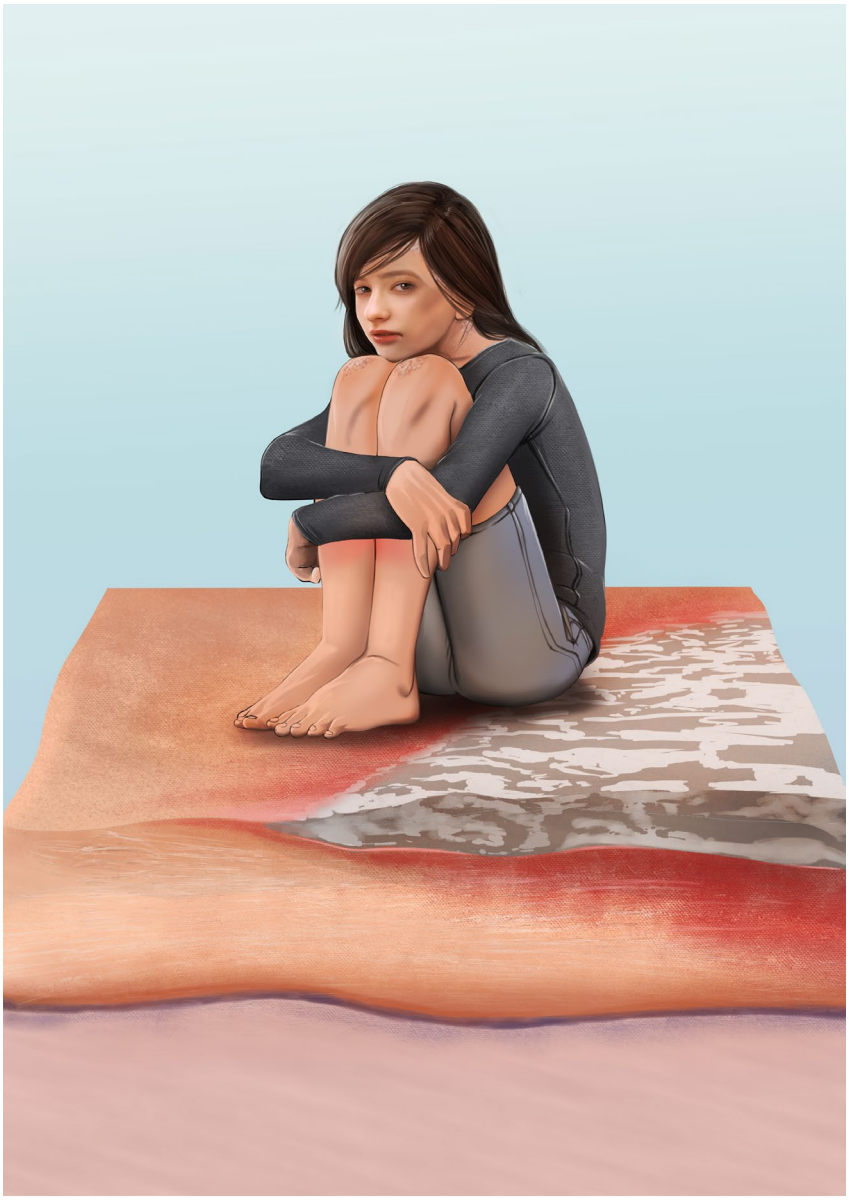
UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

The epidemiology and burden of psoriasis



Doctoral dissertation

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The Faculty of Health and Medical Sciences at the University of Copenhagen has accepted this dissertation for public defence for the doctoral degree in Medical Science. Copenhagen, 27 January 2021.

Ulla M. Wewer, Head of Faculty

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Preface

This thesis was drafted during the spring of 2018. And the summer of 2018. And the fall of 2018. You get the picture. These things take time, and often much longer than we expect. Because how do you thoroughly cover all relevant aspects of a disease affecting upwards of 100 million people worldwide? How do you contribute with new angles and improve the scientific understanding in a field where more than 50,000 scientific papers have already been published? The 10 papers selected for this thesis are in no way sufficient to adequately capture the nature, epidemiology, and burden of psoriasis, and they make up only a tiny fraction of my work in the field of dermato-epidemiology. They are a small representation of my ongoing efforts to understand, characterize, and define the scope and boundaries of the inflammatory immune-dysfunction that we like to call "psoriasis".

While it is impossible to give due credit to all in this preface, there are a few people that warrants particular mentioning. I am truly grateful to my partner in crime, Jacob P. Thyssen for his support, enthusiasm, and crazy ideas, but most of all for his friendship. During our endeavors, you have thought me that kindness is a free and inexhaustible resource. I also thank the scientific journal editors for regularly rejecting my papers, thus forcing me to do better. While many other people also deserve credit, Lotus Mallbris stands out. From her remote supremacy, she has shaped me through her invaluable mentorship and support over the years on both a professional and personal level.

Without the support and love from Yuki, this would not have been worthwhile. Beyond comparison, you are my biggest achievement.

No work, however big or small, has ever been done without the contribution of others. I am grateful to all the people I have met over the past few years – some of who have inspired me, some of who were involved in this work, and some of who have changed the trajectory of my life. Through my inherent nature I continue to have audacious goals, and one day looking back, this will be but a single pebble at the foot of a mountain.

Alexander Egeberg (2019)

List of papers

I. Prevalence and characteristics of psoriasis in the Denmark – findings from the Danish Skin Cohort.
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II. Clinical characteristics, symptoms, and burden of psoriasis and atopic dermatitis in adults.
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III. Incidence and prevalence of psoriatic arthritis in Denmark: a nationwide register linkage study.
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IV. Prevalence of psoriatic arthritis in patients with psoriasis: A systematic review and meta-analysis of observational and clinical studies.
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V. Incidence and prognosis of psoriasis and psoriatic arthritis in patients undergoing bariatric surgery.
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VI. Chronological order of immune mediated inflammatory diseases relative to diagnosis of psoriasis.
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J Am Acad Dermatol. 2019 Apr 19. pii: S0190-9622(19)30624-3.

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VIII. Risk of first-time and recurrent depression in patients with psoriasis – a population-based cohort study.
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IX. Risk of self-harm and non-fatal suicide attempts, and completed suicide in patients with psoriasis – a population-based cohort study.
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X. Factors associated with patient-reported importance of skin clearance among adults with psoriasis and atopic dermatitis.
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Contents

List of abbreviations

BMI	Body mass index
BSA	Body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CD	Crohn's disease
CI	Confidence interval
CV	Cardiovascular
CVD	Cardiovascular disease
DLQI	Dermatology life quality index
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
HR	Hazard ratio
IBD	Inflammatory bowel disease
IL	Interleukin
LDL	Low-density lipoprotein
MI	Myocardial infarction
OR	Odds ratio
PASI	Psoriasis area and severity index
PGA	Physician's global assessment
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
SD	Standard deviation
TNF	Tumor necrosis factor
UC	Ulcerative colitis
VLDL	Very low-density lipoprotein

Summary in Danish

Psoriasis er en kronisk og hyppigt forekommende inflammatorisk sygdom der kan omfatte langt mere end blot huden. Forekomsten af komorbiditet, dvs. andre legemlige eller psykiatriske tilstande er beskrevet at forekomme hyppigere blandt psoriasispatienter end hos personer uden psoriasis. En lang række faktorer, der omfatter systemisk inflammation, genetiske samt udefrakommende faktorer (især modificerbare livsstilssygdomme) er blevet brugt til at forklare den øgede forekomst af komorbiditet der ses ved psoriasis. I takt med at nye og mere effektive behandlingsmuligheder bliver tilgængelige til psoriasis, er der et stadig stigende behov for at forstå sygdomsbyrden, både den fysiske og psykiske, for tilstrækkeligt at kunne håndtere disse patienter og for at finde frem til den bedst passende langsigtede behandlingsstrategi.

Denne afhandling indeholder ti originalartikler, der hver på sin måde forsøger at øge vores forståelse af epidemiologien og sygdomsbyrden ved psoriasis på et fysisk og psykisk niveau, såvel som den potentielle påvirkning af behandlingen af disse patienter.

Ved at bruge spørgeskema-data fandt jeg at livstidsforekomsten af psoriasis var 7.9% i Danmark, og at periodeprævalensen (”nuværende psoriasis”) var 5.0%, hvilket understøtter opfattelsen af at psoriasis er hyppigere end tidligere antaget. Vi beskrev endvidere fundamentale kliniske sygdomsaspekter omkring psoriasis, såsom den anatomiske fordeling, og viste at forekomsten af risikofaktorer for livsstilssygdomme var høj, hvilket tyder på at visse komorbiditeter hos psoriasispatienter i stor grad kan forebygges ved rettidig indgriben. Ved at sammenkoble landsdækkende danske registerdata demonstrerede jeg at vægttab som følge af fedmekirurgi var forbundet med en nedsat risiko for efterfølgende at blive diagnosticeret med psoriasis, og viste at forekomsten af psoriasisgigt er stigende på befolkningsniveau. Ydermere viste et systematisk review og meta-analyse at mere end hver fjerde psoriasispatient vil udvikle psoriasisgigt i løbet af deres liv. Desuden demonstrerede jeg ikke blot at forekomsten og risikoen for inflammatorisk tarmsygdom hos psoriasispatienter varierer alt efter alder og køn, men også at denne og andre immun-medierede inflammatoriske sygdomme i de fleste tilfælde forekommer inden psoriasisdiagnosen bliver stillet første gang. Herudover demonstrerede og beskriv jeg ikke kun en betydelige emotionel byrde hos psoriasispatienter, men også at selvom risikoen for depression var øget iblandt psoriasispatienter så førte det

kun yderst sjældent til at patienterne begik selvmord. Alt i alt fremhæver disse videnskabelige fund den anseelige emotionelle byrde som følge af psoriasis, hvilket blev yderligere understøttet af patient-rapporterede data, der viste at patienterne har et højt ønske om komplet eller næsten komplet fravær af psoriasis uanset deres sygdoms sværhedsgrad.

Selvom skræddersyet psoriasisbehandling ideelt set skulle omfatte en pallette af faktorer, herunder komorbiditet risikovurdering, så bør fokus altid være på klinisk relevans og absolut risiko. De ti studier i denne afhandling forsøger at nuancere den eksisterende litteratur, og den efterfølgende diskussion forsøger at udfordre den nuværende (mis)forståelse omkring psoriasis og udviklingen af følgesygdomme. Selvom der er er lang række af andre følgesygdomme og aspekter af psoriasisbyrden som kunne have været inddraget, giver denne afhandling et helikopter-overblik over den samlede nuværende viden og fremhæver områder hvor forskningen med fordel kan fokuseres i de kommende år.

Summary in English

Psoriasis is a chronic inflammatory disease which may have implications far beyond the skin. Presence of comorbidity, i.e. concurrent medical or psychiatric conditions, is reported with higher frequency in patients with psoriasis compared with non-psoriasis individuals. A number of factors, including systemic inflammation, genetic and exogenous (in particular modifiable life-style) risk factors, have been put forward to explain this increased prevalence of comorbidity. With the emergence of new and more effective treatments for psoriasis, there is a still-increasing need to understand the disease burden, both physically and emotionally, to properly manage patients and find the most appropriate long-term treatment strategy.

This thesis included ten original articles, which each in their own way attempts to deepen our understanding of the epidemiology and burden of psoriasis on a physical and emotional level, as well as the potential impact of treatment in these patients.

Using questionnaire-based data, I found a lifetime psoriasis prevalence of 7.9% in Denmark, and a point-prevalence ("current psoriasis") of 5.0%, supporting the notion that psoriasis is more frequent than previously believed. We further described key clinical aspects of psoriasis, including the anatomical distribution and showed that presence of lifestyle-associated comorbidity risk factors was high, suggesting that certain comorbidities in psoriasis to a large degree may be preventable through timely intervention. By linking nationwide registry data from Denmark, we showed that weight-loss through bariatric surgery was associated with reduced future risk of being diagnosed with psoriasis, and we demonstrated that the incidence of diagnosed psoriatic arthritis (PsA) is increasing on a population-level. Furthermore, through a systematic review and meta-analysis, we showed that more than one in every four psoriasis patients will develop PsA during their life course. Moreover, we demonstrated not only that the incidence and risk of inflammatory bowel disease varies with age and sex in patients with psoriasis, but that this and other immune-mediated inflammatory diseases occurs before psoriasis is diagnosed in the majority of cases. In addition, I demonstrated and described a considerable emotional burden in patients with psoriasis, but also found that although the risk of depression was increased in patients with psoriasis, this very rarely led to suicide. All in all, these findings highlight the immense emotional burden of psoriasis, which was further

supported by patient-reported data showing a high need for complete or almost complete skin clearance regardless of disease severity.

While patient-tailored psoriasis management should ideally consider a multitude of factors including comorbidity risk assessment, the clinical relevance and absolute risks should always be kept in mind. The ten studies included in this thesis attempt to add nuances to the existing literature, and the subsequent discussion section seeks to challenge current (mis)-conceptions regarding psoriasis and comorbidity development. Although a multitude of other comorbid conditions and aspects of the psoriasis burden could have been included, the current thesis gives a high-level overview of the current sum of knowledge and highlights areas where future research efforts may be directed in the coming years.

Introduction

Psoriasis is a common, chronic inflammatory cutaneous disease. In the most common form, psoriasis vulgaris (plaque psoriasis), it is characterized by thick elevated silvery-white scaling plaques that may be either localized or widespread. The etymology stems from the Greek word *ψώρα* (*psṓra*) meaning "itch", a symptom which also is frequently occurs in patients with psoriasis. While the disease was previously believed to be limited to the skin and nails, it is now increasingly understood that psoriasis is a systemic condition that may, directly or indirectly, affect other organs, including the joints, liver, spleen, gastrointestinal tract, and cardiovascular (CV) system.

Within the past two decades, significant advances have been made in our understanding of the impact of psoriasis on patients. It has been suggested that psoriasis itself may be an independent risk factor for the development of CV disease (CVD).[1] Moreover, psoriasis has detrimental effects on patients' quality of life and inflict a tremendous burden of disease.[2]

At the same time, development of systemic therapies, including biologics, have expanded the physician's therapeutic options to a point where complete skin clearance is no longer an unattainable ambition.[3] However, the need for newer and more effective treatment options has not diminished, and while rapid effect on cutaneous symptoms may instill hope for long-term remission in affected individuals, many patients still fail even on the most potent of therapies.[4] Furthermore, patients may have had psoriasis for several years before they receive appropriate therapy and may have to endure several unsuccessful treatment modalities before finding a suitable treatment for their psoriasis. Importantly, an increasing awareness of comorbid conditions in these patients has highlighted the need for an individualized and holistic treatment approach, in which concurrent diseases are included in the decision process when choosing the appropriate therapeutic option for these patients. Importantly, treatment should not only be focused on pharmacotherapy, but behavioral modifications and lifestyle interventions such as weight loss, smoking cessation, dietary changes, and physical activity should be cornerstones in management of people with psoriasis with or without comorbidities.

Pathogenesis

Heritability, genetics and inflammation

Reports of family clustering of psoriasis, i.e. the observation that patients often have multiple family members with the same condition, dates back to the late nineteen-thirties,[5] and this phenomenon suggest that psoriasis has substantial genetic contributions. Indeed, studies have shown a considerably increased risk of psoriasis in patients with one or more family members already affected by psoriasis.[6] Moreover, twin-studies have found greater concordance in monozygotic than in dizygotic twins, with genetic factors explaining up to two thirds of the variance in psoriasis susceptibility, and environmental factors believed to account for the remaining variation.[7] The almost exponentially decreasing cost of genome sequencing, have led to millions of genomes being sequenced, and at present day multiple psoriasis risk loci have been identified.[8-11] Psoriasis has repeatedly and consistently been associated with the major histocompatibility complex human leukocyte antigen (HLA), class I, Cw6 (HLA-Cw6), and more than half of all patients with psoriasis display HLA-Cw*0602, i.e. the major risk gene on psoriasis susceptibility locus 1, which is associated with a 20-fold increased risk of psoriasis.[12-14] Moreover, the presence of HLA-Cw*0602 has been linked to early disease onset and with a more severe disease course.[14,15] However, other culprits have also been identified through genome-wide association studies, e.g. the interleukin (IL)-23 pathway.[16] The complexity of psoriasis is further exemplified by recent experimental data suggesting that psoriasis may in fact be an autoimmune condition, although this remains debated.[17-19] Importantly, while psoriasis was previously considered to be a Th1 cell driven disease, the discovery of IL-17-producing cells, e.g. Th17 cells, as the major drivers of the inflammatory response in psoriasis has deepened the immunological understanding of psoriasis and led to new therapeutic targets.[16,20-22]

Environmental triggers

Endogenous risk factors aside, while genes may be inherited, so can lifestyle. Indeed, a number of environmental risk factors, including distinct lifestyle characteristics have been associated with future development of psoriasis.[23,24] For example, smoking, obesity, and stressful life events have all been linked to development or exacerbation of psoriasis.[23-25] Whether alcohol consumptions is a risk factor for psoriasis

remains controversial,[26-29] however, the association between external factors such as physical trauma (i.e. the Koebner phenomenon) and subsequent onset or worsening of psoriasis remains well-established. Along these lines, one of the most consistent environmental psoriasis risk factors is streptococcal or viral infections, e.g. tonsillitis or pharyngitis, following which patients may develop guttate psoriasis. Indeed, since pharyngeal tonsillitis is one of the most common upper respiratory tract infections and since HLA-Cw*0602 has been associated with streptococcal infections, tonsillectomy have been put forward as a potential treatment for some patients with psoriasis.[30-32] Collectively, a number of internal and external factors are involved in the start and upkeep of the inflammatory response in psoriasis, and the disease thus remains multifactorial in nature.

Epidemiology

Incidence and prevalence

The incidence and prevalence of psoriasis has been a topic of intense research. Psoriasis is generally considered to affect men and women equally, and may be present in all ethnicities. While psoriasis can occur at any age and although the prevalence is roughly linear over the life course,[33] the disease onset is traditionally described with bimodal incidence peaks between ages of 16-22 and 57-60, respectively.[13] The disease is considered lifelong, although extended periods of disease-free remission may occur. Estimates of the prevalence of psoriasis have ranged from 0.09% to 11.4%.[34,35] Such differences may in part be attributable to diagnostic research methods, and although the prevalence in developed countries is generally considered to be between 1.5% to 5%,[36] studies from the Nordic countries suggests that the prevalence may in fact be increasing.[35]

Exact incidence estimates are difficult to ascertain, especially from routinely collected administrative healthcare data, since patients may not seek treatment for their psoriasis and thus the diagnosis may be delayed for several years or even decades. Population-based data from general practitioners in the United Kingdom have suggested a stable incidence but an increasing prevalence of psoriasis.[37] The highest reported prevalence has been found in Norway,[35] based on questionnaire-based data. Although such data may capture

undiagnosed psoriasis cases in patients not seeking medical treatment, misclassification of other skin diseases remains a risk in such studies. Nonetheless, since Nordic countries generally have produced higher psoriasis prevalence estimates, correlations between geographical latitude and psoriasis incidence and prevalence have been suggested,[37] however this remains debated.[38-40]

Severity of psoriasis

Several classifications have been used for psoriasis severity assessment, the most common being the percentage of affected Body Surface Area (BSA), the Psoriasis Area and Severity Index (PASI), or the Physician Global Assessment (PGA) scale. From the patients' perspective, severity of their psoriasis may be assessed as the impact on quality of life, using the Dermatology Life Quality Index (DLQI).

The BSA is a relatively easy method for severity assessment and may be applied by physicians without formal training in dermatology, and even by the patients themselves, to obtain an objective and reproducible severity estimate for skin diseases. Indeed, self-reported BSA has been show to accurately reflect BSA assessed by a physician.[41] However, assessment using the BSA may be challenging e.g. in patients with widespread small plaques as seen with guttate psoriasis. Moreover, this method does not consider differences in plaque quality, e.g. fine thin plaques as opposed to thick and very scaly plaques. On the other hand, PASI is an index (from 0 to 72) which incorporates qualitative aspects (erythema, infiltration, and desquamation) of the plaques in a weighted score based on the extent of skin involvement in four different anatomical regions (face, trunk, arms, and legs, respectively). While the qualitative assessment aspects of PASI may provide some benefits over BSA in objective estimation of psoriasis severity, PASI provides very little discriminative value among patients with mild-to-moderate psoriasis, or in those with predominantly palmoplantar, scalp or genital involvement, and the use in such patients can therefore be problematic. Similarly, in PASI, erythema, infiltration and desquamation are all weighted equally, and while erythema may present differently with varying skin types, assessment of infiltration and desquamation may be perceived differently based whether the patient has showered and/or used moisturizer shortly prior to PASI evaluation. As a scale from zero, where there are no signs of psoriasis (but where post-inflammatory discoloration may still be present) to four, with very marked plaque elevation, scaling, and erythema, the

PGA is quick and easy to use, but provides very little granularity as it is limited to only five categories. Importantly, while different objective severity estimates may describe the visible psoriasis severity, these estimates may not necessarily correlate with the magnitude of systemic inflammation. Furthermore, measures such as BSA, PASI, and PGA can provide useful and objective evaluations of psoriasis severity based on the visual extent and distribution of the disease but may fail to adequately describe the direct impact of psoriasis on the individual patient. Indeed, even if the area of involvement is very limited, psoriasis can be located in places that are either very difficult to treat (e.g. scalp and nails), provide physical or emotional discomfort (e.g. psoriasis on the hands, feet, ears, or genitals), or in highly visible places (e.g. the face). Such parameters are not adequately captured in the aforementioned severity measurements but may be better assessed using patient reported evaluations such as the DLQI.

In large-scale observational studies such as those that use routinely collected data from administrative healthcare systems, objective psoriasis severity measures such as PASI or BSA are rarely available. Consequently, severity assessment is often based on treatment patterns, e.g. the use of systemic anti-psoriatic therapy. Indeed, it is generally accepted that patients with mild psoriasis for the most part can be managed on topical therapy alone,[33] whereas those patients who are candidates for systemic therapy may be classified as having moderate-to-severe disease.[42,43]

Regardless of severity classification method, an overwhelming number of studies that have examined associations between psoriasis and various comorbid conditions, have reported so with markedly higher estimates among patients with moderate-to-severe disease, compared with patients with mild psoriasis.[44-47]

Burden of disease

Physical and emotional impact of psoriasis

Psoriasis may confer major psychosocial disability, and the disease has a considerable negative impact on patients' quality of life. Visible psoriasis skin lesions and consequent disfigurement may itself be a psychological stressor, and may also trigger negative reactions in others thereby leading to social stigmatization of patients with psoriasis.[48,49] Along these lines, studies have found that patients with visible

psoriasis skin lesions have worse physical as well as mental health,[50,51] and presence of facial and palmar psoriasis lesions is associated with considerably increased prevalence of psychiatric disorders.[52] It is recognized that mood disorders and anxiety may not only be worsened, but also influence the development or aggravation of underlying medical conditions,[53] including psoriasis.[54] The augmented mental burden in patients with psoriasis is increasingly being recognized, and has led to examination of patient-reported outcomes in observational and clinical trials of treatments for psoriasis,[4,55] as well as population-based studies examining the psoriasis-associated risk of mental disorders, e.g. anxiety, depression, and suicidal ideation, respectively.[56-59]

Quality of life

Collectively, quality of life includes physical, emotional, social, sexual, and occupational well-being.[60] Unsurprisingly, psoriasis affects not only those aspects, but also patients' self-esteem and self-image.[61,62] Moreover, work and family life may also be affected by psoriasis, thus impairing quality of life, with the greatest psychosocial impact occurring among patients with early disease onset (typically before the age of 30).[63] Studies have found that the impact on quality of life conferred by psoriasis is greater than other chronic diseases such as cancer, diabetes, heart disease, and arthritis,[2] and since these conditions also tend to occur with a higher prevalence among patients with psoriasis,[64] this emphasizes the tremendous collective quality of life impairment that patients with psoriasis may suffer from. Since no cure currently exist, management of psoriasis should be aimed at reducing the impact of the disease on comorbidities (e.g. CVD),[65] and to minimize the impact on patients' quality of life.[66]

Physical discomfort

As much as 80% of patients with psoriasis report that psoriasis has a significant negative impact of their daily life and activities,[61,62] with disruption of daily activities occurring up to 10% of the time.[61] Moreover, pruritus occurs on a daily basis in approximately three out of four patients,[67] and scaling occurs in 94% of patients according to one survey.[61] Severity of pruritus is associated with increased levels of stress[68] and depressive symptoms.[69] In addition, oozing, bleeding and skin pain may be present in psoriasis,[61,70] and

psoriasis may affect sleep[71-74] and restrict movement e.g. when located to hands and feet,[75,76] and nail psoriasis and PsA may limit patients use of their hands for daily activities.[77]

Sexual impact

Not only may psoriasis skin lesions affect patients' self-esteem and feelings of unattractiveness, but the extent and location of these lesions e.g. in the genital area, may also significantly impair the sexual frequency and function in these patients.[78] Psoriasis negatively affects patients' wish for physical intimacy,[77] and is associated with decreased libido.[79] For example, insecurities may arise as feelings of physical unattractiveness, which occurs in as much as 75% of patients with psoriasis,[61] can lead to concerns about a potential new partners reaction to the disease. Indeed, studies have found an increased prevalence and risk of erectile dysfunction in men with psoriasis,[80,81] albeit that impaired sexual activity appears to be even more profound among women.[82] An inverse association with frequency of sexual relations is seen with psoriasis severity and symptoms such as pruritus and scaling.[79] However, data have also suggested that, in patients with psoriasis, sexual impairment is more strongly mediated by the presence of non-genital skin lesions than by genital lesions alone,[83] and that the prevalence of genital lesions is comparable among male psoriasis patients with and without erectile dysfunction.[84] However, genital involvement of psoriasis was found to significantly contribute to the variance and risk of depression.[50] Moreover, genital psoriasis is associated with feelings of stigmatization, poor quality of life, and higher levels of psychological distress.[85-87] Psoriasis lesions, especially when located to the genital regions, may include fissure, pruritus, pain, and burning sensations.[88] Although genital psoriasis may be present in 33% to 63% of patients during their life course,[89] genital involvement is not routinely discussed during clinical consultations, and clinical examination often do not include the genital region in patients with psoriasis.[86,88]

Alcohol abuse

Although the relationship between psoriasis and alcohol intake has been controversial,[90,91] some studies in recent years suggest that alcohol abuse occurs more frequently in patients with psoriasis,[92,93] and is associated with increased incidence and severity of psoriasis.[94,95] However, while research has suggested there to be no direct effects of alcohol on psoriasis plaques,[96] psoriasis patients with high alcohol intake tend

to display distinct features such as either severe skin inflammation with minimal scaling, or very hyperkeratotic lesions.[94,97] Presence of alcohol abuse may also complicate psoriasis treatment, as some therapies, e.g. methotrexate, may not be suitable, and alcoholic liver cirrhosis have been shown to exacerbate psoriasis and is associated with decreased response to therapy.[92,94,98] Moreover, abstaining from alcohol have been reported to induce disease remission, whereas relapse can be seen once alcohol consumption is resumed.[94,99]

Depression

Numerous studies have reported an increased prevalence of depression and depressive symptoms in patients with psoriasis,[56,57,59,100] even among children and adolescents.[101] Depression also occurs more often in patients with psoriasis compared with many other skin disorders.[100]

In a population-based cohort study of patients with psoriasis where patients were followed to a maximum of 20 years, 18.4% of patients developed depression, versus 14.7% among a similar group of people without psoriasis.[102] Notably, it was found that the risk of first-time depression was increased in patients with psoriasis, independent of traditional risk factors, and patients with severe disease requiring biologic therapy aged 40 to 50 appeared to have the highest risk. Indeed, this supports the notion that psoriasis itself may be an independent risk factor for depression. On the other hand, the presence of depression may increase the risk of developing psoriasis,[103,104] likely due to detrimental lifestyle and behavioral factors (e.g. smoking) or through common etiopathogenic mechanisms as suggested by the increased levels of pro-inflammatory cytokines which are found in psoriasis as well as in depression.[21,54,105-108] To further highlight the complicated relationship in managing psoriasis patients and their CVD risk factors, it has been shown that the risk of major adverse CV events is significantly increased during active episodes of depression,[109] likely reflecting the poor adherence to medical treatment as well as harmful behavioral patterns during depression. Interestingly however, while presence of PsA may be associated with a higher risk of depression in patients with psoriasis,[57,110,111] the independent effect of PsA appears to be lower than that of cutaneous psoriasis.[102]

Anxiety

Studies have reported an increased prevalence of anxiety among patients with psoriasis, albeit that the relationship is less well-established than for depression. Estimates have ranged from less than 2% to more than 20%, dependent on diagnostic method and study composition.[112,113] In contrast with many other comorbid conditions, the relationship between psoriasis and anxiety have not been correlated with severity of psoriasis, as most but not all studies have reported a similar anxiety prevalence among patients with mild and severe psoriasis.[59,100,112] Interestingly, among patients with psoriasis, presence of PsA is associated with a higher prevalence of depression and anxiety compared with psoriasis alone.[111]

Suicidality

Depression, anxiety and generally impaired quality of life may lead to suicidal thoughts and behavior. Several studies have reported increased suicidal ideation among patients with psoriasis, but whether the risk of completed suicide is increased in psoriasis patients remains a controversial issue. The topic has been extensively investigated, but data remain conflicting. For example, while one study from the United Kingdom found a 72% increased risk of suicidality among psoriasis patients,[59] another study using the same data sources and an overlapping time frame could not replicate this finding.[114] In support of the latter study, the risk of suicide was assessed in Danish patients with psoriasis. While self-harm and suicide attempts occurred more frequently among psoriasis patients, the risk of completed suicide was not increased.[58] This is further supported by epidemiological data from the United States again failing to associate psoriasis with increased suicide risk.[57] Taken together, most data suggest that psoriasis impair quality of life and increases the risk of depression and possibly suicidal ideation, but not suicide.

Medical comorbidity

Prevalence of major medical comorbidity is higher in patients with psoriasis than in subjects without psoriasis.[64] While it may tempting to speculate that increased medical scrutiny due to frequent contacts with the health care system could explain some of these findings, studies have also found that the prevalence and

risk of medical comorbidities is markedly increased in patients with psoriasis compared with other inflammatory skin diseases such as atopic dermatitis.[44]

Psoriatic arthritis

The cooccurrence of psoriasis and arthritis was first described in 1822 by the French dermatologist Jean-Louis Alibert, whereas the term "arthritic psoriasis" coined by the French physician Pierre Bazin in 1860. In 1964, PsA was classified by the American College of Rheumatology as a distinct disease entity separate from rheumatoid arthritis.[115] The classical features of PsA were first described in 1973 by Moll and Wright,[116] and were formalized into the Classification Criteria for Psoriatic Arthritis (CASPAR criteria) in 2006.[117]

The disease is classified as a seronegative spondyloarthropathy due to the frequent presence of spondylitis, which is found in as much as 42% of patients according to some studies.[118] PsA is now considered one of the most frequent comorbidities in patients with psoriasis. On a population level, the incidence of diagnosed PsA is increasing, which may reflect increased symptom awareness by patients and physicians.[119] While wide variation in prevalence estimates have been reported, e.g. due to geographical region, approximately one in every five patients with psoriasis will develop PsA, with onset occurring on average 5 to 10 years after development of psoriasis. In Denmark specifically, the prevalence of PsA among psoriasis patients is estimated to be 24.1%.[120] Men and women with psoriasis appear to be affected equally frequent, and as with other comorbidities, PsA prevalence appears to be lower in patients with mild psoriasis (15.5%) and higher in patients with severe psoriasis (24.6%).[120] The prevalence among children with psoriasis is markedly lower (3.3%),[102] among whom the age of onset peaks between 11 and 12 years.[121] However, it has been suggested that 15% of patients with psoriasis may have undiagnosed PsA.[122] Currently, no specific biomarkers for PsA exist, and the diagnosis is therefore based on clinical symptoms and imaging findings. While the onset of PsA has classically been described to occur several years after onset of psoriasis, this may at least in part be due to some physician's reluctance to formally diagnose a patient with PsA without the presence of current psoriasis skin lesions or a history hereof.

Obesity

Numerous studies have reported an increased prevalence of obesity among patients with psoriasis.[123] One meta-analysis of 16 observational studies assessed the association between psoriasis and obesity, and found a pooled OR of 1.66.[123] Indeed, in one study[42] of Danish patients with psoriasis referred to an academic hospital dermatology clinic, the mean (standard deviation [SD]) BMI was 25.3 (4.7) for patients with mild psoriasis (i.e. those receiving topical treatment) and 27.8 (6.3) for patients with moderate psoriasis (i.e. those receiving systemic non-biologic therapy). Correspondingly, mean body weight was 78.0 kg (SD 15.8) for mild, and 83.2 kg (SD 20.1) for moderate psoriasis, respectively, whereas the mean body weight among patients with severe psoriasis (at time of initiation of biologic therapy) was 88.6 kg (SD 21.1).[124] Along these lines, one study from the UK found a positive disease-severity dependent association between affected BSA and obesity.[125] Interestingly, data suggest that obesity is an independent risk factor for development of psoriasis,[25,126,127] in a BMI-dependent manner.[128] Notably, obesity is a predictor for poor response to psoriasis treatment.[129] While obesity may increase the risk of psoriasis, weight loss may favorably affect psoriasis severity,[130] and successful weight loss may lead to long-term maintained PASI reductions.[131] Indeed, one population-based Danish study of 13,435 patients undergoing bariatric surgery found a decreased risk of psoriasis and PsA development, and an improved psoriasis prognosis following gastric bypass surgery.[132] Such favorable impact on psoriasis development and prognosis have also been reported in other Scandinavian countries[133] and around the world.[134]

Dyslipidemia

Dyslipidemia, an undisputed CV risk factor, is a collective term for abnormalities in either plasma lipid levels or composition.[135,136] It is well-established that reductions in high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol levels, respectively, occur in patients with immune-mediated inflammatory conditions, likely due to cytokine-induced activation of the reticuloendothelial system.[137] Notably however, even around the time of incident disease onset, patients with psoriasis display an abnormal lipoprotein composition, including increased very low density lipoprotein (VLDL) and elevated HDL

cholesterol fractions compared to patients without psoriasis.[138] While this could argue for a genetic predisposition for CVD and CV risk factors in patients with psoriasis,[139] this may also in part be explained by the aforementioned association between obesity (and a thereto related detrimental lifestyle) and risk of psoriasis. Moreover, several of the drugs which are commonly prescribed for psoriasis, including cyclosporine and acitretin can worsen dyslipidemia.[140] Nonetheless, the relationship between psoriasis and dyslipidemia remains complex, as proinflammatory cytokines including IL-1, IL-6, and TNF-α may affect hepatocyte activity as well as the function of smooth muscle cells in the arterial walls, thus conferring an altered lipoprotein composition.[141] Furthermore, an inverse correlation have been made between psoriasis severity and HDL cholesterol efflux capacity, which has been suggested as a better predictor of CV risk than HDL concentrations.[142]

Hypertension

The prevalence of hypertension is higher in patients with psoriasis compared to patients with other skin diseases such as AD,[44] and compared to the general population in some but not all studies.[143,144] One systematic review and meta-analysis previously reported a pooled OR of 1.58 (95% CI 1.42-1.76) for the association between psoriasis and co-occurring hypertension.[143] Among two prospective cohort studies, very modest increased risks of hypertension were reported in cohorts from the UK (HR 1.09, 95% CI 1.05-1.14)[145] and the US (HR 1.17, 95% CI 1.06-1.30),[146] respectively. In a Danish hospital cohort, (systolic/diastolic) blood pressure was not significantly different among patients with psoriasis (median 130/80 mmHg) when compared to a historical (unmatched) non-psoriasis general population cohort (median 130.6/81.9 mmHg).[144] Interestingly however, in a cohort of Danish psoriasis patients treated with biologics, mean (systolic/diastolic) blood pressure was 142.8/87.1 mmHg and 145.1/86.0 mmHg at treatment initiation with secukinumab and ustekinumab, respectively.[147] More importantly however, while studies have suggested that severity of hypertension appears to correlate with psoriasis severity,[148,149] hypertension in patients with psoriasis appears to be markedly undertreated[150] and lack of hypertension control is found in a psoriasis-severity dependent manner.[149]

Metabolic syndrome

Although many definitions have been proposed,[151-153] metabolic syndrome may be used as the collective term for the concurrence of abdominal obesity, dyslipidemia, hypertension, and hyperglycemia.[153] Metabolic syndrome is a well-established and widely used predictor of future diabetes and CVD risk.[154,155] Since studies have reported an increased prevalence of these individual CV risk factors, it is unsurprising that the clustering of these conditions, i.e. metabolic syndrome, also occurs more frequently in patients with psoriasis compared with non-psoriasis individuals.[156] The prevalence of metabolic syndrome has been reported as high as 40.9% when based on clinical assessment,[157] although wide variations have been reported.[156] Of note, older as well as very recent studies have found that metabolic syndrome appears to be an issue in patients with psoriasis even among children.[158,159]

Diabetes

Observational and experimental studies have associated psoriasis with diabetes and insulin resistance. In a single-center study of 32 Danish normal glucose-tolerant patients with moderate-to-severe psoriasis, insulin sensitivity was significantly reduced compared to patients matched on age, sex, and BMI.[160] Along these lines, a similar study found a significantly reduced incretin effect and gastrointestinal-mediated glucose disposal, impaired postprandial glucose tolerance, fasting hyperinsulinaemia, and increased beta-cell secretory responses, respectively, among 12 non-obese patients with psoriasis when compared to non-psoriasis control subjects matched on age, sex, and BMI.[161,162] In support hereof, a number of studies[46,47,163] have reported an increased diabetes incidence and prevalence among patients with psoriasis. Very recently, a UK population-based study suggested a potential association between historical physician-reported BSA involvement in patients with psoriasis with future risk of diabetes.[46] Furthermore, a study of 33,588 Danish twins found a significant association between psoriasis and diabetes even after adjustment for potential confounding factors.[164] Taken together, the association between psoriasis and insulin resistance and diabetes, has by some been interpreted as that psoriasis itself may represent a pre-diabetic condition.[160-162]

Cardiovascular disease

Psoriasis is strongly associated with cardiovascular disease. In line with the abovementioned risk factors, numerous epidemiological studies have found an increased risk of myocardial infarction (MI), stroke, and death due to CVD in patients with psoriasis compared with the general population. Almost half a century ago reports of thromboembolic diseases in patients with psoriasis were published,[165] and around 2004,[166] epidemiological data on CV mortality in inpatients with psoriasis emerged, leading to increased investigations of the CVD risk among people with psoriasis. Throughout numerous investigations, the most consistent association has been observed for MI, where most studies have concluded that psoriasis itself may represent an independent risk factor. However, a fundamental limitation of such large-scale epidemiological studies is the lack of detailed information on CV risk factors. Most notably, data on physical activity are rarely captured, and residual confounding must always be kept in mind when assessing the 'independent' risk of MI and other CV endpoints in psoriasis studies. Nonetheless, advanced imaging studies have demonstrated increased vascular inflammation in patients with psoriasis, suggesting that systemic inflammation and duration hereof, may also play a role.[167] Indeed, a noticeable number of publication in recent years have focused on whether treating psoriasis with systemic therapy may decrease this systemic inflammation and in turn reduce the future MI risk in these patients.[168-172] In this regard, studies have been conflicting, as observational studies consistently suggest a CV-protective effect of systemic (especially biologic) treatments whereas large-scale clinical and experimental studies have yielded somewhat opposing findings. For example, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) examined the effect of targeted IL-1β inhibition in 10,061 individuals followed for a median of 3.7 years.[173] The study found that reduction in inflammation with canakinumab (which does not significantly alter lipid levels) was associated with a statistically significant, albeit clinically modest, reduction in future CV events. Thereby, CANTOS provided irrefutable evidence that dampening of inflammation, through selected cytokine signaling pathways, may reduce CV risk, but also provide mechanistic evidence to support that chronic low-grade inflammation as seen e.g. in psoriasis, may be an independent risk factor for CVD.[174] Again, however, it is important to consider the absolute effect size, and whether such findings are of academic rather than

clinical importance. For example, the Cardiovascular Inflammation Reduction Trial (CIRT) demonstrated that weekly treatment with 15-20mg of methotrexate (which works on the same inflammatory pathway as canakinumab) had no effect in reducing future CV events among 4,786 high-risk patients.[175] Moreover, targeted and potent anti-psoriatic biologics such as TNF inhibitors, have generally shown no or only very modest effect of vascular inflammation and other CV risk markers.[170-172]

Inflammatory bowel disease

The proclamation that "all the diseases begin in the gut" and "death sits in the bowels" was made by Hippocrates and emphasize the importance of the gastrointestinal system and microbiota in the role of health and disease. In recent years, there has been an overwhelming interest in the relationship between psoriasis and gastrointestinal disorders,[176-180] in particular Crohn's disease (CD) and ulcerative colitis (UC), which together are called inflammatory bowel disease (IBD). This interest has been sparked not only due to the relatively frequent concurrence between these conditions and psoriasis, but also in light of newer psoriasis treatment modalities that may either aggravate existing IBD (or potentially induce new-onset IBD),[181,182] or be efficacious in treating both conditions.[183] In Denmark, psoriasis was associated with a significantly increased risk of new-onset CD and UC, in a psoriasis-severity dependent manner, where the highest risk was seen in patients with PsA.[180] The reasons for the apparent link between psoriasis and IBD may be multifold, including shared genetics, systemic inflammation, medication and lifestyle. For example, while the IL-23/IL-17 pathway is crucial in psoriasis, it is also involved in microbial defense and intestinal inflammation in IBD.[21,184] Notably, while reduction of IL-17 has noticeable benefits in psoriasis treatment, this may weaken the intestinal epithelial barrier and in turn lead to increased gastrointestinal inflammation.[185,186] Other potential explanations may be that psoriasis and IBD share important overlaps in risk factors including genes, smoking and possibly also diet.[187] Furthermore, psoriasis have been reported as a paradoxical reaction to several treatment modalities used for IBD.[188] No matter the cause, overwhelming evidence exists for the strong relationship between psoriasis and IBD.

