Underexposed Areas in Psoriasis Care:

Insights from Real-World Evidence

Malak Al-Gawahiri

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CHAPTER 1

General introduction and thesis outline

Introduction

Psoriasis is a complex and often underestimated inflammatory disease, the impact of which stretches well beyond dermatological symptoms, affecting many aspects of patients' lives. It is estimated that approximately 2-4% of the population in western countries is affected.[1, 2] In about one-third of patients onset of psoriasis is before the age of 18 years.[3, 4] Despite this, the majority of psoriasis research has historically centered on adults, resulting in knowledge gaps in pediatric patients. Although the number of studies on pediatric patients with psoriasis have increased in recent years,[5-8] there are still some unattended areas including the lack of definitions for disease severity, limited data on treatment outcomes in specific subgroups, including sex-specific differences, and insufficient knowledge about the development of psoriatic arthritis. Addressing these topics is important for improving pediatric psoriasis care.

Even in adult psoriasis, some aspects of psoriasis care have only recently started to receive adequate attention. For example, while research has addressed comorbidities, relatively little attention has been given to patients' lifestyle,[9-14] despite its potential role in the prevention and management of comorbidities. At the start of this PhD trajectory, little was known about lifestyle behaviors among adults with psoriasis and their motivation to change their habits. Additionally, it is increasingly recognized that the impact of psoriasis extends beyond physical symptoms, affecting patients' quality of life and their psychological and social well-being. Adults living with psoriasis often report emotional distress and reduced mental health, yet the underlying psychosocial and socioeconomic factors contributing to this burden remained insufficiently understood.

These overlooked patient groups and facets of care reflect the underexposed areas in psoriasis that this thesis aims to illuminate, using insights from real-world data and everyday clinical practice.

Clinical features

Psoriasis is a chronic, immune-mediated inflammatory disease, with several clinical subtypes, such as plaque psoriasis, guttate psoriasis, pustular psoriasis, and erythrodermic psoriasis.[15] Plaque psoriasis is the most common subtype overall, characterized by well-demarcated erythematous scaly

patches or plaques that may cause itching, pain or burning.[16] Psoriasis affects both adults and children, but its clinical presentation varies between the groups. In adults, plaque psoriasis typically involves extensor surfaces such as elbows and knees, though it can also affect intertriginous skin, scalp, nails, palms and soles.[16, 17]

In pediatric patients, plaque psoriasis accounts for 68-90% of cases,[18-21] and often presents with smaller erythematous lesions and less pronounced scaling and induration than in adult patients.[20] In pediatric patients, psoriasis commonly affects the scalp, postauricular region, face, umbilicus, anogenital region and elbows and knees. Nail psoriasis occurs less frequently in children than in adult patients with psoriasis.[22] However, when present, it may serve as a potential clinical predictor for more severe disease course over time.[22] The clinical presentation of psoriasis often varies with age. In young infants, psoriasis commonly affects the diaper area, often referred to as "napkin psoriasis".[20, 23-25] In older children and adolescents, however, the clinical presentation more closely resembles that observed in adults.

The second most common subtype of psoriasis in pediatric psoriasis is guttate psoriasis, which occurs more frequently in children than adults, accounting for 14-29% of pediatric cases compared to approximately 2% in adults.[16, 19, 20, 26] Guttate psoriasis manifests as multiple small droplet-like erythematous scaly papules on extremities and trunk.[19] The development of guttate psoriasis is often preceded by infections, especially group A beta hemolytic streptococcus of the pharyngeal or perineal area. Guttate psoriasis following streptococcal infection may spontaneously remit, but in a portion of patients, it eventually evolves into plaque psoriasis.[19, 27]

Burden of disease

Pediatric psoriasis is known to substantially impact the quality of life of those affected.[6, 28] Pediatric patients particularly experience itch and problems with psoriasis treatment. Both have shown to have a pronounced impact on the quality of life of these patients.[28, 29] A large study with data from >1000 pediatric patients with psoriasis across six countries showed that itching affected multiple areas of a patients' life, including sleep, school, social and physical activities, and that the most frequently reported treatment goal was 'to relieve itching'.[28] The visibility of psoriasis has also shown to result in social

discomfort, embarrassment and anxiety in children.[4, 25] Children can also experience social exclusion by peers, teasing, and name calling,[4, 19] which can negatively impact their self-esteem and anxiety levels, potentially leading to a significant psychiatric burden.[4] Supporting these findings, a recent systematic review showed that psoriasis negatively affects the pediatric patients life in various domains, including quality of life, physical burdens, psychological burdens, social burdens, and family burdens, although research in some of these domains is limited and many studies use unvalidated tools or tools without well-defined cutoffs.[6] For a detailed discussion on the psychological and mental health impact of (adult) psoriasis, see the 'mental health' subsection under Comorbidities.

Immunopathogenesis

Historically, psoriasis was characterized as a skin disorder involving abnormal keratinocyte differentiation and proliferation. However, since the 1980s, advances in immunology have shifted this perspective significantly, highlighting the important role of T cells and the complex involvement of both innate and adaptive immunity.[15, 16, 30, 31] Since then, considerable research has aimed to better understand the complex immunopathogenesis of psoriasis. Current evidence suggests that psoriasis arises from an interaction involving innate and adaptive immune systems, influenced by environmental factors and genetic susceptibility.[15, 32-34]

In complex diseases such as psoriasis, genetic susceptibility is typically mediated by multiple genetic variants across the genome. These variants are located at specific positions on chromosomes, known as loci. Genome-wide association studies (GWAS) are a key method for uncovering these loci. The most recent GWAS meta-analysis by Dand et al. examined data from 18 studies involving nearly 500.000 unrelated individuals of European ancestry, of which about 36000 psoriasis cases, and identified a total of 109 distinct loci, including 50 novel loci previously unreported in this population.[33] Among these, the Major Histocompatibility Complex (MHC) class I allele *HLA- C*06:02*, stands out as the most significant genetic risk factor, accounting for a substantial portion of the genetic risk for psoriasis.[33, 34] This allele is a specific variant of the *HLA-C* gene, which is located within the MHC region on the short arm of chromosome 6 (6p21.13). It has been strongly associated with early-onset psoriasis and is more frequently observed in patients with a more severe psoriasis.[15, 35-37]

Environmental factors have also been found to play a large role in the pathogenesis of psoriasis, including infections (particularly streptococcal), stress, skin trauma (Koebner phenomenon), smoking, obesity, and certain medications.[15, 38] The influence of environmental triggers points to a potential role for epigenetic modifications, which can dynamically regulate gene expression without altering the DNA sequencing. In psoriasis, epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNA activity have been shown to affect immune responses and keratinocyte behavior, contributing to disease development and severity.[34, 38]

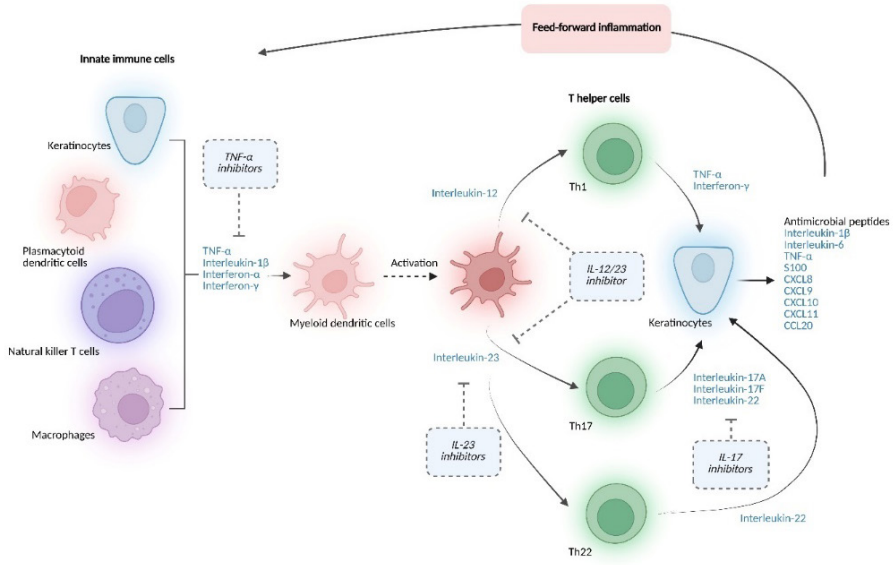

Figure 1. Immune pathogenesis of psoriasis. Abbreviations: TNF-α, tumor necrosis factor alfa; IL, interleukin; Th, T helper; CXCL, chemokine ligand; CCL, chemokine ligand.

The interplay of the innate and adaptive immune system in psoriasis is complex. The innate immune system acts as the body's initial line of defense, identifying invading pathogens in a non-specific manner. Plasmacytoid dendritic cells, macrophages, natural killer T-cells, and keratinocytes belong to the innate immunity.[39] These cells secrete cytokines, including tumor necrosis factor-alpha (TNF-α), Interferon-gamma (IFN-γ), Interferon-alpha (IFN-α) and Interleukin-1 beta (IL-1β), which activate myeloid dendritic cells (Figure 1).[15] Other important triggers in this process are antimicrobial peptides, such as LL-37, which are produced by keratinocytes. These antimicrobial peptides can bind to self-DNA released from damaged cells, to form complexes that

activates myeloid dendritic cells through toll-like receptor pathways.[15, 31] This results in the initiation of the adaptive immune phase. After activation, myeloid dendritic cells migrate to draining lymph nodes and secrete Interleukin-12 (IL-12) and Interleukin-23 (IL-23), which activate the differentiation of naïve T-cells into T-helper cells Th1, Th17 and Th22. [15, 40] These T-helper cells subsequently secrete IFN-γ, TNF-α, IL-17, and IL-22. These cytokines drive keratinocyte proliferation, stimulate the production of angiogenic mediators that promote blood vessel formation, upregulate adhesion molecules expression on endothelial cells, and facilitate immune cell infiltration onto the affected skin, driving the inflammatory cascade characteristic of psoriasis.[15] This expanded perspective on the immunopathogenesis in psoriasis has shaped a more comprehensive understanding of the disease, facilitating the development of targeted therapeutic strategies.

Treatment options, with a special focus on pediatric psoriasis

Treatment of psoriasis in pediatric patients has come a long way, and currently includes therapeutic options such as topical therapy, photo therapy, conventional systemic treatments, biologics and oral targeted therapy (Figure 2).[19, 25]

Topical therapy

Topical treatments are considered the first line of therapy in (pediatric) psoriasis. Whereas research on the safety and effectiveness of the use of topical therapies in pediatric psoriasis remains limited, extensive clinical experience support the use of these topical therapies.[19, 41, 42] Other reasons for the use of topical therapy include the ease of application, accessibility and low costs, as well as, safety when used properly.[42] Commonly used topical agents include topical corticosteroids, vitamin D analogues, calcineurin inhibitors, or a combination of these therapies. Topical corticosteroids have anti-inflammatory, antiproliferative and immunosuppressant properties, and are frequently used in pediatric patients.[42] Potential adverse events include cutaneous atrophy, striae, and telangiectasia. Other less frequently observed adverse events, particularly with extensive, widespread, and occlusive use of potent topical corticosteroids, may include systemic effects such as suppression of the hypothalamic-pituitary-adrenal axis.[43] Consequently, topical corticosteroids should be applied intermittently and alternated with nonsteroidal topical treatment to minimize risks.[25] Nonsteroidal topical treatment which can be used

include vitamin D analogues, namely calcipotriol and calcitriol, or calcineurin inhibitors, such as tacrolimus and pimecrolimus.[19, 44]

Dithranol (anthralin)

Another nonsteroidal topical agent demonstrated to be effective for moderate-to-severe (pediatric) psoriasis is dithranol, or anthralin, which shows both anti-proliferative and anti-inflammatory properties.[42, 45, 46] In our hospital, dithranol is available as cream or ointment in various concentrations and is applied in a day-care setting using two treatment approaches. In the 24-hour treatment, dithranol ointment is started at a low concentration (0.05%, or 0.03% in fair-skinned patients) and gradually increased every 3-4 days. In the short-contact therapy, dithranol cream is applied once daily, with concentration and contact time gradually increased from 15 to 45 minutes until skin clearance is (almost) achieved.[46] Possible adverse effects include skin irritation and staining at the application site or clothing.[45]

Phototherapy

Narrow-band Ultraviolet UBV (NB-UVB) has also proven to be an effective option in pediatric patients, particularly in adolescent patients that have failed topical treatment. This is especially beneficial for guttate and thin plaque psoriasis.[25, 47] However, phototherapy should be administered with caution in pediatric patients, particularly pre-adolescent and fair-skinned patients, due to potential long-term side effects. Although the long-term safety of NB-UVB phototherapy in pediatric patients is not well documented, in adults it has been shown to cause actinic damage, premature photoaging, and an increased risk of non-melanoma skin cancers such as squamous cell carcinoma.[47, 48] Short-term side effects are usually mild and include blistering, pruritus, burning, and erythema.[47]

Systemic therapy

Systemic treatments for psoriasis include conventional systemic treatments, such as methotrexate, fumaric acid, acitretin, and ciclosporin, as well as biologics and targeted oral systemics/small molecule inhibitors. While conventional systemic therapies are commonly prescribed, they are often used off-label in pediatric psoriasis. The emergence of biologic therapies has expanded treatment options for pediatric patients with moderate-to-severe psoriasis.[25, 49] The first biologic approved for the treatment of moderate-to-severe pediatric psoriasis by the European Medicine Agency (EMA) was etanercept, a recombinant human protein that acts by inhibiting the activity of TNF-α, a key cytokine involved in inflammatory processes.[50, 51] At present,

five biologics are approved by the European Medicine Agency (EMA) for the treatment of moderate-to-severe psoriasis in pediatric patients: the TNFα-inhibitors adalimumab and etanercept, the IL 12/23 inhibitor ustekinumab, and IL17 inhibitors secukinumab and ixekizumab.[52]

Other biologic therapies, such as the TNFα-inhibitors infliximab and certolizumab, the IL17 inhibitors brodalumab and bimekizumab, and the IL23 inhibitors guselkumab, risankizumab and tildrakizumab, are also used in the treatment of moderate-to-severe psoriasis, although currently only approved in adults and not yet in pediatric psoriasis patients.[5, 52, 53]

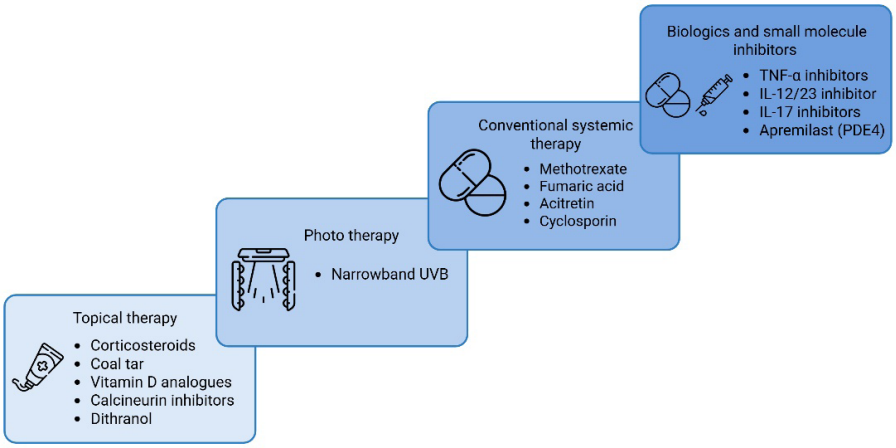

Figure 2. Treatment options for pediatric patients with psoriasis. Some of the listed therapies are not formally approved for pediatric use (off-label use). Abbreviations: UVB, ultraviolet B; TNF-α, tumor necrosis factor alfa; IL, interleukin; PDE4, phosphodiesterase-4.

Recently, oral targeted therapy has also found its way into pediatric psoriasis treatment. Apremilast, a small molecule inhibitor of phosphodiesterase-4 (PDE-4), was approved by the EMA for the treatment of pediatric patients with psoriasis in October 2024.[54] Deucravacitinib, an oral selective Tyrosine Kinase 2 (TYK2) inhibitor, which is approved for treatment of adult patients with psoriasis has also shown promising results among adults,[53, 55, 56] but is not yet approved for use in pediatric psoriasis patients.[5]

Initiation of systemic therapy among pediatric patients

Although there are several systemic therapy options available for pediatric patients with psoriasis, there are currently no definitions to assist physicians in determining when to initiate systemic treatment. A common definition

used in adult psoriasis, is the Rule of Tens (R10), in which severe psoriasis is defined as having at least one of the following: Body Surface Area (BSA) >10%, Psoriasis Area and Severity Index (PASI) >10 or Dermatology Life Quality Index (DLQI) >10.[57] More recently, the International Psoriasis Council consensus statement (IPCcs) was proposed as a new definition to categorize adult patients as candidates for either topical or systemic therapy.[58] Patients were considered candidates for systemic therapy if they met at least one of the following criteria: BSA >10%, disease involving special areas (face, palms, soles, intertriginous skin, scalp or nails), or failure of topical therapy.[58] The definitions R10 and IPCcs have been developed for adults, and although they are occasionally applied to children, it is unclear whether these definitions are suitable for application in the decision making process for initiation of systemic therapy in pediatric patients with psoriasis. Notably, while R10 focusses on psoriasis extent and quality of life, it does not consider other clinically relevant factors such the involvement of high impact sites and failure of topical treatment, which are included in IPCcs.

Additionally, upon starting systemic therapy, it is also important to consider factors that may influence treatment outcomes. In adult patients with psoriasis that are treated with biologics, sex differences in disease severity, treatment satisfaction, adverse events, and drug survival have been observed.[59-64] Males often present with more severe disease at biologic initiation,[59, 60] while females report lower quality of life and higher rates of treatment discontinuation due to adverse effects.[60-64] However, it remains unclear whether these sex-disparities are also present among pediatric or young adult patients with psoriasis, as research in these populations is limited.

Comorbidities

The understanding of psoriasis has evolved considerably. Psoriasis is now recognized as a systemic inflammatory disease, rather than a condition once thought to be confined to the skin.[65-68] This is supported by immunopathogenesis insights showing the involvement of numerous proinflammatory cytokines, including but not limited to tumor necrosis factor (TNF)-α, interleukin (IL)-17, IL-22, IL-23, and IL-1β, and interferon (IFN)-γ.[65] These cytokines stimulate keratinocyte hyperproliferation and sustain a cycle of chronic inflammation, which is associated with various comorbidities which are observed in patients with psoriasis. In adult psoriasis, common comorbidities include cardiovascular

disease, obesity, metabolic disorders such as hypertension, dyslipidemia, and type 2 diabetes mellitus, inflammatory bowel disease, mental health disorders, and psoriatic arthritis.[65, 66, 69, 70] While studies on comorbid diseases in pediatric patients with psoriasis are limited, accumulating evidence has shown similar associations, including obesity, hyperlipidemia, hypertension, diabetes mellitus, psychiatric disorders, Crohn's disease and psoriatic arthritis.[3, 4, 25, 71-73]

Psoriatic arthritis

Although juvenile psoriatic arthritis (JPsA) was first described several decades ago, it remains a diagnostic challenge in pediatric patients without visible psoriasis lesions. JPsA is currently recognized by pediatric rheumatologists as a distinct category within the broader classification of juvenile idiopathic arthritis (JIA), accounting for approximately 8% (range 4-11%) of all JIA cases.[74-78] However, the clinical presentation of JPsA in pediatric patients is highly heterogeneous, which complicates early and accurate diagnosis.[79, 80] Although widely used, both historic and recent classification systems, such as the Vancouver criteria and ILAR (international League of Associations for Rheumatology) criteria,[81, 82] have proven insufficiently specific in identifying patients with juvenile psoriatic arthritis. Limitations include concerns about the age cutoff at 16 years and the exclusion of certain clinical and laboratorial presentations.[83]

Notably, most existing literature on JPsA is derived from rheumatology-based cohorts, which often consist of mixed populations including children with arthritis with or without a confirmed diagnosis of psoriasis.[79, 84-87] To date, no large-scale cohorts have been described from a dermatological perspective, containing patients with pediatric onset psoriasis that develop juvenile psoriatic arthritis subsequent to skin symptoms. Furthermore, identifying clinical features in these patients could enhance early detection and management of JPsA. However, data on these features remain limited. Additional research is needed to better understand the timing of psoriatic arthritis onset in this population and to identify clinical characteristics associated with its development.

Mental health

Patients with psoriasis face physical and social challenges,[88-90] which contribute to heightened psychological burden. This is reflected by the increased rates of mental health conditions among the adult psoriasis population. According to a recent review by Hedemann et al., adult patients with psoriasis experience

depressive symptoms 1.5 times more often than individuals without psoriasis, while anxiety symptoms affect between 20% and 50% of patients.[14] Previous research has extensively examined factors associated with depression and anxiety in adult patients with psoriasis. However, these studies have mainly focused on well-known factors such as sex, age, and disease severity,[13, 91, 92] while the influence of psychological and socioeconomic factors remains underexplored. This highlights an important gap in the literature that needs to be assessed.

Cardiometabolic comorbidities and the role of lifestyle

Patients with psoriasis have an increased risk for cardiovascular and metabolic diseases compared to controles.[93-97] In addition, moderate-to-severe psoriasis is associated with up to a 2.5 fold risk of cardiovascular mortality,[96, 98, 99] underscoring the importance of prevention, and management of cardiometabolic comorbidities. Many cardiometabolic comorbidities observed in adult patients with psoriasis, such as obesity, hypertension, diabetes mellitus type 2 and dyslipidemia, have been found to be positively influenced by healthy lifestyle changes. Previous studies have demonstrated that particularly weight loss through dietary changes and increased physical activity are associated with significant improvements in both psoriasis severity and metabolic risk factors.[9, 10, 100-102] A narrative review by Van Acht et al. identified 34 intervention studies in adult patients with psoriasis, covering the lifestyle domains of diet, physical exercise and relaxation.[9] No interventional studies were found regarding smoking, alcohol and sleep. The review highlights that dietary modifications, especially weight loss and calorie restriction, combined with or without physical exercise, in overweight and obese patients, can have a positive impact on reduction of psoriasis severity and improvement of quality of life.

Successfully implementing lifestyle changes in psoriasis patients requires an understanding of their motivation to change and identifying which lifestyle domains they are most willing to address. However, such data are lacking. Gaining comprehensive insight into patients' current lifestyle habits is essential, yet most existing studies are small and focus on only one or two lifestyle factors, such as diet or physical activity.[103-105] A more complete understanding of patients' lifestyle, including all six lifestyle domains (physical activity, diet, alcohol, smoking, stress and sleep) could provide more insight and potentially reveal new opportunities for intervention.

Real-world evidence

There are various methodologies and study designs available to generate data for research. Historically, randomized controlled trials (RCTs) have been considered the gold standard due to their experimental design, which minimizes the risk of bias. However, RCTs present several limitations: they require a fixed, predefined follow-up schedule, consistent investigator(s), strict adherence to the protocol without deviation in response to unforeseen events, and most importantly, a homogeneous study population.[106] These constraints often limit the external validity and practical applicability of RCT findings.

In contrast, real-world evidence (RWE) enables investigation within a real-world clinical setting, reflecting routine practice. This approach allows inclusion of more diverse patient populations typically excluded from RCTs, such as children, women, and elderly individuals, resulting in a more heterogeneous cohort. Moreover, RWE studies are not restricted to evaluating a single intervention, thereby broadening the scope of research possibilities.[106, 107]

In this thesis, we utilized real-world data through two prospective daily practice registries, as well as patient questionnaires.

ChildCAPTURE

Data on pediatric and young adults with psoriasis used in this thesis originated from the ChildCAPTURE (Continuous Assessment of Psoriasis Treatment Use REgistry) registry, a prospective, daily clinical practice registry of children and adolescents treated at the Department of Dermatology at the Radboud University Medical Center in Nijmegen, the Netherlands.[7] Since its inception in 2008, the registry has included over 700 pediatric patients with psoriasis. Children under the age of 18 are enrolled at their first visit to the department, following informed consent provided by themselves and/or their parents or legal guardians.

Data collected at the initial visit include demographics, treatment history, medical history, and family medical history. Additionally, at both the baseline and each follow-up visit, disease severity scores, such as the Psoriasis Area and Severity Index (PASI), Physician Global Assessment (PGA), and Body Surface Area (BSA) affected are assessed, alongside patient-reported outcomes, including the Children's Dermatology Life Quality Index (CDLQI)

and/or the Dermatology Life Quality Index (DLQI). Data management is conducted using the electronic data capture systems CASTOR and DRE. The registry was reviewed and approved by the local ethics committee.

BioCAPTURE

Data of the BioCAPTURE registry were utilized in this thesis to gain further knowledge on young adults (between 18 and 30 years) with plaque psoriasis treated with biologics. The BioCAPTURE registry is a prospective, observational, long-term, daily clinical practice of adult patients (>18 years) treated with biologics, who received care at four academic and twenty-four non-academic centers in the Netherlands, since 2005. Similar to the ChildCAPTURE registry, data collected at the initial visit include demographics, treatment history, medical history, and family medical history. In addition, disease severity score, such as the Psoriasis Area and Severity Index (PASI), Physician Global Assessment (PGA), and Body Surface Area (BSA) are assessed at both the baseline and each follow-up visit, alongside with patient-reported outcomes, including the Dermatology Life Quality Index (DLQI). Data management is conducted using the electronic data capture systems CASTOR and DRE. The registry was reviewed and approved by the local ethics committee.

Surveys

Surveys play an important role in the collection of qualitative and quantitative data and have been widely used in dermatology for various purposes, including gathering information on patients attitudes and behaviors, treatment satisfaction, and assessment of quality of life.[108-110] Web based surveys particularity enable the inclusion of a broader and more diverse patient population beyond those attending a hospital setting. To explore lifestyle habits, attitudes towards lifestyle changes, and psychological well-being among adult patients with psoriasis, a national web-based survey was conducted in this thesis. This approach allowed for the inclusion of patients with a disease severity varying from mild to severe. The survey consisted of multiple-choice and open-ended questions, and collected information on demographic and clinical characteristics. While the primary focus of the survey was on lifestyle behaviors and patients' motivation to change them, it also incorporated validated psychological instruments, including the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder-7 (GAD-7) to assess symptoms of depression and anxiety, and the ENRICHD Social Support Instrument (ESSI) to evaluate perceived social support.

Outcome measures

Psoriasis severity

Commonly used psoriasis severity score measures are the Psoriasis Area and Severity Index (PASI, range 0-72), the Body Surface Areas (BSA, range 0-100%) and the Physician Global Assessment (PGA, range 0-5).[57, 111, 112] The BSA quantifies skin involvement in patients with psoriasis by measuring the affected area as a percentage of the total body surface.[113, 114] Accurate estimation requires using the entire palmar surface including fingers, rather than the palm alone, to obtain a reliable approximation of 1% of BSA.[114] The PASI combines this measure of affected body surface area with the intensity of clinical symptoms. The body is divided into four regions: head, upper limbs, trunk, and lower limbs, and for each region, the percentage of affected skin is estimated. Within these regions, three clinical symptoms are evaluated: erythema, induration, and desquamation, with each symptoms receiving a score ranging from 0 (absent) to 4 (severe). To calculate the score for each region, the clinical symptoms severity scores are multiplied by the proportion of affected skin. However, as each body region accounts for different percentage of the total body surface area, the scores are weighted accordingly. Finally, the weighted scores from all regions are summed to yield the total PASI score. The total PASI score ranges from 0 to 72,[111] with a PASI of >10 generally being considered as severe psoriasis.[57] The PGA is a subjective clinician-rated scale that provides an overall assessment of disease severity. Although several variants of the PGA exist, our hospital uses a 6-point scale (0-5), ranging from 'clear' to 'severe'.[112, 115-117]

Health-related quality of life (HRQoL)

The Children's Dermatology Life Quality Index (CDLQI) and the Dermatology Life Quality Index (DLQI) are widely used patient-reported outcome measures to assess the impact of skin diseases on quality of life.[118, 119] The CDLQI is specifically developed and validated for children aged 4 to 16 years and includes questions about symptoms and feelings, leisure, school or holiday, personal relationships, sleep, and treatment. The DLQI is validated for patients over 16 years of age and focuses on leisure, work or school, personal relationships, and treatment. Both instruments consist of 10 questions. Total scores range from 0 to 30, where higher scores reflect a greater impact on quality of life. While the number of items is the same, the content differs to reflect age-appropriate themes.

Psychosocial questionnaires

The Patient-Health Questionnaire-9 (PHQ-9) is a widely used screening tool for the assessment of depressive symptoms.[120-122] The PHQ-9 consists of nine items scored from 0 to 3, resulting in a total score ranging from 0 to 27. Higher scores indicate more severe depressive symptoms.[120] The General Anxiety Disorder-7 (GAD-7) questionnaire assesses the severity of general anxiety disorder symptoms. The GAD-7 includes seven items scored from 0 to 3, with a maximum score of 21. Higher scores indicate more severe symptoms of anxiety.

The ENRICHD Social Support Instrument (ESSI) evaluates patients' perceived social support.[123, 124] The ESSI is a 7-item self-report questionnaire, rated on a 5-point Likert scale and designed to measure four key aspects of social support: emotional, instrumental, informational, and appraisal.[125] ESSI scores of 3 or less on at least two items, with a total score of 18 or below, is considered as low perceived social support according to standard criteria.[123]

Outline and aims of this thesis

In this thesis, we aimed to improve the care of patients with psoriasis by addressing underexposed areas in both pediatric psoriasis (chapter 2, 3 and 4) and adult psoriasis (chapter 5 and 6).

Underexposed areas in pediatric psoriasis care

CHAPTER 2

An important underexplored aspect of pediatric psoriasis care involves up to date criteria for the initiation of systemic therapy in pediatric patients with psoriasis. Accurately identifying pediatric patients who are candidates for systemic therapy remains challenging and criteria do not exist yet. In adult psoriasis care, definitions for disease severity, such as the Rule of Tens (R10)[57] and the International Psoriasis Council consensus statement (IPCcs),[58] are used. It is yet unclear whether these definitions can be applied to pediatric patients with psoriasis. While R10 focusses on psoriasis extent and quality of life, IPCcs includes the involvement of high impact sites (face, palms, soles, intertriginous skin, scalp or nails) and failure of topical treatment as important criteria alongside psoriasis extent. However, the influence of clinical characteristics such as involvement of high impact sites on the quality of life in pediatric patients with psoriasis has not been investigated yet.

In chapter 2 we aimed to propose criteria for the initiation of systemic therapy in pediatric psoriasis patients.

To do so the following sub-aims were formulated:

1a. To determine the percentage of pediatric patients with psoriasis fulfilling the adult R10 and IPCcs definitions for initiation of systemic therapy.

