as at baseline had dropped significantly (M6 159/169 – 94%, M12 99/127 – 78%, P<0.001). Both objective skin disease activity, as well as skin-specific QoL, improved in comparison to baseline (PASI: baseline 11.2 ±7.2; M6 3.9 ±4.6, P <0.001; M12 3.9 ±4.0, P <0.001; DLQI: baseline 4, IQR 1-10; M6 1, IQR 0-4, P <0.001; M12 2, IQR 2-5, P <0.001). Moreover, also general physical and mental functioning improved significantly (PCS: baseline 43.6 ±10.2; M6 46.1 ±10.3, P <0.001; M12 45.4 ±11.0, P= 0.01; MCS: baseline 48.1 ±11.4; M6 50.1 ±10.8, P= 0.01; 12 months 51.0 ±10.0, P= 0.01).

Work-for-pay and work impairment during 12 months follow-up

Table 2 shows the course of work-related parameters over a 12-month period, again using GEE with the different timepoints as independent variables to test for differences between timepoints. At baseline, 110/94 (57%) had work-for-pay. When comparing the baseline percentage of work-for-pay between the study population to the general Dutch population, the study population showed a lower employment rate than expected (work-for-pay BioCAPTURE 53% versus general population 67%, $\chi 2$ test, *P*=0.01). The percentage of patients with work-for-pay did not change during follow-up (M6 53%, *P*=0.09; M12 52%, *P*=0.13).

Regarding work impairment, absenteeism was low throughout the entire follow-up (baseline 0% of maximum work hours, IQR 0-5; M6 0%, IQR 0-0, *P*=0.01; M12 0%, IQR 0-5, *P*=0.76), whereas presenteeism showed a statistically significant improvement at 12 months, but not at 6 months (baseline 5% of maximum theoretical productivity, IQR 0-18; M6 0%, IQR 0-15, *P*=0.17; M12 0%, IQR 0-10, *P*=0.04). Overall work impairment showed improvement over time, which was significant at 6 months but not 12 months (baseline 14%, IQR 0-26; M6 months 3%, IQR 0-20, *P*=0.01; M12 2%, IQR 0-23, *P*=0.49).

Associations between work impairment and disease-related characteristics/contextual factors

Table 3 shows the results of the GEE, exploring relationships for work impairment with disease-related characteristics and contextual factors. In a logistic GEE model, being in a relationship (OR 2.12, 95%CI 1.04-4.33, *P*=0.04) and remaining on the same biological/smi (OR 3.22, 95%CI 1.00-10.39, *P*=0.05) were positively associated with the likelihood of having work-for-pay. However, female sex (OR 0.48, 95%CI 0.25-0.93, *P*=0.03), a higher age (OR 0.89, 95%CI 0.86-0.92, *P*<0.001), and a higher amount of comorbidity (low vs high OR 0.22, 95%CI 0.07-0.67, *P*=0.01) were negatively associated with the likelihood of having work-for-pay. Disease activity and QoL parameters showed no significant relationship with work-for-pay status.

Next, we explored relationships for presenteeism (a quantitative marker of work impairment) with disease-related characteristics and contextual factors using a linear GEE model. Remaining on the same biological/smi (B=13.20, 95%CI 2.52, 23.89, *P*=0.02) and a higher amount of comorbidity (low vs intermediate B=5.75, OR 1.04-10.46, *P*=0.02) showed a positive association with a higher presenteeism (more impairment at work). Skin-related QoL (DLQI: B=0.42, 95%CI 0.06-0.79, *P*=0.02), and physical and mental functioning (PCS: B= -0.64, 95% CI -0.87 – -0.41, *P*<0.001; MCS: B= -0.57, 95% CI -0.78 - -0.37, *P*<0.001) showed a negative association with a higher presenteeism. In other words, deterioration of skin-related QoL by 1 point is associated with an increase in presenteeism of 0.4 percent, on a population level.

ADL impairment during 12 months follow-up

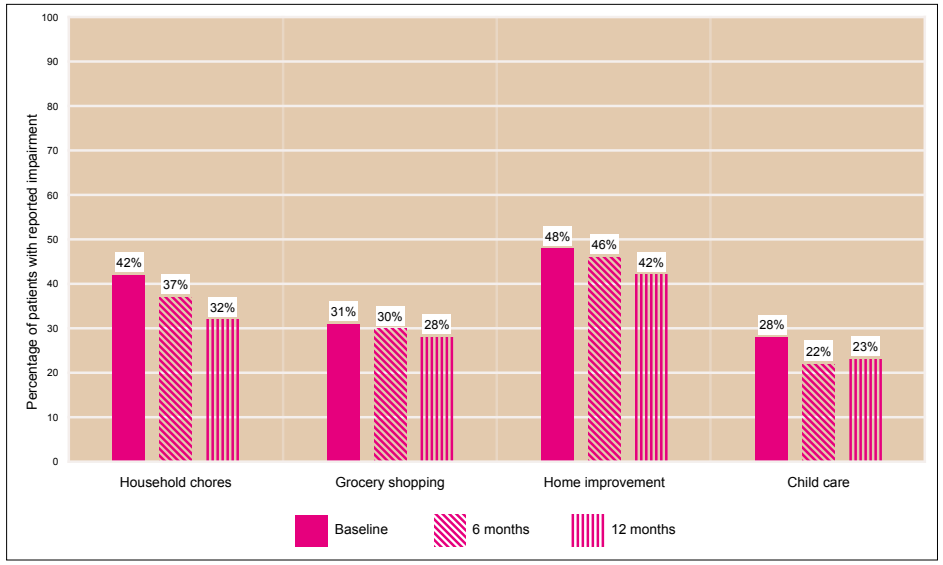
Table 2 and figure 2 show the baseline and follow-up data of the ADL-related parameters, using GEE with the different timepoints as independent variables to test for differences between timepoints. A substantial part of patients reported impairment in their ADL at baseline, of which home maintenance was most affected (impairment in household chores 37%; impairment in grocery shopping 31%; impairment in home maintenance 48%; impairment in childcare 28%). None of the ADL impairments changed during follow-up.

Table 2: Disease characteristics, work and ADL impairment at baseline and during follow-up.

			Baseline	6 months	12 months
N			194	169	127
Disease characteristics					
Same biological/smi			194/194 (100%)	159/169 (94%)[a] P > 0.05	99/127 (78%)[b] **P < 0.001**
PASI		Mean, SD	11.2 (7.2)[c]	3.9 (4.6)[d] **P < 0.001**	3.9 (4.0)[e] **P < 0.001**
DLQI		Median, IQR	4 (1, 10)[f]	1 (0, 4)[g] **P < 0.001**	2 (0, 5)[h] **P < 0.001**
SF36	PCS	Mean, SD	43.6 (10.2)[i]	46.1 (10.3)[j] **P < 0.001**	45.4 (11.0)[k] **P = 0.04**
	MCS	Mean, SD	48.1 (11.4)[i]	50.1 (10.8)[j] **P = 0.01**	51.0 (10.0)[k] **P = 0.01**
Work impairment					
Work for pay			110/194 (57%)	90/169 (53%) P = 0.09	66/127 (52%) P = 0.13
Absenteeism		Median, IQR	0 (0,5)[l]	0 (0, 0)[m] **P = 0.01**	0 (0, 5)[n] P = 0.76
Presenteeism		Median, IQR	5 (0, 18)[o]	0 (0, 15)[p] P = 0.17	0 (0, 10)[f] **P = 0.04**
Overall work impairment		Median, IQR	14 (0,26)[l]	3 (0, 20)[m] **P = 0.01**	2 (0, 23)[q] P = 0.49
ADL impairment					
Household chores		Impaired	71/183 (37%)[r]	60/160 (38%)[t] P = 0.74	41/126 (32%)[o] P = 0.13
Grocery shopping		Impaired	57/184 (31%)[s]	48/160 (30%)[t] P = 0.75	35/126 (28%)[o] P = 0.44
Home maintenance		Impaired	89/184 (48%)[s]	73/160 (46%)[t] P = 0.43	53/126 (42%)[o] P = 0.13
Childcare		Impaired	23/83 (28%)[u]	18/83 (22%)[v] P = 0.28	16/68 (23%)[y] P = 0.50

Values are given in number and percentage unless stated otherwise. Differences were tested using generalized estimating equations (GEE). P-values are expressed in comparison to baseline. Significant differences are highlighted in bold.
a = missing in 25 patients; b = missing in 67 patients; c = missing in 19 patients; d = missing in 84 patients; e = missing in 110 patients; f = missing in 3 patients; g = missing in 27 patients; h = missing in 71 patients; i = missing in 14 patients; j = missing in 29 patients; k = missing in 72 patients; l = missing in 36 patients; m = missing in 32 patients; n = missing in 24 patients; o = missing in 1 patient; p = missing in 2 patients; q = missing in 25 patients; r = missing in 11 patients; s = missing in 10 patients; t = missing in 34 patients; u = missing in 12 patients, not applicable in 99 patients; v = missing in 33 patients, not applicable in 78 patients; y = missing in 1 patient, not applicable in 57 patients
ADL = activities of daily life; DLQI = dermatology life quality index; IQR = interquartile range; MCS = mental component summary scale; PASI = psoriasis area and severity index; PCS = physical component summary scale; SD = standard deviation; SF36 = short form 36; smi = small molecule inhibitor

Figure 2: Impairments in ADL, from baseline to one year after start of biologicals/smi
The bar charts depict the amount of patients who report any impairment in the mentioned area of activities of daily life.



Associations between ADL impairment and disease-related characteristics/contextual factors

Table 3 shows the results of the GEE, exploring relationships for ADL impairment with disease-related characteristics and contextual factors. Being in a relationship showed a negative relation with being impaired in household chores (OR 0.40, 95%CI 0.18-0.87, *P*=0.02). Disease activity showed a negative association with being impaired in household chores (OR 0.95, 95%CI 0.91-1.00, *P*=0.05) and being impaired in home maintenance (OR 0.94, 95%CI 0.89-0.99, *P*=0.02). A higher amount of comorbidity showed a positive association with being impaired in grocery shopping (low vs intermediate OR 3.95, 95%CI 1.70-9.17, *P*=0.001). Physical and mental functioning showed a negative association with being impaired in all ADL domains (e.g. household chores: PCS OR 0.85, 95%CI 0.82-0.89, P<0.001; MCS OR 0.94, 95%CI 0.91-0.97; *P*<0.001).

Association between treatment success and work/ADL impairment

Supplemental table 1 shows the percentage of patients with work/ADL impairment, split per timepoint. Comparisons were made between patients with and without treatment success, where treatment success was defined as PASI ≤ 1.0, PASI ≤ 3.0, or retainment of the same biological/smi as used at baseline. Reaching PASI ≤ 1.0 after 12 months of treatment was associated with higher likelihood of having work-for-pay. Having treatment success was not associated with any of the outcomes on ADL impairment.

Table 3: Associations between work-for-pay status, presenteeism, impairments in ADL, and disease-related characteristics/contextual factors

	Work-for-pay		Presenteeism		Household chores		Grocery Shopping		Home Maintenance	
	OR (95% CI)	P-value	B (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Female Sex	**0.48 (0.25, 0.93)**	**P=0.03**	-1.77 (-6.39, 2.86)	P=0.45	1.17 (0.56, 2.41)	P=0.68	1.12 (0.51, 2.42)	P=0.78	1.31 (0.62, 2.78)	P=0.48
Age	**0.89 (0.86, 0.92)**	**P=<0.001**	-0.01 (-0.25, 0.23)	P=0.94	1.01 (0.98, 1.04)	P=0.40	0.97 (0.94, 1.01)	P=0.11	1.00 (0.97, 1.03)	P=0.84
Being in a Relationship	**2.12 (1.04, 4.33)**	**P=0.04**	3.78 (-1.05, 8,63)	P=0.13	**0.40 (0.18, 0.87)**	**P=0.02**	0.53 (0.24, 1.18)	P=0.12	0.51 (0.22, 1.18)	P=0.11
Higher Education	1.87 (0.93, 3.79)	P=0.08	1.19 (03.31, 5.69)	P=0.60	0.88 (0.40, 1.96)	P=0.76	0.87 (0.37, 2.04)	P=0.74	1.15 (0.50, 2.64)	P=0.74
Disease Duration Pso	1.02 (1.00, 1.04)	P=0.10	0.03 (-0.15, 0.20)	P=0.79	1.00 (0.98, 1.03)	P=0.98	0.99 (0.97, 1.02)	P=0.57	1.02 (0.99, 1.04)	P=0.20
Presence of PsA	1.32 (0.68, 2.56)	P=0.41	-0.23 (05.14, 4.68)	P=0.93	1.47 (0.67, 3.21)	P=0.33	1.95 (0.85, 4.47)	P=0.41	1.53 (0.68, 3.46)	P=0.31
Comorbidity Low vs Intermed	0.54 (0.28, 1.04)	P=0.07	**5.75 (1.04, 10.46)**	**P=0.02**	1.57 (0.73, 3.39)	P=0.25	**3.95 (1.70, 9.17)**	**P=0.001**	2.01 (0.04, 4.51)	P=0.07
Comorbidity Low vs High	**0.22 (0.07, 0.67)**	**P=0.01**	-5.40 (-17.20, 6.40)	P=0.37	1.22 (0.37, 4.00)	P=0.74	2.45 (0.69, 8.76)	P=0.17	3.39 (0.93, 12.33)	P=0.06
Same Biological	**3.22 (1.00, 10.39)**	**P=0.05**	**13.20 (2.52, 23.89)**	**P=0.02**	2.38 (0.63, 9.01)	P=0.20	1.63 (0.40, 0.64)	P=0.50	2.09 (0.52, 8.43)	P=0.30
PASI	0.99 (0.95, 1.04)	P=0.74	-0.25 (-0.54, 0.05)	P=0.10	**0.95 (0.91, 1.00)**	**P=0.05**	0.96 (0.92, 1.01)	P=0.13	**0.94 (0.89, 0.99)**	**P=0.01**
DLQI	0.97 (0.93, 1.03)	P=0.33	**0.42 (0.06, 0.79)**	**P=0.02**	1.00 (0.94, 1.06)	P=0.94	1.04 (0.98, 1.10)	P=0.11	1.00 (0.97, 1.03)	P=0.84
PCS	1.00 (0.97, 1.04)	P=0.95	**-0.64 (-0.87, -0.41)**	**P<0.001**	**0.85 (0.82, 0.89)**	**P<0.001**	**0.85 (0.81, 0.89)**	**P<0.001**	**0.82 (0.78, 0.87)**	**P<0.001**
MCS	1.02 (0.99, 1.05)	P=0.32	**-0.57 (-0.78, 0.37)**	**P<0.001**	**0.94 (0.91, 0.97)**	**P<0.001**	**0.94 (0.91, 0.98)**	**P<0.001**	**0.94 (0.90, 0.97)**	**P<0.001**

Table 3 shows associations between work-for-pay status, presenteeism, impairments in ADL, and disease/patient characteristics over all time points. Associations were explored using generalized estimating equations. Significant associations are highlighted in bold (P<0.05).. B = regression coefficient; CI = confidence interval; DLQI = dermatology life quality index; MCS = mental component summary scale; OR = odds ratio; PASI = psoriasis area and severity index; PsA = psoriatic arthritis; Pso = psoriasis; PCS = physical component summary scale

Discussion

Using prospective, longitudinal data from the BioCAPTURE cohort, we show that Dutch patients with plaque psoriasis who use biologicals/smi are less likely to have work-for-pay than the general Dutch population. Those who had work-for-pay reported a low percentage of overall work impairment, and this improved further over a 12 month period. Work-for-pay status was related to demographic variables (i.e. sex, age, and relationship status), while presenteeism was related to retainment of the first biological/smi, comorbidity, and mental/physical functioning. Moreover, up to half of patients report impairments in ADL. Improvement of objective disease activity was associated with improvement in ADL impairments. However, despite treatment success, the percentage of patients who experience impairments in ADL did not improve in the first year.

Regarding work-for-pay, patients with psoriasis were less likely to have paid employment than the Dutch general population. Although in this study we did not ask for the reason for not having work-for-pay, a survey in the United States showed that 92% of patients with psoriasis who did not have work-for-pay reported that having psoriasis was the main reason for their unemployment[4]. Interestingly, patients with longstanding PsA are also less likely to have work-for-pay than the general population, while this is not the case for patients with early PsA[30,31]. Note that patients in this cohort had a disease duration of 19 years on average, before initiating the biological. Hypothetically, as in PsA, it could also be the case that patients with long-standing psoriasis are less likely to have work-for-pay than patients with early disease, i.e. that patients with Pso become unemployed during their disease. In the future, the possible relationship between disease duration and employment deserves future exploration in a psoriasis cohort with less longstanding disease to see if loss of work-for-pay arises during the disease, and to see if effective treatment could be protective against loss of work-for-pay.

In patients who have work-for-pay, we found an overall work impairment of 14% at baseline. This is comparable to other observational psoriasis cohort studies[8,32-35], while interventional studies with psoriasis patients report a higher level of overall work impairment up to 34%[15,18,20,36]. This discrepancy between observational and interventional studies may be explained by a difference in the studied populations. In interventional studies, patients with a more pronounced disease are usually selected to ascertain that the intervention can achieve a beneficial effect; while in observational studies a more representative cross-selection of all patients is studied. Thus, interventional studies usually select patients with worse disease status, who presumably might have more work impairment. Indeed, previous studies have shown that a higher disease activity is associated with more work impairment[34,37-39].

During follow-up, we saw an improvement in both presenteeism and overall work impairment after treatment, which is in line with other interventional studies[14,15,18-21,36,40]. Although we found no association of presenteeism over-time with disease activity over-time, several studies did report that a larger treatment effect (e.g. a larger decrease in disease activity) was associated with more improvement in work impairment[9,16,17], while another study found no significant correlation[14]. This difference may be partly explained by group size, differences in study setting [clinical trial versus registry], or by differences between countries[32]. In conclusion, the relationship between presenteeism and disease activity needs further exploration.

Up to half of the patients in our study reported an impairment in ADL. This is in line with other international cohorts[14,33,41]. During 12 month follow-up, we found no change in the percentage of patients who felt impaired in ADL over time. However, other studies do report a decrease in the "amount" of impairment in ADL per person[14,15,19-21,36]. We did observe a significant positive relationship between disease activity and ADL impairment. Tentatively, this suggests that while ADL impairment can improve after treatment, a significant number of patients do not reach a disease status in which they feel no ADL impairments at all.

Limitations of our study are the missing data in the registry, and the dichotomous way in which we measured ADL impairments. Perhaps, a more sensitive scale (i.e. Likert-scale, visual analogue scale or numerical rating scale) would have revealed differences in ADL impairments between baseline and follow-up. Moreover, our BioCAPTURE registry only contains patients with moderate-to-severe psoriasis treated with biologicals/smi, which may hamper external validity in patients with less severe psoriasis.

Strengths of our study are the exploration of different aspects of ADL impairment, identifying home maintenance as one of the most affected areas. Moreover, our study is the first to report changes in work impairment in patients with psoriasis after treatment with biologicals/smi in a non-trial, real-world setting. This setting may make our results more transferable to daily clinical practice.

In conclusion, our BioCAPTURE registry data revealed that Dutch psoriasis patients who are treated with biologicals/smi are less likely to have work-for-pay than the general population. During one year of treatment with biologicals/smi, we saw improvements in presenteeism and overall work impairment. Moreover, we saw a significant relationship between less disease activity and less ADL impairment, suggesting that effective treatment has a positive influence on the daily life of patients. Since patients state that one of their main treatment goals is "to experience less influence of psoriasis on daily activities, such as working, studying or sports"[12], future research should be aimed at unravelling what causes these perceived impairments, with the ultimate goal to diminish them. We suggest that mapping out work and ADL impairments in a cohort with shorter disease duration would be a good starting point for this exploration, where a possible early intervention might have a protective effect against these impairments.

7

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Supplemental table 1: impairments in work and activities of daily life split by successful treatment.

Results were split by treatment success, either defined as a PASI ≤ 3 or continuation of the baseline treatment. Work-for-pay and ADL impairments are presented as absolute numbers. Presenteeism is presented as median with IQR.
Biol=biological, MWU = Mann-Whitney U; IQR = interquartile range; PASI = psoriasis area and severity index

Work-for-pay		6 months				12 months			
		Yes	No	Total	χ^2/ Fisher	Yes	No	Total	χ^2/ Fisher
PASI	≤ 1.0	9	12	21	0.46	12	4	16	**0.03**
	> 1.0	40	34	74		23	32	54	
	Total	49	46	95		35	36	71	
PASI	≤ 3.0	27	25	52	0.94	21	18	39	0.47
	> 3.0	22	21	43		14	17	31	
	Total	49	46	95		35	35	70	
Same Biol	No	5	5	10	1.00	13	15	28	0.53
	Yes	85	74	159		53	46	99	
	Total	90	79	169		66	61	127	

Presenteeism		6 months			12 months		
		Median	IQR	MWU	Median	IQR	MWU
PASI	≤ 1.0	0	0,20	0.91	0	0,10	0.58
	> 1.0	0	0, 20		0	0,21	
PASI	≤ 3.0	0	0, 20	0.29	0	0, 23	0.21
	> 3.0	5	0, 20		0	0, 8	
Same Biol	No	0	0, 8	0.66	0	0, 0	0.11
	Yes	0	0, 15		0	0, 15	

Household chores		6 months				12 months			
		Yes	No	Total	χ^2 / Fisher	Yes	No	Total	χ^2 / Fisher
PASI	≤ 1.0	8	13	21	1.00	4	12	16	0.76
	> 1.0	27	43	70		17	37	54	
	Total	35	56	91		21	49	70	
PASI	≤ 3.0	20	32	52	1.00	14	25	39	0.30
	> 3.0	15	24	39		7	23	30	
	Total	35	56	91		21	48	69	
Same Biol	No	3	5	8	1.00	6	22	28	0.25
	Yes	57	93	150		34	63	97	
	Total	60	98	158		40	85	125	

Grocery shopping		6 months				12 months			
		Yes	No	Total	χ^2 / Fisher	Yes	No	Total	χ^2 / Fisher
PASI	≤ 1.0	8	13	21	0.80	4	12	16	1.00
	> 1.0	24	46	70		15	39	54	
	Total	32	59	91		19	51	70	
PASI	≤ 3.0	18	34	52	0.90	12	27	39	0.59
	> 3.0	14	25	39		7	23	30	
	Total	32	59	91		19	50	69	
Same Biol	No	3	5	8	0.70	6	22	28	0.48
	Yes	45	105	150		29	68	97	
	Total	48	110	158		35	90	125	

Home maintenance		6 months				12 months			
		Yes	No	Total	χ^2 / Fisher	Yes	No	Total	χ^2 / Fisher
PASI	≤ 1.0	10	11	21	1.00	6	10	16	0.78
	> 1.0	33	37	70		24	30	54	
	Total	43	48	91		30	40	70	
PASI	≤ 3.0	25	27	53	0.86	18	21	39	0.61
	> 3.0	18	21	39		12	18	30	
	Total	43	48	91		30	39	69	
Same Biol	No	3	5	8	0.73	12	16	28	0.96
	Yes	70	80	150		41	56	97	
	Total	73	85	158		53	72	125	