Other immune-mediated inflammatory diseases

Although the link between psoriasis and IBD has been highlighted, studies have shown additional associations between psoriasis and a number of other immune-mediated inflammatory diseases (IMIDs).[189,190] For example, while celiac disease has been demonstrated in observational[189,191] as well as experimental studies,[192,193] the reported associations between several other conditions such as systemic lupus erythematosus, systemic sclerosis, and chronic glomerulonephritis[189] remains to be further tested in well-designed confounder-controlled studies and the potential explanatory mechanisms remain elusive. Indeed, while one study[194] found a significant association between psoriasis and rheumatoid arthritis (RA), the same study reported an OR of 33.0 (95% CI 27.1-40.3) for the association between PsA and RA, thus emphasizing the risk of diagnostic misclassification in such studies.

Methodological considerations

The present studies were epidemiological in nature, with all their inherent limitations and strengths, the most important being that observational studies can assess associations but not establish causality.

Registry studies

While epidemiological studies using routinely collected administrative data have been conducted for decades within the fields of oncology and cardiovascular medicine, registry-based dermato-epidemiology is a relatively new field in Denmark. Numerous registries exist in Denmark, most of which can be linked on an individual-level and used for research purposes. Due to the setup of the Civil Registration System,[195] Denmark provides unique opportunities for nationwide epidemiological studies, using the entire country's population as a cohort from cradle to grave with almost no loss to follow-up. Increasing requirements for registration and the introduction of harmonized coding systems have led to increasing specificity of diagnostic codes and registration procedures on a population level. Today, it is possible to link not only in- and outpatient visits, vital statistics and prescribed medication to the individual patient and to the specific

disease, but also to follow patient's disease trajectory over several decades using prospectively collected data.[194] However, important limitations of such registries also exist. As with all administrative health care systems, registration is dependent on the individual health care provider, and important behavioral and lifestyle factors are not routinely captured on a national level. Oftentimes, data may not be missing completely at random. For example, body weight, blood pressure, and smoking status may be recorded only in specialized registries of selected patients or if patients are seen in certain clinical settings where these measurements are routinely captured, and may therefore be overrepresented in "high risk" populations (e.g. patients with diabetes). Similarly, in an increasingly busy clinical setting, non-essential measurements and diagnoses may not be fully captured.

Meta-analyses

Meta-analyses, i.e. the statistical combination of data from multiple studies, enable aggregation of information from several sources, leading no only to increased statistical power, but may also allow for more robust analyses across countries and different time periods. Results from well-conducted meta-analyses are generally considered as some of the highest level of evidence, however, the quality of such studies is strongly dependent on the researcher's scrutiny and quality assessment of the studies that are included and form the source of the analyzed data. Consequently, if the included studies are either heterogenous or poorly conducted, this will diminish the value of the meta-analysis in the same way as recording errors and missing data would in registry-studies. Nonetheless, if conducted properly with application of appropriate quality assessment tools, meta-analyses may enable generalization of study results to larger populations, than what would be prudent using single-study data.

Questionnaire-based studies

Questionnaire-based studies, whether these are conducted through face-to-face interviews, over the phone, or using electronic web-based solutions, can provide unique insights into disease aspects and patient perspective that would otherwise be unavailable in register-based settings. For example, the Nord-Trøndelag Health Study (the "HUNT" study) is one of the largest population-based health examinations ever performed. Notably, such questionnaire-based data has been used in psoriasis research to establish links and

associations[24,196,197] that would be difficult to conduct using conventional administrative data. However, the quality of data, and studies derived from questionnaires are often limited by the selected study cohort, and when studies use questionnaire-based data to answer e.g. questions on skin diseases, for which the questionnaire was not initially designed to answer, this may lead to biased results. Furthermore, questionnaires may suffer from recall bias, and individuals with a certain disease may be more interested in answering a questionnaire about their particular condition than healthy individuals, thereby leading to skewed populations and result in false-high disease-prevalence estimates. The unique setup of the Danish Civil Registration System furthermore enables linkage of Danish questionnaire-based data with the individual respondent's administrative data, including medical diagnoses and treatment history. The need for more in-depth disease-specific information, together with the unique availabilities for register-based research in Denmark, led to the establishment of The Danish Skin Cohort, a prospective inception cohort nested in the Danish Civil Registration System. Initially, we identified 10,000 individuals from the general population, randomly sampled among all adults alive and resident in Denmark. Hereafter, we identified 10,000 patients with a dermatologist verified diagnosis of atopic dermatitis and psoriasis, respectively. To reduce the risk of participation bias, subjects were invited to participate without being told the specific areas in which the project was focused. Thus, patients were unaware that the data collection centered around atopic dermatitis and psoriasis, and patients were unaware that they had been selected based on their diagnosis of atopic dermatitis or psoriasis. The initial questionnaire contained information on lifestyle parameters and family history, as well as more disease-specific questions such as age of disease onset, disease location, and patient reported outcomes such as itch and pain. Collectively, this information was linked to data from the national administrative registries, thus enabling prospective data collection.

Study designs

Choice of study design is an important and often complex decision. Several considerations play into the decision including the type, quality, and completeness of the data sources. Indeed, even within administrative databases, a design that works in one country or health care system, may not be suitable to answer the same question in another setting. Moreover, the same research question may be answered using several different

study designs, each with their own advantages and limitations. The choice of the appropriate study design will most often depend on how the particular research question is stated.

Cross-sectional studies

Descriptive study designs may be useful to define certain patient or disease characteristics, e.g. the clinical features of patients with psoriasis. A defining feature of a descriptive cross-sectional study (sometimes referred to as prevalence studies) is the absence of a control group, i.e. there is only one single sample of individuals which are being investigated. Although administrative databases may enable multiple designs with already collected data, cross-sectional studies (with de novo data collection) can be completed in much shorter time than e.g. prospective cohort studies, since data are only required for a single point in time.

A characteristic of a cross-sectional study is that the study examines a representative sample (cross-section) from the population, in order to generalize the results to the entire population. Several consecutive cross-sectional studies may collectively provide information on temporal trends, e.g. changes in disease incidence and prevalence. While associations between a risk factor and an outcome (e.g. presence of psoriasis and a history of MI) can be assessed using cross-sectional data (usually presented as an OR), both the exposure and the outcome is being measured at the same time, and most often such studies cannot determine whether the exposure actually preceded the outcome.

Data obtained cross-sectionally, e.g. clinical information from the Danish Skin Cohort, may through linkage with additional registries be used as an inception cohort in future studies.

Case-control studies

As opposed to cross-sectional studies, a case-control study is traditionally divided based on the outcome, into "disease" and "no disease" groups. Such studies are particularly useful, when the outcome of interest is very rare, or to test several risk factors for as single outcome. When two or more groups within the sample of a cross-sectional study are being compared, this is considered an analytical cross-sectional study, and can thereby function as a case-control study. While case-control studies are useful to examine e.g. the exposure

to a drug among patients with and without a subsequent outcome, temporal changes and time at risk is more difficult to assess using this study design.

Cohort studies

Cohort studies offer many advantages in registry-based research. Using longitudinal data, cohort studies allows for time-to-event analysis whereby absolute risk can be quantified. This is often presented in the form of incidence rates, e.g. number of events per person per year. Cohort studies furthermore allows for adjustment of covariates that may change over time, e.g. exposure to medication, and allows for examination of several outcomes with the same exposure. However, since such studies often compares time-at-risk in two groups (e.g. exposed vs. unexposed), they are highly dependent of accurate risk-time allocation. For example, while a patient experiencing a MI will presumably have their diagnosis recorded on the date of the event, a patient may have had psoriasis for several years before they consult a physician, and the date of diagnosis may not necessarily be the date when the disease started.

Recap of studies

Prevalence of psoriasis [I]

Using cross-sectional questionnaire data from a randomly chosen population-based sample of 3,490 adults, we determined the lifetime prevalence of psoriasis in Denmark to be 7.9% (95% CI 7.0%-8.8%), and the one-year period prevalence was 5.0% (95% CI 4.4%-5.8%). The majority (221 of 275 [80.4%]) of patients reported that a physician had diagnosed their psoriasis, with 68.3% of these (151/221) being dermatologist-diagnosed. Physician-diagnosed psoriasis was slightly more common in women than men (6.8% vs. 5.7%), whereas slightly more men reported having undiagnosed psoriasis (1.8% vs. 1.4%) and more women had been diagnosed by a dermatologist (5.0% vs. 3.5%), suggesting potential gender differences in health-seeking behavior. Family history of psoriasis was reported in 13.7% of individuals without a personal history of psoriasis, whereas 44.4% of people with psoriasis had at least one family member with psoriasis.

Validation of psoriasis based on questionnaires yielded a sensitivity 78.8%-84.4%, and a specificity of 88.2%-93.6%.

Clinical characteristics of patients with psoriasis [II]

Using data from the Danish Skin Cohort, we found a bimodal peak in the age of psoriasis onset. Notably, in early-onset psoriasis the peak age for women was slightly earlier than that of men, whereas the peak incidence of late-onset was around age 50 for both men and women. The genetic allele HLA-Cw6 has firmly been associated with early onset psoriasis in numerous studies. In line with such reports, we found a striking association between having a positive family history of psoriasis (and thus a potentially higher likelihood of being HLA-Cw6 positive) and early onset psoriasis in our cohort.

Figure 1 – Age of onset of psoriasis in patients with and without a reported family history of psoriasis.

Importantly, when stratified by current disease state, patients with more severe disease tended to have early disease onset whereas more patients that were currently asymptomatic, mild, or moderate, had late onset psoriasis, suggesting that age of onset may in fact predict severity of psoriasis later in life.

In line with previous literature, we found the most frequent sites of psoriasis lesions to be the scalp and elbows, whereas other common sites included ears, back of the head, nails, buttocks, legs, and the knees. The differences in the proportion of patients with mild, moderate, and severe psoriasis having lesions in the scalp, back of head, elbows, and nails were relatively small, whereas large variations were seen e.g. in the arms, torso, legs and feet depending on psoriasis severity.

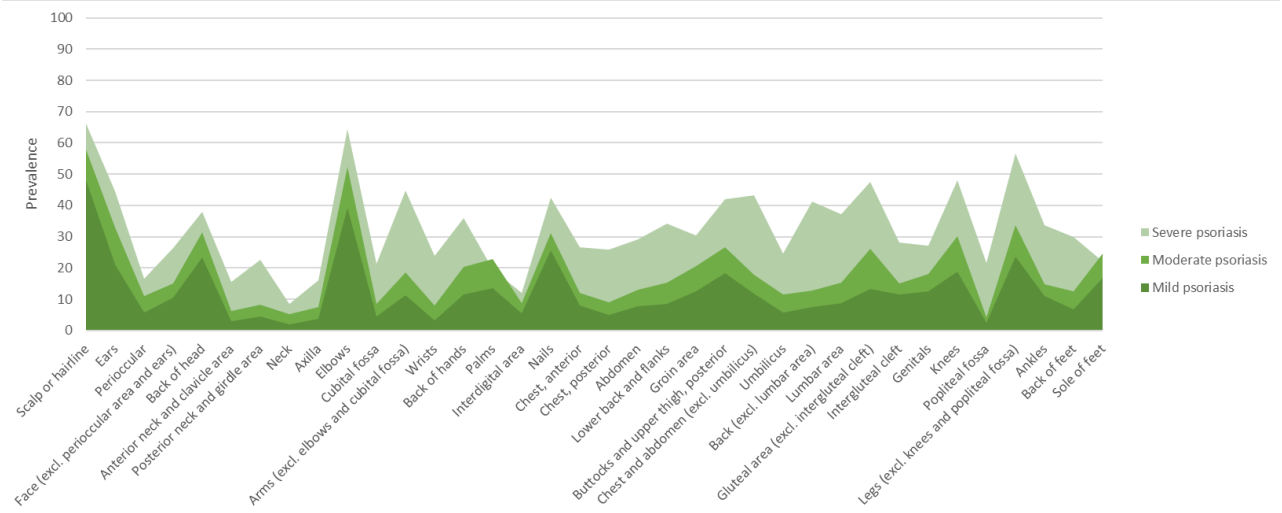

Figure 2 – Anatomical distribution of psoriasis according to current disease severity. Psoriasis severity is categorized into mild psoriasis (BSA<3), moderate psoriasis (BSA 3-9), and severe psoriasis (BSA≥10).

Notably, patients with moderate or severe psoriasis also tended to report more frequent flares compared with mild or no current psoriasis, suggesting that these patients may have a more unstable disease course. This was further substantiated by the finding many patients had extensive disease even while treated with systemic therapies, including biologics.

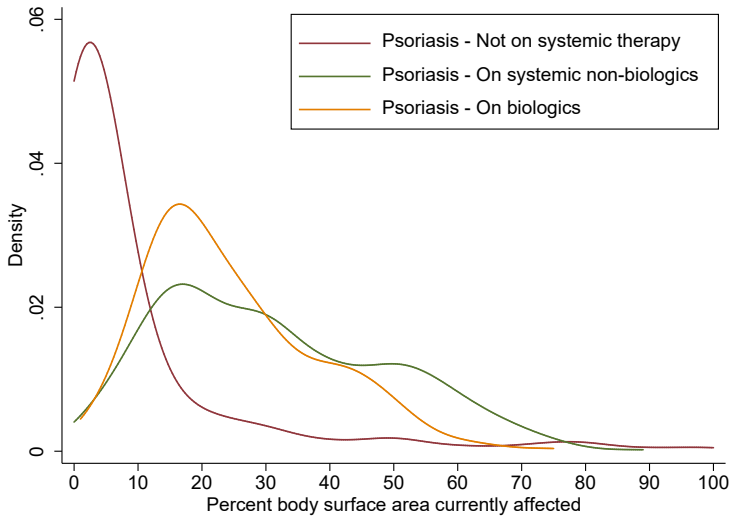

Figure 3 – Percent of body surface area currently affected by psoriasis in patients with or without systemic (or biologic) treatment

As demonstrated in studies time and time again, we found that patients with psoriasis have a greater prevalence of overweight and obesity compared with the general population. In a disease-severity dependent manner, the mean (SD) BMI was 27.1 (5.9) in people with minimal psoriasis, 27.2 (5.4) in mild psoriasis, 27.7 (6.5) in moderate psoriasis, and 28.6 (7.7) in severe psoriasis, as opposed to 26.3 (5.9) in the general population. Not only was the mean BMI higher in psoriasis patients than in the general population without psoriasis, but the prevalence of patients being moderately obese (BMI 30-35), severely obese (BMI 35-40), and very severely/morbidly obese (BMI >40) was noticeably higher in the psoriasis population. Along these lines, joint pain was noticeably higher in patients with more severe psoriasis, possibly due to a higher prevalence of subclinical or overt PsA in these patients, or due to mechanical joint stress due to increased body weight in these patients.

In addition, patients with psoriasis were found to be much less physical active compared with their healthy peers. Indeed, one-third of patients with severe psoriasis reported having a sedentary activity level, compared with only one in five of people in the general population.

Incidence and prevalence of psoriatic arthritis [III, IV]

Following full-text screening of 1,343 studies, 266 studies were meta-analyzed to obtain the prevalence of PsA among patients with psoriasis. We found wide variations in the prevalence of PsA in different geographical regions, and based on psoriasis severity, study design and study size. An almost inverse correlation was seen between the PsA prevalence and study size, possibly explained by increase symptom surveillance and scrutiny in smaller studies, whereas larger (e.g. studies utilizing administrative databases) may tend to identify only patients with symptoms severe enough for patients to seek medical advice and treatment. Overall, the global prevalence of PsA in patients with psoriasis was 19.7% (95% CI 18.5-20.9%). When limited to patients diagnosed according to CASPAR, the prevalence of PsA in psoriasis patients was found to be 23.8% (95% CI, 20.1%-27.6%).[120] In Denmark, the reported prevalence was 24.1% (9.2%-43.2%) among patients with psoriasis, and the prevalence in the overall Danish population was 0.22%.[119] Distinct differences were also found based on psoriasis severity. For example, the prevalence of PsA was 15.8% (95% CI 14.3%-17.2%) in patients with mild psoriasis, and 24.6% (95% CI 22.9%-26.4%) in patients with severe psoriasis. When systematically reviewing the published literature, the incidence of PsA ranged from 0.27 to 2.7 per 100 patients with psoriasis per year. On the other hand, using a general population sample, the incidence of psoriasis in Denmark increased substantially over a 15-year period, especially in people aged between 40-69.

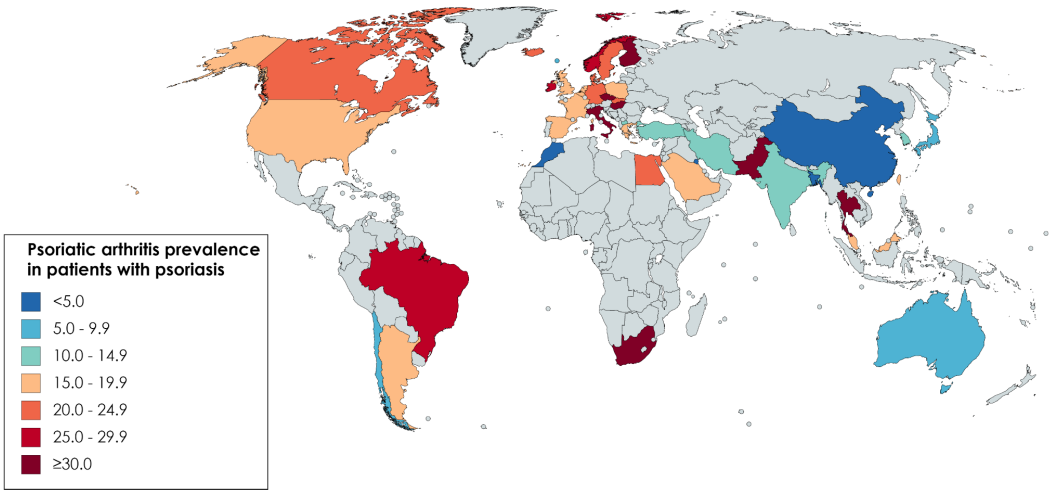

Figure 4 – Worldwide prevalence of psoriatic arthritis among patients with psoriasis

Effect of bariatric surgery on psoriasis [V]

Previous studies have suggested that weight loss may improve psoriasis symptoms and severity. Using nationwide administrative registry data, we examined 12,364 and 1,071 patients undergoing gastric bypass and gastric banding, respectively. Among these patients, we compared the incidence of psoriasis before surgery to the post-surgery incidence of psoriasis. For both procedures, three out of four patients were women, and patients were in or around their fourth decade at time of surgery. In line with previous reports, we found that patients receiving bariatric surgery with gastric bypass had a significantly reduced risk of developing first-time psoriasis (adjusted HR 0.52, 95% CI 0.33-0.81) as well as PsA (adjusted HR 0.29, 95% CI 0.12-0.71). Moreover, among patients with psoriasis, the risk of psoriasis progressing to severe disease that required treatment with systemic therapy was also significantly reduced following their gastric bypass surgery (adjusted HR 0.44, 95% CI 0.23-0.86). Interestingly, this phenomenon was not observed for patients undergoing gastric banding, a method generally associated with a much smaller weight loss than gastric bypass.

Relationship with other immune-mediated inflammatory diseases [VI, VII]

A number of IMIDs have been associated with psoriasis. Among 10,923 patients with dermatologist-verified psoriasis and 109,230 individuals without psoriasis, we examined the association and temporal relationship between psoriasis and 16 pre-specified IMIDs, including PsA. Importantly, we found that while a number of IMIDs tend to co-occur in patients with psoriasis, the majority of IMIDs occurs before the initial psoriasis diagnosis. Unsurprisingly, the strongest association was seen with PsA, which occurred more frequently after diagnosis of psoriasis (IRR 266.08, 95% CI 196.16-360.93). Although that most conditions occurred before psoriasis diagnosis, the risk of developing an additional IMID after psoriasis was increased five-fold compared with the general population (IRR 5.49, 95% CI 5.16-5.83). Moreover, the risk of developing two or more IMIDs following psoriasis diagnosis was also noticeably increased (IRR 15.06, 95% CI 11.45-19.82).

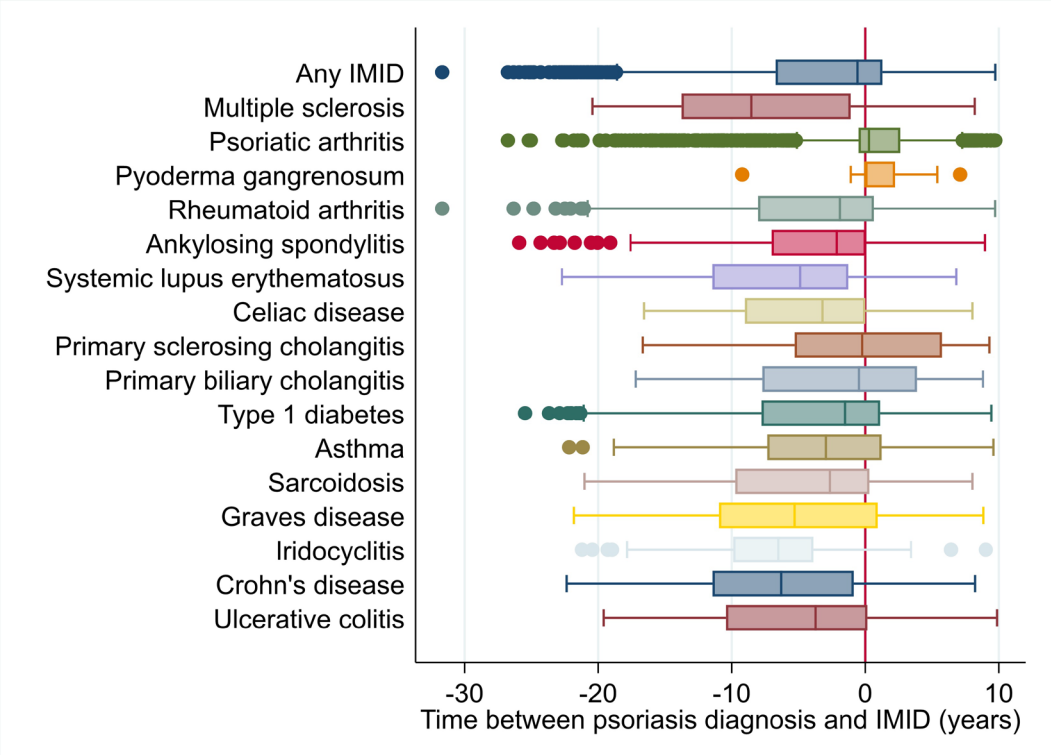

Figure 5 – The temporal relationship between different immune-mediated inflammatory diseases in relation to the time when psoriasis is first diagnosed. The box comprises the 25th and 75th percentile, and the vertical line inside the box is the median.

While CD and UC most often preceded a diagnosis of psoriasis, the incidence and risk is also significantly increased after psoriasis onset. To quantify this risk, we performed a cohort study spanning up to 20 years, to assess the incidence of CD and UC among patients with psoriasis. Psoriasis was significantly associated with risk of incident CD (HR 1.88, 95% CI 1.51-2.34) and UC (1.49, 95% CI 1.30-1.71). Interestingly, among patients with concurrent PsA, the risk of CD was noticeably higher (HR 3.10, 95% CI 1.90-5.06), whereas the risk of CD was not significantly increased in this subset of patients (1.29, 95% CI 0.85-1.98, p=0.2341). Notably however, while the prevalence of CD and UC in psoriasis remains low, considerable fluctuations in disease incidence was seen depending on age and sex. For example, the highest incidence of CD was seen among younger women with psoriasis (aged <30 years), whereas the incidence of UC was most frequent among men with psoriasis aged 30-40 years and >70 years.

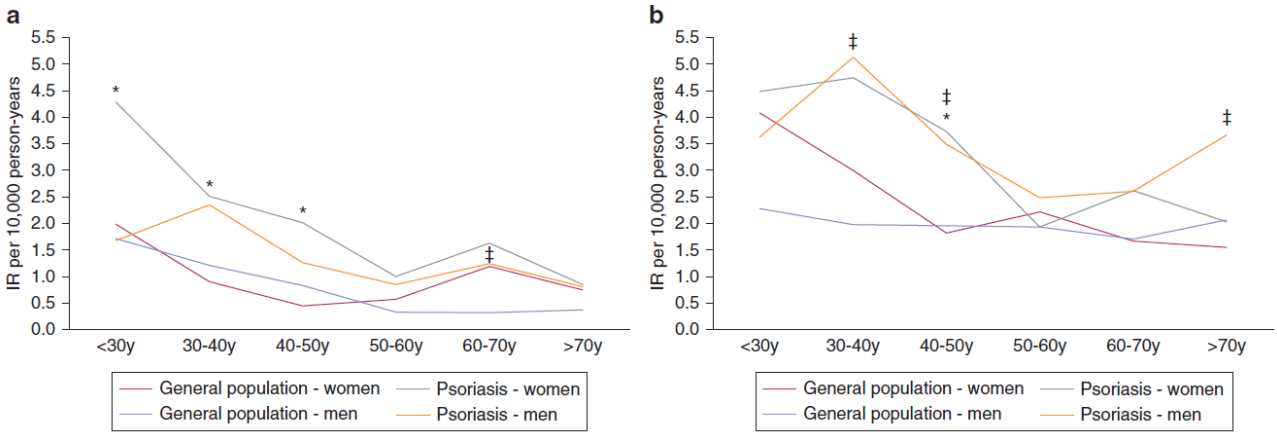

*Figure 6 – (a) Incidence of Crohn disease according to age and sex among psoriasis patients and in the general population. (b) Incidence of ulcerative colitis according to age and sex among psoriasis patients and in the general population. *Significantly higher for women with psoriasis compared with women without psoriasis. ǂSignificantly higher for men with psoriasis compared with men without psoriasis.*

Psychological and emotional burden of psoriasis [VIII, IX]

Having psoriasis considerably impairs patient's quality of life. This is evident from the DLQI score, which shows a greater DLQI impairment with increasing psoriasis severity. Importantly, in psoriasis patients without any current psoriasis lesions (i.e. a BSA of 0), the DLQI is comparable to the general population without psoriasis. Several factors may impact the DLQI in psoriasis. More extensive and widespread psoriasis is associated with increased skin pain, pruritus, and trouble sleeping, all of which may contribute to an impaired DLQI and in turn potentially lead to depression.

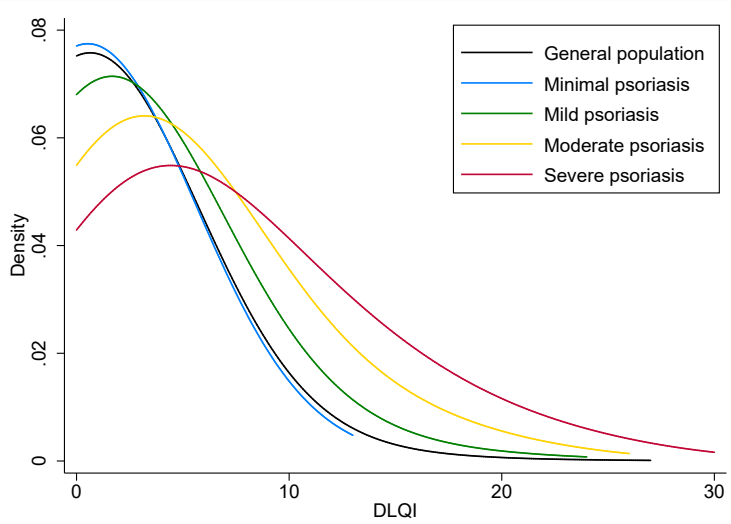

Figure 7 – DLQI scores stratified by current disease state in patients with psoriasis compared with the general population. Psoriasis severity is categorized into "minimal psoriasis" (BSA 0), mild psoriasis (BSA<3), moderate psoriasis (BSA 3-9), and severe psoriasis (BSA≥10).

Indeed, we found that, compared with the general population, patients with psoriasis had a higher risk of developing incident depression. The annual incidence of depression per 1,000 persons with psoriasis was 32.3 (95% CI 32.0-32.6) as opposed to 25.2 (95% CI 24.9-25.4) in the general population. Notably, while the risk was only marginally increased in patients with mild psoriasis, i.e. those that could be managed on topical therapy or patients treated with systemic non-biologic therapy, the risk was noticeably increased in patients requiring biologic therapy, i.e. arguably the most severe patient population. Of note, we found that female

sex, smoking, alcohol abuse, low socioeconomic status and cardiometabolic comorbidity were significant predictors of depression in psoriasis patients. Importantly however, presence of PsA only appeared to have marginal impact on the risk of depression.

Along these lines, we found an increased risk of non-fatal self-harm and suicide attempts in patients with severe psoriasis (IRR 1.69, 95% CI 1.00-2.84), albeit that the risk of completed suicide was not increased (IRR 1.00, 95% CI 0.81-1.24).[58] Importantly, out of 68,511 patients with psoriasis, only 107 completed suicides were reported, with an incidence rate of 2.42 per 10,000 psoriasis patients per year (95% CI 2.00-2.93).

Patient-perceived importance of skin clearance [X]

Cumulatively, the physiological and emotional burden of psoriasis is emphasized by the fact that patients generally report that obtaining complete or almost complete skin clearance is of major importance. Using a numeric rating scale (0 = least important, 10 = most important), psoriasis patients from the Danish Skin Cohort with mild, moderate, and severe psoriasis reported mean (SD) scores of 7.5 (3.0), 8.2 (2.5) and 8.5 (2.2), respectively, when asked to rate how important they felt it was for them to obtain almost complete skin clearance (i.e. virtually complete skin clearance). Similarly, when asked about the importance of complete (100%) skin clearance, the reported scores were 6.5 (2.9), 7.3 (2.9), and 7.9 (2.7), respectively. Increasing psoriasis severity, and involvement of specific anatomical locations (e.g. hands and feet) were significantly associated with higher need for skin clearance.

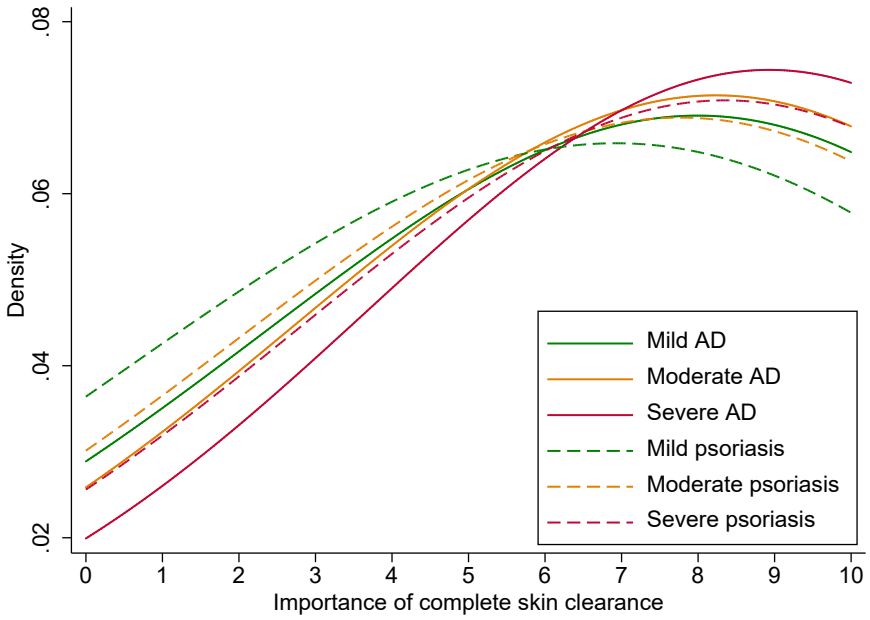

Figure 8 – Importance of complete skin clearance according to patients with psoriasis or atopic dermatitis. Patients reported their perceived importance on a numeric rating scale from 0 (least important) to 10 (most important).

Discussion

Psoriasis is a common skin disease, likely affecting more people than was previously thought. The efforts and resources that have been put into psoriasis research in recent years have expanded our knowledge and understanding of the disease considerably. Nonetheless, there remain an abundance of psoriasis research gaps, even relating to simple questions such as disease incidence and prevalence. Most published research so far has been inconsistently gathered and has predominantly consisted of data from middle-to-high income countries. Study methods may considerably affect prevalence estimates, which is evident from the almost inverse correlation between study size and PsA prevalence that has been recently reported.[120] Furthermore, prevalence estimates have been limited by the fact that although psoriasis is considered a chronic disease, the intermittent nature of the disease means that some patients may develop a single episode of manifest psoriasis in their youth and remain symptom free for several decades' hereafter. Moreover, since the extent and personal interpretation of disease impact may vary considerably, many cases may go undiagnosed for several years if patients never seek medical treatment for their disease, or, in cases where psoriasis is common in the family, patients may share topical treatments with their relatives whereby their need and incentive for consulting a physician is diminished.

The most well-established concurring disease in psoriasis is inarguably PsA. Several environmental and genetic factors have been suspected to play a role in the development of PsA. On an epidemiological level, the incidence of PsA have been increasing in the past two decades.[119] While this may in large part be explained by increased focus of PsA symptoms by patients and physicians, along with the development of improved diagnostic PsA criteria, the increasing prevalence of obesity may also play an influential role. The exact effect of adipose tissue on PsA remains unclear, but may be due to proinflammatory cytokines including TNF-α, IL-6, and leptin, which are released from the metabolically active adipose tissue and are all overexpressed in patients with PsA. In potential support of this link, weight loss is associated with reduced inflammation and less disease activity in PsA,[198] and bariatric surgery has been associated with a reduced risk of future psoriasis and PsA development.[132,199] While PsA is generally believed to occur 5-10 years after the first visible psoriasis skin lesions, a subset of patients may also experience clinical symptoms of PsA

several years before being diagnosed with psoriasis. While this may be due diagnostic uncertainty of skin lesions, or incomplete physical examination, e.g. of potential genital psoriasis lesions, this phenomenon appears to be particularly frequent among children, suggesting that this may represent a different PsA subtype similar to "early onset psoriasis". On the other hand, the latency in diagnosis of PsA among psoriasis patients may also be due to the fact that many rheumatologists may prefer to have a dermatologist verification of psoriasis to support the diagnosis of PsA as opposed to other inflammatory rheumatological diseases. This may lead to protraction of the time until the diagnosis of PsA is made.

Psoriasis skin lesions, whether located in visible places or in burdensome areas such as ears, genitals, or feet may have severe negative consequences for patients, and significantly impair their quality of life. The prevalence and risk of depression is increased among patients with psoriasis, which in turn may lead to unhealthy lifestyle, weight gain, lack of treatment adherence, and further worsening of their psoriasis. Whether psoriasis remains an independent risk factor for completed suicide remains debated, with conflicting results being reported at times even from the same country. [57-59,114,200] The detrimental effect of depression in psoriasis is exemplified by the fact that the risk of major CV events in patients with psoriasis are significantly increased during episodes of acute and chronic depression, and largely appears to normalize once patients recover from their depressive episodes.[109] Indeed, such findings should provide physicians with strong and compelling arguments for assessment of depressive symptoms and intervention or timely referral to appropriate specialists among psoriasis patients that may be at risk of depression.

Shared genetic risk loci and overlapping inflammatory pathways, together with the development of biologic therapies for both indications, have led to a surge in the interest in the psoriasis-IBD overlap. From a clinical perspective, gastroenterologists may consider psoriasis an extraintestinal manifestation of IBD, whereas dermatologists may perceive CD as psoriatic plaques in the intestines. Mechanistically, Th17 cells display different properties when located in the skin and the gut, respectively, which may explain why targeted inhibition of IL-17 in psoriasis patients with concurrent IBD may be problematic. While the onset of IBD in most cases precedes that of psoriasis, the incidence of CD and UC is also increased following the diagnosis of psoriasis. Notably, this incidence may be influenced by a variety of factors including sex, age, concurrent

PsA, and smoking status. Nonetheless, while the relative risk of e.g. CD is 3-fold increased in patients with psoriasis and concurrent PsA, in absolute numbers the risk remains very small, and CD and UC is prevalent in less than 1% of all patients with psoriasis.

For the past 2 decades, the focus on comorbidities in psoriasis have been immense, and blaming systemic inflammations for all the ills seen in psoriasis might seem tempting. It is an indisputable fact that patients with psoriasis have a greater prevalence of CV risk factors and incidence of CV disease. However, most epidemiological and experimental studies to date have failed to adjust for important risk factors, and residual confounding remains an important concern. Nonetheless, vast sums of money have been put into assessing whether the systemic inflammation is to blame for the observed associations, and in turn whether systemic treatment of psoriasis would reduce the risk of CVD in these patients. So far, the research has been conflicting at best, and experimental studies have failed to produce convincing and reproducible data to support such speculations. The reason for this may be multifold, and may at least in part be due to complications in adequately assessing vascular inflammatory changes in various parts of the body.[201] Notably, while studies like the CANTOS trial[173] supports the role of inflammation in CVD, the magnitude of the observed cardioprotective effects associated with systemic dampening of inflammation has been modest, and the clinical relevance thus remains questionable. Importantly, the enormously large randomized controlled trial investigating the potential cardioprotective effect of methotrexate in 4,786 patients (the CIRT trial) was stopped ahead of schedule, since the study failed to detect even the faintest of signals suggesting a CV benefit of reducing inflammation with methotrexate.[175]

On an epidemiological level, bias and confounding remains a major concern. As one of many examples, the risk of diabetes has been assessed in a UK cohort of 8,124 patients with psoriasis.[46] When assessed by affected BSA, patients with most severe psoriasis, i.e. a BSA of 10% or greater, had a higher risk of developing diabetes within the next four years. There are several issues with this approach. First, the severity of psoriasis was ascertained by contacting general practitioners and asking them to recall the severity of psoriasis in patients that they had seen in their practice within the last two years, which likely have led to considerable recall bias. Second, the proportion of missing data was more than 10% for many variables, and

while the study did adjust for a number of confounders (e.g. never, current, or former smoking), residual confounding due to missing key data is likely to have influenced the results. As demonstrated in a number of studies,[202,203] patients with psoriasis engage in less physical activity than their healthy peers. Indeed, even among patients with a normal BMI, and in those without joint pain or skin pain, psoriasis patients are more physically inactive in a manner correlated directly to the severity of psoriasis when assessed by current BSA. Similarly, not only is the prevalence of active smoking increased in psoriasis patients, but the number of cigarettes smoked per day is higher for patients with psoriasis. Whether alcohol consumption is a risk factor for psoriasis remains controversial and vigorously debated, however, excessive drinking has been reported to occur more frequently among patients with psoriasis than in the general population.[27-29,204] The impact and causality of such observations is further complicated by factors affecting patients' ability to consume alcohol, e.g. methotrexate, whereby the prevalence of alcohol consumption in these patients may be lower than among patients with similar severity that are not treated with methotrexate. Notwithstanding this, taken together the detrimental lifestyle observed in many psoriasis patients likely confers a considerable CVD risk and is generally not captured by most epidemiological studies. In support hereof, the "independent" effect of psoriasis on CVD risk is more or less abolished when risk estimates are adjusted for confounders such as a family history of CVD,[205] serving as a marker of lifestyle patterns. Consequently, there are overriding data to suggest that CVD among psoriasis is predominantly due to detrimental lifestyle rather than systemic inflammation. Even though systemic psoriasis-associated inflammation on a mechanistic level may cause CVD, it is likely of more academic interest rather than of major clinical relevance. Furthermore, systemic toxicity and diabetogenic effect of topical corticosteroids, a frequently used treatment modality for patients with psoriasis, remains yet another often-overlooked CVD risk factor in patients with psoriasis. Indeed, casuistic and epidemiological data supports the fact that prolonged exposure to topical corticosteroids, in particular on lesioned skin and large areas of the body, may lead to metabolic changes including diabetes.[206-208]

When reading and interpreting results of epidemiological psoriasis studies, relative risk estimates must always be seen in the context of an absolute risk. For example, although the risk of CD is increased

approximately two-fold in psoriasis compared with the general population, in absolute numbers this only translates into one additional case of CD per ten thousand psoriasis patients a year. On the other hand, overwhelming evidence exist on the high prevalence of PsA in patients with psoriasis, in whom early and aggressive treatment may possibly prevent development of irreversible joint damage. As the cumulative amounts of psoriasis research are being presented and interpreted, clinicians and researchers should always aim to balance the evidence, and not be seduced by narrative bias, i.e. the illusion of causality of events. While psoriasis and other chronic diseases are indisputably associated with other conditions, some of these incredibly rare comorbidities should be seen in the right context, and the clinical relevance should always be the main focus when drawing conclusions with direct implications for patients and their treatment. Similarly, when considering using systemic anti-psoriatic therapies as a way to reduce the burden of comorbidity (e.g. the CV risk), the number needed to treat must be balanced carefully against the number needed to harm. On the other hand, addressing frequently reported issues such as joint and skin pain, quality of life impairment, detrimental lifestyle/behavior, should be priorities in the future research and guideline developments in order to advance patient care, identify barriers to treatment adherence, and reduce the impact and burden of disease in patients with psoriasis.