1b. To investigate the influence of clinical characteristics, such as involvement of high impact sites, on the quality of life as measured by the Children's Dermatology Life Quality Index (CDLQI)

CHAPTER 3

In adult patients with psoriasis treated with biologics, notable sex-differences have been observed, revealing differences in disease characteristics and treatment responses between females and males.[59-61, 63, 64] Despite this, comparable studies in pediatric and young adult patients with psoriasis remain

scarce, highlighting significant gaps in our understanding of how sex may impact psoriasis care in young patients.

In chapter 3 we aimed to investigate whether sex-differences should be taken into account in pediatric psoriasis care.
The following sub-aim was proposed:

2. To investigate whether sex-differences in drug survival, adverse events, disease severity, effectiveness of biologics, and HR-QoL are present in pediatric and young adult patients with psoriasis treated with biologics.

CHAPTER 4

Early identification of arthritis in patients with psoriasis is important, as delayed diagnosis can lead to joint damage and reduced quality of life.[126, 127] However, data on the development of (juvenile) psoriatic arthritis (JPsA) in patients with pediatric onset psoriasis is limited.[128] Existing JPsA cohorts described by pediatric rheumatologists comprise a heterogeneous population in which psoriatic lesions are often not present. These cohorts may therefore not reflect the patients seen in a dermatology setting in which psoriasis precedes the onset of the development of juvenile psoriatic arthritis.

In chapter 4 we aimed to increase the evidence and awareness on the development of arthritis in pediatric and young adult patients with psoriasis.

We, therefore, formulated the following sub-aims:

3a. To describe a real-world cohort of patients with pediatric onset psoriasis who subsequently developed psoriatic arthritis at pediatric age or in young adulthood (JPsA/PsA), focusing on their clinical features and timing of onset.
3b. To compare these clinical features to the characteristics of a large cohort of pediatric psoriasis patients without JPsA/PsA.

Underexposed areas in adult psoriasis care

CHAPTER 5

Patients with psoriasis have a higher prevalence of depression and anxiety compared to the general population.[14] Studies examining associations with depression and anxiety in patients with psoriasis have mainly focused on well-known factors such as sex, age, and psoriasis severity. [13, 91, 92, 129-131] Yet, little is known about the role of psychosocial and socioeconomic factors,

even though these are clearly linked to mental health outcomes in the general population.[132-134]

In Chapter 5 we aimed to gain more insight in the association between psoriasis and depression and anxiety.
Therefore, we aimed:

4. To identify the most relevant factors associated with symptoms of depression and/or anxiety (DA) in patients with psoriasis, taking into account both well-known patient characteristics from literature (sex, age, and disease severity) and psychological (visibility of psoriasis lesions and stress) and socioeconomic (level of education, level of income and social support) factors.

CHAPTER 6

Despite the recognized importance of lifestyle factors in psoriasis management, detailed knowledge about the current lifestyle of adult patients with psoriasis is lacking. Most existing studies focused primarily on a few lifestyle domains, such as diet and physical activity, while other domains, including smoking, alcohol, stress and sleep, received less attention. Additionally, although patient motivation is central to the success of lifestyle interventions, this motivation has not been explored yet among patients with psoriasis.

In chapter 6 we aimed to gain a better understanding of the lifestyle of adult patients with psoriasis and the motivation to change lifestyle.

The following sub-aims were formulated:

5a. To assess the motivation of psoriasis patients to change their lifestyle and which lifestyle domains they are most willing to adapt
5b. To assess their current lifestyle in six lifestyle domains (physical activity, smoking, alcohol, diet, stress and sleep)
5c. To compare the lifestyle of patients who are motivated with patients who are unmotivated or uncertain to change their lifestyle.

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CHAPTER 2

Investigation of the applicability of adult definitions of disease severity for psoriasis in a pediatric cohort: a prospective registry study

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To the editor,

In pediatric patients with psoriasis, there are no definitions or considerations to assist the decision to initiate systemic therapy. In adults, the Rule of Tens (R10) identifies severe psoriasis as having at least one of the following: Body Surface Area (BSA) >10%, Psoriasis Area and Severity Index (PASI) >10, or Dermatology Life Quality Index (DLQI) >10.[1] The International Psoriasis Council consensus statement (IPCcs) categorizes patients with psoriasis as candidates for either topical or systemic therapy. The latter are patients who meet at least one of the following criteria: BSA>10%, disease involving special areas (face, palms, soles, intertriginous skin, scalp or nails) or failure of topical therapy.[2] Psoriasis extent is important in both definitions, but while R10 uses DLQI to assess health related quality of life (HRQoL), IPCcs focuses on high-impact site involvement as a factor that impacts HRQoL. This study aimed to determine the percentage of pediatric patients with psoriasis fulfilling R10 and IPCcs definitions and to investigate the influence of high-impact site involvement and other clinical characteristics (age, sex, psoriasis duration, therapy, extent of psoriasis) on the Children's DLQI (CDLQI).

Data of all patients <18 years with psoriasis enrolled in the prospective daily practice Child-CAPTURE registry[3] were used to assess percentages, and logistic regression was used to study influence of clinical characteristics on CDLQI. For full methods see supplementary material.

Of 641 pediatric patients, 49.0% fulfilled R10 and 92.4% IPCcs definition, despite only 16.9% having PASI>10 and 29.8% BSA>10% (Table 1). The high percentage for IPCcs reflected high-impact site involvement (90.6%), especially scalp involvement (84.1%), in the overall cohort. This high percentage of scalp involvement was not found in an adult cohort on which IPCcs definition was applied (45.9% scalp involvement).[4] Raising the threshold for scalp psoriasis from any involvement (>0%) to 5%, 10%, 20% and 50% of scalp affected, still resulted in high percentages of patients meeting IPCcs definition (Supplementary Tables 1 and 2).

Table 1. Clinical characteristics of all patients, patients meeting the Rule of Tens (R10) definition and patients meeting the IPC Consensus Statement (IPCcs) definition

	All patients	Patients with severe psoriasis according to R10	Candidates for systemic therapy according to IPCcs
Total patients	641	314	592
Sex, *n (%)*			
Male	257 (40.1)	124 (39.5)	238 (40.2)
Female	384 (59.9)	190 (60.5)	354 (59.8)
Age, years, median [IQR]	11.0 [7.0]	11.0 [6.0]	11.0 [7.0]
Age distribution, *n* (%)	112 (17.5)	52 (16.6)	104 (17.6)
0-6 years	293 (45.7)	132 (42.0)	266 (44.9)
7-12 years	236 (36.8)	130 (41.4)	222 (37.5)
13-17 years			
Family history of psoriasis[a,b], *n (%)*	207 (52.9)	99 (51.3)	185 (51.5)
PsA, *n (%)*	5 (0.8)	2 (0.6)	5 (0.8)
Psoriasis duration, years, median [IQR]	1.4 [3.4]	1.5 [3.6]	1.3 [3.4]
Psoriasis severity, median [IQR]			
PASI (0-72)b	5.7 [4.8]	8.0 [6.3]†	5.9 [4.7]†
PGA (0-5)[b]	3.0 [1.0]	3.0 [1.0]	3.0 [1.0]
BSA (0-100%)[b]	6.0 [8.4]	11.5 [12.9]†	6.5 [9.5]†
CDLQI (0-30)[b], median [IQR]	8.0 [7.0]	12.0 [6.0]†	8.0 [7.0]†
Numbers and percentage of patients fulfilling the criteria according to R10, n (%)			
PASI > 10	108 (16.9)	108 (34.5)	108 (18.3)
BSA > 10%	191 (29.8)	191 (61.0)	191 (32.3)
CDLQI > 10	199 (31.5)	199 (65.5)	192 (33.0)
Numbers and percentage of patients fulfilling the criteria according to IPCcs, n (%)			
Failure of topical therapy	121 (18.9)	92 (29.3)	121 (20.4)
Involvement of high-impact sites	581 (90.6)	298 (94.9)	581 (98.1)
Face	169 (26.4)	101 (32.2)	169 (28.5)
Intertriginous skin[c]	236 (36.8)	157 (50.0)	236 (39.9)
Palms and soles	10 (1.6)	10 (3.2)	10 (1.7)
Nails	101 (15.8)	61 (19.4)	101 (17.1)
Scalp[d]	539 (84.1)	275 (87.6)	539 (91.0)
BSA > 10 %	191 (29.8)	191 (61.0)	191 (32.3)

Abbreviations: BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PsA, psoriatic arthritis

[a]Psoriasis in parents or siblings

[b]In case of missing data, scores were calculated over available data. Variables with missing data include: family history of psoriasis (n=10), PASI (n=1), PGA (n=2), BSA (n=1) and CDLQI (n=10), percentage of psoriasis involvement on the scalp (n=6).

[c]Intertriginous skin refers to the body folds, including axillary, anogenital and inframammary skin.

[d]The assessment of scalp psoriasis involvement was based on any degree of affected scalp (>0%).

†Both Mann-Whitney U- test and median test showed a statistically significant higher PASI, BSA and CDLQI in the R10 compared to the IPCcs group (*p<0.001*).

Impaired HRQoL (CDLQI>10) was associated with high-impact site involvement (OR 1.9, 95%CI 1.2-3.0), BSA>10% (OR 1.8, 95%CI 1.2-2.7) and teen age (13-17 years) (OR 1.8, 95%CI 1.0-3.1) (Table 2). Sensitivity analysis substituting PASI>10 for BSA>10% showed similar results (Supplementary Table 3).

Since this is a single-center study, it might lack generalizability. However, patients are referred from various general practitioner and dermatologist offices across the country, offering a diverse patient population that mirrors a typical pediatric psoriasis population within a hospital setting.

Table 2. Influence of clinical characteristics on CDLQI with BSA as severity measure: univariable and multivariable logistic regression model[a, b, c]

Variables	Univariable analysis[f]		Multivariable analysis[g]	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age 7-12 years vs 0-6 years (ref)	0.894 (0.638-1.253)	0.517	1.445 (0.854-2.447)	0.170
Age 13-17 years vs 0-6 years (ref)	1.506 (1.068-2.125)	0.020	**1.767 (1.012-3.082)**	**0.045**
Sex (Female)	1.372 (0.968-1.944)	0.076	1.372 (0.956-1.968)	0.086
Psoriasis duration (per year)	1.020 (0.961-1.082)	0.523		
Type of therapy (systemic)	2.294 (1.525-3.451)	<0.001	1.482 (0.934-2.352)	0.095
BSA (>10%)	2.148 (1.497-3.081)	<0.001	**1.806 (1.223-2.666)**	**0.003**
Involvement of high-impact sites (yes) [d,e]	2.218 (1.391-3.535)	<0.001	**1.864 (1.151-3.018)**	**0.011**

Abbreviations: BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index

[a]The dependent variable was CDLQI with a cut-off value at 10.

[b]BSA was used as severity measure because it is present in both the Rule of Tens and IPC consensus statement. A sensitivity analysis using PASI is shown in Supplementary Table 3.

[c]In case of missing data, scores were calculated over available data. Variables with missing data include: BSA (n=1) and CDLQI (10). A total of 630 cases were included in the analyses.

[d]High-impact sites: face, palms and soles, intertriginous skin, scalp and nails

[e]In this analysis, patients were classified as having scalp psoriasis if >10% of the scalp was affected.

[f]Variables with a *P <0.20* in the univariable analysis were analyzed in the multivariable logistic regression model.

[g]In the multivariable logistic regression model, variables with a *p <0.05* were considered statistically significant and are displayed in bold.

This study showed that R10 (49.0%) qualifies fewer pediatric patients as candidates for systemic treatment than IPCcs (92.4%), given that almost all pediatric patients have high-impact site involvement. It also demonstrated a clear association between high-impact site involvement in pediatric patients and impaired HRQoL, which was shown before in adult patients with psoriasis.[5]

In addition, CDLQI>10 was found to be associated with extent of psoriasis and teen age. Data from this study highlight the need to establish a new definition for systemic therapy initiation in pediatric patients with psoriasis, in which the (newly) identified associations between clinical characteristics and impaired HRQoL should be taken into account.

Acknowledgement
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Supplementary Material

Methods

Patient selection and study design

This prospective registry study was conducted in children (aged <18 years at baseline) diagnosed with plaque psoriasis, who attended the outpatient clinic of the Department of Dermatology at the Radboud University Medical Center in Nijmegen between September 2008 and August 2023 (data lock). Data were extracted from the ChildCAPTURE registry (Continuous Assessment of Psoriasis Treatment Use Registry), a prospective, observational, daily clinical practice registry of children and adolescents with psoriasis.[33] Patients were referred by various general practitioners and dermatologists across the Netherlands.

Data collection and outcome measures

Baseline data (corresponding to patient's first visit in ChildCAPTURE) were extracted from the registry, including patient and psoriasis characteristics: localization (face, intertriginous skin, palms and soles, nails and scalp) and psoriasis severity scores [PASI, BSA and Physician Global Assessment (PGA)], with higher scores indicating more severe psoriasis. The CDLQI, a patient reported outcome measure, was also collected, with a higher score indicating a larger influence on quality of life.

Patients were treated according to daily clinical care. Treatments were clustered in two groups: (1) topical therapy, which includes corticosteroids, vitamin D analogues, calcineurin inhibitors, and dithranol (anthralin), and (2) photo- or systemic therapy, including methotrexate, fumaric acid esters, cyclosporine, oral acitretin, and biologics (etanercept, adalimumab, ustekinumab, secukinumab, ixekizumab).

Both R10 and IPCcs were applied to ChildCAPTURE data and the percentage of patients fulfilling the criteria of these definitions were calculated. In this study, patients were classified as having 'failure of topical therapy' if they started photo or systemic therapy within the first three months after their first visit to our outpatient clinic or if they already were using systemic- or phototherapy at first visit. Patients potentially eligible for systemic therapy at referral first underwent optimization of topical therapy. If this approach is not effective within approximately six weeks, patients were transitioned to systemic treatment.

As the prevalence of scalp involvement in pediatric patients with psoriasis is high (up to 90%), this would implicate that, solely based on scalp involvement, up to 90% of patients would classify as candidates for systemic therapy according to the IPCcs definition. Therefore, the influence of the extent of scalp involvement on the percentage of patients fulfilling the IPCcs was investigated by exploring different thresholds for percentage of scalp involvement: >0%, >5%, >10%, >20% and >50%.

Statistical analysis

Patient characteristics were presented as numbers (percentages) for categorical variables and medians (interquartile ranges [IQRs]) and means (± standard deviation (SD)) for continuous variables depending on the distribution. Mann Whitney U-test and median test were used to compare clinical characteristics (PASI, BSA and CDLQI) for patients fulfilling R10 versus IPCcs definition. Univariable logistic regression was used to study whether age, sex, psoriasis duration, type of therapy, extent of psoriasis (BSA or PASI), and involvement of high impact sites were associated with CDLQI>10. A cut-off value of CDLQI>10 was used because it is the threshold for the R10[1] and known to have substantial impact on the quality of life. All variables with a $P<0.20$ in univariable logistic regression analysis were entered in a multivariable logistic regression model (standard method of regression). Two-sided $P<0.05$ was considered statistically significant for the multivariable logistic regression analysis.

Supplementary Table 1. Total number of pediatric psoriasis patients, number of patients meeting R10 definition and number of patients meeting IPCcs definition[a]

	No. (%)
All patients	641 (100)
Patients with severe psoriasis according to R10	314 (49.0)
Candidates for systemic therapy according to IPCcs[a]	592 (92.4)
Candidates for systemic therapy according to IPCcs [scalp >5% affected][a]	551 (86.0)
Candidates for systemic therapy according to IPCcs [scalp >10% affected][a]	531 (82.8)
Candidates for systemic therapy according to IPCcs [scalp >20% affected][a]	511 (79.7)
Candidates for systemic therapy according to IPCcs [scalp >50% affected][a]	474 (73.9)

[a]Those considered for systemic therapy as per the IPC consensus statement were evaluated five times–first with the original IPC criteria and then with the adjusted consensus statements, which includes scalp involvement thresholds at >5%, >10%, >20% and >50%.

Supplementary Table 2. Clinical characteristics of patients meeting the IPC Consensus Statement (IPCcs) definition, with consideration of scalp psoriasis thresholds (>5%, >10%, >20% and >50%)

	Candidates for systemic therapy according to IPCcs (scalp >5%[a])	**Candidates for systemic therapy according to IPCcs (scalp >10%[a])**	**Candidates for systemic therapy according to IPCcs (scalp >20%[a])**	**Candidates for systemic therapy according to IPCcs (scalp >50%[a])**
Total patients	551	531	511	474
Sex, *n (%)*				
Male	224 (40.7)	218 (41.1)	214 (41.9)	198 (41.8)
Female	327 (59.3)	313 (58.9)	297 (58.1)	276 (58.2)
Age, years, median [IQR]	11.0 [7.0]	11.0 [7.0]	11.0 [7.0]	11.0 [7.0]
Age distribution, *n* (%)	97 (17.6)	93 (17.5)	87 (17.0)	82 (17.3)
0-6 years	245 (44.5)	234 (44.1)	226 (44.2)	212 (44.7)
7-12 years	209 (37.9)	204 (38.4)	198 (38.7)	180 (38.0)
13-17 years				
Family history of psoriasis[b, c], *n (%)*	172 (51.2)	169 (51.7)	164 (51.9)	151 (51.2)
PsA, *n (%)*	5 (0.9)	5 (0.9)	5 (1.0)	5 (1.1)
Psoriasis duration, years, median [IQR]	1.3 [3.4]	1.3 [3.4]	1.3 [3.4]	1.3 [3.4]
Psoriasis severity, mean (SD)				
PASI (0-72)[c]	6.2 [4.8]	6.2 [4.7]†	6.3 [4.7]	6.6 [5.1]†
PGA (0-5)[c]	3.0 [1.0]	3.0 [1.0]	3.0 [1.0]	3.0 [1.0]
BSA (0-100%)[c]	7.0 [9.5]	7.2 [9.9]†	7.5 [10.1]	8.0 [10.6]†
CDLQI (0-30)[c], mean (SD)	8.0 [7.0]	9.0 [7.0]†	9.0 [6.0]	9.0 [6.0]†
Numbers and percentage of patients fulfilling the criteria according to R10, n (%)				
PASI > 10	108 (19.6)	107 (20.2)	107 (21.0)	107 (22.6)
BSA > 10%	191 (34.7)	191 (36.0)	191 (37.5)	191 (40.3)
CDLQI > 10	186 (34.4)	182 (34.9)	180 (35.9)	174 (37.5)

Supplementary Table 2. Continued

	Candidates for systemic therapy according to IPCcs (scalp >5%[a])	Candidates for systemic therapy according to IPCcs (scalp >10%[a])	Candidates for systemic therapy according to IPCcs (scalp >20%[a])	Candidates for systemic therapy according to IPCcs (scalp >50%[a])
Numbers and percentage of patients fulfilling the criteria according to IPCcs, n (%)				
Failure of topical therapy	121 (22.0)	121 (22.8)	121 (23.7)	121 (25.5)
Involvement of high impact sites	540 (98.0)	520 (97.9)	500 (97.8)	463 (97.7)
Face	169 (30.7)	169 (31.8)	169 (33.1)	169 (35.7)
Intertriginous skin[d]	236 (42.8)	236 (44.4)	236 (46.2)	236 (49.8)
Palms and soles	10 (1.8)	10 (1.9)	10 (2.0)	10 (2.1)
Nails	101 (18.3)	101 (19.0)	101 (19.8)	101 (21.3)
Scalp[e]	441 (80.9)[c, e]	385 (73.3)[c, e]	324 (64.2)[c, e]	164 (35.0)[c, e]
BSA > 10 %	191 (34.7)	191 (36.0)	191 (37.5)	191 (40.4)

Abbreviations: BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PsA, psoriatic arthritis

[a]Patients considered for systemic therapy as per the IPCcs were evaluated five times–first with the original IPC criteria (seen in Table 1) and then with adjusted scalp involvement thresholds at >5%, >10%, >20% and >50%. Please note that patients are considered candidates for systemic therapy if they meet any criterion of the IPCcs, including involvement of any of the high impact sites.

[b]Psoriasis in parents or siblings

[c]In case of missing data, scores were calculated over available data. Variables with missing data include: family history of psoriasis (n=10), PASI (n=1), PGA (n=2), BSA (n=1) and CDLQI (n=10), percentage of psoriasis involvement on the scalp (n=6).

[d]Intertriginous skin refers to the body folds, including axillary, anogenital and inframammary skin.

[e]These percentages are calculated based on the minimum percentage of affected scalp psoriasis according to the specified threshold, thus exceeding >5%, >10%, >20%, or >50%.

[†]Both Mann-Whitney U- test and median test showed a statistically significant higher PASI, BSA and CDLQI in R10 group compared to the IPCcs group (scalp >10%) ($p<0.001$) group and in R10 group compared to the IPCcs group (scalp >50%) ($p<0.001$).

Supplementary Table 3. Influence of clinical characteristics on CDLQI with PASI as severity measure: univariable and multivariable logistic regression model[a,b]

Variables	Univariable analysis[e]		Multivariable analysis[f]	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age 7-12 years vs 0-6 years (ref)	0.894 (0.638-1.253)	0.517	1.406 (0.831-2.378)	0.204
Age 13-17 years vs 0-6 years (ref)	1.506 (1.068-2.125)	0.020	1.649 (0.948-2.869)	0.077
Sex (Female)	1.372 (0.968-1.944)	0.076	1.381 (0.963-1.982)	0.079
Psoriasis duration (per year)	1.020 (0.961-1.082)	0.523		
Type of therapy (systemic)	2.294 (1.525-3.451)	<0.001	1.548 (0.982-2.441)	0.060
PASI (>10)	2.585 (1.683-3.970)	<0.001	**2.071 (1.314-3.263)**	**0.002**
Involvement of high impact sites (yes)[c,d]	2.218 (1.391-3.535)	<0.001	**1.914 (1.185-3.092)**	**0.008**

Abbreviations: BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index

[a]The dependent variable was CDLQI with a cut-off value at 10.

[b]In case of missing data, scores were calculated over available data. Variables with missing data include: CDLQI (10). A total of 631 cases were included in the analyses.

[c]High impact sites: face, palms and soles, intertriginous skin, scalp and nails.

[d]In this analysis, patients were classified as having scalp psoriasis if >10% of the scalp was affected.

[e]Variables with a *P <0.20* in the univariable analysis were analyzed in the multivariable logistic regression model

[f]In the multivariable logistic regression model, variables with a *p <0.05* were considered statistically significant and are displayed in bold.

CHAPTER 3

Sex-disparities in pediatric and young adult patients with psoriasis treated with biologics: differences in adverse events and disease activity

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Abstract

Background

Sex-differences in biological treatment outcomes in adult patients with psoriasis are well known. Potential sex-differences in a real-world cohort of pediatric and young adult patients with psoriasis using biologics were investigated in this study.

Methods

Data on pediatric (<18 years) and young adult (≥18 to ≤30 years) patients were obtained from the prospective, daily practice, ChildCAPTURE and BioCAPTURE registries. Drug survival and adverse event rates were compared between sexes. Confounder-corrected linear mixed models were used to compare Psoriasis Area and Severity Index (PASI) and (Children's) Dermatology Life Quality Index ((C)DLQI) scores between sexes.

Results

We included 117 pediatric (65 females) and 243 young adult (124 females) patients on biologics (753.4 observation years). Young adult males had a significantly higher PASI at biologic initiation compared to females, with the same trend for pediatric patients. A higher adverse event rate was observed in females compared to males in both pediatric and young adult patients. Drug survival, PASI and (C)DLQI course during the first treatment year, were comparable between pediatric and young adult females and males.

Conclusion

Awareness on sex-differences (start PASI and adverse event rates) in pediatric and young adult patients with psoriasis is important for timely initiation and adjustment of appropriate treatment.

Introduction

Sex-differences in disease severity and treatment outcomes, including drug survival, have gained significant attention in adults with psoriasis undergoing biologic treatment, but their relevance in pediatric patients has yet to be examined.[1] Although prevalence of psoriasis is comparable between females and males, previous cohort studies in adult patients reported more severe psoriasis in males at initiation of biologic treatment.[2, 3] In contrast, females reported a lower health-related quality of life (HR-QoL) due to their psoriasis, and expressed lower satisfaction with their biological treatment compared to males.[3-7] Previous studies also showed that females discontinued their biologic earlier and reported more adverse events compared to their male counterparts.[3, 7-11] However, these studies were performed in adult cohorts, with an average age ranging between 45.6 and 50.0 years.[4, 6, 7, 9-11] It is unknown whether these differences in sexes are present in pediatric or young adult patients with psoriasis. Studies on drug survival, adverse events, disease severity, and HR-QoL in pediatric and young adult patients with psoriasis treated with biologics are limited,[12-15] and not stratified for sex. Only one previous study among young adults with psoriasis reported that females had a worse quality of life and greater impairment of social functioning compared to males.[16] Awareness of potential sex-differences in the pediatric and young adult population could offer valuable insights for enhancement of personalized treatment in clinical practice. We, therefore, aimed to investigate whether sex-differences in drug survival, adverse events, disease severity, effectiveness of biologics, and HR-QoL are present in pediatric and young adult patients with psoriasis.

Methods

This explorative study was conducted in pediatric patients (<18 years) and young adult patients (≥18 to ≤30 years) diagnosed with plaque psoriasis and treated with biologics. Data were extracted from the ChildCAPTURE registry (Continuous Assessment of Psoriasis Treatment Use REgistry), a prospective, daily clinical practice registry of children and adolescents treated at the Department of Dermatology at the Radboud University Medical Center in Nijmegen, the Netherlands, since 2008,[17] and the BioCAPTURE registry, a prospective, observational, long-term, daily clinical practice of adult patients treated with biologics, who received care at four academic and nineteen non-academic centers in the Netherlands, since 2005. (www.biocapture.nl). Both

registries were reviewed and approved by the local ethics committee and written informed consent was obtained from every patient.

Data collection

Data from the first biologic treatment episode of patients registered in ChildCAPTURE or BioCAPTURE were extracted in May 2024. Biologics included were: infliximab, etanercept, adalimumab, certolizumab, ustekinumab, secukinumab, ixekizumab, brodalumumab, bimekizumab, guselkumab, risankizumab and tildrakizumab.

As only one treatment episode was included per patient, the number of treatment episodes is equal to the number of patients included. A treatment episode referred to a period, without interruptions of more than ninety days, in which a patient was treated with a particular biologic. Data on sex, age, body mass index (BMI), disease duration, family history of psoriasis, psoriatic arthritis (PsA), psychiatric comorbidities, biological therapy, Psoriasis Area and Severity Index (PASI) scores, (Children's) Dermatology Life Quality Index ((C)DLQI), and reported adverse events were extracted. Pediatric patients and young adult patients were analyzed separately. Biological sex was obtained based on the information in electronic health records.

Adverse events

(Serious) adverse events were systematically collected. Medical Dictionary for Regulatory Activities (MedDRA) was used to classify adverse events.[18]

Disease severity and treatment effects

To visualize baseline severity at start of a biologic and treatment effectiveness, PASI scores were analyzed. A PASI score was selected at baseline and at three-month intervals during the first year for each treatment episode, using the assessment date nearest to each corresponding time point. Additionally, the number of patients reaching a PASI score ≤1, ≤3 and ≤5 at six months of treatment, as well as PASI scores at the time of treatment discontinuation due to ineffectiveness, were assessed.

Health-related quality of life

Patients included in the registries were requested to complete (C)DLQI questionnaires at baseline and at three-month intervals during the first year for each treatment episode. The (C)DLQI, a validated and dermatology-specific tool, which comprises of 10 questions related to HR-QoL and produces

a score between 0 (indicating no impairment) and 30 (indicating maximum impairment).[19-21] The CDLQI was assessed for pediatric patients (<18 years) and DLQI was assessed for young adult patients (≥18 to ≤30 years).

Statistical analysis

All analyses were performed in SPSS version 29.0 (IBM Corporation, Armonk, NY, USA) and R version 4.4.1). A p-value of less than 0.05 was regarded as statistically significant. Descriptive statistics were used to present baseline patient and treatment characteristics (n (%), mean (95% confidence interval (CI)) for variables with a normal distribution, median [interquartile range (IQR)] for variables with a skewed distribution). The N-1 Chi-square was used to test to compare proportions between patients groups and calculate the 95%CI of proportions.[22] The Mann-Whitney U test was used to compare continuous variables with skewed distributions between patient groups.

Missing data was addressed to enhance reliability of the results. Linear interpolation was initially used to estimate missing PASI scores, provided that a baseline PASI and at least one follow-up PASI during the first year of treatment were available. Multiple imputation was applied for PASI scores that could not be estimated using linear interpolation. Multiple imputation was also applied for missing values in disease duration, BMI and (C)DLQI scores. Forty imputed datasets were generated using mice R-package version 3.16.0.

Drug survival rates were analyzed using Kaplan–Meier estimates. For overall drug survival all reasons of discontinuation were considered an event, including ineffectiveness, adverse events, death and pregnancy. Patients who were lost to follow-up or who remained on the biologic at the time of data lock were censored. Additionally, drug survival was assessed separately for discontinuation due to ineffectiveness and adverse events. For these sub-analyses, patients were censored when they discontinued their biologic for a reason other than the reason of interest. To examine the relationship between sex and drug survival of biologics, multivariable Cox regression models were used. We included potential confounders based on clinical relevance: age at start of the biologic, baseline PASI score, BMI, duration of psoriasis until the start of the biologic, experience with prior biologics, presence of psoriatic arthritis, psychiatric disease and type of biologic. All confounding factors were assessed at baseline. The proportional hazard assumption was checked.

Adverse event rates were described in events per observation year stratified by sex. Adverse event rates with confidence intervals were calculated and compared between groups using the exact Poisson method.[23]

A linear mixed model was used to analyze the effect of sex on the course of PASI and (C)DLQI during the first year of treatment, accounting for repeated measurements for each patient. For each outcome measure, a separate model was constructed, with the outcome defined as the dependent variable and sex as the independent variable. Each model included the same clinically relevant potential confounders used in the multivariable Cox regression analyses. Residual plots were used to assess model assumptions (normality using a histogram, homoscedasticity with a scatterplot with residuals on the y-axis, and predicted values on the x-axis). The effect of sex on reaching a PASI score of ≤1, ≤3 or ≤5 was assessed using a multivariable logistic regression model, with sex as independent variable and duration of psoriasis until the start of the biologic, baseline PASI score, BMI and experience with prior biologics as potential confounders (selected based on clinical relevance). The same potential confounders were incorporated in a multivariable linear regression model to analyze the effect of sex on PASI or (C)DLQI score upon treatment discontinuation. The effect of sex on reaching a (C)DLQI score of ≤1, ≤3 or ≤5 was assessed using a multivariable logistic regression model, with sex as independent variable and baseline (C)DLQI as potential confounder.