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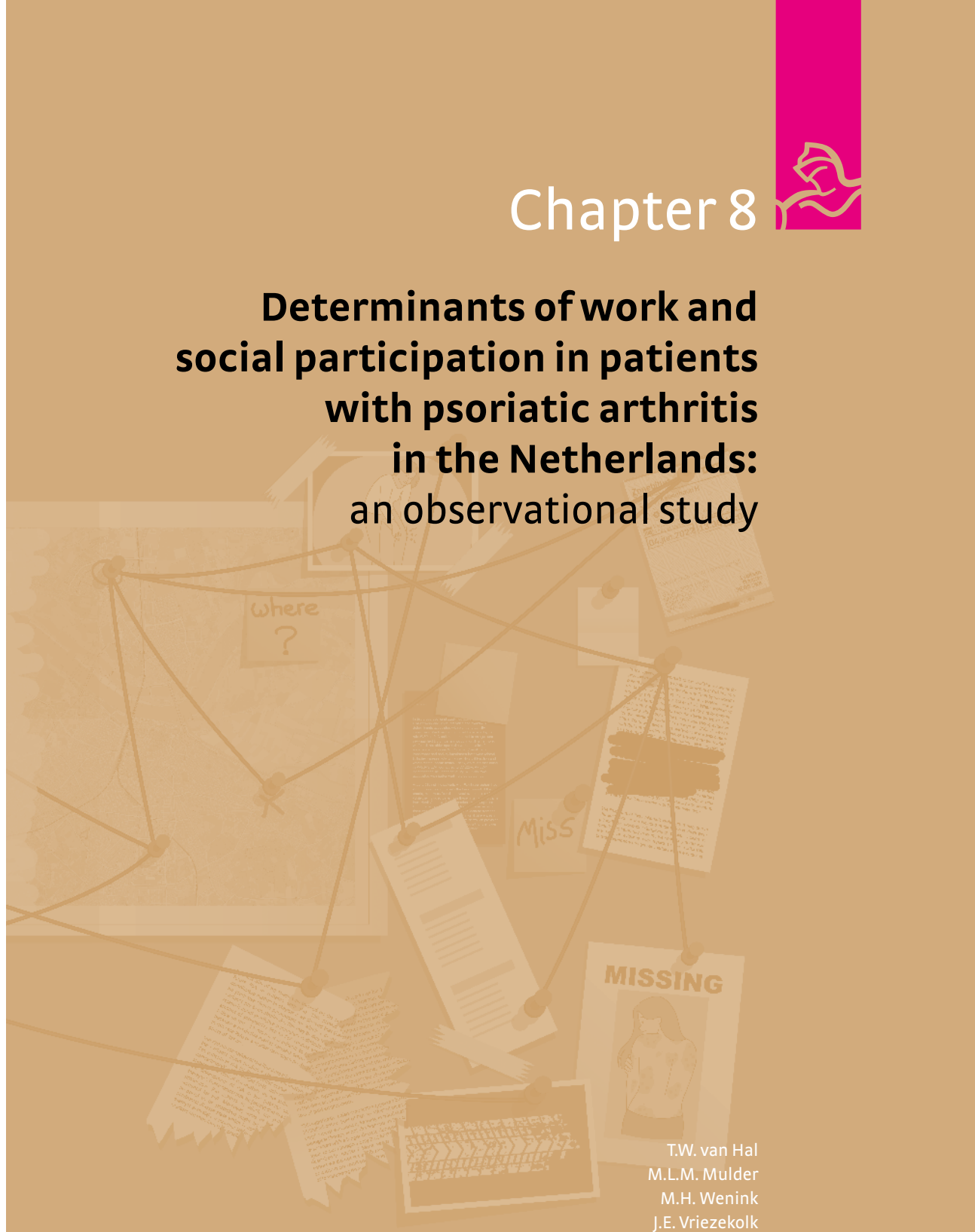
Chapter 8

Determinants of work and social participation in patients with psoriatic arthritis in the Netherlands: an observational study



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Abstract

Background
Psoriatic arthritis (PsA) can cause pain, disability, and permanent joint damage. This can lead to impairments in work and social participation. Little is known about the extent of these impairments in routine practice. With this study, we aim to examine the extent of work and activity impairment in (subgroups of) Dutch patients with PsA, and to examine determinants associated with this impairment.

Methods
This is an observational study using data collected from the electronic health records of PsA patients treated at the Sint Maartenskliniek, the Netherlands. Data about work and activity impairment were collected via the Work Productivity and Activity Impairment questionnaire. To compare our PsA-cohort with the Dutch general population, we used age- and sex-matched data derived from the Central Bureau of Statistics. Regression analyses were performed to examine determinants of work and activity impairment.

Results
In total, 246 patients were included, of which 126 (51.2%) were female. Mean age (S.D.) was 55.7 (13.2) years. Compared with the Dutch general population, work for pay (WFP) was significantly lower in PsA (52.9% versus 62.6%, $P < 0.001$). In PsA, younger age and better physical function were associated with WFP status ($P< 0.05$). Higher disease activity, worse physical function, and worse mental health-related quality of life were associated with both more work and activity impairment ($P< 0.05$). Furthermore, reaching low disease activity status (LDA) according to Psoriatic ArthritiS Disease Activity Score (PASDAS; ≤3.2) was associated with less work and activity impairment than reaching LDA according to DAS28-CRP (≤2.9) ($P< 0.05$).

Conclusions
In PsA patients, worse physical function was associated with a lower likelihood of having WFP, and with higher work and activity impairment. PASDAS LDA as a goal for treat to target, compared to DAS28-CRP, appears to favour the reduction of work and activity impairment.

Background

Psoriatic arthritis (PsA) is an immune-mediated inflammatory disease of joints and entheses, which can lead to pain, disability, and a loss of quality of life (QoL)[1]. All these may culminate in impairments in work, leading to a loss in employment and productivity. PsA patients are less likely to have work-for-pay (WFP) than healthy controls[2]. Even when having WFP, the work impairment caused by PsA is reported to be between 24 and 38 percent of total potential work productivity[3-5]. PsA may also lead to impairment in social activities, which can have a direct impact on social relations, intimacy, and community participation[6]. When identifying which areas of impairment are most important to patients, the "activities and participation" domain is mentioned most often[7]. To thoroughly assess the impact of disease on daily life, for example with the aim of evaluating whether a treatment is cost-effective, a better understanding of the extent of work and social participation and its influencing factors is vital.

Work and social participation are influenced by both disease-related and societal factors. In spondyloarthritis (SpA), a multinational study showed differences in work participation and work impairment between countries, which can be partly explained by economic factors (e.g., health care expenditure), or by cultural differences (e.g., perceived importance of employment)[8]. The effect of disease-related factors on work participation is exemplified by the fact that higher levels of disease activity and disability have been associated with an increase in work impairment, while in clinical trials treatment of active disease led to a decrease in both work and social impairment[9-11]. However, the differences in setting (clinical trial versus real-world, international versus national) make it hard to extrapolate international data to other countries and patient populations. A valid estimation of the societal impact of a disease is, however, crucial when allocating resources for treatment.

The aim of this study was to examine the employment status of PsA patients in a Dutch routine practice cohort, compared with an age- and sex-matched Dutch general population. We also examined the associations of work impairment and activity impairment with patient and disease characteristics. Finally, we examined the association of low disease activity (LDA) status, measured by PsA-specific Psoriatic Arthritis Disease Activity Score (PASDAS) and Disease Activity Score of 28 joints (DAS28-CRP), with work and activity impairment.

Material and methods

Aim of the study
To examine the extent of work and activity impairment in (subgroups of) patients with PsA , and to examine determinants associated with this impairment.

Study design and population
This study describes the baseline data of a longitudinal study, conducted at the department of Rheumatology in the Sint Maartenskliniek in Nijmegen, the Netherlands. Patients with rheumatologist-diagnosed PsA, aged ≥ 18 years, were eligible for this study. Patients were treated according to local protocol, which is based on PASDAS driven treat-to-target (T2T) from March 2019 onwards. Before March 2019, patients were treated according to a DAS28-CRP based protocol[12]. We approached patients by sending them a questionnaire about work and

activity impairment at the moment they were switching from the DAS28-CRP to the PASDAS driven strategy. Only the clinical data of those patients who returned the questionnaire were gathered for further analysis. Data was collected between July 2019 and December 2020.

Data collection

The Work Productivity Activity Impairment: Specific Health Problem (WPAI-SHP) questionnaire was used to collect data about work and activity impairment[13]. With the WPAI-SHP, patient's WFP status, absenteeism (percentage of the time being away from work due to the specific health problem) and presenteeism (percentage of productivity loss while at work due to the specific health problem) and activity impairment (percentage of "productivity" loss during non-work activities due to the specific health problem) are assessed. The work parameters can be combined to estimate overall work impairment as follows:
*Absenteeism + ((1 – absenteeism) * presenteeism)*

The electronic health record of patients with PsA was used to extract data about demographics, treatment, disease activity, functional impairment, and health-related QoL (HR-QoL). Disease activity was measured via DAS28-CRP and/or PASDAS[14]. The PASDAS is a PsA-specific composite disease activity score that consists of a 68 tender joint count, a 66 swollen joint count, a six entheses Leeds enthesitis index (LEI)[15], a twenty digit dactylitis count, and a C-reactive protein (CRP). These are complemented with a visual analogue scale (VAS) of global disease activity by both patient and physician (range: 0 – 100 mm) and the physical summary component score (PCS) of the Short Form 12 (SF-12; range: 0-100). Next to the PCS, the SF-12 also yields a mental summary component score (MCS; range: 0-100)[16]. A higher score in PASDAS defines a higher disease activity. Cut-off points for near-remission and LDA state are 1.9 and 3.2, respectively[17].

To strengthen our analysis of the effect of LDA status on work and activity impairment, we used both the PsA-specific PASDAS and the DAS28-CRP. While this latter composite disease activity score was originally developed for use in rheumatoid arthritis (RA), and despite the fact that a 28 joint based score is not advised for PsA[18], the DAS28-CRP is still often used for PsA[19,20]. A higher score in DAS28-CRP defines a higher disease activity. We used the cut-off points as defined for RA: 2.4 for remission and 2.9 for LDA, respectively[21].

Physical impairment was measured routinely with the Health Assessment Questionnaire-Disability Index (HAQ). This questionnaire evaluates physical disability in eight different domains (dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities). Scores range from zero (no impairment at all) to three (unable to perform a certain task). Although originally developed for RA, the HAQ has been validated for PsA[22].

Statistical analysis

Continuous data were described with the mean (with standard deviation, SD) or median (with interquartile ranges, IQR), when appropriate. Categorical data were described as absolute frequencies and percentages.

To compare our PsA-cohort with the Dutch general population, we used an age- and sex-matched model based on data from the Central Bureau of Statistics (CBS) of the Netherlands[23]. The CBS provided data on WFP status, stratified for sex and age groups (per five years of age). Differences between our PsA-cohort and the general population were tested using a Chi square test.

Using complete cases only, the relationship between WFP and demographics, disease activity, functional impairment, mental component HR-QoL, and therapy modality (no systemic treatment, conventional systemic DMARD (csDMARD) or biological/targeted DMARD (b/tsDMARD)) was investigated with a logistic regression model. WFP status (yes/no) was the dependent variable. The relationships of overall work impairment and activity impairment with demographics, disease activity, functional impairment, HR-QoL and therapy modality were tested with a linear regression model. Overall work impairment or activity impairment were the dependent variables. After univariable regression analyses, independent variables with a $P < 0.157$ (Akaike criterion) were entered in a multivariable regression model using backward stepwise selection.

Differences with respect to WFP/overall work impairment/activity impairment between groups of different disease activity states (i.e. remission/LDA) were tested using Chi square or Mann-Whitney U.

As a sensitivity analysis, we created a dataset where missing data were imputed using multiple imputation with chained equations (MICE); 54 complete data sets were iterated [24]. Imputed variables included: WFP, overall work impairment, activity impairment, absenteeism, presenteeism, PASDAS, DAS28-CRP, PCS, MCS, 28/68 tender joint count, 28/66 swollen joint count, LEI, dactylitis count, patient global VAS, physician global VAS, CRP, and HAQ. All statistical procedures were carried out in STATA v13.0 (StataCorp, USA).

Results

Response rate and patient characteristics

Four hundred sixty patients were approached for this study; 264 patients filled out the WPAI questionnaire (response rate 53.5%). Of these 246 patients, 162 (65.9%) had a valid PASDAS score, 173 (68.1%) had a valid SF-12 score, and 113 (45.9%) had a valid HAQ.

Table 1 shows the demographic and disease characteristics of the study population. Fifty-one percent of the participants was female and mean age was 55.7 years (S.D. 13.2 years). Hundred and sixteen patients (47.5%) used csDMARD only, 94 (38.2%) used b/tsDMARD (with or without csDMARD), whereas 36 patients (14.6%) used no systemic treatment. Mean PASDAS was 3.04 (S.D. 1.40); 54% of patients were in PASDAS LDA (≤3.2). Mean DAS28-CRP was 2.17 (S.D. 0.93); 80% were in DAS28CRP LDA (≤2.9).

Work for pay, overall work impairment, and activity impairment

Table 2 shows the WFP status and degree of overall work impairment and activity impairment in our PsA-cohort. 52.9% of the patients with PsA (N=130) had WFP, compared to 62.6% in the age- and sex-matched model of the general population ($P < 0.001$). In patients who had WFP, median absenteeism, presenteeism, and overall work impairment were 0% (IQR 0%-0%), 20% (IQR 0%-40%), and 10% (IQR 0%-40%), respectively. Activity impairment for the whole sample (N=246) was 30% (IQR 10%-60%).

Table 1: Patient and disease characteristics of PART2-cohort

Age (years)		55.7 (13.2)
Female - N (%)		126 (51.2%)
PASDAS[a]	Mean	3.04 (1.40)
	LDA (≤3.2) – N (%)	87 (53.7%)
	Remission (≤1.9) – N(%)	37 (22.7%)
DAS28-CRP	Mean	2.17 (0.93)
	LDA (2.9) – N (%)	183 (79.9%)
	Remission (2.4) – N (%)	159 (69.4%)
SJC68 - N (%)	0	169 (68.7%)
	1-4	60 (24.4%)
	5 or more	12 (5.3%)
TJC68 – N (%)	0	117 (47.6%)
	1-4	79 (32.1%)
	5 or more	45 (18.3%)
LEI – N (%)	0	185 (75.2%)
	1	22 (8.9%)
	2 or more	22 (8.9%)
Active dactylitis – N (%)		5 (2.0%)
Global VAS	Physician	14.4 (15.3)
	Patient	31.6 (23.5)
CRP		3.76 (8.6)
SF12	PCS[b]	41.6 (10.2)
	MCS[b]	49.1 (10.6)
HAQ[c]		0.63 (0.6)
DMARD use – N (%)	None	36 (14.6%)
	csDMARD	116 (47.5 %)
	b/tsDMARD	94 (38.2%)

All in mean (SD), unless stated otherwise. Variables with >10% missing are marked:
a PASDAS was known in 162 patients
b SF12 was known in 173 patients
c HAQ was known in 113 patients
b/ts DMARD = biological / targeted systemic DMARD; CRP = C-reactive Protein; csDMARD = conventional systemic DMARD; DAS28-CRP = Disease Activity Score of 28 joints using CRP; DMARD = disease modifying antirheumatic drug; HAQ = Health Assessment Questionnaire Disability Index; MCS = Mental summary Component Score; PASDAS = Psoriatic ArthritiS Disease Activity Score; PCS = Physical summary Component Score; SF12 = Short Form-12; SJC66 = Swollen Joint Count of 68 joints ; TJC68 = Tender Joint Count of 66 joints; VAS = Visual Analog Scale

Associations between work / activity impairment and patient / disease characteristics

Table 3 shows the results of both univariable and multivariable regression analyses, of the associations between WFP/impairment, and both patient and disease characteristics.

Work for pay

Univariable logistic regression analyses showed significant associations between a positive WFP status and younger age (OR= 0.91, $P < 0.001$), lower PASDAS (OR= 0.57, $P < 0.001$), and lower HAQ scores (OR=0.32, $P < 0.001$). In the multivariable model, only age (OR=0.89, $P < 0.001$) and HAQ (OR=0.22, $P= 0.001$) remained significant, explaining 34% of the variance.

Overall work impairment

Univariable linear regression analyses showed significant associations between higher overall work impairment and female sex ($B= 16.1$, $P = 0.002$), higher PASDAS ($B = 15.7$, $P < 0.001$), lower MCS ($B= - 1.4$, $P < 0.001$), and higher HAQ ($B= 25.1$, $P < 0.001$). In the multivariable model, the associations between overall work impairment and PASDAS (β= 0.32, $P = 0.014$), HAQ (β= 0.46, $P < 0.001$), and MCS (β= -0.24, $P= 0.04$) remained significant, explaining 61% of the variance.

Activity impairment

Univariable linear regression analyses showed significant associations between higher activity impairment and female sex ($B= 12.8$, $P < 0.001$), higher PASDAS ($B= 14.3$, $P < 0.001$), lower MCS ($B= -1.3$, $P < 0.001$), and higher HAQ ($B= 25.8$, $P < 0.001$). In the multivariable model, the associations between activity impairment and PASDAS (β= 0.35, $P < 0.001$), MCS (β= -0.17, $P = 0.03$), and HAQ (β= 0.45, $P < 0.001$) remained significant, explaining 61% of the variance.

Sensitivity analyses with imputed data set

Supplementary table 1 shows the results of univariable and multivariable regression analyses using the imputed data set. These results are in line with the complete case analyses, with the following differences. For WFP, in the multivariable model, HAQ was no longer associated with WFP. Instead, a lower PASDAS showed a significant relationship with a positive WFP status (OR= 0.59, $P < 0.001$). Moreover, the multivariable model showed an additional significant association of a higher activity impairment with female sex ($B= 5.2$, $P= 0.04$).

Differences in work and activity impairment between patients in low disease activity according to either PASDAS or DAS28-CRP

Supplementary table 2 shows the number and frequency of patients by disease activity status (LDA or remission). Of the 163 patients with valid PASDAS scores, 129 (79%) were in LDA according to DAS28-CRP (≤2.9), and 88 (54%) were in LDA according to PASDAS (≤3.2). Forty three patients (26%) were in LDA according to DAS28-CRP, but not according to PASDAS.

Table 4 and figure 1 show WFP, overall work and activity impairment of patients in LDA according to either PASDAS or DAS28-CRP. Subgroup analyses between patients in PASDAS LDA (N= 88) and patients in DAS28-CRP LDA (N= 129) showed that patients in PASDAS LDA were more likely to have WFP than patients in DAS28-CRP LDA (respectively 63% and 54%). In patients who had WFP, median overall work impairment did not differ between the patients in PASDAS LDA or DAS28-CRP LDA (i.e. 10% in both groups). Median activity impairment was lower in patients in PASDAS LDA compared to patients in DAS28-CRP LDA (20% versus 30%).

Table 2: Percentage employment and impairment in PART2-cohort

Work for pay – N (%)		**130 (52.9%)**
Absenteeism	when working	0% (0%-0%)
Presenteeism	when working	20% (0%-40%)
Overall work impairment	when working	10% (0%-40%)
Activity impairment	all participants	30% (10%-60%)

All in median (IQR), unless stated otherwise.

Table 3: Determinants associated with work for pay, overall work impairment and activity impairment

	Low disease activity			(Near) Remission		
	DAS28-CRP (all) N = 127	DAS28-CRP (not in PASDAS) N = 42	PASDAS N = 87	DAS28-CRP (all) N = 108	DAS28-CRP (not in PASDAS) N=71	PASDAS N = 37
Work for pay	106 (54.3%)	15* (35.8%)	55 (63.2%)	61 (56.5%)	36 (50.7%)	25 (67.6%)
Overall work impairment	10% (0%, 30%)	35%* (20%, 70%)	10% (0%, 20%)	10% (0%, 30%)	20%* (10, 40%)	0% (0%, 10%)
Activity impairment	30% (10%, 50%)	50%* (30%, 70%)	20% (0%, 30%)	20% (0%, 50%)	30%* (20%, 60%)	0% (0%, 20%)

Associations between work for pay and independent variables were studied using logistic regression. Associations between overall work impairment/activity impairment and independent variables were studied using linear regression. Number of patients included in the multivariable model is shown above the table. Regression coefficients with 95% confidence intervals are shown, unless stated otherwise.
b/tsDMARD = biological / targeted synthetic DMARD; DMARD = Disease Modifying Anti Rheumatic Drug; HAQ = Health Assessment Questionnaire Disability Index; MCS = Mental summary Component Score; PASDAS = Psoriatic ArthritiS Disease Activity Score
* P = < 0.05

Further subgroup analyses showed that patients who were in DAS28-CRP LDA, but not in PASDAS LDA (N=43), were less likely to have WFP than patients who were also in PASDAS LDA (N=86): 34% versus 63%, *P*= 0.02. Patients who were in DAS28-CRP LDA, but not in PASDAS LDA, showed more overall work impairment (20% versus 0%, *P* < 0.001) and more activity impairment (30% versus 0%, *P* < 0.01) than patients who were also in PASDAS LDA.

Table 4 shows WFP, overall work impairment, and activity impairment of patients in (near)-remission according to either PASDAS or DAS28-CRP. Comparable results were found.

Discussion

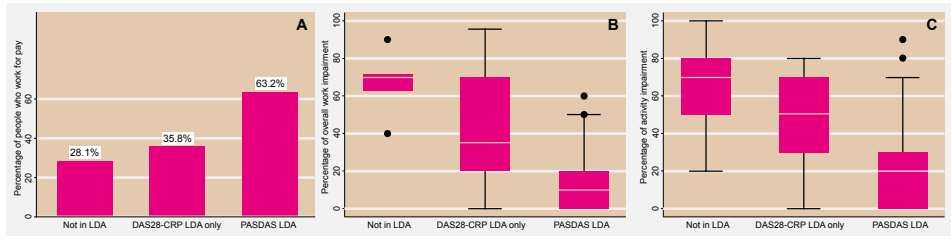
In this cross-sectional study, we explored the impact of PsA on work and social activities and examined determinants associated with work and activity impairment. We found a significant lower employment rate (WFP) in PsA patients compared to an age- and sex-matched Dutch general population. Furthermore, we found that older age and a worse physical function were related to poorer WFP status. Overall work impairment and activity impairment both were related to higher disease activity, worse physical function and worse mental health status. Lastly, we found that being in PASDAS LDA (compared to DAS28-CRP LDA) increased the

Table 4: Proportion of patients with work for pay, work impairment and activity impairment by low disease activity and remission statu

	Low disease activity			(Near) Remission		
	DAS28-CRP (all) N = 127	DAS28-CRP (not in PASDAS) N = 42	PASDAS N = 87	DAS28-CRP (all) N = 108	DAS28-CRP (not in PASDAS) N=71	PASDAS N = 37
Work for pay	106 (54.3%)	15* (35.8%)	55 (63.2%)	61 (56.5%)	36 (50.7%)	25 (67.6%)
Overall work impairment	10% (0%, 30%)	35%* (20%, 70%)	10% (0%, 20%)	10% (0%, 30%)	20%* (10, 40%)	0% (0%, 10%)
Activity impairment	30% (10%, 50%)	50%* (30%, 70%)	20% (0%, 30%)	20% (0%, 50%)	30%* (20%, 60%)	0% (0%, 20%)

Work for pay is expressed in N (%). Overall work impairment and activity impairment are expressed in median (IQR). Outcomes of patient in DAS28-CRP LDA/remission (but not in PASDAS LDA/remission) were tested against outcomes of patients in PASDAS LDA/remission using either Chi-square or Mann Whitney U.
CRP = C-reactive protein; DAS28-CRP = Disease Activity Score of 28 joints using CRP; LDA = Low Disease Activity; PASDAS

Figure 1: Work for pay, overall work impairment and activity impairment by disease activity status.