Concluding remarks

Through my work in dermato-epidemiology, including the ten papers presented in this thesis, I have strived to increase the understanding and interplay between disease burden, comorbidity, and exogenous factors in patients with psoriasis as well as other inflammatory skin diseases. There remains a considerable number of unanswered research questions, and although dermato-epidemiology remains at infancy, it is time to move to more well-defined prospectively designed cohorts of deeply phenotyped patients, to improve our understanding of the natural history of psoriasis. Through increased understanding of the underlying disease mechanisms and the interaction between psoriasis and comorbid conditions, we will hopefully be able to alter the individual patient's disease trajectory going forward.

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Appendix

Papers I-X

BMJ Open

Prevalence and characteristics of psoriasis in Denmark: findings from the Danish skin cohort

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ABSTRACT

Background Wide-ranging psoriasis prevalence estimates have been reported, possibly due to methodological differences.

Objectives To assess the prevalence of psoriasis in Denmark and to validate the use of questionnaire-based data to identify patients with psoriasis.

Methods We used data from the Danish Skin Cohort, a prospective cohort comprising general population adults, as well as patients with dermatologist-verified psoriasis and atopic dermatitis, respectively. The general population cohort was interviewed to assess the psoriasis prevalence in Denmark, and validation of the questions was performed.

Results From 3490 general population participants, 7.9% (n=275) were found to have self-reported psoriasis. Of these, 221 (prevalence 6.3%) had their disease diagnosed by a physician (the dermatologist-diagnosed prevalence was 4.3%), whereas 54 (prevalence 1.6%) were not diagnosed by a physician. A total of 176 (5%) had active psoriasis within the last 12 months. More than half of patients had at least one disease flare in the last 12 months, and 44.4% of patients with psoriasis had at least one family member with psoriasis, whereas this was only the case for 13.7% of non-psoriasis individuals. Validation of the psoriasis diagnosis yielded a high sensitivity and specificity, with little incremental value of limiting diagnoses to those diagnosed by a physician.

Conclusion The lifetime-prevalence of self-reported psoriasis was found to be 7.9%, whereas the 1-year prevalence (ie, currently active psoriasis) was 5.0%. If used appropriately, questionnaire-based data may accurately identify patients with psoriasis.

Strengths and limitations of this study

- ► Studies from Scandinavian countries have reported some of the highest psoriasis prevalence estimates in the world, but wide-ranging estimates could be explained by methodological differences and unvalidated outcome definitions. We validated the use of questionnaire data for psoriasis prevalence estimation, and demonstrated a high sensitivity and specificity of patient-reported psoriasis.
- ► To reduce the chance of participation bias, subjects were not informed about the content of the research project until they had agreed to participate.
- ► Questionnaire-based studies like the present one are subject to recall bias.

INTRODUCTION

In the past decades there has been a dramatic increase in the number of studies that have investigated the epidemiology of common inflammatory skin diseases; either based on data routinely collected in clinics, observational data from administrative registries, or questionnaire-based data from general population or patient surveys.[1–6] While these studies have predominantly focused on psoriasis,[1–5] research in other skin diseases such as atopic dermatitis (AD), hidradenitis suppurativa and rosacea have also gained considerable momentum.[7–13] Previous efforts to describe the disease prevalence, comorbidities, treatment and prognosis of psoriasis have overall led to increased awareness and understanding of the disease burden, however, studies have often yielded different and even conflicting results.[14] For example, the prevalence of psoriasis has previously been assessed with great variation in Scandinavian countries, ranging from 2.2% to 11.4%.[15–18] Several reasons may exist, including disease misclassification and recall-bias in retrospective questionnaire-based studies,[19] differences in sample size, study design, as well as validity of the data and data sources. Moreover, large-scale epidemiological studies using routinely collected healthcare data often lack important information about disease-specific clinical characteristics and patient reported outcomes.

The present article describes the prevalence and clinical characteristics of patients with psoriasis, using baseline data from the Danish Skin Cohort, a prospective cohort of patients with psoriasis and AD in Denmark.

MATERIALS AND METHODS

All Danish residents have free, equal and universal healthcare access in Denmark.

This, includes general practitioners, as well as specialists in private or hospital clinics. Patients initially consult their general practitioner, and from there they can be referred to a private or hospital dermatologist if the general practitioner finds it necessary, eg, to establish a firm diagnosis or provide certain treatments, for example, phototherapy. Referral does not necessitate severe disease.

Danish skin cohort

The Danish Skin Cohort is a prospective cohort established with the aim of studying the natural history and disease course of psoriasis and AD in Denmark. The Danish Skin Cohort is composed of three independent samples. Sample A comprised randomly sampled adults (≥18 years) from the Danish general population. Sample B contained a group of adult patients with a clinical dermatologist verified diagnosis of plaque psoriasis. Sample C comprised a group of adult patients with a clinical dermatologist verified diagnosis of AD. Initially, the Civil Registration System[20] was used to randomly select 10 000 adults from the general population alive and resident in Denmark at time of cohort establishment (Sample A). The entire Danish population, aged 18 years or older, was eligible for selection. Second, the Danish National Patient Register[21] was used to identify a total of 10 000 adults with a clinician diagnosis of psoriasis (Sample B). The Danish National Patients Register contains information on all diagnoses given from public and private hospitals (including outpatient/ambulatory clinics), as well as diagnoses from a number of private practice dermatology clinics in Denmark. Patients with psoriasis were randomly selected among all patients that had at least one dermatologist diagnosis of psoriasis occurring in adulthood (ie, after their 18th birthday), regardless of whether or not this was their first-ever diagnosis. Third, a total of 10 000 adults with a clinician diagnosis of AD were identified from the Danish National Patient Register (Sample C). To qualify, patients had to have at least one diagnosis of AD verified by a dermatologist after their 18th birthday, regardless of whether or not this was their first-ever diagnosis. Importantly, to further reduce the chance of misclassification, patients with psoriasis were required to never had a recorded diagnosis of AD, and vice versa for AD patients, regardless of the type diagnosing physician. To reduce the chance of participation bias, subjects were not informed about the content of the research project until they had agreed to participate. Consequently, the invited subjects were simply informed that the project was 'Research regarding the people in the Danish population' an were thus unaware that the content related to skin diseases. Upon accepting the invitation, and throughout the study, patients had the opportunity to withdraw from participation. A total of 3490 (adult general population), 4016 (adults with psoriasis) and 3834 (adults with AD), accepted the invitation to participate in the prospective cohort.

Patient interviews

Among the 30 000 individuals that were invited to participate in the Danish Skin Cohort, those who accepted the invitation were systematically interviewed. In Denmark, all communications from the government and other official institutions are sent to a personal and secure digital mailbox, which citizens are obligated to check on a regular basis. Eligible subjects were sent an invitation to participate in the Danish Skin Cohort. In case of non-response, patients were sent a reminder after 1 week. Continued non-responders were contacted by phone or mail up to a total of five times. Subjects were interviewed in a structured manner by professional researchers over the phone, but had the option to answer the survey electronically if they preferred. Digital photographs were provided to all participants where applicable (eg, for assessment of Patient-Oriented SCORing Atopic Dermatitis. The survey was conducted between 15 May 2018 and 15 July 2018. Information on lifestyle and general health included height in cm, weight in kg, smoking history and quantity, current alcohol consumption and physical activity. Specific to skin diseases, patients were asked if they currently or at any point in time had psoriasis or AD, and if they recalled whether a dermatologist, or any other type of physician had informed them about their diagnosis, respectively. Family history of psoriasis or AD was recorded, as was information about disease activity, including number of flares in the past 12 months, measurements of the currently affected body surface area (BSA). Use of patient-reported BSA has previously been validated and shown to accurately reflect physician-reported BSA scores.[22] A flare was defined as one or more consecutive days with significant worsening of symptoms requiring escalation of treatment or seeking additional medical advice.[23] Quantitative measures of touch avoidance, skin and joint pain, as well as pruritus, was obtained using a numeric rating scale (NRS).[24–27] Information on Dermatology Life Quality Index (DLQI) was obtained regardless of whether they had ever had any skin disease.

Statistical analysis

Summary statistics were created and presented as frequencies with percentages for categorical variables and means with SDs for continuous variables. Furthermore, IQR were estimated for non-normally distributed continuous outcome variables. To validate the use of self-reported psoriasis, we calculated the sensitivity, specificity, positive and negative likelihood ratios of patient-reported psoriasis ('any psoriasis', 'physician diagnosed psoriasis' and 'dermatologist diagnosed psoriasis', respectively). As true-positive cases we used patients in the Danish Skin Cohort with dermatologist diagnosed psoriasis vulgaris (ie, the psoriasis sample), whereas patients with a dermatologist diagnosed AD (ie, the AD sample) were used as true-negative controls. By chart review of 100 patients with psoriasis and 100 patients with AD, we have previously

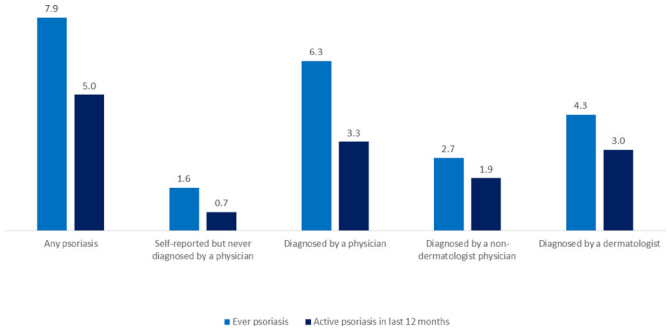

Figure 1 Prevalence of psoriasis in Denmark. Data were drawn from Sample A, that is, a general population sample of 3490 Danish adults.

validated these diagnoses with positive predictive values of 98% and 95%, respectively. Importantly, during the validation of these diagnoses, no cases of psoriasis were reported among AD patients and vice versa. Analyses were performed using Stata software V.13.0.

Patient and public involvement

Patients and or public were not involved in the design or conduct of the current study.

Data sharing

There is no plan to share raw data from this study.

RESULTS

In the following, only findings from the baseline assessment of the general population sample (Sample A) are reported. Data on the entire invited population and non-responders are provided in online supplementary table 1 . Out of a total of 3490 general population participants, 41 individuals (1.2%) were excluded from the study (values treated as missing), since they did not wish to participate after being informed that the study was focused on skin diseases. Overall, the prevalence of self-reported psoriasis (n=275) in the general population was 7.9% (95% CI 7.0% to 8.8%), with an age and sex distribution comparable to that of the general population participants without self-reported psoriasis. A total of 221 (80.4%) of psoriasis patients reported that their disease had been diagnosed by a physician (predominantly dermatologists, [151 of 221]), whereas 54 (19.6%) of the population reported having undiagnosed psoriasis, yielding a prevalence of 1.6% for undiagnosed psoriasis (figure 1). When limited to active psoriasis within the last 12 months, the prevalence of psoriasis was 5.0% (n=176). Stratified by sex, the prevalence of psoriasis was 8.2% and 7.5% among women and men, respectively. Active psoriasis within the last 12 months was reported by 5.3% of women, and 4.7% of men (figure 2).

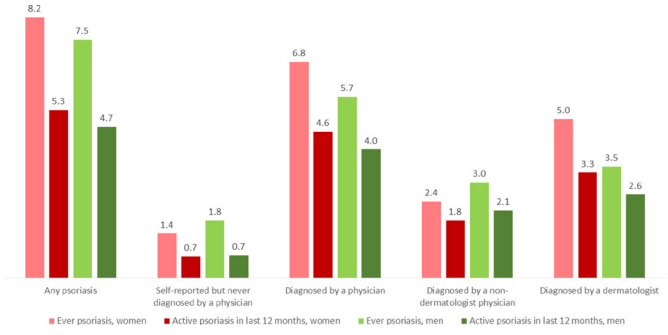

Figure 2 Sex-specific prevalence of psoriasis in Denmark. Data were drawn from Sample A, that is, a general population sample of 3490 Danish adults.

Physician diagnosed psoriasis among general population adults

Among the total 221 individuals reporting physician-diagnosed psoriasis, there was a strong female predominance (59.7%) as shown in table 1. This gender disproportionality was driven by dermatologist-diagnosed psoriasis (63.6% women vs 36.4% men) whereas the sex-distribution was equal among patients diagnosed by non-dermatologists (51.4% women vs 48.6% men). The majority of patients had mild disease (63.8%) with a current BSA less than 3. Roughly one in every 10 patients (11.8%) had severe psoriasis, ie, a BSA of 10 or greater. Of note, 46.6% reported having at least one family member with psoriasis, with 12.2% of patients having more than one family member with psoriasis. The mean (SD) DLQI was 2.3 (3.6), and the NRS score (0=no pain, 10=worst pain imaginable) for joint pain was 3.3 (2.8). One-third of patients (37.6%) reported stable disease, ie, no disease flares in the past 12 months.

Self-reported psoriasis among general population adults

Among patients responding that they had psoriasis that had never been diagnosed by a physician, there was an equal sex distribution. Interestingly, a family history of psoriasis was lower among patients with self-reported psoriasis than among dermatologist-verified psoriasis patients, although that a positive family history was still twice as frequent as in non-psoriasis individuals. In total 44.4% (n=24) of these patients reported that there had been visible psoriasis lesions within the last 12 months, and their median DLQI was 3 (IQR 1–4) versus 0 (IQR 0–1) among patients with self-reported psoriasis that did not have visible lesions within the last 12 months. Joint pain was comparable (mean NRS 3.2 vs 3.3) among patients with self-reported and physician diagnosed psoriasis, respectively. Generally, patients with self-reported psoriasis had more stable disease, ie, less disease flares, an a numerically higher occurrence of mild psoriasis, compared with physician-reported psoriasis, respectively. A list of questions obtained during the survey is shown in online Supplementary table 2 .

Validating the use of a questionnaire-based approach for identification of psoriasis

To examine the validity of questions aiming at identifying psoriasis, the dermatologist diagnosed psoriasis sample of 4016 patients (Sample B) and the dermatologist diagnosed AD sample of 3834 AD patients (Sample C) were

Table 1 Characteristics of people with psoriasis from an adult general population sample

				Physician diagnosed psoriasis		
	No psoriasis	Any psoriasis	Self-reported psoriasis	Any physician	Non-dermatologist	Dermatologist
	(n=3174)	(n=275)	(n=54)	(n=221)	(n=70)	(n=151)
Age, n (%)						
18–24 years	239 (7.5)	13 (4.7)	4 (7.4)	9 (4.1)	4 (5.7)	5 (3.3)
25–34 years	312 (9.8)	27 (9.8)	7 (13.0)	20 (9.1)	4 (5.7)	16 (10.6)
35–44 years	414 (13.0)	28 (10.2)	6 (11.1)	22 (10.0)	6 (8.6)	16 (10.6)
45–54 years	567 (17.9)	28 (10.2)	9 (16.7)	41 (18.6)	15 (21.4)	26 (17.2)
55–64 years	615 (19.4)	57 (20.7)	9 (16.7)	48 (21.7)	15 (21.4)	33 (21.9)
65–74 years	646 (20.4)	72 (26.2)	13 (24.1)	59 (26.7)	16 (22.9)	43 (28.5)
≥75 years	381 (12.0)	28 (10.2)	6 (11.1)	22 (10.0)	10 (14.3)	12 (8.0)
Sex, n (%)						
Women	1756 (55.3)	158 (57.5)	26 (48.2)	132 (59.7)	36 (51.4)	96 (63.6)
Men	1418 (44.7)	117 (42.6)	28 (51.9)	89 (40.3)	34 (48.6)	55 (36.4)
Family history of psoriasis, n (%)						
Any family member	434 (13.7)	122 (44.4)	19 (25.2)	103 (46.6)	32 (45.7)	71 (47.0)
Sibling	120 (3.8)	39 (14.6)	7 (13.7)	32 (14.8)	15 (21.7)	17 (11.5)
Mother	115 (3.7)	39 (11.2)	4 (7.8)	26 (12.0)	8 (12.6)	18 (12.2)
Father	92 (2.9)	40 (14.9)	7 (13.7)	33 (15.2)	9 (13.0)	4 (16.2)
Grandparent	63 (2.0)	35 (13.1)	2 (3.9)	33 (15.2)	5 (7.3)	28 (18.9)
Children	96 (3.1)	14 (5.2)	3 (5.9)	11 (5.1)	3 (4.4)	8 (5.4)
More than one family member	47 (1.5)	31 (11.3)	4 (7.4)	12 (12.2)	7 (10.0)	20 (13.3)
Age at psoriasis onset, mean (SD)	–	32 (21)	32 (24)	32 (20)	37 (23)	31 (20)
Flares in last 12 months, n (%)						
None	–	108 (39.3)	25 (46.3)	83 (37.6)	29 (42.4)	54 (35.8)
one flare	–	33 (12.0)	5 (9.3)	28 (12.7)	6 (8.6)	22 (14.6)
two to five flares	–	64 (23.3)	9 (16.7)	55 (24.9)	18 (25.7)	37 (24.5)
6–10 flares	–	25 (9.1)	4 (7.4)	21 (9.5)	5 (7.1)	5 (7.1)
>10 flares	–	26 (9.5)	4 (7.4)	22 (10.0)	7 (10.0)	15 (9.9)
Unknown	–	19 (6.9)	7 (13.0)	12 (5.4)	5 (7.1)	7 (4.6)
Current psoriasis severity, n (%)						
Mild psoriasis (BSA<3)	–	178 (64.7)	37 (68.5)	141 (63.8)	46 (65.7)	95 (62.9)
Moderate psoriasis (BSA 3–10)	–	53 (19.3)	7 (13.0)	46 (20.8)	11 (11.7)	35 (23.2)
Severe psoriasis (BSA>10)	–	32 (11.6)	6 (11.1)	26 (11.8)	8 (11.4)	18 (11.9)
Unknown	–	12 (4.4)	4 (7.4)	8 (3.6)	5 (7.1)	3 (2.0)
Current DLQI, mean (SD)	0.9 (2.1)	2.3 (3.7)	2.4 (4.4)	2.3 (3.6)	2.0 (3.3)	2.4 (3.7)
Joint pain (NRS 0–10) in last 7 days, mean (SD)	2.7 (2.8)	3.3 (2.8)	3.2 (3.0)	3.3 (2.8)	3.5 (2.8)	3.2 (2.8)

BSA, body surface area; DLQI, Dermatology Life Quality Index; NRS, numerical rating scale.

used. The sensitivity of patient-reported psoriasis ('Have you ever had psoriasis?') was 84.4% (95% CI 83.2% to 85.5%) and the specificity was 88.2% (95% CI 87.1% to 89.2%). Asking specifically about physician-diagnosed psoriasis ('Has a doctor ever told you that you have/had psoriasis?') yielded a comparable sensitivity and specificity (table 2). Asking patients 'Has a dermatologist ever told you that you have/had psoriasis?' yielded the a sensitivity

Table 2 Validation of the use of questionnaire-based surveys for identification of psoriasis

	Sensitivity (%)	95% CI	Specificity (%)	95% CI	LR+	95% CI	LR-	95% CI
Patient-reported psoriasis (regardless of whether or not this was diagnosed by a physician)	84.4	83.2 to 85.5	88.2	87.1 to 89.2	7.14	6.54 to 7.80	0.18	0.16 to 0.19
Patient-reported physician diagnosed psoriasis	83.3	82.2 to 84.5	91.8	90.8 to 92.6	10.11	9.08 to 11.26	0.18	0.17 to 0.20
Patient-reported dermatologist diagnosed psoriasis	78.8	77.6 to 80.10	93.6	92.8 to 94.4	12.31	10.90 to 13.91	0.23	0.21 to 0.24

True positive cases were drawn from Sample B. True negative cases were drawn from Sample C.
Sensitivity = true positive / (true positive + false negative).
Specificity = true negative / (false positive + true negative).
LR+ = sensitivity / (1 – specificity).
LR- = (1 – sensitivity) / specificity.
LR+, positive likelihood ratio; LR-, negative likelihood ratio.

of 78.8 (95% CI 77.6% to 80.1%), with a specificity of 93.6% (95% CI 92.8% to 94.4%).

DISCUSSION

In this population-based study of adult Danes, the lifetime prevalence of self-reported psoriasis was 7.9%, whereas the 1 year period prevalence of was 5.0%. The majority of patients reported one or more disease flares within the last 12 months, but the majority of patients had mild disease. Noticeable differences were seen based on diagnostic methodology (self-diagnosed, physician diagnosed or dermatologist diagnosed), yet use of a questionnaire-based approach for identification of patients with psoriasis generally yielded high sensitivity, and specificity, with little added value of limiting the question to whether psoriasis had been diagnosed by a physician or dermatologist.

In our study, there was a strong female predominance among patients reporting dermatologist-diagnosed psoriasis, whereas the male-to-female ratio was more balanced (and comparable to the general population) in the overall group of patients diagnosed solely by non-dermatologists (eg, general practitioners). Although speculative, this could be explained by differences in healthcare seeking behaviour, whereby women may be more prone to consult a physician about skin problems and furthermore request a referral to a dermatologist for treatment of their psoriasis. In agreement with our findings, a previous survey-based study examined the prevalence of psoriasis among 3471 residents in the Copenhagen between 2006–2008 using the question 'Have you ever been told by a physician that you had psoriasis?', and found a prevalence of 7.1%.[16] Interestingly, while the study did not distinguish between the type of diagnosing physician, 57% of the affirmative responders were woman, versus 55% of sampled individuals without psoriasis. In contrast, a recent European questionnaire-based study showed that overall, the same proportions of men and women with psoriasis were treated by general physicians and dermatologists.[28] However, stratification by country showed considerable differences in access to dermatologists.

Our findings in the validation study support that survey data may adequately identify adult patients with psoriasis, although that prevalence estimates may tend to slightly underestimate the true prevalence as evident by the sensitivity in our validation study. This is in stark contrast to AD, where survey-based data are generally considered inapplicable in adult population due to very high risk of misclassification.[19] Previously, registry-based studies have suggested a somewhat lower prevalence of psoriasis in Denmark and other European countries such as the UK.[15 29] While registry based studies using routinely collected administrative data may hold information on large numbers of patients, such studies most often require that patients consult their physicians in order to be accurately captured. Accordingly, such studies may tend to underestimate the true prevalence, in particular since family knowledge about psoriasis and its treatment may prevent for example, men from seeking medical help.[17] In general, questionnaire-based studies may suffer from non-response, sampling bias and misclassification leading to a false-high prevalence.

Certain strength and limitations apply to the methodology, robustness and interpretation of these data. In our study, the majority of patients reporting a history of psoriasis were diagnosed by a physician, whereas a smaller proportion reported a positive history of self-diagnosed psoriasis. Interestingly, a positive family history was more frequent in these patients than in non-psoriasis individuals, but remained conspicuously more uncommon when compared with patients with physician-diagnosed psoriasis. Indeed, this could suggest that patients with

other skin diseases may incorrectly believe that they have psoriasis. Notably, unlike for example, the USA, where advertisements with pictures of psoriasis are frequently displayed on television and in newspapers, pharmaceutical advertisements towards non-healthcare professionals are not allowed in Denmark. Thus, Danish residents may be less likely to recognize psoriasis lesions, which could potentially lead to disease misclassification if they never consult a physician about their skin condition. Our specificity estimates were calculated using a cohort of patients with AD as true-negative controls, which may slightly limit the generalisability to the general population. The Danish Skin Cohort originally had 30 000 people invited to participate, and approximately 40% of people agreed to be enrolled. This is in line with response rates from other studies, in comparable populations.[30] Importantly, our cohort was comparable to the general population in terms of baseline demographics suggesting that results may be generalisable on a national level. Furthermore, since only 1.2% of patients declined to participate, we feel fairly confident that our study was not significantly affected by participation bias (ie, patients with skin disease being more willingly to participate). Nevertheless, some degree of selection bias may have occurred, as the age and gender distribution of responders compared with invitees were marginally skewed (online supplementary table 1). Furthermore, recall bias could have affected the results, since we only surveyed adults, some may have consulted a physician in childhood due to psoriasis or not even remember it. Furthermore, patients may have received treatment for their psoriasis by their physician without the physician actually telling them that they in fact had psoriasis.

CONCLUSION

We found a life-time self-reported psoriasis prevalence of 7.9% (95% CI 7.0% to 8.8%) in Denmark, whereas the 1 year period prevalence was 5.0%. Physician-diagnosed psoriasis had a lifetime prevalence of 6.3%, and a 1 year period prevalence of 3.3%. The majority of patients had mild disease, although approximately two-thirds of patients had at least one psoriasis flare in the last 12 months. Our data showed that questionnaire-based assessment of psoriasis prevalence is a valid approach with a high sensitivity and specificity.

Contributors AE had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: AE, YMFA, JPT. Acquisition, analysis and interpretation of data: AE, YMFA, JPT. Drafting of the manuscript: AE. Critical revision of the manuscript for important intellectual content: AE, YMFA, JPT. Statistical analysis: AE. Obtained funding: None. Administrative, technical or material support: AE. Study supervision: AE. Substantial contributions to the conception or design of the work and/or to acquisition, analysis or interpretation of data for the work: AE, YMFA, JPT. Drafting the work or revising it critically for important intellectual content: AE, YMFA, JPT. Final approval of the version to be published: AE, YMFA, JPT. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: AE, YMFA, JPT.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval All relevant study approvals were obtained (ref. 2012-58-0004, j.no. VD-2018–286, I-Suite no.: 6528). Review of an ethics committee is not required in Denmark for studies not involving human tissue.

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Clinical characteristics, symptoms and burden of psoriasis and atopic dermatitis in adults

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Summary

Background There is debate as to whether psoriasis and atopic dermatitis (AD) belong to the same disease spectrum.
Objectives To describe and compare disease characteristics, lifestyle factors and disease burden in adult patients with psoriasis and AD.
Methods We linked registry data with clinical and patient-reported outcomes from the Danish Skin Cohort, containing 3348 and 3834 adults with dermatologist-verified psoriasis or AD respectively, and 2946 adults from the general population.
Results The participants were predominantly women and middle-aged. Patients with psoriasis mostly reported disease onset throughout adulthood, but with a distinct early incidence peak in those with a positive family history or severe disease. AD predominantly began in childhood, with only a very discrete incidence peak in adulthood. Scalp, extremity, chest and abdomen involvement was common to both diseases. Scalp/hairline, elbows, nails, intergluteal cleft, umbilicus, knees and legs were most frequently affected in patients with psoriasis. In AD, periocular, neck, antecubital fossae, back of the hands, interdigital areas and popliteal fossae were commonly affected. Patients with psoriasis (but not AD) were generally more overweight, obese and physically inactive, and had a positive smoking history, compared with the general population. Patients with both diseases experienced more frequent flares with increasing disease severity. Patients generally displayed uncontrolled disease despite being on systemic therapies. Itch and skin pain were much more severe in patients with AD, whereas joint pain was more common in patients with psoriasis.
Conclusions We identified important similarities and differences in the clinical characteristics of adults with psoriasis and AD; these should help clinicians to prioritize and improve patient management.

What's already known about this topic?

- Psoriasis and atopic dermatitis in adults are increasingly being compared, and there is discussion as to whether they are part of the same disease spectrum.

What does this study add?

- In this comparative study, patient-reported disease burden was markedly higher in atopic dermatitis than in psoriasis, whereas lifestyle-associated cardiometabolic risk factors were more frequent in psoriasis.
- In both disease groups, the condition in the majority of patients was uncontrolled even while they were on systemic therapy.
- The contrasting presentations highlight that these diseases are two distinct and different entities rather than belonging to the same spectrum.

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Conflicts of interest
A.E. has received research funding from Pfizer, Eli Lilly, the Danish National Psoriasis Foundation and the Kgl Hofbundtmager Aage Bang Foundation; and honoraria as a consultant and/or speaker from AbbVie, Almirall, LEO Pharma, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly and Company, Novartis, Galderma, Dermavant, Bristol-Myers Squibb and Janssen Pharmaceuticals. C.E.M.G. has received honoraria and/or research grants from AbbVie, Almirall, BMS, Celgene, Galderma, GSK, Janssen-Cilag, LEO Pharma, Lilly, Novartis, Pfizer, Sandoz, Sanofi and UCB Pharma. H.C.W. and Y.M.F.A. have no conflicts of interest to declare. J.P.T. has attended advisory boards for Sanofi-Genzyme, Union Therapeutics, AbbVie, Pfizer and Eli Lilly & Co; received speaker honoraria from LEO Pharma and Sanofi-Genzyme; and been an investigator for Sanofi-Genzyme, Eli Lilly & Co, LEO Pharma and AbbVie.

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Psoriasis and atopic dermatitis (AD) are two common chronic skin diseases.[1] With the advent of new therapies to treat psoriasis and AD, the two diseases are increasingly being discussed and presented together in publications and scientific symposia.[2–4] It has even been suggested that psoriasis and AD are part of the same disease spectrum,[5,6] the rationale being the overlap in T-cell-mediated skin and systemic inflammation that responds to cytokine-specific antagonism.

While a unifying and novel disease view may lead to a clearer understanding, it can also mask some of the key differences between psoriasis and AD. Even subtle variations in disease expression and characteristics are important in clinical work, and there is therefore an inherent risk of losing an appreciation of discriminatory differences if the perception of these two skin diseases is reduced to them simply being cutaneous inflammation. This blurring of key differences may in turn negatively affect patient management. Important differences may be obscured in further epidemiological investigations if the two diseases are lumped together.

Very few studies have described and compared the characteristics of adult patients with psoriasis and AD using the same methods.[4,7] Further study may improve the distinction of the two diseases and help to improve overall patient management, for example through better addressing of patient needs, reduction of risk factors and identification of clinically relevant comorbidities. We therefore examined and compared how clinical features were expressed in adults with psoriasis or AD.

Patients and methods

All appropriate study approvals were obtained: Danish Data Agency reference 2012-58-0004, j.no. VD-2018-286, I-Suite no. 6528; The Danish Patient Safety Authority reference 3-3013-2765/1, j.no. EMGW.

Danish Skin Cohort

The prospective Danish Skin Cohort was established to study psoriasis and AD among adults in Denmark; data collection and selection have been described in detail previously.[8] Briefly, the cohort consists of three independent samples: sample A, random adults (age ≥ 18 years) from the Danish general population; sample B, adult patients with dermatologist-verified plaque psoriasis; and sample C, adult patients with dermatologist-verified AD. Data from the Danish Skin Cohort were linked at an individual level to national databases in Denmark to obtain detailed information that included medication use,[9] socioeconomic status[10] and comorbid conditions.[11]

To obtain disease-specific data, including patient-reported outcome measures, participants were interviewed in a structured manner over the phone by professional researchers, but they could optionally complete a survey electronically. Digital photographs of skin lesions were provided to all participants, for example for assessment of Patient-Oriented Scoring Atopic Dermatitis (PO-SCORAD).[12] The survey was conducted between 15 May 2018 and 15 July 2018. Information on lifestyle and general health included height in cm, weight in kg, current alcohol use, smoking history and current use of tobacco, and levels of physical activity. All participants were interviewed about their family history of psoriasis or AD.

Disease activity and severity were recorded, including the number of self-reported flares that patients had experienced in the past 12 months. Patients' currently affected body surface area (BSA) was recorded. Use of patient-reported BSA has previously been validated and shown to reflect physician-reported BSA scores accurately.[13] Among patients with psoriasis and AD, respectively, we defined minimal or no current disease (henceforth 'minimal disease') as BSA = 0% or PO-SCORAD = 0, mild disease as BSA < 3% or PO-SCORAD 1–25, moderate disease as BSA 3–9% or PO-SCORAD 25–50, and severe disease as BSA ≥ 10% or PO-SCORAD > 50. Categorization of the current disease severity was made regardless of which treatment patients were currently receiving; however, only relatively few were on systemic therapy (including biologics), as detailed elsewhere.[14]

For both psoriasis and AD, a flare was defined as one or more consecutive days with significant worsening of symptoms requiring escalation of treatment or additional medical advice.[15] For quantitative measures such as skin pain, touch avoidance, joint pain and pruritus, we used a numerical rating scale ranging from 0 (least affected) to 10 (most highly affected).[16–18] To ensure comparability with the general population, we obtained information on Dermatology Life Quality Index (DLQI) regardless of whether participants had ever had any skin disease.

Statistical analysis

Summary statistics were created and are presented as frequencies with percentages for categorical variables and means with SDs for continuous variables. Interquartile ranges (IQRs) were estimated for non-normally distributed continuous outcome variables. Analyses were performed using SAS statistical software version 9·4 (SAS Institute Inc., Cary, NC, U.S.A.) and Stata software version 13·0 (StataCorp, College Station, TX, U.S.A.).

Results

In total of 3834 and 3348 patients with AD and psoriasis, respectively, and 2946 referents from the general population without a history of either of these diseases were included. The mean age of study participants was 58·6 ± 14·4 years for psoriasis, 48·8 ± 14·5 years for AD and 54·7 ± 17·6 years for the general population. Women were more commonly represented across all groups (Table 1).

The prevalence of physician-diagnosed asthma was 9·0% in the general population, and slightly higher among patients with psoriasis (11·9–14·6%). Among patients with AD with minimal disease (PO-SCORAD = 0) the prevalence of asthma was 21·1%, and with increasing AD severity the prevalence reached 59·4%. A strong family history was observed for both

diseases, with 25·3–55·2% of patients with AD across severities and 49·0–59·8% of patients with psoriasis reporting at least one family member (parent, sibling, grandparent or offspring) with the same disease.

Distribution and characteristics of age at disease onset

Psoriasis onset showed a bimodal age distribution, most pronounced among women, but it became less apparent when patients were categorized according to current disease severity (Fig. 1). Patients with a family history of psoriasis and more severe psoriasis displayed mostly early onset. For AD, the disease predominantly began in childhood, and only a very discrete incidence peak was observed among adult patients. Similarly to psoriasis, women with AD and those with severe disease tended to have a slightly earlier disease onset.

Anatomical localization of psoriasis and atopic dermatitis

The anatomical distribution varied markedly between psoriasis and AD, as well as across current disease severity (Fig. 2). Sites commonly affected by psoriasis included the scalp or hairline, elbows, nails, intergluteal cleft, umbilicus, knees and legs, whereas the face, neck, trunk and upper extremities were most frequently affected in AD. Overall, psoriasis tended to affect extensor areas, whereas folds and flexural areas were more commonly involved in AD. Both diseases affected the palms and dorsal hands, but AD predominantly gave interdigital lesions. Psoriasis tended to affect the soles more often than AD.

Lifestyle

Patients with AD generally had a body mass index (BMI) that was similar to or lower than in the general population (Fig. 3). Patients with psoriasis were more often overweight and obese, and this was associated with increasing psoriasis severity ($P < 0·05$ for all groups compared with the general population). Compared with the general population, the proportion of people who formerly, daily or occasionally smoked was not increased in AD, albeit that the prevalence of people who smoked daily was numerically higher among patients with severe AD (19·6% vs. 13·3%, $P = 0·11$). Across psoriasis disease severities, more patients with psoriasis currently or previously smoked ($P < 0·001$) compared with the general population.

Patients with mild and moderate AD reported slightly lower alcohol use than the general population, whereas no significant difference was observed for psoriasis overall compared with the general population. However, when patients were stratified by ever use of methotrexate, a higher proportion of patients with severe psoriasis (not treated with methotrexate) reported consumption of more than 15 units of alcohol per week, compared with the general population (Fig. S1; see Supporting Information). Physical activity among patients with AD was comparable with that in the general population, although fewer patients with mild AD had a sedentary lifestyle ($P < 0·05$). Patients with mild, moderate and severe psoriasis less often engaged in vigorous physical activity ($P < 0·05$), and those with moderate and severe psoriasis more often had a sedentary lifestyle ($P < 0·001$) compared with the general population. Limiting analyses to patients without joint pain or skin pain yielded similar findings (data not shown).

Disease burden

The frequency of disease flares in the past 12 months increased with increasing disease severity (Fig. 4). When comparing with patients with similar disease severity, we found that patients with severe AD had significantly more (median 12, IQR 7–30; $P < 0·001$) flares in the past year than patients with severe psoriasis (median 4, IQR 2–11). The median BSA was 3 (IQR 1–10) for both psoriasis and AD ($P = 0·19$). More severe disease measured by either BSA (psoriasis) or PO-SCORAD (AD) was seen among patients who were currently on systemic or biologic therapy (Fig. 4). The DLQI was higher for AD (mean 4·1 ± 4·8, median 2, IQR 1–6) than for psoriasis (mean 3·5 ± 4·7, median 2, IQR 0–5, $P < 0·05$) and increased with disease severity in both diseases. Among patients with minimal disease (for psoriasis, BSA = 0; for AD, PO-SCORAD = 0), the DLQI scores were virtually identical to those of the general population (Fig. 4).

Joint pain was significantly higher (mean 3·8 ± 3·0, $P < 0·05$) among patients with psoriasis (across all psoriasis severities, $P < 0·05$) compared with the general population (mean 2·7 ± 2·8), and increased with psoriasis severity. Joint pain was comparable between patients with AD (2·6 ± 2·8, $P = 0·08$) and the general population. However, interestingly, patients with severe AD reported higher levels of joint pain (3·9 ± 3·1, $P < 0·05$; Fig. 5) than the general population (Fig. S2; see Supporting Information), although they were significantly lower than in patients with severe psoriasis (4·6 ± 3·1, $P < 0·05$).

Symptoms such as skin pain, itch and touch avoidance were significantly worse ($P < 0·05$) in patients with AD than in patients with psoriasis, whereas no difference were seen in trouble sleeping ($P = 0·10$) between these diseases. Itch was generally higher in AD than in psoriasis, and a major proportion of patients with AD with minimal disease reported that they generally did not itch at all. While those with mild disease (especially AD) reported that itch was mostly confined to lesional skin, those with more severe disease also reported itch from uninvolved areas (Fig. S3; see Supporting Information).

Discussion

This large descriptive study identified important clinical differences and similarities between adult patients with AD and psoriasis. Our observations should serve as a guide for healthcare providers to distinguish better between patients, to prioritize and to tailor patient management.