Results

Baseline characteristics

This study included a total of 117 pediatric (65 females (F) and 52 males (M)) and 243 young adult (F: 124, M: 119) patients on biologics (Table 1). The total observation years were 234.1 years for pediatric patients (F: 125.5 years, M: 108.6 years), and 519.3 years for young adult patients (F: 263.7 years, M: 255.6 years). The vast majority of the patients was biologic naïve at inclusion in the registry; 96.6% of pediatric and 85.6% of young adult patients. The mean age at start of the biologic was 14.5 (95%CI=13.9-15.0) years for pediatric patients and 24.7 (95%CI=24.4-25.2) years for young adults. The median baseline PASI was comparable in pediatric (7.6 [6.6]) and young adult patients (8.5 [7.8]). Pediatric patients used ustekinumab more often than young adult patients (difference: 22.1%, 95%CI= 11.3-32.5; *p<0.001*), while young adult patients used adalimumab more often than pediatric patients (difference: 8.3%, 95%CI= -2.4-18.8; *p=0.126*). Young adult males had a significantly higher median baseline PASI compared to females, (F: 10.6 [8.4] vs M: 6.8 [6.0], *p<0.001)*. In pediatric patients, the median baseline PASI for females was 8.3 [6.6] and for males 6.8 [7.3] (*p=0.279)*.

Table 1. Patient and treatment characteristics of the first biologic treatment episode in ChildCAPTURE or BioCAPTURE

	Pediatric patients (n=117)			Young Adult patients (n=243)		
	Total	**Males**	**Females**	**Total**	**Males**	**Females**
Number of patients	117	52 (44.4%)	65 (55.6%)	243	119 (49.0%)	124 (51.0%)
Age at onset, years[a]	8.3 (7.5-9.0)	8.3 (7.1-9.5)	8.3 (7.3-9.2)	14.5 (13.8-15.1)	15.4 (14.5-16.4)	13.6 (12.7-14.5)
Range	0.4-17.3	0.5-14.9	0.4-17.3	2.0-27.0	3.1-27.0	2.0-27.0
Age at start biologic, years	14.5 (13.9-15.0)	14.2 (13.2-15.1)	14.7 (14.1-15.1)	24.7 (24.4-25.2)	24.8 (24.2-25.6)	24.2 (23.5-25.6)
Range	4.7-17.9	4.7-17.9	6.2-17.9	18.2-30.9	18.3-30.9	18.2-30.9
Disease duration at start biologic, years	6.2 (5.5-6.9)	5.8 (4.9-6.7)	6.5 (5.5-6.7)	10.0 (9.4-10.7)	9.4 (8.5-10.3)	10.6 (9.7-11.6)
Psoriatic arthritis[a]	10 (8.5%)	6 (11.5%)	4 (6.2%)	32 (15.2%)	13 (12.4%)	19 (16.2%)
Family history with psoriasis[b]	63 (53.8%)	30 (57.7%)	33 (50.8%)	141 (58.0%)	70 (58.8%)	71 (57.3%)
Baseline BMI[a]	20.7 [4.9]	19.8 [3.5]	21.8 [6.5]	24.4 [7.3]	24.6 [6.2]	24.1 [8.8]
Baseline PASI[a,c]	7.6 [6.6]	8.3 [6.6]	6.8 [7.3]	8.5 [7.8]	**10.6 [8.4]**	**6.8 [6.0]**
Baseline CDLQI[a,c,d]	8.0 [9.0]	8.0 [8.5]	9.0 [8.5]	-	-	-
Baseline DLQI[a,c,d]	-	-	-	5.0 [7.3]	3.0 [4.0]	6.0 [8.0]
Biologic naive	113 (96.6%)	50 (96.2%)	63 (96.9%)	208 (85.6%)	104 (87.4%)	104 (83.9%)
Type of biologic,						
Etanercept	13 (11.1%)	8 (15.4%)	5 (7.7%)	31 (12.8%)	17 (14.3%)	14 (11.3%)
Adalimumab	36 (30.8%)	16 (30.8%)	20 (30.8%)	95 (39.1%)	47 (39.5%)	48 (38.7%)
Ustekinumab	61 (52.1%)	24 (46.2%)	37 (56.9%)	73 (30.0%)	38 (31.9%)	35 (28.2%)
Ixekizumab	5 (4.3%)	3 (5.8%)	2 (3.1%)	7 (2.9%)	4 (3.4%)	3 (2.4%)
Guselkumab	2 (1.7%)	1 (1.9%)	1 (1.5%)	6 (2.5%)	2 (1.7%)	4 (3.2%)
Risankizumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (4.5%)	6 (5.0%)	5 (4.0%)
Certolizumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (4.5%)	0 (0.0%)	11 (8.9%)
Secukinumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.2%)	2 (1.7%)	1 (0.8%)
Tildrakizumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.8%)	0 (0.0%)
Bimekizumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.2%)	2 (1.7%)	1 (0.8%)
Brodalumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.8%)
Infliximab	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.8%)

Table 1. Continued

	Pediatric patients (n=117)			Young Adult patients (n=243)		
	Total	**Males**	**Females**	**Total**	**Males**	**Females**
Observation years[e]	1.4 [2.1]	1.2 [2.15]	1.6 [2.2]	1.5 [2.3]	1.4 [2.3]	1.5 [2.3]
Registry						
ChildCAPTURE	117 (100%)	52 (100%)	65 (100%)	67 (27.6%)	29 (24.4%)	38 (30.6%)
BioCAPTURE	0 (0.0%)	0 (0.0%)	0 (0.0%)	176 (72.4%)	90 (75.6%)	86 (69.4%)

Data is presented as n (%), mean (95%CI) or median [IQR].

Percentages are calculated using the total number of available data for that characteristic per group

Abbreviations: BMI, body mass index; (C)DLQI, (Children's) Dermatology Life Quality Index; CI, confidence interval; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

[a] Variables with missing data include age at onset (young adult, n=15), disease duration at start of biologic (young adult, n=15), psoriatic arthritis (young adult; n=21), baseline BMI (pediatric, n=27; young adult; n=62), baseline PASI (pediatric, n=7; young adult; n=30), baseline CDLQI (pediatric, n=14), baseline DLQI (young adult, n=181)

[b] Psoriasis in (grand)parents or siblings

[c] Mann-Whitney U test was performed to test statistical significant difference between sexes within age groups. Statistical significant differences ($p<0.05$) are bold.

[d] For pediatric patients CLDQI and for young adult patients DLQI was assessed.

[e] The observation years covered the time from the start of the first biologic treatment registered in the ChildCAPTURE or BioCAPTURE registries until data lock or until the discontinuation of treatment

Drug survival

Kaplan Meier survival curves showed comparable drug survival for females and males in both pediatric and young adult patients (Figure 1). Multivariable Cox regression analyses, corrected for confounders, showed no association between sex and overall drug survival, ineffectiveness related drug survival and adverse event related drug survival in both pediatric and young adult patients (Supplemental Table 1).

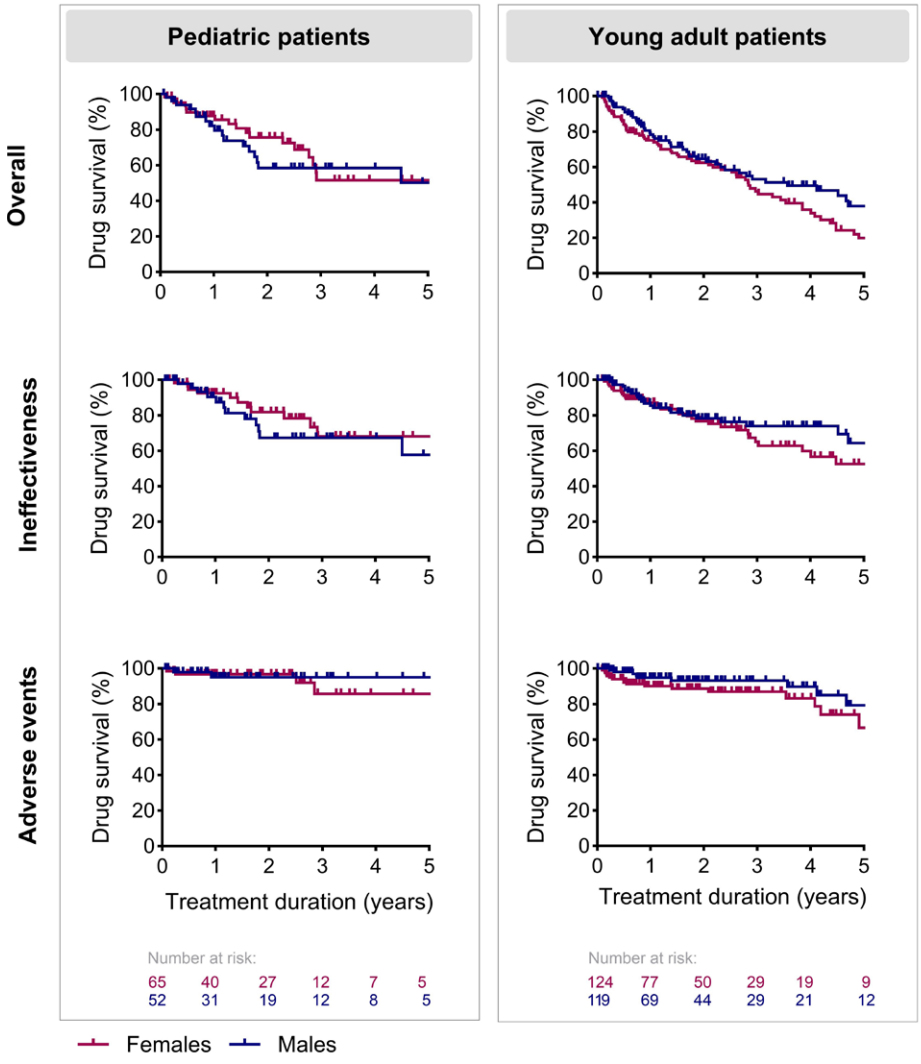

Figure 1. Drug survival of biological therapy in female and male pediatric and young adult patients, split according to reason of discontinuation.

Adverse events

The number of adverse events per observation year (adverse event rate) was significantly higher in females compared to males in both pediatric patients (F: 2.41, 95%CI=2.15-2.70 vs M: 1.56, 95%CI=1.33-1.82; *p<0.001*) and young adult patients (F: 1.48, 95%CI=1.34-1.64 vs M: 0.99, 95%CI=0.87-1.12; *p<0.001*) (Table 2). In both age categories, and for both sexes, "infections and infestations" and "general disorders (mainly fatigue) and administration site conditions" were the most common adverse events (Supplemental Table 2a). Serious adverse event rates (number of events per observation year) were very low in both pediatric patients (F: 0.02, 95%CI=0.00-0.07 vs M: 0.02, 95%CI=0.00-0.07) and young adult patients (F: 0.03, 95%CI= 0.02-0.06 vs M: 0.02, 95%CI= 0.00-0.04) regardless of sex (Supplemental Table 2b). Of 5 serious adverse events in the pediatric group 3 (cholesteatoma, abdominal pain and surgical intervention due to appendicitis) were deemed to be possibly related to the biologic. In young adults 4 out of 13 serious adverse events (sinusitis, hospitalization due to psoriasis exacerbation, type I hypersensitivity reaction to biologic, and surgical intervention due to appendicitis) were deemed possibly related to the biologic. Among these, one serious adverse event in pediatric patients (abdominal pain) and one in young adult patients (type 1 hypersensitivity reaction to biologic) resulted in treatment discontinuation.

Table 2. Adverse event rates in pediatric and young adult patients with psoriasis using biologics, split for sex.

		Males	Females
Pediatric patients	N patients	52	65
	N patients with ≥1 AE	37	52
	Sum AE	169	304
	Sum observation years	108.2	126.1
	AE rate (95%CI)	1.56 (1.33 -1.82)	2.41 (2.15-2.70)
		P<0.001	
Young adult patients	N patients	119	124
	N patients with ≥1 AE	62	70
	Sum AE	252	392
	Sum observation years	255.6	263.7
	AE rate (95%CI)	0.99 (0.87-1.12)	1.48 (1.34-1.64)
		P<0.001	

Abbreviations: AE, adverse event; CI, confidence interval.
Adverse event rates with confidence intervals were calculated and compared between groups using the "Exact Poisson Method".[23]

Disease severity and treatment effects

Longitudinal analysis of PASI scores showed for both sexes a rapid decrease during the first three months of treatment with a biologic, followed by stabilization, for both pediatric and young adult patients (Figure 2). After correction for confounders, the linear mixed model showed that the PASI course during the first year of treatment was comparable between females and males for both pediatric and young adult patients (Supplemental Table 3).

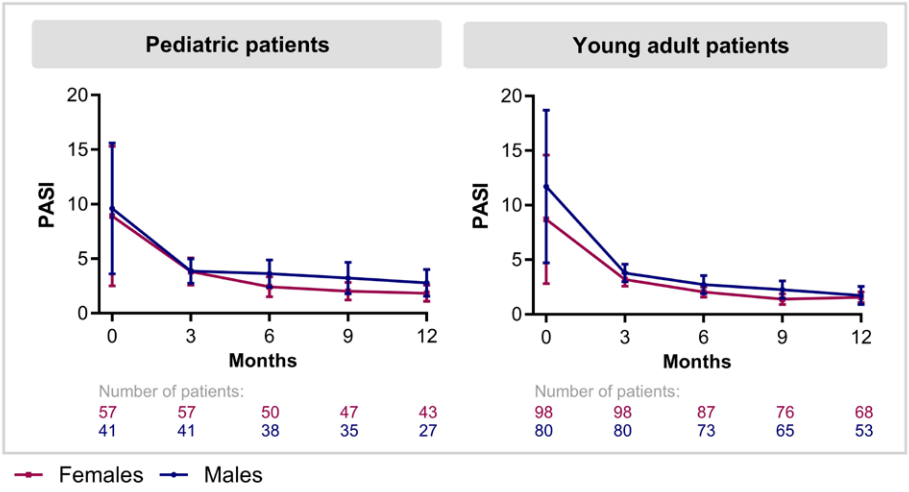

Figure 2. Mean PASI scores for pediatric and young adult patients during the first year of treatment, split for sex. Whiskers show 95% confidence intervals.

Also the percentage of patients reaching a PASI score of ≤1, ≤3 and ≤5 at six months of treatment were comparable between females and males in both pediatric patients (≤1: F: 49.1% vs M: 26.8%, ≤3: F: 71.9% vs M: 68.3%, ≤5: F: 82.5% vs M: 80.5%) and young adult patients (≤1: F: 38.8% vs M: 35.0%, ≤3: F: 79.6% vs M: 71.3%, ≤5: F: 99.0% vs M: 82.5%). After correcting for confounding, in both pediatric and young adult patients, sex was not associated with the number of patients reaching a PASI score of ≤1, ≤3 or ≤5 at six months (Supplemental Table 4).

The mean PASI scores at moment of treatment discontinuation due to ineffectiveness were comparable between females and males in both pediatric patients (F: 7.9, 95%CI=3.41-12.38 vs M: 7.74, 95%CI=4.03-11.44), and young adults (F: 4.65, 95%CI=2.84-8.27 vs M: 5.56, 95%CI=2.84-8.27). After correction for confounders, also no sex-differences were found (Supplemental Table 5).

Health-related quality of life

Longitudinal analysis of CDLQI scores for pediatric patients and DLQI scores for young adult patients showed for both sexes a rapid decrease during the first three months of treatment with a biologic followed by stabilization (Figure 3). After correction for confounders, the linear mixed model showed that (C)DLQI scores during the first year of treatment were comparable between females and males for both pediatric and young adult patients (Supplemental Table 6).

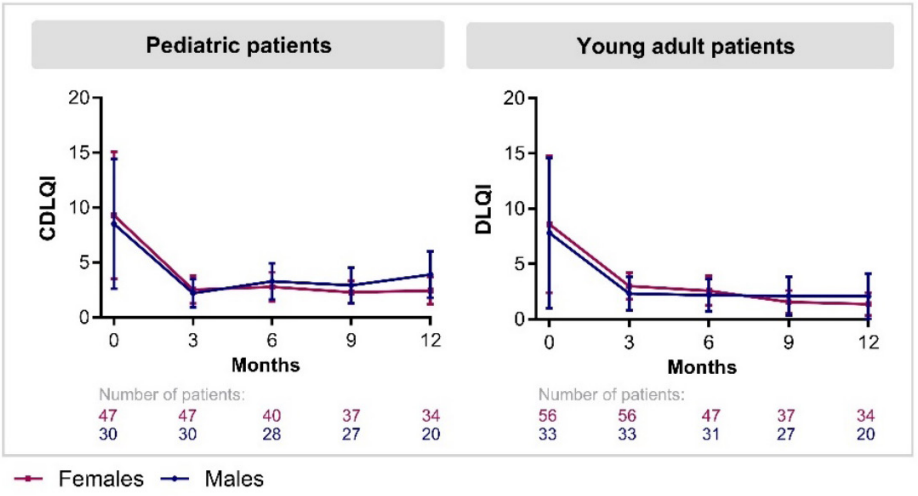

Figure 3. Mean (C)DLQI scores for pediatric and young adult patients with psoriasis during the first year of treatment with biologics, split for sex. Whiskers show 95% confidence intervals.

The percentage of pediatric patients reaching a CDLQI score of ≤1, ≤3 and ≤5 at six months of treatment were comparable between females and males (≤1: F: 68.1% vs M: 63.3%, ≤3: F: 80.9% vs M: 83.3%, ≤5: F: 89.4% vs M: 93.3%) and the number of young adult patients reaching a DLQI score of ≤1, ≤3 and ≤5 at six months of treatment were comparable between females and males (≤1: F: 74.5% vs M: 78.8%, ≤3: F: 80.7% vs M: 78.8%, ≤5: F: 84.2% vs M: 97.9%). After correcting for confounding, in both pediatric and young adult patients, sex was not associated with patients reaching a PASI score of ≤1, ≤3 or ≤5 at six months (Supplemental Table 7).

The mean (C)DLQI scores at moment of treatment discontinuation due to ineffectiveness were comparable between females and males in both pediatric patients (F: 9.60, 95CI%=2.27-16.94 vs M: 5.50, 95%CI=2.11-8.89), and young adults (F: 7.18, 95%CI=3.04-11.33 vs M: 5.09, 95%CI=0.16-10.02). The confounder corrected model showed no sex-differences (Supplemental Table 8).

Discussion

This study investigated sex-differences in drug survival, adverse events, disease severity, effectiveness of biologics and HR-QoL of pediatric and young adult patients with psoriasis treated with biologics using real-world data. Young adult males had significantly higher baseline PASI scores compared to young adult females (F: 6.8 [6.0] vs M: 10.6 [8.4]), and male pediatric patients (8.3 [6.6]) also had a higher baseline PASI score than female pediatric patients (6.8 [7.3], albeit not statistically significant. Both pediatric and young adult female patients had statistically higher adverse event rates compared to males. The drug survival, course of PASI and (C)DLQI during the first year of treatment, as well as reaching threshold scores of ≤1, ≤3, ≤5, and the scores at treatment discontinuation due to ineffectiveness, were comparable between females and males for both pediatric and young adult patients.

Young adult males had a higher PASI score at baseline compared to young adult females, indicating more severe disease at initiation of a biologic, which aligns with previous cohort studies on adult patients with psoriasis treated with biologics.[2] A similar trend was seen among pediatric patients in our study, with boys having a higher baseline PASI compared to girls, albeit not statistically significant. It is intriguing to speculate why male patients have a higher baseline PASI at start of a biologic. This could be due to a longer delay in starting biologic therapy in males compared to females, possibly because the decision is subjective and influenced by the choices of physicians and patients and/or parents. However, in our cohort, both pediatric and young adult males had a shorter disease duration prior to start of a biologic than females, suggesting that a longer delay before initiation of a biologic is not an explanation for this finding. Another hypothesis for the finding that male patients have a more severe disease at initiation of a biologic might be the fact that male patients with psoriasis overall have a more severe disease course than female patients. The fact that male sex was shown to be a predictor for the development of severe psoriasis in pediatric patients could support this theory.[24] Additionally, sex hormones may play an underlying role. Previous research has shown that testosterone, the primary male sex hormone known for its immunosuppressive functions, is present at lower levels in male patients with psoriasis compared to healthy males.[25, 26] In contrast, estrogens, the primary female sex hormones, are thought to have a protective effect on psoriasis.[27] Together, these hormonal differences may contribute to the disparity in disease severity at biologic initiation between males and females. Although sex-differences in baseline

PASI were found, we did not find sex-differences in the course of PASI during the first year of treatment with a biologic, as well as the percentage of patients reaching PASI thresholds of ≤1, ≤3, ≤5 during their treatment. Hence, there seems to be no sex-difference in effectiveness of the biologics.

We found higher adverse event rates in females compared to males, in both pediatric and young adult patients, which is also consistent with previous studies in adults.[3, 7, 28, 29] The fact that differences in adverse event rates between females and males are already present in pediatric patients suggest a more physiological and sex-related explanation, rather than attributing these differences to social-cultural factors that become more pronounced with age. Evidence from prior research indicates that sex hormones can modulate the pharmacokinetics and dynamics of medications.[30] Our findings on sex-differences in adverse event rates instigate to further explore whether these differences are also present in pediatric and young adult patients with other immune mediated inflammatory diseases, as sex-differences in adverse event rates might not be exclusive to psoriasis. Indeed, previous studies among adult patients with inflammatory bowel disease and rheumatic diseases treated with biologics have also shown that females experience adverse events more often than male patients, regardless of whether they were treated with conventional systemic agents or biologics.[31, 32] The most common types of adverse events were similar across sexes in pediatric and young adult patients with psoriasis, which was also previously shown in adults.[29] Notably, serious adverse event rates were extremely low in both pediatric and young adult patients, providing reassurance that biologics can be safely used in pediatric and young adult patients.

Our study showed that HR-QoL was comparable between sexes at baseline and during treatment for both pediatric and young adult patients. This is in contrast with previous literature in adults, where it has been shown that adult female patients with psoriasis perceived a greater impact on quality of life and mental health.[33, 34] It could be hypothesized that the emotional and social challenges associated with psoriasis become more pronounced with age, potentially due to increased social pressure, and thereby explain the presence of sex-differences in HR-QoL in adults but not (yet) in younger patients.

A notable strength of this study is its use of the longstanding, prospective, and highly detailed ChildCAPTURE and BioCAPTURE registries. Additionally, our use of linear mixed models to analyze PASI and (C)DLQI scores over the first

year of biologic treatment allowed for a thorough longitudinal assessment of these outcomes. Furthermore, adjusting for confounders in the drug survival, PASI and (C)DLQI analyses enhanced the reliability and validity of the findings.

A limitation of this study was that, although there was a relatively large number of pediatric patients, the sample size was not large enough to further stratify the cohort into more subgroups, such as children and adolescents. The latter would be particularly beneficial for examining the influence of puberty on the timing of the emergence of sex-differences. Additionally, data of the pediatric patients were obtained from a single-center registry. Nevertheless, since pediatric patients were referred by general practitioners and dermatologists from across the Netherlands, we believe this study cohort represents a regular pediatric psoriasis population. Furthermore, investigating the impact of sex can be affected by unmeasured confounding. Moreover, determining the actual occurrence of adverse events is challenging, as it relies on patient-reported data, which can be subjective.

Our data fill a scientific gap regarding insights in sex-differences in pediatric and young adult patients with psoriasis, showing that female patients with psoriasis on biologics reported more adverse events than males. This sex-disparity was already present in childhood. Adult male psoriasis patients had a significantly higher disease activity (PASI) at biologic treatment initiation, with a similar trend observed in pediatric male patients. Awareness for these sex-differences in pediatric and young adult patients with psoriasis is crucial for ensuring timely initiation and adjustment of appropriate treatment.

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Supplementary Material

Supplemental Table 1. Multivariable Cox regression analyses assessing the effect of sex on drug discontinuation in pediatric and young adult patients with psoriasis.

	Pediatric patients				Young adult patients			
Variable	**HR**	**95% CI**		**p-value**	**HR**	**95% CI**		**p-value**
Overall drug survival								
Sex (Female)	1.18	0.75	1.86	0.476	0.91	0.65	1.28	0.578
Age at start biologic (Years)	0.96	0.88	1.04	0.272	1.00	0.95	1.0	0.988
Disease duration until start of biologic (Years)	0.96	0.91	1.03	0.255	0.99	0.95	1.03	0.644
BMI	1.00	0.94	1.07	0.935	1.02	0.99	1.06	0.207
Psoriatic arthritis (Yes)	1.96	0.88	4.35	0.099	1.57	0.94	2.63	0.083
Psychiatric disease (Yes)	0.98	0.53	1.80	0.944	1.11	0.69	1.80	0.659
Biologic class (ref TNF-α)[a]								
IL-12/23	0.89	0.56	1.44	0.639	0.94	0.66	1.33	0.705
IL-17	1.41	0.32	6.20	0.649	1.36	0.67	2.73	0.394
IL-23	NA	NA	NA	NA	1.47	0.80	2.70	0.208
Previous use of biologics (Yes)	0.39	0.11	1.41	0.150	0.89	0.48	1.63	0.698
Baseline PASI	0.99	0.95	1.03	0.698	0.95	0.92	0.98	0.001
Ineffectiveness related drug survival								
Sex (Female)	0.99	0.30	3.21	0.981	0.93	0.42	2.06	0.856
Age at start biologic (Years)	098	0.80	1.20	0.836	0.96	0.86	1.07	0.420
Disease duration until start of biologic (Years)	0.87	0.73	1.04	0.115	0.97	0.89	1.05	0.413
BMI	1.06	0.93	1.21	0.334	1.10	1.02	1.19	0.014
Psoriatic arthritis (Yes)	0.61	0.14	2.61	0.462	0.94	0.58	6.49	0.273

Supplemental Table 1. Continued

	Pediatric patients				Young adult patients			
Variable	**HR**	**95% CI**		**p-value**	**HR**	**95% CI**		**p-value**
Psychiatric disease (Yes)	0.80	0.15	4.21	0.768	0.85	0.28	2.57	0.770
Biologic class (ref TNF-α)[a]								
IL-12/23	0.23	0.06	0.87	0.034	0.24	0.09	0.66	0.008
IL-17	2.18	0.18	26.44	0.495	0.65	0.15	2.87	0.556
IL-23	NA	NA	NA	NA	0.00	0.00	NA	0.996
Previous use of biologics (Yes)	0.19	0.01	2.59	0.182	0.33	0.10	1.05	0.059
Baseline PASI	1.04	0.96	1.11	0.287	0.95	0.90	1.01	0.117
Adverse event related drug survival								
Sex (Female)	5.56	0.00	NA	0.538	1.15	0.30	4.38	0.808
Age at start biologic (Years)	0.87	0.00	NA	0.755	0.93	0.78	1.111	0.384
Disease duration until start of biologic (Years)	1.04	0.00	NA	0.874	1.05	0.91	1.20	0.456
BMI	0.84	0.00	NA	0.804	1.08	0.95	1.22	0.198
Psoriatic arthritis (Yes)	0.49	0.00	NA	0.740	1.19	0.20	7.18	0.826
Psychiatric disease (Yes)	0.00	0.00	NA	0.99	1.92	0.46	8.03	0.320
Biologic class (ref TNF-α)[a]								
IL-12/23	0.22	0.00	NA	0.587	0.45	0.11	1.86	0.230
IL17	NA	NA	NA	NA	0.66	0.08	5.59	0.660
IL-23	NA	NA	NA	NA	0.00	0.00	??	0.998
Previous use of biologics (Yes)	141732040.98	0.00	NA	1.000	0.21	0.03	1.35	0.088
Baseline PASI	0.88	0.00	210652258 12813.00	0.654	0.96	0.86	1.06	0.365

Abbreviations: BMI, body mass index; CI, confidence interval; IL, Interleukin; NA, not applicable; PASI, Psoriasis Area and Severity Index; TNF-α, Tumor Necrose Factor-alfa.

Values that could not be estimated because of small sample size are described as 'NA' or not applicable.