A Work for pay
B Work impairment
C Activity impairment
Work for pay in N (%). Overall work impairment and activity impairment in median (IQR). Overall work impairment only described in patient who have work for pay.
CRP = C-reactive protein; DAS28-CRP = Disease Activity Score of 28 joints using CRP; PASDAS = Psoriatic ArthritiS Disease Activity Score

likelihood of having WFP, and was associated with better work-related outcomes.

Around 53% of the patients with PsA in our cohort had WFP; this corresponds with the lower bound of the employment rates found in several systematic reviews[25-27]. While the included patients in these latter reviews came from North America, South America, and Europe, no Dutch patients were included. Also, in these reviews there was a predominance of clinical centers from the United States and Canada. International differences in both the accessibility of health care as well as provision of unemployment benefits could account for the lower amount of patients with WFP in our cohort. Dutch employers are obliged to provide paid

sick leave for up to two years, after which there is a possibility to apply for social disability benefits. An absence of paid sick leave or social disability benefits could urge employees to keep working while sick. Also, the Dutch sociopolitical system provides access to reimbursed healthcare via mandatory health care insurance. With this insurance, a wide range of effective DMARD's is accessible to all citizens. This access to effective treatments may lead to better disease control, and therefore to less loss of work force or less work impairment. Noteworthy, the employment rates found in our PsA-cohort was also lower than another Dutch cohort of patients with early PsA (mean symptom duration 1.0 years, employment rate 74%)[28]. Given that our routine practice cohort comprises PsA patients with various disease duration, this suggests that a longer disease duration could negatively affect the likelihood of having WFP. Unfortunately, we were not able to explore the relationship between disease duration and WPF, as disease duration data were not available for our study.

In both multivariable models, over 60% of work and activity impairment was explained by the combined effects of higher disease activity, worse mental HR-QoL, and worse physical function. This suggests that these determinants are highly relevant factors to decrease the societal burden of PsA. First, with respect to disease activity, the association between work impairment and a higher disease activity in this routine care cohort is in line with the results of previous clinical trials. When compared with placebo, treatment with tumor necrosis alpha inhibitors or ixekizumab either improved work productivity or lowered overall work impairment[11,29,30]. This would even support a causal relationship between disease activity and work impairment. However, in contrast to previous studies, we did not find an association between therapy modality and work impairment[28,31]. In contrast to our study, the study of Tillett et al.[31] showed a large difference in disease activity between patients who were treated with csDMARD or bDMARD. Given that disease activity was related to work and activity impairment in our cohort, while therapy modality was not, this may indicate that a stringent disease control is key to preventing impairment (either in work or non-work activities), regardless of the way this disease control is achieved.

Second, a worse mental HR-QoL was robustly associated with both work and activity impairment. To our knowledge, this association has not been reported before. With this current design, we cannot infer a causal relationship between mental well-being and impairment. Given that mental HR-QoL remained significant in the multivariable model together with disease activity and physical function, this indicates that the relationship is independent of disease activity and functional impairment. Longitudinal and interventional data are needed to determine the directionality of the relationship between mental HR-QoL and work and social impairment.

Third, a worse physical function was also associated with both work and activity impairment. This finding is consistent with a study of Tillett et al[11]. In fact, this study even used the HAQ as an anchor to find the minimal clinical important difference of the WPAI:SPH in PsA. While our analyses cannot infer a causal relationship, it is tempting to speculate that a worse physical function leads to more impairment in both work and non-work activities.

Last, we found that being in PASDAS LDA (compared to DAS28-CRP LDA) increases the likelihood of having WFP, and is associated with lower overall work impairment and activity impairment. We previously reported that the PsA-specific PASDAS revealed residual inflammation when compared to the DAS28-CRP[32]. In line with these findings, we observed more WFP and less work and activity impairment when employing the LDA criteria of the PASDAS instead of the DAS28-CRP. All these results may indicate that T2T using PsA-specific targets may lead to better disease control, and thus less impairment.

A major strength of our study is the study setting. The PsA-cohort of the Sint Maartenskliniek is a real world cohort, which facilitates extrapolation of our results to real world cohorts in other out-patient clinics. Our cohort is treated following a PASDAS-driven T2T strategy, which entails that on every visit we collect data about disease activity and QoL[12]. However, this real world outpatient setting (in contrast to a dedicated study setting such as a randomized controlled trial) also means that parameters not essential to the primary treatment goal may be missing more often.

One limitation of our study was indeed a substantial amount of missing data, mostly regarding the SF-12 or the HAQ questionnaires. To examine whether this may have led to biased results, we conducted sensitivity analyses with an imputed data set. For WFP, the multivariable analysis using the original data set with only complete cases showed a significant association between having WFP and a higher HAQ, but not with PASDAS. The multivariable analysis using the imputed data set showed a significant association between having WFP and a lower PASDAS, but not with HAQ. In our opinion, there is an interplay between WFP on the one hand and disease activity/physical function on the other hand. Our study design, however, limits inferences about the directionality of these relationships.

Regarding activity impairment, the imputed multivariable model showed an additional association with female sex. Earlier research by our group showed significant differences between men and women in disease activity scores[33]. Further research is needed to explore whether the association between activity impairment and female sex is a true association or a spurious relationship, when in reality the differences in activity impairment are related to the differences in disease activity between the sexes.

Another limitation is the possibility of responder bias. Privacy regulations limited us in gathering data about the non-responders. However, we compared the patient and disease characteristics of our responders with previously published data about the PsA cohort in our clinic[32]. Our subset of this population showed a slight overrepresentation of women (51% in our study versus 46% in the study of Mulder et al.), but comparable PASDAS and HAQ scores, and use of DMARD'S, making it conceivable that our results are valid.

Taking together, our study findings imply that PsA has an impact on those aspects of life that patients hold most dearly[7]. We showed robust relationships between work and activity impairment, and disease activity. Also, we showed that reaching LDA by definition of the PsA-specific PASDAS (in comparison to the widely-used, but not PsA-specific DAS28-CRP) is associated with a higher likelihood of being employed, and less work and activity impairment. Therefore, it is conceivable that stringent T2T with a PsA-specific disease activity score may improve patients' ability to perform both work and non-work activities. Supported by the results of Wervers et al[28], we suggest that early achievement of LDA may prevent loss of employment.

Conclusions

Our study revealed that approximately 53% of patients in our routine practice PsA-cohort were employed. Higher disease activity, worse physical function, and mental wellbeing independently contributed to work and activity impairment. Furthermore, patients with a PASDAS LDA status reported less impairment in work and social activities than patients with a DAS28-CRP LDA status. Whether a T2T approach with a PsA-specific disease activity score has a positive effect on work and activity impairment remains to be investigated.

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Supplementary table 1: Determinants associated with work for pay, overall work impairment and activity impairment using the imputed data set

	Work for pay (n=243)		Overall work impairment (n=130)		Activity impairment (n=246)	
	Univariable (OR)	Multivariable (OR)	Univariable	Multivariable	Univariable	Multivariable
Age	0.91 (0.89, 0.94)	0.91* (0.89, 0.94)	- 0.19 (- 0.67, 0.28)		0.10 (- 0.16, 0.37)	
Female sex	0.85 (0.52, 1.42)		17.31* (6.94, 27.68)		12.92* (6.22, 19.62)	5.12* (0.10, 10.14)
PASDAS	0.62* (0.50, 0.77)	0.59* (0.46, 0.75)	15.56* (11.78, 19.34)	8.36* (3.54, 13.18)	13.61* (11.59, 15.63)	8.07* (5.53, 10.61)
MCS	1.01 (0.98, 1.04)		- 1.40* (- 1.95, - 0.86)	- 0.86* (- 1.39, - 0.34)	- 1.14* (- 1.48, - 0.80)	- 0.59* (- 0.91, - 0.26)
HAQ	0.48* (0.29, 0.80)		25.72* (16.36, 35.07)	15.50* (6.16, 24.84)	23.69* (17.91, 29.48)	14.15* (8.93, 19.37)
No DMARD	0.69 (0.34, 1.42)		2.26 (- 14.26, 18.78)		6.65 (- 3.09, 16.40)	
bDMARD	1.21 (0.72, 2.03)		- 1.82 (- 12.83, 9.19)		- 0.77 (- 7.86, 6.32)	

Associations between work for pay and independent variables were studied using logistic regression. Associations between overall work impairment/activity impairment and independent variables were studied using linear regression. Number of patients included in the multivariable model is shown above the table. Regression coefficients with 95% confidence intervals are shown.
b/tsDMARD = biological / targeted synthetic DMARD; DMARD = Disease Modifying Anti Rheumatic Drug; HAQ = Health Assessment Questionnaire Disability Index; MCS = Mental summary Component Score; PASDAS = Psoriatic ArthritiS Disease Activity Score
* P = < 0.05

Supplementary table 2: patients split by LDA and remission status

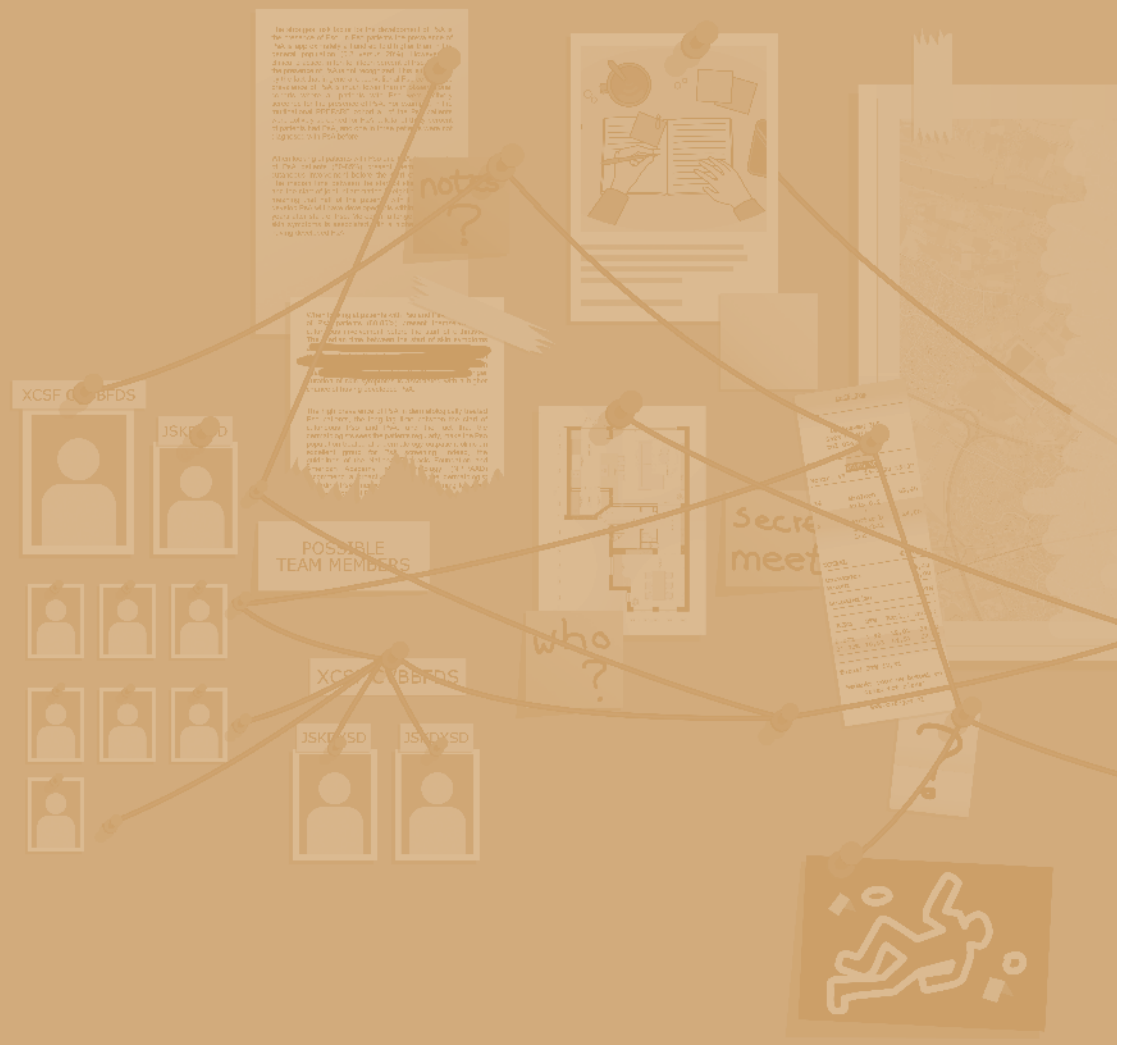
		PASDAS LDA	
		No	Yes
DAS28-CRP LDA	No	32 (19.6%)	2 (1.2%)
	Yes	43 (26.4%)	86 (52.8%)

		PASDAS Near-remission	
		No	Yes
DAS28-CRP Remission	No	53 (32.5%)	0 (0%)
	Yes	72 (44.2%)	38 (23.3%)

CRP = C-reactive protein; DAS28-CRP = Disease Activity Score of 28 joints using CRP; LDA = Low Disease Activity; PASDAS = Psoriatic ArthritiS Disease Activity Score

Chapter 9

Summary and general discussion



Summary of this thesis

Psoriasis (Pso) and psoriatic arthritis (PsA) are both presentations of psoriatic disease, and represent immune-mediated inflammatory diseases of predominantly skin and nails, and joints and entheses, respectively. Both are chronic diseases, characterized by a large inter- and intra-individual variation in course and presentation.

Pso is characterized by erythrosquamous plaques, which can lead to physical (pain, itching) and psychological (stigma, shame) problems for the patients. PsA is characterized by an asymmetrical oligo- to polyarthritis and enthesitis, which can lead to irreparable joint damage and loss of function. One in three Pso patients will develop PsA. Guidelines recommend an active approach of the dermatologist towards PsA, but currently used screening methods leave room for improvement. Moreover, these screening methods are not always routinely used in clinical practice.

Pso and PsA share a common immunological background (the interleukin (IL) 23- IL17 pathway), and common therapeutical options (systemic immune modulation). These therapeutical options can be divided into three classes, in rising potency: topical medications (creams, UV therapy or local injections), conventional systems drugs (immune-modulating drugs targeting the immune system as a whole), and biologicals/small molecule inhibitors (smi; immune-modulating drugs targeting a specific protein in the immune cascade). The latter two are used in the form of pills, injections or intravenously, and are also known as systemic medication (in contrast to topical, local medication).

Although the last two decades have shown an enormous rise in therapeutic options, and although current treatment strives to minimize disease activity, many patients with Pso and PsA still experience impairment in their activities at work or in daily life. This is particularly important since Pso and PsA can start early in life, and can be disruptive in career and family planning.

In this thesis, we aimed to research how to diminish the burden of disease for patients with Pso and PsA, by determining the following aims for our studies:

1. To determine (clinical) characteristics useful to predict future PsA in Pso patients treated at a dermatology outpatient clinic
2. To determine (clinical) characteristics useful to identify concomitant, current PsA in Pso patients treated at the dermatology outpatient clinic
3. To determine the impact of Pso and PsA on patients' work and activities of daily life

Chapters 2 and 3 focus on the first aim: to determine (clinical) characteristics useful to predict future PsA in Pso patients treated at the dermatology outpatient clinic.

Chapter 2 describes the results of a systematic literature review of the clinical, laboratory, and genetic markers for the development or presence of PsA in patients with Pso. We conducted a systematic search for studies assessing markers (clinical, laboratory, genetic) associated with the development or presence of PsA in patients with Pso. We performed a best evidence synthesis to determine the level of evidence for a marker and its association with the development or presence of PsA. Overall, 119 studies were selected, yielding a total

of 259 possible markers. The only marker with a strong level of evidence for association with the future development of PsA was the laboratory marker CXCL10. Moreover, four laboratory markers related to inflammation and bone metabolism reached a strong level of evidence for association with the current presence of PsA in patients with Pso. No clinical or genetic marker reached a strong level of evidence for association with the development or presence of PsA.

Chapter 3 describes the results of a study investigating the prevalence, incidence and risk factors for the development of PsA in patients from the BioCAPTURE cohort. The BioCAPTURE cohort is a multicenter prospective registry of patients with moderate to severe plaque Pso, who use biologicals/smi. We assessed the prevalence and incidence of PsA in these patients, and the predictive value of demographic and clinical characteristics for the development of PsA. In this cohort of 427 patients, 117 patients had rheumatologist-confirmed PsA (27%). The incidence of PsA was 1.0 per 100 psoriasis years. Except for a lower risk for PsA in males, no clinical factors were significantly associated with an altered risk of developing PsA. During biologic therapy, 32 patients (9.4%) newly developed PsA. In conclusion, clinical risk factors might be insufficient to predict PsA onset in patients with moderate-to-severe psoriasis on biologics. Even with low disease activity of the skin, psoriasis patients on biologics are still prone to develop PsA.

Chapters 4, 5 and 6 focus on the second aim: to determine (clinical) characteristics useful to identify concomitant, current PsA in Pso patients treated at the dermatology outpatient clinic. These chapters describe the results of the prospective, cross-sectional study investigating the prevalence and predicting factors for concomitant PsA in patients with Pso in the dermatology outpatient clinic: Discovery of Arthritis in Psoriasis Patients for Early Rheumatological Referral (DAPPER).

Chapter 4 describes the DAPPER study protocol. We aimed to include 300 patients with Pso who were treated at the dermatology outpatient clinic of the Radboudumc. Patients with known concomitant PsA were not excluded. All patients were screened extensively for signs and symptoms of PsA by a trained rheumatologist. During this screening visit, patient and disease characteristics (e.g. comorbidity, treatment history, joint complaints) were collected, which were later used to develop a new screening instrument. If there was clinical suspicion of untreated PsA, the patient was referred to the rheumatology department for confirmation of diagnosis and further care. After one year, data on changes in quality of life (QoL) and disease activity were gathered from the referred patients, to evaluate the effect of referral.

Chapter 5 describes the DAPPER study population, the prevalence of PsA in this cohort, and the one-year follow-up of referred patients. The total prevalence of PsA in this observational, prospective cohort (n=303) was 24%. Prevalence was higher in patients who received more intense treatment for their Pso: 12% in patients who used topicals only, 18% in patients who used conventional systemic drugs but not biologicals/smi, and 44% in patients who used biologicals/smi. Moreover, Pso patients with concomitant PsA had longer skin disease duration. In this academic, specialized setting, we detected 7 patients (2.3 percent) who were not receiving rheumatological care despite having active PsA. These patients were characterized by a combination of low (perceived) disease burden and a low sensitivity of existing screening questionnaires, making it hard for the dermatologist to discover PsA in these patients.

Chapter 6 describes the development of a referral tool identifying patients with Pso with concomitant PsA, based on the results of the DAPPER study. Using multivariable regression analyses, we identified five predictive variables for the presence of concomitant PsA in patients with Pso at the dermatology outpatient clinic: treatment history with conventional systemic drugs, treatment history with biologicals/smi, patient-reported history of joint pain not caused by trauma, patient-reported history of swollen joints, and patients-reported history of sausage-like swollen fingers. With these variables in mind, we created a four-point checklist which can aid the dermatologist in selecting those patients who may benefit from referral to a rheumatologist. When using a cut-off of three or higher, this referral tool has a sensitivity of 79% and a specificity of 69%.

Chapters 7 and 8 focus on the third aim: To determine the impact of Pso and PsA on patients' work and activities of daily life.

Chapter 7 describes the results of a study investigating the impairments in work and activities of daily life (ADL) experienced by patients with Pso from the BioCAPTURE cohort. In patients who started a biological/smi, we assessed patient, disease and treatment characteristics, as well as work/ADL impairments at baseline, six and twelve months after start. In this cohort of 194 patients, disease activity improved significantly after initiation of biological/smi. Work-for-pay was significantly lower in the psoriasis cohort than in the Dutch general population (53% versus 67%). In patients who had work-for-pay, presenteeism improved over time. Up to half of the patients reported impairment in ADL, which did not change over time. Associations between work/ADL impairment and contextual factors varied, but all impairments were associated with worse mental and physical general functioning.

Chapter 8 describes the results of a cross-sectional observational study investigating the impairments in work and non-work activities experienced by patients with PsA receiving regular treatment. This study used data from the electronic health record and questionnaires of PsA patients treated at a rheumatology outpatient clinic at the Sint Maartenskliniek. In this cohort of 246 patients, we saw that work-for-pay was significantly lower in the PsA cohort than in the Dutch general population (53% versus 63%). Younger age and better physical functioning were associated with work-for-pay status. Higher disease activity, worse physical functioning, and worse mental functioning were associated with both more work and activity impairment. Furthermore, reaching low disease activity status (LDA) according to Psoriatic ArthritiS Disease Activity Score (a PsA specific disease activity score) was associated with less work and activity impairment than reaching LDA according to DAS28-CRP, a disease activity score developed for rheumatoid arthritis (RA). In conclusion, in PsA patients worse physical function was associated with a lower likelihood of having work-for-pay, and with higher work and activity impairment.

Finally, this chapter, **chapter 9**, describes a summary of the studies forming the body of this thesis and extrapolates from these studies the main overlapping findings, limitations, and future perspectives for Pso/PsA research and care.

9

Main finding 1:

To investigate the prediction of future PsA or the detection of current, concomitant PsA in patients with Pso (aim 1 and 2), we first need to establish the prevalence of PsA in patients with Pso. In chapter 5, we found that the prevalence of PsA in patients with Pso attending a dermatology outpatient clinic was approximately 25%, i.e. one in four patients. The prevalence of PsA was higher in groups with more potent treatment for Pso[1,2]. However, this does not mean more potent treatment is a cause of PsA.

To investigate the prevalence of PsA in patients with Pso, I performed the DAPPER study. As explained in chapter 4, all patients from our DAPPER study were screened by a rheumatologist for the presence of PsA. This was done by chart review, structured interview, and physical examination[3]. In chapter 5 I describe that this cohort showed an overall prevalence of PsA of 24%. Interestingly, the prevalence increased as the treatment potency increased: it was lowest in patients using topical therapy only, and highest in patients using biologicals/smi[1]. Moreover, in chapter 6 we use this data to develop a referral tool. In this process, I discovered that the use of systemic anti-psoriatic treatment was an independent predicting factor for the presence of PsA[2].

Prevalence of PsA in other Pso cohorts

The prevalence of PsA in our cohort is somewhat higher than the 20% described in the systematic literature review of Alinaghi et al[4]. This can be explained by differences in methodology and population. Our cohort describes an actively screened population of Pso patients in a Dutch academic hospital setting. Meanwhile, the studies used for the analysis of Alinaghi are performed worldwide, in both general practices as well as dermatology clinics, and describe both actively screened cohorts as well as routine care (not actively screened) cohorts.

First, the prevalence of PsA is higher in Europe when compared to Asia/Africa, probably due to genetic differences[5]. Therefore, a worldwide pooled prevalence will be lower than the prevalence in a Western European (Dutch) cohort. Second, the prevalence in a hospital setting is higher than in the general population[6], again leading to a lower prevalence in a study where patients from general practices and hospitals are pooled. Third, the active screening of our cohort may yield a higher prevalence of PsA: if you don't look for it, you don't find it. Indeed, several studies have shown that without active screening, a significant part of PsA will be undiscovered[7,8].

Prevalence of PsA is higher in patients with Pso using systemic therapy

In chapter 5, I show that more potent treatment (i.e., biologicals) is associated with a higher chance of presence of concomitant PsA[1]. However, especially in this case, association must not be confused with causation. In fact, the association between systemic treatment and the presence of PsA might be due to the fact that the risk factor "systemic treatment" combines several other risk factors.