Table 1 Characteristics of patients with psoriasis and atopic dermatitis vs. the general population

	General population (*no AD or psoriasis*)	Atopic dermatitis (*dermatologist verified*)				Psoriasis vulgaris (*dermatologist verified*)			
	(n = 2,946)	Asymptomatic (n = 261)	Mild (n = 2,126)	Moderate (n = 1,304)	Severe (n = 143)	Asymptomatic (n = 408)	Mild (n = 1,166)	Moderate (n = 851)	Severe (n = 923)
Age, mean (SD)	54·7 (17·6)	56·1 (15·9)	49·7 (14·3)	46·1 (13·7)	47·3 (15·1)	61·0 (14·5)	59·1 (13·9)	57·1 (15·9)	58·3 (14·5)
Women, n (%)	1,587 (53·9)	167 (64·0)	1,492 (70·2)	888 (68·1)	97 (67·8)	261 (64·0)	618 (53·0)	455 (53·5)	492 (53·3)
Socioeconomic status, n (%)									
Lowest	717 (24·3)	41 (15·7)	336 (15·8)	238 (18·3)	34 (23·8)	88 (21·6)	184 (15·8)	149 (17·5)	188 (20·4)
Below average	575 (19·5)	55 (21·1)	327 (15·4)	209 (16·0)	36 (25·2)	81 (19·9)	233 (20·0)	176 (20·7)	272 (29·5)
Average	604 (20·5)	40 (15·3)	399 (18·8)	260 (20·0)	27 (18·9)	67 (16·4)	255 (21·9)	189 (22·2)	201 (21·8)
Above average	530 (18·0)	58 (22·2)	480 (22·6)	296 (22·7)	24 (16·8)	87 (21·3)	249 (21·4)	194 (22·8)	153 (16·6)
Highest	520 (17·7)	67 (25·7)	584 (27·5)	301 (23·1)	22 (15·4)	85 (20·8)	245 (21·0)	143 (16·8)	109 (11·8)
Asthma, n (%)									
Physician diagnosed	266 (9·0)	55 (21·7)	676 (31·8)	648 (49·7)	85 (59·4)	54 (13·2)	139 (11·9)	105 (12·3)	135 (14·6)
Self-reported but never diagnosed	63 (2·1)	3 (1·2)	71 (3·3)	40 (3·1)	4 (2·8)	14 (3·4)	36 (3·1)	21 (2·5)	33 (3·6)
Allergic rhinitis, n (%)									
Physician diagnosed	371 (12·6)	74 (29·3)	909 (42·8)	800 (61·4)	90 (62·9)	52 (12·8)	169 (14·5)	143 (16·8)	131 (14·2)
Self-reported but never diagnosed	189 (6·4)	16 (6·3)	140 (6·6)	57 (4·4)	7 (4·9)	20 (4·9)	81 (7·0)	52 (6·1)	51 (5·5)
Family history of atopic dermatitis, n (%)									
Any family member	388 (13·2)	66 (25·3)	927 (43·6)	825 (63·3)	79 (55·2)	78 (19·1)	214 (18·4)	160 (18·8)	176 (19·1)
Sibling	90 (3·1)	20 (8·1)	328 (15·6)	287 (22·3)	33 (23·6)	22 (5·5)	65 (5·7)	40 (4·9)	50 (5·7)
Mother	31 (1·1)	8 (3·2)	199 (9·5)	208 (16·2)	16 (11·3)	10 (2·5)	19 (1·7)	30 (3·7)	39 (4·5)
Father	15 (0·5)	7 (2·8)	216 (10·3)	208 (16·2)	25 (17·6)	13 (3·2)	27 (2·4)	23 (2·8)	31 (3·5)
Grandparent	8 (0·3)	5 (2·0)	125 (6·0)	173 (13·4)	20 (14·1)	5 (1·3)	20 (1·8)	11 (1·3)	28 (3·2)
Children	266 (9·2)	37 (15·0)	423 (20·1)	321 (24·9)	28 (19·6)	42 (10·5)	105 (9·2)	72 (8·8)	79 (9·0)
More than 1 family member	21 (0·7)	11 (4·2)	287 (13·5)	289 (22·2)	28 (19·6)	11 (2·7)	20 (1·7)	15 (1·8)	40 (4·3)
Family history of psoriasis, n (%)									
Any family member	401 (13·6)	41 (15·7)	422 (19·9)	274 (21·0)	29 (20·6)	200 (49·0)	644 (55·2)	507 (59·6)	552 (59·8)
Sibling	113 (3·9)	10 (4·1)	118 (5·6)	63 (4·9)	10 (7·1)	65 (16·1)	222 (19·2)	156 (18·7)	193 (21·3)
Mother	108 (3·7)	7 (2·9)	107 (5·1)	67 (5·2)	7 (4·9)	52 (12·9)	192 (16·6)	158 (18·9)	166 (18·3)
Father	85 (2·9)	14 (5·7)	127 (6·0)	85 (6·6)	7 (4·9)	68 (16·9)	217 (18·8)	171 (20·5)	184 (20·3)
Grandparent	51 (1·8)	7 (2·9)	125 (5·9)	94 (7·3)	6 (4·2)	59 (14·6)	215 (18·6)	174 (20·8)	205 (22·6)
Children	92 (3·2)	9 (3·7)	46 (2·2)	27 (2·1)	4 (2·8)	30 (7·4)	113 (9·8)	78 (9·3)	128 (14·1)
More than 1 family member	44 (1·5)	6 (2·3)	83 (3·9)	52 (4·0)	5 (3·5)	61 (15·0)	244 (20·9)	175 (20·6)	226 (24·5)

AD, atopic dermatitis; SD, standard deviation

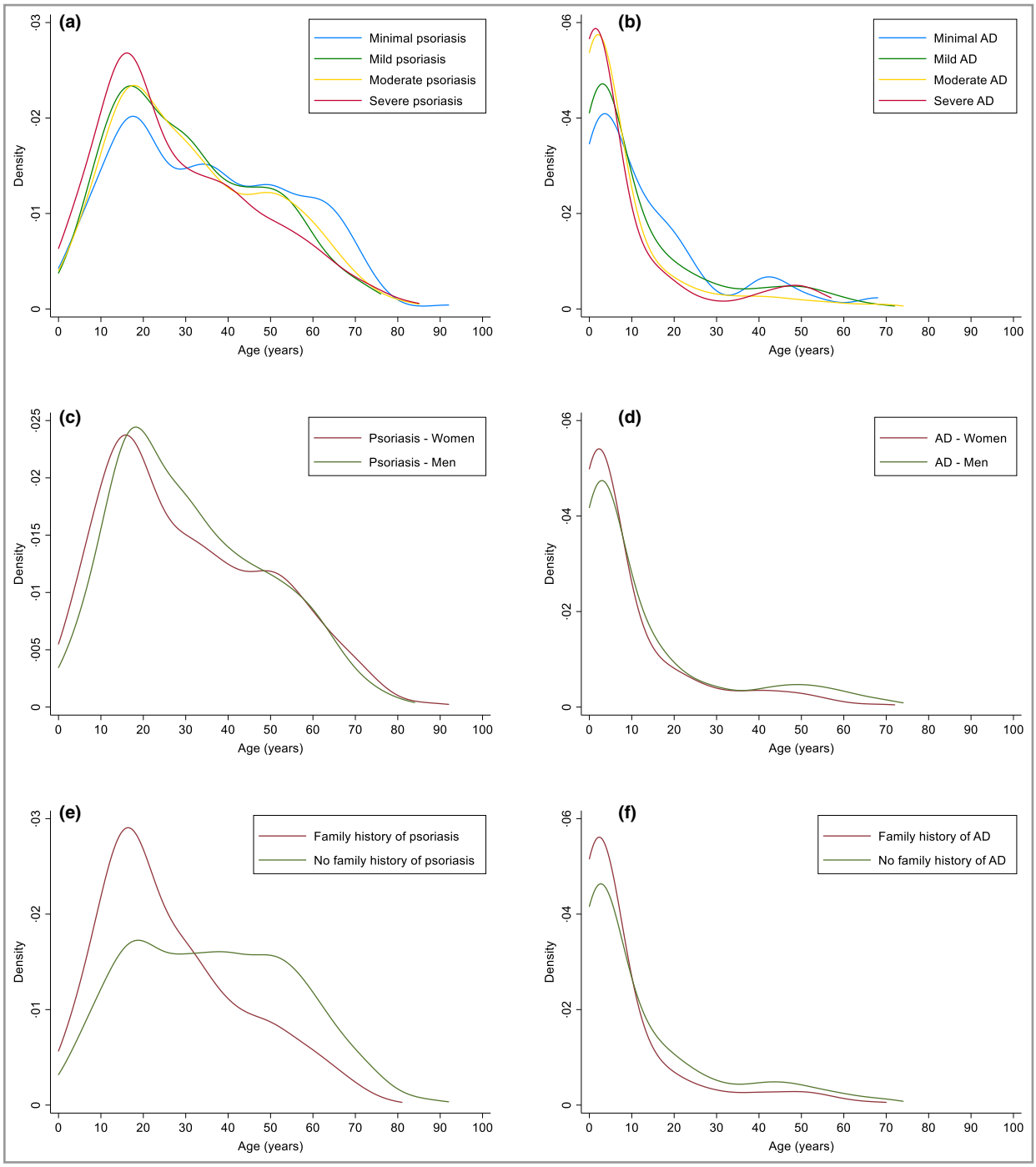

Fig 1. Age of onset among patients with psoriasis and atopic dermatitis according to (a) psoriasis severity, (b) atopic dermatitis (AD) severity, (c) sex (psoriasis), (d) sex (AD), (e) family history of psoriasis and (f) family history of AD.

While psoriasis does occur in patients of all ages, we confirmed the existence of bimodal incidence peaks for psoriasis (i.e. early- and late-onset psoriasis) and a pattern dominated by onset in early infancy and childhood for AD.[19,20] For both conditions, early onset was seen more frequently in those with severe disease. Women reported marginally earlier onset of psoriasis and AD than men. Patients with psoriasis with a family history of psoriasis had an earlier onset of disease, but this was less apparent in patients with AD. This supports the notion that early-onset psoriasis has a stronger genetic component than late-onset psoriasis.[19] Due to the different patterns of disease onset, some children with early-onset psoriasis may initially be misdiagnosed as having AD, yet our data suggest that a family history of psoriasis can help in the diagnostic work-up of children with inflammatory skin disease.

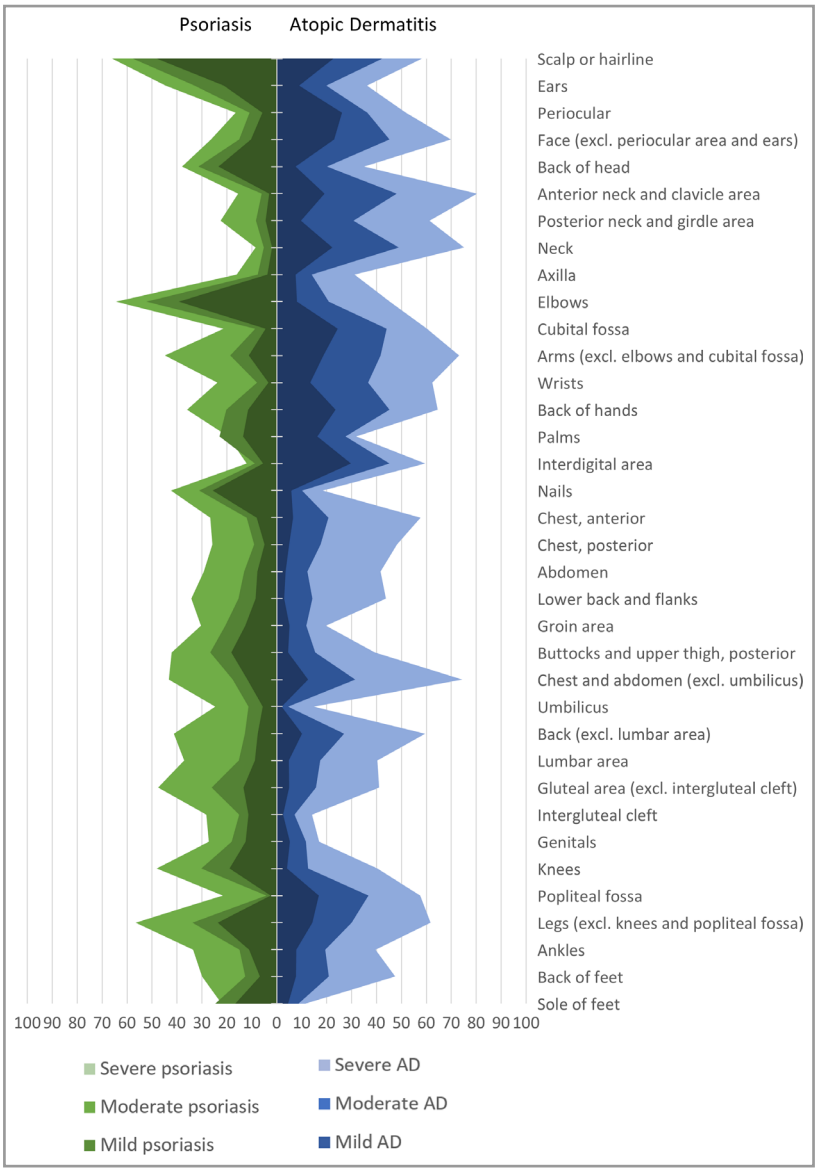

Fig 2. Anatomical distribution of psoriasis and atopic dermatitis.

Our study did not confirm the recent suggestion that late-onset AD is a common occurrence.[21,22] One valid explanation is that a significant proportion of patients with AD with 'adult-onset' AD simply do not recall having the disease in childhood.[4,23] However, it is possible that in milder AD, cases not captured by this study, adult onset can be more common. A recent Italian study showed that certain clinical characteristics are associated with adult-onset AD[22] and that it may be less atopic than childhood AD, a finding that has been replicated by others.[24,25]

Stereotypical descriptions of the anatomical distribution of psoriasis (e.g. extensor surfaces and scalp) and AD (e.g. flexural sides and face) are often applied. However, few reports provide complete and detailed mapping of the involved anatomical sites by severity. We showed that patients were affected by their skin disease in anatomical regions beyond those that are traditionally thought of in psoriasis and AD. The direct graphic comparison in Figure 2 shows that both diseases can be widespread and highlights key contrasting areas, such as the neck (more common in AD), interdigital area (more common in AD) and nails (more common in psoriasis). In patients with mild-to-moderate disease, anatomical involvement may indeed provide important clues that may serve to distinguish the two diseases. However, in patients with severe and widespread disease, it can be more difficult to rely on anatomical distribution alone, as many nonspecific areas are affected. Clinicians may here, along with other factors such as family history, use the morphology of skin lesions as clues to help establish the correct diagnosis.

In recent years, the association between major cardiometabolic comorbidity and psoriasis has to a large extent been attributed to systemic low-grade inflammation, which is present in both psoriasis and AD. While the increased

Fig 3. Prevalence of cardiometabolic risk factors in the general population, in patients with psoriasis and in patients with atopic dermatitis (AD). (a) Body mass index (BMI, in kg m^{-2}), (b) smoking, (c) leisure-time physical activity level and (d) weekly alcohol consumption in units; 1 unit = one beer (330 mL), one glass of wine (120 mL) or a single measure of spirits.

prevalence of cardiometabolic disease in psoriasis is reasonably well established, convincing data on an association between cardiometabolic disease and AD are lacking.[26] However, to date few studies have been able to adjust adequately for all appropriate cardiovascular risk factors, including smoking, physical activity and BMI. Our study showed that patients with all severities of psoriasis had a higher BMI than their healthy peers, in particular those with severe psoriasis, while the relationship in patients with AD was less clear cut. Notably, a higher proportion of patients with severe AD had BMI > 30 kg m^{-2}, but high proportions of patients with mild or moderate AD had BMI < 25 kg m^{-2}.

Self-reported sedentary lifestyle and physical inactivity were also more commonly seen in patients with psoriasis, especially those with severe disease, and even among individuals of normal weight. This is in line with previous findings, where psoriasis was less common in physically active than in non-physically active individuals, and data suggested beneficial effects of exercise on psoriasis and AD.[27,28] While this may, at least in part, be due to subjective symptoms such as worsening of pruritus following physical activity, as well as skin pain and joint pain, it is also plausible that decreased physical activity may lead to a detrimental body composition with increased adipose tissue, which in turn could lead to the initial development of psoriasis.[29] Conversely, patients with AD had similar or slightly better levels of physical activity compared with the general population, despite the common belief that patients with AD exercise less due to itch.

Patients with severe AD and psoriasis had slightly lower alcohol consumption, which may be explained by certain contraindications such as methotrexate use. This was supported by analyses restricted to severe psoriasis where, compared with the general population, higher alcohol consumption (> 15 units per week) was seen among those never treated with methotrexate, whereas this was not seen for patients treated with methotrexate. Notably, while current smoking was only marginally more frequent in patients with AD (predominantly those with severe disease) than in the general population, the vast majority of patients with psoriasis were either former or current smokers, and less than one-third of patients with psoriasis had never smoked. Our findings emphasize that such detailed information about lifestyle-related risk factors should be taken into account in future large epidemiological studies, as they represent important confounding factors when assessing causal links between inflammatory skin diseases and comorbidities. Moreover, they emphasize that clinicians should address and treat cardiometabolic risk factors in their patients.

Disease flares were frequent in patients with severe psoriasis and even more so in AD, emphasizing the highly fluctuating nature of AD. Many patients with psoriasis and AD had poor disease control despite treatment with systemic (including biologic) therapies. In both patient groups, DLQI followed a severity-dependent pattern, where patients with minimal disease had a DLQI almost identical to that of the normal population. Notably, many of these patients and general population controls did not report a DLQI of zero, despite being considered to have minimal disease. This could represent other unrelated complaints and concerns about their skin. When it was developed, the DLQI was tested not only in patients with various skin diseases, but also among healthy volunteers. Therefore, the use of the DLQI among our general population sample seems appropriate.[30]

The patient-reported outcomes regarding joint pain, skin pain, itch, sleep disturbance and touch avoidance correlated

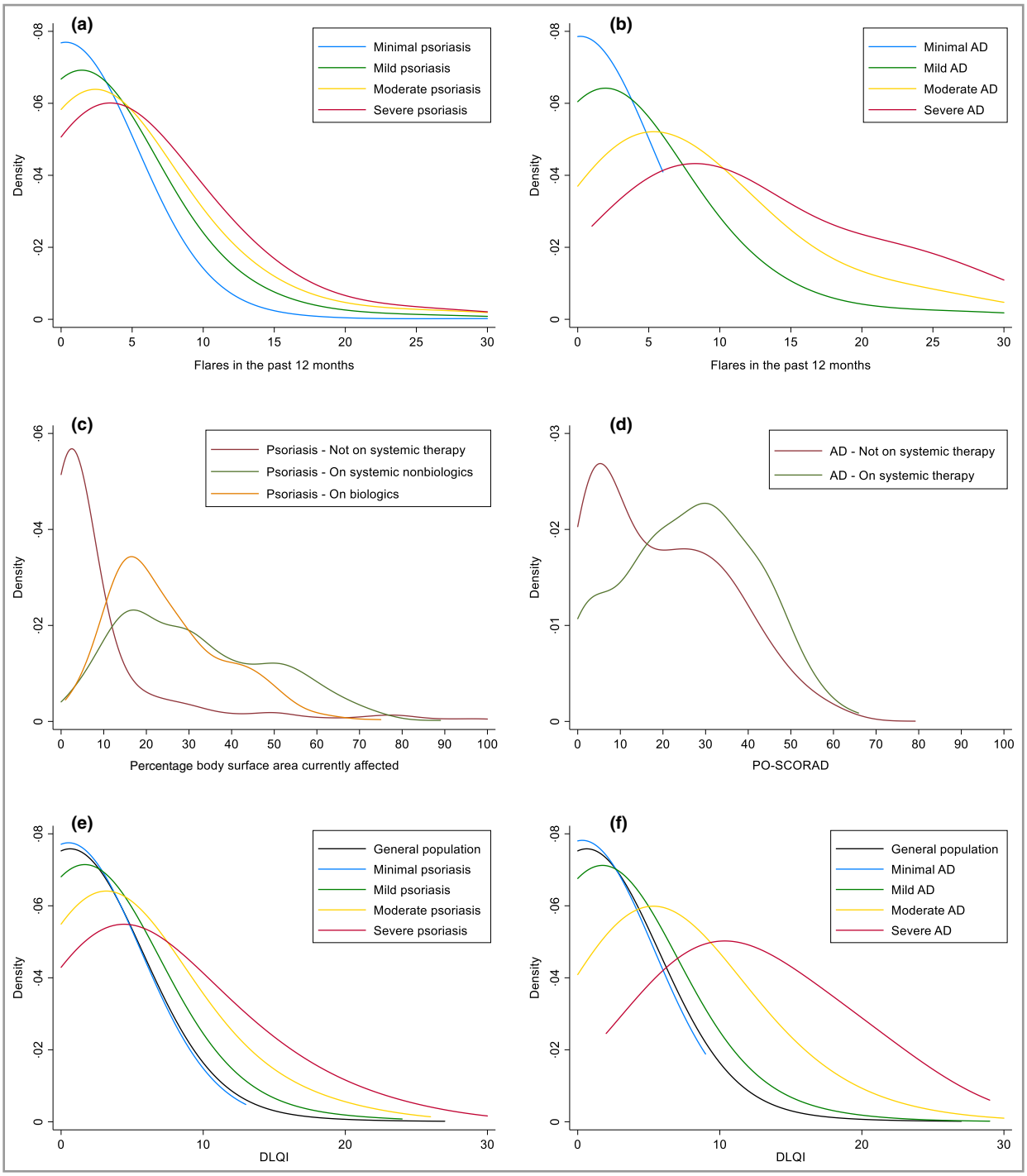

Fig 4. Disease impact among patients with psoriasis and atopic dermatitis (AD). Density plots of (a) disease flares stratified by current disease state among patients with psoriasis, (b) disease flares stratified by current disease state among patients with AD, (c) percentage of body surface area currently affected by psoriasis in patients with or without systemic (or biologic) treatment, (d) Patient-Oriented Scoring Atopic Dermatitis (PO-SCORAD) in patients with AD with or without systemic treatment, (e) Dermatology Life Quality Index (DLQI) scores stratified by current disease state in patients with psoriasis and (f) DLQI scores stratified by current disease state in patients with AD.

with disease severity in both diseases. Patients with severe AD reported noticeably worse outcomes than the psoriasis group, indicating that the burden of AD and stigmatization may be somewhat underestimated and could exceed those of psoriasis. Such observations highlight the importance of the patient's perspective when managing these chronic conditions. Importantly, while itch was located mainly on lesional skin in those with mild disease, more patients with severe AD or psoriasis also reported itch from nonlesional skin, which could indicate an underlying effect of systemic inflammation, or that the

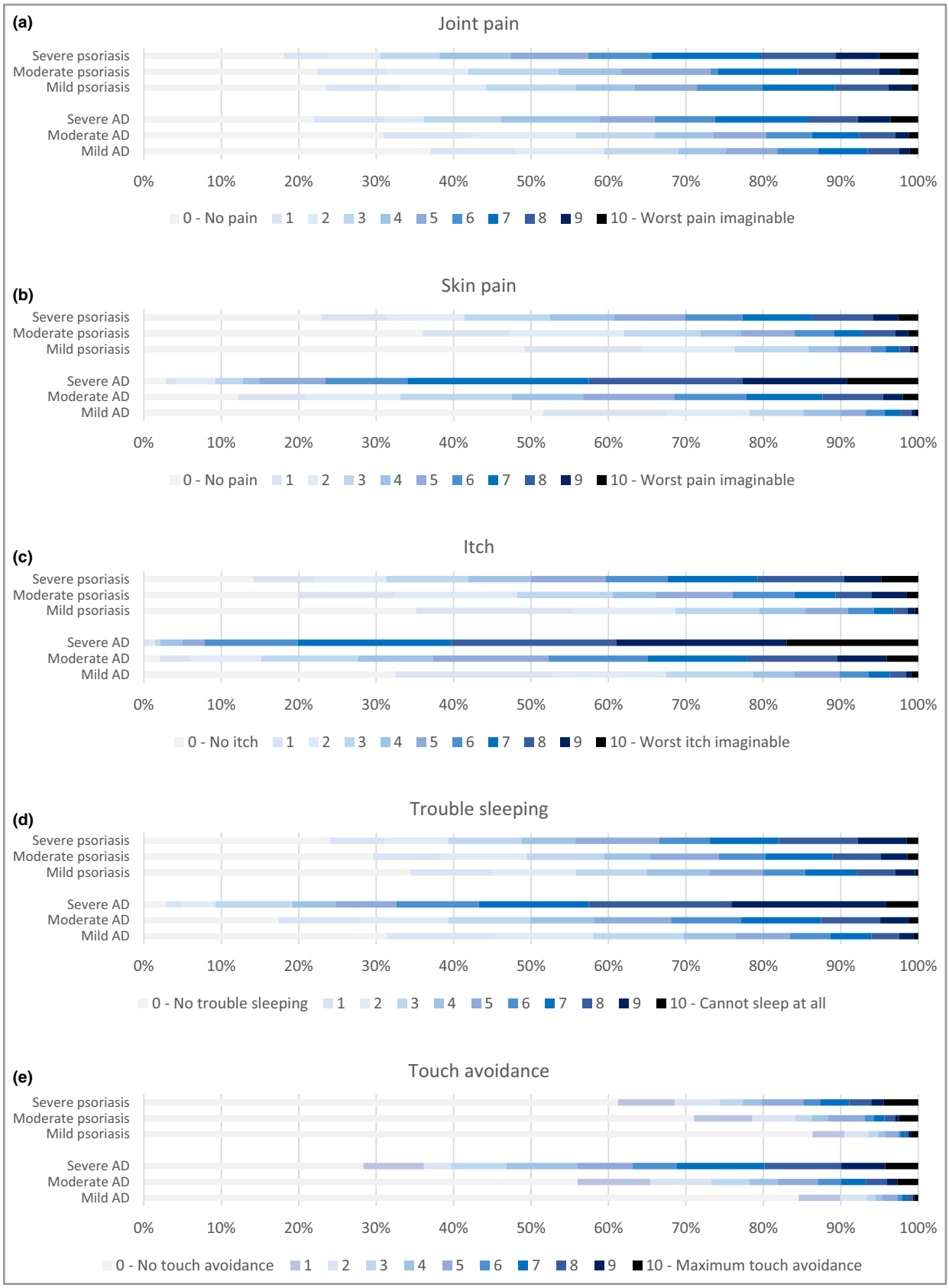

Fig 5. Patient-reported outcome measures. Data are presented on a numerical rating scale, where 0 is least affected and 10 is most greatly affected. AD, atopic dermatitis.

overall skin barrier is dysfunctional in these patients. We recently showed that particular patients with severe AD, facial AD and severe itch reported a higher need for complete skin clearance than patients with other severities of AD and psoriasis.[14]

Certain limitations and strengths warrant discussion in the present manuscript. The self-reported nature of many of the recorded variables in this study, for example alcohol consumption, may have led to reporting bias. However, this would arguably be nondifferential between psoriasis, AD and the general population. Although all patients with psoriasis or AD had their diagnosis verified by a dermatologist, reporting bias may have influenced our findings, as patients were not examined in person on the date of the survey. Furthermore, the age difference between the groups may have influenced certain outcomes, albeit that estimates such as age of disease onset were weighted according to the respondent's current age. Nonetheless, we presented unadjusted estimates for lifestyle factors such as BMI and smoking, as there is good evidence that these can be viewed as stable.[31,32]

While these data provide unique insights into many hitherto unexplored aspects of psoriasis and AD, several disease characteristics may vary over time. However, such differences would likely even out due to the large number of patients in this study. We used BSA as a severity measure for psoriasis and PO-SCORAD for AD, as these are well-established severity assessment tools for the respective diseases, although they may only capture certain aspects of the disease impact. This was evident as some patients with minimal disease appeared to experience considerable symptoms, such as flares, or report high DLQI. While assessment of AD and psoriasis by dermatologists ensured the clinical accuracy of the diagnoses, the Danish population is predominantly white, and symptoms, characteristics and patient perspectives may differ in other ethnicities and geographical regions.

Psoriasis and AD are chronic inflammatory skin diseases affecting high proportions of the global adult population. We identified important similarities and differences in clinical characteristics, which should help clinicians to interpret better the risks for presence of comorbidity, establish correct diagnoses and address patient needs. From an epidemiological and biological standpoint, psoriasis and AD do not appear to belong to the same disease spectrum, and we recommend that they are viewed as two distinct and different entities.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig S1. Weekly alcohol consumption among patients with severe psoriasis with and without methotrexate, compared with the general population.

Fig S2. Joint pain in patients with atopic dermatitis compared with the general population.

Fig S3. Localization of itch across disease severity in psoriasis and atopic dermatitis.

EXTENDED REPORT

Incidence and prevalence of psoriatic arthritis in Denmark: a nationwide register linkage study

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ABSTRACT

Objectives To examine the incidence and temporal trends of psoriatic arthritis (PsA) in the general population in Denmark.

Methods Using nationwide registry data, we estimated the number of patients with incident PsA within each 1-year period between 1997 and 2011 and calculated the rate of PsA cases within gender and age subgroups. Incidence rates were presented per 100 000 person-years.

Results There was a female predominance ranging from 50.3% (1998) to 59.2% (2010), and the mean age at time of diagnosis was 47–50 years. We identified a total of 12 719 patients with PsA (prevalence=0.22%), including 9034 patients where the PsA diagnosis was made by a rheumatologist (prevalence=0.16%). Incidence rates of PsA (per 100 000 person-years) increased from 7.3 in 1997 to a peak incidence of 27.3 in 2010. Incidence rates were highest for women and patients aged 50–59 years, respectively. The use of systemic non-biologic agents, that is, methotrexate, leflunomide, ciclosporin or sulfasalazine increased over the 15-year study course and were used in 66.3% of all patients. Biologic agents (etanercept, infliximab, adalimumab, certolizumab pegol, golimumab or ustekinumab) were used in 17.7% of patients with PsA.

Conclusions We found a clear trend of rising PsA incidence on a national level. While the cause remains unclear, our findings might be explained by increased attention by patients and physicians.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease, which frequently develops in patients with cutaneous psoriasis.[1] PsA is characterised by inflammation of the peripheral and axial joints as well as at the sites of tendon and ligament insertion into bone (enthesitis) and inflammation of the whole digit (dactylitis) and extra-articular manifestations, including nail dystrophy.[2 3] Severity and prevalence of the different disease manifestations vary greatly, and the clinical picture may overlap with that of seronegative rheumatoid arthritis and ankylosing spondylitis.[3]

Although the prevalence of PsA is unclear, primarily due to lack of consensus on diagnostic criteria, it is estimated to occur in 0.04–0.1% of the general population; however, this figure may be underestimated.[4] Studies have suggested that approximately 30% of patients with cutaneous psoriasis suffer from PsA, and one study reported that 42% of Danish patients with psoriasis had PsA when examined by rheumatologists, albeit that this may be limited to patients seen in a hospital setting.[5] Although PsA may occur at any age, the onset typically begins in the patients mid-to-late 30s and affects men and women equally.[2 3]

Studies on the incidence of PsA in the general population remain scarce. While recent data suggest an incidence rate ranging from 3.6 to 7.2 per 100 000 person-years, older studies have reported a much wider incidence range (ie, from 0.1 to 23.1 per 100 000 person-years).[6–10] The most recent study and the only prospective study of PsA in patients with psoriasis demonstrated an annual incidence of 2.8%.[11] Consequently, the incidence and temporal trends of PsA in the general population remain poorly understood. In the present work, we therefore examined the incidence and prevalence of PsA in a Danish nationwide cohort.

MATERIALS AND METHODS

Data sources and study population

Study approval was obtained from the Danish Data Protection Agency (ref. 2007-58-0015, int. ref. GEH-2014–018, I-Suite 02736) and approval from an ethics committee is not required for registry studies in Denmark. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology recommendations.[12]

Using the unique personal identification number assigned to all Danish citizens, we linked individual-level information from nationwide administrative registers. The Civil Registration System[13] contains information on sex, date of birth and updated information on vital status and emigration, thus minimising loss to follow-up. All inpatient and outpatient (ambulatory) hospital consultations are recorded in the Danish National Patient Register[14] (DNPR), including 1 primary and up to 19 secondary diagnoses coded by discharging physicians according to the International Classification of Diseases, eighth revision (ICD-8) (prior to 1994) and according to the tenth revision (ICD-10) thereafter. The primary diagnosis is the main reason for the hospital consultation or hospitalisation, and secondary diagnoses are additional conditions, including complications. Since 1994, detailed and accurate information on all pharmacy-dispensed medications has been registered in the Danish Registry of Medicinal Products Statistics according to the Anatomical Therapeutic

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Table 1 Characteristics of patients diagnosed with first-time psoriatic arthritis (PsA) in Denmark, all specialties

PsA—diagnoses from all specialties

	1997		1999		2001		2003		2005		2007		2009		2011	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Population	5 799 626		5 796 301		5 790 440		5 775 643		5 763 587		5 748 752		5 730 728		5 699 167	
Women	2 929 404	50.5	2 925 814	50.5	2 920 591	50.4	2 910 527	50.4	2 902 514	50.4	2 893 295	50.3	2 882 814	50.3	2 866 063	50.3
Men	2 870 222	49.5	2 870 487	49.5	2 869 849	49.6	2 865 116	49.6	2 861 073	49.6	2 855 457	49.7	2 847 914	49.7	2 833 104	49.7
PsA																
Mean age, years	47.7		48.0		48.0		47.8		47.2		48.6		48.7		49.7	
Any	376	0.01	466	0.01	447	0.01	566	0.01	714	0.01	894	0.02	1118	0.02	1128	0.02
Women	215	57.2	268	57.5	242	54.1	320	56.5	396	55.5	497	55.6	659	58.9	655	58.1
Men	161	42.8	198	42.5	205	45.9	246	43.5	318	44.5	397	44.4	459	41.1	473	41.9
Age groups																
0–19	8	2.1	10	2.1	17	3.8	29	5.1	25	3.5	35	3.9	44	3.9	42	3.7
20–29	27	7.2	41	8.8	43	9.6	45	8.0	67	9.4	62	6.9	77	6.9	85	7.5
30–39	75	19.9	90	19.3	78	17.4	96	17.0	136	19.0	143	16.0	191	17.1	184	16.3
40–49	95	25.3	119	25.5	104	23.3	124	21.9	166	23.2	219	24.5	255	22.8	257	22.8
50–59	109	29.0	107	23.0	112	25.1	156	27.6	192	26.9	241	27.0	302	27.0	254	22.5
60–69	39	10.4	58	12.4	51	11.4	72	12.7	86	12.0	122	13.6	179	16.0	192	17.0
≥70	23	6.1	41	8.8	42	9.4	44	7.8	42	5.9	72	8.1	70	6.3	114	10.1
Systemic Tx*																
Any	163	43.4	168	36.1	183	40.9	257	45.4	337	47.2	431	48.2	536	47.9	504	44.7
Non-biologic	163	43.4	168	36.1	183	40.9	257	45.4	337	47.2	416	46.5	496	44.4	479	42.5
Biologic	0	0.0	0	0.0	0	0.0	0	0.0	6	0.8	32	3.6	98	8.8	79	7.0

*Systemic Tx: methotrexate, leflunomide, ciclosporin, sulfasalazine, etanercept, infliximab, adalimumab, certolizumab pegol, golimumab, ustekinumab.
Tx, therapy.

Chemical classification.[15] Hospital-administered pharmacotherapy is coded in the DNPR as treatment procedure (SKS) codes. We defined patients with incident PsA as those recorded with a corresponding first-time ICD-10 code (M07.0–3 and M09.0) and thus excluded all patients with a history of PsA before 1 January 1997. In estimations of prevalence, these patients were not excluded. The study period was divided into 1-year groups from 1997 to 2011. We identified the use of systemic therapy, that is, methotrexate, leflunomide, ciclosporin, sulfasalazine, etanercept, infliximab, adalimumab, certolizumab pegol, golimumab and ustekinumab. Although uncommon, methotrexate, sulfasalazine and ciclosporin can be prescribed by general practitioners in Denmark, whereas leflunomide and biologics are only prescribed by specialists. We did not consider corticosteroids, as these may be used primarily for short-term management and did not include non-steroidal anti-inflammatory drugs as these may also be purchased over the counter in Denmark.

Statistical analysis

We estimated the number of incident PsA cases within each of the predefined 1-year periods and calculated the frequency of PsA cases within gender and age subgroups (0–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70+ years). We computed the incidence rate within each 1-year period as the number of newly diagnosed PsA cases divided by the risk time of the underlying population. We estimated the population size in each of the 1-year periods as the number of Danes alive in the mid-year of each period, as recorded in the Civil Registration System, and the risk time as 1 year times the estimated number of Danes in each period. The prevalence of PsA was estimated among all Danes alive and resident in the source population on 31 December 2012. Since it is possible that younger individuals may have been coded as having juvenile idiopathic arthritis (JIA) instead of PsA, we performed additional analyses to examine the incidence of having either PsA or JIA in individuals aged 0–19 years. Due to data security requirements, data on one or two subjects are shown as 'less than 3', and the derived percentages are not shown. SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina, USA) was used for statistical analysis.

RESULTS

During the study period, the total Danish population comprised approximately 5.7 million individuals with equal gender distribution. Among patients diagnosed with PsA, there was a female

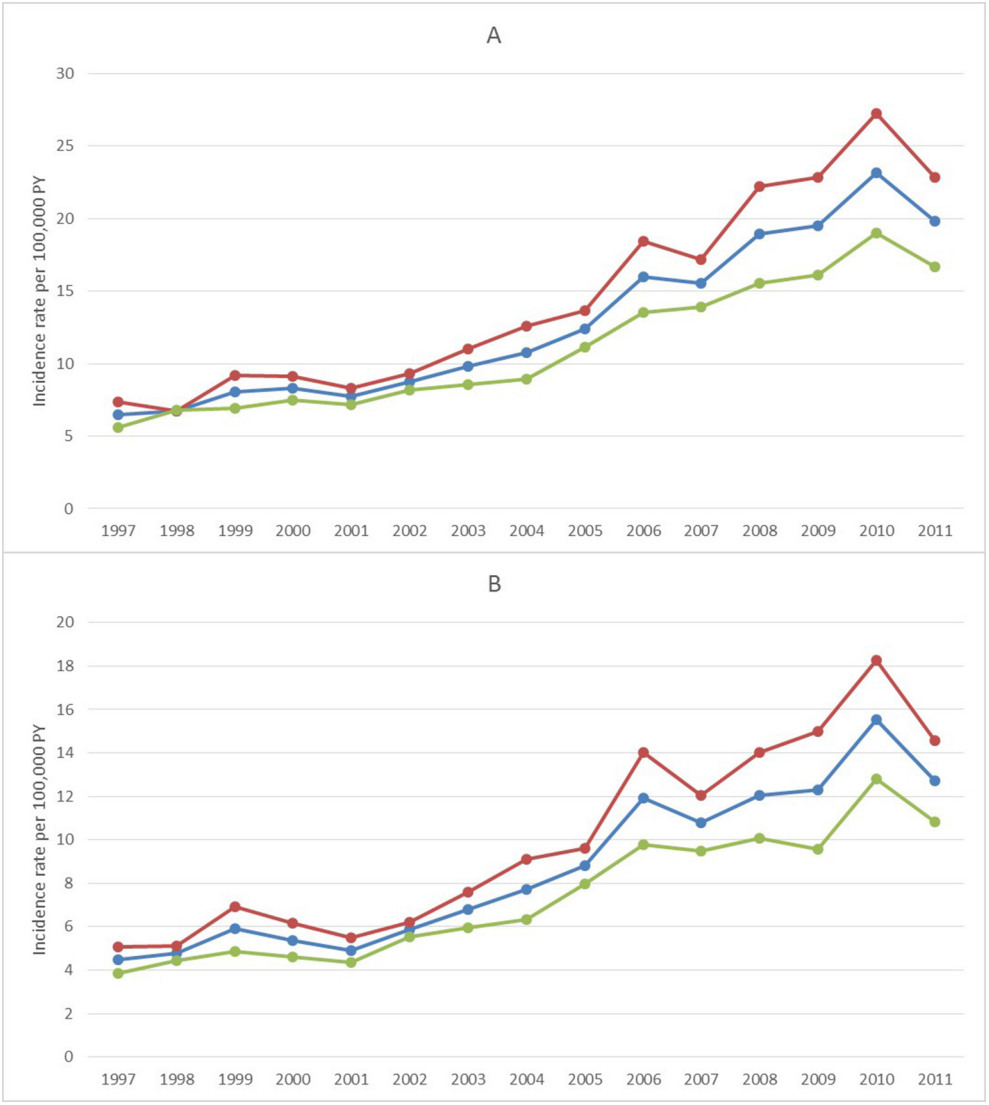

Figure 1 Incidence rates of psoriatic arthritis (PsA). Total and gender-specific incidence rates per 100 000 person-years of PsA over the study period 1997–2011. (A) Diagnoses from all specialties. (B) Diagnoses made by rheumatologists. Blue,Overall; Red, Women; Green, Men.

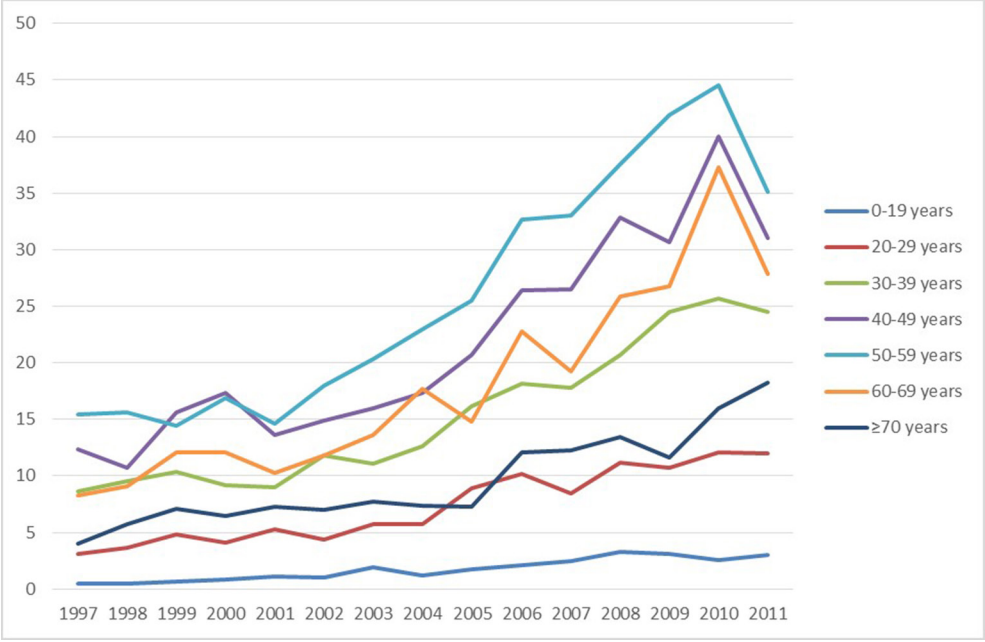

Figure 2 Age-specific incidence rates per 100 000 person-years of psoriatic arthritis over the study period 1997–2011.

predominance ranging from 50.3% (1998) to 59.2% (2010), and the mean age at time of diagnosis was 47–50 years (table 1 and see online Supplementary table S1). The incidence of PsA (presented as incidence rates per 100 000 person-years) increased almost fourfold, from 7.3 in 1997 to a maximum of 27.3 in 2010 (see online Supplementary Table S2 and figure 1). The highest percentage of patients with incident PsA was among individuals aged between 50 and 59 years, whereas PsA was the least frequent among younger individuals aged 0–19 years (table 1 and figure 2). Similarly, age-specific incidence rates revealed the greatest absolute increase in PsA incidence among subjects aged 50–59 years and the lowest increase among individuals aged 0–19 years (see online Supplementary table S2 and supplementary figure S1).

The use of systemic non-biologic agents, that is, methotrexate, leflunomide, ciclosporin or sulfasalazine increased over the 15-year study course. The first recorded use of biologic agents (etanercept, infliximab, adalimumab, certolizumab pegol, golimumab or ustekinumab) for patients diagnosed with PsA within the same year occurred in 2004 from whereon their use steadily increased (table 1 and see online supplementary table S1).