[a]Type of biologics included are for TNF-α: etanercept, adalimumab, infliximab, certolizumab; IL-12/23: ustekinumab; IL-17: secukinumab, ixekizumab, bimekizumab and brodalumab and for IL-23: guselkumab, risankizumab, tildrakizumab

Supplemental Table 2. Adverse events, and serious adverse events, in pediatric and young adult patients using a biologic, split for sex.

a. Adverse events

Adverse events (MedDRA classification)	**Total**	**Pediatric patients**			**Young adult patients**		
		Total	Male	Female	Total	Male	Female
Total number of patients	360	117	52	65	243	119	124
Total number of patients with AEs	221	89	37	52	132	62	70
Total number of AEs	1117	473	169	304	644	252	392
Blood and lymphatic system disorders	6 (0.5%)	4 (0.8%)	1 (0.6%)	3 (1.0%)	2 (0.3%)	1 (0.4%)	1 (0.3%)
Cardiac disorders	6 (0.5%)	2 (0.4%)	0 (0%)	2 (0.7%)	4 (0.6%)	1 (0.4%)	3 (0.8%)
Ear and labyrinth disorders	6 (0.5%)	5 (1.1%)	0 (0%)	5 (1.6%)	1 (0.2%)	1 (0.4%)	0 (0%)
Endocrine disorders	1 (0.09%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)	1 (0.3%)
Eye disorders	6 (0.5%)	4 (0.8%)	1 (0.6%)	3 (1.0%)	2 (0.3%)	1 (0.4%)	1 (0.3%)
Gastrointestinal disorders	62 (5.6%)	46 (9.7%)	19 (11.2%)	27 (8.9%)	16 (2.5%)	2 (0.8%)	14 (3.6%)
General disorders and administration site conditions	142 (12.7%)	81 (17.1%)	28 (16.6%)	53 (17.4%)	61 (9.5%)	28 (11.1%)	33 (8.4%)
Fatigue	49 (4.4%)	35 (7.4%)	11 (6.5%)	24 (7.9%)	14 (2.1%)	5 (2.0%)	9 (2.3%)
Injection site reactions	22 (1.9%)	22 (3.8%)	9 (5.3%)	13 (4.3%)	0 (0%)	0 (0%)	0 (0%)
Other	75 (6.7%)	24 (5.1%)	8 (4.7%)	16 (5.3%)	47 (7.1%)	20 (7.9%)	27 (6.9%)
Hepatobiliary disorders	7 (0.6%)	1 (0.2%)	1 (0.6%)	0 (0%)	6 (0.9%)	3 (1.2%)	3 (0.8%)
Immune system disorders	23 (2.1%)	1 (0.2%)	0 (0%)	1 (0.3%)	22 (3.4%)	5 (2.0%)	17 (4.3%)
Infections and infestations	564 (50.5%)	191 (40.4%)	68 (40.2%)	123 (40.5%)	373 (57.9%)	154 (61.1%)	219 (55.9%)
Upper respiratory tract infections	373 (30.2%)	133 (28.1%)	45 (26.2%)	88 (28.9%)	208 (32.3%)	88 (34.9%)	120 (30.6%)
Other	227 (20.3%)	58 (12.3%)	23 (13.6%)	35 (11.5%)	165 (25.6%)	66 (26.2%)	99 (25.3%)
Injury, wounds and complications	19 (1.7%)	9 (1.9%)	3 (1.8%)	6 (2.0%)	10 (1.6%)	8 (3.2%)	2 (0.5%)
Investigations	30 (2.7%)	25 (5.3%)	13 (7.7%)	12 (3.9%)	5 (0.8%)	1 (0.4%)	4 (1.0%)

Supplemental Table 2. Continued

a. Adverse events							
Metabolism and nutrition	4 (0.4%)	4 (0.8%)	2 (1.2%)	2 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders	37 (3.3%)	14 (3.0%)	3 (1.8%)	11 (3.6%)	23 (3.6%)	7 (2.8%)	16 (4.1%)
Neoplasms benign, malignant and unspecified	1 (0.09%)	1 (0.2%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)
Nervous system disorders	29 (2.6%)	20 (4.2%)	4 (2.4%)	16 (5.3%)	9 (1.4%)	0 (0%)	9 (2.3%)
Pregnancy, puerperium and perinatal conditions	7 (0.6%)	0 (0%)	0 (0%)	0 (0%)	7 (1.1%)	1 (0.4%)	6 (1.5%)
Psychiatric disorders	15 (1.3%)	6 (1.3%)	2 (1.2%)	4 (1.3%)	9 (1.4%)	4 (1.6%)	5 (1.4%)
Renal urinary disorders	4 (0.4%)	4 (0.8%)	2 (1.2%)	2 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Reproductive system and breast disorders	11 (1.0%)	6 (1.3%)	1 (0.6%)	5 (1.6%)	5 (0.8%)	0 (0%)	5 (1.3%)
Respiratory, thoracic, and mediastinal disorders	24 (2.1%)	14 (3.0%)	4 (2.4%)	10 (3.3)	10 (1.6%)	3 (1.2%)	7 (1.8%)
Skin and subcutaneous tissue disorders	68 (6.1%)	26 (5.5%)	12 (7.1%)	14 (4.6%)	42 (6.5%)	13 (5.2%)	29 (7.4%)
Social circumstances	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Surgical and medical procedures	40 (3.6%)	7 (1.5%)	4 (2.4%)	3 (1.0%)	33 (5.0%)	18 (7.1%)	15 (3.8%)
Vascular disorders	5 (0.4%)	2 (0.4%)	1 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.4%)	2 (0.5%)
b. Serious adverse events							
Total number of patients	14	4	1	3	10	3	7
Total number of SAEs	18	5	2	3	13	4	9
Ear and labyrinth disorders	1	1[a]	0	1	0	0	0
Gastrointestinal disorders	1	1[a]	0	1	0	0	0
Immune system disorders	1	0	0	0	1[a]	0	1
Infections and infestations	3	1[a]	1	0	2[a]	1	1
Injury, wounds and complications	1	1	0	1	0	0	0
Pregnancy, puerperium and perinatal conditions	5	0	0	0	5[a]	1	4

Supplemental Table 2. Continued

b. Serious adverse events							
Reproductive system and breast disorders	1	1	1	0	0	0	0
Skin and subcutaneous tissue disorders	3	0	0	0	3	1	2
Surgical and medical procedures	2	0	0	0	2	1	1

Abbreviations: AE, adverse events; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse events.
Data expressed as n (%).
Percentages are calculated by dividing the number of AEs per AE category, by the total number of adverse events per group.
[a] For pediatric patients three serious adverse events were possibly related to the biologic (cholesteatoma, abdominal pain and surgical intervention due to appendicitis), and for young adults four serious adverse events were possibly related to the biologic (sinusitis, hospitalization due to psoriasis exacerbation, type I hypersensitivity reaction to biologic, and surgical intervention due to appendicitis).

Supplemental Table 3. Linear mixed model assessing the effect of sex on the course of PASI during the first year of treatment in pediatric and young adult patients with psoriasis.

	Pediatric patients				Young adult patients			
Variable	**Estimate**	**95% CI**		**p-value**	**Estimate**	**95% CI**		**p-value**
Intercept	1.17	-4.35	6.70	0.676	1.64	-2.17	5.45	0.397
Sex (Female)	-0.21	-1.55	1.12	0.753	-0.28	-1.10	0.53	0.498
Age at start biologic (Years)	-0.09	-0.34	0.17	0.515	-0.06	-0.18	0.05	0.278
PASI at time points (ref 3 months)								
6 months	-0.73	-1.23	-0.24	0.004	-0.98	-1.35	-0.61	0.000
9 months	-1.05	-1.56	-0.55	0.000	-1.34	-1.71	-0.96	0.000
12 months	-1.01	-1.54	-0.48	0.000	-1.46	-1.86	-1.05	0.000
Disease duration until start of biologic (Years)	0.08	-0.10	0.26	0.390	-0.01	-0.10	0.08	0.860
BMI	0.11	-0.07	0.29	0.223	0.09	0.01	0.17	0.036
Psoriatic arthritis (Yes)	1.08	-1.27	3.42	0.367	0.86	-0.41	2.13	0.186
Psychiatric disease (Yes)	-0.43	-2.35	1.49	0.660	-0.06	-1.26	1.15	0.929
Biologic class (ref TNF-α)[a]								
IL-12/23	-1.78	-3.15	-0.41	0.011	-0.49	-1.36	0.39	0.273
IL17	-1.96	-6.49	2.57	0.395	-1.13	-2.94	0.69	0.222
IL23	NA	NA	NA	NA	-0.93	-2.39	0.54	0.213
Previous use of biologics (Yes)	-0.52	-4.21	3.17	0.781	0.09	0.01	0.17	0.036
Baseline PASI	0.30	0.18	0.41	0.000	0.14	0.07	0.20	0.000

Abbreviations: BMI, body mass index; CI, confidence interval; IL, Interleukin; NA, not applicable; PASI, Psoriasis Area and Severity Index; TNF-α, Tumor Necrose Factor-alfa.

Values that could not be estimated because of small sample size are described as 'NA' or not applicable.

[a]Type of biologics included are for TNF-α: etanercept, adalimumab, infliximab, certolizumab; IL-12/23: ustekinumab; IL-17: secukinumab, ixekizumab, bimekizumab and brodalumab and for IL-23: guselkumab, risankizumab, tildrakizumab.

Supplemental Table 4. Logistic regression model assessing the effect of sex on the number of patients reaching PASI scores of ≤1, ≤3 and ≤5 at six months of treatment, in pediatric and young adult patients with psoriasis.

		Pediatric patients				Young adult patients			
	Variable	**OR**	**95% CI**		**p-value**	**OR**	**95% CI**		**p-value**
	Intercept	0.42	0.01	24.05	0.673	2.87	0.19	43.77	0.449
PASI ≤1	Sex (Female)	2.48	0.92	6.73	0.078	0.85	0.42	1.70	0.642
	Disease duration until start of biologic (Years)	0.95	0.84	1.08	0.453	1.05	0.97	1.12	0.244
	BMI	1.01	0.91	1.12	0.878	0.94	0.87	1.02	0.132
	Previous use of biologics (Yes)	1.01	0.06	17.95	0.993	1.11	0.30	4.09	0.874
	Baseline PASI	0.93	0.85	1.02	0.113	0.98	0.93	1.04	0.467
PASI ≤3	Intercept	29086.74	0.00	NA	0.992	22.74	1.41	366.86	0.030
	Sex (Female)	1.05	0.37	3.00	0.926	1.04	0.45	2.40	0.932
	Disease duration until start of biologic (Years)	0.99	0.86	1.15	0.922	1.03	0.94	1.13	0.548
	BMI	1.02	0.90	1.14	0.798	0.95	0.88	1.02	0.148
	Previous use of biologics (Yes)	0.00	0.00	NA	0.993	0.69	0.16	3.05	0.625
	Baseline PASI	0.89	0.81	0.98	0.024	0.96	0.90	1.03	0.292
PASI ≤5	Intercept	564312.89	0.00	NA	0.991	57.53	2.18	1520.47	0.017
	Sex (Female)	0.93	0.26	3.33	0.914	0.88	0.31	2.49	0.816
	Disease duration until start of biologic (Years)	0.91	0.77	1.08	0.267	1.02	0.90	1.15	0.767
	BMI	1.02	0.88	1.19	0.762	0.95	0.88	1.03	0.184
	Previous use of biologics (Yes)	0.00	0.00	NA	0.993	0.89	0.16	4.97	0.891
	Baseline PASI	0.86	0.76	0.97	0.016	0.95	0.88	1.02	0.134

Abbreviations: BMI, body mass index; CI, confidence interval; NA, not applicable; OR, odds ratio; PASI, Psoriasis Area and Severity Index.
Values that could not be estimated because of small sample size are described as 'NA' or not applicable.

Supplemental Table 5. Linear regression model assessing the effect of sex on the PASI score at treatment discontinuation, in pediatric and young adult patients with psoriasis.

	Pediatric patients				Young adult patients			
Variable	**Effect**	**95% CI**		**p-value**	**Effect**	**95% CI**		**p-value**
Intercept	3.92	-9.31	17.16	0.530	-0.35	-10.15	9.45	0.942
Sex (Female)	0.31	-4.62	5.25	0.891	-0.24	-3.28	2.81	0.220
Disease duration until start of biologic (Years)	0.63	-0.05	1.31	0.066	0.05	-0.27	0.36	0.768
BMI	-0.10	-0.67	0.47	0.702	0.06	-0.22	0.34	0.670
Previous use of biologics (Yes)	-4.38	-14.24	5.48	0.355	2.72	-1.32	6.75	0.176
Baseline PASI	0.56	0.15	0.97	0.012	0.15	-0.09	0.38	0.220

Abbreviations: BMI, Body Mass Index; CI: Confidence Interval; PASI, Psoriasis Area and Severity Index.

Supplemental Table 6. Linear mixed model assessing the effect of sex on the course of CDLQI in pediatric patients and DLQI in young adult patients with psoriasis, during the first year of treatment.

	Pediatric patients (CDLQI)				Young adult patients (DLQI)			
Variable	**Effect**	**95% CI**		**p-value**	**Effect**	**95% CI**		**p-value**
Intercept	2.37	-3.49	8.24	0.426	13.64	3.40	23.88	0.009
Sex (Female)	0.05	-1.57	1.67	0.954	0.20	-1.48	1.89	0.811
(C) DLQI at time points (ref 3 months)[a]								
6 months	0.73	-0.07	1.53	0.073	0.04	-0.55	0.64	0.884
9 months	0.50	-0.39	1.39	0.265	-0.43	-1.10	0.23	0.195
12 months	0.83	-0.14	1.80	0.091	-0.65	-1.36	0.06	0.074
Age at start biologic (Years)	-0.33	-0.67	0.00	0.049	-0.03	-0.33	0.28	0.854
Disease duration until start of biologic (Years)	-0.07	-0.31	0.17	0.562	0.07	-0.17	0.30	0.590
BMI	0.24	0.04	0.43	0.016	-0.19	-0.41	0.03	0.093
Psoriatic arthritis (Yes)	0.95	-1.48	3.38	0.441	-0.63	-3.34	2.08	0.650
Psychiatric disease (Yes)	-1.78	-4.69	1.13	0.229	2.00	-0.68	4.68	0.143
Biologic class (ref TNF-α)[b]								
IL-12/23	-0.54	-2.15	1.08	0.513	-2.23	-4.10	-0.36	0.020
IL17	-5.94	-12.75	0.87	0.087	-7.15	-12.32	-1.98	0.007
IL23	NA	NA	NA	NA	-3.08	-6.09	-0.06	0.046
Previous use of biologics (Yes)	-2.24	-6.22	1.75	0.269	-7.47	-11.25	-3.70	0.000
Baseline CDLQI[a]	0.25	0.09	0.41	0.002	NA	NA	NA	NA
Baseline DLQI[a]	NA	NA	NA	NA	0.16	0.02	0.31	0.030

Abbreviations: BMI, Body Mass Index; CI: Confidence Interval; (C)DLQI: (Children's) Dermatology Life Quality Index; IL, Interleukin; NA, not applicable; PASI, Psoriasis Area and Severity Index; TNF-α, Tumor Necrose Factor-alfa.

Values that could not be estimated because of small sample size are described as 'NA' or not applicable.

[a]The CDLQI was used in pediatric patients (<18 years) and the DLQI was used in young adult patients (18-30 years).

[b]Type of biologics included are for TNF-α: etanercept, adalimumab, infliximab, certolizumab; IL-12/23: ustekinumab; IL-17: secukinumab, ixekizumab, bimekizumab and brodalumab and for IL-23: guselkumab, risankizumab, tildrakizumab.

Supplemental Table 7. Logistic regression model assessing the effect of sex on the number of pediatric patients reaching CLDQI scores, and young adult patients reaching DLQI scores, of ≤1, ≤3 and ≤5 at six months of treatment.

		Pediatric patients (CDLQI)				Young adult patients (DLQI)			
	Variable	**OR**	**95% CI**		**p-value**	**OR**	**95% CI**		**p-value**
(C)DLQI ≤1[a]	Intercept	2.34	0.26	20.98	0.451	4.57	0.60	34.84	0.148
	Sex (Female)	1.43	0.43	4.78	0.566	0.65	0.22	1.96	0.447
	Baseline (C)DLQI	0.93	0.83	1.04	0.202	0.97	0.90	1.04	0.368
(C)DLQI ≤3[a]	Intercept	13.15	0.44	390.99	0.146	3.40	0.41	28.36	0.263
	Sex (Female)	0.82	0.13	5.20	0.831	1.33	0.40	4.39	0.647
	Baseline (C)DLQI	0.95	0.84	1.08	0.440	0.96	0.88	1.04	0.304
(C)DLQI ≤5[a]	Intercept	372321.09	0.00	NA	0.996	11.31	0.78	163.28	0.080
	Sex (Female)	0.01	0.00	NA	0.997	0.94	0.23	3.90	0.938
	Baseline (C)DLQI	0.92	0.77	1.10	0.366	0.94	0.85	1.03	0.205

Abbreviations: BMI, Body Mass Index; CI: Confidence Interval; (C)DLQI: (Children's) Dermatology Life Quality Index; NA, not applicable; OR, odds ratio. Values that could not be estimated because of small sample size are described as 'NA' or not applicable.

[a]The CDLQI was used in pediatric patients (<18 years) and the DLQI was used in young adult patients (18-30 years).

Supplemental Table 8. Linear regression model assessing the effect of sex on the CLDQI scores in pediatric patients, and DLQI scores in young adult patients with psoriasis, at treatment discontinuation.

	Pediatric patients (CDLQI)				Young adult patients (DLQI)			
Variable	**Effect**	**95% CI**		**p-value**	**Effect**	**95% CI**		**p-value**
Intercept	4.99	-17.18	27.16	0.625	14.71	-17.00	46.41	0.329
Sex (Female)	4.79	-7.57	17.15	0.402	1.13	-5.97	8.23	0.736
Disease duration until start of biologic (Years)	0.06	-.125	1.37	0.913	-0.14	-1.17	0.90	0.772
BMI	0.25	-0.48	0.97	0.456	-0.37	-1.11	0.36	0.283
Previous use of biologics (Yes)	-11.30	-28.26	5.66	0.169	-3.65	-17.64	10.34	0.563
Baseline (C)DLQI	-0.03	-1.04	0.97	0.939	0.31	-0.24	0.85	0.240

Abbreviations: BMI, Body Mass Index; CI: Confidence Interval; (C)DLQI: (Children's) Dermatology Life Quality Index.

CHAPTER 4

Development of arthritis in a large real-world cohort of patients with pediatric onset psoriasis

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Abstract

Background
Early identification and treatment of psoriatic arthritis (PsA) among patients with psoriasis is important to prevent joint damage. Insights in arthritis onset and the associated clinical factors among pediatric and young adult patients with psoriasis is scarce.

Objectives
To describe pediatric patients with psoriasis who subsequently developed psoriatic arthritis at pediatric age or in young adulthood (JPsA/PsA). We focused on clinical features and timing of onset, and compared clinical features to characteristics of a large cohort of pediatric psoriasis patients.

Methods
Data on patients with pediatric onset of psoriasis were obtained from the prospective, daily practice, ChildCAPTURE registry. Descriptive statistics were used. ILAR and CASPAR criteria were used for classification of JPsA and PsA, respectively. The time to JPsA/PsA diagnosis following psoriasis onset was analyzed using Kaplan-Meier survival analysis.

Results
Among 717 pediatric and young adult patients with psoriasis, 15 (2.1%) developed arthritis, of which 8 patients before the age of 18 years (1.1%, JPsA) and 7 patients in young adulthood (1.0%, PsA), with an estimated incidence of 2.8% within 10 years after psoriasis diagnosis. The median interval between psoriasis onset and JPsA/PsA development was 4.8 years. Male sex, obesity, and nail involvement were common clinical features of patients developing JPsA/PsA, and these were observed more frequently compared to the total pediatric psoriasis cohort.

Conclusion
The incidence of JPsA/PsA among patients with pediatric onset of psoriasis is low. If the clinical features male sex, obesity and nail involvement are present, extra awareness for the development of JPsA/PsA is warranted.

Introduction

Early diagnosis of psoriatic arthritis (PsA) in patients with psoriasis is important for prevention and interception of PsA.[1] Many potential risk factors for PsA development in adult patients with psoriasis have been suggested in the literature including obesity, nail involvement, psoriasis severity, familial history, and arthralgia.[1-4] However, little is known about the development of PsA in pediatric patients with psoriasis.

At the moment, the largest body of evidence on the development of arthritis in pediatric patients with psoriasis originates from pediatric rheumatology cohorts, describing patients with Juvenile Psoriatic Arthritis (JPsA). JPsA is a subtype of Juvenile Idiopathic Arthritis (JIA) and accounts for approximately 8% (range 4-11%) of the JIA population.[5-9] Despite its prevalence, diagnosing JPsA remains challenging, particularly in patients without psoriatic lesions (in 40-60% of JPsA cases[10,11]), due to the heterogeneous patient population characterized by diverse clinical presentations and laboratory findings.[5,12-14] Consequently, the clinical features of these JPsA cohorts may not correspond to the clinical characteristics of pediatric patients with psoriasis subsequently developing JPsA, who are primarily seen in a dermatology setting.

Only one claims-based study reported on the development of JPsA in pediatric patients with psoriasis and its associated risk factors, finding that 2% of children with psoriasis developed JPsA during a mean follow-up of five years. Older age at the time of first psoriasis diagnosis and the presence of uveitis were identified as risk factors for developing JPsA.[10] Especially in pediatric and young adult patients with psoriasis, little is known about the presenting clinical features of psoriatic arthritis and potential risk factors thereof. This study aims to describe a real-world cohort of pediatric patients with psoriasis who subsequently developed psoriatic arthritis at pediatric age or in young adulthood (JPsA/PsA), focusing on their clinical features and timing of onset. In addition, we compare these clinical features with the characteristics of pediatric psoriasis patients from the same cohort who did not develop psoriatic arthritis.

Methods

This explorative study was conducted among pediatric patients with plaque psoriasis. Data were extracted from the ChildCAPTURE registry (Continuous

Assessment of Psoriasis Treatment Use REgistry), a prospective, daily clinical practice registry in which pediatric patients with psoriasis (<18 years) treated at the Department of Dermatology at the Radboud University Medical Center in Nijmegen, the Netherlands, are included since 2008.[15] All patients with dermatologist-confirmed psoriasis (ranging from mild to severe psoriasis) were included. Only those in whom the diagnosis could not be clearly established were excluded from the registry. Patients were referred by various general practitioners and dermatologists across the Netherlands to our dermatology department. Because pediatric patients included in the ChildCAPTURE registry are followed into young adulthood, data on psoriatic arthritis onset beyond the age of 18 years were also extracted. Follow-up duration varied between individuals, with data collection extending up to 30 years of age. This study was reviewed and approved by the local ethics committee. Written informed consent was obtained from the parents or guardians and/or from the participating pediatric patients according to applicable rules.

Data collection

At the time of registry inclusion (baseline), data were extracted on patient characteristics, including sex, age at onset of psoriasis, psoriasis treatment history, family history of psoriasis and psoriatic arthritis. The following clinical characteristics were extracted: Psoriasis Area and Severity Index (PASI) score, Body Surface Area (BSA), Body Mass Index (BMI), and nail involvement. At each follow-up visit, the following data were recorded: PASI score, BSA, BMI, and nail involvement. The age at onset of JPsA (defined as PsA <18 years of age) or PsA (defined as PsA ≥18 years of age) was recorded,[16] either at baseline if already diagnosed, or during follow-up if the diagnosis occurred later. The total group was designated as JPSA/PsA.

For BMI, children (<18 years) were classified as underweight, normal weight, overweight or obese according to International Obesity Task Force criteria.[17,18] For young adults (>18 years), BMI categories were defined according to the World Health Organization reference ranges.[19] Nail involvement was defined as the presence of nail psoriasis features such as pitting, onycholysis or oil drop phenomenon.

Diagnosis of JPsA/PsA

Patients were referred to a rheumatologist based on clinical assessment by the treating physician. Factors considered for referral included persistent joint complaints, morning stiffness lasting more than 30 minutes, and elevated

PEST scores (>3). Patients were referred to a (pediatric) rheumatologist at the patient's preferred hospital, either at the Radboud University Medical Center or another medical center of their choice. Medical records from these evaluations at the time of the arthritis diagnosis, as well as laboratory results and imaging studies, were obtained retrospectively for this study. Children <18 years were diagnosed with JPsA by a pediatric rheumatologist according to the ILAR classification criteria.[20,21] [16]The ILAR criteria define JPsA as psoriasis and arthritis, or arthritis without psoriasis and at least two of the following: 1) dactylitis, 2) nail pitting or onycholysis, 3) psoriasis in a first-degree relative.[21]

Young adults (≥ 18 years) were diagnosed with PsA by a rheumatologist according to the CASPAR criteria.[22] The CASPAR criteria require the presence of inflammatory articular disease (affecting joints, spine, or entheses) along with a score of ≥3 points from the following categories: (1) current psoriasis, personal or family history of psoriasis; (2) typical psoriatic nail dystrophy; (3) negative rheumatoid factor; (4) current or past dactylitis; and (5) radiographic evidence of juxta articular new bone formation.[22]

Statistical analysis

Analyses were performed in SPSS version 29.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were used to summarize patient characteristics, including demographics and clinical features. Categorical variables were presented as numbers and percentages, and continuous variables as medians with interquartile ranges [IQRs] or means with standard deviation (SD), depending on data distribution. Baseline characteristics between patients with JPsA/PsA and the total cohort were compared descriptively; numbers of patients with JPsA/PsA were low therefore statistical comparisons were not made. The time to arthritis diagnosis following psoriasis onset was analyzed using Kaplan-Meier survival analysis in R studio version 2024.04 (R Foundation for Statistical Computing, Vienna, Austria). Here, JPsA/PsA diagnosis was considered an event, and patients that were lost-to-follow up or patients who remained arthritis-free until data lock were censored.

Results

A total of 717 pediatric patients with psoriasis were included in the study, with a cumulative observation period of 2850 years following inclusion in the ChildCAPTURE registry. The majority of patients were female (60.1%)

and the median age at psoriasis diagnosis was 8.0 [6.2] years (Table 1). Of 717 patients, 15 patients (2.1%) developed JPsA/PsA. Over a 10-year period following psoriasis onset, the cumulative incidence of development of JPsA/PsA was 2.8% (95%CI=1.0%-4.6%) as shown in the Kaplan-Meier analysis in Supplemental Figure 1.

Table 1. Clinical characteristics of pediatric patients in the ChildCAPTURE registry

	All patients (n=717)	**Patients diagnosed with JPsA/PsA (n=15)**
Sex, *n (%)*		
Male	286 (39.9)	10 (66.7)
Female	431 (60.1)	5 (33.3)
Age at psoriasis diagnosis, years, median [IQR]	8.0 [6.2]	12.0 [7.4]
Age at registry inclusion, years, median [IQR]	11.2 [6.8]	14.6 [4.4]
Age at arthritis diagnosis, years, median [IQR]	-	17.3 [9.6]
Follow-up duration in registry, years, median [IQR][a]	2.8 [5.6]	9.7 [7.6]
Time from psoriasis onset to arthritis diagnosis, years, median [IQR]	-	4.8 [7.5]
First degree family history, *n (%)*[a]	228 (31.8)	5 (33.3)
Psoriasis	19 (3.8)	0 (0.0)
Psoriatic arthritis		
BMI category at registry inclusion, *n (%)*[b]		
Underweight	86 (15.6)	0 (0.0)
Normal weight	361 (65.4)	8 (61.5)
Overweight	68 (12.3)	1 (7.7)
Obese	37 (6.7)	4 (30.8)
BMI category at arthritis diagnosis, *n (%)*[a,b]		
Underweight	-	0 (0.0)
Normal weight		5 (41.7)
Overweight		4 (33.3)
Obese		3 (25.0)
Nail involvement at registry inclusion, *n (%)*[a]	129 (18.0)	6 (40.0)
Nail involvement at arthritis diagnosis, *n (%)*[a]	-	7 (50.0)
Disease severity at registry inclusion, median [IQR]		
PASI (0-72)	5.6 [4.8]	6.3 [2.7]
BSA (0-100%)	6.0 [8.0]	6.6 [7.0]

Table 1. Continued

	All patients (n=717)	Patients diagnosed with JPsA/PsA (n=15)
Disease severity at arthritis diagnosis, median [IQR][a]	-	
PASI (0-72)		3.9 [7.6]
BSA (0-100%)		2.5 [6.9]

Notes: Percentages were calculated using the total number of available data for that characteristic per group.

Abbreviations: BSA, Body surface area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; JPsA/PsA, juvenile psoriatic arthritis or psoriatic arthritis; PASI, Psoriasis Area and Severity Index; PEST, Psoriasis Epidemiology Screening Tool; PGA, Physician Global Assessment; PsA, psoriatic arthritis

[a]Variables with *missing* data include: family history of psoriasis (all patients, n=1), family history of psoriatic arthritis (all patients, n=220; patients diagnosed with JPsA/PsA, n=7), BMI category at registry inclusion (all patients, n=165; patients diagnosed with JPsA/PsA, n=2), BMI category at arthritis diagnosis (n=3), nail involvement at registry inclusion (all patients, n=1), nail involvement at arthritis diagnosis (n=1), PASI at arthritis diagnosis (n=3), BSA at registry inclusion (all patients, n=11), BSA at JPsA/PsA diagnosis (n=3).

[b]Children (<18 years) were classified as underweight, normal weight, overweight or obese according to International Obesity Task Force criteria. These criteria are based on pooled BMI data from six countries (including the Netherlands) and provide internationally recognized cut-off points for BMI categorization in children.[17,18] For young adults (>18 years), BMI categories were defined according to the World Health Organization reference ranges: underweight (<18.5), normal weight (18.5–24.9), overweight (>25.0), and obese (>30.0).[19]

Among the 15 patients that developed JPsA/PsA, the median age at psoriasis diagnosis was 12.0 [7.4] years and the age at arthritis diagnosis was 17.3 [9.6] years (Table 1). The median time between onset of psoriasis and development of JPSA/PsA was 4.8 [7.5] years. Eight patients developed JPsA before the age of 18 years. Among all patients with JPsA/PsA, half of them had nail involvement and 58.3% were overweight or obese at the time of arthritis diagnosis. Furthermore, PASI and BSA were lower at time of JPsA/PsA diagnosis than at time of registry inclusion (PASI, 3.9 [7.6] vs 6.3 [2.7]; BSA, 2.5 [6.9] vs 6.6 [7.0]). At the time of JPsA/PsA diagnosis, five patients used topical therapy only, six were treated with conventional systemic therapy (methotrexate (n=5) and fumaric acid (n=1)), and four patients were treated with a biologic (adalimumab (n=1), ustekinumab (n=2) and certolizumab (n=1)). More details on the treatments of these patients before and after diagnosis of JPsA/PsA are depicted in Figure 1.

Table 2. Clinical and laboratory findings by (pediatric) rheumatologists in pediatric and young adult psoriasis patients at time of JPsA/PsA diagnosis

Patient	Sex	Age at psoriasis diagnosis, years	Age at JPsA/PsA diagnosis, years	Arthritis	Dactylitis	Nail involvement	Enthesitis	Oligo- or poly-arthritis	Asymmetry
1	Female	2.4	9.8	Yes	No	No	No	Poly	Yes
2	Male	5.9	9.8	Yes	No	Yes	No	Oligo	Yes
3	Male	7.4	10,2	Yes	Yes	Yes	No	Poly	Yes
4	Male	10.5	11.2	Yes	No	Yes	No	Poly	n.a.
5	Male	12.0	13.0	Yes	No	Yes	No	Poly	No
6	Female	14.6	15.5	Yes	n.a.	n.a.	n.a.	n.a.	n.a.
7	Male	4.0	16.5	Yes	No	No	No	Oligo	No
8	Male	14.2	17.3	Yes	n.a.	No	n.a.	n.a.	n.a.
9	Female	14.4	19.3	Yes	Yes	No	No	Oligo	Yes
10	Male	14.6	19.3	Yes	No	No	No	Poly	No
11	Female	14.6	20.2	Yes	No	Yes	No	Oligo	Yes
12	Male	9.8	20,8	Yes	No	No	No	Poly	Yes
13	Male	12.2	22.8	Yes	No	Yes	No	Oligo	Yes
14	Male	13.7	23.4	Yes	No	No	No	Oligo	Yes
15	Female	7.0	26.0	Yes	No	Yes	No	Oligo	Yes

Abbreviations: n.a., not available; NEG, negative; POS, positive; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; HLA-B27, human leukocyte antigen B27; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibodies; DIP, distal interphalangeal joint; PIP, proximal interphalangeal joint.

[a]To assess whether CRP and ESR were elevated, the interpretation of the (pediatric) rheumatologist was used when available. If no interpretation was provided, CRP was considered elevated if ≥10 mg/L, and ESR was considered elevated if ≥15 mm/hour.