First, a more potent treatment of Pso is indicated when the psoriasis is more severe, i.e. when there is higher disease activity. Indeed, several studies show that the prevalence of concomitant PsA is higher in groups with higher disease activity of the skin[9-11]. Second, patients with Pso are usually treated in a step-up strategy, meaning that more potent therapy is usually associated with longer disease duration[12]. Because the incidence of PsA per year of disease duration of Pso remains equal over the years[10], patients with a longer disease duration have a higher chance of having developed PsA[13,14]. Third, dermatologists might be more inclined to prescribe systemic medication to patients they already suspect of having PsA: a one-shot-treats-all tactic that has been discussed in literature[15]. This leads to confounding by indication[16].

Possible protective effect of biologicals on development of PsA

While the *prevalence* of PsA may be higher in patients with Pso who use biologicals, there are some observational studies suggesting that the *incidence* might be lower[17-19]. First, using an insurance database, Rosenthal et al found that Pso patients using biologicals had a lower incidence than Pso patients using conventional systemic drugs (11% during 10 years follow-up for patients using biologicals versus 16% during 10 years follow-up for patients using conventional systemic drugs)[17]. These results remained robust after propensity score matching for several known risk factors for PsA (e.g. age, sex, BMI, smoking).

Second, using a case-control approach, Acosta Felquer et al also found that the incidence rate of PsA in Pso patients was lower in patients using biologicals than in patients using other treatment modalities[18]. Moreover, they found a dose-effect relationship, showing that a more potent treatment for Pso is associated with a lower incidence of PsA: the incidence rate in patients using topical therapy was 1.67 per 100 patient-years, in patients using conventional systemic drugs 0.81 per 100 patient/years, and in patients using biologicals 0.55 per 100 patient-years. Results remained significant after adjustment for sex, BMI and psoriatic nail involvement.

Third, the retrospective non-randomized study described by Gisondi et al reports a lower annual incidence rate of PsA in patients using biologicals versus patients using UVB therapy (1.20 per 100 patients/year versus 2.17 per 100 patients/year)[19]. However, the results might be biased by baseline dissimilarities between the groups, since the difference in incidence rate was non-significant when using propensity score matching for baseline skin disease activity.

Contradictory to these studies suggesting a protective effect of conventional systemic drugs/biologicals for the development of PsA, the retrospective cohort study of Meer et al reports an opposite dose-response effect of treatment potency and PsA[20]. In this study, the incidence rate of PsA was 0.59 per 100 patient-years for patients using no therapy, 6.20 per 100 patient-years for patients using conventional systemic drugs, and 7.73 per 100 patient-years for patients using biologicals. These results remained significant after adjustment and propensity score matching for age, sex, comorbidity and BMI.

The different results of these studies could be explained by the nature of their design. In these retrospective cohorts, the two compared groups (biologicals versus other treatment modalities) were not comparable at baseline. First, patients using biologicals tend to have a more severe skin disease. Second, they also tend to have a longer follow-up time. Moreover, when applying propensity score matching, a significant part of the cohort may fall out of the analysis (having no match). This is even more important when the amount of events is low, as was the case in these cohorts. Last, propensity score matching cannot account for unmeasured biases, such as confounding by indication[16].

In conclusion, in chapter 5 and 6 we show that a more potent treatment for Pso (i.e. systemic drugs) is associated with a higher prevalence of PsA[1,2]. This finding might be explained by the fact that more potent treatment is associated with a more severe skin disease, a longer disease duration, and a higher arthritis awareness of physician and patient (confounding by indication). Moreover, retrospective observational studies suggest that treatment with biologicals might even lower the incidence of PsA. A prospective study investigating the effect of treatment of Pso on PsA prevalence is necessary to clarify the relationship between systemic treatment and the incidence of PsA.

Main finding 2:

The first aim of my thesis was focused on the prediction of future PsA in patients with Pso. This proved to be a complicated matter: in chapter 2 we showed that there were no predictive clinical parameters for which a strong level of evidence has been obtained[21]. This may be due to the fact that research about predictive parameters is difficult due to a low amount of prospective Pso to PsA cohorts with a sufficient follow-up time. Moreover, it is difficult to make a distinction between a predictive marker (present before start of disease, in this case PsA) or a marker denoting a prodromal, subclinical phase of disease.

Our systematic review of the literature (chapter 2) showed that the evidence about predictive clinical parameters to identify Pso patients at risk for PsA is either scarce, of low quality, or contradictory[21]. The BioCAPTURE cohort (chapter 3) also showed that clinical parameters are not sufficient to predict the development of PsA in Pso patients using biological therapy[22]. These results may be (partly) due to a low amount of prospective Pso cohorts in which are patients regularly screened for PsA. Moreover, some of the clinical markers proposed to be predictive might be more indicative of a prodromal disease state which is not yet full blown PsA, for example arthralgia or morning stiffness. It is debatable if these markers are therefore truly predictive for the onset of PsA.

Designing a study to identify predictors for the future development of PsA

Prospective cohort studies are the holy grail in the search for predictive parameters. A prospective cohort design allows the researchers to use predefined, clear, consistent definitions of predictors and outcomes. As with all study designs, a clear patient selection (Pso patients without PsA) and a correct assessment of the outcome of interest (incident PsA) are of the utmost importance in this design. Moreover, the sample size should be large enough, and the follow-up time long enough, to allow for a sufficient amount of events of the outcome of interest to happen.

When looking at predictive parameters for PsA research, a few problems arise considering outcome assessment and follow-up time. First, the correct assessment of PsA requires an interview and physical assessment by a trained physician. As illustrated by the fact that one in three Pso patients with concomitant PsA remain undiscovered in clinical practice, one cannot rely on merely the information acquired in daily clinical practice to assess the outcome (PsA)[8]. This makes data gathered in prospective database registries -such as the THIN database or the Rochester Epidemiology Project- less reliable, since these are based on diagnostic codes gathered in daily clinical practice[23,24]. Moreover, the median time between the start of skin Pso and joint PsA is ten years, requiring a long follow-up for prospective cohorts[10,25]. Moreover, to avoid overfitting of a predictive model, a sufficient amount of events is necessary, requiring a large amount of patients to start with [26].

The large amount of patients, the long follow-up time needed, and the need to perform diagnostic procedures outside of daily clinical practice, make it a time- and money-consuming effort to design and perform such a study. Currently, only two prospective cohorts with a sufficient amount of patients are described in literature (box 2)[27,28]. Unfortunately, even in these cohorts follow-up time is limited, up to 48 months.

An observational prospective cohort studying clinical parameters: Toronto Psoriasis Cohort

The most relevant prospective Pso to PsA cohort is located in Toronto, Canada[29]. In this cohort, patients with psoriasis from the Greater Toronto Area were recruited mainly via dermatology and phototherapy clinics. PsA was excluded before start of the cohort by interview and musculoskeletal examination, and additional imaging if indicated. After inclusion, patients are reviewed yearly by a trained physician. Diagnosis of PsA (the outcome of interest) is made based on the ClASsification criteria for Psoriatic Arthritis (CASPAR criteria), after review of the clinical data by two independent rheumatologists. In this way, 695 patients were screened, of which 611 patients entered the cohort. At time of the last scientific publication, 402 patients provided data for one or more follow-up visits, and thus could be included for analyses regarding predictive parameters[30].

The Toronto Psoriasis Cohort provided a lot of information about the development of PsA in patients with Pso. For example, it showed us that the annual incidence rate of PsA in Pso patients is approximately 2.5 cases per 100 psoriasis years[27,31]. Moreover, it provided us with clues about possible predictive parameters for PsA in Pso patients. Regarding Pso phenotype, the presence of nail pitting, a higher disease activity of Pso, and the use of retinoids were associated with a higher chance of developing PsA[31]. Regarding joint related parameters, the presence and severity of heel pain, joint pain, and joint stiffness were associated with a higher chance of developing PsA[30]. Last but not least, this cohort provided us with the only PsA predictor with a strong level of evidence as stated in chapter 2[21]: the height and dynamics of the serum level of the cytokine CXCL10[32,33].

True predictor of future disease, or merely indicator of preclinical phase?

When looking at the predictive parameters we found, it is important to distinguish between true predictors of disease (i.e., parameters which are present before the disease has started) and indicators of preclinical disease (i.e., parameters which are present before the disease has been diagnosed, but are in fact due to the already present disease)[34]. This realization sheds a different light on the finding that joint complaints associated with enthesitis and arthritis (e.g. the beforementioned heel pain and joint stiffness) are shown to be predictive of PsA development[30]. Moreover, a smaller prospective cohort in Germany found that structural changes of the entheses seen on ultrasound are also predictive of the development of PsA in Pso patients[28,35]. Could this mean that the beforementioned joint complaints can be explained by a preclinical phase of PsA, for instance low-grade enthesitis?

An interesting finding in this context is the fact that subclinical enthesitis on ultrasound in seen more often in patients with Pso than in healthy controls[36,37]. In patients with PsA, the prevalence of subclinical enthesitis is even higher[37]. Maybe PsA and Pso should not be seen as two “distinct but related” disease entities, but more as a continuum of disease severity. In this theory of psoriatic disease, prediction of future PsA would be a contradiction *in terminis*,

as joint involvement would already be part of the concept of psoriatic disease. An interesting thought in this theory would be the question if every patient with Pso would develop PsA, given enough exposure (both in time and disease severity).

In conclusion, there are no clinical parameters with a strong level of evidence for the prediction of PsA in Pso patients. This is due to two caveats in Pso to PsA prospective cohorts: active screening by a trained physician is required, and the necessary follow-up time is several years. Moreover, possible predictive parameters identified may not be truly predictive, but instead be indicative of subclinical arthritis or enthesitis.

Box 2
Prospective cohorts studying the development of PsA in patients with Pso
University of Toronto Psoriasis cohort
Based in: Toronto, Canada
Follow-up at last publication: Jan 2006 – Dec 2014
Follow-up time per patient: 45.7 months (SD 25.7)
Amount of patients with Pso at start of follow-up: 410
Amount of patients with PsA at end of follow-up: 57 (13.9%)
Based upon Eder et al, A&R 2017[30]
University of Erlangen-Nuremberg cohort
Based in: Nuremberg, Germany
Follow-up at last publication: Jan 2011 – Jul 2018
Follow-up time per patient: 28.2 months (SD 17.7)
Amount of patients with Pso at start of follow-up: 114
Amount of patients with PsA at end of follow-up: 24 (21.1%)
Based upon Simon et al, A&R 2022[35]

Main finding 3:

The second aim of my thesis was focused on the identification of Pso patients with concomitant Pso. In cohorts described in literature, one in three Pso patients with concomitant PsA remains undiscovered. However, in our academic cohort in a Pso expertise center, the amount of undiscovered PsA was less than ten percent. Hence, it must be possible to detect (almost) all cases of PsA in the dermatology clinic.

In our DAPPER cohort (chapter 5), I found an overall prevalence of PsA in Pso of 24%: 22% of patients were already known to have PsA, and 2% of patients were newly discovered[1]. However, in literature a prevalence of undiscovered PsA of up to 15% is described[8]. This means that our cohort is in some ways different than the cohorts usually described in studies investigating prevalence or screening.

DAPPER cohort: Pso patients visiting outpatient clinic of an academic Pso expertise center

An important characteristic of our DAPPER cohort is its setting in an academic Pso expertise center: the Radboudumc. To understand the low prevalence of undiscovered PsA in our cohort, we need to dive deeper into the characteristics of three key elements: the patients, the dermatologists, and the general organization of the outpatient clinic.

The first key element is the patients. One possible explanation for the high number of undiscovered cases of PsA in Pso patients may be that patients do not link joint complaints to their skin disease, and therefore do not mention these joint complaints to their doctors (be it dermatologists or general practioner)[38]. On the other hand, patients who are aware of all aspects of their disease (both skin and joints) may be more alert to joint complaints and report them sooner. In psoriasis, it has been shown that a higher self-reported disease activity is associated with a higher health literacy: knowing better what to do, and whom to alert, when experiencing different disease aspects[39]. I hypothesize that patients who visit an academic center are more likely to have a higher health literacy: they were either referred by a second-line non-academic dermatologist because of therapy-resistant psoriasis with most often a high disease activity (associated with a higher health literacy), or found the expertise center when researching their disease (which requires a certain amount of health literacy). Therefore, these academic patients may be more likely to have knowledge about all aspects of their disease, and thus to report their joint complaints, leading to a low prevalence of undiscovered PsA.

The second key element is the dermatologist. It is conceivable that dermatologists in a psoriasis expertise center are more aware of possible comorbidities and how to screen for them, when compared to dermatologists in a non-academic setting. Lack of knowledge about PsA and the existing screening questionnaires has been identified as a barrier for implementation of screening[40].

A third key element is the general organization of the outpatient clinic. This element comprises several aspects, such as duration of consults, paramedical assistance, and the use of information technology. In general, duration of consults is longer in academic than in non-academic centers. Since time constraints are a major barrier for addressing comorbidities such as PsA, this longer consultation time makes it more likely for an academic dermatologist to address these comorbidities[40,41]. Moreover, in the Radboudumc specialized consultation hours are arranged for pre-specified groups of Pso patients, such as pediatric patients [42], or patients who use biologicals/smi[43]. Before a planned visit to one of these specialized consultation hours, patients are digitally asked to fill in online questionnaires, one of those being a PsA screening questionnaire. In addition, these specialized consultation hours are supported by dedicated (research) nurses, who (among other things) take time to help patients fill in patient-reported outcome measurements. During the consult, the physician can address the results and refer a patient to a rheumatologist if necessary. By taking away barriers (time constraints) and implementing facilitators (paramedical support, information technology), compliance with PsA screening is higher and therefore less Pso patients with PsA remain undiscovered. This approach to PsA screening, with the use of a prefilled questionnaire, is also employed in other hospitals in the Netherlands, such as Maasstad Ziekenhuis and ErasmusMC in Rotterdam, and Amsterdam UMC in Amsterdam.

Ideas for achieving a find-all goal in PsA screening at the dermatology clinic

When trying to find all PsA patients in a Pso cohort, there are several ways to increase the discovery rate. The diagnosis of PsA in Pso patients at the dermatology clinic can be considered

a process involving three key players: the patient, the dermatologist, and the rheumatologist.

The first player in this process is the patient. Awareness of the importance of joint complaints is an important factor, but it is hard to put into numbers how much of the undiscovered PsA diagnoses are due to patient delay. Moreover, it is hard to influence this factor. There have been public awareness campaigns, for example the symptom check by Novartis (www.psoriasishuid.nl/symptomencheck). However, just presenting the patient with more information does not lead to higher participation in screening programs for PsA[44]. Education programs involving face-to-face information by healthcare professionals do increase the patients' knowledge about psoriatic disease[45,46]. Unfortunately, face-to-face education is time-consuming for already busy healthcare professionals.

The second player in this process is the dermatologist. The role of the dermatologist is to refer patients with (a high risk of) PsA to the rheumatologist for further diagnosis and treatment. One way to identify patients with a high risk of PsA is by implementing the routine use of screening questionnaires. Arguably, none of the existing questionnaires (e.g. PEST, PASE, Topas2) are perfect in terms of specificity and sensitivity, with both metrics estimated to be between sixty and eighty percent[40,47]. Moreover, none of the questionnaires have been tested for repeated use. Still, I think that the first step in improving the detection of PsA is implementing any form of screening, faulty as it may be. Providing a PsA screening questionnaire via an automated process before a visit to the outpatient clinic, as is done in the Radboudumc, is a reachable first step in the routine implementation of this strategy. Disappointingly, an inquiry in Spain reported that only one in three dermatology centers actively employed any form of PsA screening at all[40].

The third player in this process is the rheumatologist. Difficult access to rheumatological care has been mentioned as a barrier to implementing PsA screening[40]. This means that, at least, a rheumatologist must be available to assess patients who are referred by a dermatologist. In addition, several models have been proposed for a "shared-care" principle in Pso patients with concomitant PsA: a joint consultation (both dermatologist and rheumatologist addressing the same patient, in the same room, at the same time), a parallel consultation (dermatologist and rheumatologist in adjacent rooms at the same department, directly referring a patient to the colleague physician when deemed necessary), and a preferential consultation (dermatologist and rheumatologist at different departments, consulting each other remotely when deemed necessary)[48]. However, the latter two options still require an estimation of the dermatologist whether or not to involve rheumatological care. The first option, a joint consultation of all patients with Pso, is likely not feasible in current medical practice, as it requires a huge rheumatological workforce.

In conclusion, in our DAPPER cohort the amount of Pso patients with undiscovered PsA is low in comparison to literature. PsA awareness in patients and dermatologists, facilitating the implementation of screening, and direct access to a rheumatologist may be key in identifying Pso patients with concomitant PsA.

Main finding 4:

The second aim of my thesis was to find characteristics associated with the presence of PsA in Pso patients. In my studies I found that there were specific joint symptoms which were associated with the presence of PsA in patients with Pso, such as joint pain not caused by trauma, swollen joints, and sausage-like swollen digits. However, even when I combined multiple predictors in one prediction model in chapter 6, it remained difficult to adequately distinguish between Pso patients with and without PsA based purely clinical characteristics[2].

The DAPPER cohort forms the basis of chapters 4, 5, and 6 of this thesis. In these chapters, I showed that some Pso characteristics are associated with the presence of concomitant PsA in univariable analyses, such as ever having erythroderma, or ever having nail pitting. However, these were overruled in the multivariable analysis by variables describing treatment history and joint complaints[2].

Skin disease characteristics associated with PsA

Several characteristics associated with the cutaneous phenomena of Pso have been linked with a higher chance of PsA, such as a more active skin disease, or Pso in certain locations.

Regarding the association between PsA and skin disease activity, our systematic review of the literature (chapter 2) found conflicting evidence for an association between the chance of developing PsA and higher disease activity[21]. The DAPPER cohort (chapter 5) did not show a significant difference in either body surface area (BSA) affected by Pso or Psoriasis Area and Severity Index (PASI) between patients with Pso only and patients with Pso and concomitant PsA[1]. However, several other reviews did show an association between higher disease activity of the skin and the presence of PsA[9,49-51]. When I reflected on the differences between these studies, several discrepancies and uncertainties became clear.

First of all, skin disease activity is not a permanent status: even during the natural course of the disease, it differs over time, experiencing seasonal influences or occasional exacerbations[52]. Therefore, it is essential to clarify when it is measured: at the start of disease, at the worst status, or at a random moment. This variable nature may explain differences between studies, where comparing different timings of measurement could be as comparing apples to oranges. Furthermore, skin disease activity may change even more during treatment at the dermatology outpatient department, and treatment for Pso may influence the prevalence of PsA[17,18,20]. Moreover, skin disease activity is probably related to other possible risk factors.

Regarding the association between PsA and Pso in certain locations, the presence of Pso in fingernails (psoriasis unguium) and in the intergluteal fold (sometimes comically referred to as the "natal cleft phenomenon") has since long been considered as associated with PsA. However, when systematically reviewing the literature, the association between intergluteal psoriasis and PsA is debatable, to say the least[49,51]. When one would investigate this association retrospectively through chart reviews, specific mentioning of the intergluteal region is more likely when it is the only site which shows Pso lesions. This could lead to misclassification bias: patients with more obvious Pso are less likely to have the intergluteal region specifically mentioned. The best way to investigate this association would be a prospective cohort with a predefined case report form mentioning the intergluteal region, such as the DAPPER cohort. As described in chapter 5, we did not see an association between intergluteal Pso and PsA[53].

When looking at the association of nail psoriasis and PsA, we found evidence for an association in both our systematic review of the literature (chapter 2), as well as in the DAPPER cohort

(chapter 6)[2,21]. Moreover, the presence of nail psoriasis is a variable in many screening questionnaires[40]. Looking deeper into this association between joints and nails, two things are worth mentioning specially. First, nail psoriasis can present in different forms, representing involvement of the nail matrix and the nail bed[54]. However, there is evidence that not all forms of nail psoriasis are equally related to PsA: in particular onycholysis and pitting show an association with PsA[55,56]. This may explain why studies reporting nail psoriasis in general do not show an association [50]. Second, nail psoriasis is subject to some of the same issues as skin disease activity: it is variable over time, (hopefully) changes after visiting a dermatologist and starting treatment, and this treatment may influence the prevalence of PsA.

Joint complaints associated with PsA

When trying to distinguish Pso patients with joint inflammation from Pso patients without joint inflammation, joint complaints seem a logical first step for screening. In agreement with this, all screening questionnaires include questions about joint complaints, for example pain or swelling in any joint, pain or swelling in the heel, and dactylitis (sausage-like swelling of an entire digit)[40].

However, joint complaints are highly prevalent generally, both in patients with and without arthritis[57]. This is exemplified by the fact that in our DAPPER cohort, 75 percent of patients reported current joint pain (chapter 5)[2]. Therefore, a more fine-tuned definition of "joint complaints" is necessary to improve diagnostic value. Both rheumatologists and dermatologists identified "inflammatory pain in peripheral joints" as the most important symptom to look for during screening[58,59]. To distinguish inflammatory pain from non-inflammatory pain, prolonged morning stiffness and joint swelling have been identified as key characteristics[60]. Indeed, in chapter 6 I showed that joint swelling and morning stiffness were associated with PsA in our DAPPER cohort, showing a strong and medium effect respectively[2].

With the CASPAR criteria in mind[61], only screening for peripheral arthritis would miss out on patients with sole enthesitis or axial spondyloarthritis (axSpA). Indeed, screening tools falsely identify patients with musculoskeletal problems other than PsA (e.g. fibromyalgia and osteoarthritis), but have trouble identifying patients with enthesitis and/or axial spondyloarthritis[62]. The difficulty In screening for enthesitis is mainly caused by the large overlap of symptoms between (poly)enthesitis and fibromyalgia[63]. The difficulty in screening for axial spondyloarthritis in PsA is mainly caused by the fact that the phenotype of axSpA in PsA is different than the classical phenotype of axSpA seen in ankylosing spondylitis (AS). For example: the classical "inflammatory back pain" symptoms are much less pronounced in axSpA associated with PsA than in axSpA associated with AS, making the distinction with non-inflammatory general back pain very hard[64,65].

Physical examination: the gold standard

In the assessment of joint complaints by a rheumatologist, physical examination of the joints is the most important step in differentiating arthralgia (joint pain) from arthritis (joint inflammation). Laboratory or imaging examinations may be used to find the underlying cause of arthritis, but the diagnosis is foremost dependent on physical examination. Moreover, the addition of laboratory or imaging examinations does not improve the diagnostic accuracy of screening for PsA in patients with Pso[7]. In other words, the diagnosis of PsA is most often made solely on the medical interview and physical examination.

With this in mind, it has been suggested that one way to improve the detection rate of PsA by dermatologists would be for them to carry out a physical examination of the joints[38]. Of course, training beforehand would be necessary. When comparing the joint examinations of dermatologists with rheumatologists, two independent studies showed that there is substantial agreement between dermatologists and rheumatologists in examining tender joints (joints painful upon standardized palpation). However, in assessing joint swelling, dermatologists and rheumatologists only have fair agreement, i.e. are consistent with each other in about 25% of the cases[66,67]. Unfortunately, a single training session did not improve these results[66]. To be fair, the educational plan for rheumatology residents anticipates a learning period of up to six months to be able to distinguish between inflammatory and non-inflammatory joint complaints by interview and physical examination[68]. Therefore, only one training session is probably not enough to acquire the necessary skills for assessing joint inflammation.