As shown in table 2, we identified a total of 12 719 patients with PsA (prevalence=0.22%), including 9034 patients where the PsA diagnosis was made by a rheumatologist (prevalence=0.16%). When limited to adults (≥18 years), the PsA prevalence was 0.28% across specialties and 0.20% when the diagnosis was made by a rheumatologist. Among patients not diagnosed by a rheumatologist, the majority received their diagnosis from a dermatologist. Patients were predominantly women (58%) with a mean age of 47 years. The highest prevalence was among patients aged between 50 and 59 years, followed by those aged 60–69 years (table 2 and figure 3). Approximately two-thirds of patients had received treatment with systemic non-biologic agents, whereas biologics were used in one-fifth of patients (table 2). Similar characteristics were observed when analyses were limited to patients diagnosed by a rheumatologist (see online Supplementary figures S2-3). The trend in incidence of PsA and JIA combined for individuals aged 0–19 years are shown in online Supplementary figure S4.

Table 2 Characteristics and prevalence of patients diagnosed with psoriatic arthritis (PsA)

	All specialties		Rheumatologists	
	n	%	n	%
Population	5 677 138		5 677 138	
Women	2 854 985	50.29	2 854 985	50.29
Men	2 822 153	49.71	2 822 153	49.71
PsA				
Mean age, years	46.7		47.4	
Any	12 719	0.22	9034	0.16
Women	7318	57.54	5257	58.19
Men	5401	42.46	3777	41.81
Age groups				
0–19	183	1.44	26	0.29
20–29	501	3.94	318	3.52
30–39	1256	9.87	916	10.14
40–49	2505	19.69	1833	20.29
50–59	3168	24.91	2314	25.61
60–69	3124	24.56	2303	25.49
≥70	1982	15.58	1324	14.66
Systemic Tx*				
Any	8519	66.98	6307	69.81
Non-biologic	8434	66.31	6246	69.14
Biologic	2250	17.69	1759	19.47

*Systemic Tx: methotrexate, leflunomide, ciclosporin, sulfasalazine, etanercept, infliximab, adalimumab, certolizumab pegol, golimumab and ustekinumab.

DISCUSSION

In this nationwide study of the Danish population, we observed an increasing incidence of PsA between 1997 and 2011. This finding is in contrast to cutaneous psoriasis which appears to have a stable or even slightly decreasing incidence in Northern Europe.[16] Notably, the increasing incidence was most pronounced among older individuals, and a strong female predominance was observed. Overall, the prevalence of PsA in Denmark was 0.22%, whereas the prevalence was 0.16% when limited to diagnoses

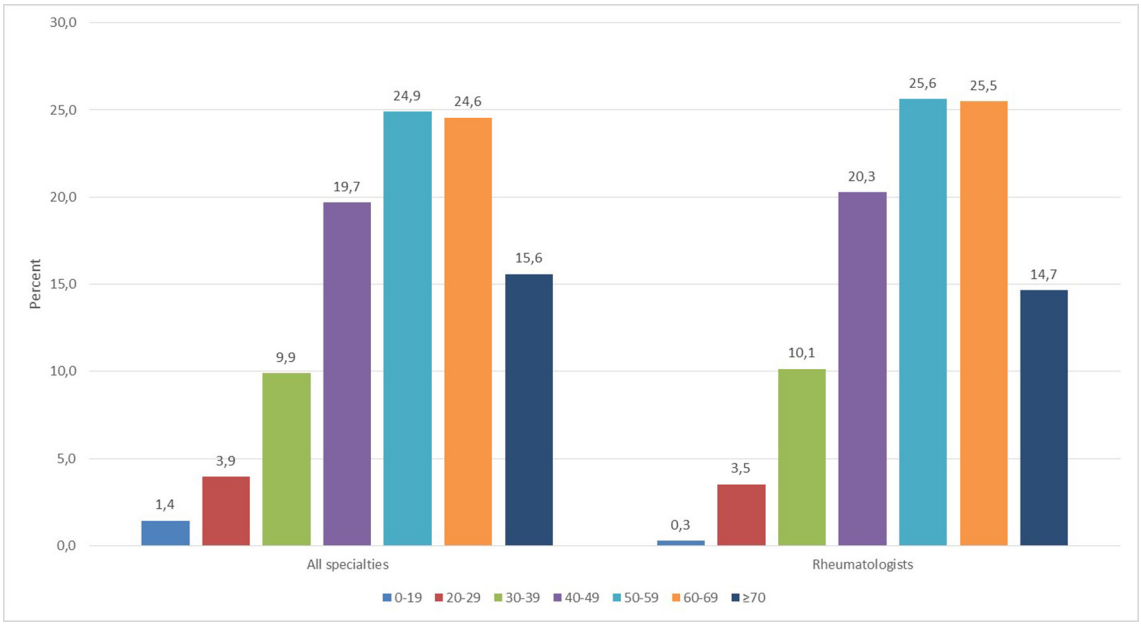

Figure 3 Distribution of prevalent psoriatic arthritis, stratified by age.

made by rheumatologists. Two-thirds of patients received treatment with systemic non-biologic therapy, and one-fifth of patients were at some point treated with biologics.

While the aim of the present study was to examine the incidence and prevalence of PsA in the general population, studies have reported that most patients with PsA develop cutaneous psoriasis prior to the development of arthritic symptoms.[17 18] Notably, however, data suggest that the risk of PsA remains constant following diagnosis of cutaneous psoriasis.[19] Several studies have examined the incidence and prevalence of PsA in patients with cutaneous psoriasis, yet general population studies of PsA incidence remain conflicting, although a recent meta-analysis reported a PsA prevalence of 0.19% in Europe.[20] Based on self-reported questionnaire data from 2006 to 2008, a Norwegian study of 50 806 citizens found a PsA incidence rate of 41.3 per 100 000 person-years and a prevalence of 0.67% among individuals older than 20 years.[21] In one previous study from Denmark, 34 944 Danish twins were surveyed in 2002, and reported an incidence rate of 6 per 100 000 person-years.[22] The observed differences between previous studies and our findings may be due to methodological differences, as well as the time period in which the incidence and prevalence was examined. A fundamental limitation of the aforementioned studies is the lacking assessment of the developments in PsA incidence over time. However, one small study comprising a total of 147 patients with incident PsA reported an increasing incidence from 3.6 to 9.8 per 100 000 person-years between the periods from 1970–1979 to 1990–1999.[23] Similarly, a study from Taiwan reported an increasing PsA prevalence from 1014 in 2003 (prevalence rate: 0.45/10 000 individuals) to 3072 in 2013 (prevalence rate: 1.31/10 000 individuals).[24] Until now, only one prospective study has been published of patients with psoriasis developing PsA. The study reported a constant risk in these patients.[11] Indeed, this finding was corroborated by a cross-sectional observational study of 1560 patients with psoriasis, of which 126 had PsA.[19]

We found a mean age of 47–50 years at time of PsA diagnosis, a somewhat higher estimate compared with certain other studies.[25] Our population-based study also included cases diagnosed by dermatologists only, which together with milder more insidious cases of onset could explain the higher mean age of diagnosis identified in this study. The female predominance observed in our study is supported by some previous publications, including data from biologics registers.[20 21 26] Although the cause remains speculative, it is conceivable that female patients may be more likely to seek medical treatment for arthritic symptoms compared with men. The increasing PsA incidence is in contrast to rheumatoid arthritis, for example, where recent population-based studies have reported a reduction in incidence and prevalence.[27] Although speculative, decreasing number of active smokers together with less air pollution in the major cities over the last decades, together with an increase in obesity may explain these differences. Moreover, we observed an increase in use of systemic therapies, in particular biologics, in newly diagnosed patients with PsA. It is plausible that the increasing PsA incidence may reflect use of screening questionnaires as well as increased targeted educational initiatives provided to patients and physicians. The increasing use of systemic therapies may also be due to emerging data suggesting that early and aggressive treatment results in improved prognosis,[28 29] and the introduction of the classification criteria for psoriatic arthritis (CASPAR) criteria which may have enabled increased focus on specific symptoms, consequently resulting in earlier disease recognition. However, in daily practice few clinicians use the CASPAR criteria outside of clinical trials and computerised databases. Also, the lack of evidence supporting the use of synthetic disease-modifying antirheumatic drugs may have influenced the use of biologics. For example, studies have suggested that methotrexate does not significantly modify relevant disease outcome measures in PsA,[30] whereas a tight control of disease activity was recently shown to significantly improve PsA.[31]

Strengths and limitations

Because of its nationwide and population-based design within a setting with equal access to healthcare for the entire population, our study is virtually unaffected by referral and selection biases and is likely to provide highly generalisable results. Nonetheless, a few limitations need to be addressed. Although we find it unlikely that misclassification can explain our findings, we acknowledge that an increase in the completeness of PsA coding over time might play a role in the observed increase in PsA incidence. The ICD-10 classification has been

used in Denmark since 1995. Selection of patients with PsA in this study was based on ICD codes recorded, which may introduce a selection bias towards more severe cases being included while failing to capture patients with mild disease who are managed entirely at primary care units. However, according to a previous study in Sweden (a neighbouring Scandinavian country closely resembling Denmark), this is a minor problem and would only increase the number of cases by less than 4%, at the expense of a larger degree of misclassification.[32]

Regarding the case definitions of PsA used in this study, data and results from another group suggest that rheumatic misclassification occurs in less than 10%.[33] Moreover, our findings were corroborated by analyses limited to diagnoses given by rheumatologists, which yielded similar results as our primary analyses. Nevertheless, we cannot refute that our results may be underestimated. Indeed, a recent meta-analysis found that up to 15.5% of patients with cutaneous psoriasis may have undiagnosed PsA.[34] Since we dealt with confounding by age and gender in stratified analyses, we find it unlikely that confounding plays a substantial role in our findings of an increase in PsA incidence over time. We lacked data on clinical measures of disease severity and used systemic treatment as a measure thereof, which may have biased our results slightly. Lastly, our study was limited by the lack of information on clinical as well as radiographic findings among patients with PsA and we were therefore unable to evaluate the impact of the systemic treatment, for example, on time trends of disease severity and progression.

In conclusion, we found a clear trend of rising PsA incidence on a national level in Denmark. While the cause remains unclear, it is likely that our findings are partly explained by increased attention by patients and physicians, the availability of classification criteria, increased information on disease severity and a need for earlier therapy. Future research is warranted to examine whether early and aggressive treatment of cutaneous psoriasis, for example, with systemic agents such as biologics, may prevent a continuous increase in PsA incidence.

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Contributors AE and GHG had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: AE. Acquisition, analysis and interpretation of data: all authors. Drafting of the manuscript: AE. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: AE and GHG. Obtained funding: AE and LM. Administrative, technical or material support: AE and GHG. Study supervision: AE and GHG.

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Patient consent Patient consent is not required for register studies per Danish law.

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Prevalence of psoriatic arthritis in patients with psoriasis: A systematic review and meta-analysis of observational and clinical studies

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Background: Wide-ranging prevalence estimates of psoriatic arthritis (PsA) in patients with psoriasis have been reported.

Objectives: To assess the prevalence and incidence of PsA in patients with psoriasis.

Methods: Two authors independently searched 3 databases for studies reporting on the prevalence or incidence of PsA in patients with psoriasis. A proportion meta-analysis was performed to calculate the pooled proportion estimates of PsA in patients with psoriasis.

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Drs Alinaghi and Calov had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Egeberg and Thyssen take responsibility for study concept and design. All the authors take responsibility for acquisition, analysis, and interpretation of the data and for critical revision of the manuscript for important intellectual content. Drs Alinaghi and Egeberg take responsibility for drafting of the manuscript. Dr Egeberg takes responsibility for statistical analysis. Drs Egeberg and Thyssen take responsibility for administrative, technical, or material support and for study supervision.

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Results: A total of 266 studies examining 976,408 patients with psoriasis were included. Overall, the pooled proportion (95% confidence interval [CI]) of PsA among patients with psoriasis was 19.7% (95% CI, 18.5%-20.9%). In children and adolescents (<18 years of age), the pooled prevalence was 3.3% (95% CI, 2.1%-4.9%). The PsA prevalence was 22.7% (95% CI, 20.6%-25.0%) in European patients with psoriasis, 21.5% (95% CI, 15.4%-28.2%) in South American patients with psoriasis, 19.5% (95% CI, 17.1%-22.1%) in North American patients with psoriasis, 15.5% (95% CI, 0.009%-51.5%) in African patients with psoriasis, and 14.0% (95% CI, 95% CI, 11.7%-16.3%) in Asian patients with psoriasis. The prevalence of PsA was 23.8% (95% CI, 20.1%-27.6%) in studies in which the Classification Criteria for Psoriatic Arthritis were applied. The incidence of PsA among patients with psoriasis ranged from 0.27 to 2.7 per 100 person-years.

Limitations: Between-study heterogeneity may have affected the estimates.

Conclusions: We found that 1 in 4 patients with psoriasis have PsA. With the growing recognition of the Classification Criteria for Psoriatic Arthritis, more homogenous and comparable prevalence estimates are expected to be reported. (J Am Acad Dermatol 2019;80:251-65.)

Key words: arthritis; arthropathy; incidence; prevalence; psoriasis; psoriatic.

CAPSULE SUMMARY

- Wide-ranging estimates have been reported for the occurrence of psoriatic arthritis in patients with psoriasis.
- We found an overall pooled prevalence of 19.7% for psoriatic arthritis in patients with psoriasis and 24.6% in patients with moderate-to-severe disease.
- Screening patients with psoriasis for psoriatic arthritis may be warranted, especially for those with moderate-to-severe disease.

Psoriatic arthritis (PsA), which is classified as a seronegative spondyloarthropathy, is strongly associated with cutaneous psoriasis; dactylitis and enthesitis are the hallmarks of the disease.[1] Since its formal acceptance as a distinct entity, several attempts have been made to devise the most sensitive and specific set of diagnostic criteria.[2-10] In 1973, Moll and Wright defined PsA as the presence of inflammatory arthritis with the concurrent existence of psoriasis and seronegativity for rheumatoid factor,[2] and in 2006 the Classification Criteria for Psoriatic Arthritis (CASPAR) were introduced.[10]

Despite the increasing recognition of PsA as a distinct disease, the lack of a widely accepted and validated case definition has yielded considerable variability in estimates of the prevalence of PsA.[11-15] Several observational studies have investigated the latter issue,[16,17] but no meta-analysis has yet been performed to estimate the exact prevalence in patients with psoriasis. Applying a broad and inclusive search strategy, we examined the occurrence of PsA in patients with psoriasis in a systematic review and meta-analysis.

METHODS

Literature search

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and a study protocol was developed a priori.

All articles from inception of the databases through November 2017 were potentially eligible for inclusion. Two authors independently screened the 3 databases (PubMed, Web of Science, and EMBASE) using the following search terms: (*psoriasis*) AND (*psoriatic* OR *arthritis* OR *arthropathy* OR *incidence* OR *prevalence*).

Inclusion and exclusion criteria

To qualify for inclusion, studies had to (1) be original, (2) be written in English and available in full text, (3) have a source population of patients with psoriasis, and (4) include absolute numbers or the percentage of PsA cases to calculate a prevalence of PsA among patients with psoriasis. Studies were excluded if they reported the occurrence of arthritis without distinctly specifying the type of arthritis. Studies of juvenile idiopathic arthritis (JIA) were not included because the term might comprise several different types of arthritis. Furthermore, we distinguished PsA from psoriatic arthropathy, as the latter is a vague term referring to musculoskeletal pain and complaints in general that may be unrelated to PsA.

Data extraction and quality assessment

Records were screened according to the title and abstract. The relevant abstracts, or articles without an

Abbreviations used:

CASPAR:	Classification Criteria for Psoriatic Arthritis
CI:	confidence interval
HLA:	human leukocyte antigen
JIA:	juvenile idiopathic arthritis
PsA:	psoriatic arthritis

abstract, were selected for full-text review. References from the included studies were also screened for additional studies not identified through the initial search strategy. The extracted data from each study are presented as a supplemental data set on Mendeley and can be accessed at http://dx.doi.org/10.17632/48xm3bwkdr.1. Quality assessment was performed by using the Newcastle-Ottawa Scale.[18] An adapted version was used for cross-sectional studies, in which case a maximum score of either 8 or 10 could be achieved. Thus, studies receiving a score of 6 or higher and 7 or higher, respectively, were considered of high quality. For case-control studies and cohort studies, those receiving a score of 7 or higher were considered of high quality.

Data analysis

All statistical analyses were performed with StatsDirect software (version 3.1.4, StatsDirect Ltd, Cheshire, UK). The Freeman-Tukey double arcsine method was applied to transform proportions,[19] and an inverse-variance weighted random effects meta-analysis was performed by using the DerSimonian and Laird method.[20] A priori, we opted for the DerSimonian-Laird random effects methods because we expected to find significant between-study heterogeneity. A proportion meta-analysis was completed to obtain pooled proportions with 95% confidence intervals (CIs) of PsA in patients with psoriasis. The heterogeneity of the included studies was assessed using the Cochran Q test and I^2 statistics, and forest plots were constructed. Furthermore, we calculated the prevalence of PsA in patients with psoriasis for the following stratifications: all studies, sex, period published (before 2000, 2000-2009, and 2010-2017), child and adolescent populations only (ie, those <18 years), studies of adults only (those ≥18 years), diagnosis according to CASPAR, diagnosis according to the Moll and Wright criteria, population size (<500, 500-1000, and ≥1000), study type (clinical, register-based, population-based, and observational studies), geographic area and country, Newcastle Ottawa Scale score (good quality or fair/poor quality), and severity of psoriasis disease defined as moderate-to-severe disease (Psoriasis Area Severity Index score ≥10 or body surface area ≥10) and mild disease (Psoriasis Area Severity Index score <10 or body surface area <10).

RESULTS

We identified 6331 records through database searching (2139 in PubMed, 1217 in Web of Science, and 2975 in EMBASE); 4323 nonduplicate records were screened by title and abstract, yielding 1302 articles for full-text assessment. Counting the additional 41 studies identified by screening references, 287 studies were included for data extraction and 266 studies were selected for quantitative analysis (Fig 1); together, these studies included 976,408 patients with psoriasis (12,884 children and adolescents). The results of all analyses performed are summarized in Table I.

Prevalence of PsA in patients with psoriasis

Overall, quantitative analysis of 266 studies yielded a pooled PsA prevalence of 19.7% (95% CI, 18.5%-20.9%) in patients with psoriasis (Supplemental Fig 1; available at http://www.jaad.org). A total of 21 studies[21-41] reported data on children and/or adolescents, yielding a pooled prevalence of 3.3% (95% CI, 2.1%-4.9%) (Supplemental Fig 2; available at http://www.jaad.org), and a total of 245 studies[11-17,42-279] reported data for PsA in adults with psoriasis with a pooled prevalence of 21.6% (95% CI, 20.3%-22.9%) (Supplemental Fig 3; available at http://www.jaad.org). A total of 36 studies* reported data on PsA stratified by sex (Supplemental Figs 4 and 5; available at http://www.jaad.org), with the prevalences for men and women being 23.3% (95% CI, 19.4%-27.5%) and 24.0% (95% CI, 20.1%-28.1%), respectively. A total of 45 studies† used CASPAR as the underlying diagnostic approach for assessment of PsA, with a pooled prevalence of 23.8% (95% CI, 20.1%-27.6%) (Supplemental Fig 6; available at http://www.jaad.org). Similarly, 20 studies‡ used the Moll and Wright criteria, yielding a prevalence of 24.1% (95% CI, 15.0%-34.5%) (Supplemental Fig 7; available at http://www.jaad.org).

*11,14,22,42,44,48,49,52,57,63,64,69,70,80,91,99,100,112,117,140,156,159,169,177,179,188,189,200,208,214,217,223,239,241,245,275.

†11,14,90,99,119,129,130,135,137,141,142,146-148,155,156,159,163,164,174,177,180,186,197,198,200,208-210,217,218,229,231,233,235,241,245,247,249,257-259,271,273,275.

‡43,44,47,49,57,63,75,80,87,88,92,93,102,157,199,219,239,240,276,280.

Variations in PsA prevalence by geographic region and country

There were 119 studies[§] from Europe, with a resultant pooled prevalence of 22.7% (95% CI, 20.6%-25.0%). From Asia there were 59 studies[¶] included for analysis, yielding a pooled prevalence of 14.0% (11.7%-16.3%). Furthermore, 47 studies[‖] were included from North America, with a pooled prevalence of 19.5% (95% CI, 17.1%-22.1%). There were 10 studies[#] from South America, resulting in a pooled estimate of 21.5% (95% CI, 15.4%-28.2%). We included 3 studies[40,43,119] from Africa; the pooled prevalence was 15.5% (95% CI, 0.009%-51.5%).

By country, the following estimates were calculated: 30.5% (95% CI, 24.8%-36.4%) from Italy,[**] 18.7% (95% CI, 15.0%-22.7%) from Spain,[††] 20.5% (95% CI, 17.6%-23.5%) from Germany,[‡‡] 19.2% (95% CI, 9.2%-31.8%) from the Netherlands,[§§] 22.4% (95% CI, 16.4%-29.0%) from Sweden,[16,33,55,57,66,140,188,265] 24.1% (95% CI, 9.2%-43.2%) from Denmark,[16,42,189,203,260] 18.2% (95% CI, 3.6%-40.6%) from Greece,[31,45,131,239,276] 17.0% (95% CI, 6.2%-31.7%) from Poland,[62,151,268,272] 30.0% (95% CI, 25.3%-35.0%) from Finland,[16,48] 27.1% (95% CI, 13.3%-43.7%) from Norway,[16,51] 16.3% (95% CI, 7.9%-26.9%) from France,[34,41,78,189,202,226,253] 19.4% (95% CI, 12.5%-27.6%) from the United Kingdom,[¶¶] 22.0% (95% CI, 10.7%-35.9%) from Iceland,[16,68] 14.2% (95% CI, 8.6%-21.0%) from Turkey,[‖‖] 13.5% (95% CI, 7.8%-20.6%) from India,[##] 8.3% (95% CI, 1.6%-19.6%) from Japan,[13,60,94,273,275] 4.9% (95% CI, 1.9%-9.3%) from China,[15,73,130,132,146] 35.5% (95% CI, 11.8%-64.0%) from Thailand,[14,184,222,240] 18.5% (95% CI, 5.8%-36.3%) from Taiwan,[206,255,267] 10.4% (95% CI, 8.3%-12.8%) from South Korea,[54,217,245] 13.0% (95% CI, 5.5%-23.0%) from Iran,[80,117] 41.8% (95% CI, 35.8%-48.0%) from Pakistan,[88,246] 19.0% (95% CI, 16.3%-21.8%) from the United States,[***] 24.6% (95% CI, 17.3%-32.7%) from Canada,[91,95,99,189,196,218,236] 25.2% (95% CI, 18.6%-32.3%) from Brazil,[†††] and 17.8% (95% CI, 12.4%-24.0%) from Argentina[145,177] (Fig 2 and Supplemental Table I [available at http://www.jaad.org]).

Prevalence estimates by population size

The population size per study ranged from 25 to 198,366 patients with psoriasis.

There were 173 studies[‡‡‡] with a population of fewer than 500 patients with psoriasis, with a pooled prevalence of 22.2% (95% CI, 20.0%-24.4%). A total of 35 studies[§§§] had a study population between 500 and 1000 patients, with a pooled prevalence of 18.5% (95% CI, 15.0%-22.3%), and 57 studies[¶¶¶] had a study population of 1000 or more, resulting in a prevalence of 14.4% (95% CI, 12.5%-16.3%).

Prevalence of PsA by publication year and study design

Stratified by year of publication, there were 13 studies[21,42-53] from before 2000, resulting in a pooled prevalence estimate of 22.0% (95% CI, 16.1%-28.5%). There were 51 studies[12,16,17,22-25,54-97] and 202 studies[‖‖‖] published between 2000-2009 and 2010-2017, respectively. The respective pooled prevalence estimates were 16.5% (95% CI, 13.1%-20.3%) and 20.4% (95% CI, 19.1%-21.8%).

There were 34 clinical studies,[###] resulting in a pooled prevalence of 22.9% (95% CI, 20.7%-25.2%). Moreover, there were 160 observational studies,[****] yielding a pooled prevalence of 20.7% (95% CI, 18.3%-23.2%). With regard to the register-

§11,16,17,21,31-36,41,42,44,45,48,49,51,52,55,57,58,62,65,66,68-71,74,78,90,93,100,104,106,107,111-113,115,116,123,127,129,131,133,135,136,139-142,149-153,156-159,162-164,167,168,170,171,173-176,178-180,188,191,192,194,197,199,200,202-205,211,215,220,223-227,229-231,234,235,237-239,242,249-251,253,254,260,261,264,265,268-270,272,276,277,279.

¶12-15,22-24,27,37,39,54,59,60,63,72,73,80,88,94,102,103,105,108,110,117,128,130,132,138,146,147,155,160,184,186,198,206,216,217,221,222,233,240,241,244-248,255,257,258,263,266,267,271,273-275.

‖25,28,29,46,47,50,53,56,61,64,75,76,79,81,86,87,91,95-99,109,118,120,121,125,134,143,144,148,154,161,169,183,193,196,201,212,214,218,232,236,243,252,259,262.

#126,137,145,172,177,190,208,209,219,228.

**11,21,35,44,49,52,65,69,71,74,112,115,116,135,136,139,141,142,150,158,163,164,173,174,178,179,191,197,199,211,220,225,229,230,238,253.

††58,113,123,133,149,170,175,176,192,194,200,205,215,224,250,253,254.

‡‡17,36,70,93,107,129,171,180,189,231,237,253.

§§26,32,104,127,152,162,167,168,235,261,279.

¶¶90,153,156,204,223,227,242,253,270,277.

‖‖12,23,27,39,59,63,72,102,103,138,160,198,241,248,258.

##22,105,108,110,128,147,186,216,233,244,247,257,263,266,271.

***28,29,46,47,50,53,56,61,64,75,79,86,87,96-98,109,118,120,121,125,134,144,148,154,169,183,189,193,201,212,214,232,243,252,262.

†††137,172,190,208,209,219,228.

‡‡‡11,12,21-26,29,30,32-34,36-45,47,50-55,57,59,62,63,66,67,69,72,74-76,78-81,85-88,90,92,98,99,102-105,107,108,110,113,115-119,122-129,131,136-142,144-147,149-153,155-160,163-170,172-181,184,185,190,191,194,196-200,205,229,230,233,234,236,238-248,250,257-259,263,266-268,271-273,275-277,279.

§§§27,31,49,61,64,65,70,73,77,82,91,94,95,101,106,109,111,114,121,133,189,193,195,208,211,213-215,218,249,251,253,264,270,274.

¶¶¶13,15,17,28,46,48,56,58,60,68,71,83,84,89,93,96,97,100,112,120,130,132,134,135,143,148,154,161,162,171,182,183,186-188,192,201,203,204,207,212,221,227,231,232,235,237,252,254-256,260-262,265,269,278.

‖‖‖‖11,13-15,26-41,98-279.

###25,42,61,67,76-78,81-85,101,111,114,118,121,122,124,125,143,161,165,166,181,185,187,195,207,213,256,264,273,278.

****11-15,21,23,24,26,27,29-31,33-41,43-47,49,50,52,54,55,62,63,65,66,69,70,72-75,79,80,87,88,92,98-100,102-108,110,113,116,117,119,123,126-133,135-142,145,147,149-151,153,155,157-160,163,164,167,169,170,172-180,184,186,189-191,194,195,197-200,205,206,208-211,214-220,222,224,225,228-230,233,238-241,243-248,253,257-259,263,266-268,270-273,275-277.

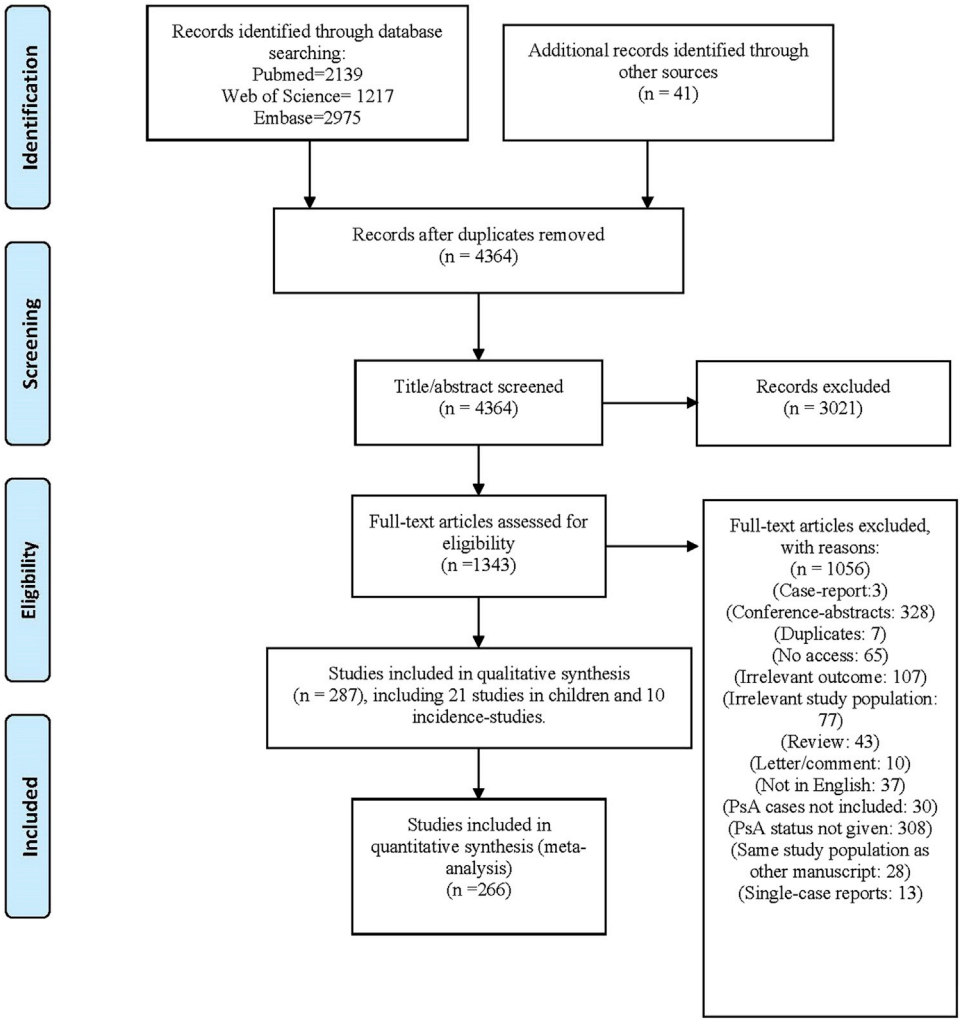

Fig 1. PRISMA flow chart.

based studies, 48 such studies[††††] were included in the analysis, with a pooled prevalence of 15.1% (95% CI, 13.3%-17.1%). Finally, 46 population-based studies[‡‡‡‡] were included, yielding a pooled prevalence estimate of 15.6% (95% CI, 13.7%-17.7%).

Prevalence of PsA by severity of disease

There were 122 studies[§§§§] that included patients with moderate-to-severe psoriasis, resulting in a pooled prevalence of 24.6% (95% CI, 22.9%-26.4). Furthermore, there were 58 studies[¶¶¶¶] with mild disease, resulting in a pooled estimate of 15.8% (95% CI, 14.3%-17.2%).

Study quality and bias assessment

A total of 134 studies[‖‖‖‖‖‖] had good quality according to the Newcastle-Ottawa Scale, with a pooled prevalence of 18.1% (95% CI, 16.6%-19.6%). Furthermore, there were 84 studies[####] categorized

††††22,28,32,35,53,56,57,59,86,90,94-97,112,115,120,144,148,152,154,168,171,182,188,201,203,204,212,221,223,226,227,232,234-236,250,252,254,255,260-262,265,269,274,279.

‡‡‡‡16,17,48,51,56-58,60,64,68,71,86,89-91,93,95-97,109,112,120,134,146,148,154,156,162,183,188,192,193,201,202,212,221,223,227,231,235,237,242,249,251,260,262.

§§§§17,25,32,35,36,38,42,46,47,61,67,69,70,74,76-78,80-85,87,88,91-93,95,100,101,104,106,107,109,111-119,121-125,127,129,136,138,141,143,152,153,157,161-163,165,166,168,171,173-175,178,179,181,182,184,185,187,191,192,194-197,201,203-207,210,211,213,214,216,217,220,222,224,226,229,230,233,234,236,241,243,250,252-254,256-258,264-269,273,274,277-279.

¶¶¶¶11,12,16,28,31,33,52,53,59,64,65,79,90,99,102,103,105,120,130,135,139,140,142,144,145,147,149,155,156,160,164,167,170,172,183,186,198,200,212,215,223,225,227,228,235,237,238,240,242,245,247,248,251,259,260,263,270,272.

‖‖‖‖‖‖15-17,21,22,27-34,36,38,39,41,54,56,57,62,63,65,68-71,74,79,80,92-95,97,98,100,103,104,106,107,112,115,117,119,120,127-132,134,136,137,141,142,144,147-149,154,156-160,162-164,167,170-173,175-178,180,182-184,186,188-192,194,197,199,201-204,206,209,211,212,215,218-221,226,227,229,231,232,235,237,240,242,243,246-248,250-252,254,255,260,262,263,265,268-270,274-276,279.

####11-14,23,24,40,43-53,55,58-60,64,66,72,73,75,86-91,99,102,105,108,110,113,116,125,126,133,135,138-140,145,146,151,153,155,169,174,193,198,200,205,208,210,214,216,217,223,225,228,230,233,234,236,238,239,241,244,245,249,253,257,258,261,266,267,271,272.

Table I. Prevalence estimates according to different population characteristics

Group	Number of studies	Prevalence	95% CI
All studies	266	19.7%	18.5%-20.9%
Men	36	23.3%	19.4%-27.5%
Women	36	24.0%	20.1%-28.1%
Children	21	3.3%	2.1%-4.9%
Adults	245	21.6%	20.3%-22.9%
Studies using CASPAR	45	23.8%	20.1%-27.6%
Studies using Moll and Wright	20	24.1%	15.0%-34.5%
Mild disease*	58	15.8%	14.3%-17.2%
Moderate-to-severe disease**	122	24.6%	22.9%-26.4%
Population size: < 500	173	22.2%	20.0%-24.4%
Population size: 500-1000	35	18.5%	15.0%-22.3%
Population size: ≥ 1000	57	14.4%	12.5%-16.3%
Publication year (pre-2000)	13	22.0%	16.1%-28.5%
Publication year (2000-2009)	51	16.5%	13.1%-20.3%
Publication year (2010-2017)	202	20.4%	19.1%-21.8%
Study design (clinical)	34	22.9%	20.7%-25.2%
Study design (observational)	160	20.7%	18.3%-23.2%
Study design (register-based)	48	15.1%	13.3%-17.1%
Study design (population-based)	46	15.6%	13.7%-17.7%
Continent (Europe)	119	22.7%	20.6%-25.0%
Continent (Asia)	59	14.0%	11.7%-16.3%
Continent (North America)	47	19.5%	17.1%-22.1%
Continent (South America)	10	21.5%	15.4%-28.2%
Continent (Africa)	3	15.5%	0.009%-51.5%

*BSA/PASI < 10
**BSA/PASI ≥ 10

as being of fair or poor quality, with a pooled prevalence of 21.5% (95% CI, 17.7%-25.6%). The studies categorized as being of fair or poor quality scored a maximum of 2 with regard to representativeness of the study population. Correspondingly, of the 134 studies with good quality, 66 scored at least 4, with a minimum score of 3 for all the studies (Supplemental Table II; available at http://www.jaad.org).

Furthermore, the Egger test indicated a significant risk of bias for all the studies included ($P < .0001$). There was a very high level of heterogeneity between all studies included (given by the I^2 of 99.5% [95% CI, 99.5% to 99.5%]). The high level of heterogeneity persisted in all subgroups except for studies from Pakistan, South Korea, and Argentina from the subgrouping by country, in which case the Cochran Q test result was not significant (Supplemental Table III; available at http://www.jaad.org).

Incidence of PsA among patients with psoriasis

A total of 10 studies reported incidence estimates of PsA among patients with psoriasis. Wilson et al[96] conducted a population-based retrospective cohort study based on review of the medical charts of 1593 patients with psoriasis from the United States. Patients were followed for up to 30 years (1970-1999) and the incidence rate was 2.7 per 1000 person-years. Furthermore, cumulative incidences of 1.7%, 3.1%, and 5.1% were reported at 5-, 10-, and 20-years' follow-up, respectively. Li et al[281] reported an annual incidence of 2.1% during 15-years of follow-up (1991-2005) in a US population–based setting of women from the Nurses' Health Study. Furthermore, in a population-based cohort study from the United Kingdom[282] an incidence rate of 26.5 per 10,000 person-years was reported during 15-years of follow-up (1995-2010). In a European study enrolling patients from the United Kingdom, Italy, France, Spain, and Germany, Christophers et al[100] followed 1560 patients with plaque psoriasis from secondary care units for a total of 30 years. The cumulative incidence of PsA was 13% at 20-years' follow-up. Eder et al[283] followed 313 Canadian patients with psoriasis for 4 years (2006-2010), most of whom were enrolled from secondary care clinics, and reported an incidence rate of 1.9 per 100 person-years.

In a study from Italy[139] an annual mean incidence of 1.7% was reported at the 3-year follow-up (2008-2011) for patients with psoriasis who were being seen at an outpatient dermatology clinic. Also from

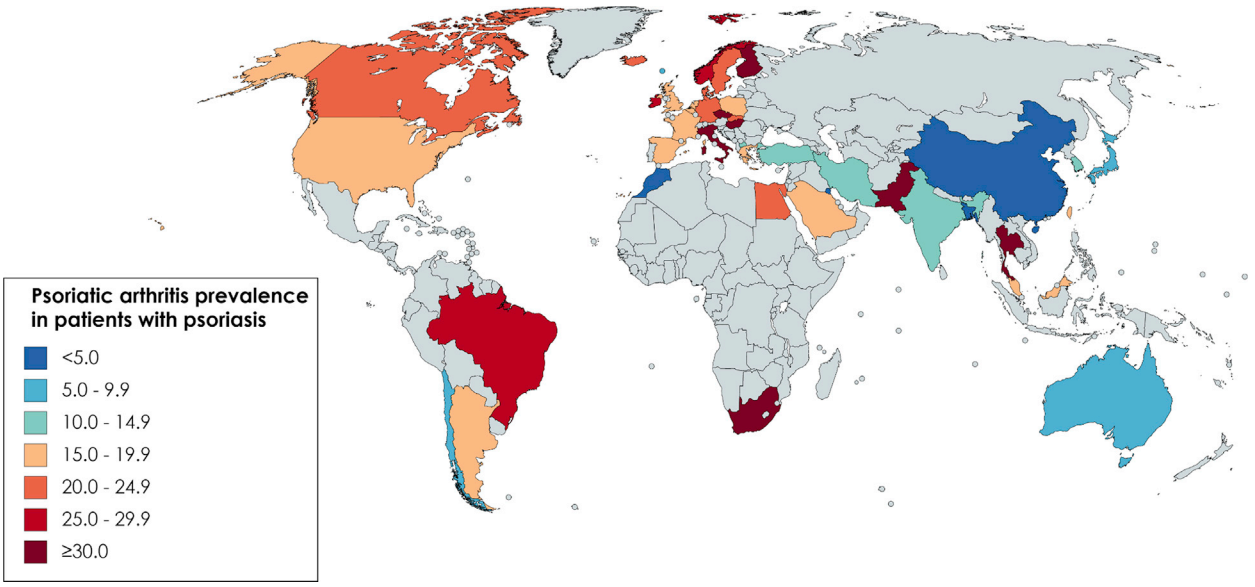

Fig 2. Worldwide prevalence of psoriatic arthritis among patients with psoriasis. Number of studies included per country: Argentina (n = 2), Australia (n = 1), Bangladesh (n = 1), Belgium (n = 1), Brazil (n = 7), Canada (n = 8), Chile (n = 1), China (n = 5), Czech Republic (n = 1), Denmark (n = 5), Egypt (n =1), Faroe Islands (n = 1), Finland (n = 2), France (n = 7), Germany (n = 12), Greece (n = 5), Hungary (n = 1), Iceland (n = 2), India (n = 15), Iran (n = 2), Ireland (n = 1), Israel (n = 1), Italy (n = 36), Japan (n = 5), Kuwait (n = 1), Macedonia (n = 1), Malaysia (n = 1), Morocco (n = 1), Netherlands (n = 11), Norway (n = 2), Pakistan (n = 2), Poland (n=4), Saudi Arabia (n = 1), Scotland (n = 1), Slovakia (n = 1), South Africa (n = 1), South Korea (n = 3), Spain (n = 17), Sweden (n = 8), Taiwan (n = 3), Thailand (n = 4), Turkey (n = 15), United Kingdom (n = 10), United States (n = 36).

Italy, Tinazzi et al[11] reported a cumulative incidence of 8.4% at 12-months' follow-up in a study that enrolled patients with severe psoriasis, and Brunasso et al[115] reported an incidence rate of 22.7 per 1000 person-years during a mean follow-up of 39 months for 55 patients with psoriasis who were treated with efalizumab. In a study from Canada[218] a cumulative incidence of 8.4% was reported during 8-years of follow-up (2006-2014). In another prospective cohort study from Canada[284] the incidence rate was reported to be 2.7 per 100 person-years at 8-years' follow-up (2006-2014).