Involvement of lower back	Change in therapy	Lab results					Erosions on imaging
		ANA	HLA-B27	CRP or ESR[a]	RF	Anti-CCP	
No	Already on methotrexate, start ibuprofen	NEG	POS	Elevated	NEG	NEG	n.a.
No	Start Naproxen	NEG	n.a.	n.a.	NEG	NEG	n.a.
No	Already on Fumaric acid, start Naproxen	NEG	n.a.	Not elevated	NEG	NEG	yes
No	Already on methotrexate	NEG	NEG	n.a.	NEG	n.a.	No
No	Start Naproxen	NEG	NEG	Not elevated	NEG	NEG	No
n.a.	Already on methotrexate	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Yes	Already on methotrexate, start Diclofenac	NEG	NEG	Not elevated	NEG	NEG	No
n.a.	Initially start meloxicam, later Enbrel	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
No	Already on ustekinumab, start sulfasalazine	POS	NEG	Elevated	NEG	NEG	No
No	Start Naproxen	n.a.	n.a.	Elevated	NEG	NEG	Yes
No	Injection Kenacort, start naproxen and higher dosage methotrexate	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
No	Already on adalimumab	NEG	n.a.	Not elevated	n.a.	NEG	No
No	Already on ustekinumab, Injection Kenacort	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
No	Start methotrexate	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
No	Already on certolizumab, start Naproxen and Injection Depomedrol	n.a.	NEG	Not elevated	NEG	NEG	No

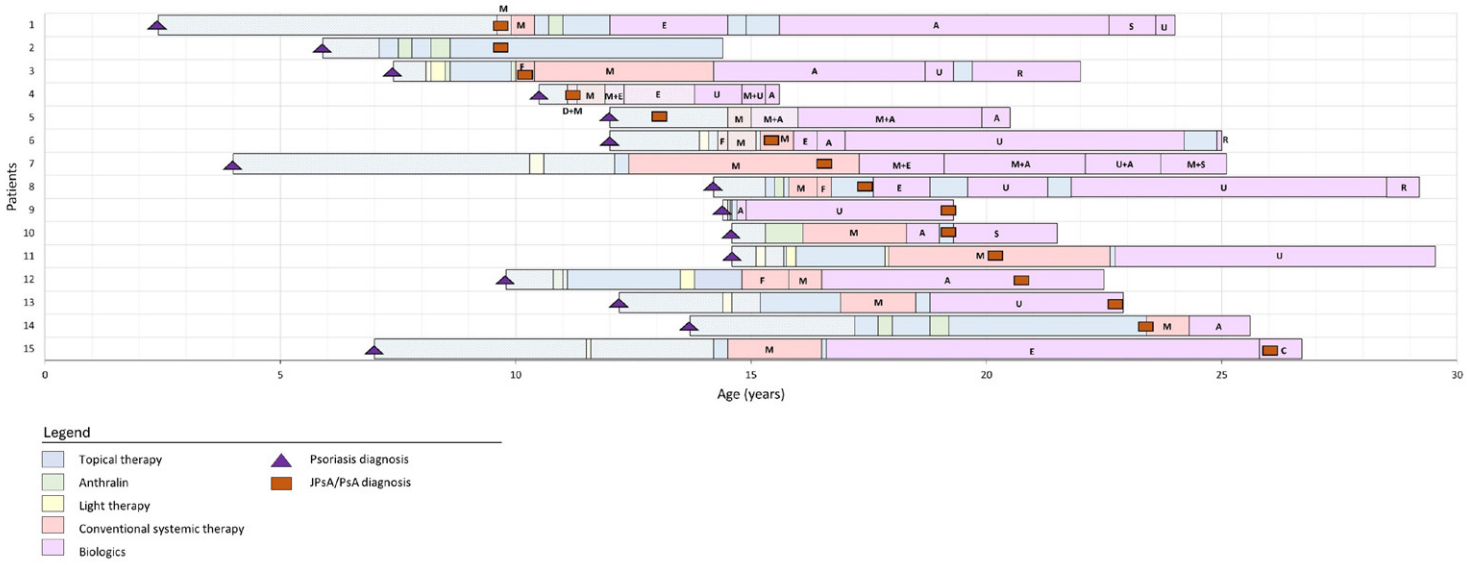

Figure 1. Psoriasis and JPsA/PsA onset and treatments of 15 pediatric and young adult patients with arthritis

Abbreviations: JPsA/PsA, juvenile psoriatic arthritis or psoriatic arthritis; Ci, ciclosporin; M, methotrexate; F, fumaric acid. A, adalimumab; C, certolizumab; E, etanercept; S, secukinumab; R, rituximab; U, ustekinumab

A detailed rheumatological assessment at the time of JPsA/PsA diagnosis is described in Table 2. The age at psoriasis diagnosis ranged from 2.4 years to 14.6 years and diagnosis of JPsA/PsA ranged from 9.8 years to 26 years. The most common clinical findings at the time of JPsA/PsA diagnosis were asymmetry of the affected joints (9/12 patients) and involvement of the nails (7/14 patients). Oligoarthritis and polyarthritis were equally present in this group (7/13 vs 6/13 patients). Only 2 patients reported dactylitis, diagnosed based on clinical symptoms. Symptoms of enthesitis were not observed, and lower back pain was only observed in one patient, who was followed up with MRI and X-ray by the rheumatologist and revealed sacroiliitis and arthritis of the hip joints.

Comparison between baseline characteristics of JPsA/PsA patients and the total pediatric psoriasis cohort.

When comparing baseline characteristics between JPsA/PsA patients and the total pediatric psoriasis cohort (Table 1), it was observed that patients with JPsA/PsA were more often male (66.7% vs 39.9%), were more often obese (30.8% vs 6.7%) and their nails were more often affected at registry inclusion compared to the total psoriasis cohort (40.0% vs 18.0%). Also, the median age at psoriasis diagnosis is relatively higher (12 vs 8 years). Patients with JPsA/PsA had a longer median follow-up duration in the registry compared to the total cohort (9.7 [7.6] years vs 2.8 [5.6] years). Family history for psoriasis and PsA was comparable between groups.

Discussion

This prospective registry study investigated the development of juvenile psoriatic arthritis and psoriatic arthritis (JPsA/PsA) among a large real-world cohort of patients with pediatric onset of psoriasis. It was shown that 2.1% of patients developed JPsA/PsA in this cohort. Age of arthritis onset was before the age of 18 years in eight patients (1.1%) and in young adulthood in seven patients (1.0%). The estimated cumulative risk of the development of JPsA/PsA was 2.8% within 10 years after the diagnosis of pediatric onset psoriasis. The median interval between psoriasis onset and JPsA/PsA development was 4.8 years. Patients with JPsA/PsA were predominantly male, more often obese, and had more often nail involvement compared to the total cohort.

In our cohort, with detailed characterization and follow-up, the pediatric patients with psoriasis that developed JPsA was 1.1%. Only one US based study

using administrative claims data of children (0-16 years) identified that 2% of pediatric patients had diagnosis codes for both psoriasis and JPsA.[10] However, after excluding the patients where the JPsA diagnosis preceded the psoriasis diagnosis, only 1.6% (70/4312) of pediatric patients with psoriasis developed JPsA.[10] Our data confirm the fact that the percentage of pediatric patients with psoriasis that develops JPsA at pediatric age over time is low. In our study, we uniquely followed pediatric patients with psoriasis into young adulthood and showed that an additional 1.0% of patients developed PsA between the ages of 18 and 30 years.

In the present study, a median time from psoriasis to JPsA/PsA diagnosis of 4.8 years was found. Until now, only two studies mentioned the time from psoriasis diagnosis to development of arthritis in pediatric patients. In a US data claims study, the median time to index code for arthritis after index code for psoriasis was reported to be 17.6 months [IQR 4.1– 38.1],[10] and in a retrospective case-control study among 14 pediatric patients, the mean time between psoriasis onset and arthritis diagnosis was 3.8 (± 3.5) years.[23] While the time from psoriasis to JPsA/PsA diagnosis in our cohort is somewhat longer than previous mentioned pediatric reports, it remains considerably shorter than the 9-13 years that have been reported in adult cohorts.[23-25] Although it is tentative to speculate that arthritis tends to occur relatively early in pediatric patients with psoriasis, this conclusion cannot be drawn with certainty due to the relative short follow-up and small number of patients.

Within our group of pediatric patients with psoriasis, the proportion of males was notably higher in the group that developed JPsA/PsA compared to the overall psoriasis group (66.7% vs. 39.9%). In JPsA literature two distinct clinical subgroups with a bimodal age distribution for arthritis onset are identified, with incidence peaks occurring at approximately 2–3 years and 10–12 years of age.[12,24-26] The later-onset peak more often presents with features characteristic of spondyloarthritis, including male predominance, enthesitis, axial involvement, and HLA-B27 positivity.[25] The male predominance and later onset of arthritis found in our cohort supports this finding, although only one of our patients had axial involvement, HLAB27 positivity was only found in one female patient and enthesitis was not recorded in any of our patients. These differences in clinical characteristics between JPsA cohorts derived from pediatric rheumatology practices and our dermatology derived cohort underline the importance of publications of pediatric cohorts in which psoriasis precedes arthritis.

In adults with psoriasis, obesity is the most significant modifiable risk factor for the development of PsA, as many studies have shown a relationship between high BMI and development of PsA.[2,27,28] As there are limited studies focusing on pediatric patients with psoriasis who develop JPsA, the potential risk factors for PsA in the pediatric population remain poorly defined. However, a recent cross-sectional study identified higher BMI as possible predictor for the development of JPsA in children with psoriasis.[29] In our cohort, 38.5% of patients that developed JPsA/PsA over time were overweight or obese at registry inclusion compared to 19.0% of the total cohort. At the time of JPsA/PsA diagnosis, 58.3% of patients was overweight or obese. Our data show a potential association between higher BMI and arthritis, and underscore previous literature in which a higher BMI was found to be a possible predictor for the development of JPsA in children with psoriasis.[29]

Interestingly, at the time of JPsA/PsA diagnosis, 6 of 15 patients were treated with conventional systemic therapy (methotrexate (n=5) and fumaric acid (n=1)), and four patients were on a biologic, including adalimumab (n=1), ustekinumab (n=2) and certolizumab (n=1). Despite this, they still developed JPsA/PsA. We also observed that psoriasis severity was lower around the time of JPsA/PsA diagnosis compared to the time of registry inclusion for these 15 patients (PASI, 3.9 vs 6.3; BSA, 2.5 vs 6.6). Both findings suggest that JPsA/PsA can arise in pediatric and young adult patients when the psoriasis is clinically well-controlled.

Nail involvement has often been reported as a potential risk factor for PsA in adults, although findings across studies are somewhat inconsistent.[30-32] While several adult cohorts have shown an increased risk of PsA in patients with nail changes, particularly nail pitting and onycholysis, others have not found a statistically robust association. This variability may reflect differences in how the presence of nail involvement is assessed. One pediatric study has likewise noted nail involvement as a possible predictor for JPsA development, although it is unclear whether the analysis accounted for confounding factors.[29] In our cohort, patients diagnosed with JPsA/PsA had a higher prevalence of nail involvement at the time of registry inclusion compared to the total population (40.0% resp. 18.0%).

One of the strengths of this study is the use of the longstanding, prospective ChildCAPTURE registry. The prospective design enabled detailed follow-up of disease progression and tracking of clinical features. A limitation of this

study is the relatively low number of JPsA/PsA development events, which restricts the study's statistical power and may affect the robustness of the findings. To identify patients with JPsA/PsA, joint complaints and PEST scores were prospectively collected in the ChildCAPTURE registry, and patients were actively referred to a rheumatologist with persistent joint complaints, morning stiffness >30 min and/or PEST scores >3. Nevertheless, the ChildCAPTURE registry was not solely designed to identify patients who develop arthritis, which could theoretically have resulted in an underreporting of the number of patients with arthritis.

Another limitation of this study is that, despite the use of a longstanding registry cohort with a substantial number of observation years (2850 years), the number of patients who may still develop arthritis remains uncertain. This is reflected by the shorter median follow-up for the entire cohort (2.8 years) compared with those who have developed JPsA/PsA (9.7 years). To mitigate this, we performed Kaplan Meier analysis taking differences in follow-up duration into account.

In this study, a unique real-world cohort of patients with pediatric onset of psoriasis who subsequently developed JPsA/PsA was described. Approximately 1% of patients developed JPsA before the age of 18 years and another 1% during young adulthood, with an estimated incidence of 2.8% within 10 years after psoriasis diagnosis. The median interval between psoriasis onset and JPsA/PsA development was 4.8 years, and frequently found clinical features of patients developing arthritis included male sex, obesity, and nail involvement. These findings may help the early recognition of JPsA/PsA in pediatric and young adult patients with psoriasis and contribute to the ongoing efforts to refine classification criteria for juvenile psoriatic arthritis.

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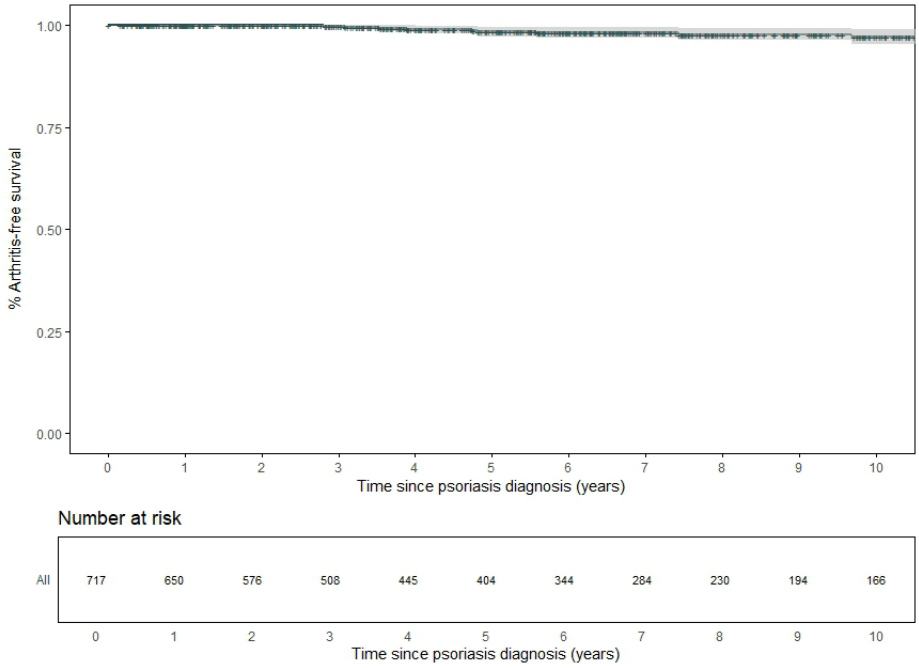
Supplementary Material



Supplemental Figure 1. Kaplan-Meier curve of time to JPsA-PsA development in pediatric and young adult patients with psoriasis[a]

Abbreviation: JPsA/PsA, juvenile psoriatic arthritis or psoriatic arthritis

[a]Using Kaplan-Meier survival analysis in R, the 10-year cumulative incidence of JPsA/PsA development after psoriasis diagnosis was estimated at 2.8% (95% CI: 1.0%–4.6%).

CHAPTER 5

Psychological and socioeconomic factors associated with depression and anxiety among patients with psoriasis

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Abstract

Background

Patients with psoriasis have an increased prevalence of depression and anxiety compared to the general population. Previous studies linked sex, age and psoriasis severity to depression and/or anxiety (DA), but research on factors like psoriasis visibility, stress, socioeconomic status and social support is limited. This study explored factors associated with moderate-to-severe DA in patients with psoriasis, assessing both well-known patient characteristics (sex, age and disease severity) and psychological and socioeconomic factors.

Methods

A web-based survey among psoriasis patients was conducted. The Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder scale (GAD-7) were used to assess symptoms of depression and anxiety respectively. Multivariable logistic regression analyses were used to assess associations between moderate-to-severe DA and possible contributing factors.

Results

Of 267 patients, 54 (20.2%) screened positive for symptoms of depression (PHQ-9≥10) and/or symptoms of anxiety (GAD-7≥10). Stress (OR 23.34, 95%CI=3.01-181.21), low income (OR 2.90, 95%CI=1.14-7.35), and low education level (OR 2.32, 95%CI=1.04-5.15) were associated with DA, while sex (OR 1.40, 95%CI=0.60-3.26), age (OR 0.82, 95%CI=0.65-1.05) and psoriasis severity (OR 1.98, 95%CI=0.97-4.03) were not significantly associated. Sensitivity analysis showed association of low perceived social support (OR 11.30, 95%CI=4.02-31.79), psoriasis severity (OR 2.25, 95%CI=1.01-4.97), and age (OR 0.71, 95%CI=0.54-0.93) with DA.

Conclusion

Stress and low perceived social support were strongly associated with moderate-to-severe DA in patients with psoriasis. Less strong associations were found for low income, low education level, psoriasis severity, and age. This emphasizes the need for additional support beyond the medical domain to address the mental health of patients with psoriasis.

Introduction

Patients with psoriasis have an increased prevalence of depression and anxiety compared to the general population.[1] Depression and anxiety often go hand in hand, with about half of individuals diagnosed with one disorder also diagnosed with the other.[2, 3] As such, this study investigates depression and/or anxiety collectively, hereafter referred to as DA. Previous research has placed considerable attention on identifying factors associated with DA in patients with psoriasis. Whereas studies have consistently found a positive association between female sex and DA,[4-9] findings regarding age were more inconsistent, linking both younger and older age to DA in patients with psoriasis.[4, 7-12] Additionally, previous studies have found that a more severe psoriasis was positively associated with DA.[5, 11, 13, 14] It is, however, questionable whether factors like sex, age, and disease severity are the primary factors associated with DA in patients with psoriasis or if other, less explored factors may hold greater significance.

The association between visibility of psoriasis lesions and DA is less explored,[6, 12, 15] despite the fact that patients with visible lesions might be at higher risk of developing psychiatric illnesses as they often feel more stigmatized than patients without visible lesions.[16, 17] Additionally, limited focus has been placed on factors beyond the skin, such as stress, level of education, level of income, and social support,[6-8, 10, 11, 13] while psychological and socioeconomic factors are known to be associated with psychiatric illnesses in the general population.[18-22] Therefore, the objective of this study was to identify the most relevant factors associated with DA in patients with psoriasis, taking into account both well-known patient characteristics from literature (sex, age, and disease severity) and psychological (visibility of psoriasis lesions and stress) and socioeconomic (level of education, level of income and social support) factors.

Methods

Patient selection and study design

A cross-sectional study was performed between August 2021 and February 2022, in which Dutch patients with psoriasis ≥16 years were asked to fill out an open web-based survey. A link to the survey was promoted nationally through the Dutch Psoriasis Patients Association (via their website and newsletter)

and via social media. Patients excluded from the study were those who failed to complete the psychological questionnaires and those who indicated in the survey that their psoriasis diagnosis was not confirmed by a physician. This study was reviewed by the regional Ethics Committee and was deemed not to fall within the scope of the Medical Research Involving Human Subjects Act. Data was collected anonymously via Qualtrics Survey Software.

Data collection and outcome measures

The survey was initially created for the BENEFIT for All lifestyle program designed for patients with cardiovascular diseases,[23] and was modified to incorporate specific psoriasis-related questions in collaboration with the Dutch Psoriasis Patients Association and the Dutch Psoriasis Scientific Research Foundation (SWOP). Its adaptation resulted in a large survey with multiple choice questions as well as open-ended questions, primarily aimed to study the lifestyle of patients with psoriasis.[24] Elements of this adapted survey are employed in this current study. The survey included questions on demographic characteristics (sex, age, education, income and the presence of stress in the past year [including stress at home, at work, financial stress and the occurrence of a stressful event]) and clinical characteristics, such as type of treatment, presence of psoriasis on visible areas, and psoriasis severity. Psoriasis severity was assessed with the self-assessment version of the simplified psoriasis index (saSPI)[25], which reflects the overall state of psoriasis on a 0-5 scale, with higher scores reflecting more severe psoriasis, as experienced by the patient at the time of the survey completion. Furthermore, assessment of social support was performed using the ENRICHD Social Support Instrument (ESSI). The ESSI is a 7-item self-report survey that assesses four defining attributes of social support: emotional, instrumental, informational, and appraisal.[26] Using standard criteria, a low perceived social support was defined as a score of ≤3 on at least 2 items and a total score ≤18.[27]

Assessment of depression and/or anxiety (DA) symptoms

Symptoms of DA were assessed by means of two sets of psychological questionnaires, the Patient-Health Questionnaire-9 (PHQ-9) and the General Anxiety Disorder-7 (GAD-7). The PHQ-9 is a widely used and validated tool to assess the severity of depressive symptoms.[28] The questionnaire consists of nine questions with an individual maximum score of 3 per question. The total score ranges from 0 to 27, with a score of 0 indicating the absence of depressive symptoms and a score of 27 reflecting severe symptoms. The cut-off values for none, mild, moderate, moderately severe and severe depression are 0 to 4,

5 to 9, 10 to 14, 15 to 19 and 20 to 27, respectively.[28] In line with this categorization, we used the threshold of ≥10 to identify patients with symptoms of moderate-to-severe depression. The GAD-7 is a widely recognized and validated tool to screen for and assess the severity of General Anxiety Disorder symptoms.[29] The questionnaire consists of seven questions with an individual maximum score of 3 per question. The total score ranges from 0 to 21, with 0 indicating absence of anxiety symptoms and 21 indicating severe anxiety symptoms. The cut-off values for none, mild, moderate and severe anxiety were 0 to 4, 5 to 9, 10 to 14 and 15 to 21, respectively.[30] In this study, the threshold of ≥10 was used to identify patients with symptoms of moderate-to-severe anxiety. Both PHQ-9 and GAD-7 questionnaires are based on the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria. Patients that scored ≥10 on either one or both screening tools, PHQ-9 and GAD-7, were classified as having symptoms of moderate-to-severe DA.

Statistical analysis

Baseline characteristics were displayed using descriptive statistics (median [interquartile range], N (%)).

Multivariable logistic regression models without stepwise selection were used to identify factors associated with moderate-to-severe DA. The number of clinically relevant variables for this analysis was determined following recommendations by van Smeden et al.,[31] using the recommended interactive calculation tool (https://mvansmeden.shinyapps.io/BeyondEPV/). Accordingly, seven variables were included. Three variables were chosen based on factors identified from previous literature (sex, age, and disease severity) using the same screening tools,[4, 5, 13] and four additional psychological and socioeconomic factors deemed clinically relevant (psoriasis in visible areas, education level, and monthly net income and stress). Due to missing values in education level and monthly net income, multiple imputation was applied, with imputation performed ten times. The pooled data was used for the regression analyses.

Due to the bidirectional relationship between stress and DA, a sensitivity analysis was performed in which stress was excluded from the multivariable logistic regression analysis to examine which factors emerged in its absence. Another sensitivity analysis was performed incorporating ESSI scores in order to explore the association between social support and moderate-to-severe DA. Social support was not incorporated in the main analysis to minimize

patient exclusion due to incomplete response, given that the ESSI survey was in the final part of the questionnaire. Statistical analyses were performed with SPSS version 27.0 (IBM, SPSS inc., Chicago Il, USA). A two-sided $p<0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 448 patients participated in the online lifestyle survey. Of these 448 patients, 277 patients (58.0%) successfully completed the PHQ-9 and GAD-7. After excluding 10 patients in which the psoriasis diagnosis was not confirmed by a physician, a total of 267 patients could be included in the analysis. Data on demographic and clinical characteristics are shown in Table 1. Fifty-four patients (20.2%) had symptoms of moderate-to-severe DA. Almost half of them screened positive for symptoms of both disorders (n=25, 46.3%) (Figure 1). The majority of the patients with moderate-to-severe DA was female (n=44, 81.5%) and had a median age of 47.5 years, ranging from 16.7 years to 71.1 years. About half of the patients with moderate-to-severe DA had severe psoriasis (46.3%) and one-third used phototherapy or systemic treatments for their psoriasis (33.3%).

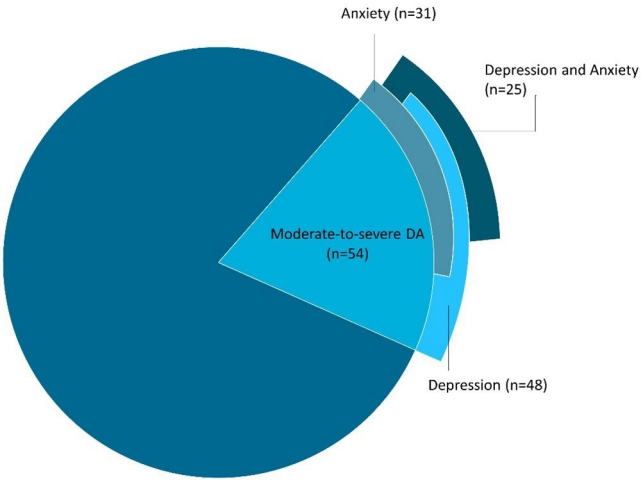

Figure 1. The prevalence and co-occurrence of moderate-to-severe depression and anxiety[A]
Abbreviations: DA, depression and/or anxiety
[A]Patients were classified as having moderate-to-severe DA if they had symptoms of moderate-to-severe depression (PHQ-9 ≥ 10), anxiety (GAD-7 ≥ 10), or both.

Table 1. Baseline characteristics

	Total patients(n=267)	Patients without moderate-to-severe DA (n=213)	Patients with moderate-to-severe DA (n=54)[a]
Sex			
Male	85 (31.8)	75 (35.2)	10 (18.5)
Female	182 (68.2)	138 (64.8)	44 (81.5)
Age, years, median [IQR]	53.9 [22.8]	55.0 [20.2]	47.5 [23.2]
Min-max	16.7-84.0	18.1-84.0	16.7-71.1
BMI ≥25 kg/m^2*	164 (61.2)	130 (61.6)	34 (63.0)
Family history of psoriasis (First or second degree)			
Yes	161 (60.3)	126 (59.2)	35 (64.8)
No	106 (39.7)	87 (40.8)	19 (35.2)
Psoriasis severity at time of survey[b]			
0, 1, 2 (mild)	169 (63.3)	740 (65.7)	29 (53.7)
3, 4, 5 (severe)	98 (36.7)	73 (34.3)	25 (46.3)
Psoriasis in visible areas			
Yes	229 (85.8)	180 (84.5)	49 (90.7)
No	38 (14.2)	33 (15.5)	5 (9.3)
Self-reported psoriatic arthritis			
Yes	73 (27.3)	57 (26.8)	16 (29.6)
No	194 (72.7)	156 (73.2)	38 (70.4)
Current psoriasis treatment			
No therapy/Topical therapy	153 (57.3)	117 (54.9)	36 (66.7)
Phototherapy/Systemic (+ topical) therapy	114 (42.7)	96 (45.1)	18 (33.3)
Daily life affected by psoriasis			
Yes	156 (58.4)	116 (54.5)	40 (74.1)
No	111 (41.6)	97 (45.5)	14 (25.9)
Physical activity according to Dutch recommended guidelines[c]			
Yes	92 (34.5)	74 (34.7)	18 (33.3)
No	175 (65.5)	139 (65.3)	36 (66.7)
Smoking			
Yes	46 (17.2)	30 (14.1)	16 (29.6)
No	221 (82.8)	183 (85.9)	38 (70.4)
Excessive alcohol use[d]			
Yes	13 (4.9)	11 (5.2)	2 (3.7)
No	254 (95.1)	202 (94.8)	52 (96.3)
Level of education*[e]			
Lower to medium education level	124 (56.6)	92 (52.3)	32 (74.4)
Higher education level	95 (43.4)	84 (47.7)	11 (25.6)
Net income per month*			
Low ≤ €1500	55 (26.1)	36 (21.1)	19 (47.5)
Medium to high > €1500	156 (73.9)	135 (78.9)	21 (52.5)

Table 1. Continued

	Total patients(n=267)	Patients without moderate-to-severe DA (n=213)	Patients with moderate-to-severe DA (n=54)[a]
Stress[f]			
Yes	210 (78.7)	157 (73.7)	53 (98.1)
No	57 (21.3)	56 (26.3)	1 (1.9)
Social support*[g]			
Low perceived social support	33 (12.4)	14 (7.0)	19 (38.0)
Medium to high perceived social support	217 (81.3)	186 (93.0)	31 (62.0)

Abbreviations: BMI, Body Mass Index; DA, depression and/or anxiety

*Missing values for the following variables: BMI (n = 2), level of education (n = 48), net income per month (n = 56), and social support (n = 17).

[a]Patients were classified as having moderate-to-severe DA if they had symptoms of moderate-to-severe depression (PHQ-9 ≥ 10), anxiety (GAD-7 ≥ 10), or both.

[b]Psoriasis severity was measured by using Part 1B of the self-assessment version of the simplified psoriasis index (saSPI).[25]

[c]The 2017 Dutch Physical Activity Guidelines recommends at least 150 minutes of moderate to intense physical activity each week and exercises to strengthen the muscles and bones at least two times a week for adults, as advised by The Health Council of the Netherlands.

[d]According to the Trimbos Institute, excessive drinking is defined as drinking more than 14 glasses of alcohol per week for women and more than 21 glasses of alcohol per week for men.

[e]The level of education was determined according to the definition of the Centraal Bureau voor Statistiek (CBS)

[f]Stress factors included are stress at home, stress at work, financial stress, and stressful events from the past year

[g]Social support was measured by ENRICHD Social Support Instrument (ESSI). Low perceived social support was indicated by a score of <3 on 2 or more items (1,2,3, 5 & 6) and a total score below 18.[27]

Factors associated with moderate-to-severe DA

The multivariable logistic regression analysis showed that stress (OR 23.34, 95%CI=3.01-181.21; *p=0.003*), low income (OR 2.90, 95%CI=1.14-7.35, *p=0.026*) and low education level (OR 2.32, 95%CI=1.04-5.15; *p=0.039*) were associated with moderate-to-severe DA, while sex (OR 1.40, 95% CI=0.60-3.26, *p=0.433*) showed no association. A trend was observed for severe psoriasis (OR 1.98, 95%CI=0.97-4.03; *p=0.060*) and for an inverse association with older age (OR 0.82, 95%CI=0.65-1.05; *p=0.112*), although neither were statistically significant (Table 2). A sensitivity analysis without stress revealed that older age was inversely associated with moderate-to-severe DA (OR 0.78, 95%CI=0.63-0.97; *p=0.028*). Furthermore, while not statistically significant anymore, a trend was seen for low income (OR 2.38, 95%CI=1.00-5.69; *p=0.051*) and low education level (OR 1.99, 95% CI=0.91-4.36; *p=0.084*) (Supplementary Table 1).