In conclusion, identifying Pso patients with concomitant PsA solely on patient-reported characteristics or medical interview seems to be insufficient. The addition of findings during physical examination may be key in differentiating between mere arthralgia and inflammatory arthritis.

Main finding 5:

The third aim of my thesis was to investigate the impact of Pso and PsA on patients' work and activities of daily life (ADL). Our observational studies in chapter 7 and 8 show that patients with Pso and/or PsA are less likely to have work-for-pay than the general Dutch population[53].

We used two real-world observational cohorts to evaluate the impact of Pso and/or PsA on the working life of patients. In chapter 7, we made use of longitudinal data from the multicenter prospective BioCAPTURE registry to examine the effect of starting biological/smi therapy on the professional life of Pso patients. Furthermore, in chapter 8, we made use of data from the cross-sectional, regular-care PART2 study to examine the impact of disease on the professional life of PsA patients[53]. Both of these cohorts were located in the Netherlands. Since the working environment and social security differs widely between countries, country-specific information is adamant for a correct estimation about the effect of disease on the working life of patients. So, our cohorts offer a valuable insight into the Dutch situation.

Cost estimates of psoriatic disease: international differences

Estimation of costs of disease are important in determining the impact of a disease on society. Total cost of disease is a combination of direct costs and indirect costs. Direct costs are costs made directly for medical care, such as doctors' fees and medication. Indirect costs are costs not directly related to medical care, such as work productivity losses. Both can be influenced by treatment decisions: a more expensive treatment can lead to higher direct costs, a more effective treatment can lead to lower indirect costs. The ratio of direct versus indirect costs differs per disease, and changes with the appearance of new treatment options. For example, the ratio of direct : indirect costs is 1:3 in fibromyalgia[69] and 2:1 in psoriasis[70]. In the estimation of indirect costs, a large proportion of the costs are due to work productivity losses (WPL). Since Pso and PsA are both diseases which start before or during working age[71,72], these diseases can lead to high WPL.

When looking at employment and work productivity parameters, getting real-life country-specific evidence is paramount. Contextual factors such as compensation for sick leave, reimbursement for medications or medical procedures, but also childcare arrangements are highly likely to be of influence on work-related outcomes[73]. In PsA, it has been reported that better economic circumstances in a country (e.g. healthcare expenditure, human development index) are associated with less WPL[74]. Both in Pso and PsA, differences in WPL between countries have been linked to differences in treatment and disease severity[75,76]. Moreover, sociocultural differences between countries, for example regarding the role of women in the workplace, may lead to international differences in WPL[74,77].

Preventing unemployment: treating the disease earlier

In PsA literature, the (prevention of) work loss has been described in several studies, more so than in Pso. This may be partly due to the fact that disability leave and/or unemployment is higher in patients with Pso and concomitant PsA, compared to patients with Pso only[78-81]. It is clear that both in Pso and PsA, a higher disease activity is related to a higher chance of unemployment or long-term disability leave[82-84]. Moreover, a longer disease duration is also related to a higher chance of unemployment/disability leave[77,79,82,85]. Furthermore, in chapter 8 we showed that unemployment in a cohort of long-standing PsA (a cross-section of all patients visiting our outpatient clinics) was higher than the unemployment rate of the Dutch general population[53]. Around the same time, another Dutch cohort of early PsA showed a much lower rate of unemployment[86]. This leads to my hypothesis that there is a window of opportunity early in the disease, when reaching a lower disease activity may prevent loss of paid employment.

This hypothesis is also indirectly supported by the fact that in a biological-only cohort of PsA no effect of disease duration on employment was shown, keeping in mind that the start of biological therapy is not the first step in PsA treatment (and is thus associated with a longer disease duration)[79]. This could also apply to our biological-only BioCAPTURE cohort of Pso patients as described in chapter 7. Moreover, the fact that in the BioCAPTURE cohort we did not see a difference in WPL between patients with or without concomitant PsA may be due to the "overruling" effect of longstanding disease.

This "window of opportunity" and the importance of early intervention is in line with the concept of cumulative life course impairment (CLCI) in Pso[87,88]. The CLCI concept had been proposed to describe the impact of psoriasis during a life time. Essential to this concept is the idea that Pso may induce life-changing events early in the disease. These life-changing events may lead to cumulative "damage" later in life. Again, an example could be job loss early in the disease due to a high disease activity, after which return to paid work can be quite difficult even if the disease becomes mild[88,89]. According to this theory, early intervention with effective treatment (i.e., starting sooner with systemic treatment in order to reach quick skin clearance) may prevent this cumulative damage.

In conclusion, we show that in longstanding psoriatic disease the employment rate is considerably lower than in the general population. However, there are indications that early effective treatment of Pso/PsA may prevent loss of paid employment. The economic effect of preservation of employment may offset the costs associated with systemic treatment.

Overall limitations

Looking at this thesis overall, there are three overall limitations which must be addressed: patient selection, dichotomizing continuous variables, and missing data.

Patient selection : three different cohorts

Ideally, the patients who are included in a study should be a representative sample of the patients in daily clinical practice. This ensures high external validity: the results obtained during the study are applicable in daily practice.

This thesis used data from three different, but partly overlapping study cohorts: DAPPER, BioCAPTURE, and PART2. DAPPER is a cohort of Pso patients, treated in an academic Pso expertise center. This setting may hamper the external validity: these patients probably have more active disease, are harder to treat, and may have more comorbidity when compared to patients in "regular" second line dermatology clinics. Next to these differences, there is a difference in physicians and organization between this academic center and a peripheral clinic, which may lead to another treatment regime and a different implementation of screening techniques. Therefore, affirmation of our results in a non-academic setting would provide vital information.

BioCAPTURE is a prospective, multicenter, real-world, observational cohort of Pso patients who use biologicals or smi. The multicenter setting, which includes multiple peripheral and academic centers, improves its external validity. However, this cohort only contains Pso patients who meet the requirements to start with biological therapy. This means that results obtained may not be applicable to patients with less severe Pso.

PART2 is a monocenter cohort of PsA patients, treated in regular care at a specialized, categorical hospital. However, this hospital is not specifically specialized in PsA care, meaning that in theory these patients should be representable for PsA patients at a rheumatological outpatient clinic. Some selection bias does apply, as patients with very long standing remission might visit the clinic less often or might be referred back to their GP, and thus are less likely to be included in a study.

In conclusion, every monocenter research cohort deals with selection bias. While multicenter, daily practice cohorts make bias less likely, findings of any study should be replicated to determine the impact of patient selection.

Working with continuous data: to dichotomize or not?

When constructing a data model using continuous quantitative data, the researcher can choose how to work with this data: i.e. continuous, categorized, or dichotomized. The best choice is dependent on the intended use of the final model.

In our systematic review of the literature, we found numerous studies in which continuous data was compared between two groups (in our case, patients with Pso with or without concomitant PsA). Statistical tests (e.g. students t-test, Mann-Whitney U) were used to compare the values of both groups, and to determine if there was a statistical significant difference. With this method, it can be determined whether the "average" patient from group

A differs from the “average” patient of group B. However, there still may be an area in which both groups overlap. This makes it hard to determine whether an individual patient belongs to a certain group based on their value: is it a “high scoring” A, or a “low scoring” B? This concept is shown in figure 1.

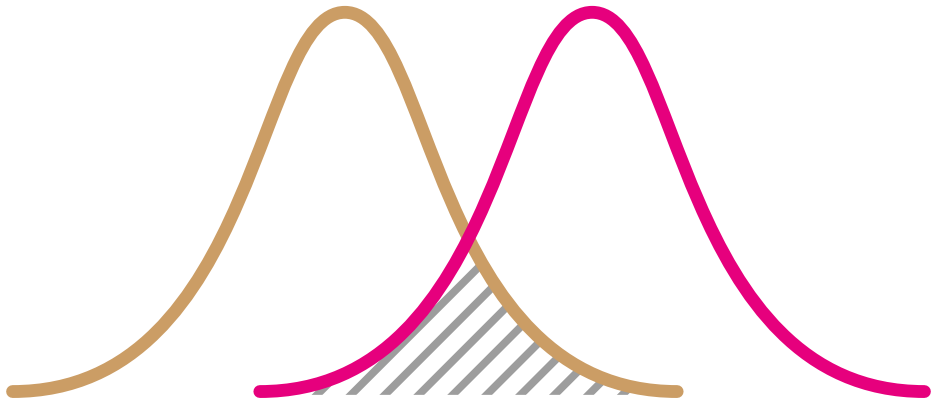


Figure 1: two distinct populations, showing overlap
Both groups are statistically different. However, when a certain observation is located in the “gray area”, it is impossible to determine whether it belongs to group A or group B

In the development of our prediction model for the presence of concomitant Pso in PsA patients, we decided to only use dichotomous (yes/no) parameters. In the exploratory phase, we did find continuous parameters which differed between patients with and without concomitant PsA, for instance disease duration of skin disease. Using these continuous variables as is may improve the diagnostic accuracy of the model. However, we preferred ease of use over a small increase in accuracy, and chose to “keep it simple, stupid” by using only dichotomous variables. This choice was made to improve implementation of a screening tool in clinical practice. In the end, using a less-than-perfect model is better than not using a perfect model at all due to time constraints.

In the study examining ADL impairments in Pso patients using biologicals, we made use of a questionnaire which divided impairment in four categories: no impairment, impaired but capable, uncapable/fully impaired, and not applicable. Based on the distribution of the data, we decided to dichotomize these categories into impaired or not impaired at all. Using these dichotomization, we could not find any effect of treatment on impairment. However, other studies using continuous data did find effects of treatment. Probable, the resolution of data points in our study was too low to detect relative differences: patients with impairment might have improved, but did not reach a state of no impairment at all.

In conclusion, the choices made in the construction of a statistical model can influence the outcome of the study. Advantages of dichotomization are ease of use and better distinctive capabilities. A major disadvantage is the loss of information, which may lead to a type II statistical error.

Missing data: filling in the blanks

In all kinds of studies, there is a certain amount of missing data. Although there are several statistical techniques to “fill in the blanks”, the missing data can influence the results of the analysis and therefore cause bias.

In this thesis, we used several techniques for data collection: literature search, questionnaires, and observational data both from daily clinical practice as well as dedicated study visits. The latter is least prone to missing data, since the researcher themselves collects all the data with the final goal (the analysis) in mind. In contrast, in our daily clinical practice PART2 cohort, I noticed that one of the variables (Health Assessment Questionnaire – HAQ) was often missing. This was due to an error in the administrative process: part of the patients did not receive this questionnaire. We deemed this to be a case of data missing completely at random (MCAR), and used imputation techniques as a work-around.

In both the BioCAPTURE and the PART2 studies, we also used questionnaires outside of daily clinical practice. However, more often than not, questionnaires were not returned by patients. This introduces a form of selection bias: patients who are interested in, or who experience problems with the study topic, are more likely to respond. Therefore, I deemed this data to be missing not at random (MNAR). This may lead to an overestimation of the experienced impairment.

In our systematic review of the literature, we could only use information available in published articles. This of course introduces publication bias: a phenomenon where results of positive, confirmative studies are more likely to get published than negative results. Moreover, due to word constraints, negative results are less likely to get mentioned in a paper. We tried to overcome this bias by only evaluating the variables who were studied in multiple studies, or in one study of good quality. However, some form of bias can not be excluded.

In conclusion, missing data is present in almost all studies. Recognizing the reason for missingness is an important tool in estimation the effect of the missingness on the result of the analysis, and recognizing and mentioning possible bias.

Future perspectives: research themes

After reviewing the main findings of this thesis, I would like to propose some knowledge gaps where future research can help improve our knowledge of and care for (patients with) Pso and PsA.

Regarding prediction of future PsA in Pso patients, DNA profiling might help to build a “risk profile”. It is already known that Pso patients with and without concomitant PsA differ in, for example, HLA-profile[21]. I would like to investigate what the absolute risk of PsA is for patients who are HLA-B*27 and/or HLA-C*06 positive, and if such a risk profile at the start of skin disease can help identify patients at higher risk for PsA. Prediction of the (future) risk of PsA can help select the patients most at risk. This may be helpful when studying preventive strategies, and may assist the implementation of a screening strategy for concomitant PsA. When studying a possible preventive strategy, the number of (expected) events must be large enough to detect

differences between the two experimental arms. By selecting patients at higher risk, a smaller amount of patients need to be recruited, which improves feasibility of such a trial. Currently, one finished and one ongoing trial are studying the effect of the early use of biologicals in patients with Pso on the incidence of PsA[90,91]. Already, the European Alliance of Associations for Rheumatism (EULAR) identified joint complaints and entheseal lesions as markers for a higher risk of PsA[92]. I would like to see if DNA profiling could improve the selection of these high risk patients.

Regarding identification of concomitant PsA in Pso patients, several questions remain. There are models indicating that the implementation of active screening for concomitant PsA in patients with Pso would be cost-effective. These models presume that, when using screening questionnaires, PsA would be found earlier, and loss of function could be prevented[93]. However, screening with questionnaires is far from perfect with regard to sensitivity and specificity. Use of questionnaires will lead to unnecessary referrals to the rheumatology department, while still missing a considerate amount of PsA patients. This increased referral rate will put a burden on the already taxed healthcare system, increasing the workload of dermatologists and rheumatologist, as well as increasing the healthcare expenses[2]. I propose that individual, hands-on screening by a trained health care professional (e.g. a trained nurse of physician assistant) could minimize the unnecessary referrals. Although the initial costs of such trained personnel might be higher than the implementation of a questionnaire, the improved predictive value might make this approach worthwhile. Ideally, I would like to compare regular care with two forms of screening: the use of questionnaires, and screening by a trained health care professional. The outcome of patients after several years should be compared, taking into account the costs (of screening and treatment), complications (of treatment and undiscovered disease), and benefits (in terms of less disease burden and higher QoL).

Furthermore, a huge knowledge gap in the world of PsA screening is the repetitive use of screening protocols over time. Pso is a chronic disease, and the risk of incident PsA stays the same during the disease[10]. This could imply that Pso patients need to be re-screened for PsA at certain intervals. Currently, there is no evidence regarding the repeated use of screenings: how often and in which way should this be done? Moreover, it is unknown what should be done when a patient with a positive screening test visited the rheumatologist, and a diagnosis of PsA was deemed unlikely. Should the patient be screened again after a certain amount of time, and if positive, referred to the rheumatologist again? I would like to investigate the outcome of repeated screening test in a prospective cohort of Pso cohorts: what is the additive predictive value when repeating the screening after one or several year(s)? Do we identify more patients with PsA, and/or does the amount of false positives increase?

Regarding the impact of Pso and PsA on patients work and activities of daily life, there are some clues that reaching early remission might prevent job loss in PsA[86]. Moreover, we found that in longer-standing Pso and PsA, the employment rate is lower in patients than in the general population[53]. Interestingly, in a Danish PsA cohort, average yearly income of PsA patients is lower than in the general population already five years before start of arthritis[94]. I would like to investigate what the employment rate is in Dutch patients with early Pso and PsA, and whether this is associated with reaching (early) disease remission. A longitudinal cohort of patients with early Pso or PsA (for example, first visit to the dermatologist/rheumatologist less than one year ago) could for the basis for such a study. Using questionnaires such as the Work Productivity and Activity Impairment questionnaires (WPAI) on regular intervals, the "survival" of employment could be plotted. When combining this with disease activity parameters, a relationship with reaching disease remission could be inferred. Such data is missing especially for the group of patients treated with conventional systemic drugs.

Future perspectives: how to improve care

With regard to implications for current medical practice, there are three themes which I would like to address: cooperation between disciplines, aiming for low disease activity as soon as possible, and attention for measuring the correct end goals of treatment.

Cooperation between disciplines: let's connect

First, psoriatic disease is an excellent example of a disease entity which surpasses the organ-specific way in which our current Dutch healthcare system is organized. Ideally, a patient should be treated by a physician with knowledge of all aspects of the disease. However, in daily clinical practice, combined dermatology-rheumatology clinics are not the standard. In my opinion, we should reach out more to each other, for example via multidisciplinary meetings, by sharing the physical space of the outpatient clinic, or by organizing combined clinics[95,96]. Even the implementation of a screening for joint complaints in dermatology clinics, or skin complaints in rheumatology clinics, could be a first step[97].

Aiming for low disease: why wait?

Second, we see that even in treated PsA and Pso patients there is still a considerable burden, which affects work and ADL[53]. However, even in this treated everyday cross-sectional selection of patients, the disease is not in complete remission, i.e. there is still skin disease, and there are still inflamed joints. Moreover, both in Pso as in PsA we found clues that prolonged disease activity is associated with more impairment. There are even studies which suggest that treatment of Pso patients with biologicals may prevent the development of PsA[17,18,90]. Despite this evidence, especially in Pso, patients more often than not have endured several years of skin disease before getting access to systemic medication[12]. I would like to plead for a more "aggressive" approach to treatment, where we strive for low disease activity (or remission) of Pso and PsA as soon as possible.

End goals: a "normal" life

Third, I want to emphasize that low disease activity as defined by medical professionals is possibly not the treatment goal which benefits patients the most. I would like to state that "low disease activity" is not the end goal at all: it is the means to an end. In the end (pun intended), patients want to live their life as "normal" as possible, with the disease having little to no effect on their life choices and self image[98]. While achieving a state of low disease activity is a way to achieve this end goal, it is important to also measure this end goal itself. For example, the burden of treatment, or the impact of disease on emotional well-being or interpersonal relationships, are topics that are important to patients which are not measured in disease activity scores[99,100]. The Dutch Society of Rheumatology (Nederlandse Vereniging voor Reumatologie; NVR) already advises to pay attention to employment in patients with rheumatoid arthritis (RA)[101]. In other words, I would like to ask you to strive for an optimal treatment considering a patients' life in total, not only their joints or skin.

In conclusion, with the studies described in this thesis we have contributed to the increasing knowledge base about the prevalence and risk factors for PsA in Pso patients. Moreover, we have tried to shed light on the impact of disease on professional and home life. In the future, cooperation between patients, dermatologists and rheumatologist is key to improving Pso and PsA care.

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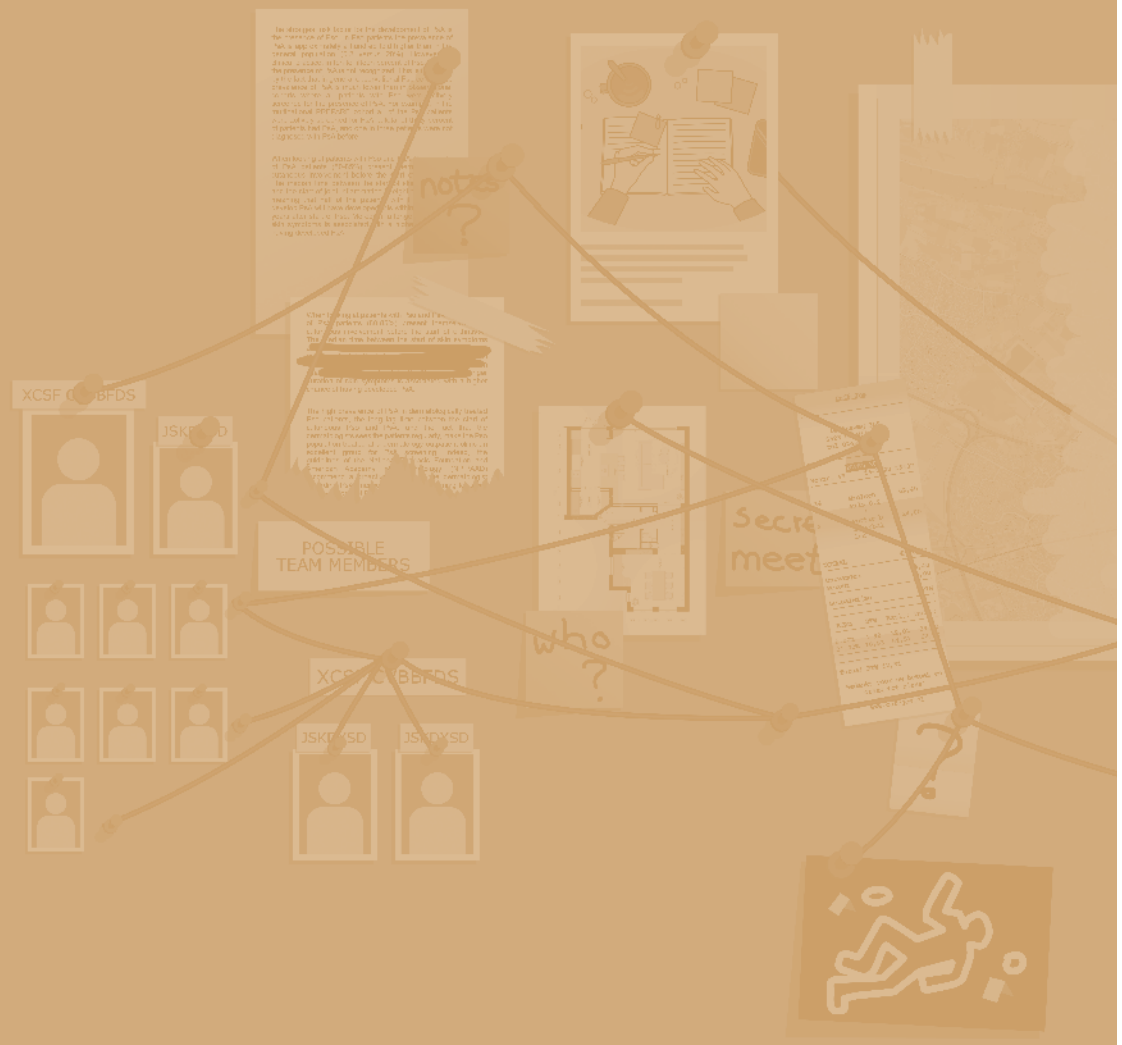
Chapter 10

Nederlandse samenvatting



Nederlandse samenvatting

Dit proefschrift (“boekje”) is een verzameling van verschillende onderzoeken. Deze onderzoeken gaan over de ziektes *psoriasis* en *artritis psoriatica*.

Psoriasis is een ziekte met ontsteking van de huid en de nagels. Patiënten kunnen last hebben van rode, verdikte en schilferende plekken op hun huid. Dit kan pijn doen of jeuken. Mensen kunnen zich er ook voor schamen.

Artritis psoriatica is een begrip uit het Latijn. Het betekent: ontsteking van de gewrichten bij *psoriasis*. *Artritis psoriatica* is een ziekte met ontsteking van de gewrichten en van de plek waar de pees vastzit aan het bot (de aanhechting). Patiënten kunnen pijn hebben, of de gewrichten minder goed gebruiken. Als de ontsteking van de gewrichten er lang blijft, kunnen de gewrichten zelfs beschadigd raken. We noemen dat erosies.

Patiënten met *artritis psoriatica* worden behandeld door de reumatoloog. De reumatoloog kan medicijnen gebruiken om de ontsteking in de gewrichten te onderdrukken. Het is belangrijk dat de ontsteking aan de gewrichten zo snel mogelijk wordt behandeld. Dan wordt de schade aan de gewrichten tegengehouden.

Patiënten met *psoriasis* kunnen behandeld worden door de huidarts (dermatoloog). Eén op de drie patiënten met *psoriasis* krijgt ook *artritis psoriatica*. In de adviezen voor dermatologen staat dat zij ook moeten kijken naar *artritis psoriatica*. Voor een dermatoloog is het lastig om in te schatten of een patiënt ook ontsteking in zijn gewrichten heeft.