DISCUSSION

Quantitative analysis of 266 studies yielded a PsA prevalence of 19.7% among 976,408 patients with psoriasis. The prevalence of PsA was markedly lower in children and adolescents than in adults but equally frequent in both sexes. Notably, higher estimates were found in patients with moderate-to-severe psoriasis than in patients with mild psoriasis, suggesting that increased attention among this group of patients is warranted.

The prevalence of PsA among patients with psoriasis was lowest in Asia. Previously, Tam et al[285] reported a prevalence range of 1% to 9% in patients with psoriasis from Asia. Moreover, our data show congruence in the estimates from Europe and North America, which is supported by previous findings. Furthermore, the pooled estimate for South America was unexpectedly high in light of a previous review that reported complete absence of psoriasis in the Andean region.[286] Studies have shown that both psoriasis and PsA have strong genetic components.[99,287] Accordingly, human leukocyte antigen (HLA)-C*06 positivity in patients with psoriasis is generally higher in whites than in Asians.[288] Moreover, strong genetic associations have linked HLA-B7, HLA-B27, and HLA-B39 with PsA in particular,[289] and data have shown higher occurrence of HLA-B27 in non-Hispanic whites.

It is generally accepted that PsA is uncommon in children, which is supported by the pooled prevalence of 3.3%. This low estimate might, at least in part, be explained by lack of clear segregation of PsA from JIA. However, juvenile PsA accounts for approximately 5% of patients with JIA, emphasizing the importance of discerning it from JIA as a distinct entity.[290] Moreover, PsA in children often presents before psoriasis.[291] We examined studies of only

those children with psoriasis, and thus children with PsA who developed cutaneous manifestations later on could have been missed in our study. Furthermore, we observed decreasing proportion estimates as the population size increased. This observation might partly be explained by more thorough examination of patients with psoriasis in smaller studies and underdiagnosis of PsA in larger ones (eg, in register-based studies in which assessment of PsA is based on diagnostic codes), as such studies may tend to predominantly capture those patients with more severe joint symptoms.

The reported incidence rates ranged from 0.27 per 100 person-years, as reported by Wilson et al[96] and Love et al,[282] to 2.7 per 100 person-years, as reported in a prospective setting by Eder et al.[284] Interestingly, both studies reporting the lowest estimates were conducted in a nonselected population–based setting. However, the higher incidence rates could also be explained by improving diagnostic abilities, as there seems to be a link between more recent studies and higher incidence rates.

High levels of heterogeneity were observed between studies both overall and across subgroups. Such heterogeneity may be attributed to the lack of widely accepted diagnostic criteria in the past, different study designs, geographic variations, ethnicity, the remitting and relapsing nature of the disease, and different study inclusion criteria (eg, whether patients with psoriasis were selected from primary, secondary, or tertiary care settings).

In 2015, Villani et al. reported a 15.5% prevalence of undiagnosed PsA among patients with psoriasis in a systematic review and meta-analysis.[292] However, the focus was directed only on the occurrence of newly diagnosed PsA among patients with cutaneous psoriasis. Few review articles have examined the prevalence of PsA among patients with plaque psoriasis,[292-294] and they have generally applied a narrow search strategy, thus excluding a vast number of relevant studies.

Strengths of this study include the sheer number of studies, the focused inclusion of patients with PsA rather than any type of arthritis, the liberal inclusion of various types of study populations and designs, and lastly the inclusion of all types of diagnostic methods for PsA. On the other hand, our study was limited by the few studies from Africa and Australia, thus complicating an accurate assessment of the prevalence of PsA among patients with psoriasis in these regions. The exclusion of studies written in languages other than English and a significant risk of publication bias may also have affected our estimates. Furthermore, because of a lack of available data, we were not able to assess whether severity of psoriasis could explain the lower prevalence of PsA observed in children and in patients from Asia and Africa.

In conclusion, this meta-analysis showed that 1 in 5 patients with psoriasis have PsA, with very consistent results across numerous strata. However, high levels of heterogeneity were observed between the included studies, which may have affected interpretation.

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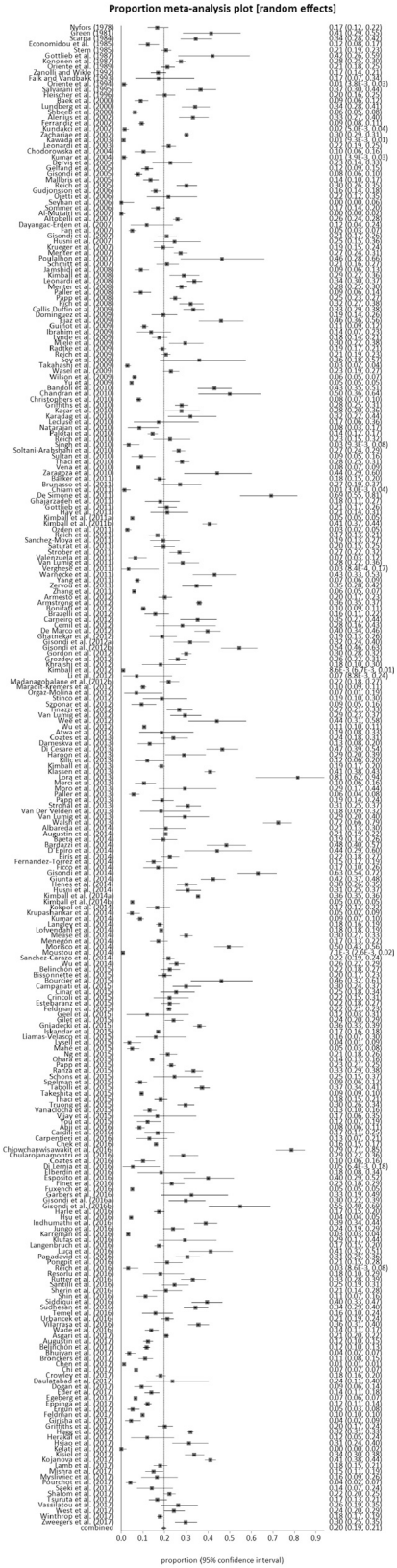
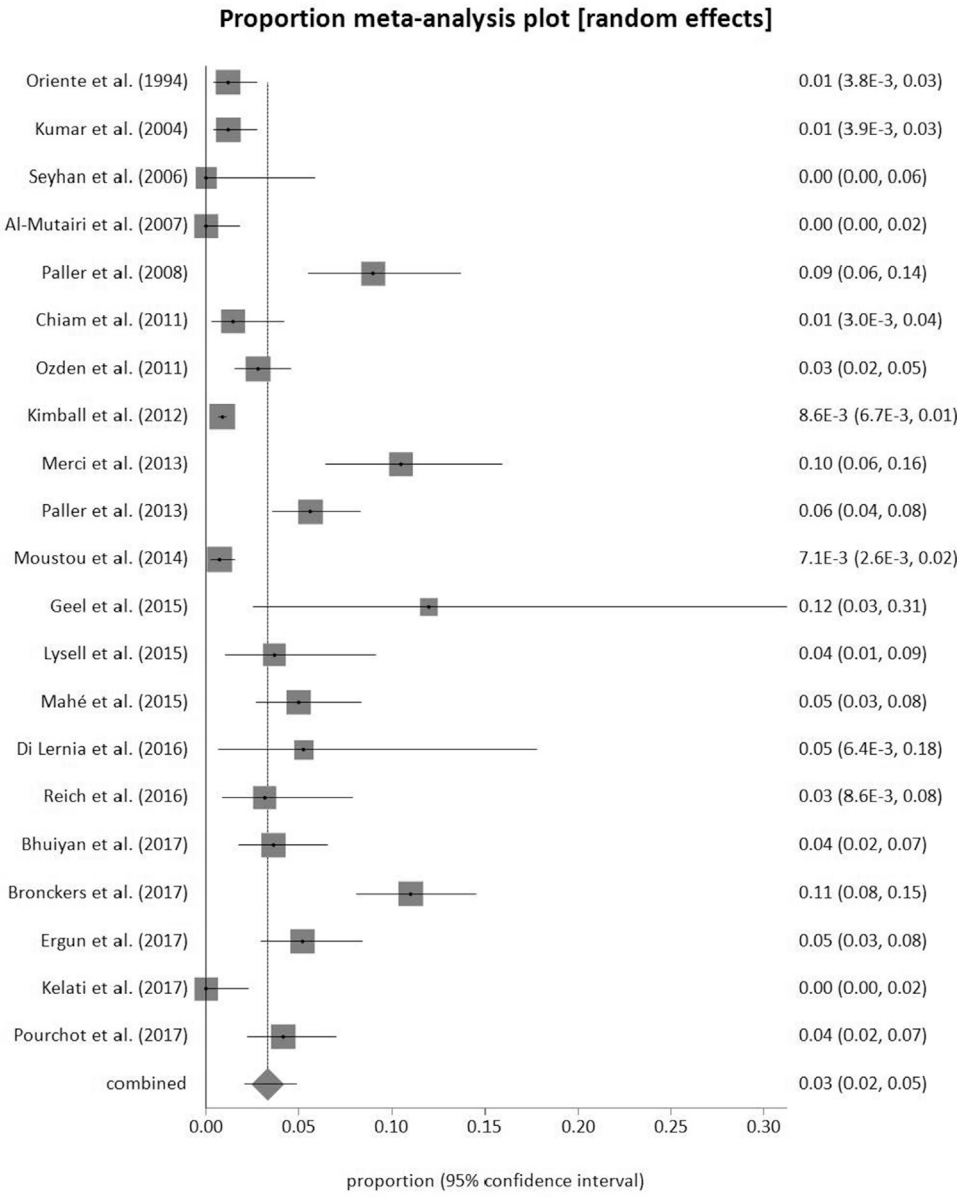
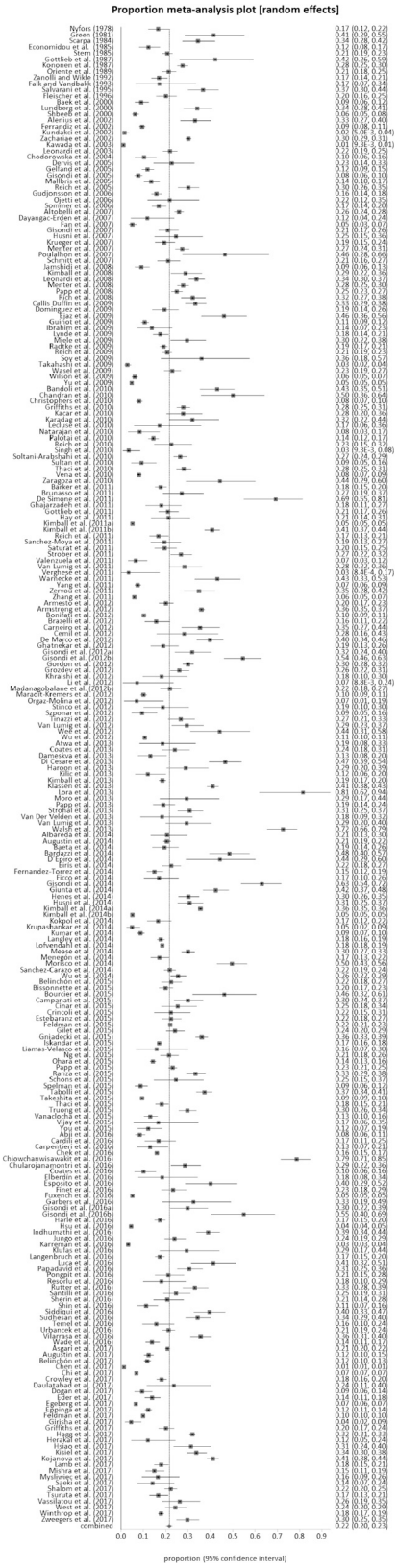


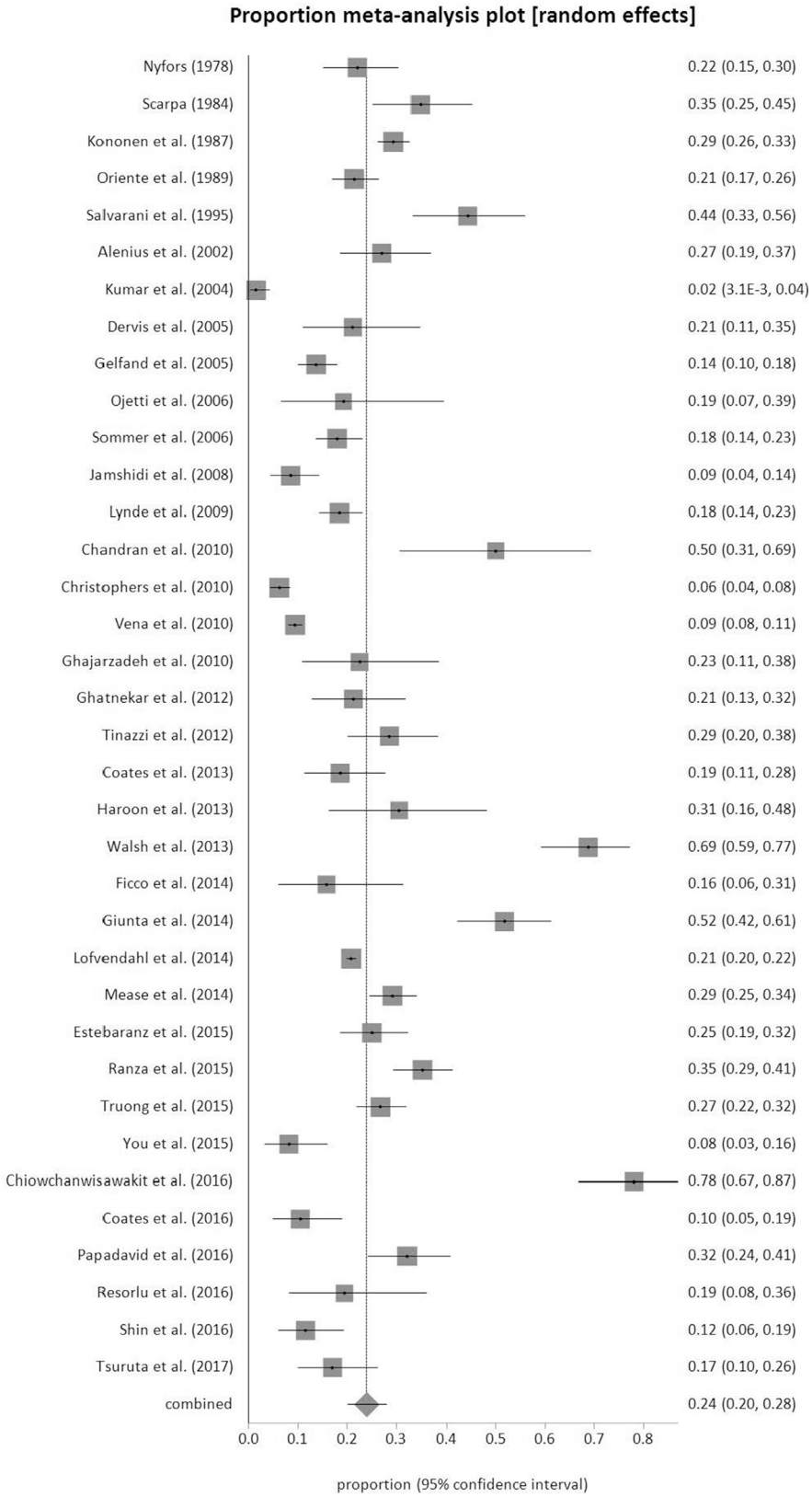
Supplemental Fig 1. Psoriatic arthritis in patients with psoriasis (all studies).



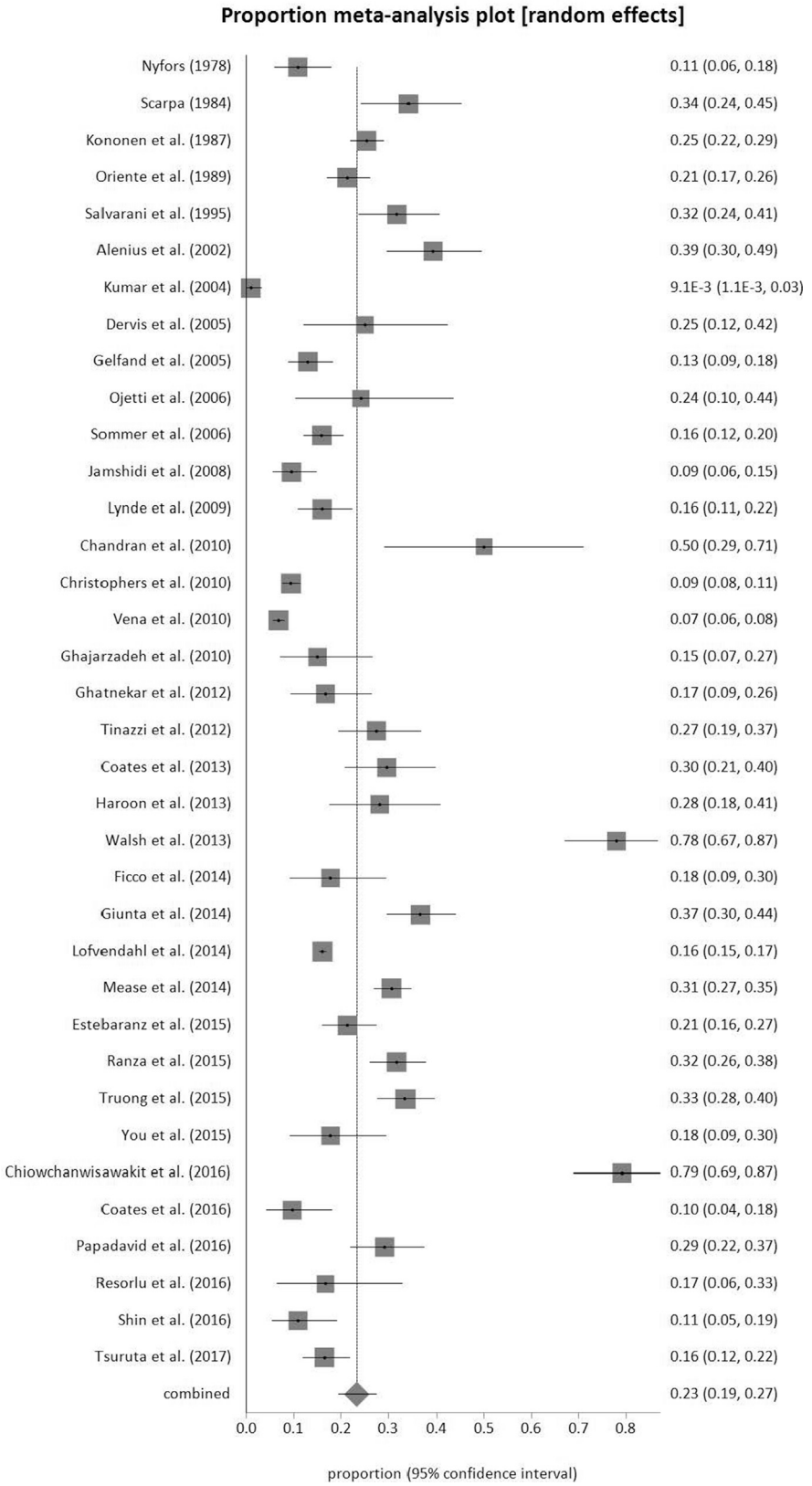
Supplemental Fig 2. Psoriatic arthritis in children with psoriasis.



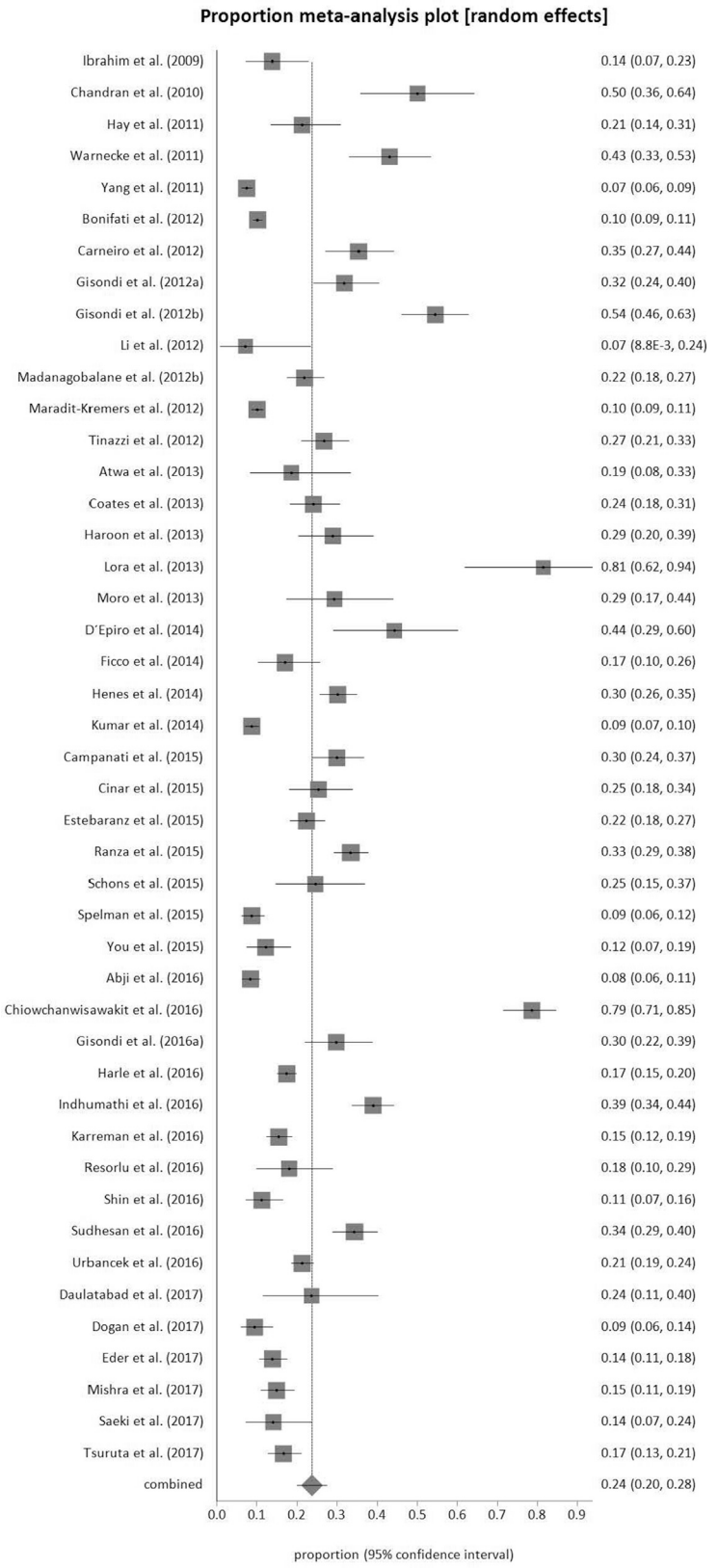
Supplemental Fig 3. Psoriatic arthritis in adults with psoriasis.



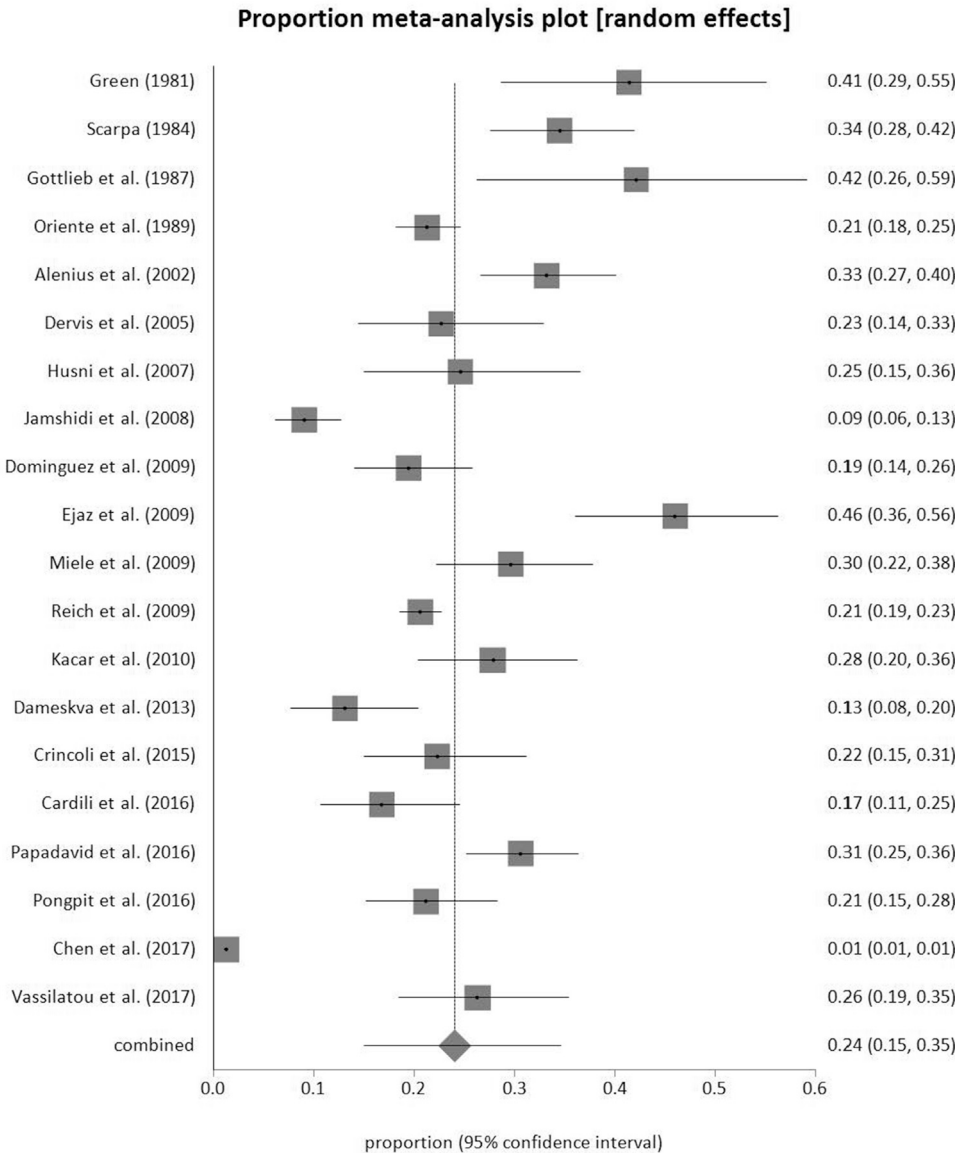
Supplemental Fig 4. Psoriatic arthritis in men with psoriasis.



Supplemental Fig 5. Psoriatic arthritis in women with psoriasis.



Supplemental Fig 6. Psoriatic arthritis according to CASPAR.



Supplemental Fig 7. Psoriatic arthritis according to Moll and Wright.

Supplemental Table I. Prevalence of PsA in patients with psoriasis by geographic region and country

Region/country	Prevalence	95% CI
Australia	8.7%	Not applicable
Africa	15.5%	(0.009%-51.5%)
Egypt	21.3%	Not applicable
Morocco	0%	Not applicable
South Africa	41.6%	Not applicable
Asia	14.0%	(11.7%-16.3%)
Bangladesh	3.6%	Not applicable
China	4.9%	(1.9%-9.3%)
India	13.5%	(7.8%-20.6%)
Iran	13.0%	(5.5%-23.0%)
Israel	22.3%	Not applicable
Japan	8.3%	(1.6%-19.6%)
Kuwait	0%	Not applicable
Malaysia	16.0%	Not applicable
Pakistan	41.8%	(35.8%-48.0%)
Saudi Arabia	18.6%	Not applicable
South Korea	10.4%	(8.3%-12.8%)
Taiwan	18.5%	(5.8%-36.3%)
Thailand	35.5%	(11.8%-64.0%)
Turkey	14.2%	(8.6%-21.0%)
Europe	22.7%	(20.6%-25.0%)
Belgium	18.0%	Not applicable
Czech Republic	41.0%	Not applicable
Denmark	24.1%	(9.2%-43.2%)
Faroe Islands	8.8%	Not applicable
Finland	30.0%	(25.3%-35.0%)
France	16.3%	(7.9%-26.9%)
Germany	20.5%	(17.6%-23.5%)
Greece	18.2%	(3.6%-40.6%)
Hungary	37.9%	Not applicable
Iceland	22.0%	(10.7%-35.9%)
Ireland	29.0%	Not applicable
Italy	30.5%	(24.8%-36.4%)
Macedonia	13.1%	Not applicable
Norway	27.1%	(13.3%-43.7%)
Poland	17.0%	(6.2%-31.7%)
Scotland	13.8%	Not applicable
Slovakia	21.3%	Not applicable
Spain	18.7%	(15.0%-22.7%)
Sweden	22.4%	(16.4%-29.0%)
The Netherlands	19.2%	(9.2%-31.8%)
United Kingdom	19.4%	(12.5%-27.6%)
North America	19.5%	(17.1%-22.1%)
Canada	24.6%	(17.3%-32.7%)
United States	19.0%	(16.3%-21.8%)
South America	21.5%	(15.4%-28.2%)
Argentina	17.8%	(12.4%-24.0%)
Brazil	25.2%	(18.6%-32.3%)
Chile	6.5%	Not applicable

CI, Confidence interval; *PsA*, psoriatic arthritis.

Supplemental Table II. Results from quality assessment according to the Newcastle-Ottawa Scale

Author	Selection	Comparability	Outcome/exposure	Total
Green et al[S1] (1981)	2	0	2	4/10
Scarpa et al[S2] (1984)	2	—	2	4/8
Economidou et al[S3] (1985)	1	2	2	5/9
Stern[S4] (1985)	2	—	3	5/8
Gottlieb et al[S5] (1987)	2	—	3	5/8
Kononen et al[S6] (1987)	2	0	2	4/10
Oriente et al[S7] (1989)	2	—	2	4/8
Zanolli and Wikle[S8] (1992)	1	—	1	2/8
Falk and Vandbakk[S9] (1993)	2	—	2	4/8
Oriente et al[S10] (1994)	3	—	3	6/8
Salvarani et al[S11] (1995)	2	2	2	6/10
Fleischer et al[S12] (1996)	2	—	3	5/8
Baek et al[S13] (2000)	2	2	3	7/10
Lundberg et al[S14] (2000)	1	2	2	5/10
Shbeeb et al[S15] (2000)	5	—	3	8/8
Alenius et al[S16] (2002)	3	—	3	6/8
Ferrandiz et al[S17] (2002)	2	—	3	5/8
Kundakci et al[S18] (2002)	2	—	3	5/8
Zachariae et al[S19] (2002)	3	—	3	6/8
Kawada et al[S20] (2003)	1	—	2	3/8
Chodorowska et al[S21] (2004)	4	2	2	8/9
Kumar et al[S22] (2004)	3	—	3	6/8
Dervis[S23] (2005)	4	2	2	8/9
Gelfand et al[S24] (2005)	2	—	3	5/8
Gisondi et al[S25] (2005)	3	—	3	6/8
Mallbris et al[S26] (2005)	2	—	3	5/8
Gudjonsson et al[S27] (2006)	3	—	3	6/8
Ojetti et al[S28] (2006)	4	2	2	8/9
Seyhan et al[S29] (2006)	2	0	3	5/10
Sommer et al[S30] (2006)	4	2	3	9/9
Al-Mutairi et al[S31] (2007)	2	—	3	5/8
Altobelli et al[S32] (2007)	2	2	3	7/10
Dayangac-Erden et al[S33] (2007)	0	2	2	4/9
Fan et al[S34] (2007)	2	—	3	5/8
Gisondi et al[S35] (2007)	4	2	2	8/9
Husni et al[S36] (2007)	2	—	3	5/8
Schmitt and Ford[S37] (2007)	3	—	3	6/8
Jamshidi et al[S38] (2008)	4	—	2	6/8
Callis Duffin et al[S39] (2009)	2	—	3	5/8
Dominguez et al[S40] (2009)	2	—	3	5/8
Ejaz et al[S41] (2009)	2	—	3	5/8
Guinot et al[S42] (2009)	2	—	3	5/8
Ibrahim et al[S43] (2009)	2	—	3	5/8
Lynde et al[S44] (2009)	2	2	2	6/10
Miele et al[S45] (2009)	4	2	2	8/9
Radtke et al[S46] (2009)	4	—	3	7/8
Reich et al[S47] (2009)	4	1	3	8/10
Soy et al[S48] (2009)	0	2	2	4/9
Takahashi et al[S49] (2009)	4	—	3	7/8
Wasel et al[S50] (2009)	3	—	3	6/8
Yu et al[S51] (2009)	4	2	3	9/9
Bandoli et al[S52] (2010)	4	2	2	8/9
Chandran and Raychaudhuri[S53] (2010)	2	2	2	6/9
Christophers et al[S54] (2010)	4	2	3	9/10
Kacar et al[S55] (2010)	2	0	3	5/10

Continued

Supplemental Table II. Cont'd

Author	Selection	Comparability	Outcome/exposure	Total
Karadag et al[S56] (2010)	4	2	2	8/9
Lecluse et al[S57] (2010)	4	2	3	9/9
Natarajan et al[S58] (2010)	2	—	2	4/8
Palotai et al[S59] (2010)	4	—	3	7/8
Reich et al[S60] (2010)	3	2	3	8/10
Singh and Singh[S61] 2010	1	2	1	4/9
Sultan et al[S62] (2010)	2	2	2	6/9
Vena et al[S63] (2010)	4	2	3	9/9
Zaragoza et al[S64] (2010)	2	—	3	5/8
Brunasso et al[S65] (2011)	4	2	2	8/9
De Simone et al[S66] (2011)	2	2	1	5/9
Ghajarzadeh et al[S67] (2011)	4	2	2	8/9
Hay and Rashed[S68] (2011)	4	2	2	8/9
Kimball et al[S69] (2011)	4	2	3	9/9
Ozden et al[S70] (2011)	4	2	3	9/9
Strober et al[S71] (2011)	2	—	3	5/8
Valenzuela et al[S72] (2011)	3	2	1	6/10
Van Lumig et a[S73] (2011)	3	—	3	6/8
Verghese et al[S74] (2011)	4	2	2	8/9
Warnecke et al[S75] (2011)	4	2	2	8/9
Yang et al[S76] (2011)	3	—	3	6/8
Zervou et al[S77] (2011)	4	2	2	8/9
Zhang et al[S78] (2011)	3	2	2	7/9
Armesto et al[S79] (2012)	2	2	2	6/9
Armstrong et al[S80] (2012)	2	2	3	7/10
Bonifati et al[S81] (2012)	2	—	3	5/8
Brazelli et al[S82] (2012)	3	—	3	6/8
Carneiro et al[S83] (2012)	3	—	3	6/8
Cemil et al[S84] (2012)	2	2	2	6/9
De Marco et al[S85] (2012)	2	—	3	5/8
Ghatnekar et al[S86] (2012)	2	—	2	4/8
Gisondi et al[S87] (2012)	3	2	2	7/9
Gisondi et al[S88] (2012)	3	2	2	7/9
Grozdev et al[S89] (2012)	3	2	3	8/10
Khraishi et al[S90] (2012)	2	—	3	5/8
Kimball et al[S91] (2012)	4	2	3	9/9
Li et al[S92] (2012)	1	—	2	3/8
Madanagobalane and Anandan[S93] (2012)	3	2	2	7/9
Maradit-Kremers et al[S94] (2012)	4	2	3	9/9
Orgaz-Molina et al[S95] (2012)	4	2	3	9/9
Szponar et al[S96] (2012)	2	2	2	6/9
Tinazzi et al[S97] (2012)	2	—	3	5/8
Wee et al[S98] (2012)	2	2	2	6/10
Wu et al[S99] (2012)	4	2	3	9/9
Atwa et al[S100] (2012)	2	2	2	6/10
Coates et al[S101] (2013)	2	2	3	7/10
Dameskva et al[S102] (2013)	4	2	2	8/9
Di Cesare et al[S103] (2013)	3	2	2	7/9
Haroon et al[S104] (2013)	3	—	3	6/8
Kilic et al[S105] (2013)	4	2	2	8/9
Klassen et al[S106] (2013)	3	—	3	6/8
Lora et al[S107] (2013)	3	2	2	7/9
Mercy et al[S108] (2013)	3	—	3	6/8
Moro et al[S109] (2013)	3	2	3	8/10
Paller et al[S110] (2013)	3	2	3	8/10

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Supplemental Table II. Cont'd

Author	Selection	Comparability	Outcome/exposure	Total
Van Der Velden et al[S111] (2013)	4	2	3	9/9
Walsh et al[S112] (2013)	2	—	3	5/8
Albareda et al[S113] (2014)	4	2	2	8/9
Augustin et al[S114] (2014)	4	—	3	7/8
Baeta et al[S115] (2014)	2	2	3	7/10
Bardazzi et al[S116] (2014)	2	2	3	7/10
D'Epiro et al[S117] (2014)	1	—	3	4/8
Eirís et al[S118] (2014)	3	2	2	7/9
Fernandez-Torrez et al[S119] (2014)	3	—	3	6/8
Ficco et al[S120] (2014)	3	—	3	6/8
Gisondi et al[S121] (2014)	4	2	2	8/9
Henes et al[S122] (2014)	2	2	3	7/10
Kimball et al[S123] (2014)	4	—	3	7/8
Kimball et al[S124] (2014)	4	2	3	9/9
Kokpol et al[S125] (2014)	4	2	3	9/9
Kumar et al[S126] (2014)	3	—	3	6/8
Lofvendahl et al[S127] (2014)	5	—	3	8/8
Mease et al[S128] (2014)	5	—	3	8/8
Menegón et al[S129] (2014)	4	2	2	8/9
Morisco et al[S130] (2014)	2	2	3	7/8
Moustou et al[S131] (2014)	5	—	3	8/8
Sanchez-Carazo et al[S132] (2014)	3	2	2	7/8
Wu et al[S133] (2014)	2	—	3	5/8
Belinchón et al[S134] (2015)	4	2	3	9/10
Campanati et al[S135] (2015)	3	2	3	8/10
Cinar et al[S136] (2015)	2	—	3	5/8
Crincoli et al[S137] (2015)	3	2	2	7/9
Estebaranz et al[S138] (2015)	2	2	2	6/10
Feldman et al[S139] (2015)	4	2	3	9/9
Geel et al[S140] (2015)	4	—	3	7/8
Gilet et al[S141] (2015)	4	—	3	7/8
Gniadecki et al[S142] (2015)	5	2	3	10/10
Iskandar et al[S143] (2015)	3	2	3	8/10
Liamas-Velasco et al[S144] (2015)	2	2	2	6/10
Lysell et al[S145] (2015)	2	2	3	7/10
Mahé et al[S146] (2015)	4	2	2	8/9
Ng et al[S147] (2015)	4	2	3	9/10
Ohara et al[S148] (2015)	2	—	3	5/8
Ranza et al[S149] (2015)	1	—	3	4/8
Schons et al[S150] (2015)	2	2	3	7/10
Spelman et al[S151] (2015)	2	—	3	5/8
Tabolli et al[S152] (2015)	4	2	3	9/10
Takeshita et al[S153] (2015)	5	2	3	10/10
Truong et al[S154] (2015)	2	—	3	5/8
Vanaclocha et al[S155] (2015)	3	2	3	8/10
Vijay[S156] (2015)	2	—	3	5/8
You et al[S157] (2015)	2	—	3	5/8
Abji et al[S158] (2016)	3	2	3	8/10
Cardili et al[S159] (2016)	3	2	2	7/9
Carpentieri et al[S160] (2016)	4	2	3	9/10
Chek et al[S161] (2016)	5	2	3	10/10
Chiowchanwisawakit et al[S162] (2016)	2	—	3	5/8
Coates et al[S163] (2016)	2	2	2	6/10
Esposito et al[S164] (2016)	2	—	3	5/8
Finet et al[S165] (2016)	3	2	3	8/10

Continued

Supplemental Table II. Cont'd

Author	Selection	Comparability	Outcome/exposure	Total
Fuxench et al[S166] (2016)	4	2	3	9/9
Garbers et al[S167] (2016)	2	—	3	5/8
Gisondi et al[S168] (2016)	3	2	2	8/9
Gisondi and Girolomoni[S169] (2016)	2	—	3	5/8
Harle et al[S170] (2016)	3	—	3	6/8
Hsu et al[S171] (2016)	3	2	3	8/10
Indhumathi et al[S172] (2016)	2	2	2	6/9
Jungo et al[S173] (2016)	2	1	2	5/10
Karreman et al[S174] (2016)	3	—	3	6/8
Klufas et al[S175] (2016)	1	—	3	4/8
Langenbruch et al[S176] (2016)	3	—	3	6/8
Luca et al[S177] (2016)	2	—	3	5/8
Papadavid et al[S178] (2016)	1	2	2	5/10
Pongpit et al[S179] (2016)	3	2	3	8/10
Reich et al[S180] (2016)	3	—	3	6/8
Resorlu et al[S181] (2016)	1	2	2	5/10
Rutter et al[S182] (2016)	3	2	3	8/10
Santilli et al[S183] (2016)	4	2	2	8/9
Sherin and Udaykumar[S184] (2016)	2	—	3	5/8
Shin et al[S185] (2016)	2	—	3	5/8
Siddiqui et al[S186] (2016)	4	—	32	7/8
Sudhesan et al[S187] (2016)	3	2	2	7/9
Temel et al[S188] (2016)	3	2	3	8/9
Urbancek et al[S189] (2016)	2	—	3	5/8
Vilarrasa et al[S190] (2016)	3	—	3	6/8
Wade et al[S191] (2016)	4	—	3	7/8
Asgari et al[S192] (2017)	4	2	3	9/9
Augustin et al[S193] (2017)	2	2	2	6/10
Belinchón et al[S194] (2017)	3	2	3	8/10
Bronckers et al[S195] (2017)	2	2	3	7/10
Chen et al[S196] (2017)	4	2	3	9/10
Chi et al[S197] (2017)	4	2	3	9/9
Daulatabad et al[S198] (2017)	2	—	2	4/8
Dogan et al[S199] (2017)	2	—	3	5/8
Egeberg et al[S200] (2017)	4	2	3	9/9
Eppinga et al[S201] (2017)	1	2	2	5/10
Ergun et al[S202] (2017)	3	2	3	7/9
Feldman et al[S203] (2017)	4	2	3	9/9
Girisha and Thomas[S204] (2017)	3	2	3	8/9
Hagg et al[S205] (2017)	4	2	3	9/10
Herakal et al[S206] (2017)	2	2	2	6/9
Hsiao et al[S207] (2017)	1	2	1	4/10
Kelati et al[S208] (2017)	2	—	3	5/8
Kisiel et al[S209] (2017)	2	2	3	7/9
Kojanova et al[S210] (2017)	3	2	2	7/10
Lamb et al[S211] (2017)	3	2	2	7/10
Mishra et al[S212] (2017)	2	—	3	5/8
Mysliwiec et al[S213] (2017)	2	2	2	6/9
Pourchot et al[S214] (2017)	3	2	2	7/10
Shalom et al[S215] (2017)	3	2	3	8/10
Tsuruta et al[S216] (2017)	4	2	3	9/9
Vassilatou et al[S217] (2017)	4	2	3	9/9
Zweegers et al[S218] (2017)	3	2	2	7/10