Table 2. Multivariable logistic regression model assessing risk factors associated with moderate-to-severe DA[a]

	Multivariable analysis	
Variables	**OR (95% CI)**	**p-value**
Sex (female)	1.401 [0.603-3.259]	0.433
Age/10 years	0.823 [0.648-1.047]	0.112
Psoriasis severity (severe)	1.980 [0.972-4.033]	0.060
Psoriasis in visible areas (yes)	1.581 [0.524-4.772]	0.416
Stress (yes)[b]	**23.339 [3.006-181.210]**	**0.003**
Level of education (lower to medium education level)	**2.315 [1.042-5.145]**	**0.039**
Net income per month (low ≤ €1500)	**2.896 [1.142-7.346]**	**0.026**

Abbreviations: CI, confidence interval; DA, depression and/or anxiety; OR, odds ratio.
[a]atients were classified as having moderate-to-severe DA if they had symptoms of moderate-to-severe depression (PHQ-9 ≥ 10), anxiety (GAD-7 ≥ 10), or both.
[b]Stress factors included are stress at home, stress at work, financial stress, and stressful events from the past year

The second sensitivity analysis, in which the ESSI score was incorporated (250 patients included), revealed that stress (OR 15.27, 95%CI=1.89-123.33; *p=0.011*), low perceived social support (OR 11.30, 95%CI=4.02-31.79; *p<0.001*), and severe psoriasis (OR 2.25, 95%CI=1.01-4.97; *p=0.046*) were associated with moderate-to-severe DA, and older age was inversely associated with moderate-to-severe DA (OR 0.71, 95%CI=0.54-0.93; *p=0.013*) (Supplementary Table 2).

Discussion

In this study, we aimed to identify the most relevant factors associated with symptoms of moderate-to-severe depression and/or anxiety (DA) in patients with psoriasis. Stress and low perceived social support were found to be strongly associated with moderate-to-severe DA. In addition, low income and low education level were associated with moderate-to-severe DA, albeit less strong. The patient characteristics sex, age and psoriasis severity, which were often found to be associated with DA in previous literature, were not found to be associated with moderate-to-severe DA in the primary analysis, in which stress was included. However, in the sensitivity analyses, severe psoriasis and younger age did show an association with moderate-to-severe DA.

Our study showed that stress and low perceived social support clearly exhibited the most pronounced associations with moderate-to-severe DA in patients with psoriasis. The strong contribution of stress is likely driven by its complex bidirectional relationship with DA. While stress has been linked to worsening mental health, mental health issues themselves, in turn, can also lead to stress.[32] This vicious cycle, along with the strong association found in this study, underscores the importance of recognizing stress in patients with psoriasis, whether as a precursor to or a consequence of moderate-to-severe DA.

Sensitivity analysis showed that low perceived social support was strongly associated with moderate-to-severe DA. This association between social support and DA is well-established in the general population.[33, 34] While literature on the impact of this association among patients with psoriasis is limited, two previous studies showed that higher social support was negatively associated with depressive symptoms in patients with psoriasis.[6, 35] Our findings underscore the crucial role of social support in the mental health of patients with psoriasis, emphasizing the need for increased attention and awareness.

Although less prominent than stress and social support, low income and low education level were also identified as factors associated with moderate-to-severe DA in the present study. The relationship between income or education and DA has been well-documented in the general population.[19, 36] In patients with psoriasis, studies have shown that higher income is associated with reduced odds for both depression and anxiety.[7, 8] Higher education was associated with reduced odds of specifically depression in one study,[11] while another observed that patients with only primary education have higher odds of anxiety, although no such association was found for depression.[10] These findings emphasize the significant role that socioeconomic factors have in mental health outcomes among patients with psoriasis, and highlight the need for a more comprehensive approach in both research and clinical practice.

Although sex, age and disease severity were not associated with moderate-to-severe DA in the primary analysis in which the association with stress was very prominent, associations for younger age and severe psoriasis with DA were identified in the sensitivity analyses. Younger age was associated with DA in patients with psoriasis before in several studies,[7, 9, 11] but also older age was associated with DA in other studies.[4, 8, 10] Therefore, a robust conclusion on the association between age and DA is hampered, likely due to differences in study population size and age distribution.[4, 7-12] Our findings in the sensitivity

analysis underline the well-known association between psoriasis severity and DA,[5, 11, 13, 14] underscoring the importance of effectively managing psoriasis to enhance patients' mental health. However, as stress and social support seem to play a more prominent role, psoriasis treatment alone seems insufficient to fully address the mental health challenges these patients may suffer. This highlights the need for additional support beyond dermatological care.

A strength of this study was the broad scope of the questionnaire, covering psychological and socioeconomic factors, in addition to the more frequently studied patient and disease related factors in patients with psoriasis. As this study was part of a large lifestyle survey study, respondents may have had a stronger interest in lifestyle than the general psoriasis population, which could have introduced selection bias. It is possible that these individuals experienced different mental health outcomes compared to those less engaged with lifestyle. Our survey did not include questions regarding (previous) mental health diagnoses, and as a result, we were unable to check whether individuals experiencing symptoms of depression and/or anxiety according to PHQ-9 and GAD-7 questionnaires, also had DA according to an (psychiatric) expert in the field. Although these questionnaires have not been specifically validated for patients with psoriasis, previous research has shown that they maintain high sensitivity and specificity across various settings, including primary, secondary, and tertiary care. For the PHQ-9, a cut-off score of 10 yielded a sensitivity of 78% and a specificity of 91%.[37] Similarly, the GAD-7, with a cut-off score of 10, showed a sensitivity of 74% and a specificity of 83%.[29]

This study highlights that stress and low perceived social support are strongly associated with moderate-to-severe DA in patients with psoriasis. Alongside these strong associations, low income, low education level, severe psoriasis and younger age were also linked to moderate-to-severe DA, though these associations were less pronounced. This emphasizes that, while treatment of psoriasis by dermatologists remains crucial due to the link between disease severity and moderate-to-severe DA, addressing the mental health of patients with psoriasis requires a broader, interdisciplinary approach beyond the medical domain.

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Supplementary Material

Supplementary Table 1. Sensitivity analysis of logistic regression model assessing risk factors associated with moderate-to-severe DA with exclusion of stress[a]

	Multivariable analysis	
Variables	**OR (95% CI)**	**p-value**
Sex (female)	1.487 [0.657-3.367]	0.341
Age/10 years	**0.781 [0.626-0.973]**	**0.028**
Psoriasis severity (severe)	1.789 [0.915-3.498]	0.089
Psoriasis in visible areas (yes)	1.371 [0.471-3.991]	0.562
Level of education (lower to medium education level)	1.993 [0.911-4.361]	0.084
Net income per month (low ≤ €1500)	2.379 [0.995-5.690]	0.051

Abbreviations: CI, confidence interval; DA, depression and/or anxiety; OR, odds ratio.

[a]Patients were classified as having moderate-to-severe DA if they had symptoms of moderate-to-severe depression (PHQ-9 ≥ 10), anxiety (GAD-7 ≥ 10), or both.

Supplementary Table 2. Multivariable logistic regression model with ENRICHD Social Support Instrument (ESSI), assessing risk factors associated with moderate-to-severe DA[a]

	Multivariable analysis	
Variables	**OR (95% CI)**	**p-value**
Sex (female)	2.467 [0.903-6.740]	0.078
Age/10 years	**0.712 [0.544-0.932]**	**0.013**
Psoriasis severity (severe)	**2.246 [1.014-4.973]**	**0.046**
Psoriasis in visible areas (yes)	2.452 [0.670-8.969]	0.175
Stress (yes)[b]	**15.268 [1.890-123.330]**	**0.011**
Level of education (lower to medium education level)	1.647 [0.685-3.957]	0.265
Net income per month (low ≤ €1500)	2.401 [0.876-6.577]	0.088
Social support (Low)[c]	**11.297 [4.015-31.785]**	**<0.001**

Abbreviations: CI, confidence interval; DA, depression and/or anxiety; OR, odds ratio.

[a]Patients were classified as having moderate-to-severe DA if they had symptoms of moderate-to-severe depression (PHQ-9 ≥ 10), anxiety (GAD-7 ≥ 10), or both.

[b]Stress factors included are stress at home, stress at work, financial stress, and stressful events from the past year

[c]Social support was measured by ENRICHD Social Support Instrument (ESSI). Low perceived social support was indicated by a score of <3 on 2 or more items (1,2,3, 5 & 6) and a total score below 18.[27]

CHAPTER 6

The lifestyle of psoriasis patients and their motivation to change

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Abstract

Background
Knowledge about the lifestyle of patients with psoriasis and the motivation to change their lifestyle enhances development of targeted lifestyle interventions.

Objectives
To assess motivation of psoriasis patients to change their lifestyle, to assess lifestyle in six lifestyle domains, and to compare lifestyle of patients who are motivated with patients who are unmotivated to change their lifestyle.

Methods
A web-based survey among Dutch psoriasis patients ≥16 years was conducted between August 2021 and February 2022. Questions addressed patients' motivation to change lifestyle, their current lifestyle within the domains physical activity, smoking, alcohol, diet, stress and sleep, and their preferred domains to change lifestyle.

Results
Of 448 included patients, most were motivated (48.5%) or possibly motivated (36.8%) to change their lifestyle, whereas 5.1% of patients was unmotivated and 9.6% was uncertain. Motivated and possibly motivated patients were most willing to change physical activity and dietary habits. Only one third of 308 motivated and unmotivated patients answering questions on current lifestyle complied to the recommended Dutch physical activity and dietary guidelines. Unmotivated patients were older ($p=0.005$), had less psoriasis in visible areas ($p=0.010$) and used systemic- or phototherapy more often than motivated patients ($p=0.024$). Except for the fact that unmotivated patients were more often smokers than motivated patients ($p=0.041$), current lifestyle of both groups did not significantly differ.

Conclusion
The majority of patients was motivated to change their lifestyle, with exercise and diet being the most popular lifestyle domain targets. A large number of patients did not meet the Dutch guidelines for healthy physical activity and/or diet, regardless of their motivation to change lifestyle. As the current lifestyle in these domains is suboptimal and there is a genuine motivation to make a positive change, interventions aiming at incitement of more physical activity and a healthier diet seem most promising.

Introduction

Psoriasis is a chronic inflammatory skin disorder with an estimated prevalence around 2-4% in western countries[1] and is associated with various comorbidities including obesity, hypertension, cardiovascular diseases and type 2 diabetes.[2, 3] In medicine, lifestyle and lifestyle changes to improve general health are increasingly gaining attention.[4, 5] It has already been shown that some of the comorbidities associated with psoriasis (e.g. diabetes, cardiovascular diseases) can be positively influenced by lifestyle changes.[6, 7] A recent review on the effect of lifestyle changes on psoriasis severity showed that dietary and relaxation interventions could be promising in improving psoriasis severity and the quality of life.[8] In order to be able to implement lifestyle changes in the psoriasis population, knowledge on the motivation of psoriasis patients to change lifestyle, and on differences in lifestyles of motivated versus unmotivated patients is essential. If patients are willing to change their lifestyle, it is also important to know which lifestyle domain they prefer to change. Until now, this information is lacking. In addition, literature on the current lifestyle habits of psoriasis patients is limited to small studies focusing on one or two lifestyle domains.[9-11] Thus, a complete overview of current lifestyle including six lifestyle domains adds to the existing literature. In this study, lifestyle will be assessed as the presence or absence of healthy behaviors and will be subdivided into six domains: physical activity, smoking, alcohol, diet, stress and sleep.[12] We aim (1) to assess the motivation of psoriasis patients to change their lifestyle and which lifestyle domains they are most willing to adapt, (2) to assess their current lifestyle in six lifestyle domains (physical activity, smoking, alcohol, diet, stress and sleep) and (3) to compare the lifestyle of patients who are motivated with patients who are unmotivated or uncertain to change their lifestyle.

Methods

Study design and population

A national survey study was performed between August 2021 and February 2022, in which Dutch patients with psoriasis, aged 16 years or older, filled out an open web-based survey. The regional Ethics Committee reviewed the study protocol and declared that our study did not fall within the scope of the Medical Research Involving Human Subjects Act. Data was collected anonymously via Qualtrics Survey Software. Promotion by the Dutch Psoriasis Patients Association and on social media brought the survey under national attention.

Survey

The questionnaire was based on a survey used for the BENEFIT for all lifestyle program, designed for patients with cardiovascular diseases.[12] Specific psoriasis-related questions were added with the help of the Dutch Psoriasis Patients Association. The survey consisted of multiple choice questions, open-ended questions, and Likert scales. Subjects were asked whether they were motivated to change their lifestyle and, depending on their answer, were categorized in three different groups: patients that were (1) motivated, (2) possibly motivated and (3) unmotivated or uncertain about their motivation. Motivated and possibly motivated patients were subsequently asked which two lifestyle domains they were willing to change. All patients, regardless of motivation, received questions about their current lifestyle, subdivided into six domains (physical activity, smoking, alcohol, diet, stress and sleep). Questions regarding physical activity, alcohol and diet were asked with precise details (e.g. physical exercise intensity and duration, alcohol intake in glasses and amount of vegetables, fruit and oily fish intake per day). Insight in these habits were used to determine whether patients complied with the Dutch guidelines for physical activity and diet and whether they met the Dutch criteria for excessive and/or heavy drinking.[13-16] The 2017 Dutch Physical Activity Guidelines, advised by the Health Council of the Netherlands for a healthy lifestyle, recommend at least 150 minutes of moderate to intense physical activity and muscle and bone strengthening exercises at least two times each week for adults.[13] The 2015 Dutch food-based dietary guidelines advised by the Health Council of the Netherlands recommends at least an intake of 200 grams of vegetables and 200 grams of fruit per day and at least one serving of (oily) fish per week. [15] The Trimbos Institute (the national knowledge institute for alcohol use in the Netherlands) defines excessive drinking as drinking more than 14 glasses and more than 21 glasses of alcohol per week for women and men, respectively, and heavy drinking as drinking more than 4 glasses and more than 6 glasses of alcohol per day for women and men, respectively.[14]

Data analysis

Descriptive analyses were performed using standard parameters such as frequencies, medians and interquartile ranges [IQR]. Baseline characteristics of responders to the lifestyle questions were compared to non-responders. Group comparisons between motivated and unmotivated patients were performed using Pearson Chi square test for categorical variables. Patients were categorized as unmotivated if they were unmotivated or uncertain about their motivation to change their lifestyle. Continuous variables were statistically tested by an

independent T test or Mann-Whitney U test depending on the distribution. Statistical analyses were performed with SPSS version 27.0 (IBM, SPSS inc., Chicago Il, USA). A two-sided $p<0.05$ was considered statistically significant.

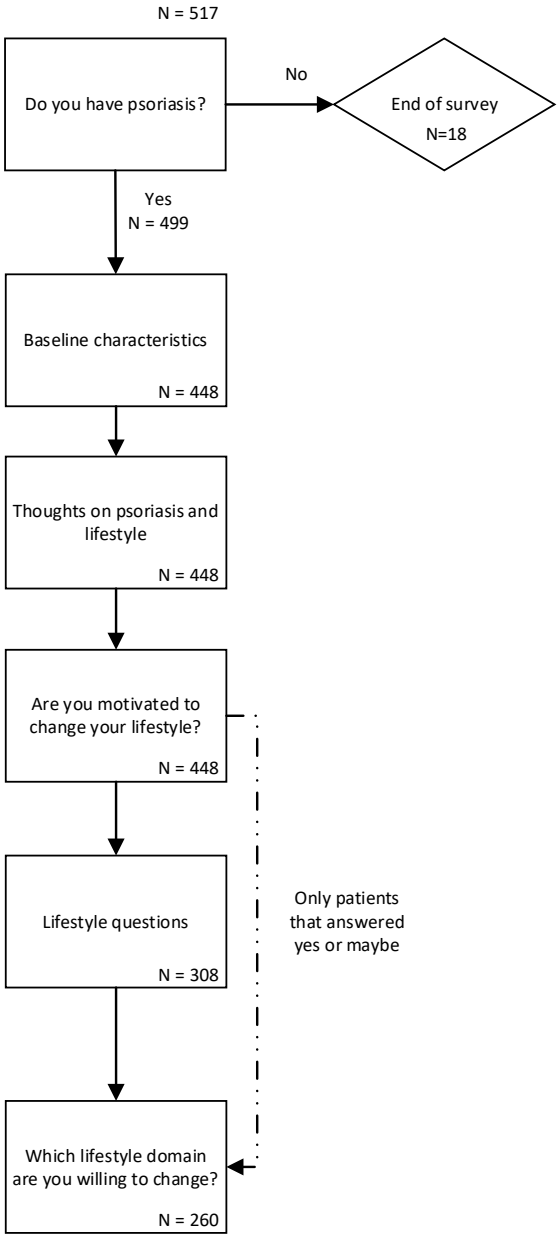

Figure 1. Respondents flowchart

Results

Patient characteristics

Of 517 respondents, 69 were excluded from the analyses because they did not have psoriasis (n=18) or due to lack of response on the question whether they are motivated to change their lifestyle (n=51). A respondents flowchart is provided in Figure 1.

In total, the answers of 448 psoriasis patients were analyzed (Table 1). Respondents were predominantly female (69.9%) with a median age of 54 years. Most patients had psoriasis for at least one year (97.1%) and had a positive family history for psoriasis (60.5%). At time of survey, more than a third of respondents (38.8%) considered their psoriasis to be severe using the self-assessment version of the simplified psoriasis index (saSPI),[17, 18] and the majority (85.3%) of patients had psoriasis in visible areas. Psoriatic arthritis, diagnosed by a rheumatologist, was present in 27.7% of patients. Current therapy consisted of systemic treatment or phototherapy in 44.0% of patients. More than half of respondents (58.3%) reported that their daily life was affected by psoriasis.

Attitudes on lifestyle and motivation to change

Data on attitudes on lifestyle were available from 448 patients. Although few patients (2.7%) thought that lifestyle was the cause of their psoriasis, almost half of respondents (46.9%) believed that lifestyle influenced the severity of their psoriasis (Table 1). Most patients were either motivated (48.5%) or possibly motivated (36.8%) to change their lifestyle. The question "which lifestyle domain are you willing to change" was asked at the end of the survey, after the questions about the current lifestyle (Figure 1), which led to 260 motivated or possibly motivated patients that answered this question. They were most willing to change lifestyle habits in the physical exercise and diet domain, followed by the stress and sleep domain. To stop smoking and to reduce or stop drinking alcohol were the least favorable lifestyle changes (Table 1).

Table 1. Baseline characteristics and thoughts about lifestyle and motivation (n=448)

	Total patients (n=448) No. (%)	Motivated (n=217) No. (%)	Possibly motivated (n=165) No. (%)	Unmotivated/ uncertain (n=66) No. (%)	P value (motivated vs unmotivated/ uncertain)
Baseline characteristics					
Psoriasis diagnosis by					
General practitioner	94 (21.0)	46 (21.2)	33 (20.0)	15 (22.7)	NS
Dermatologist	337 (75.2)	161 (74.2)	128 (77.6)	48 (72.7)	
Self-diagnosed	17 (3.8)	10 (4.6)	4 (2.4)	3 (4.5)	
Gender					
Male	135 (30.1)	59 (27.2)	53 (32.1)	23 (34.8)	NS
Female	313 (69.9)	158 (72.8)	112 (67.9)	43 (65.2)	
Age, median [IQR]	54.0 [24.6]	53.0 [26.0]	52.0 [23.9]	59.5 [18.1]	0.005
Psoriasis duration					
< 1 year	13 (2.9)	9 (4.1)	3 (1.8)	1 (1.5)	NS
≥ 1 year	435 (97.1)	208 (95.9)	162 (98.2)	65 (98.5)	
Family history of psoriasis (1st or 2nd degree)					
Yes	271 (60.5)	135 (62.2)	96 (58.2)	40 (60.6)	NS
No	177 (39.5)	82 (37.8)	69 (41.8)	26 (39.4)	
Psoriasis severity at time of survey[a]					
0, 1, 2 (mild)	274 (61.2)	135(62.2)	89 (53.9)	50 (75.8)	0.054
3,4,5 (severe)	174 (38.8)	82 (37.8)	76 (46.1)	16 (24.2)	
Psoriasis in visible areas					
Yes	382 (85.3)	191 (88.0)	142 (86.1)	49 (74.2)	0.010
No	66 (14.7)	26 (12.0)	23 (13.9)	17 (25.8)	
Psoriatic arthritis[b]	124 (27.7)	59 (27.2)	44 (26.7)	21 (31.8)	NS

Table 1. Continued

	Total patients (n=448) No. (%)	**Motivated (n=217) No. (%)**	**Possibly motivated (n=165) No. (%)**	**Unmotivated/ uncertain (n=66) No. (%)**	**P value (motivated vs unmotivated/ uncertain)**
Current psoriasis therapy					
No therapy/topical therapy	251 (56.0)	130 (59.9)	92 (55.8)	29 (43.9)	0.024
Photo therapy/ systemic (+topical) therapy	197 (44.0)	87 (40.1)	73 (44.2)	37 (56.1)	
Daily life affected by psoriasis					
Yes	261 (58.3)	138 (63.6)	95 (57.6)	28 (42.4)	0.003
No	187 (41.7)	79 (36.4)	70 (42.4)	38 (57.6)	
Thoughts on lifestyle and motivation					
Do you think lifestyle is the cause of your psoriasis?					NS
Yes or I have a suspicion	63 (14.1)	37 (17.1)	21 (12.7)	5 (7.6)	
No or I don't know	385 (85.9)	180 (82.9)	144 (87.3)	61 (92.4)	
Do you think lifestyle influences the severity of your psoriasis?					<0.001
Yes or a little	210 (46.9)	116 (53.5)	80 (48.5)	14 (21.2)	
No or I don't know	238 (53.1)	101 (46.5)	85 (51.5)	52 (78.8)	
Are you motivated to change your lifestyle in one of the lifestyle domains?					
Yes	217 (48.5)	-	-	-	-
Possibly	165 (36.8)				
No	23 (5.1)				
Uncertain	43 (9.6)				

Table 1. Continued

	Total patients (n=448) No. (%)	Motivated (n=217) No. (%)	Possibly motivated (n=165) No. (%)	Unmotivated/ uncertain (n=66) No. (%)	P value (motivated vs unmotivated/ uncertain)
Which parts of your lifestyle would you like to change?[c] (n=260)					
Physical activity		63 (44.1)	59 (50.4)	-	-
Smoking		6 (4.2)	15 (12.8)		
Alcohol		7 (4.9)	10 (8.5)		
Diet		64 (44.8)	40 (34.2)		
Stress		52 (36.4)	35 (29.9)		
Sleep		53 (37.1)	34 (29.1)		
Don't know (yet)		31 (21.7)	23 (19.7)		
Is there a specific reason you do not want to change your lifestyle? (n=34)					
Yes	-	-	-	26 (76.5)	-
I'm okay with my current lifestyle				9 (34.6)	
I've already changed my lifestyle				5 (19.2)	
Too busy/tired				3 (11.5)	
I've tried before with no success				1 (3.8)	
It's not worth the effort				3 (11.5)	
Other illness				3 (11.5)	
Unclear				1 (3.8)	
I'm too old				1 (3.8)	
No				8 (23.5)	

[a]Psoriasis severity was measured by using part 1B of the self-assessment version of the simplified psoriasis index (saSPI)[17,18]

[b]Diagnosis made by a rheumatologist

[c]Patients were able to choose a maximum of two lifestyle domains they are willing to change

Current Lifestyle

All questions regarding current lifestyle were answered by 308 patients (Figure 1). Comparison of responders to non-responders revealed no differences regarding baseline characteristics. Only a third of patients (33.8%) complied with the Dutch guideline for physical activity. In addition, 17.2% were smokers and 74.4% drank alcohol, while a small percentage of those patients were excessive (9.2%) or heavy alcohol drinkers (7.0%), according to the Trimbos Institute (Table 2). About one third of respondents complied with the Dutch dietary guidelines for vegetables intake (28.2%) and fruits intake (29.5%) whereas 49.4% complied with the dietary guidelines for oily fish intake.[15] Almost half of patients reported having much stress at home (41.9%) or work (48.7%). The majority of patients reported sleeping seven hours per day, and patients evaluated their sleeping quality as seven out of ten.

Comparing motivated patients to unmotivated patients

Group comparison between motivated and unmotivated (or uncertain) patients revealed that unmotivated patients were older ($p=0.005$), had less psoriasis in visible areas ($p=0.010$) and were treated with systemic therapy or phototherapy for their psoriasis more often than motivated patients ($p=0.024$) (Table 1). Remarkably, the unmotivated group stated less often that psoriasis affected their daily life than the motivated group ($p=0.003$). In addition, more patients in the unmotivated group did not think that lifestyle influenced the severity of their psoriasis ($p<0.001$) than patients in the motivated group (Table 1). Except for the fact that unmotivated patients were more often smokers ($p=0.041$) lifestyle of motivated and unmotivated patients did not show any statistical differences. (Table 2).

Table 2. Current lifestyle (n=308)[a]

Lifestyle characteristics	Total patients (n=308) No. (%)	Motivated (n=147) No. %	Possibly motivated (n=124) No. %	Unmotivated/ uncertain (n=37) No. %	P value (motivated vs unmotivated/ uncertain)
Exercise					
At least 150 minutes of moderate to intense physical activity and muscle and bone strengthening exercises two times per week[b]					
Yes	104 (33.8)	58 (39.5)	36 (29.0)	10 (27.0)	NS
No	204 (66.2)	89 (60.5)	88 (71.0)	27 (73.0)	
Smoking					
Do you smoke?					
Yes	53 (17.2)	13 (8.8)	32 (25.8)	8 (21.6)	0.041
Cigarettes/day on an average week, median [IQR]	9.1 [12.7]	10.0 [13.7]	9.6 [10.6]	6.5 [9.7]	
No	255 (82.8)	134 (91.2)	92 (74.2)	29 (78.4)	
Alcohol					
Do you drink alcohol?					
Yes	229 (74.4))	106 (72.1)	100 (80.6)	23 (62.2)	NS
Excessive drinker (>14 (F) or >21 (M) glasses alcohol per week)[c]					
Yes	21 (9.2)	7 (6.6)	13 (13.0)	1 (4.3)	NS
No	208 (90.8)	99 (93.4)	87 (87.0)	22 (95.7)	
Heavy drinker (>4 (F) or >6 (M) glasses alcohol per day)[d]					
Yes	16 (7.0)	3 (2.8)	11 (11.0)	2 (8.7)	NS
No	213 (93.0)	103 (97.2)	89 (89.0)	21 (91.3)	
No	79 (25.6)	41 (27.9)	24 (19.4)	14 (37.8)	

Table 2. Continued

Lifestyle characteristics	Total patients (n=308) No. (%)	Motivated (n=147) No. %	Possibly motivated (n=124) No. %	Unmotivated/ uncertain (n=37) No. %	P value (motivated vs unmotivated/ uncertain)
Diet					
At least 200g vegetables daily[e]					
Yes	87 (28.2)	55 (41.6)	24 (19.4)	8 (21.6)	NS
No	221 (71.8)	92 (63.2)	100 (80.6)	29 (78.4)	
At least 200g fruits daily[e]					
Yes	91 (29.5)	52 (35.4)	26 (21.0)	13 (35.1)	NS
No	217 (70.5)	95 (64.6)	98 (79.0)	24 (64.9)	
At least one serving of oily fish weekly[e]					
Yes	152 (49.4)	84 (57.1)	50 (40.3)	18 (48.6)	NS
No	156 (50.6)	63 (42.9)	74 (59.7)	19 (51.4)	
Stress					
Do you experience stress at home?					
Little stress	179 (58.1)	75 (51.0)	81 (65.3)	23 (62.2)	NS
Much stress	129 (41.9)	72 (49.0)	43 (34.7)	14 (37.8)	
Did you experience stress at work?[f]					
Little stress	119 (51.3[g])	59 (53.2[g])	48 (49.5[g])	12 (50.0[g])	NS
Much stress	113 (48.7[g])	52 (46.8[g])	49 (50.5[g])	12 (50.0[g])	
Sleep					
Hours sleep per day, median [IQR]	7.0 [2.0]	7.0 [2.0]	7.0 [2.0]	7.0 [2.0]	NS
Sleep quality (1-10)	7.0 [2.0]	7.0 [3.0]	7.0 [2.0]	7.0 [3.0]	NS

Table 2. Continued

Abbreviations: F, female; M, male.

[a]Only patients that responded to all lifestyle questions were included in the analyses.

[b]The 2017 Dutch Physical Activity Guidelines as advised by The Health Council of the Netherlands recommends at least 150 minutes of moderate to intense physical activity each week and muscle and bone strengthening exercises at least two times per week for adults.[13]

[c]According to the Trimbos Institute excessive drinking is defined as drinking more than 14 glasses of alcohol per week for women and more than 21 glasses of alcohol per week for men.[14]

[d]According to the Trimbos Institute heavy drinking is defined as drinking more than 4 glasses of alcohol per day for women and more than 6 glasses of alcohol per day for men.[14]

[e]The 2015 Dutch dietary guidelines as advised by the Health Council of the Netherlands recommends at least 200 grams of vegetables, 200 grams of fruit per day and at least one serving of (oily) fish per week.[15]

[f]Patients who do not work were excluded from this question

[g]Percentage of all patients who work

Discussion

This cross-sectional open web-based survey among patients with psoriasis showed that nearly half of all respondents thought that lifestyle influenced the severity of their psoriasis. The majority of respondents was motivated or possibly motivated to change their lifestyle, especially in the domains physical activity and diet. With regard to the current lifestyle of respondents, however, there is still room for improvement, as only one third of patients complied to the Dutch physical activity guidelines and only one third of patients met the Dutch recommended dietary criteria for vegetables and fruits. Patients that were unmotivated to change their lifestyle were older, had less often psoriasis in visible areas, used more often systemic treatments for psoriasis and smoked more often than motivated patients. Unmotivated patients reported that psoriasis affected their daily life less often than motivated patients, and they also thought less often that lifestyle influenced the severity of their psoriasis than motivated patients.