Om de dermatoloog te helpen, zijn verschillende testen ontwikkeld. Dit zijn meestal vragenlijsten. Na het invullen van de vragenlijst, komt er een advies of het nodig is om de patiënt door te sturen naar de reumatoloog. Maar deze testen zijn niet precies genoeg. Soms wordt een patiënt doorgestuurd terwijl er geen *artritis psoriatica* is. Soms wordt een patiënt niet doorgestuurd terwijl er wel *artritis psoriatica* is. Ook worden deze vragenlijsten niet altijd en overal gebruikt.

De laatste twintig jaar zijn er veel nieuwe behandelingen gekomen voor *psoriasis* en *artritis psoriatica*. De behandelingen worden ingedeeld in drie categorieën: plaatselijke behandeling, “conventionele” middelen en biologicals. Plaatselijke behandeling kan bestaan uit zalven/crèmes en lichttherapie voor de huid, en spuiten in de gewrichten. Conventionele middelen bestaan al lange tijd. Het zijn meestal pillen. Zij verminderen ontsteking in het algemeen, dus ook in de huid en de gewrichten. Biologicals, of biologische medicijnen, bestaan sinds ongeveer twintig jaar. Het zijn meestal spuitjes of infusen. Deze medicijnen werken op een heel precies deel van de ontstekingsreactie. Vaak gebruiken patiënten eerst lokale therapie en conventionele middelen. Als dit niet genoeg helpt, schrijft de dokter een biological voor.

Met deze behandelingen kunnen we *psoriasis* en *artritis psoriatica* steeds beter aanpakken. We willen dat patiënten geen plekken op de huid en geen ontstekingen in de gewrichten meer hebben. Toch hebben patiënten vaak nog last van hun ziekte in het dagelijks leven. Dit kan invloed hebben op hun werk of gezin. Dit is voor patiënten een belangrijk onderwerp.

Onze onderzoeken draaien om de volgende drie vragen:
1. Kunnen we voorspellen welke patiënten met *psoriasis* in de toekomst ook *artritis psoriatica* krijgen?
2. Kunnen we herkennen welke patiënten met *psoriasis* op dit moment ook *artritis psoriatica* hebben?
3. Wat is de invloed van de ziekte op het werk en het dagelijks leven van de patiënten?

1. Kunnen we voorspellen welke patiënten met psoriasis in de toekomst ook artritis psoriatica krijgen?

In **hoofdstuk 2** hebben we een overzicht gemaakt van eerdere onderzoeken, die hebben gekeken naar patiënten met *psoriasis* die ook *artritis psoriatica* hebben (gekregen). Hebben deze patiënten bepaalde kenmerken? Bijvoorbeeld: roken ze, of drinken ze alcohol? Of hebben ze sommige stofjes in hun bloed of in hun DNA? We hebben 119 onderzoeken gevonden die hiernaar gekeken hebben. Uit deze 119 onderzoeken kwamen 259 verschillende kenmerken naar voren. Er was 1 kenmerk dat kan helpen bij het voorspellen of patiënten in de toekomst *artritis psoriatica* krijgen: het stofje CXCL10 in het bloed. Patiënten met een hogere waarde van CXCL10 in het bloed, hebben een grotere kans om in de toekomst *artritis psoriatica* te krijgen. Er waren 2 kenmerken voor het hebben van *artritis psoriatica* op dit moment. Dit zijn stofjes in het bloed die te maken hebben met ontsteking, en met de opbouw van botten. Er zijn geen DNA-kenmerken, of kenmerken van de patiënt zelf, die kunnen voorspellen of een patiënt met *psoriasis* ook *artritis psoriatica* heeft of zal krijgen.

In **hoofdstuk 3** hebben we gekeken naar patiënten met *psoriasis* die een biological gebruiken. Dit soort medicijnen wordt voorgeschreven als de *psoriasis* ernstig is. Of als andere medicijnen niet goed genoeg werken. We hebben gekeken naar een grote groep Nederlandse patiënten die deze medicijnen gebruiken. Deze groep noemen we het BioCAPTURE cohort. Er deden 427 patiënten met *psoriasis* mee aan dit onderzoek. Van deze patiënten hadden 117 patiënten ook *artritis psoriatica*. Dat is 27 procent, ongeveer 1 op de 4. De *artritis psoriatica* was er meestal al voordat de patiënt begon met het gebruiken van de biological. Maar, bij 32 patiënten ontstond de *artritis psoriatica* na het starten van de biological. Dat is 9 procent, ongeveer 1 op 11. Dat betekent dat ook patiënten met *psoriasis* die sterke medicatie gebruiken (biologicals) nog steeds *artritis psoriatica* kunnen krijgen.

2. Kunnen we herkennen welke patiënten met psoriasis op dit moment ook artritis psoriatica hebben?

In **hoofdstuk 4** gaat het over de DAPPER-studie. In deze studie heb ik als reumatoloog gewerkt op de polikliniek van de dermatologie. Ik heb 300 patiënten met *psoriasis* onderzocht. Dit waren 100 patiënten die alleen zalven/crémes gebruikten, 100 patiënten met conventionele middelen, en 100 patiënten met biologicals. Ik heb gekeken of zij naast *psoriasis* ook *artritis psoriatica* hadden. Van al deze patiënten heb ik gegevens verzameld. Bijvoorbeeld hun leeftijd, of welke medicijnen zij gebruiken. Wanneer een patiënt *artritis psoriatica* had, hebben we gevraagd of zij behandeld werden door een reumatoloog. Als ze niet behandeld werden door een reumatoloog, hebben we ze doorgestuurd. Na een jaar hebben we gekeken welke patiënten zijn doorgestuurd. Deze mensen hebben we opnieuw opgespoord om te vragen hoe het met hen gegaan was.

In **hoofdstuk 5** vertel ik meer over de patiënten in de DAPPER-studie. In deze studie zaten in totaal 303 patiënten met *psoriasis*. Een op de 4 patiënten (24%) had ook *artritis psoriatica*. We ontdekten dat patiënten die conventionele middelen of biologicals gebruikten voor hun *psoriasis*, vaker *artritis psoriatica* hadden. Patiënten die alleen zalven/crèmes gebruikten voor hun *psoriasis*, hadden minder vaak *artritis psoriatica*. Patiënten die langer *psoriasis* hadden, hadden ook vaker *artritis psoriatica*. De meeste DAPPER-patiënten met *artritis psoriatica* hadden al een reumatoloog. Er waren 7 patiënten die *artritis psoriatica* hadden, maar (nog) geen behandeling bij de reumatoloog kregen. Deze patiënten hadden weinig klachten van hun gewrichten. Zij waren moeilijk te “vinden” voor de dermatoloog.

In **hoofdstuk 6** probeer ik de dermatoloog te helpen om patiënten met *artritis psoriatica* te vinden. Ik heb de gegevens van de DAPPER-studie gebruikt. Er zaten verschillen tussen de patiënten die wel, en de patiënten die geen *artritis psoriatica* hadden. Daarmee hebben we een lijst gemaakt voor de dermatoloog. Patiënten met *artritis psoriatica* hadden vaker: pillen of spuitjes voor hun *psoriasis*, of ze zeiden dat er pijn in hun gewrichten was zonder dat er een ongeluk gebeurd was, er gezwollen gewrichten waren, en vingers of tenen die eruit zagen als een worstje. Deze kenmerken kan een dermatoloog gebruiken om patiënten met *artritis psoriatica* op te sporen.

3. Wat is de invloed van de ziekte op het werk en het dagelijks leven van de patiënten?

In **hoofdstuk 7** heb ik weer gekeken naar patiënten met *psoriasis* die een biological gebruiken: de BioCAPTURE groep. Dit keer keek ik naar patiënten die net gingen beginnen met een biological. Ik heb deze mensen vragen gevraagd: Heeft de *psoriasis* invloed op uw dagelijks gezinsleven of op het werk? Er deden 194 patiënten mee aan het onderzoek. De helft van de patiënten (53%) had een betaalde baan. In vergelijking: van alle Nederlanders heeft 67% een betaalde baan. Patiënten met *psoriasis* hebben dus minder vaak een baan dan de gemiddelde Nederlander. Op het werk hebben mensen ook last van hun *psoriasis*. Zij kunnen hun werk minder goed doen. Ook thuis lukken dingen minder goed. We hebben na een jaar gekeken hoe het met deze mensen ging. Op het werk ging het beter met ze. Het meedoen aan het gezinsleven ging niet beter of slechter.

In **hoofdstuk 8** heb ik gekeken naar patiënten met *artritis psoriatica*. Deze patiënten bezochten de reumatoloog in de Sint Maartenskliniek. Ook aan deze patiënten heb ik gevraagd wat de ziekte deed op hun gezinsleven en hun werk. Er deden 246 patiënten mee aan het onderzoek. Ook hier had de helft van de patiënten een betaalde baan. Dat is minder vaak dan de gemiddelde Nederlander. Op hun werk en thuis hebben mensen problemen door hun *artritis psoriatica*. Ze kunnen minder goed (mee)doen aan werk en andere activiteiten. Patiënten kunnen vooral minder goed (mee)doen als de ontsteking actiever is. Of, als zij last hebben van hun lichaam. Bijvoorbeeld pijn, of niet meer goed kunnen bewegen.

Conclusie:
In mijn onderzoeken zie ik dat ongeveer een op de vier patiënten met *psoriasis* ook *artritis psoriatica* krijgt. Als mensen sterkere medicijnen nodig hebben voor hun *psoriasis*, hebben zij ook vaker *artritis psoriatica*. Zelfs tijdens het gebruik van deze sterke medicijnen kan toch *artritis psoriatica* ontstaan.

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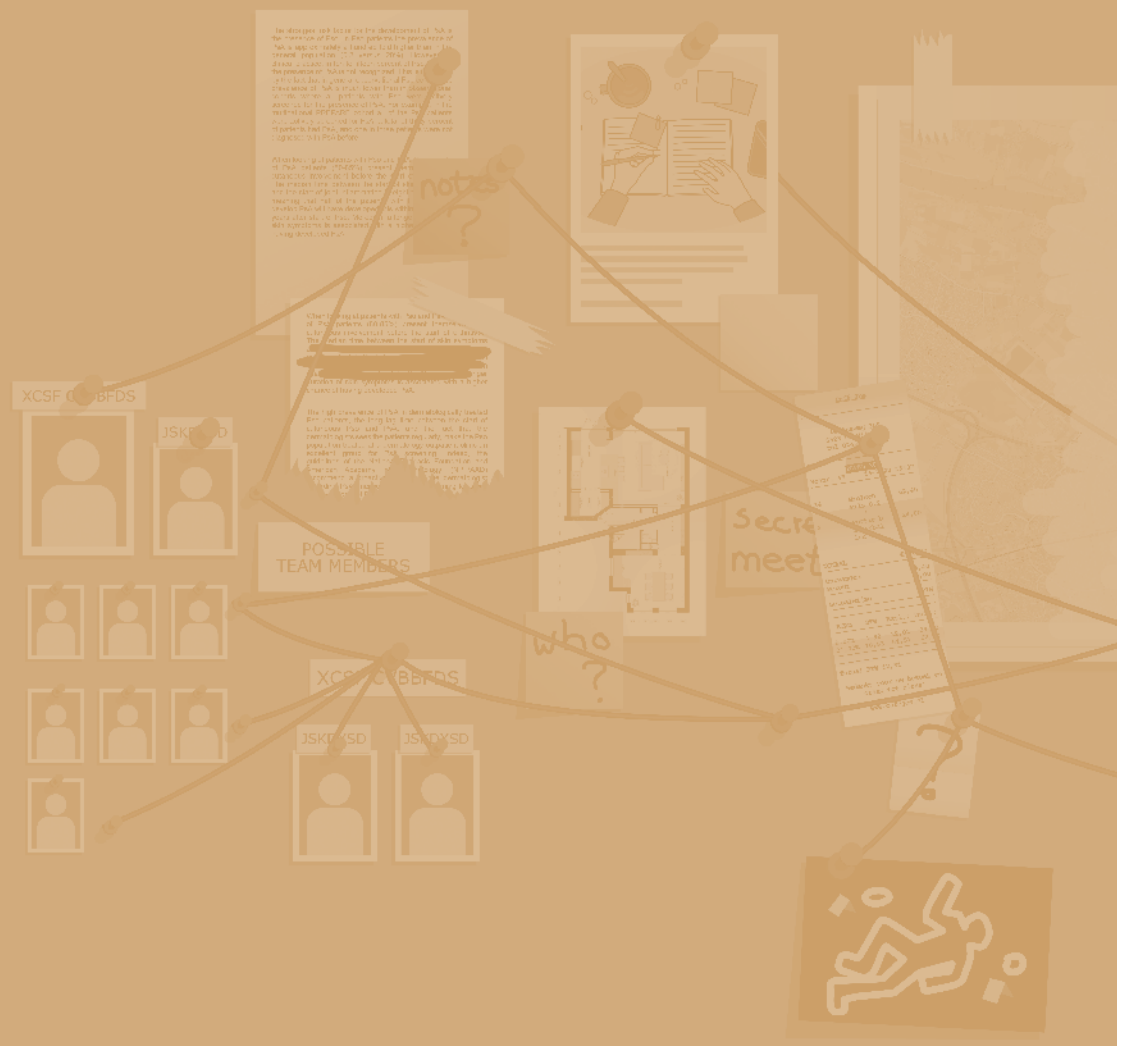
Naast het gebruik van medicijnen zijn er ook bepaalde gewrichtsklachten die wijzen op het hebben van *artritis psoriatica*. Maar, zelfs met deze verschillen is het moeilijk om patiënten met *artritis psoriatica* goed te herkennen in de groep patiënten met *psoriasis*.

Patiënten met *psoriasis* of *artritis psoriatica* hebben minder vaak een betaalde baan. Ook kunnen ze minder goed hun werk doen door hun ziekte. Mensen met een zeer actieve ontsteking worden het meest gehinderd in hun werk. Behandeling met biologicals laat wel verbetering op het werk zien, maar niet in het gezinsleven.

In de toekomst hoop ik dat beter en meer onderzoek ons meer aanwijzingen geeft om mensen met *artritis psoriatica* beter en sneller te herkennen. Als we deze mensen eerder opsporen en eerder behandelen, kunnen we misschien voorkomen dat ze door hun ziekte beperkt worden in hun werk en gezinsleven.

List of abbreviations



List of abbreviations

AAD	**A**merican **a**ssociation of **d**ermatology
ACE	**A**ngiotension **c**onverting **e**nzym
ACPA	**A**nti-**c**itrullinated **p**rotein **a**ntibodies
ADAMTS	**A** **d**isentegrin **a**nd **m**etalloproteinase with **t**rombo**s**pondin motifs
ADL	**A**ctivities of **d**aily **l**ife
Ala	**Ala**nine
Anti-CCP	**Anti**-**c**ylic **c**itrillunated **p**rotein
APF	**A**nti**p**erinuclear **f**actor
Apo	**Apo**lipoprotein
Arg	**Arg**inine
AS	**A**nkylosing **s**pondylitis
ASAS	**A**ssessment of **s**pondylo**a**rthritis international **s**ociety
Asn	**As**paragi**n**e
Asp	**Asp**artic acid
AUA	**A**cute **u**veitis **a**nterior
AUC	**A**rea **u**nder the **c**urve
axSpA	**Ax**ial **sp**ondylo**a**rthritis
B	Regression coefficient
BES	**B**est **e**vidence **s**ynthesis
BioCAPTURE	**C**ontinuous **A**ssessment of **P**soriasis **T**reatment **U**se **Re**gistry with **Bio**logics
Biol	**Biological drug**
BMI	**B**ody **m**ass **i**ndex
BSA	**B**ody **s**urface **a**rea
b/tsD	**B**iological/**t**argeted **s**ynthetic **d**rug
C16ORF1	Endosomal protein sorting factor like (VSP35L)
C2C	Collagen fragment neoepitopes Col2-3/4 (long mono)
C9	**C**omplement factor **9**
CASPAR	**Cla**ssification criteria for **p**soriatic **ar**thritis
CBS	**C**entral **b**ureau of **s**tatistics
CCI	**C**harlson **C**omorbidity **I**ndex
CCL	**C-C** chemokine **l**igand
CCR	**C-C** chemokine **r**eceptor
CD	**C**luster of **d**ifferentiation
CD5L	**CD5 l**igand
CER	**Cer**amide
CI	**C**onfidence **i**nterval
Cig	**Cig**arettes
CM	**C**entral **m**emory
COMP	**C**artilage **o**ligomeric **m**atrix **p**rotein
CPII	**C-p**ropeptide of type **II** collagen
CPN2	**C**arboxy**p**eptidase **N** subunit **2**
CRP	**C**-**r**eactive **p**rotein
csD	**C**onventional **s**ynthetic **d**rug
CTx	**C**ollagen **t**ype I C-telopeptide
CX3CL	**C-X3-C** motif **l**igand

CXCL	**C-X-C** motif **l**igand
CXCR	**C-X-C** motif **r**eceptor
DAPPER	**D**iscovery of **a**rthritis in **p**soriasis **p**atients for **e**arly **r**heumatological referral
DAS28	**D**isease **a**ctivity **s**core of **28** joints
DIP	**D**istal **i**nter**p**halangeal joint
DKK	**D**ic**kk**opf
DLQI	**D**ermatological **l**ife **q**uality **i**ndex
DMARD	**D**isease **m**odifying **a**nti-**r**heumatic **d**rug
DNA	**D**eoxyribo**n**ucleid **a**cid
EARP	**E**arly **a**rthritis for **p**soriatic patients questionnaire
EM	**E**ffector **m**emory
ESR	**E**rythrocyte **s**edimentation **r**ate
EULAR	**Eu**ropean **al**liance of **a**ssociation for **r**heumatism
FAIR	**F**indable, **a**ccessible, **i**nteroperable, **r**eusable
FCI	**F**unctional **c**omorbidity **i**ndex
FHL1	**F**our and a **h**alf **L**IM domains
GEE	**G**eneralized **e**stimating **e**quations
Glu	**Glu**tamic acid
Gly	**Gly**cine
GP	**G**eneral **p**ractioner
GPS	**G p**rotein pathway **s**uppressor
HAQ	**H**ealth **a**ssessment **q**uestionnaire – disability index
HAT	**H**uman **a**irway **t**rypsin-like protein
HDL	**H**igh-**d**ensity **l**ipoprotein
HLA	**H**uman **l**eukocyte **a**ntigen
Hp	**H**ydroxy**p**roline
HR	**H**azard **r**atio
HR-QoL	**H**ealth-**r**elated **q**uality **o**f **l**ife
hs	**H**igh **s**ensitivity
HT	**H**yper**t**ension
IBD	**I**nflammatory **b**owel **d**isease
IFI	**I**nter**f**eron-**i**nducible protein
IFN	**I**nter**fero**n
Ig	**I**mmuno**g**lobulin
IL	**I**nter**l**eukin
IL1RN	**IL-1 r**eceptor a**n**tagonist
IL2R	**I**nter**l**eukin **2 r**eceptor
IL23R	**I**nter**l**eukin **23 r**eceptor
IQR	**I**nter**q**uartile **r**ange
ISG	**I**nterferon **s**timulated **g**ene
ITGB	**I**n**teg**rin **b**eta
JAK	**Ja**nus **k**inase
K17	**K**eratin **17**
KIR	**K**iller-cell **i**mmunoglobuline-like **r**eceptor
L	**L**iter
lb	International pound (weight)
LDA	**L**ow **d**isease **a**ctivity

LDL	**L**ow-**d**ensity **l**ipoprotein
LEI	**L**eeds **e**nthesitis **i**ndex
Leu	**Leu**cine
Lys	**Lys**ine
LZIC	**L**eucine **zi**pper and **C**TNNBIP1 domain containing
M2BP	**M**ac-**2**-**b**inding **p**rotein
MACE	**M**ajor **a**dverse **c**ardiovascular **e**vent
MAGI	**M**embrane-**a**ssociated **g**uanylate **k**inase
MCAR	**M**issing **c**ompletely **a**t **r**andom
MCS	**M**ental **c**omponent **s**ummary score
M-CSF	**M**acrophage **c**olony **s**timulating **f**actor
MCV	**M**utated **c**itrullinated **v**imentin
Met	**Met**hionine
mg	**M**illi**g**ram
MHC	**M**ajor **h**istocompatibility **c**omplex
MI	**M**yocardial **i**nfarction
MICA	**M**HC **c**lass **I** polypeptide-related sequence **A**
miRNA	**Mi**cro-**RNA**
MMP	**M**atrix **m**etallo**p**roteinase
MNAR	**M**issing **n**ot **a**t **r**andom
MPO	**M**yelo**p**er**o**xidase
MPV	**M**ean **p**latelet **v**olume
mRNA	**M**essenger **RNA**
MWU	**M**ann-**W**hitney **U**
N/A	**N**ot **a**vailable
NAPSI	**Na**il **p**soriasis **s**everity **i**ndex
NFKB	**N**uclear **f**actor **k**appa-**B**
NKFBIA	**NFKB i**nhibitor **a**lpha
NLR	**N**eutrophile to **l**ymphocyte **r**atio
N-NAIL	**N**ijmegen **nail** psoriasis activity index
NPF	**N**ational **P**soriasis **F**oundation
NRP	**N**eu**ro**pilin
NSAID	**N**on-**s**teroidal **a**nti-**i**nflammatory **d**rug
NVR	**N**ederlandse **v**ereniging voor **r**eumatologie
OA	**O**steo**a**rthritis
OCP	**O**steo**c**last **p**recursor
OPG	**O**steo**p**roteg**e**rin
OR	**O**dds **r**atio
oxLDL	**Ox**idated **LDL**
PAFAH1B2	**P**latelet **a**ctivating **f**actor **a**cetyl**h**ydrolase **1b** catalytic subunit **2**
PART2	**Part**icipation in **p**soriatic **art**hritis
PASDAS	**P**soriatic **a**rthriti**s** **d**isease **a**ctivity **s**core
PASE	**P**soriatic **A**rthritis **S**creening and **E**valuation Tool
PASI	**P**soriasis **a**rea and **s**everity **i**ndex
PBMC	**P**eripheral **b**lood **m**ononuclear **c**ells
PCS	**P**hysical **c**omponent **s**ummary score
PDCD	**P**rogramme**d** **c**ell **d**eath 1

PDE	**P**hospho**die**sterase
PEST	**P**soriasis **e**pidemiology **s**creening **t**ool
PLR	**P**latelet to **l**ymphycte **r**atio
POSTN	**P**eri**ostin**
PPP2R4	**P**rotein **p**hos**p**hatase **2** phosphatase activato**r**
PREPARE	**Pre**valence of **p**soriatic **ar**thritis in adults with psoriasis: an **e**stimate from dermatology practice
PRISMA	**P**referred **r**eporting **i**tems for **s**ystematic reviews and **m**eta-**a**nalysis
PRODISQ	**Pro**ductivity and **dis**ease **q**uestionnaire
PRL	**Pro**lactin
PsA	**Ps**oriatic **a**rthritis
PsAID	**Ps**oriatic **a**rthritis **i**mpact of **d**isease
Pso	**Pso**riasis
PTPN22	**P**rotein **t**yrosine **p**hosphatase **n**on-receptor type **22**
PUVA	**P**soralen-**UVA**
QoL	**Q**uality **o**f **l**ife
RA	**R**heumatoid **a**rthritis
Radboudumc	**Radboud u**niversity **m**edical **c**enter
RANK	**R**eceptor **a**ctivor of **N**F-κB
RANKL	**RANK l**igand
RF	**R**heumatoid **f**actor
RNA	**R**ibo**n**ucleid **a**cid
ROC	**R**eceiver **o**perating **c**haracteristics
RR	**R**elative **r**isk
SD	**S**tandard **d**eviation
Ser	**Ser**ine
SETD	**SET d**omain protein
SF12	**S**hort **f**orm **12**
SFA	**S**aturated **f**atty **a**cids
sIL-2R	**S**oluble **IL-2 r**eceptor
SJC	**S**wollen **j**oint **c**ount
SMI	**S**mall **m**olecule **i**nhibitor
SNCA	**Sy**n**uc**lein **a**lpha
SNP	**S**ingle **n**ucleotide **p**olymorphism
SpA	**Sp**ondylo**ar**thritis
SPARCC	**Sp**ondylo**ar**thritis **r**esearch **c**onsortium of **C**anada
sRANKL	**S**oluble **RANKL**
SRP	**S**ignal **r**ecognition **p**article
SRPX	**S**ushi **r**epeat containing **p**rotein **X**-linked
STAT	**S**ignal **t**ransducer and **a**ctivator of **t**ranscription
STIP	**St**ress-**i**nducible **p**hosphoprotein
SYK	**S**pleen associated t**y**rosine **k**inase
T2T	**T**reat-**to**-**t**arget
TBX	**T**-**bo**x
TC	**T**otal **c**holesterol
T-EM	**E**ffector **m**emory **T**-cell
T-EMRA	**TEM** re-expressing CD45**RA**