Supplemental Table III. Results from the heterogeneity assessment analysis

Analysis	Cochran Q	I^2 (inconsistency)
All studies	51,353.956365 (df = 265), $P < .0001$	99.5% (95% CI = 99.5%-99.5%)
Children/adolescents	257.50413 (df = 20), $P < .0001$	92.2% (95% CI = 89.9%-93.8%)
Adults	49,850.155111 (df = 244), $P < .0001$	99.5% (95% CI = 99.5%-99.5%)
Women	851.049548 (df = 35), $P < .0001$	95.9% (95% CI = 95.3%-96.4%)
Men	944.758517 (df = 35), $P < .0001$	96.3% (95% CI = 95.8%-96.7%)
CASPAR	1,375.560066 (df = 44), $P < .0001$	96.8% (95% CI = 96.4%-97.1%)
Moll and Wright criteria	2,106.084629 (df = 19), $P < .0001$	99.1% (95% CI = 99.0%-99.2%)
Europe	20,268.547922 (df = 118), $P < .0001$	99.4% (95% CI = 99.4%-99.4%)
Asia	6,606.785307 (df = 58), $P < .0001$	99.1% (95% CI = 99.1%-99.2%)
North America	12,837.963169 (df = 46), $P < .0001$	99.6% (95% CI = 99.6%-99.7%)
South America	88.934535 (df = 9), $P < .0001$	89.9% (95% CI = 83.9%-92.9%)
Africa	93.720955 (df = 2), $P < .0001$	97.9% (95% CI = 96.6%-98.5%)
Italy	1,885.727292 (df = 35), $P < .0001$	98.1% (95% CI = 98.0%-98.3%)
Spain	281.89573 (df = 16), $P < .0001$	94.3% (95% CI = 92.7%-95.4%)
Germany	128.502938 (df = 11), $P < .0001$	91.4% (95% CI = 87.5%-93.7%)
The Netherlands	1,113.346677 (df = 10), $P < .0001$	99.1% (95% CI = 99.0%-99.2%)
Sweden	562.515846 (df = 7), $P < .0001$	98.8% (95% CI = 98.5%-98.9%)
Denmark	1,287.043367 (df = 4), $P < .0001$	99.7% (95% CI = 99.7%-99.7%)
Greece	360.162616 (df = 4), $P < .0001$	98.9% (95% CI = 98.6%-99.1%)
Poland	65.734974 (df = 3), $P < .0001$	95.4% (95% CI = 91.9%-97.0%)
Finland	7.536024 (df = 1), $P = .006$	Not available
Norway	4.509611 (df = 1), $P = .0337$	Not available
France	146.803591 (df = 6), $P < .0001$	95.9% (95% CI = 94.2%-96.9%)
United Kingdom	1,827.634289 (df = 9), $P < .0001$	99.5% (95% CI = 99.5%-99.5%)
Iceland	28.63972 (df = 1), $P < .0001$	Not available
Turkey	237.463501 (df = 14), $P < .0001$	94.1% (95% CI = 92.3%-95.3%)
India	406.101175 (df = 14), $P < .0001$	96.6% (95% CI = 95.8%-97.1%)
Japan	1,022.726575 (df = 4), $P < .0001$	99.6% (95% CI = 99.6%-99.7%)
China	330.786131 (df = 4), $P < .0001$	98.8% (95% CI = 98.5%-99.0%)
Thailand	186.146537 (df = 3), $P < .0001$	98.4% (95% CI = 97.8%-98.8%)
Taiwan	137.701857 (df = 2), $P < .0001$	98.5% (95% CI = 97.9%-98.9%)
South Korea	1.489581 (df = 2), $P = .4748$	0% (95% CI = 0-72.9%)
Iran	5.514712 (df = 1), $P = .0189$	Not available
Pakistan	1.152595 (df = 1), $P = .283$	Not available
United States	11,629.796979 (df = 35), $P < .0001$	99.7% (95% CI = 0 to $-\infty$)
Canada	122.287039 (df = 7), $P < .0001$	94.3% (95% CI = 91.5%-95.8%)
Brazil	46.80496 (df = 6), $P < .0001$	87.2% (95% CI = 74.8%-92.0%)
Argentina	0.047787 (df = 1), $P = .827$	Not available
Population size <500	3,980.059445 (df = 172), $P < .0001$	95.7% (95% CI = 95.4%-95.9%)
Population size 500-1000	1,949.067349 (df = 34), $P < .0001$	98.3% (95% CI = 98.1%-98.4%)
Population size ≥1000	35,372.117945 (df = 56), $P < .0001$	99.8% (95% CI = 99.8%-99.8%)
Published before 2000	338.550153 (df = 12), $P < .0001$	96.5% (95% CI = 95.6%-97.1%)
Published in 2000-2009	10,168.059791 (df = 50), $P < .0001$	99.5% (95% CI = 99.5%-99.5%)
Published in 2010-2017	39,582.143547 (df = 201), $P < .0001$	99.5% (95% CI = 99.5%-99.5%)
Clinical trials	595.721927 (df = 33), $P < .0001$	94.5% (95% CI = 93.5%-95.2%)
Observational studies	9,007.731995 (df = 160), $P < .0001$	98.2% (95% CI = 98.1%-98.3%)
Register-based studies	22,975.476167 (df = 47), $P < .0001$	99.8% (95% CI = 99.8%-99.8%)
Population-based studies	20,547.466663 (df = 45), $P < .0001$	99.8% (95% CI = 0 to $-\infty$)
NOS, good quality	36,374.576652 (df = 133), $P < .0001$	99.6% (95% CI = 0 to $-\infty$)
NOS, fair or poor quality	8,789.763402 (df = 83), $P < .0001$	99.1% (95% CI = 99.0%-99.1%)

CASPAR, Classification Criteria for Psoriatic Arthritis; *CI*, confidence interval; *df*, degrees of freedom; *NOS*, Newcastle-Ottawa Scale.

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JAMA Surgery | Original Investigation

Incidence and Prognosis of Psoriasis and Psoriatic Arthritis in Patients Undergoing Bariatric Surgery

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IMPORTANCE Psoriasis and obesity are strongly linked, and weight loss appears to improve psoriasis symptoms and severity. Bariatric surgery may induce remission of psoriasis, but data are limited to small studies and case series.

OBJECTIVE To examine the incidence and prognosis of psoriasis and psoriatic arthritis in patients undergoing bariatric surgery (gastric bypass and gastric banding).

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study used individual-level linkage of administrative and public health registers in Denmark. All Danish citizens who received gastric bypass or gastric banding between January 1, 1997, and December 31, 2012, were included in the study. Data analysis was performed from February 4 to April 14, 2016.

MAIN OUTCOMES AND MEASURES The outcomes were incident (new-onset) psoriasis or psoriatic arthritis, or progression to severe psoriasis. Incidence rates per 1000 person-years were calculated, and crude and adjusted hazard ratios (HRs) were estimated by Cox regression models and presented with 95% CIs. The HRs were obtained by comparing the risk in the cohort of patients presurgery and postsurgery, with the presurgery groups serving as the reference groups.

RESULTS We identified 12 364 and 1071 patients receiving gastric bypass and gastric banding, respectively. The gastric bypass subset was composed of 9480 (76.7%) women and 2884 (23.3%) men at the study start; the mean (SD) age of these patients was 27.8 (10.1) years at the study start and 41.0 (10.0) years at the time of surgery. The gastric banding subset was composed of 800 (74.7%) women and 271 (25.3) men; the mean (SD) age of these patients was 32.3 (10.1) years at the study start and 41.7 (10.0) years at the time of surgery. Adjusted HRs of psoriasis were 0.52 (95% CI, 0.33-0.81) and 1.23 (95% CI, 0.40-3.75) for gastric bypass and gastric banding, respectively. Similarly, adjusted HRs of progression to severe psoriasis were 0.44 (95% CI, 0.23-0.86) and 1.18 (95% CI, 0.12-11.49) for gastric bypass and gastric banding, respectively. Adjusted HRs of psoriatic arthritis were 0.29 (95% CI, 0.12-0.71) and 0.53 (95% CI, 0.08-3.56) for gastric bypass and gastric banding, respectively.

CONCLUSIONS AND RELEVANCE Gastric bypass was associated with a significantly reduced risk and improved prognosis of psoriasis and psoriatic arthritis, whereas gastric banding was not. This finding may be caused by the postoperative differences in nutrient intake and/or weight loss as well as differences in the secretion of hormones that potentially modulate inflammation.

Invited Commentary
page 349

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Psoriasis is a chronic inflammatory disease of which the exact cause is not fully understood, but both genetic and environmental factors have been implicated in its onset and progression.[1] The prevalence is approximately 2% to 3% in Europe and up to 9% in some Nordic countries.[2] Psoriasis is characterized by localized or widespread thick, raised, silvery white scaling and pruritic plaques. It is also a systemic disease that affects joints, vasculature, and other tissues.[1,3] Approximately one-third of patients with psoriasis develop psoriatic arthritis, and patients with severe psoriasis have a shortened life expectancy (most likely because of cardiovascular disease).[1,3] Obesity is significantly and independently associated with the presence and severity of psoriasis,[4] likely as a result of obesity-induced, systemic low-grade inflammation.[5,6] Obese patients show a slowed response to antipsoriatic therapy,[7] so weight loss has been suggested as a potential therapeutic option for patients with psoriasis.[8,9]

Gastric banding is considered a purely restrictive procedure that involves the laparoscopic placement of an adjustable band around the cardia of the stomach, creating an approximately 15-mL proximal pouch. However, gastric bypass, in particular Roux-en-Y gastric bypass, is the favored surgical treatment for patients who are morbidly obese and accounts for more than 95% of bariatric surgical procedures in Denmark (in accordance with national and international guidelines).[10] In this procedure, the stomach is divided into a small proximal pouch from which ingested nutrients are diverted to the jejunum with a Roux-en-Y gastrojejunostomy and thus bypass a large segment of the proximal small bowel. Gastric bypass results in robust and sustained weight loss. Interestingly, the procedure also causes a rapid improvement of the glucose tolerance in patients with type 2 diabetes (or even complete remission of the diabetic state), even before any significant weight loss has occurred.[11] This phenomenon is most likely mediated by multifarious factors. One of the most well-described factors is the rerouting of ingested nutrients directly from the stomach to the distal part of the small intestine where there are abundant enteroendocrine cells that secrete the insulinotropic, glucagonostatic, and appetite-reducing hormone glucagon-like peptide-1 (GLP-1).

Research has suggested that bariatric surgery has antipsoriatic effects, as evidenced by some patients who are in complete remission of psoriasis after undergoing gastric bypass, but these data are limited to small studies and case series; even less is known about the effects of gastric banding.[12-15] Therefore, we examined the incidence and prognosis of psoriasis and psoriatic arthritis in patients treated with gastric bypass or gastric banding. We identified a nationwide Danish cohort and observed them for a maximum of 16 years.

Key Points

Question Does bariatric surgery affect the risk and prognosis of psoriasis?

Findings In a population-based cohort study, gastric bypass was associated with reduced risk and improved prognosis of psoriasis and psoriatic arthritis, whereas gastric banding was not.

Meaning The results may be due to postoperative differences in nutrient intake and/or weight loss, but differences in the secretion of hormones that potentially modulate inflammation may also play a role.

Methods

Data Sources and Study Population

In Denmark, the population-based health registry provides an opportunity to perform a population-based cohort study. Each citizen is assigned a unique civil registration number at birth or on immigration, allowing for unambiguous linkage among all population-based administrative and health registries in the country.[16] The Danish National Health Service provides all residents with tax-supported health care that includes unrestricted access to hospitals and general practitioners. Information on all patients admitted to Danish hospitals is stored in the Danish National Patient Register, in accordance with the Danish version of *the International Classification of Diseases*; hospital-based treatments, such as surgical procedures, are recorded by treatment procedure (Sundhedsvæsnets Klassifikation System [SKS]) codes.[17] In addition, all pharmacy-dispensed prescriptions in the country are recorded in the Register of Medicinal Product Statistics, and all drugs are classified according to the Anatomical Therapeutic Chemical Classification System.[18]

Using data from the Danish National Patient Registry, we identified all patients who received bariatric surgery, including gastric bypass (SKS code KJDF1) and gastric banding (SKS code KJDF2), between January 1, 1997, and December 31, 2012. All patients were included at the study start (January 1, 1997) and followed up until migration, death from any cause, the occurrence of an endpoint, or December 2012, whichever came first. Patients with psoriatic disease prior to study start were excluded to enable examination of incident (new-onset) cases of psoriasis or psoriatic arthritis.

Covariates (ie, alcohol abuse and diabetes, smoking, and socioeconomic status) were assessed up to 5 years prior to study start or surgery, as appropriate. Information on tax-reported household income was obtained from Statistics Denmark to calculate an age-standardized index of socioeconomic status between 0 (lowest group) and 4 (highest group) on the basis of mean gross annual income. Diabetes was defined by either a hospital diagnosis or use of glucose-lowering drugs. Collection of proxy data on smoking history and alcohol abuse was performed as described previously.[19,20] The end points were the first occurrence of psoriasis or psoriatic arthritis and the classification of psoriasis as a severe disease. Patients were classified with severe psoriasis when they received systemic antipsoriatic therapy (biological drugs, cyclosporine, psoralens, retinoids, or methotrexate). A previous study described and validated this method for psoriasis identification and severity classification with a sensitivity of 98%.[19] The end points were analyzed separately, and the occurrence of an end point in one analysis (eg, risk of psoriasis) did not result in censoring in the other analysis (eg, risk of psoriatic arthritis). We followed recommendations from Strengthening the Reporting of

Table 1. Characteristics of the Study Population[a]

Characteristic	Gastric Bypass (n = 12 364)		Gastric Banding (n = 1071)	
	At Study Start	At Time of Surgery	At Study Start	At Time of Surgery
Sex				
Women	9480 (76.7)		800 (74.7)	
Men	2884 (23.3)		271 (25.3)	
Age, mean (SD)	27.8 (10.1)	41.0 (10.0)	32.3 (10.1)	41.7 (10.0)
Socioeconomic status				
Lowest income group	2492 (20.2)	2472 (20.0)	218 (20.4)	215 (20.1)
Below-average income group	2468 (20.0)	2473 (20.0)	213 (19.9)	214 (20.0)
Average income group	2468 (20.0)	2473 (20.0)	214 (20.0)	214 (20.0)
Above-average income group	2468 (20.0)	2473 (20.0)	213 (19.9)	214 (20.0)
Highest income group	2468 (20.0)	2473 (20.0)	213 (19.9)	214 (20.0)
Alcohol abuse	96 (0.8)	93 (0.8)	14 (1.3)	13 (1.2)
Diabetes	142 (1.2)	2271 (18.4)	18 (1.7)	191 (17.8)
Smoking	926 (7.5)	1850 (15.0)	56 (5.2)	174 (16.3)

[a] Data are given as number (percentage) unless otherwise noted.

Observational Studies in Epidemiology to conduct and report this study.[21]

This study was approved by the Danish Data Protection Agency. Danish law does not require ethical approval or written patient consent when nationwide registries are used for registry studies. Data analysis was performed from February 4 to April 14, 2016.

Statistical Analysis

We described patient characteristics with means (SDs) for continuous variables, and frequencies and percentages for categorical variables. To ensure accurate registration of time at risk, we included surgery status as a time-dependent variable. This means patients, before surgery, contributed risk time in the presurgery groups and, after surgery, allocated risk time to the postsurgery groups. Consequently, events (diagnosis of psoriasis or psoriatic arthritis) that occurred before the surgery date were allocated to the presurgery groups, and events that occurred after the surgery date were allocated to the postsurgery groups. However, if a patient was diagnosed with psoriasis in the presurgery group, this individual was censored and did not contribute risk time in the postsurgery groups during the analysis of incident psoriasis. Rather than use a healthy (eg, general population) comparison group, we compared the risk in the same group of individuals presurgery and postsurgery because the direct effect of the intervention can be observed with minimal risk of introducing bias that occurs because of between-group (eg, demographic) differences. Throughout this article, the presurgery groups constitute the reference groups.

We used SAS, version 9.4 (SAS Institute Inc), and STATA, version 13 (StataCorp), to summarize incidence rates per 1000 person-years. We also used Cox proportional hazards regression models to obtain hazard ratios (HRs) for the risk of any psoriasis, severe psoriasis, and psoriatic arthritis. The HRs were calculated as crude, age-adjusted and sex-adjusted, and fully adjusted (ie, age, sex, alcohol abuse, and socioeconomic, smoking, and diabetes status were considered). These covariates were chosen a priori because they are independently associated with psoriasis. Alcohol abuse data as well as smoking and diabetes status were continually updated throughout the study. The Cox proportional hazards assumption was tested and found to be valid. All statistical tests were conducted using a level of significance of .05, and results were reported with 95% CIs, where applicable. Because the Danish Data Protection Agency does not permit the presentation of data on groups composed of fewer than 3 individuals, the results of 1 or 2 events or individuals are described as "fewer than 3" and derived results are shown as approximations.

Results

The study comprised 12 364 patients undergoing gastric bypass and 1071 patients undergoing gastric banding between January 1, 1997, and December 31, 2012. There was a female predominance in both cohorts. Patient characteristics are shown in **Table 1**.

From study start until the time of surgery, there were 272 (2.2%) and 16 (1.5%) cases of incident psoriasis in the gastric bypass and gastric banding groups, respectively, including 84 (0.8%) and fewer than 3 cases of severe psoriasis, respectively. Before bariatric surgery, there were 56 patients (0.5%) in the gastric bypass group and 3 patients (0.3%) in the gastric banding group who developed psoriatic arthritis. After bariatric surgery, there were 49 (0.5%) and 15 (1.4%) cases of incident psoriasis in the gastric bypass and gastric banding groups, respectively, including 20 (0.0%) and 5 (0.5%) cases of severe psoriasis, respectively, and 11 (0.1%) and 6 (0.6%) cases of incident psoriatic arthritis, respectively. Follow-up time and incidence rates per 1000 person-years are shown in **Table 2**. There was a significantly decreased risk of psoriasis (adjusted HR, 0.52; 95% CI, 0.33-0.81), severe psoriasis (adjusted HR, 0.44; 95% CI, 0.23-0.86), and psoriatic arthritis (adjusted HR, 0.29; 95% CI, 0.12-0.71) in patients following gastric bypass. Interestingly, there were no significant differences in risk of psoriasis (adjusted HR, 1.23; 95% CI, 0.40-

Table 2. Summary of Follow-up Time, Number of Events, and Event Rates per 1000 Person-years

Characteristic	Gastric Bypass		Gastric Banding	
	Presurgery	Postsurgery	Presurgery	Postsurgery
Any psoriasis				
Person-years	158 404.6	33 175.8	9939.1	6724.1
No.of events	272	49	16	15
Incidence rate per 1000 person-years (95% CI)	1.72 (1.52-1.93)	1.48 (1.12-1.95)	1.61 (0.99-2.63)	2.23 (1.34-3.70)
Severe psoriasis				
Person-years	159 529.2	33 729.6	10 000.5	6848.4
No. of events	84	20	<3[a]	5
Incidence rate per 1000 person-years (95% CI)	0.59 (0.43-0.65)	0.53 (0.38-0.92)	<0.30 (0.05-0.80)	0.73 (0.30-1.75)
Psoriatic arthritis				
Person-years	159 652.1	33 823.2	9999.4	6844.4
No. of events	56	11	3	6
Incidence rate per 1000 person-years (95% CI)	0.35 (0.27-0.46)	0.33 (0.18-0.59)	0.30 (0.10-0.93)	0.88 (0.39-1.95)

[a] Because the Danish Data Protection Agency does not permit presentation of data on groups composed of fewer than 3 individuals, results of 1 or 2 events or individuals are described as "<3" and derived results are shown as approximations.

Table 3. Crude and Adjusted Hazard Ratios of Psoriasis, Severe Psoriasis, and Psoriatic Arthritis in Patients Undergoing Bariatric Surgery

Characteristic	Crude		Age Adjusted and Sex Adjusted		Fully Adjusted[a]	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Gastric bypass						
Any psoriasis	0.54 (0.34-0.84)	.006	0.52 (0.32-0.81)	.004	0.52 (0.33-0.81)	.004
Severe psoriasis	0.45 (0.23-0.88)	.02	0.44 (0.22-0.73)	.02	0.44 (0.23-0.86)	.02
Psoriatic arthritis	0.31 (0.13-0.76)	.01	0.30 (0.12-0.73)	.01	0.29 (0.12-0.71)	.01
Gastric banding						
Any psoriasis	1.42 (0.47-4.30)	.54	1.23 (0.41-3.74)	.71	1.23 (0.40-3.75)	.72
Severe psoriasis	1.32 (0.14-12.11)	.81	1.28 (0.14-11.85)	.83	1.18 (0.12-11.48)	.89
Psoriatic arthritis	0.62 (0.10-3.89)	.61	0.58 (0.09-3.68)	.57	0.53 (0.08-3.56)	.52

[a] Fully adjusted considered age, sex, alcohol abuse, and socioeconomic, smoking, and diabetes status.

3.75), severe psoriasis (adjusted HR, 1.18; 95% CI, 0.12-11.48), or psoriatic arthritis (adjusted HR, 0.53; 95% CI, 0.08-3.56) following gastric banding (**Table 3**).

Discussion

In this nationwide study of patients undergoing bariatric surgery, gastric bypass was associated with a significantly reduced risk and progression of psoriasis and psoriatic arthritis whereas gastric banding was not. To date, this is the largest study to examine the effect of bariatric surgery on psoriatic disease, and our results suggest that the type of bariatric procedure is important for the antipsoriatic effects associated with surgical weight loss therapy; gastric bypass stands out as a bariatric procedure with antipsoriatic effects. One of the features that distinguishes gastric bypass from gastric banding is the dramatically changed secretory profile of a number of gut hormones released during meal intake (eg, GLP-1). According to our results, these postoperative hormonal changes may, in addition to the weight loss, be important for the antipsoriatic effect of gastric bypass. Both gastric bypass and gastric banding have been shown to lead to sustained weight loss, suggesting that the observed differences in our study might be caused by factors other than weight loss.[22]

It is well established that obesity is a risk factor for psoriasis and psoriatic arthritis,[4,23] and obese patients with psoriatic disease are less likely than leaner individuals with psoriatic disease to achieve a satisfactory treatment response.[8] Similarly, numerous studies suggest that a low-calorie diet is associated with greater improvement in objective disease measurements, such as the Psoriasis Area and Severity Index and the Dermatology Life Quality Index.[8] Previously, a study of 33 morbidly obese patients found an improvement of psoriasis symptoms in 39.4% of patients after bariatric surgery. Interestingly, and in potential agreement with our findings, more patients who underwent gastric bypass reported improvements compared with those who received nonbypass procedures (ie, sleeve gastrectomy or laparoscopic adjustable gastric banding).[12] Similarly, Hossler et al[24] found that, following

bariatric surgery, 21 of 34 patients showed improvement in their psoriasis and patients tended to need less systemic antipsoriatic therapy. To date, available evidence regarding gastric bypass in the context of psoriasis is limited to these small studies and case series, and even less is known about the effect of gastric banding on psoriasis. Therefore, our study of 12 364 patients undergoing gastric bypass and 1071 patients undergoing gastric banding expands the existing literature by suggesting important differences in psoriasis outcome and prognosis following these procedures.

Both gastric bypass and gastric banding lead to weight loss and improvements in certain obesity-related comorbidities, but gastric bypass also elicits endocrine changes. The procedure increases postprandial secretion of the gut-derived hormone GLP-1, which is renowned for lowering glucose (because of its insulinotropic and glucagonostatic effects) and reducing appetite (because it activates GLP-1 receptors in the brain), whereas gastric banding does not.[25] Patients who are glucose intolerant see improvements of their glucose and insulin levels within days after gastric bypass, seemingly uncorrelated with postsurgical weight loss.[11] Such apparent changes are believed to be caused by the rerouting of ingested nutrients, bypassing a large segment of the proximal small bowel and entering the distal part of the jejunum directly.[26] Postprandial GLP-1 plasma levels increase 20-fold following gastric bypass, but not after gastric banding.[25,27] It has been suggested that the antipsoriatic effects of weight loss could be explained, at least in part, by increased GLP-1 levels.[28] Along this line, some but not all studies have demonstrated improvements in psoriasis following treatment with liraglutide, a GLP-1 receptor agonist used in treatment of type 2 diabetes and obesity.[29-31] Interestingly, GLP-1 has demonstrated anti-inflammatory effects in vitro and in vivo,[32,33] with down-regulation of tumor necrosis factor and the nuclear factor κβ pathway.[34,35] Indeed, tumor necrosis factor and nuclear factor κβ are crucial in the initiation and maintenance of the inflammatory cycle in psoriasis,[36] and it is tempting to speculate if the antipsoriatic effects observed in our study is, in part, mediated by decreased systemic inflammation because of GLP-1.

Important strengths of the study include the high accuracy of the nationwide registries as well as the available information on household income, which minimized bias regarding sex, age, comorbidity, and/or socioeconomic status. In addition, the statistical adjustments for covariates for which data were continually updated during follow-up, as well as the length and accuracy of follow-up, add credibility to our findings.

Limitations

Several limitations and strengths apply to the interpretation of our results. Because of the observational nature of our study, we cannot determine causality. We lacked information on presurgical and postsurgical body weight, and whether the observed effect is due, in part, to postsurgical differences in GLP-1 response; whether the findings are mainly due to differences in weight loss, lifestyle factors, or other mechanisms requires further examination. Some but not all studies have suggested that sustained weight loss may be greater for gastric bypass than gastric banding. Moreover, the Danish population is predominantly of Caucasian descent, which may limit extrapolation of the results to other ethnicities. Furthermore, the sample sizes and absolute number of events were limited, and the risk estimates should be interpreted accordingly.

Conclusions

In conclusion, gastric bypass was associated with a significantly reduced risk and improved prognosis of psoriasis and psoriatic arthritis, whereas gastric banding was not. Although speculative, these findings may be the result of postoperative differences in weight loss and nutrient uptake as well as differences in the postsurgical secretion of a number of gut hormones, including GLP-1.

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Correction: This article was corrected on March 7, 2018, to fix the heading for the last column of data in Table 2 so that it reads "Postsurgery" instead of "Presurgery."

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Study concept and design: Egeberg, Sørensen, Skov.
Acquisition, analysis, or interpretation of data: Egeberg, Gislason, Knop.
Drafting of the manuscript: Egeberg.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Egeberg, Gislason, Knop.
Obtained funding: Egeberg.
Administrative, technical, or material support: Egeberg, Gislason.
Study supervision: All authors.

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ORIGINAL ARTICLE

Chronologic order of appearance of immune-mediated inflammatory diseases relative to diagnosis of psoriasis

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Background: Psoriasis is a common inflammatory skin disease associated with several immune-mediated inflammatory diseases (IMIDs); however, little is known of the chronology of disease development.

Objective: To investigate the chronology of IMIDs relative to psoriasis.

Methods: We utilized routinely collected data from Danish nationwide administrative registries to examine the occurrence of IMIDs in patients with psoriasis (n = 10,923) and general population controls (n = 109,230).

Results: Approximately 20% of patients with psoriasis developed ≥1 IMID, with a 5-fold increased risk compared with the general population. Most IMIDs were diagnosed before psoriasis, except for psoriatic arthritis. Psoriasis was significantly associated with having multiple IMIDs (odds ratio 15.2, 95% confidence interval 11.6-20.0). Human leukocyte antigen B27 positivity was significantly more frequent among psoriasis patients.

Limitations: Clinical measurements were unavailable.

Conclusion: IMIDs occur frequently in patients with psoriasis and most are diagnosed before psoriasis. The observed chronology might represent important mechanisms of disease development. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2019.04.033.)

Key words: autoimmune; comorbidity; epidemiology; HLA-B27; inflammation; psoriasis; psoriatic arthritis.

Psoriasis is a common, chronic cutaneous immune-mediated inflammatory disease (IMID). Patients with psoriasis are more likely than those in the general population to have other IMIDs during their life course, the most frequent IMID being psoriatic arthritis (PsA) which occurs in ~1 in 5 psoriasis patients.[1] Presence of IMIDs might add considerably to the disease burden and confer

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excess morbidity and mortality in patients with psoriasis. Indeed, among patients with PsA, the presence of comorbidities is associated with impaired response to therapy with biologics.[2] Moreover, in a cohort of patients with inflammatory bowel disease (IBD), the presence of 1 IMID increased the susceptibility of developing other IMIDs, but whether the same holds true for psoriasis patients remains unclear.[3,4]

A number of IMIDs share genetic risk loci with psoriasis,[5] and previous epidemiologic studies have shown significant associations between psoriasis and certain IMIDs, including celiac disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, and systemic lupus erythematosus, but data on the frequency of IMIDs in large populations of patients with psoriasis remain scarce.[4,6] Importantly, a chronologic assessment of the appearance of IMIDs relative to diagnosis of psoriasis has not been done.

CAPSULE SUMMARY

- Psoriasis has been associated with a number of immune-mediated inflammatory diseases, but the chronology of these remains poorly understood.
- For most immune-mediated inflammatory diseases, onset occurred several years before diagnosis of psoriasis; however, psoriatic arthritis most often occurred after the diagnosis of psoriasis. These findings might lower the need for continuously screening for comorbidities in patients followed for psoriasis.

MATERIALS AND METHODS

Data sources and study population

Danish nationwide administrative registries served as data sources for this study. All citizens of Denmark are assigned a unique identification number at birth or migration. The number is used in all public records and enables linkage of information across several registries. The Civil Registration System contains demographic information on all citizens of Denmark, including date of birth, death, and migration.[7] Health care data were obtained through the Danish National Patient Registry (DNPR), which contains prospectively collected data on inpatient and outpatient contacts at all Danish hospitals, as well as a few private clinics.[8] Detailed records of contacts, including diagnostic codes according to the International Classification of Diseases, Tenth Revision (ICD-10), system were available. In addition, information regarding hospital procedures and hospital-dispensed medication are recorded in the DNPR by specific procedure code.[9] Routinely measured data, such as height, weight, and blood pressure, are also recorded by using specific procedure codes in the DNPR. On a national level, ~95% of data from routinely performed laboratory tests are recorded in the Register of Laboratory Results for Research. Data on all pharmacy-dispensed medication (including drug, drug strength, drug formulation, drug quantity, and indication for the prescription) are recorded in the Registry of Medicinal Products Statistics by anatomical therapeutic codes. Last, tax-reported income levels for each individual were obtained through Statistics Denmark.[10]

We identified all adult (persons ≥18 years of age) Danish patients with a first-time psoriasis diagnosis during January 1, 2007-December 31, 2016. To qualify, patients had to have received ≥1 diagnostic code for psoriasis (ICD-10 L40); the diagnosis date was defined as the date of the first of either of 2 events: the assignment of the first ICD code or receipt of the first prescription prescribed for the indication psoriasis (for cases in which patients received their first treatment by their general practitioner before they received a formal diagnosis of psoriasis in the DNPR). Patients who had ever been diagnosed with psoriasis before January 1, 2007, were excluded from the study population. For each patient, the date of their first-ever psoriasis diagnosis served as the index date. To enable comparison with the general population, each psoriasis patient was matched on sex and date of birth with 10 individuals from the general population by using incidence density sampling, ie, controls were persons who did not have psoriasis but were alive and resident in the source population at the time that the corresponding psoriasis patient received their diagnosed.

Outcomes

The following IMIDs were selected a priori: multiple sclerosis, PsA, pyoderma gangrenosum, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, celiac disease, primary sclerosing cholangitis, primary biliary cholangitis, type 1 diabetes, asthma, sarcoidosis, Graves' disease, iridocyclitis, ulcerative colitis, and Crohn's disease. IMID diagnoses were identified by the first record of the ICD-10 code. Moreover, because a considerable proportion of patients with iridocyclitis or asthma probably received their diagnoses and had their conditions managed exclusively by their general

Abbreviations used:

CI:	confidence interval
DNPR:	Danish National Patient Registry
ICD-10:	International Classification of Diseases, Tenth Revision
IBD:	inflammatory bowel disease
IL:	interleukin
IMID:	immune-mediated inflammatory disease
IQR:	interquartile range
IRR:	incidence rate ratio
OR:	odds ratio
PsA:	psoriatic arthritis
SD:	standard deviation

practitioner, we also identified such patients using prescription data. Thus, patients with iridocyclitis were identified by either ICD-10 code or by their first receipt of topical corticosteroids or anticholinergics for ocular use prescribed for the treatment of iridocyclitis. Likewise, patients with asthma were identified by either ICD-10 code or by receipt of ≥2 inhalation medications prescribed for the treatment of asthma.

Statistical analysis

Descriptive statistics were made by using means and medians (with standard deviations [SDs] and interquartile ranges [IQRs]) for continuous variables and frequencies with percentages for categorical variables. Age at inclusion was handled as a continuous variable. Socioeconomic status was presented as percentiles of age-standardized means of tax-reported income during the 5 years before study inclusion. Medication use was presented as a binary variable of never-ever exposure during the study period. Odds ratios (ORs) were estimated by using conditional logistic regression. Incidence rates were calculated per 10,000 person-years, and incidence rate ratios (IRRs) were estimated by using Poisson regression models adjusted for age and sex. To test whether the risk was significantly different before and after psoriasis was diagnosed, we compared the incidence during the 10 years before the psoriasis diagnosis (serving as the reference group) with the incidence after psoriasis diagnosis because this would yield IRRs of comparable risk time within the same population. In these analyses, significantly increased IRRs would suggest the risk of IMIDs was greatest after psoriasis diagnosis, and decreased IRR estimates would suggest that the risk was highest before psoriasis diagnosis. All OR and IRR estimates were presented with 95% confidence intervals (CIs). Graphic depictions of study results were presented by box plots and bar charts. All analyses were performed by using SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC) and STATA software version 13.0 (StataCorp, College Station, TX).

RESULTS

We identified a total of 10,923 patients with a first-ever diagnosis of psoriasis during the study period. These patients were matched with 109,230 individuals from the general population. The mean (SD) age at time of psoriasis diagnosis was 52.1 (15.5) years, and 52.9% were women. The prevalence of human leukocyte antigen B27 positivity was significantly higher among the psoriasis group (P = .03), whereas no significant differences were observed in the immunologic laboratory profile between psoriasis patients and the general population (Table I).

Before diagnosis of psoriasis (or the corresponding index date for the general population), 2181 (20.0%) psoriasis patients received a diagnosis of an IMID, compared with 8153 (7.4%) people in the general population (OR 3.10, 95% CI 2.94-3.26) (Table II). The highest number of coexisting IMIDs in a single individual before diagnosis of psoriasis was 5. After diagnosis of psoriasis, 14.7% (1607/10,923) of psoriasis patients developed ≥1 IMID, compared with 2.7% (2928/109,230) of people in the general population (OR 6.26, 95% CI 5.87-6.68). Likewise, after diagnosis of psoriasis, 1.2% (128/10,923) of psoriasis patients and 0.1% (85/109,230) of the general population received ≥2 IMID diagnoses (OR 15.2, 95% CI 11.6-20.0). The OR of ever (either before or after onset of psoriasis) having an IMID was 4.33 (95% CI 4.14-4.53) and ever having ≥2 IMIDs was 8.58 (95% CI 7.75-9.51). Excluding PsA from the models yielded no significant changes compared with our primary results (data not shown). To examine whether the observed associations could be explained by increased interaction with the health care system, we also examined the association with syphilis (serving as a negative control). In Denmark, syphilis is managed by dermatologists, and because the disease unlikely has a mechanistic link to psoriasis, increased health care contact with dermatologists observed in patients with syphilis would, therefore, suggest a positive association if the findings were affected by surveillance bias. Compared with the general population, there was no significant difference before psoriasis diagnosis (P = .171) or after psoriasis diagnosis (P = .264), and psoriasis was not significantly associated with syphilis (P = .271) when compared with the general population.

The most commonly occurring IMIDs before a psoriasis diagnosis were PsA (7.2%), followed by asthma (3.7%), rheumatoid arthritis (3.4%), and type

Table I. Characteristics of the study population

Characteristic	General population, n = 109,230	Psoriasis, n = 10,923
Age, years		
Mean (SD)	52.1 (15.5)	52.1 (15.5)
Median (IQR)	52.4 (40.4-63.2)	52.4 (40.4-63.2)
Sex, n (%)		
Women	57,770 (52.9)	5777 (52.9)
Men	51,460 (47.1)	5146 (47.1)
Socioeconomic status, n (%)		
Lowest	21,840 (20.0)	2190 (20.1)
Below average	21,627 (19.8)	2404 (22.0)
Average	21,778 (19.9)	2253 (20.6)
Above average	22,018 (20.2)	2013 (18.4)
Highest	21,967 (20.1)	2063 (18.9)
Body weight, kg, mean (SD)	76.9 (19.5)	81.8 (23.0)
Body mass index, mean (SD)	26.3 (6.5)	27.8 (7.4)
Blood pressure, mmHg, systolic/diastolic, mean (SD)	138/81 (22/13)	136/82 (21/13)
Medication, n (%)		
Acitretin	106 (0.1)	1244 (11.4)
Cyclosporine	139 (0.1)	231 (2.1)
Methotrexate	1601 (1.5)	2668 (33.6)
TNF inhibitors	325 (0.3)	783 (7.2)
HLA-B27, positive/total (%)	84/651 (12.9)	60/334 (18.0)
Immunologic laboratory profile,* positive/total (%)		
anti-dsDNA IgG	122/321 (38.0)	52/177 (29.4)
Anti-histidyl-tRNA-synthase IgG, Jo-1	5/98 (5.1)	<3/74 (NS)
ANA IgG	<3/82 (NS)	<3/66 (NS)
Anti-SSA IgG	10/128 (7.8)	5/98 (5.1)
Anti-SSB IgG	8/132 (6.1)	3/99 (3.0)
U1 snRNP IgG	6/108 (5.6)	3/79 (3.8)
Anti-topoisomerase antibody IgG, Scl-70	5/104 (4.8)	<3/76 (NS)
Anti-major centromere B IgG	5/98 (5.1)	<3/171 (NS)
Smiths antibody IgG	5/108 (4.6)	0/79 (0)
Rheumatoid factor IgM	222/645 (34.4)	114/344 (33.1)
Anti-CCP IgG	26/456 (5.7)	25/340 (7.4)

ANA, Antinuclear antibody; *CCP*, cyclic citrullinated peptide; *HLA*, human leukocyte antigen; *IQR*, interquartile range; *NS*, not shown for data security purposes; *SD*, standard deviation; *snRNP*, small nuclear ribonuclear protein; *TNF*, tumor necrosis factor; *tRNA*, transfer RNA.
*Only measurements within 1 year of psoriasis diagnosis are shown.

1 diabetes (2.5%). After psoriasis onset, the dominating comorbidity was PsA (10.5%).