Data on the motivation of patients with psoriasis to change their lifestyle is scarce. Only one study performed in the United States assessed the motivation behind dietary behaviors of patients with psoriasis and showed that 86% of 1206 patients tried to remove something from their diet at least once. Forty percent of these respondents even tried a special diet for their psoriasis. About 40% of these patients reported that the reason to improve their diet was that their diet might improve other health problems.[9] In our study, 85.3% of patients were motivated or possibly motivated to change their lifestyle, with diet being the second most favorable lifestyle domain patients wanted to change. As less than a third (28.2%) of patients with psoriasis complied with the Dutch guidelines for vegetable intake, this high motivation to change diet provides opportunity for interventions. In the general Dutch population, a similar percentage (29.3%) was found to comply with these guidelines, according to the 2022 Dutch Health Survey/ Lifestyle monitor conducted on behalf of the Ministry of Health, Welfare and Sports. [16, 19] However, with respect to fruit and fish intake, patients with psoriasis did better than the general Dutch population: 29.5% and 49.4% of patients in our cohort complied to the fruits and fish guidelines, respectively, compared to 18.5% and 28.0% of the general Dutch population, respectively.[19] These data complement findings of a large United States national survey in which psoriasis patients also consumed more fruits than age- and sex-matched healthy controls.[9]

The most popular lifestyle domain for change among the surveyed patients was physical activity. Whereas the dietary habits of psoriasis patients were

comparable to the general Dutch population, and even better with respect to fruit and fish intake, the studied psoriasis population was less engaged with physical activity than the general Dutch population. Almost half (45.8%) of the general adult Dutch population (between 18 and 65 years) complied with the Dutch physical exercise guidelines, compared to only 33.8% of the respondents in our survey.[13, 20] This finding is in line with literature: a British study compared the amount of physical activity in psoriasis patients to the amount recommended by the committee on Exercise and Cardiac Rehabilitation of the American Heart Association (AHA) and found that 52.8% of psoriasis patients between 18-65 years engaged in less physical activity than the recommended amount.[21] A Portuguese study also showed reduced levels of physical activity in severe psoriasis patients compared to healthy controls with an odds ratio for low-level physical activity for psoriasis patients of 3.42.[22]

Smoking habits and alcohol use were roughly similar for the present cohort and the general Dutch population: 18.9% of the Dutch population smoked and 77.5% drank alcohol at least once the past year,[14, 23] compared to 17.2% and 74.4% in our cohort, respectively. Although a systemic literature review showed alcohol consumption to be greater in psoriasis patients than in the general population, we could not confirm this finding in our cohort.[24] In our study, a large percentage of psoriasis patients reported having either much stress at home (41.9%) or at work (48.7%).[25] This percentage is much higher than in the general Dutch population (20.6%), according to the Health monitor adults and elderly which was conducted by the Public Health Services of the Netherlands.[26] In a Brazilian cross-sectional study, it was also shown that patients with psoriasis experienced a lot of stress.[25] It is known that psychological stress and psoriasis are related,[27] and a recent study even showed that patients with chronic skin diseases may perceive and cope with stress differently in comparison to patients with work-related stress due to inherent personality traits.[28]

Regarding the comparison between motivated and unmotivated patients, some distinct differences were found. Interestingly, the unmotivated group used systemic treatments for their psoriasis more often than motivated patients. Probably partially due to these systemic treatments, they had less psoriasis in visible areas and showed a trend of less severe psoriasis (*p=0.054*) compared to the motivated group. One might hypothesize that the use of systemic treatments and the consequent improvement of visible psoriasis does not contribute to the attitude that a change in lifestyle can improve psoriasis

severity. Indeed, unmotivated patients reported less frequently to believe that lifestyle influenced the severity of their psoriasis than motivated patients. Unmotivated patients were also more content with their current lives than motivated patients and, consequently, less inclined to change their lifestyle.

A limitation of this study is the fact that respondents participating in this survey have possibly more interest in lifestyle changes than the general psoriasis population, which could have resulted in selection bias, and an overrepresentation of motivated patients. Nevertheless, this study was able to present some clear differences in attitudes and lifestyles between motivated and unmotivated patients, which can be helpful in future attempts to implement lifestyle changes in the psoriasis population.

This study provides novel insights into the attitudes and motivation of psoriasis patients to change their lifestyle and, uniquely, offers a complete overview of the lifestyle habits of these psoriasis patients. Given the current lifestyle of patients with psoriasis, there is a clear potential for improvement of lifestyle both in motivated and in unmotivated patients. Since a majority of respondents reported that they were (possibly) motivated to change their lifestyle, lifestyle education or other lifestyle interventions appear to be feasible. Ultimately, physical exercise and diet seem to be the most promising interventions for this population, as the current lifestyle in these domains is suboptimal and there is a genuine motivation to make a positive change, making the intervention likely to succeed.

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CHAPTER 7

Summary and discussion

Summary and discussion

Psoriasis is a common chronic, immune-mediated inflammatory disease that affects around 2-4% of the population in western countries, and develops in about one-third of patients during childhood. Despite the increasing evidence that is available about optimal treatment and care for patients with psoriasis, there are still underexposed areas in psoriasis care. In this thesis we aimed to improve the care for patients with psoriasis by addressing underexposed areas in both pediatric psoriasis care (chapter 2, 3 and 4) and adult psoriasis care (chapter 5 and 6).

To improve **pediatric psoriasis care** we focused on definitions for initiation of systemic therapy (Chapter 2), potential sex-differences in treatment-related aspects of care (Chapter 3) and the development of psoriatic arthritis (Chapter 4). Regarding **adult psoriasis care** we concentrated on the following underexplored areas: the psychological and socioeconomic factors associated with depression and anxiety (Chapter 5) and the lifestyle of psoriasis patients and their motivation to change (Chapter 6).

Underexposed areas in pediatric psoriasis care

Systemic therapy initiation

AIM 1: To propose criteria for the initiation of systemic therapy in pediatric psoriasis patients. To do so the following sub-aims were formulated:

1a. To determine the percentage of pediatric patients with psoriasis fulfilling the adult Rule of Tens (R10) and the adult definition of the International Psoriasis Council consensus statement (IPCcs) for initiation of systemic therapy.

1b. To investigate the influence of clinical characteristics, such as involvement of high impact sites, on the quality of life as measured by the Children's Dermatology Life Quality Index (CDLQI).

An important underexplored area in pediatric psoriasis care is the lack of a definition for the initiation of systemic treatment. In order to propose criteria for the initiation of systemic therapy in pediatric psoriasis patients, it is important to assess the applicability of currently used adult definitions in pediatric psoriasis patients. In adult psoriasis, the Rule of Tens (R10) and the

IPC consensus statement (IPCcs) are often used. The R10 classifies psoriasis as severe when the Body Surface Area (BSA) is >10%, or the Psoriasis Area and Severity Index (PASI) is >10, or DLQI Is >10. On the other hand, IPCcs classifies patients as candidates for systemic therapy if they meet at least one of the following criteria: BSA >10% or involvement of high impact sites (face, palms, soles, intertriginous skin, scalp or nails) or if patients fail to respond to topical treatment. In **Chapter 2**, we applied the R10 and IPCcs definitions to a cohort of 641 pediatric patients with psoriasis. Data of these patients were extracted from the ChildCAPTURE registry, a prospective observational daily practice registry. Logistic regression was used to analyze factors associated with CDLQI>10. We showed that the R10 classified fewer pediatric patients as eligible for systemic treatment (49.0%) compared to the International Psoriasis Council consensus statement (IPCcs) (92.4%). This high percentage of patients eligible for systemic treatment according to IPCcs was mainly due to the fact that 90.6% of all patients had involvement of high impact sites. We also found that an impaired health-related quality of life (HRQoL), defined as CDLQI >10, was associated with high impact site involvement, BSA>10%, and teen age. A sensitivity analysis replacing BSA>10% with PASI>10 showed similar results.

While the R10 incorporates measures of disease extent (PASI and BSA) and quality of life (CDLQI), it may not fully capture the burden imposed by high impact site involvement. The assessment of high impact sites among patients with psoriasis is important; as in adults, involvement of these sites were shown to be associated with worse quality of life, depression, and a greater limitation in ability to participate in activities and social roles.[1] Our study confirmed this observation in pediatric patients, as a high CDLQI was associated with the involvement of high impact sites. Furthermore, studies showed that visible psoriatic lesions in pediatric patients lead to increased social challenges, such as being bullied and stigma, and may contribute to reduced self-esteem.[2-5] Broader definitions like the IPCcs, which also account for high impact site involvement, may therefore offer a more comprehensive assessment of disease burden, particularly in patients with a limited psoriasis extent. However, the IPCcs may lack specificity, as it qualifies nearly all (92.4%) pediatric patients with psoriasis in our cohort as eligible for systemic therapy mainly due to high impact site involvement, which was present in 90.6% of all patients. Among these high impact sites, scalp involvement was observed substantially more frequently than involvement of other locations, as scalp involvement was seen in 84.1% of patients, compared with intertriginous skin (36.8%), face (26.4%),

nails (15.8%), and palms and soles (1.6%). Even when the threshold for extent of scalp involvement was adjusted to >50%, 74% of patients still met the IPCcs definition, mainly because other high impact sites were also involved. Thus, although the involvement of high impact sites is very important to consider as a criterion for initiation of systemic treatment in pediatric patients with psoriasis, it should not be the only criterion on which this decision is based.

Another criterion to consider for systemic therapy initiation in pediatric patients includes the age of the patient. We found that teen age (13-17 years), as compared to the reference group of patients aged 0-6 years, was associated with a high CDLQI. This finding is consistent with the notion that adolescence represents a particularly vulnerable developmental period, as previous literature highlights that compared to other age groups, adolescents experience unique challenges related to peer relationships, intimacy, sexuality, body image, and autonomy.[2, 6] Clinicians should therefore be particularly attentive to teen age patients and consider starting systemic therapy earlier compared to other pediatric age groups.

Another criterion to take into account when considering systemic therapy initiation is failure of topical treatment. This criterion is part of the IPCcs and is also incorporated in several current guidelines.[7-10] However, its practical applicability poses challenges, as there is no consensus on what failure of topical treatment constitutes. The IPC's Disease Severity Working Group recently proposed defining failure of topical therapy in adult patients as the inability to achieve clear/nearly clear skin (BSA ≤1% and Physician's Global Assessment (PGA) 0 or 1) after two consecutive 4-week courses of topical therapy.[7] In practice, the definition may be difficult to apply, especially in pediatric patients where treatment adherence, tolerance, parental support, and the child's willingness or to apply topical therapy may influence outcomes. It is important to apply this criterion with caution, as reliance on this single factor may result in systemic therapy being considered too early, which could especially be harmful in children with mild disease. Thus, while relevant to keep in mind, failure of topical therapy should not be applied as a strict or stand-alone criterion for systemic therapy initiation in pediatric patients.

In conclusion, when defining criteria for the initiation of systemic therapy in pediatric psoriasis, the extent and severity of the disease (as measured by PASI or BSA) remains a key criterion, also because many studies, including our study, showed a strong association with HRQoL.[11-14] However, it is essential

to look beyond classical activity scores. The involvement and extent of high-impact sites should be incorporated, but always interpreted in the context of their impact on the child's quality of life. Particular consideration should also be given to patients of teen age, in which psoriasis often has a greater psychosocial impact than in younger children. Finally, while it is good to acknowledge failure of topical therapy, this factor should not be applied as a strict or stand-alone criterion for systemic therapy initiation in pediatric patients. Furthermore, it should be recognized that initiating systemic therapy in in pediatric patients is not without consequences: potential adverse events, the invasiveness of oral medication or injections, regular blood testing, and frequent follow-up visits, can all place a considerable burden on both patients and caregivers. These aspects should therefore be carefully weighed before initiation of systemic therapy.

Sex-differences

AIM 2: To investigate whether sex-differences should be taken into account in pediatric psoriasis care. The following sub-aim was proposed:

To investigate whether sex-differences in drug survival, adverse events, disease severity, effectiveness of biologics, and HRQoL are present in pediatric and young adult patients with psoriasis.

Another underexplored aspect in pediatric and young adult patients with psoriasis is the influence of sex-differences on psoriasis care and outcomes. In Chapter 3, data from two prospective daily practice registries, ChildCAPTURE and BioCAPTURE, were obtained to explore whether sex-disparities in drug survival, adverse events, disease severity, effectiveness of biologics, and HRQoL are indeed present in pediatric (<18 years) and young adult (≥18 to ≤30 years) patients with psoriasis that are treated with biologics. The study included a total of 360 patients, of which 117 pediatric patients (65 females, 52 males) and 243 young adult patients (124 females, 119 males). We found that young adult males had a significantly higher PASI at biologic initiation compared to females, with the same trend for pediatric patients. We also found that females had a higher adverse event rate compared to males in both pediatric and young adult patients. Drug survival, improvements in PASI and (C)DLQI over the first treatment year, reaching threshold scores of ≤1, ≤3, and ≤5, and scores at treatment discontinuation due to ineffectiveness were similar between female and male patients in both pediatric and young adult patients.

The observation of a higher PASI at biologic initiation among young adult males raises the question of whether males experience a delay in seeking care, leading to later presentation and initiation of biologic therapy compared to females. However, our data showed that disease duration at the start of biologic treatment was shorter in males compared to females across both pediatric and young adult groups (pediatric males: 5.8 years vs. females: 6.5 years; young adults males: 9.4 years vs. females: 10.6 years). These findings suggest that the higher PASI scores observed in males are unlikely due to delayed treatment initiation, but may instead reflect a more severe disease course overall. Our findings suggest the importance of avoiding delays or reluctance in starting systemic therapy in males, ensuring timely treatment to address their more severe disease.

The higher adverse event rate in females compared to males in both pediatric and young adult patients, was also previously seen among adult patients with psoriasis.[15-18] While these sex differences have been documented in adults, the underlying causes remain unclear. The observation that disparities in adverse event rates between females and males are present even among pediatric patients points to a physiological, sex-related explanation rather than social-cultural influences that become more pronounced with age. Previous research has indeed showed that sex hormones can affect both the pharmacokinetics and pharmacodynamics of medications. The higher rate of adverse events observed in female pediatric and young adult patients compared to their male counterparts calls for more understanding and consideration of their specific experiences in dermatological care. Acknowledging these experiences and openly discussing potential adverse events can help patients feel better heard and supported. This approach may not only strengthen the relationship between patient and doctor, but also improve adherence, trust, and overall treatment satisfaction.[19-23]

It is important to acknowledge that children under 18 years do not represent a homogeneous group, as the immune system undergoes substantial maturation throughout childhood and adolescence.[24-28] Literature has also shown that immunological sex-differences are already present during early life and across distinct developmental stages like puberty.[26-28] Therefore, moving forward, identifying the specific age group in which sex differences in pediatric psoriasis emerge, such as during early childhood, school age, or adolescence, could support clinicians in recognizing and addressing these differences, increasing awareness and ultimately psoriasis care.

Referring back to our overarching aim, it is indeed important to take sex-differences into account in pediatric psoriasis care, especially with regards to differences in disease severity and perceived adverse events. Awareness and timely initiation of systemic therapy is important in males, as they present with more severe disease, whereas particularly in females empathy, open communication, and careful monitoring is important throughout treatment as they experience adverse events more often.

Development of Juvenile Psoriatic arthritis

AIM 3: To increase the evidence and awareness on the development of arthritis in pediatric and young adult patients with psoriasis. We therefore aimed:

3a. To describe a real-world cohort of patients with pediatric onset psoriasis who subsequently developed psoriatic arthritis at pediatric age or in young adulthood (JPsA/PsA), focusing on their clinical features and timing of onset.

3b. To compare these clinical features to the characteristics of a large cohort of pediatric psoriasis patients.

In chapter 4, data from the ChildCAPTURE registry were extracted to describe a cohort of 717 patients with pediatric onset of psoriasis, and to assess who subsequently developed JPsA/PsA. International League of Associations for Rheumatology (ILAR)[29-31] and Classification Criteria for Psoriatic ARthritis (CASPAR) criteria[32] were used for classification of JPsA and PsA, respectively. The time to JPsA/PsA diagnosis following psoriasis onset was analyzed using Kaplan-Meier survival analysis. Among 717 patients, 15 (2.1%) developed arthritis, approximately 1% before the age of 18 years (JPsA), and another 1% during young adulthood (PsA). The estimated 10-year cumulative incidence of JPsA/PsA following psoriasis diagnosis was 2.8%. The median interval between psoriasis onset and JPsA/PsA development was 4.8 years. The group of patients who developed JPsA/PsA comprised more males, and these patients were more often obese and more frequently had nail involvement, than the total cohort of pediatric patients at the time of inclusion in the registry. Obesity and nail involvement was also more frequently observed at the time of arthritis onset compared to the time of registry inclusion.

These findings highlight that the prevalence of JPsA/PsA development is relatively low among patients with pediatric onset psoriasis. However, monitoring of patients is still important to ensure early detection and

intervention, as it may prevent long term joint damage.[33-36] In our cohort, patients were routinely asked about joint complaints and completed a PEST questionnaire at each appointment. Given the relatively low prevalence of arthritis observed, such frequent and intensive screening of all patients may not be necessary and could also make patients more conscious about certain symptoms, for instance in patients with no complaints except isolated nail pitting. To reduce the burden of repeated screening, an additional focus could be considered on patients who appear to be at higher risk for developing PsA, namely patients that are male, have a high BMI and have nail involvement as these clinical characteristics were more present in our group of patients with JPsA/PsA.

In adult patients, studies have also shown an association between high BMI and development of PsA.[37-39] Research has shown that weight loss in adult patients with PsA and obesity can lead to improvements in joint and entheses symptoms.[40] Weight loss among adult patients with psoriasis has also been associated with a decrease in disease severity.[41-43] These findings underscore the importance of incorporating lifestyle counseling, particularly around nutrition and physical activity, into the care of patients with psoriasis. Although research on this topic in pediatric patients remains limited, our study identified a potential association between a higher BMI and the development of JPsA/PsA. Consistent with our findings, one previous pediatric study reported this association.[44] Given the increasing prevalence of obesity in children,[45-47] and its possible contribution to not only PsA but also other comorbidities,[48-50] lifestyle counseling may be especially relevant for pediatric patients with psoriasis.

In adult literature, the use of early systemic therapy for the prevention of comorbidities, including PsA, and worsening of psoriasis has been postulated,[51-56] however, it remains uncertain whether this approach should also be applied in pediatric patients with psoriasis. Our findings showed that patients with pediatric onset of psoriasis can develop JPsA/PsA even under systemic therapy, including both conventional and biologic treatment. However, more research is needed to establish whether early systemic treatment can prevent or delay the occurrence of psoriatic arthritis in children.

Ideally, identifying patients at risk for JPsA/PsA using biomarkers could help guide treatment decisions and allow for more timely and personalized treatment. A recent systematic review and meta-analysis found no specific diagnostic biomarkers for PsA in adult populations.[57] Among the most

frequently studied markers, Cartilage Oligomeric Matrix Protein (COMP) and Matrix Metalloproteinase-3 (MMP-3) were reported to be higher in PsA compared with controls in pooled analyses (for COMP versus healthy or osteoarthritis controls; for MMP-3 versus psoriasis controls). However, results were inconsistent between studies and varied by assay method. Another biomarker, CXCL10, has shown potential in longitudinal adult psoriasis cohorts, where elevated baseline levels preceded PsA onset.[58, 59] However, CXCL10 is not specific to PsA, as CXCL10 levels are elevated across many autoimmune diseases,[60] and has not been validated in large independent studies. Overall, while biomarker research in PsA is advancing, clinical application remains limited and requires further validation, also in pediatric psoriasis populations.

In conclusion, although the relatively low occurrence of JPsA/PsA among pediatric psoriasis patients is reassuring, clinicians should remain attentive to the development in patients presenting with joint complaints, particularly those with patient characteristics male sex, obesity, and nail involvement.

Underexposed areas in adult psoriasis

Mental health

AIM 4: To gain more insight in the association between psoriasis and depression and anxiety. Therefore, we aimed:

To identify the most relevant factors associated with symptoms of depression and/or anxiety (DA) in patients with psoriasis, taking into account both well-known patient characteristics from literature (sex, age, and disease severity) and psychological (visibility of psoriasis lesions and stress) and socioeconomic (level of education, level of income and social support) factors.

In Chapter 5, data from a national web based survey were to used to identify the most relevant factors associated with moderate-to-severe DA among 267 adult patients with psoriasis. Symptoms of depression and anxiety were assessed using the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder scale (GAD-7), respectively. A score of ≥10 on either screening tool was used to indicate moderate-to-severe depressive or anxiety symptoms. Associations between DA and the following possible contributing factors were assessed: sex, age, disease severity, psoriasis in visible areas, education level, income, stress and social support. The first three factors were

often found to be associated with DA in previous literature,[61-68] whilst the latter five are factors we deemed clinically relevant but were not frequently studied yet. We found that 54 of 267 patients (20.2%) screened positive for symptoms of DA. We also found that stress and low perceived social support were strongly associated with moderate-to-severe DA. In addition, low income and low education level were associated with moderate-to-severe DA, albeit less strong. The well known patient characteristics sex, age and psoriasis severity, which were often found to be associated with DA in previous literature, were not found to be associated with moderate-to-severe DA in our main analysis, where stress was also included.

Our findings demonstrate that psychosocial and socioeconomic factors are more strongly associated with DA than the clinical severity of psoriasis. This highlights that much of the vulnerability to psychological distress lies outside the direct scope of classic dermatological care. Initiatives based on the principles of value-based healthcare, with the aim to capture the overall impact of care on the patient beyond disease-specific measures, may provide a broader perspective. One example is the PsoPlus consultation, a structured, multidisciplinary approach in which a nurse and dermatologist systematically assess not only disease severity and quality of life, but also other factors like comorbidities and aspects relevant to mental health.[69, 70] Implementing such comprehensive care in routine clinical practice, however, remains challenging due to cost and time restraints.

In conclusion, stress and low social support are strongly linked to moderate-to-severe DA, while lower income, lower education, severe psoriasis, and younger age also contribute, albeit to a lesser extent. These findings highlight that, although dermatological treatment remains essential given the relationship between disease severity and DA, effectively addressing the mental health of psoriasis patients requires a broader approach that extends beyond current psoriasis care.

Lifestyle

AIM 5: To gain a better understanding of the lifestyle of adult patients with psoriasis and the motivation to change lifestyle. The following sub-aims were formulated:

5a. To assess the motivation of psoriasis patients to change their lifestyle and which lifestyle domains they are most willing to adapt.

5b. To assess their current lifestyle in six lifestyle domains (physical activity, smoking, alcohol, diet, stress and sleep).

5c. To compare the lifestyle of patients who are motivated with patients who are unmotivated or uncertain to change their lifestyle.

Patients with psoriasis are at increased risk of cardiovascular and metabolic diseases, many of which are influenced by lifestyle factors, underscoring the importance of healthy lifestyle as part of psoriasis care. In Chapter 6, using data from a web-based survey, we assessed attitudes towards lifestyle changes and current lifestyle habits among 448 psoriasis patients aged ≥16 years. Questions addressed patients' motivation to change lifestyle, their current lifestyle within the domains physical activity, smoking, alcohol, diet, stress and sleep, and their preferred domains to change lifestyle. Patients were categorized in three different groups based on their level of motivation: (1) motivated, (2) possibly motivated and (3) unmotivated or uncertain. We found that the majority of patients with psoriasis (85.3%) were motivated to change their lifestyle, with physical activity and diet being the most commonly mentioned domains they wished to improve. When examining their current lifestyle behaviors, these same two domains showed the greatest potential for improvement. Only about one-third of patients met the Dutch recommended guidelines for physical activity and diet. Furthermore, we found that nearly half of the patients reported experiencing high levels of stress both at home (41.9%) and at work (48.7%). Comparison between motivated and unmotivated patients revealed that unmotivated patients were older, had less psoriasis in visible areas and were treated with systemic therapy or phototherapy for their psoriasis more often than motivated patients. Unmotivated patients also less often perceived psoriasis as affecting their daily life or believed lifestyle influenced disease severity than motivated patients. Except for higher smoking rates among unmotivated patients, lifestyle factors did not differ significantly between groups.

Our findings provide insights that patients with psoriasis are motivated to make positive lifestyle changes, especially with regards to physical activity and diet, domains where current lifestyle also showed considerable room for improvement. Given that suboptimal diet and low levels of physical activity contribute to higher BMI, and considering the well-established negative impact of high BMI on both psoriasis severity and associated comorbidities,[37, 41, 71-81] this presents a valuable opportunity for intervention. However, while patients with psoriasis may benefit from lifestyle interventions,

there is also room for improvement in the lifestyle of the general Dutch population. For example, only 45.8% of adults meet guidelines for physical activity, about one-third consume the recommended amounts of fruits and vegetables, and 20.6% report experiencing high levels of stress.[82-84] These patterns reflect a broader societal challenge, with unhealthy behaviors contributing not only to individual health risks but also to the global rise in diabetes, cardiovascular disease, and obesity worldwide.[85, 86] Promoting healthier lifestyle habits should therefore be a focus for all individuals, not just patients with psoriasis.

Moreover, although addressing lifestyle factors in psoriasis patients is important, it is not feasible for dermatologists to assume the role of primary lifestyle counselors. Instead, patients with chronic diseases in which lifestyle influences a disease trajectory, such as psoriasis, would benefit from referral to specialized lifestyle support services. For instance, the "Leefstijl Loket" program at Radboudumc evaluates patients' lifestyle behaviors and provides tailored guidance to facilitate change. Ultimately, while psoriasis care provides an opportunity to initiate discussions about the lifestyle of patients, sustainable improvement in lifestyle behaviors requires systemic and societal interventions, including public health programs, educational initiatives, and accessible support services for all individuals. Currently, in the Netherlands, a referral to the general practitioner (GP) is the designated way to achieve combined lifestyle intervention to improve health.[87] The GP lead the way in joining approved intervention programs that will also be reimbursed by the medical insurance companies.

Furthermore, as unmotivated patients more often used systemic therapy and were less likely than motivated patients to perceive psoriasis as affecting their daily life or to believe that lifestyle influences disease severity, discussing lifestyle factors early in the treatment process, preferably at the first consultation, may be more effective. Addressing lifestyle at this stage can help patients recognize the connection between psoriasis and lifestyle factors, and act while their motivation to change is still relatively high, before the disease becomes well controlled. Nevertheless, continuing to engage patients in discussions about healthy lifestyle behaviors remains important, even at later stages of the treatment, as lifestyle factors influence not only psoriasis but also various comorbidities.

In conclusion, considering the limited articles on the attitude and complete overview of current lifestyle habits of patients with psoriasis at the start of this PhD trajectory, our findings provide valuable insights into these important

matters, highlighting opportunities to support patients in adopting healthier behaviors. Especially the domains physical exercise and diet are important to consider as they represent substantial room for improvement. However, addressing lifestyle factors extends beyond the scope of dermatology and represents a broader societal challenge. Effective support requires dedicated programs and public health initiatives that can provide patients with the resources and guidance needed to make sustainable changes.

New insights from this thesis

This thesis provides several new insights that contribute to improving psoriasis care in the pediatric and adult population.

In pediatric psoriasis care, our findings offer concrete guidance for clinical decision making by proposing criteria for the initiation of systemic therapy, emphasizing that treatment decisions should not rely solely on disease extent, but also on quality of life, involvement and extent of high impact sites, and the age of a patient. Furthermore, we demonstrated that sex differences in psoriasis severity and in reported adverse events are already present in pediatric patients. Boys appear to have a more severe disease course, underscoring the importance of timely treatment, whereas girls more frequently report adverse events of treatment. A greater awareness of these differences in clinical practice will improve psoriasis care. Additionally, we showed that only a small proportion of pediatric patients developed JPsA/PsA. Yet, male sex, obesity, and nail involvement were associated with an increased risk of JPsA/PsA development. Therefore, extra attention should be paid to the development of JPsA/PsA in patients with these clinical characteristics.

In adult psoriasis care, this thesis identified two key domains that require broader attention. First, we found that depression and anxiety are strongly driven by psychological and socioeconomic factors, in addition to psoriasis severity, emphasizing the need for awareness of the broader determinants of mental health. Second, we showed that patients with psoriasis have considerable room for improvement in their lifestyle behaviors, particularly in physical activity and diet, while demonstrating strong motivation to make positive changes. Given that lifestyle directly affects both psoriasis severity and comorbidities, early attention to lifestyle factors is essential to enhance treatment effectiveness and long-term health outcomes.

Future perspectives

To improve pediatric psoriasis care, we proposed several criteria for considering the initiation of systemic therapy. To incorporate these findings in daily care, a possible approach would be to develop a Delphi consensus among international experts. However, it remains uncertain whether such a consensus would be equally useful in all settings, as clinicians may need to tailor decisions based on individual patient needs and local availability of therapies. Access to therapeutic options varies widely across different regions of the world, and the availability of systemic treatments, particularly biologics, remains limited in many settings due to high costs and healthcare infrastructure challenges.[88-91] Therefore, efforts to improve global access to effective systemic therapies for pediatric patients with psoriasis are essential. Conventional systemic treatments, such as methotrexate, which are more affordable and widely accessible, should continue to play a significant role in treatment strategies. Particularly in countries and regions where access to biologics is still limited, the (timely) use of conventional systemic treatments is important to ensure fair and effective psoriasis care.

Another way to improve pediatric psoriasis care is to increase awareness and improve screening tools for comorbidities, like psoriatic arthritis. In this thesis, we identified male sex, obesity, and nail involvement as potential characteristics that may help clinicians recognize patients with pediatric onset psoriasis who are at risk of developing JPsA/PsA. However, future research with larger, prospective cohorts is needed to confirm whether these factors can truly serve as predictors of JPsA/PsA in this population. In addition to validating such predictors, optimizing clinical decision-making will also require the development of effective and pediatric-specific screening tools to support dermatologists in determining which patients should be referred to the rheumatologist. Furthermore, insights from adult studies suggests that treatment choice may play a role in the development of PsA. For instance, studies showed that patients receiving IL23 inhibitors seem at lower risk to develop PsA than those receiving TNF-α inhibitors or IL17 inhibitors.[56, 92] However, IL23 inhibitors are currently not yet approved for pediatric psoriasis. Expanding therapeutic options and evaluating the role of (newer) biologics in pediatric psoriasis therefore represents important directions for future research.

In adult psoriasis care, our findings highlight the need for a broader approach to improve patient outcomes, including greater attention to mental health

and lifestyle factors. We observed that depression and anxiety were strongly associated with psychological and socioeconomic factors such as stress, low perceived social support, low income, and low education level. Addressing these factors could therefore have a positive impact on patients' overall health and well-being. However, implementing such an approach requires additional time and resources, raising the question how this can be integrated into routine dermatological care. One potential strategy is the use of digital tools prior to the consultations, which may help identify patients who would benefit from additional support related to psychosocial factors. The POSITIVE study is one example where more holistic tools, like the WHO well-being Index (WHO-5), can be incorporated to capture psychological well-being alongside traditional clinical measures in patients with psoriasis.[93, 94] Nevertheless, while our findings suggested that psychosocial and socio-economic factors play a major role, clinical severity of psoriasis can still contribute to psychological distress. Dermatologists can actively address this not only by optimizing psoriasis treatment, but also by providing educational resources, and linking patients to support services or patient organizations. For pediatric patients, providing supportive resources, such as material to help them to give a school presentation, may improve understanding among peers. For children and adults, patient organizations and dermatologists could play an active role in increasing public visibility, for instance through awareness campaigns. The rise of social media offers additional opportunities to share patient stories, raise awareness, and facilitate peer support. Using popular platforms may help patients feel less isolated and more connected to a community that understands their experiences. However, considering the current issue of miscommunication in social media, it is important that these platforms are monetized by patient organizations or other independent health care organizations.

Lifestyle behaviors represent another key aspect of comprehensive psoriasis care. It is important to discuss the role of lifestyle behaviors in psoriasis and comorbidities early, as we showed that the motivation of patients seems to be lower at a later stage when their psoriasis is well controlled. Recent studies have explored the potential role of Glucagon-like peptide 1 (GLP-1) receptor agonists, originally developed for diabetes and obesity management, in improving cardiometabolic health and inflammatory markers in patients with psoriasis.[95-97] Early findings suggest that GLP-1 based therapies may have beneficial effects on both psoriasis severity and comorbid conditions, likely through mechanisms involving weight reduction, insulin sensitivity,

and modulation of inflammatory pathways.[96, 98-100] However, while these developments are promising, it remains essential to maintain a balanced perspective, as overreliance on pharmacological treatments may shift the responsibility for lifestyle changes away from patients.