Thr	**Thr**eonine
TICOPA	**T**ight **co**ntrol in **p**soriatic **a**rthritis
TJC	**T**ender **j**oint **c**ount
TNF	**T**umor **n**ecrosis **f**actor
TNFAIP	**TNF a**lpha-**i**nduced **p**rotein
TNFi	**TNF i**nhibitors
TNIP	**TN**FAIP2 **i**nteracting **p**rotein
ToPAS	**To**ronto **p**soriatic **a**rthritis **s**creen questionnaire
TRAF	**T**NF **r**eceptor **a**ssociated **p**rotein
TRAF3IP	**TRAF3 i**nteracting **p**rotein
TRIPOD	**T**ransparent **r**eporting of a multivariable prediction model for **i**ndividual **p**rognosis **o**r **d**iagnosis
Trp	**Tryp**tophan
TSC1	**T**uberous **sc**lerosis **1**
TWEAK	**T**NF-like **weak** inducer of apoptosis
UFA	**U**nsaturated **f**atty **a**cids
UK	**U**nited **K**ingdom
USA	**U**nited **S**tates of **A**merica
UV	**U**ltra**v**iolet
Val	**Val**ine
VAS	**V**isual **a**nalogue **s**cale
vBMD	**V**olumetric **b**one **m**ineral **d**ensity
VCP	**V**alosin-**c**ontaining **p**rotein
VEGF	**V**ascular **e**ndothelial **g**rowth **f**actor
VEGFR	**VEGF r**eceptor
VLDL	**V**ery **l**ow **d**ensity **l**ipoprotein
WFP	**W**ork-**f**or-**p**ay
WPAI-SHP	**W**ork **p**roductivity and **a**ctivity impairment: **s**pecific **h**ealth **p**roblem
WPL	**W**ork **p**roductivity **l**oss
WTCCC	**W**elcome **t**rust **c**ase **c**ontrol **c**onsortium
ZNF	**Zi**n**c f**inger protein

Curriculum vitae

Curriculum Vitae

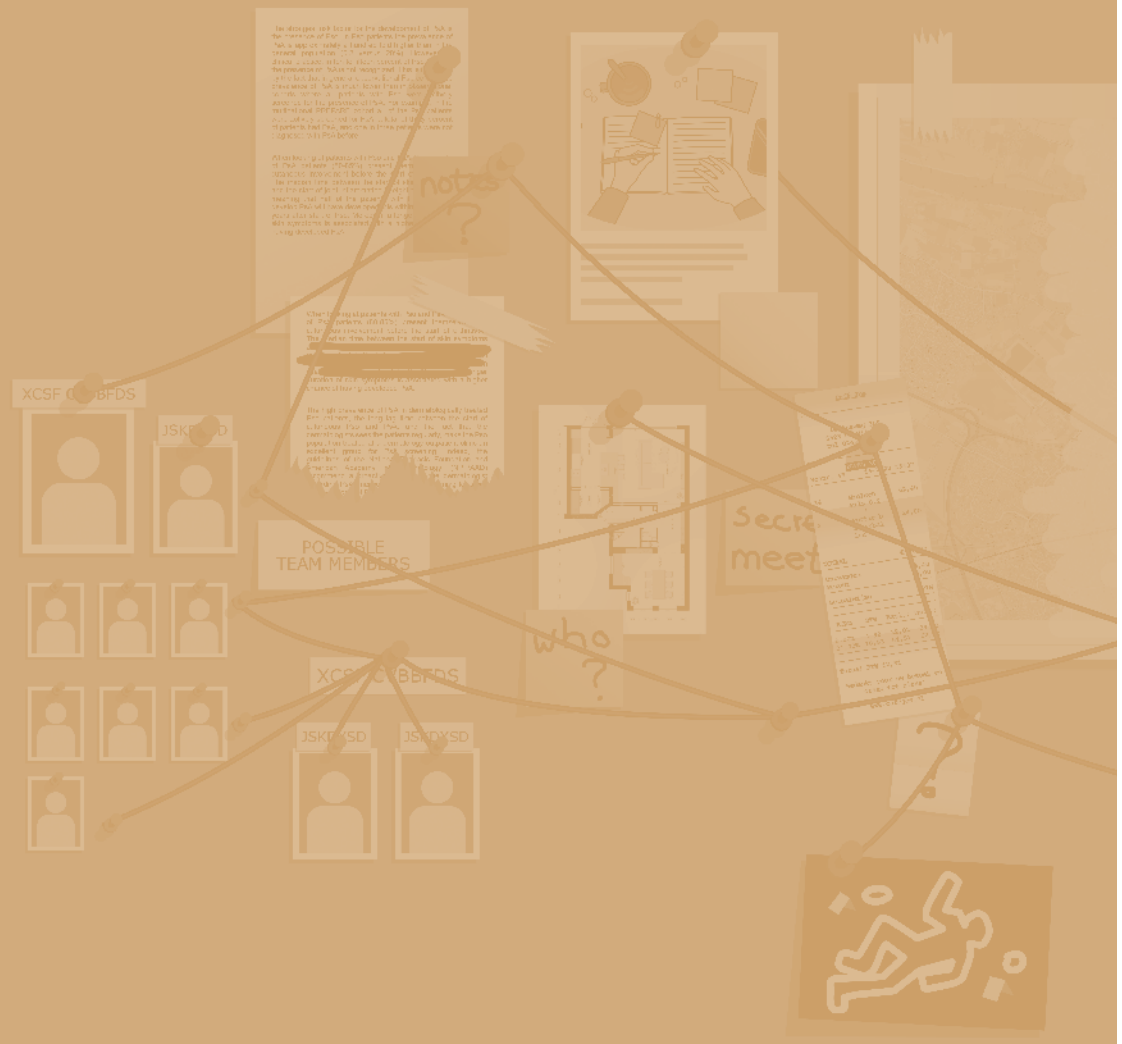
Tamara van Hal is geboren op 6 september 1984 in het toenmalige Sint Radboudziekenhuis te Nijmegen. Haar jeugd en schooltijd heeft zij doorgebracht in Doetinchem, waar ze in 2002 haar gymnasiumdiploma haalde aan het Rietveld Lyceum. Na een werkend tussenjaar begon zij in 2003 aan de studie Geneeskunde bij het inmiddels geheten Universitair Medisch Centrum St. Radboud te Nijmegen. In 2010 behaalde ze hier haar artsdiploma.

Van 2010 tot 2012 heeft ze wetenschappelijk basaal onderzoek verricht onder begeleiding van prof. dr. T.D.R.J. Radstake bij het laboratorium Experimentele Reumatologie van het UMC St. Radboud (Nijmegen) en het UMC Utrecht. In 2013 is zij vanuit het Universitair Medisch Centrum St. Radboud start met de opleiding tot reumatoloog. Van 2013 tot 2017 was zij in het kader van de vooropleiding werkzaam bij de afdeling Interne Geneeskunde van het Deventer Ziekenhuis, onder begeleiding van opleider dr. C.M. Vermeij. Van 2017 tot 2018 vervolgde zij de opleiding bij de afdeling Reumatologie van de Sint Maartenskliniek te Nijmegen, onder begeleiding van opleider dr. E.A.M. Mahler.

Vanuit de afdeling Reumatologie van de St. Maartenskliniek in samenwerking met de afdeling Dermatologie van het (inmiddels zo geheten) Radboudumc heeft Tamara van 2018 tot 2022 gewerkt aan een promotietraject naar het voorkomen van artritis psoriatica in patiënten met psoriasis, en naar de sociale en occupationele belemmeringen van patiënten met psoriasis en artritis psoriatica. Dit heeft geleid tot het proefschrift “A rheumatologist undercover. Research of psoriatic arthritis at the dermatology clinic”, wat zij op 4 juli 2024 zal verdedigen. Zij is hierbij begeleid door dr. M.H. Wenink en dr. J.E. Vriezekolk van de St. Maartenskliniek, en prof. E.M.G.J. de Jong en dr. J.M.P.A. van den Reek van het Radboudumc.

Momenteel is Tamara werkzaam als arts-assistent in opleiding tot specialist reumatologie bij de afdeling Reumatologie van het Radboudumc, onder begeleiding van drs. H.K.A. Knaapen-Hans. Zij woont in Nijmegen-Noord, samen met haar echtgenoot en dochter.

List of publications



List of publications

Publications related to this thesis

Van Hal TW, van den Reek JMPA, Wenink MH, Otero ME, Ossenkoppele PM, Njoo MD, Oostveen A, Peters B, Tjioe M, Kop NE, Körver JEM, Dodement SRP, Kleinpenning MM, Berends MAM, Veldkamp WR, van Doorn MBA, Mommers JM, Lindhout RJ, Kuijpers ALA, van Lümig PP, de Jonge CEJ, Tupker RA, Hendricksen J, Keijsers RR, van den Hoogen FHJ, Vriezekolk JE, de Jong EMG.
Impairment in work and activities of daily life in patients with psoriasis: results of the prospective BioCAPTURE registry.
J Dermatolog Treat. 2024 Dec; 35(1): 2304025.

Van Hal TW, Mulder MLM, Wenink MH, van den Hoogen FHJ, Maurits JSF, Pasch MC, van den Reek JMPA, de Jong EMGJ.
Development of a New Referral Tool to Identify Psoriasis Patients with Concomitant Psoriatic Arthritis: Results of the Prospective DAPPER Cohort.
Acta Derm Venereol. 2023 Apr 27; 103: adv5269.

Van Hal TW, Mulder MLM, Wenink MH, Pasch MC, Van den Hoogen FHJ, van den Reek JMPA, de Jong EMGJ.
Discovery of Psoriatic Arthritis in Psoriasis Patients for Early Rheumatological Referral (DAPPER) Study: A Prospective Observational Cohort.
Acta Derm Venereol. 2022 Aug 26; 102: adv00768.

Van Hal TW, Mulder MLM, Wenink MH, Vriezekolk JE.
Determinants of work and social participation in patients with psoriatic arthritis in the Netherlands: an observational study.
BMC Rheumatol. 2022 Aug 17; 6 (1): 49.

Van Hal TW, Van den Reek JMPA, Groenewoud HM, Pasch MC, van den Hoogen FHJ, Wenink MH, de Jong EMGJ.
Discovery of Arthritis in Psoriasis Patients for Early Rheumatological Referral (DAPPER): Protocol for a Longitudinal Observational Study.
JMIR Res Protoc. 2021 Nov 16; 10 (11): e31647.

Mulder MLM*, **van Hal TW***, Wenink MH, Koenen HJPM, van den Hoogen FHJ, de Jong EMGJ, van den Reek JMPA, Vriezekolk JE.
Clinical, laboratory, and genetic markers for the development or presence of psoriatic arthritis in psoriasis patients: a systematic review.
Arthritis Res Ther. 2021 Jun 14; 23 (1): 168.
* Both authors contributed equally

Van Muijen ME, **van Hal TW**, Groenewoud HMM, van den Reek JMPA, de Jong EMGJ.
The Skin May Clear But the Arthritis Won't Disappear: Focusing on Concomitant and New-Onset Psoriatic Arthritis in a Daily Practice Cohort of Psoriasis Patients on Biologic Therapy.
Psoriasis (Auck). 2020; 10: 29-37.

Publications not related to this thesis

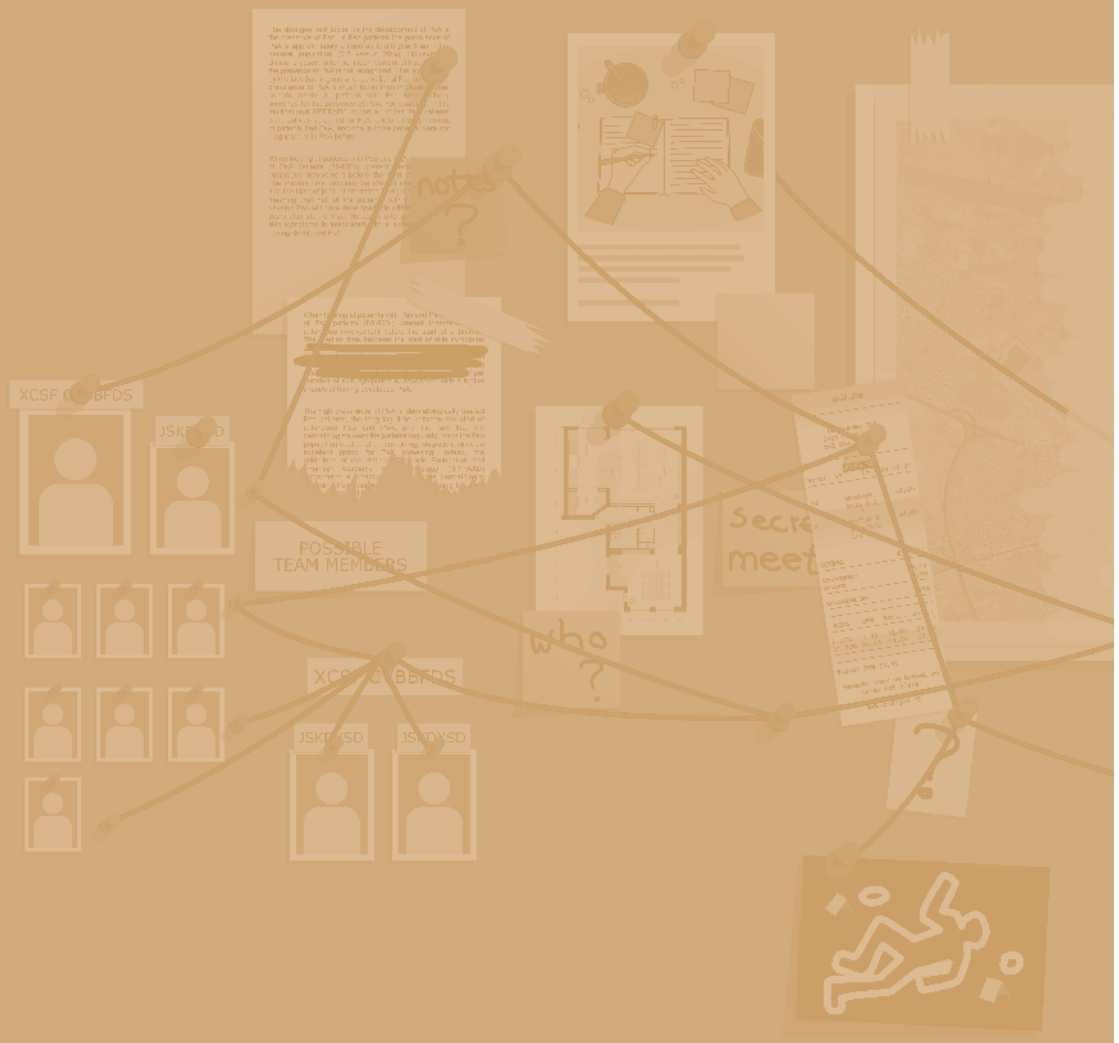
Mulder MLM, Vriezekolk JE, **van Hal TW**, Nieboer LM, den Broeder N, de Jong EMGJ, van den Hoogen FHJ, Helliwell PS, Wenink MH.
Comparing methotrexate monotherapy with methotrexate plus leflunomide combination therapy in psoriatic arthritis (COMPLETE-PSA): a double-blind, placebo-controlled, randomised trial.
Lancet Rheumatol. 2022 Apr 1; 4(4): e 252-e261.

Mulder MLM, **Van Hal TW**, van den Hoogen FHJ, de Jong EMGJ, Vriezekolk JE, Wenink MH.
Measuring disease activity in psoriatic arthritis: PASDAS implementation in a tightly monitored cohort reveals residual disease burden.
Rheumatology (Oxford). 2021 Jul 1; 60 (7): 3165-3175.

Van Hal TW, Sluiter HE, van de Scheur MR, van Ginkel CJ.
A case of acute generalised pustulosis due to amoxicillin/clavulanic acid.
Neth J Med. 2014 May; 72(4): 245-6.

Van Hal TW, van Bon L, Radstake TRDJ.
A system out of breath: how hypoxia possibly contributes to the pathogenesis of systemic sclerosis. *Int J Rheumatol.* 2011; 2011: 824972.

PhD portfolio



PhD portfolio of Tamara van Hal

Department: **department of rheumatology, Sint Maartenskliniek**

PhD period: **01/09/2018 – 31/08/2022**

PhD Supervisor: **Prof. dr. E.M.G.J. de Jong**

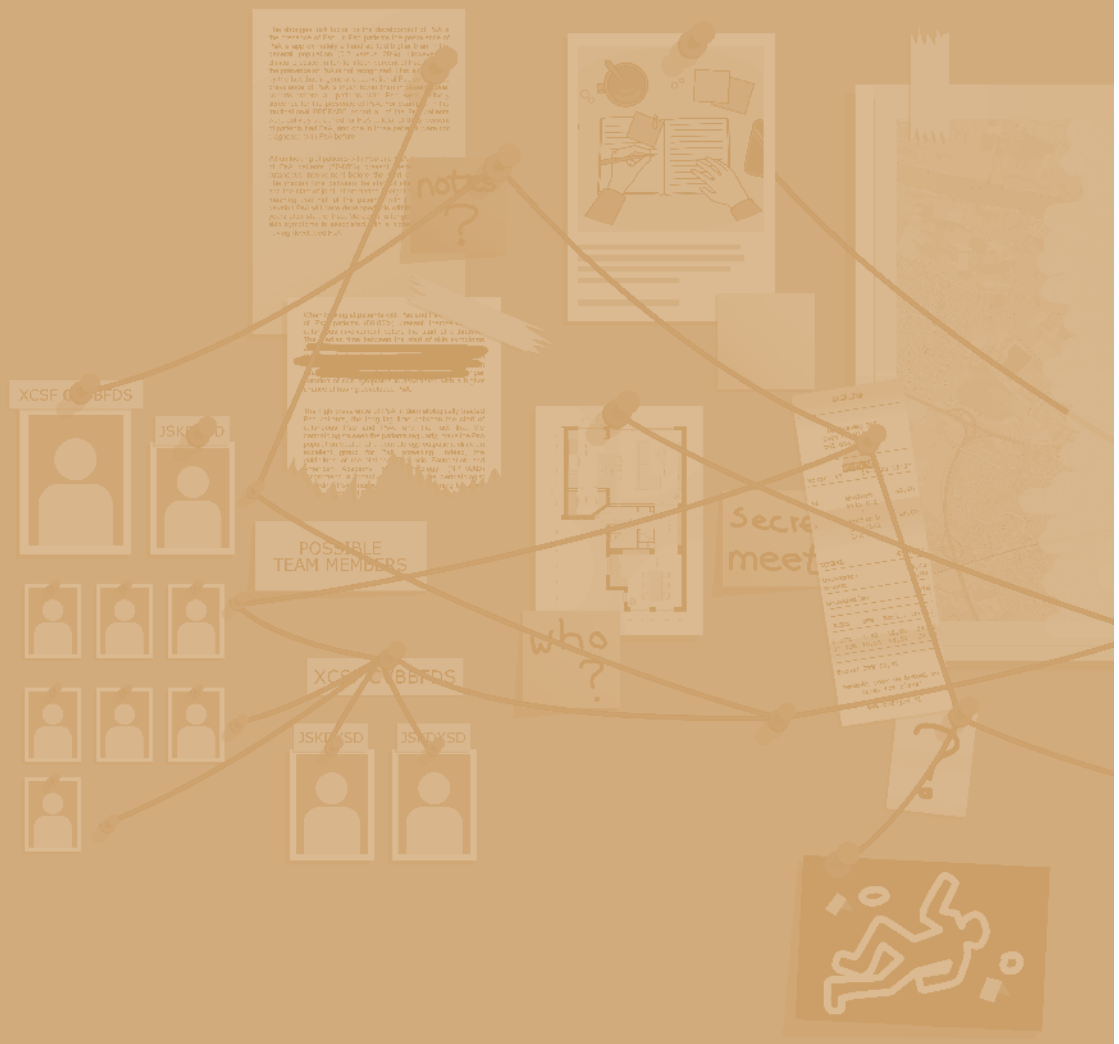
PhD Co-supervisors: **Dr. J.M.P.A. van den Reek, dr. M.H. Wenink, dr. J.E. Vriezekolk**

Training activities		Hours
Courses		
-	Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (2018)	21.00
-	Beginners course "Statistics for PhD Candidates" (2019)	42.00
-	RIHS - Introduction course for PhD candidates (2019)	15.00
-	Statistics for PhD candidates using SPSS (2020)	84.00
-	V30 Regressietechnieken (2020)	112.00
-	Scientific Writing for PhD Candidates (2021)	84.00
-	Radboudumc - Scientific integrity (2021)	20.00
-	RU - Open Science for PhD candidates (2021)	28.00
-	RU - Grant Writing and Presenting for Funding Committees (2021)	28.00
Seminars		
-	Time management voor aios (2018)	3.00
-	Regionale Refereeravond Reumatologie (2018)	3.00
-	IRON Nascholing echografie (2018)	3.00
-	STAP patiëntparticipatie avond (2018)	3.00
-	BioCAPTURE Meeting (2018)	3.00
-	ROR-onderwijs (2019)	1.00
-	Biologicals in Psoriasis (2019)	3.00
-	ROR-onderwijs (2019)	1.00
-	SpA Academy (2019)	2.00
-	Echo-onderwijs reumatologie (2020)	3.00
-	BioCAPTURE Meeting (2020)	3.00
-	Research Integrity Round (2021)	1.00
-	Workshop Communicatie - The Online Scientist (2022)	6.00
-	BioCAPTURE Meeting – oral presentation (2023)	2.00

Conferences	
- Immunology Summit (2019)	21.00
- NVR Najaarsdagen – oral presentation (2019)	21.00
- PhD Retreat (2019)	14.00
- NVED Jaarcongres – poster presentation (2020)	21.00
- AASMK Jaarsymposium (2020)	4.00
- NVR Najaarsdagen (2020)	4.00
- GRAPPA Trainee Symposium – poster presentation (2021)	21.00
- NVR Najaarsdagen – oral presentation (2021)	21.00
- ACR Symposium – poster presentation (2021)	7.00
- EULAR Yearly Symposium – poster presentation (2022)	35.00
- RIHS PhD Retreat – oral presentation (2022)	21.00
- Lage Landen Top Reumatologie – oral presentation (2023)	10.00
Other	
- Journal Club Dermatology (2019)	28.00
- Bestuur AASMK (2019)	14.00
- Journal Club Dermatology (2020)	28.00
- Journal Club Dermatology (2021)	28.00

Teaching activities	Hours
Lecturing	
- Lecture: what to know about PsA for dermatologists (2019)	4.00
- MINK07: immunologie van bench tot bedside (2020)	6.00
- MINK07: immunologie van bench tot bedside (2021)	10.00
- Student Meets Patient (2022)	4.00
- MINK07: immunologie van bench tot bedside (2022)	14.00
Supervision of internships / other	
- Research Project: Grant proposal (2021)	49.00
- Research Project: Grant proposal (2022)	49.00
Total	**905.00**

Research data management



Research data management

The articles in this thesis are based upon four studies: a literature study (chapter 2), the observational BioCAPTURE registry (chapter 3 and 7), the observational longitudinal DAPPER study (chapter 4, 5, and 6), and the observational cross-sectional PART2 study (chapter 8).

Literature study

Data collection, analysis, and storage

References were saved using Endnote. Data from the references was extracted and entered in Excel. Data files and analyses were stored at the digital archive of the Sint Maartenskliniek (V:/). Data were made reusable by adding sufficient documentation in a readme.txt.

Availability of data

The article is published open access. The dataset is not published in a repository, but is available upon reasonable request.

BioCAPTURE Registry

Ethics and privacy

The BioCAPTURE registry contains medical-scientific data from human participants. The medical ethical review Committee on Researching Involving Human Subjects Region Arnhem Nijmegen (CMO Arnhem-Nijmegen) deemed that formal ethical approval as mentioned under the Medical Research Involving Human Subjects Act (WMO) was not applicable to this observational study. However, written informed consent was obtained from all patients included in the registry. Data was pseudonymized, and access to the identification codes was limited to research personnel.

Data collection, analysis, and storage

Data from the BioCAPTURE study is currently collected through electronic Case Report Forms (eCRF) using Castor EDC, a cloud-based clinical data management platform with an incorporated audit trail, Data were converged from Castor EDC to SPSS (SPSS Inc., Chicago, Ilinois, USA) for analyses. Data were stored and analyzed in the Azure DRE. Data and analyses are only accessible to research personnel. Paper (hardcopy) data is stored in cabinets in the department of Dermatology of the Radboudumc.

Availability of data

All articles are published open access. The data will be archived for 15 years after termination of the study. The pseudonymized dataset is not published in a repository, but is available upon reasonable request.

DAPPER study

Ethics and privacy

The DAPPER study contains medical-scientific data from human participants. It was subject to the Medical Research Involving Human Subjects Acts (WMO). The medical ethical review Committee on Researching Involving Human Subjects Region Arnhem Nijmegen (CMO Arnhem-Nijmegen) has given approval to conduct this study (file number 2018-4959). Informed consent was obtained from all research participants. Technical and organizational measures were followed to safeguard the availability, integrity, and confidentiality of the

data (these measures include the use of independent monitoring, pseudonymization, access authorization, and secure data storage). The study was conducted in accordance with the ICH-GCP guidelines (Good Clinical Practice) and the Declaration of Helsinki.

Data collection, analysis, and storage

Data from the DAPPER study is collected through hard copy questionnaires and notes in Epic, the electronic patient file (EPF). Data was entered into an electronic Case Report Forms (eCRF) using Castor EDC, a cloud-based clinical data management platform with an incorporated audit trail. Data were converged from Castor EDC to SPSS (SPSS Inc., Chicago, Ilinois, USA) for analyses. Data and analyses are stored in the Azure DRE. Data and analyses are only accessible to research personnel. Paper (hardcopy) data is stored in cabinets in the department of Dermatology of the Radboudumc.

Availability of data

All articles are published open access. The data will be archived for 15 years after termination of the study. The pseudonymized dataset is not published in a repository, but is available upon reasonable request. Furthermore, during the informed consent procedure, participants were asked consent to re-use the pseudonymized data for further research concerning psoriasis and/or psoriatic arthritis.

PART2 study

Ethics and privacy

The PART2 study contains medical-scientific data from human participants. The medical ethical review Committee on Researching Involving Human Subjects Region Arnhem Nijmegen (CMO Arnhem-Nijmegen) deemed that formal ethical approval as mentioned under the Medical Research Involving Human Subjects ACT (WMO) was not applicable to this observational study. Informed consent was assured via an opt-out procedure. Technical and organizational measures were followed to safeguard the availability, integrity, and confidentiality of the data (these measures include the use of independent monitoring, pseudonymization, access authorization, and secure data storage).

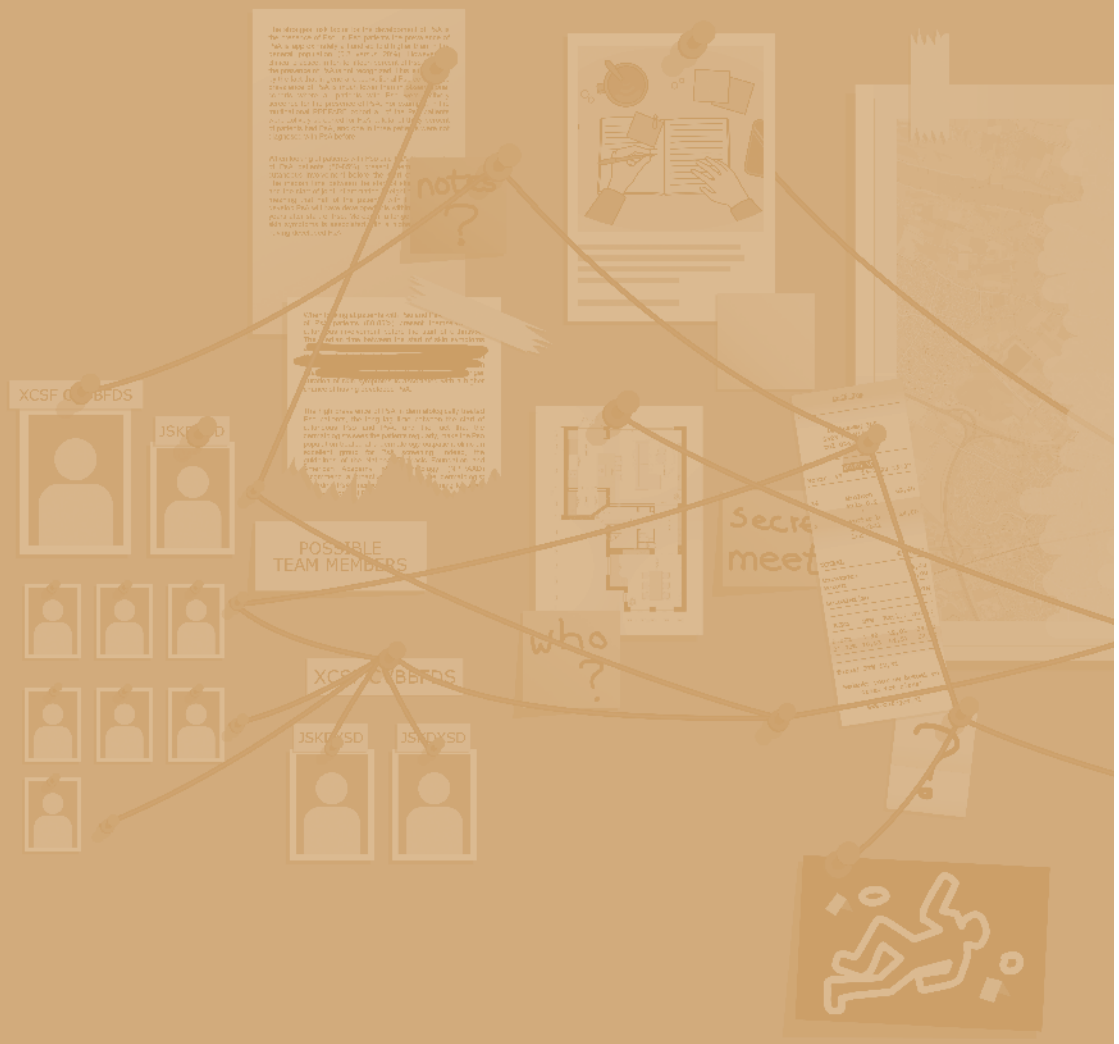
Data collection, analysis and storage

Data from the PART2 study is collected through hardcopy questionnaires and notes in HiX, the electronic patient file. Data was entered into an electronic Case Report Forms (eCRF) using Castor EDC, a cloud-based clinical data management platform with an incorporated audit trail. Data were converged from Castor EDC to Stata (StataCorp LLC, College Station, Texas, USA) for analyses. Data and analyses are stored at the digital archives of the Sint Maartenskliniek (V:/). Data and analyses are only accessible to research personnel. Paper (hardcopy) data is at the archive of the Department of Research & Innovation of the Sint Maartenskliniek.

Availability of data

The article is published open access. The data will be archived for 15 years after termination of the study. The pseudonymized dataset is not published in a repository, but is available upon reasonable request.

Theses Sint Maartenskliniek



Theses Sint Maartenskliniek

Boekesteijn, R. (2024) *Evaluating walking in lower-extremity osteoarthritis: Beyond the lab, towards the real world.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Te Molder, M. (2024). *The unhappy patient after TKA. A paradigm shift in assessing outcome.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Kuijpers, R. (2024). *Adapt your step: Clinical assessment and training of walking adaptability in children with mild motor disorders.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Den Broeder, A. (2024). *More than tapering, less than full dose - Efficient use of biologics in the treatment of rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Veenstra, F. (2024). *About gout. Studying potential targets for improvement of care.* Radboud University Nijmegen, Nijmegen. The Netherlands.

De Jong, L.A.F. (2023). *Effects of lower limb orthotic devices in people with neurological disorders.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Michielsens, C. (2023). *Tapering strategies of biologics in inflammatory disorders*. Radboud University Nijmegen, Nijmegen. The Netherlands.

Pouls, B. (2023). *Supporting patients'medication management using eHealth. Test cases in rheumatology*. Radboud University Nijmegen, Nijmegen. The Netherlands.

Stöcker, J. (2023). *Accessible and effective non-pharmacological care for persons with systemic sclerosis*. Radboud University Nijmegen, Nijmegen. The Netherlands.

Mulder, M. (2022). *Going off-road. Exploring and mapping psoriatic arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Huiskes, V. (2022). *The synergistic role of patients and healthcare providers in reducing drug-related problems.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Marsman, D. (2022). *Polymyalgia rheumatica. Clinical characteristics and new treatment opportunities.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Alingh, J. (2021). *Effect of robotic gait training on the post-stroke gait pattern. Evaluation of LOPES II.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Van Dijsseldonk, R. (2021). *Step into the future: mobility after spinal cord injury*. Radboud University Nijmegen, Nijmegen, The Netherlands.

Pelle, T. (2021). *Beating osteoarthritis by e-self management in knee or hip osteoarthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Van Heuckelum, M (2020). *Novel approaches to improve medication adherence in rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Mathijssen, E. (2020). *The voice of patients with rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Bakker, S. (2019). *Regional anesthesia and total knee arthroplasty. Anesthetic and pharmacological considerations.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Claassen, A. (2019). *Strategies for patient education in rheumatic diseases.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Fenten, M. (2019). *Optimizing locoregional anesthesia in fast track orthopaedic surgery.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Minten, M. (2019). *On the role of inflammation and the value of low dose radiation therapy in osteoarthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Verhoef, L. (2019). *Effective and efficient use of bDMARDs in rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Bekker, C. (2018). *Sustainable use of medication. Medication waste and feasibility of redispensing.* Utrecht University, Utrecht. The Netherlands.

Bikker, I.(2018). *Organizing timely treatment in multi-disciplinary care.* University of Twente, The Netherlands.

Bouman, C. (2018). *Dose optimisation of biologic DMARDs in rheumatoid arthritis: long-term effects and possible predictors.* Radboud University Nijmegen, The Netherlands.

Mahler, E. (2018). *Contributors to the management of osteoarthritis.* Utrecht University, The Netherlands.

Tweehuysen, L. (2018). *Optimising biological treatment in inflammatory rheumatic diseases. Predicting, tapering and transitioning.* Radboud University Nijmegen, Nijmegen, The Netherlands.

Geerdink, Y. (2017). *Getting a grip on hand use in unilateral cerebral palsy.* Radboud University, Nijmegen, The Netherlands.

Remijn, L. (2017). *Mastication in children with cerebral palsy.* Radboud University, Nijmegen, The Netherlands.

Selten, E. (2017). *Beliefs underlying treatment choices in osteoarthritis.* Radboud University, Nijmegen, The Netherlands.

Van Hooff, M. (2017). *Towards a paradigm shift in chronic low back pain? Identification of patient profiles to guide treatment.* VU University Amsterdam, Amsterdam, The Netherlands.

Lesuis, N. (2016). *Quality of care in rheumatology. Translating evidence into practice.* Radboud University, Nijmegen, The Netherlands.

Luites, J. (2016). *Innovations in femoral tunnel positioning for anatomical ACL reconstruction.* Radboud University, Nijmegen, The Netherlands.

Pakvis, D. (2016). *Survival, primary stability and bone remodeling assessment of cementless sockets. An appraisal of Wolff's law in the acetabulum*. Radboud University, Nijmegen, The Netherlands.

Schoenmakers, K. (2016). *Prolongation of regional anesthesia. Determinants of peripheral nerve block duration.* Radboud University, Nijmegen, The Netherlands.

Altmann, V. (2015). *Impact of trunk impairment on activity limitation with a focus on wheelchair rugby.* Leuven University, Leuven, Belgium.

Bevers, K. (2015). *Pathophysiologic and prognostic value of ultrasonography in knee osteoarthritis.* Utrecht University, Utrecht, The Netherlands.

Cuperus, N. (2015). *Strategies to improve non-pharmacological care in generalized osteoarthritis.* Radboud University, Nijmegen, The Netherlands.

Kilkens, A. (2015). *De ontwikkeling en evaluatie van het Communicatie Assessment & Interventie Systeem (CAIS) voor het aanleren van (proto-)imperatief gedrag aan kinderen met complexe ontwikkelingsproblemen.* Radboud University, Nijmegen, The Netherlands.

Penning, L. (2015). *The effectiveness of injections in cuffdisorders and improvement of diagnostics.* Maastricht University, Maastricht, The Netherlands.

Stegeman, M. (2015). *Fusion of the tarsal joints: outcome, diagnostics and management of patient expectations.* Utrecht University, Utrecht, The Netherlands.

Van Herwaarden, N. (2015). *Individualised biological treatment in rheumatoid arthritis.* Utrecht University, Utrecht, The Netherlands.

Wiegant, K. (2015). *Uitstel kunstknie door kniedistractie.* Utrecht University, Utrecht, The Netherlands.

Willems, L. (2015). *Non-pharmacological care for patients with systemic sclerosis.* Radboud University, Nijmegen, The Netherlands.

Witteveen, A. (2015). *The conservative treatment of ankle osteoarthritis.* University of Amsterdam, Amsterdam, The Netherlands.

Zwikker, H. (2015). *All about beliefs. Exploring and intervening on beliefs about medication to improve adherence in patients with rheumatoid arthritis.* Radboud University, Nijmegen, The Netherlands.

Koenraadt, K. (2014). *Shedding light on cortical control of movement.* Radboud University, Nijmegen, The Netherlands.

Smink, A. (2014). *Beating Osteoarthritis. Implementation of a stepped care strategy to manage hip or knee osteoarthritis in clinical practice.* VU University Amsterdam, Amsterdam, The Netherlands.

Stolwijk, N. (2014). *Feet 4 feet. Plantar pressure and kinematics of the healthy and painful foot.* Radboud University, Nijmegen, The Netherlands.

Van Kessel, M. (2014). *Nothing left? How to keep on the right track. Spatial and non-spatial attention processes in neglect after stroke.* Radboud University, Nijmegen, The Netherlands.

Brinkman, M. (2013). *Fixation stability and new surgical concepts of osteotomies around the knee.* Utrecht University, Utrecht, The Netherlands.

Kwakkenbos, L. (2013). *Psychological well-being in systemic sclerosis: Moving forward in assessment and treatment.* Radboud University, Nijmegen, The Netherlands.

Severens, M. (2013). *Towards clinical BCI applications: assistive technology and gait rehabilitation.* Radboud University, Nijmegen, The Netherlands.

Stukstette, M. (2013). *Understanding and treating hand osteoarthritis: a challenge.* Utrecht University, Utrecht, The Netherlands.

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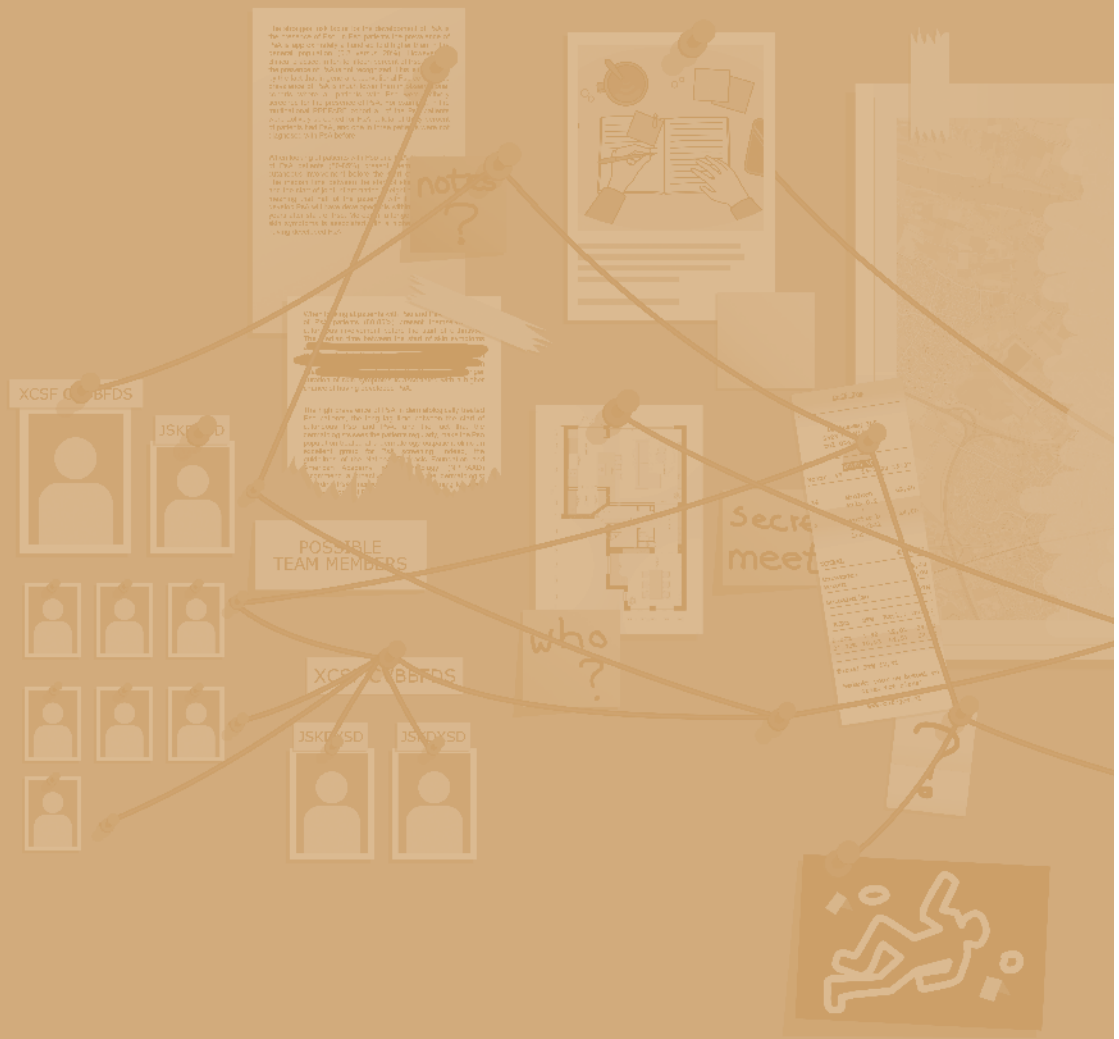
Dankwoord



Dankwoord

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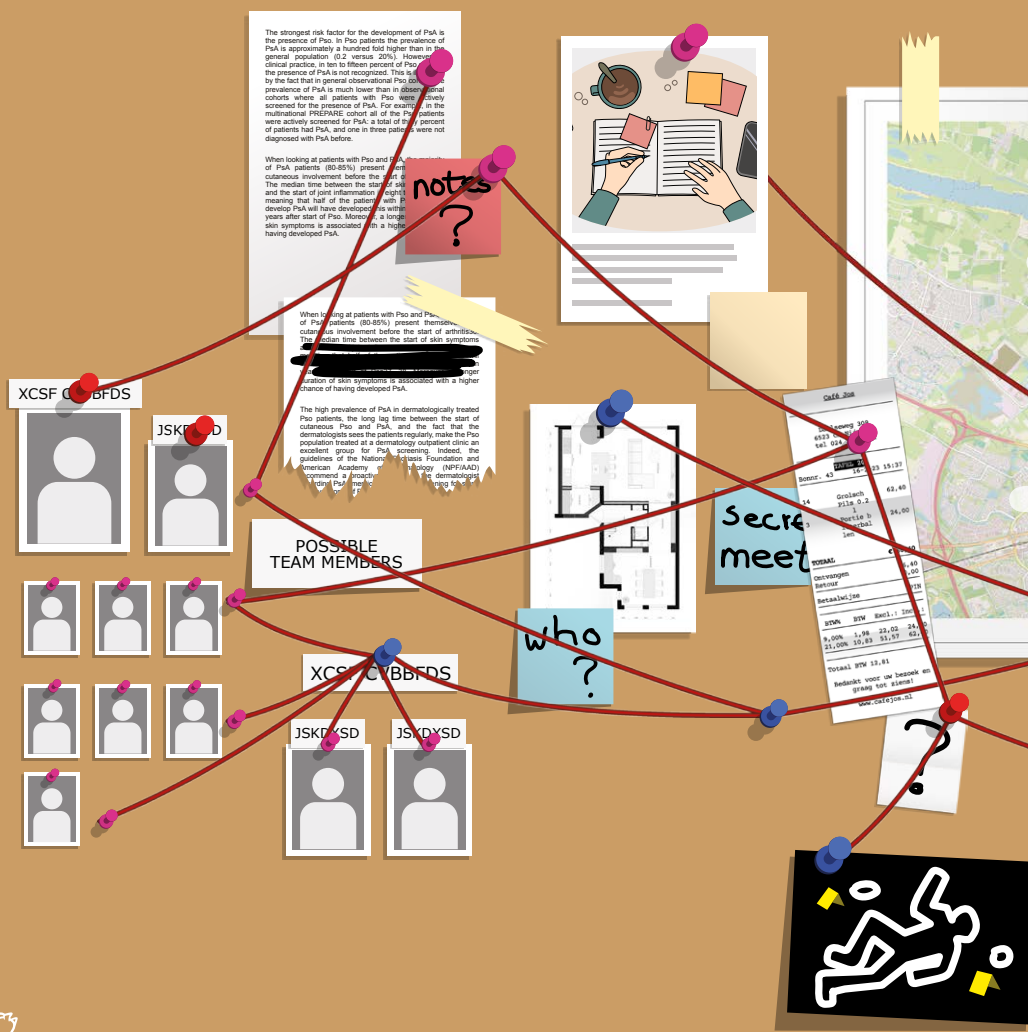

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