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CHAPTER 8

Nederlandse samenvatting

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Psoriasis is een veelvoorkomende, chronische, immuungemedieerde ontstekingsziekte die ongeveer 2-4% van de bevolking in westerse landen treft. Bij ongeveer een derde van de patiënten ontstaat psoriasis op kinderleeftijd. Ondanks de groeiende hoeveelheid kennis over optimale behandeling en zorg voor patiënten met psoriasis, bestaan er nog onderbelichte aspecten binnen de psoriasiszorg. In dit proefschrift hebben we daarom getracht de zorg voor patiënten met psoriasis te verbeteren door aandacht te besteden aan deze onderbelichte gebieden, zowel binnen de kinderpopulatie (hoofdstukken 2, 3 en 4) als bij volwassen patiënten (hoofdstukken 5 en 6).

Om de zorg voor kinderen met psoriasis te verbeteren, richtten we ons op de volgende doelen: het formuleren van criteria voor het starten van systemische therapie (Hoofdstuk 2), het onderzoeken van mogelijke sekseverschillen die van invloed kunnen zijn op behandeluitkomsten (Hoofdstuk 3) en het in kaart brengen van de ontwikkeling van artritis psoriatica (Hoofdstuk 4). Met betrekking tot de psoriasiszorg voor volwassen patiënten concentreerden we ons op de psychologische en sociaaleconomische factoren die samenhangen met depressie en angst (Hoofdstuk 5) en de leefstijl van psoriasispatiënten en hun motivatie om deze te veranderen (Hoofdstuk 6).

Onderbelichte aspecten in de psoriasiszorg voor kinderen

Initiëren van systemische therapie

Een belangrijk onderbelicht aspect in de zorg voor kinderen met psoriasis is het ontbreken van duidelijke criteria voor het starten van systemische therapie. Om criteria voor kinderen te kunnen formuleren, hebben wij de toepasbaarheid van bestaande definities voor volwassenen onderzocht. Bij volwassenen worden de Rule of Tens (R10) en het International Psoriasis Council consensus statement (IPCcs) vaak gebruikt. De R10 classificeert een psoriasis als ernstig wanneer het lichaamsoppervlak (BSA) >10% is aangedaan, of als de Psoriasis Area and Severity Index (PASI), een score die de ernst en uitgebreidheid van de psoriasis meet, > 10 is, of wanneer de Dermatology Life Quality Index (DLQI), een vragenlijst die de impact van huidziekten op de kwaliteit van leven beoordeelt, >10 is. De IPCcs classificeert volwassen psoriasispatiënten als kandidaten voor systemische therapie als zij aan ten minste een van de

volgende criteria voldoen: BSA>10%, of betrokkenheid van high impact sites (gebieden met grote klinische impact: hoofdhuid, lichaamsplooien, gezicht, nagels en handpalmen en voetzolen), of wanneer patiënten niet voldoende reageren op topicale behandeling.

In **Hoofdstuk 2** onderzochten we de toepasbaarheid van deze volwassen definities in een cohort van 641 kinderen met psoriasis uit het ChildCAPTURE register. Daarnaast analyseerden we welke klinische factoren geassocieerd waren met een verminderde kwaliteit van leven (CDLQI<10). De R10 identificeerde minder kinderen als geschikt voor systemische therapie (49.0%) dan de IPCcs (92.4%). Dit verschil werd vooral veroorzaakt door de hoge frequentie van betrokkenheid van de high impact sites, die bij 90.6% van de kinderen voorkwam. Daarnaast zagen we dat een verminderde kwaliteit van leven (CDLQI >10) geassocieerd was met betrokkenheid van high impact sites, een verhoogde ziekte-ernst (BSA>10%/ PASI>10) en tienerleeftijd (13-17 jaar).

Hoewel de R10 rekening houdt met ziekte-ernst (BSA en PASI) en met de kwaliteit van leven, wordt er mogelijk te weinig rekening gehouden met betrokkenheid van high impact sites. Studies bij volwassenen wezen namelijk uit dat deze high impact sites geassocieerd zijn met een slechtere kwaliteit van leven, depressie en grotere belemmering om deel te nemen aan dagelijkse en sociale activiteiten. Het is daarom belangrijk om te kijken naar meer definities die deze high impact sites meenemen bij de overweging om te starten met systemische therapie, zoals de IPCcs. Uit ons onderzoek bleek dat de IPCcs defintie echter te aspecifiek was, aangezien bijna alle patiënten aan de criteria voldeden (92.4%). Dit hoge percentage bleek vooral te verklaren door de frequente betrokkenheid van high impact sites (90.6%). Binnen deze high impact sites kwam met name betrokkenheid van de hoofdhuid frequent voor (84.1%), vergeleken met lichaamsplooien (36.8%), gezicht (26.4%), nagels (15.8%) en handpalmen en voetzolen (1.6%). Zelfs na het verhogen van de drempel voor betrokkenheid naar >50% van de scalp, voldeed nog altijd 74% van de patiënten aan de IPCcs definitie. Hoewel betrokkenheid van high impact sites een belangrijk criterium is bij het overwegen van systemische therapie bij kinderen met psoriasis, dient het niet het enige criterium te zijn.

Een ander criterium dat overwogen moeten worden is leeftijd. Onze studie wees uit dat tieners (13-17 jaar) een lagere kwaliteit van leven hadden vergeleken met jongere kinderen (0-6 jaar). Daarom is het aan te raden om bij deze leeftijdsgroep extra alert te zijn en systemische therapie eerder te overwegen.

Het falen van lokale therapie kan ook een reden zijn om systemische therapie te overwegen. Dit criterium maakt deel uit van de IPCcs en komt ook terug in diverse richtlijnen. De praktische toepasbaarheid van dit criterium is echter beperkt omdat factoren als therapietrouw, tolerantie, ouderlijke ondersteuning en de bereidheid van het kind om te smeren een belangrijke rol spelen. Falen van topicale therapie is dus wel relevant, maar zou geen stricte of op zichzelfstaand criterium mogen zijn voor het opstarten van systemische therapie.

Concluderend moeten bij het bepalen van criteria voor het starten van systemische therapie bij kinderen met psoriasis de ernst en uitgebreidheid van de ziekte (PASI/BSA) als belangrijke maatstaf worden meegenomen, maar moet daarnaast aandacht zijn voor betrokkenheid van high impact sites en invloed op de kwaliteit van leven. Daarbij verdient de tienerleeftijd extra aandacht. Tegelijkertijd is het van belang te realiseren dat het starten van systemische therapie bij kinderen met psoriasis niet zonder gevolgen is. Mogelijke bijwerkingen, de invasiviteit van injecties, regelmatig bloedonderzoek en frequentere controleafspraken zouden een belasting kunnen vormen voor de patiënten en hun zorgverleners. Een gezamenlijke beslissing met patient en zorgverleners waarbij de voor- en nadelen goed worden afgewogen is dan ook van belang.

Sekseverschillen

Een ander onderbelicht aspect in de zorg voor kinderen en jongvolwassenen met psoriasis is de invloed van sekseverschillen op behandeluitkomsten. In **Hoofdstuk 3** werden daarom gegevens uit de ChildCAPTURE- en BioCAPTURE registers geanalyseerd om te onderzoeken of er sekseverschillen bestaan in drug survial, gerapporteerde bijwerkingen, ziekte-ernst, effectiviteit van biologics, en kwaliteit van leven bij kinderen (<18 jaar) en jongvolwassenen (≥18 tot ≤30 jaar) die behandeld worden met biologics.

In totaal werden 360 patiënten meegenomen in de studie, waarvan 117 kinderen (65 meisjes, 52 jongens) en 243 jongvolwassenen (124 vrouwen, 119 mannen). Jongvolwassen mannen bleken een hogere PASI-score te hebben bij de start van een biologic vergeleken met jongvolwassen vrouwen, en een vergelijkbare trend werd gezien bij jongens ten opzichte van meisjes. Daarnaast rapporteerden meisjes en jongvolwassen vrouwen vaker bijwerkingen dan jongens en jongvolwassenen mannen. Er werden geen sekseverschillen gevonden in drug survival en geen sekseverschillen in de

verbetering van PASI en (C)DLQI-scores gedurende het eerste behandeljaar, noch in het bereiken van drempelwaarden (PASI/ (C)DLQI ≤1, ≤3, and ≤5) binnen deze scores. Ook de PASI-scores op het moment van het stoppen van een biologic wegens ineffectiviteit waren vergelijkbaar tussen vrouwelijke en mannelijke patiënten. Dit patroon was zichtbaar bij zowel kinderen als jongvolwassenen.

De hogere PASI-scores bij mannen lijken niet te worden verklaard door een latere start van behandeling, aangezien hun ziekteduur bij aanvang juist korter was. Dit suggereert een mogelijk ernstiger ziektebeloop in het algemeen bij mannen. De hogere frequentie van bijwerkingen bij vrouwen, ook op jonge leeftijd, wijst op fysiologische sekseverschillen in plaats van sociaal-culturele factoren. Het erkennen van deze verschillen en het bespreken van mogelijke bijwerkingen kan bijdragen aan betere begeleiding, therapietrouw en tevredenheid bij patiënten.

Het is dus van belang om sekseverschillen mee te nemen in de zorg voor kinderen en jongvolwassenen met psoriasis, vooral met betrekking tot ziekte-ernst en ervaren bijwerkingen. Bewustzijn en tijdige start van systemische therapie zijn met name van belang bij jongens, omdat zij zich vaker presenteren met een ernstigere ziekte. Bij meisjes daarentegen zijn empathie, open communicatie en zorgvuldige monitoring gedurende de behandeling van belang, aangezien zij vaker bijwerkingen ervaren.

Ontwikkelen van artritis psoriatica

Ongeveer een derde van de volwassenen met matig-ernstige psoriasis ontwikkelt artritis psoriatica. Bij kinderen is hier echter nog weinig over bekend. In **Hoofdstuk 4** werden data gebruikt uit het ChildCAPTURE register om een cohort te beschrijven van 717 patiënten waarbij psoriasis op kinderleeftijd ontstond, en te beoordelen wie van hen vervolgens een artritis psoriatica ontwikkelde op kinderleeftijd (JPsA) of op volwassen leeftijd (PsA). De International League of Associations for Rheumatology (ILAR) and Classification Criteria for Psoriatic ARthritis (CASPAR) criteria werden respectievelijk gebruikt voor de classificatie van JPsA en PsA. Een Kaplan-Meier survivalanalyse werd gebruikt om de tijd van psoriasisdiagnose tot aan de JPsA/PsA diagnose te bepalen. Van de 717 patiënten ontwikkelden 15 patiënten (2.1%) een artritis. Hiervan ontwikkelde ongeveer 1% dit op kinderleeftijd en ongeveer 1% op jongvolwassen leeftijd (PsA). De geschatte 10-jaar cumulatieve incidentie van JPsA/PsA na psoriasisdiagnose was 2.8%. Het mediane tijdsinterval tussen de psoriasisdiagnose en JPsA/PsA

ontwikkeling was 4.8 jaar. Op het moment van inclusie in het register bestond de groep die later JPsA/PsA zou gaan ontwikkelen uit relatief meer jongens. Ook hadden deze patiënten vaker obesitas en nagelbetrokkenheid dan het totale cohort kinderen met psoriasis. Ten tijde van de artritis diagnose kwamen overgewicht/obesitas en nagelbetrokkenheid zelfs nog vaker voor bij patiënten met JPsA/PsA dan op het moment van inclusie in het register.

Deze bevindingen laten zien dat de prevalentie van JPsA/PsA relatief laag is bij kinderen en jongvolwassenen patiënten waarbij psoriasis op kinderleeftijd is ontstaan. Desalniettemin blijft monitoring van deze patiënten nog altijd belangrijk voor vroege opsporing en interventie, aangezien dit op de lange termijn gewrichtsschade kan voorkomen. In ons cohort werden patiënten routinematig gevraagd naar gewrichtsklachten en vulden zij bij elke bezoek een PEST vragenlijst in. Gezien de lage prevalentie van artritis lijkt een dergelijke intensieve screening niet nodig, en kan dit patiënten ook onnodig bewust maken van milde klachten, zoals putjesnagels. Om belasting bij herhaald screenen te verminderen, kan gerichte monitoring worden overwogen bij patiënten met een verhoogd risico op het ontwikkelen van JPsA/PsA: met name jongens, patiënten met een hoog BMI en patiënten met nagelbetrokkenheid, aangezien deze kenmerken vaker voorkomen in de JPsA/PsA groep.

Concluderend kan worden gesteld dat, ondanks de relatief lage prevalentie van JPsA/PsA onder kinderen met psoriasis, alertheid op het ontstaan van artritis geboden is bij patiënten met gewrichtsklachten, vooral wanneer zij mannelijk zijn, obesitas hebben of nagelbetrokkenheid hebben.

Onderbelichte aspecten in de psoriasiszorg voor volwassenen

Mentale gezondheid

Patiënten met psoriasis hebben een hogere prevalentie van depressie en angst dan de algemene bevolking. Studies naar factoren die geassocieerd zijn met depressie en angst bij psoriasispatiënten hebben zich vooral gericht op bekende factoren zoals geslacht, leeftijd en de ernst van psoriasis. Over de rol van psychologische en socioeconomische factoren bij patienten met psoriasis is echter nog weinig bekend, terwijl deze in de algemene bevolking duidelijk verband houden met mentale gezondheidsuitkomsten. In **Hoofdstuk 5** werden gegevens uit een landelijke, online enquête onder psoriasispatiënten, gebruikt

om de meest relevante factoren te identificiëren die geassocieerd zijn met matige tot ernstige depressie en/of angst (DA) bij 267 volwassen patiënten met psoriasis. Symptomen van depressie en angst werden beoordeeld met behulp van respectievelijk de Patient Health Questionnaire (PHQ-9) en de Generalized Anxiety Disorder schaal (GAD-7). Een score van ≥10 op een van de screeningsinstrumenten werd gezien als matige tot ernstige depressieve respectievelijk angstsymptomen. We onderzochten associaties tussen DA en de volgende mogelijke beïnvloedende factoren: geslacht, leeftijd, ziekte-ernst, psoriasis op zichtbare plekken, opleidingsniveau, inkomen, stress en sociale steun. De eerste drie factoren worden in de literatuur vaak in verband gebracht met depressie en angst, terwijl de laatste vijf factoren klinisch relevant zijn maar nog maar weinig onderzocht zijn in een psoriasis populatie. We vonden dat 54 van de 267 patiënten (20.2%) positief screenden op symptomen van DA. Daarnaast bleken stress en laag ervaren sociale steun sterk geassocieerd met matige tot ernstige DA. Ook een laag inkomen en laag opleidingsniveau waren hiermee geassocieerd, zij het minder sterk. De bekende patiëntkarakteristieken geslacht, leeftijd en ziekte-ernst, die in eerdere literatuur vaak werd gekoppeld aan DA, waren in onze hoofdanalyse niet geassocieerd met matige tot ernstige DA.

Deze bevindingen benadrukken dat, hoewel dermatologische behandeling van psoriasis essentieel blijft vanwege de relatie tussen ziekte-ernst en DA, een effectieve aanpak van de mentale gezondheid van psoriasispatiënten een bredere benadering vereist die verder reikt dan de huidige psoriasiszorg.

Leefstijl

Patiënten met psoriasis hebben een verhoogd risico op cardiovasculaire en metabole aandoeningen die op hun beurt worden beïnvloed door leefstijlfactoren. Dit onderstreept het belang van een gezonde leefstijl als onderdeel van de psoriasiszorg. In **Hoofdstuk 6** onderzochten we, aan de hand van gegevens uit een landelijke online enquête, de bereidheid tot leeftstijlverandering en de huidige leefstijlgewoonten onder 448 psoriasis-patiënten van ≥ 16 jaar. Middels vragenlijsten werd de motivatie om de leefstijl te veranderen in kaart gebracht. Ook de huidige leefstijl binnen de domeinen beweging, roken, alcohol, dieet, stress en slaap werd bevraagd, alsmede binnen welke domeinen patiënten hun leefstijl het liefst zouden willen aanpassen. Patiënten werden ingedeeld in drie groepen op basis van hun motivatie om hun leefstijl aan te passen: (1) gemotiveerd, (2) mogelijk gemotiveerd en (3) ongemotiveerd of onzeker. We vonden dat de meerderheid

van de psoriasispatiënten (85.3%) gemotiveerd was om hun leefstijl te veranderen, waarbij beweging en dieet de vaakst genoemde domeinen waren die patiënten wilden verbeteren. Bij het onderzoeken van hun huidige leefstijlgewoonten bleken juist deze twee domeinen de meeste ruimte te bieden voor verbetering: slechts ongeveer een derde van de patiënten voldeed aan de aanbevolen Nederlandse richtlijn voor beweging en dieet. Daarnaast rapporteerde bijna de helft van de patiënten hoge stressniveaus, zowel thuis (41.9%) als op het werk (48.7%). De vergelijking tussen gemotiveerde en ongemotiveerde patiënten liet zien dat ongemotiveerde patiënten ouder waren, minder vaak psoriasis op zichtbare gebieden hadden en vaker behandeld werden met systemische therapie of lichttherapie dan gemotiveerde patiënten. Ongemotiveerde patiënten ervoeren bovendien minder vaak dat psoriasis invloed had op hun dagelijks leven of dat leefstijl de ernst van hun ziekte beïnvloedde. Behalve een hogere prevalentie van roken onder ongemotiveerde patiënten, verschilden leefstijlfactoren verder niet significant tussen de groepen.

Concluderend bieden onze bevindingen waardevolle inzichten over leefstijlgewoonten van psoriasispatiënten en hun motivatie om deze te veranderen, onderwerpen waarover bij aanvang van dit promotietraject weinig artikelen beschikbaar waren. Daarnaast laten onze resultaten zien welke mogelijkheden er zijn om patiënten te ondersteunen bij het aannemen van gezondere leefstijlgewoonten. Met name de domeinen beweging en dieet verdienen aandacht, omdat hier aanzienlijke ruimte voor verbetering ligt en patiënten in deze domeinen het meest gemotiveerd zijn om verandering aan te brengen. Het aanpakken van leefstijlfactoren gaat echter verder dan de dermatologie en vormt een bredere maatschappelijke uitdaging. Effectieve ondersteuning vraagt om gerichte programma's en initiatieven op het gebied van volksgezondheid die patiënten de middelen en begeleiding bieden die nodig zijn om duurzame veranderingen door te voeren.

Deze thesis biedt verschillende nieuwe inzichten die bijdragen aan het verbeteren van de psoriasiszorg voor zowel kinderen als volwassenen.

CHAPTER 9

Appendices

List of abbreviations

AE	Adverse Event
BioCAPTURE	Continuous Assessment of Psoriasis Treatment Use Registry with Biologics
BMI	Body Mass Index
BSA	Body Surface Area
CASPAR	Classification for Psoriatic Arthritis
CAPTURE	Continuous Assessment of Psoriasis Treatment Use Registry
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence Interval
COMP	Cartilage Oligomeric Matrix Protein
DA	Depression and/or Anxiety
DLQI	Dermatology Life Quality Index
DRE	Digital Research Environment
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMA	European Medicines Agency
ESSI	ENRICHD Social Support Instrument
GAD-7	General Anxiety Disorder-7
GLP-1	Glucagon-like peptide 1
GP	General Practitioner
GWAS	Genome-wide association studies
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
IFN	Interferon
IL	Interleukin
ILAR	International League of Associations for Rheumatology
IOTF	International Obesity Task Force
IPC	International Psoriasis Council
IPCcs	International Psoriasis Council consensus statement
IQR	Inter Quartile Range
JPsA	Juvenile Psoriatic Arthritis
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MMP-3	Matrix Metalloproteinase-3
N	Total number of individuals or observations
NA	Not applicable or Not assessed
NB-UVB	Narrow band UVB

NVED	Nederlandse Vereniging voor Experimentele Dermatologie
OR	Odds Ratio
PASI	Psoriasis Area and Severity Index
PEST	Psoriasis Epidemiology Screening Tool
PGA	Physician Global Assessment
PHQ-9	Patient-Health Questionnaire-9
PsA	Psoriatic Arthritis
QoL	Quality of Life
R10	Rule of Tens
RCT	Randomized Controlled trial
RWE	Real World Evidence
SD	Standard Deviation
SAE	Serious Adverse Event
SPSS	Statistical Package for Social Sciences
TNF	Tumor Necrosis Factor
UV	Ultraviolet
WHO	World Health Organization
WHO-5	WHO Five-Item Well-being Index

List of publications

Publications related to this thesis

Al-Gawahiri M, Paller AS, Skov L, van de Kerkhof PCM, de Jong EMGJ, van den Reek JMPA, Seyger MMB. Investigation of the applicability of adult definitions of disease severity for psoriasis in a pediatric cohort: A prospective registry study. J Am Acad Dermatol. 2025;92(6):1424-1427.

Al-Gawahiri M, Barenbrug L, Bronkhorst EM, de Jong EMGJ, van den Reek JMPA, Seyger MMB. Sex-disparities in pediatric and young adult patients with psoriasis treated with biologics: differences in adverse events and disease activity. J Dermatolog Treat. 2025;36(1):2532672.

Al-Gawahiri M, de Jong EMGJ, Schatorjé EJH, Hoppenreijs EPAH, van den Reek JMPA, Seyger MMB. Development of Arthritis in a Large Real-World Cohort of Patients With Pediatric Onset Psoriasis. Journal of Psoriasis and Psoriatic Arthritis. Published online ahead of print April 25, 2026.

Al-Gawahiri M, Godding LTH, de Jong EMGJ, Limbeek DR, Janssen VR, van den Reek JMPA, Seyger MMB. Psychological and Socioeconomic Factors associated with Depression and Anxiety among Patients with Psoriasis. Under review at Archives of Dermatological Research. 2026.

Al-Gawahiri M, van den Reek JMPA, van Acht MR, Evers AWM, de Jong EMGJ, Seyger MMB. The lifestyle of psoriasis patients and their motivation to change. J Eur Acad Dermatol Venereol. 2024;38(10):e836-e841.

Publications not related to this thesis

Al-Gawahiri M, van der Bent SAS, Clahsen P, Vos LE. Single and multiple keratoacanthomas after a recent black tattoo in two patients. BMJ Case Rep. 2024;17(11):e260760.

Al-Gawahiri M, Rustemeyer T, Franken SM, van Zuuren EJ, Ipenburg NA. Frequency and clinical relevance of contact allergy in dental patients. Contact Dermatitis. 2024;90(1):66-73.

Research data management

Ethics and privacy

This thesis is based on medical-scientific research involving human participants. Chapters 2, 3, and 4 utilize data from the ChildCAPTURE registry, which was exempted from formal ethical approval by the Medical Ethical Review Committee 'METC Oost-Nederland' (registration number: 2012/383). Although formal approval and informed consent were not mandatory, written consent was obtained from every enrolled patient. Additionally, chapter 3 includes data from the BioCAPTURE registry, also exempted from formal approval by the same committee (registration number: 2024/17362), with written informed consent obtained from all participants.

Data for chapters 5 and 6 were collected via a web-based survey. The regional Ethics Committee reviewed the study protocol and confirmed that it did not fall under the Medical Research Involving Human Subjects Act (registration number: 2021/13035).

Data collection and storage

For chapters 2, 3 and 4, data was collected from electronic Case Report forms (eCRF) using Castor EDC. From Castor EDC, data were extracted to SPSS (SPSS Inc., Chicago, Illinois, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

Data from chapters 5 and 6 were pseudonymously collected by the use of the password-protected web-based survey system Qualtrics (XM 2020, Provo, UT, USA).

Pseudonymized data were stored and analyzed in the Azure DRE, on the department server and in Castor EDC and are only accessible by project members working at the Radboudumc.

Availability of data

All studies are published open access. Questions regarding the existing data used from the ChildCAPTURE and BioCAPTURE registries can be addressed to onderzoek.derma@radboudumc.nl. However, reusing the data for future research is only possible after a renewed permission by the participants. The data will be archived for 15 years after termination of the study.

The new data of chapters 5 and 6 that were collected and used for the published chapters are not suitable for reuse because consent for reuse of the pseudonymized data was not obtained. This data will be archived with closed access for 15 years in a DAC of the Radboud Data Repository (DOI:10.34973/sggz-jw04) after termination of the study. Reusing the data for future research is only possible after a renewed permission by the participants.

PhD Portfolio

Department: Dermatology
PhD period: 16-10-2022 until 16-10-2025
PhD Supervisor(s): Prof. dr. E.M.G.J. de Jong
PhD Co-supervisor(s): Dr. M.M.B. Seyger and dr. J.M.P.A. van den Reek

Training activities	Hours
Courses	
• Radboudumc - Introduction day (2022)	6.00
• RadboudUMC Basic Life support course (2023)	4.00
• Radboudumc - In the lead - Radboudumc introduction for PhD candidates (2023)	12.00
• Radboudumc - eBROK course (2023)	42.00
• RU - Writing Scientific Articles (2023)	96.00
• Meet the expert - How to prepare for your PhD defense (2024)	1.50
• Radboudumc - Scientific integrity (2024)	20.00
• RU - Art of Finishing Up (2025)	10.00
• RU - Presentation Skills (2025)	42.00
Seminars	
• Radboud Research Rounds (2022)	1.50
• Real World Evidence Workshop (2023)	13.00
• Journal club Dermatology (oral presentation) (2023)	6.00
• Radboud Integrity Rounds (2023)	1.50
• Radboud Research Rounds (2023)	1.50
• Journal club Dermatology (oral presentation) (2024)	6.00
• Radboud Integrity Rounds (2024)	1.50
• Annual BioCAPTURE meeting (2024)	3.50
• Dermatology Researchers Retreat (2024)	8.00
• Research Integrity Rounds (2024)	1.50
• Meet the expert - Missing data (2025)	2.00
• Clinical demonstration Dermatology LUMC (2025)	4.50
• Spring Symposium epidemiology and personalised medicine (2025)	4.00
• Journal club Dermatology (oral presentation) (2025)	6.00
• Annual BioCAPTURE meeting (2025)	3.00
Conferences	
• Nederlandse Vereniging voor Experimentele Dermatologie (NVED) (2023)	8.00
• BENEFIT consortium meeting LUMC (2023)	3.00
• PhD Retreat (2023)	12.00
• Nederlandse Vereniging voor Experimentele Dermatologie (NVED, poster presentation) (2024)	24.00
• European Academy of Dermatology and Venereology (EADV) (2024)	24.00
• Nederlandse Vereniging voor Experimentele Dermatologie (NVED, poster presentation) (2025)	24.00
• European Society for Pediatric Dermatology (ESPD, oral presentation) (2025)	32.00
Other	
• Radboudumc - General Radboudumc introduction for research personnel (2023)	9.00
• International Psoriasis Council (IPC, oral presentation) (2023)	10.00
• International Psoriasis Council (IPC, oral presentation) (2023)	10.00
• Introduction day ANIOS, AIOS en basisartsen (2023)	4.00
• Stichting Wetenschappelijk Onderzoek Psoriasis (SWOP, oral presentation) (2023)	8.00
• Committee member annual department activity 2024 (2024)	10.00

Teaching activities	
Lecturing	
• Meet the PhD project - bachelor biomedical sciences students (2023)	42.00
Supervision	
• Supervision of medical student outpatient clinic year 1 (2023)	160.00
• Supervision medical student Research internship (2024)	30.00
• Supervision of medical student outpatient clinic year 2 (2024)	160.00
• Supervision of medical student outpatient clinic year 3 (2025)	40.00
Total	**907.00**

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Curriculum Vitae

Malak Al-Gawahiri werd geboren op 1 februari 1995 in Bagdad, Irak, en verhuisde op jonge leeftijd naar Stockholm, Zweden, waar ze enkele jaren verbleef, alvorens haar jeugd verder door te brengen in Leiden, Nederland. Na het behalen van haar gymnasiumdiploma aan het Stedelijk Gymnasium Leiden begon zij in 2015 met de opleiding Geneeskunde aan de Universiteit Leiden. Tijdens de bachelorfase ontstond haar interesse in het deelnemen aan medisch wetenschappelijk onderzoek en andere extracurriculaire activiteiten. Zo nam zij deel aan het excellentieprogramma Honours College Geneeskunde en de Vereniging Chirurgie voor Medisch Studenten (VCMS). Ook volgde zij cursussen Medisch Spaans en Students Experienced in Lifestyle and Food (SELF). Daarnaast bekleedde zij een bestuursfunctie in de Carrièrecommissie van de Medische Faculteit der Leidse Studenten (MFLS).

In de wachttijd voor de coschappen was zij werkzaam als medewerker kwaliteit en veiligheid bij DC Klinieken in Voorschoten en deed zij een klinische stage bij de afdeling thoraxchirurgie van het Consortium General University Hospital in Valencia, Spanje. Gedurende de coschappen groeide haar interesse voor dermatologie. Dit leidde tot een semiartsstage bij de afdeling dermatologie van het Haaglanden Medisch Centrum in Den Haag, gevolgd door een wetenschappelijke stage bij de afdeling dermato-allergologie van het Amsterdam Universitair Medisch Centrum.

Eind 2022 startte zij als arts-onderzoeker, onder begeleiding van prof. dr. Elke de Jong, dr. Marieke Seyger en dr. Juul van den Reek, op de afdeling dermatologie van het Radboud Universitair Medisch Centrum in Nijmegen. Het onderwerp van haar promotietraject betrof onderbelichte aspecten van de psoriasiszorg bij kinderen en (jong)volwassenen. Haar onderzoeksactiviteiten hebben geleid tot de publicatie van vijf peer-reviewed artikelen in toonaangevende tijdschriften. Deze publicaties zijn gebundeld in dit proefschrift. Haar promotieonderzoek combineerde zij met haar werkzaamheden als arts op het specialistische kinderpsoriasis spreekuur.

Sinds december 2025 werkt zij als arts-assistent dermatologie in het IJsselland Ziekenhuis te Capelle aan den IJssel.

مُقامي بينكم شُكْرُ ويَومي عندَكم دَهْرُ
سيصلُحُ منكم العُذْرُ إذا لم يصلُحِ الشِعْرُ

محمد مهدي الجواهري - شكر وعذر

Mijn aanwezigheid onder jullie is mijn dank,
en de tijd met jullie was van onschatbare waarde.
Mochten mijn woorden tekortschieten,
dan spreekt mijn dank des te meer.

Muhammad Mahdi al-Jawahiri – Dank en verontschuldiging

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