Chronologic order of IMIDs relative to psoriasis diagnosis

Fig 1 shows the time of occurrence of IMIDs relative to the time of psoriasis diagnosis. Most IMIDs occurred before diagnosis of psoriasis, except for PsA, which predominantly occurred after psoriasis (Table II, Fig 1). Of the IMIDs occurring before psoriasis, a mean (SD) of 6.4 (5.9) years or a median (IQR) of 4.8 (1.2-10.4) years occurred before psoriasis diagnosis. The mean (SD) time from psoriasis diagnosis to occurrence of an IMID after psoriasis was 2.9 (2.5) years or a median (IQR) of 2.3 (0.8-4.7) years. The overall incidence of IMID after a psoriasis diagnosis was 297.97 (95% CI 283.75-321.90)/10,000 person-years compared with 49.43 (95% CI 47.68-51.26)/10,000 person-years in the general population (Table III). Patients with psoriasis had a considerably increased risk of ≥1 IMID after psoriasis diagnosis (IRR 5.49, 95% CI 5.16-5.83) compared with general population controls. Likewise, patients with psoriasis were at higher risk of having ≥2 IMIDs (IRR 15.06, 95% CI 11.45-19.82) (Fig 2). Psoriasis was associated with an increased risk of 11 out of the 16 studied IMIDs. These included rheumatic, gastrointestinal, respiratory, and endocrine IMIDs. No significant risk was found for systemic lupus erythematosus or neurologic and biliary IMIDs. For most individually examined IMIDs, the risk was significantly higher before diagnosis of psoriasis (Table II). When comparing the time at risk before and after diagnosis of psoriasis, there was an 81%

Table II. Proportion of patients with IMID onset before and after diagnosis of psoriasis

Comorbidity, disease onset, n (%)	General population	Psoriasis
Any IMID		
Before psoriasis	8153 (7.4)	2181 (20.0)
After psoriasis	2928 (2.7)	1607 (14.7)
Multiple sclerosis		
Before psoriasis	402 (0.4)	47 (0.4)
After psoriasis	82 (0.1)	10 (0.1)
Psoriatic arthritis		
Before psoriasis	88 (0.1)	783 (7.2)
After psoriasis	43 (0.1)	1063 (10.5)
Pyoderma gangrenosum		
Before psoriasis	9 (0)	9 (0.1)
After psoriasis	9 (0)	8 (0.1)
Rheumatoid arthritis		
Before psoriasis	831 (0.8)	373 (3.4)
After psoriasis	425 (0.4)	148 (1.4)
Ankylosing spondylitis		
Before psoriasis	146 (0.1)	111 (1.0)
After psoriasis	58 (0.1)	38 (0.4)
Systemic lupus erythematosus		
Before psoriasis	95 (0.1)	37 (0.3)
After psoriasis	28 (0)	5 (0.1)
Celiac disease		
Before psoriasis	109 (0.1)	34 (0.3)
After psoriasis	40 (0.1)	11 (0.1)
Primary sclerosing cholangitis		
Before psoriasis	78 (0.1)	10 (0.1)
After psoriasis	99 (0.1)	10 (0.1)
Primary biliary cholangitis		
Before psoriasis	22 (0)	10 (0.1)
After psoriasis	23 (0)	5 (0.1)
Type 1 diabetes		
Before psoriasis	1511 (1.4)	270 (2.5)
After psoriasis	587 (0.5)	136 (1.3)
Asthma		
Before psoriasis	2639 (2.4)	406 (3.7)
After psoriasis	1055 (1.0)	183 (1.7)
Sarcoidosis		
Before psoriasis	280 (0.3)	57 (0.5)
After psoriasis	85 (0.1)	22 (0.2)
Graves disease		
Before psoriasis	883 (0.8)	89 (0.8)
After psoriasis	206 (0.2)	45 (0.4)
Iridocyclitis		
Before psoriasis	977 (0.9)	173 (1.6)
After psoriasis	53 (0.1)	5 (0.1)
Crohn's disease		
Before psoriasis	203 (0.2)	109 (1.0)
After psoriasis	61 (0.1)	24 (0.2)
Ulcerative colitis		
Before psoriasis	484 (0.4)	84 (0.8)
After psoriasis	161 (0.2)	32 (0.3)

The psoriasis diagnosis date was used as the index date for the corresponding age- and sex-matched reference group from the general population.
IMID, Immune-mediated inflammatory disease.

higher risk of IMID diagnosis after onset of psoriasis (IRR 1.81, 95% CI 1.66-1.96); however, this finding was attributable to PsA. Thus, when excluding PsA, the risk of developing any IMID was significantly lower after a diagnosis of psoriasis than before (IRR 0.83, 95% CI 0.73-0.95).

DISCUSSION

Main findings

In a cohort of 10,923 patients with psoriasis, we found that ~20% and 14% of patients with psoriasis had an IMID develop before and after the onset of psoriasis, respectively. The predominant IMID developing after the onset of psoriasis was PsA. Patients with psoriasis had a 5-fold increased risk of subsequent IMID compared with the general population.

Interpretation

The increased prevalence of immune-mediated inflammatory comorbidities in patients with psoriasis is in line with previous studies on this association. A similar observational study including 25,341 participants from the United States showed a significant association between psoriasis and having ≥1 (OR 1.6, 95% CI 1.5-1.7) and ≥2 (OR 1.9, 95% CI 1.6-2.4) autoimmune diseases.[4] This study however did not investigate PsA as a study outcome, possibly resulting in lower estimates of the collective association. Likewise, in another large study involving data from US insurance claims, psoriasis and PsA were associated with multiple autoimmune diseases.[11] A systematic review from 2012 including 28 publications showed a convincing association between psoriasis and IBD; however, the available evidence for other autoimmune diseases was limited.[6]

In contrast with previous studies, we studied the temporality of psoriasis and the development of a wide range of associated IMIDs. We demonstrated that most IMIDs occurred before the diagnosis of psoriasis, apart from PsA. Some IMIDs, such as asthma and celiac disease, were expected to appear before psoriasis due to the tendency of these diseases for early onset. The term comorbidity is frequently used to describe an excess risk of IMIDs in patients with psoriasis; however, the term can be somewhat misleading. It might give the impression that the other co-occurring diseases are triggered by systemic changes caused by psoriasis, and that psoriasis is the main contributor for excess morbidity; however, the current study results suggest a different disease trajectory. Indeed, one may speculate whether psoriasis can, at least in a subset of patients, be considered a cutaneous manifestation of a complex composition of several coexisting

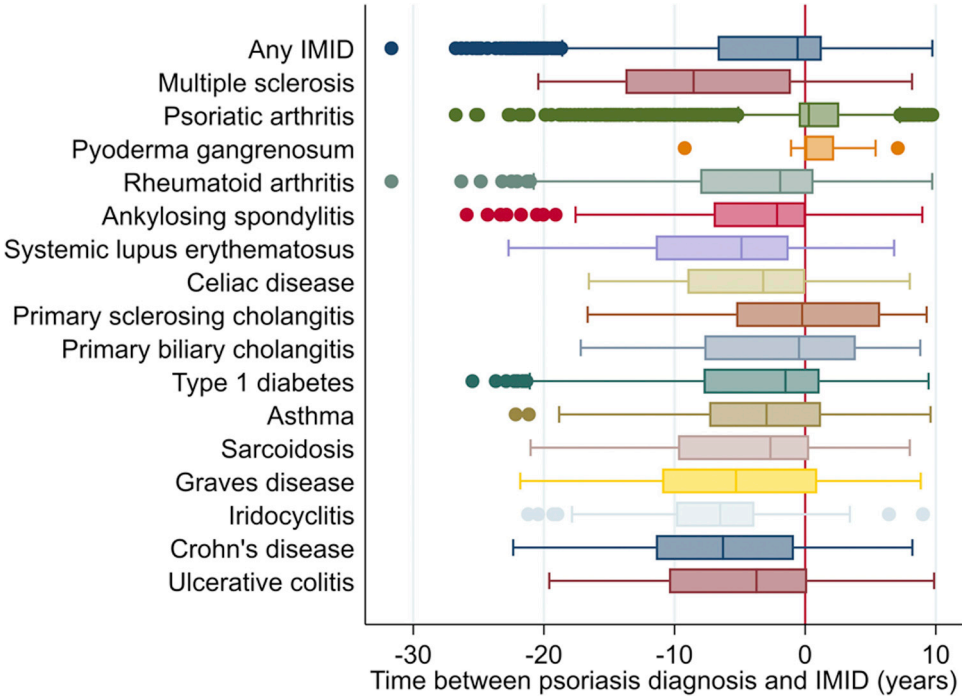

Fig 1. Appearance of different IMIDs relative to the time of psoriasis diagnosis. Data are presented as horizontal box plots where boxes represent the 25th through the 75th percentile. The vertical line inside the box is the median. Whiskers represent the 95% confidence intervals, and dots represent outliers. *IMID*, Immune-mediated inflammatory disease.

IMIDs. This observation provides new insight in possible pathophysiologic mechanisms of these associations.

Although the exact pathophysiologic mechanisms of the shown association are not yet known, collectively, the current evidence shows that psoriasis is associated with presence of other IMIDs. The associations are likely complex; however, common genetic susceptibility caused by overlapping risk genes and loci has been suggested as one of the major contributing factors in this association.[12-14] Such genetic links might further explain the tendency of disease clustering of IMIDs and supports the findings of the current study where we observed that patients with psoriasis had a 15-fold increased risk of developing ≥2 IMIDs compared with general population controls. Certain stressors, such as cigarette smoking and microbial agents, might also play a role as common trigger factors.[15-17] Higher prevalence of psoriasis and some IMIDs have also been observed in some geographic regions, especially areas with higher latitude; however, the exact environmental factors that can explain these links are unknown.[18-20] Furthermore, an upregulation of proinflammatory cells and cytokines might contribute to an environment triggering the co-occurrence of certain IMIDs. It is well-established that patients with psoriasis or PsA have increased levels of interleukin (IL) 17, IL-23, and tumor necrosis factor α and that patients with psoriasis and concurrent PsA tend to carry more inflammatory comorbidities compared with patients with skin manifestations alone.[21,22] This is in line with the findings of the current study, as we observed that PsA was highly represented in individuals with multiple IMIDs.

Beyond genetic, environmental, and common inflammatory pathways, other possible explanatory mechanisms include immune-modulating medications. Some drugs that are prescribed to treat psoriasis might contribute to the pathogenesis of certain IMIDs. Indeed, tumor necrosis factor α−inhibitors are contraindicated in patients with multiple sclerosis due to the risk of disease exacerbation.[23] Furthermore, worsening of IBD has been observed in treatment with IL-17 inhibitors.[24] In contrast, other biologics, such as adalimumab, infliximab, and ustekinumab, can be used to treat IBD.[25] Thus, certain immune-modulating drugs might interact and influence the risk of comorbidities by either preventing or triggering other IMIDs in patients with psoriasis or vice versa.

PsA was seen more frequently after the development of psoriasis. This finding is in line with the

Table III. Summary of time to IMIDs, incidence rates, and incidence rate ratios of IMIDs in patients with psoriasis compared with the general population

	Time from psoriasis to IMID, y		IMID in general population, IR (95% CI)	IMID in psoriasis population, IR (95% CI)	Psoriasis vs general population			After vs before (reference) psoriasis diagnosis*		
Category	Mean (SD)	Median (IQR)			IRR	95% CI	*P* value	IRR	95% CI	*P* value
Any IMID	2.9 (2.5)	2.3 (0.8-4.7)	49.43 (47.68-51.26)	297.97 (283.75-312.90)	5.49	5.16-5.83	<.0001	1.81[†]	1.66-1.96	<.0001
≥2 IMIDs	4.4 (2.5)	4.4 (2.1-6.5)	1.43 (1.16-1.77)	23.58 (19.89-28.04)	15.06	11.45-19.82	<.0001	2.45[‡]	1.95-3.07	<.0001
Multiple sclerosis	4.8 (3.1)	5.8 (2.5-7.4)	1.37 (1.10-1.70)	1.67 (0.90-3.11)	1.22	0.63-2.35	.5523	0.44	0.21-0.92	.0283
Psoriatic arthritis	2.8 (2.5)	2.1 (0.7-4.4)	0.72 (0.53-0.96)	206.66 (194.60-210.46)	266.08	196.16-360.93	<.0001	1.67	1.52-1.84	<.0001
Pyoderma gangrenosum	3.3 (2.6)	3.1 (1.0-5.4)	0.15 (0.08-0.29)	1.33 (0.67-2.67)	8.90	3.43-23.06	<.0001	0.89	0.34-2.31	.8098
Rheumatoid arthritis	3.7 (2.6)	3.3 (1.4-5.5)	7.12 (6.48-7.83)	25.67 (21.85-30.16)	3.58	2.97-4.31	<.0001	0.56	0.46-0.69	<.0001
Ankylosing spondylitis	2.3 (2.2)	1.3 (0.5-4.1)	0.97 (0.75-1.25)	6.41 (4.66-8.80)	6.61	4.39-9.95	<.0001	0.48	0.33-0.70	.0002
Systemic lupus erythematosus	1.9 (2.8)	0.8 (0.3-1.4)	0.47 (0.32-0.67)	0.84 (0.35-2.01)	1.79	0.69-4.63	.2304	0.20	0.08-0.52	.0010
Celiac disease	3.4 (2.7)	3.4 (0.3-5.9)	0.67 (0.49-0.91)	1.84 (1.02-3.32)	2.76	1.41-5.37	.0029	0.44	0.22-0.90	.0237
Primary sclerosing cholangitis	5.6 (2.3)	5.7 (4.9-6.6)	1.65 (1.35-2.00)	1.67 (0.90-3.10)	1.01	0.52-1.94	.9754	1.43	0.54-3.76	.4684
Primary biliary cholangitis	6.1 (3.4)	8.2 (3.9-8.4)	0.39 (0.25-0.58)	0.83 (0.35-2.00)	2.18	0.83-5.72	.1152	0.63	0.20-1.91	.4104
Type 1 diabetes	3.0 (2.4)	2.2 (1.1-4.6)	9.91 (9.14-10.74)	23.34 (19.74-27.62)	2.34	1.94-2.82	<.0001	0.73	0.58-0.91	.0048
Asthma	3.6 (2.4)	3.4 (1.6-5.4)	18.03 (16.97-19.15)	31.86 (27.56-36.83)	1.76	1.50-2.06	<.0001	0.60	0.50-0.72	<.0001
Sarcoidosis	2.5 (2.0)	1.9 (1.0-3.6)	1.42 (1.15-1.75)	3.69 (2.43-5.60)	2.60	1.62-4.15	.0001	0.58	0.34-0.98	.0427
Graves disease	3.2 (2.6)	2.5 (0.9-5.4)	3.45 (3.01-3.96)	7.57 (5.65-10.14)	2.18	1.58-3.02	<.0001	0.92	0.62-1.38	.6961
Iridocyclitis	4.5 (3.2)	3.4 (2.3-6.4)	0.89 (0.68-1.16)	0.85 (0.35-2.04)	0.95	0.28-2.38	.9127	0.04	0.02-0.10	<.0001
Crohn's disease	3.8 (2.5)	4.0 (1.6-5.4)	1.02 (0.79-1.31)	4.04 (2.71-6.02)	3.97	2.47-6.36	<.0001	0.40	0.25-0.65	.0002
Ulcerative colitis	2.7 (2.5)	2.0 (0.5-4.9)	2.69 (2.30-3.14)	5.37 (3.80-7.60)	1.99	1.36-2.91	.0004	0.60	0.38-0.92	.0202

CI, Confidence interval; *IMID*, immune-mediated inflammatory disease, *IQR*, interquartile range; *IR*, incidence rate per 10,000 person-years; *IRR*, incidence rate ratio; *SD*, standard deviation.

*In analyses of risk of IMIDs before versus after diagnosis of psoriasis, the incidence rate in the 10 years before psoriasis diagnoses serves as the reference group (ie, IRRs <1 suggests a higher risk before psoriasis diagnosis and IRRs >1 suggest a higher risk after psoriasis diagnosis).

[†]When excluding psoriatic arthritis, the IRR was 0.83 (95% CI 0.73-0.95), $P = .0046$.

[‡]When excluding psoriatic arthritis, the IRR was 0.90 (95% CI 0.61-1.32), $P = .5775$.

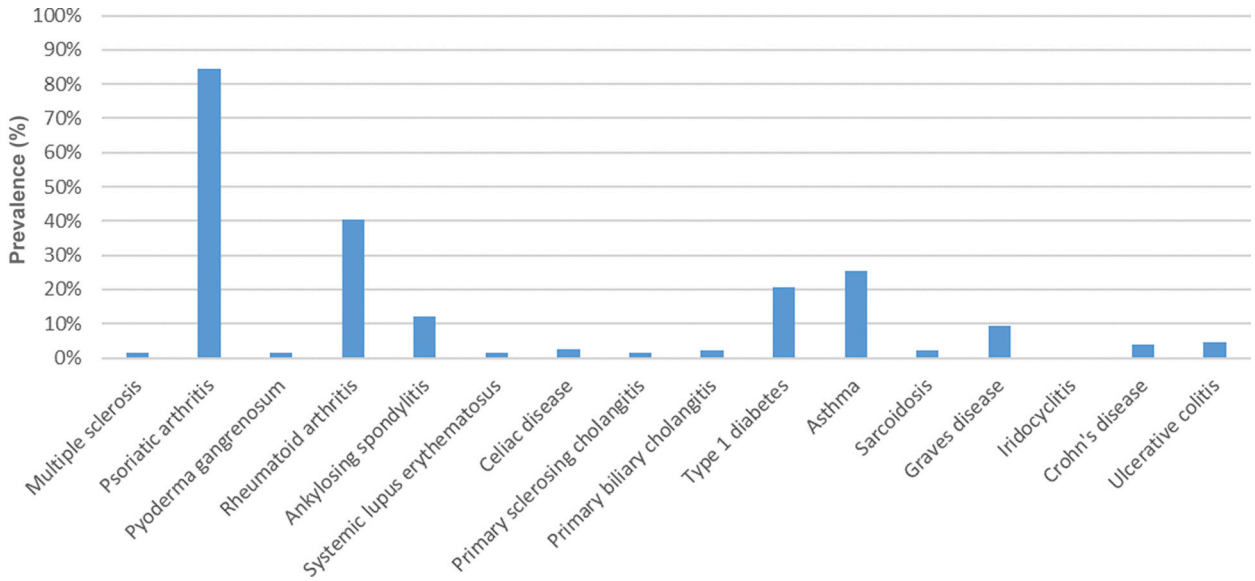

Fig 2. Prevalence of immune-mediated inflammatory diseases in patients with psoriasis that have ≥2 co-ocurring immune-mediated inflammatory diseases (in addition to psoriasis).

results of a UK observational study involving primary care and secondary care data sources that found that most participants (82.3% with primary care data and 61.3% with secondary care data) had psoriasis before PsA.[26] We further observed that PsA was associated with having multiple comorbid IMIDs. The clinical similarities between PsA and rheumatoid arthritis has been described previously, and because of overlapping symptoms, some diagnostic overlap might occur.[27] In some cases, rheumatologists depend on a psoriasis diagnosis before the PsA diagnosis is given. However, it is important to keep in mind that the date of psoriasis diagnosis does not necessarily represent the exact time of onset of skin manifestations of plaque psoriasis, as many patients might have plaques for several years before consulting a physician. This uncertainty in timing of disease onset might represent a study limitation. Furthermore, it is estimated the PsA often occurs ~10 years after a psoriasis diagnosis.[28] The association in the current study might therefore be underestimated due to the limited follow-up period. Patients with psoriasis might be seen by physicians more frequently than members of the general population, which might lead to a somewhat earlier diagnosis of IMIDs among these patients compared with the general population. However, since the total duration of this study was up to 4 decades, any such differences would arguably not lead to an overall bias of the absolute number of patients diagnosed with IMIDs during the study. Last, as with most observational studies involving routinely collected administrative data, we lacked objective measurement of psoriasis severity, such as the percentage of the affected body surface area or the Psoriasis Area and Severity Index, and we were therefore unable to assess whether more severe psoriasis was associated with a higher risk of IMID development.

Conclusion

Patients with psoriasis carried a 5-fold increased risk of developing any IMID compared with the general population. Most IMIDs were diagnosed before psoriasis, potentially providing important insight in the understanding of pathophysiologic mechanisms of concurrent IMIDs in patients with psoriasis. Presence of PsA among patients with psoriasis was strongly associated with having additional IMIDs, indicating that patients with psoriasis and concurrent PsA carry an increased burden of disease and might require increased diagnostic awareness among clinicians.

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Incidence and Risk of Inflammatory Bowel Disease in Patients with Psoriasis—A Nationwide 20-Year Cohort Study

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In psoriasis patients, incidence rates of Crohn disease (CD) and ulcerative colitis (UC) have been increased in epidemiological studies and certain clinical trials, yet the association remains poorly understood. We studied a 20-year nationwide cohort of 235,038 Danish adults with psoriasis and a 1:1 matched reference group. Less than 1% of psoriasis patients developed CD or UC during follow-up. Incidence rates of CD were highest for younger women with psoriasis and patients with concurrent psoriatic arthritis, whereas men with psoriasis had particularly high incidence rates of UC compared with their non-psoriasis peers. Adjusted hazard ratios of CD were 1.84 (95% confidence interval [CI]= 1.47−2.29) and 2.38 (95% CI = 1.62−3.49) among psoriasis patients treated with topical and systemic nonbiologic therapy, respectively. No definite CD cases occurred during biologic therapy. For UC, adjusted hazard ratios were 1.49 (95% CI = 1.29−1.72), 1.51 (95% CI = 1.14−2.01), and 1.23 (95% CI = 0.39−3.86, $P = 0.7197$) for psoriasis patients receiving topical, systemic nonbiologic, and biologic therapy, respectively. Time to CD (but not UC) diagnosis was significantly longer for psoriasis patients compared with the general population, and patients receiving systemic treatment had the longest time to CD and UC. Psoriasis was associated with increased risk of CD and UC. Particular risk factors included sex and psoriatic arthritis.

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INTRODUCTION

Psoriasis is a common chronic inflammatory skin disease characterized by T helper cell infiltrates, predominately with T helper type 1 and T helper type 17 cells, and expression of IL-17, IL-23, and TNF-α. Clinically, psoriasis is characterized by either widespread or localized sharply demarcated silvery, scaly, and erythematous plaques distributed symmetrically.

Epidemiological studies have established strong associations between psoriasis and Crohn disease (CD) and ulcerative colitis (UC), with increased risk of CD and UC in patients with psoriasis and vice versa (Egeberg et al., 2016; Eppinga et al., 2017). CD and UC represent the two forms of inflammatory bowel disease (IBD) and are believed to occur as a host response to intestinal microbes in genetically predisposed individuals (Abraham and Cho, 2009). IBD typically occurs in individuals aged 15−30 years, although it may occur at any age (Loftus and Sandborn, 2002). Indeed, not only do psoriasis and IBD share important genetic risk loci, they also have crucial overlaps in their inflammatory pathways (Ellinghaus et al., 2012; Fiorino and Omodei, 2015).

In recent years, significant advances have been made in the understanding and treatment of both psoriasis and IBD, and shared inflammatory pathways have enabled simultaneous treatment of both diseases with biologics targeting TNF-α and IL-12/23. However, although biologics inhibiting the IL-17 pathway have been shown to be efficacious for treatment of psoriasis and psoriatic arthritis (PsA) (Frieder et al., 2018), concerns have been raised regarding their potential for worsening existing IBD or perhaps even inducing first-time CD or UC (Egeberg, 2016; Hueber et al., 2012; Reich et al., 2017; Targan et al., 2016; van de Kerkhof et al., 2016).

Data on incidence rates (IRs) of CD and UC among psoriasis patients in clinical trials have been conflicting and are difficult to compare with IRs from observational studies, because patient characteristics and diagnostic methods often differ considerably. The aims of this nationwide study was to examine the incidence and risk of CD and UC in patients with psoriasis treated with topical, systemic nonbiologic, and biologic therapy and to provide strata-specific data on the IBD.

RESULTS

The study cohort comprised a total of 235,038 patients with psoriasis and 235,038 matched non-psoriasis individuals from the general population, all without a history of CD or UC at baseline. Among patients receiving topical treatment or systemic nonbiologic therapy and the general population, there was a slight female predominance, whereas the majority of biologics-treated patients were men (Table 1). The mean age at baseline was lower among patients who received treatment with biologics during the study compared

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Abbreviations: aHR, adjusted hazard ratio; CD, Crohn disease; CI, confidence interval; IBD, inflammatory bowel disease; ICD-10, International Classification of Diseases, 10th revision; IR, incidence rate; PsA, psoriatic arthritis; UC, ulcerative colitis

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Table 1. Characteristics of the the study population

Characteristic	General Population	Psoriasis		
		Topical	Systemic Nonbiologic	Biologic
Number	235,038	209,367	23,484	2,187
Age, years				
Mean (SD)	51.0 (18.6)	50.1 (18.9)	52.5 (16.0)	37.5 (13.2)
Median (IQR)	52.2 (36.6–65.1)	52.5 (36.1–65.3)	53.8 (41.5–64.1)	37.5 (27.0–47.0)
Sex, n (%)				
Women	124,342 (52.9)	110,852 (53.0)	12,729 (54.2)	761 (34.8)
Men	110,696 (47.1)	98,515 (47.1)	10,755 (45.8)	1,426 (65.2)
Available data on family history, n (%)	135,688 (57.7)	122,564 (58.5)	12,243 (52.1)	1,773 (81.1)
First-degree relative with IBD	3,845 (2.8)	4,023 (3.3)	387 (3.2)	57 (3.2)
Smoking, n (%)	33,087 (14.1)	38,158 (18.2)	5,596 (23.8)	403 (18.4)
Alcohol abuse, n (%)	15,496 (6.6)	17,506 (8.4)	2,098 (8.9)	244 (10.2)
Education level, n (%)				
Primary school	78,286 (33.3)	71,913 (34.4)	8,716 (37.1)	772 (35.3)
Middle school	14,807 (6.3)	13,181 (6.3)	896 (3.8)	165 (7.5)
High school and vocational school	78,234 (33.3)	71,147 (34.0)	9,108 (38.8)	807 (36.9)
Short higher education	30,136 (12.8)	25,813 (12.3)	2,621 (11.2)	210 (9.6)
Bachelor's degree	3,017 (1.3)	2,448 (1.2)	135 (0.6)	24 (1.1)
Master's degree	13,423 (5.7)	10,741 (5.1)	676 (2.9)	76 (3.5)
Doctorate degree and research fellowships	716 (0.3)	474 (0.2)	32 (0.1)	4 (0.2)
Other/unregistered	16,419 (7.0)	13,650 (6.5)	1,300 (5.5)	129 (5.9)
Income level, n (%)				
Lowest	48,735 (20.7)	42,528 (20.3)	3,358 (14.3)	517 (23.6)
Below average	45,353 (19.3)	42,384 (20.2)	4,903 (20.9)	289 (13.2)
Average	45,660 (19.4)	42,044 (20.1)	5,497 (23.4)	498 (22.8)
Above average	27,253 (20.1)	40,919 (19.5)	5,480 (23.3)	515 (23.6)
Highest	48,037 (20.4)	21,492 (19.8)	4,246 (18.1)	368 (16.8)
Comorbidity, n (%)				
Diabetes, at baseline	12,489 (5.3)	14,774 (7.1)	1,565 (6.7)	50 (2.3)
Diabetes, during follow-up	20,939 (8.9)	24,533 (11.7)	3,381 (14.4)	263 (12.0)
Hypertension, at baseline	30,067 (14.1)	36,492 (17.4)	3,820 (16.3)	111 (5.1)
Hypertension, during follow-up	49,479 (21.1)	51,647 (24.7)	7,051 (30.0)	443 (20.3)
Statin use, at baseline[1]	1,819 (0.8)	1,871 (0.9)	269 (1.2)	10 (0.5)
Statin use, during follow-up	53,204 (22.6)	54,833 (26.2)	7,750 (33.0)	543 (24.8)
Psoriatic arthritis, at baseline	0 (0.0)	3,134 (1.5)	2,146 (9.1)	188 (8.6)
Psoriatic arthritis, during follow-up	0 (0.0)	6,807 (3.3)	5,329 (22.7)	936 (42.8)

Abbreviations: IBD, inflammatory bowel disease; IQR, interquartile range; SD, standard deviation.
[1]Prescription within past 6 months.

with psoriasis patients receiving topical or systemic nonbiologic therapy. A positive family history (in a first-degree relative) of IBD was slightly more frequent among patients with psoriasis, with comparable estimates among those patients receiving topical, systemic nonbiologic, and biologic therapy. Patients with psoriasis had a higher prevalence of smoking, alcohol abuse, and medical comorbidity compared with the general population (Table 1).

Crohn disease

During the study period, a total of 257/464/664 and 124/252/383 cases of definite/probable/possible CD occurred among patients with psoriasis and the general population, respectively (Figure 1 and Table 2). The IR (per 10,000 person-years) of definite CD was 1.55 (95% confidence interval [CI] = 1.37–1.76) among patients with psoriasis and 0.79 (95% CI = 0.67–0.95) in the age- and sex-matched general population. Stratified by psoriasis treatment, the IRs of definite CD were 1.96 (95% CI = 1.40–2.75) among those receiving systemic nonbiologic therapy and 1.51 (95% CI = 1.32–1.73) among patients receiving topical treatment. The IRs of definite/probable/possible CD among psoriasis patients with and without concurrent PsA are presented in Supplementary Table S1 online. Incidence of CD decreased with increasing age (see Supplementary Table S2 online). After adjustment for potential confounding factors, psoriasis was significantly associated with increased risk of definite CD (adjusted hazard ratio [aHR] = 1.88, 95% CI = 1.51–2.34), probable CD (aHR = 1.74, 95% CI = 1.49–2.03), and possible CD (aHR = 1.63, 95% CI = 1.44–1.85), respectively. Although the risk of CD was increased in patients receiving topical and systemic nonbiologic treatment, the aHR of CD was not significantly increased in patients treated with biologic therapy, regardless of presence or absence of PsA (Table 3), although the sample size of patients treated with biologics was much smaller than the other treatment

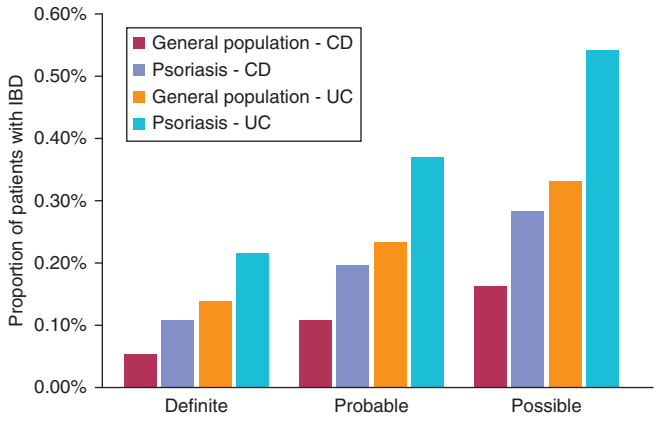

Figure 1. Prevalence of inflammatory bowel disease (IBD) in patients with psoriasis. Percentage of patients developing new-onset Crohn disease (CD) and ulcerative colitis (UC) during follow-up.

modalities. Limiting analyses of PsA to patients for whom the diagnosis had been verified by a rheumatologist, the aHR of CD was 2.90 (95% CI = 1.61−5.22).

Ulcerative colitis

During the study period, 504/870/1274 and 325/546/778 patients with psoriasis and general population referents, respectively, developed definite/probable/possible UC. The incidence of definite UC was 3.17 (95% CI = 2.90−3.46) among patients with psoriasis and 2.08 (95% CI = 1.87−2.32) in the general population. Comparable IRs were seen among patients receiving topical and systemic nonbiologic therapy, whereas lower IRs (although with wide and overlapping CIs) were seen for psoriasis treated with biologics (Table 2). The IRs in different age groups are presented in Supplementary Table S3 online. In adjusted models, there was a significantly increased risk of UC in patients with psoriasis (definite UC: aHR = 1.49, 95% CI = 1.30−1.71), although the risk of definite UC reached statistical significance only in patients without PsA (aHR = 1.50, 95% CI = 1.30−1.73) but not in patients with concurrent PsA (aHR = 1.29, 95% CI = 0.85−1.98, $P = 0.2341$) (Table 4). Among psoriasis patients with rheumatologist-verified PsA, the aHR of UC was 1.22 (95% CI = 0.80−1.87, $P = 0.3589$).

Distribution and characteristics

Uses of different systemic nonbiologic and biologic therapies are presented in Supplementary Table S4 online. Among patients with definite IBD, the UC-to-CD ratio was 2.8 in the general population and 2.3 in patients with psoriasis ($P = 0.105$). The highest age-specific IR estimate (per 10,000 person-years) of CD was in women with psoriasis younger than 30 years (IR estimate = 4.28, 95% CI = 3.14−5.83), whereas the highest IR estimate of UC was seen in men with psoriasis aged 30−40 years (IR estimate = 5.13; 95% CI = 3.36−6.81) (Figure 2a and b). Surprisingly, mean time to diagnosis of CD, but not UC, was significantly longer among patients with psoriasis, compared with the general population, even among patients receiving only topical therapy

Table 2. Summary of number of events, follow-up time, and incidence rates per 10,000 person-years

		Psoriasis			
Diagnosis	**General Population**	**Any Psoriasis**	**Topical**	**Systemic Nonbiologic**	**Biologic**
Definite Crohn disease					
Follow-up time, years	1,560,873	1,591,680	1,410,185	173,317	8,178
Number of events	124	247	213	34	0
IR per 10,000 person-years (95% CI)	0.79 (0.67−0.95)	1.55 (1.37−1.76)	1.51 (1.32−1.73)	1.96 (1.40−2.75)	Not applicable
Probable Crohn disease					
Follow-up time, years	1,560,621	1,590,573	1,409,244	173,173	8,156
Number of events	252	464	408	55	<3
IR per 10,000 person-years (95% CI)	1.62 (1.43−1.83)	2.92 (2.66−3.20)	2.90 (2.62−3.19)	3.18 (2.44−4.14)	1.23 (0.17−8.70)
Possible Crohn disease					
Follow-up time, years	1,559,716	1,589,653	1,408,477	173,039	8,136
Number of events	383	664	583	78	3
IR per 10,000 person-years (95% CI)	2.46 (2.22−2.71)	4.18 (3.87−4.51)	4.14 (3.81−4.49)	4.51 (3.61−5.63)	3.69 (1.19−11.43)
Definite ulcerative colitis					
Follow-up time, years	1,560,170	1,590,733	1,409,388	173,187	8,158
Number of events	325	504	444	57	3
IR per 10,000 person-years (95% CI)	2.08 (1.87−2.32)	3.17 (2.90−3.46)	3.15 (2.87−3.45)	3.29 (2.54−4.27)	3.68 (1.19−11.40)
Probable ulcerative colitis					
Follow-up time, years	1,558,899	1,588,525	1,407,505	172,887	8,183
Number of events	546	870	768	96	6
IR per 10,000 person-years (95% CI)	3.50 (3.22−3.81)	5.48 (5.12−5.85)	5.46 (5.08−5.86)	5.55 (4.55−6.78)	7.48 (3.31−16.42)
Possible ulcerative colitis					
Follow-up time, years	1,557,735	1,586,343	1,405,698	172,521	8,123
Number of events	778	1,274	1,123	146	5
IR per 10,000 person-years (95% CI)	4.99 (4.66−5.36)	8.03 (7.60−8.48)	7.99 (7.54−8.47)	8.46 (7.20−9.96)	6.16 (2.56−14.79)

Due to data security requirements, data on one or two events are shown as <3.
Abbreviations: CI, confidence interval; IR, incidence rate.

Table 3. HRs of the risk of Crohn disease in patients with psoriasis compared with the general population

	Definite CD			Probable CD			Possible CD		
Psoriasis Type	**Adjusted HR**	**95% CI**	***P*-Value**	**Adjusted HR**	**95% CI**	***P*-Value**	**Adjusted HR**	**95% CI**	***P*-Value**
Any psoriasis	**1.88**	**1.51–2.34**	**<0.0001**	**1.74**	**1.49–2.03**	**<0.0001**	**1.63**	**1.44–1.85**	**<0.0001**
Topical treatment	1.84	1.47–2.29	<0.0001	1.72	1.47–2.02	<0.0001	1.62	1.42–1.84	<0.0001
Systemic nonbiologic treatment	2.38	1.62–3.49	<0.0001	1.92	1.43–2.58	<0.0001	1.74	1.36–2.23	<0.0001
Biologic treatment		Not applicable		0.56	0.08–4.00	0.5622	1.20	0.38–3.75	0.7561
Psoriasis without PsA	**1.83**	**1.47–2.27**	**<0.0001**	**1.70**	**1.46–1.99**	**<0.0001**	**1.59**	**1.40–1.81**	**<0.0001**
Topical treatment	1.81	1.45–2.27	<0.0001	1.70	1.45–2.00	<0.0001	1.59	1.39–1.81	<0.0001
Systemic nonbiologic treatment	2.08	1.34–3.23	<0.0001	1.76	1.26–2.45	0.0009	1.65	1.25–2.17	0.0004
Biologic treatment		Not applicable		0.88	0.12–6.31	0.9004	1.87	0.60–5.85	0.2821
Psoriasis with PsA	**3.10**	**1.90–5.06**	**<0.0001**	**2.39**	**1.63–3.50**	**<0.0001**	**2.28**	**1.67–3.11**	**<0.0001**
Topical treatment	2.63	1.37–5.07	<0.0001	2.28	1.40–3.71	0.0009	2.40	1.65–3.51	<0.0001
Systemic nonbiologic treatment	4.11	2.13–7.93	<0.0001	2.79	1.61–4.82	0.0002	2.29	1.42–3.70	0.0007
Biologic treatment		Not applicable			Not applicable			Not applicable	

Adjusted for age, sex, socioeconomic status, smoking, and alcohol abuse. Bold text indicates "all psoriasis patients" regardless of whether they receive topical, systemic nonbiologic, or biologic therapy.

Abbreviations: CD, Crohn disease; CI, confidence interval; HR, hazard ratio.

(see Supplementary Table S5 online). However, for patients receiving systemic nonbiologic and especially biologic therapy, time to CD and UC diagnosis was significantly longer than the general population. Among patients with definite IBD, 66.6% of CD patients and 75.8% of UC patients had data specifying anatomical location, whereas the remaining patients were recorded as "unspecified" (International Classification of Diseases, 10th revision [ICD-10] codes K50.9 and K51.9, respectively). Although there were some numerical differences in anatomical involvement of CD or UC among patients with psoriasis and the general population, none of these differences were statistically significant (Table 5). Among patients developing definite CD, 9.8% (psoriasis) and 16.5% (general population) had a family history of either CD or UC ($P = 0.127$), whereas a positive family history was seen in 7.0% (psoriasis) and 8.2% (general population) of individuals who developed definite UC during the study, respectively ($P = 0.612$). Using patients without psoriasis as a reference, risk of CD, but not UC, was higher among patients with longer psoriasis duration (see Supplementary Table S6 online). Sensitivity analyses with additional adjustment for use of nonsteroidal anti-inflammatory drugs, systemic antibiotics, and oral contraceptives yielded similar findings compared with our primary analyses (see Supplementary Table S7 online). Furthermore, use of a different reference population where non-psoriasis individuals were required to have been seen in the Danish health care system within 30 days on the corresponding psoriasis patients index date did not significantly alter the findings of our primary analyses (see Supplementary Table S8 online).

DISCUSSION

In this nationwide cohort study spanning two decades, we found a significantly increased risk of CD and UC among patients with psoriasis. No differences were seen in anatomical IBD location between psoriasis patients and the general population. Higher CD (but not UC) risk was seen with longer psoriasis duration.

In line with our findings, a previous Danish study found a positive association between psoriasis and risk of CD and UC, although IBD was not limited to diagnoses made by

Table 4. HRs of the risk of ulcerative colitis in patients with psoriasis compared with the general population

	Definite UC			Probable UC			Possible UC		
	Adjusted HR	**95% CI**	***P*-Value**	**Adjusted HR**	**95% CI**	***P*-Value**	**Adjusted HR**	**95% CI**	***P*-Value**
Any psoriasis	**1.49**	**1.30–1.71**	**<0.0001**	**1.52**	**1.37–1.70**	**<0.0001**	**1.56**	**1.43–1.71**	**<0.0001**
Topical treatment	1.49	1.29–1.72	<0.0001	1.52	1.36–1.70	<0.0001	1.55	1.42–1.70	<0.0001
Systemic nonbiologic treatment	1.51	1.14–2.01	0.0041	1.54	1.24–1.92	<0.0001	1.65	1.38–1.97	<0.0001
Biologic treatment	1.23	0.39–3.86	0.7197	1.85	0.84–4.16	0.1356	1.13	0.47–2.74	0.7816
Psoriasis without PsA	**1.50**	**1.30–1.73**	**<0.0001**	**1.51**	**1.35–1.68**	**<0.0001**	**1.53**	**1.39–1.67**	**<0.0001**
Topical treatment	1.49	1.29–1.72	<0.0001	1.50	1.34–1.67	<0.0001	1.52	1.39–1.67	<0.0001
Systemic nonbiologic treatment	1.67	1.24–2.25	0.0007	1.58	1.25–2.00	0.0001	1.59	1.31–1.94	<0.0001
Biologic treatment	1.23	0.31–4.97	0.7684	1.83	0.68–4.91	0.2307	1.36	0.51–3.65	0.5370
Psoriasis with PsA	**1.29**	**0.85–1.98**	**0.2341**	**1.81**	**1.35–2.42**	**<0.0001**	**2.21**	**1.77–2.77**	**<0.0001**
Topical treatment	1.58	0.97–2.59	0.0685	2.06	1.45–2.91	<0.0001	2.42	1.85–3.18	<0.0001
Systemic nonbiologic treatment	0.85	0.38–1.92	0.6962	1.39	0.83–2.33	0.2115	1.99	1.38–2.88	0.0003
Biologic treatment	1.29	0.18–9.30	0.8010	2.09	0.62–4.50	0.3008	0.77	0.11–5.52	0.7968

Adjusted for age, sex, socioeconomic status, smoking, and alcohol abuse. Bold text indicates "all psoriasis patients" regardless of whether they receive topical, systemic nonbiologic, or biologic therapy.

Abbreviations: CI, confidence interval; HR, hazard ratio; UC, ulcerative colitis.

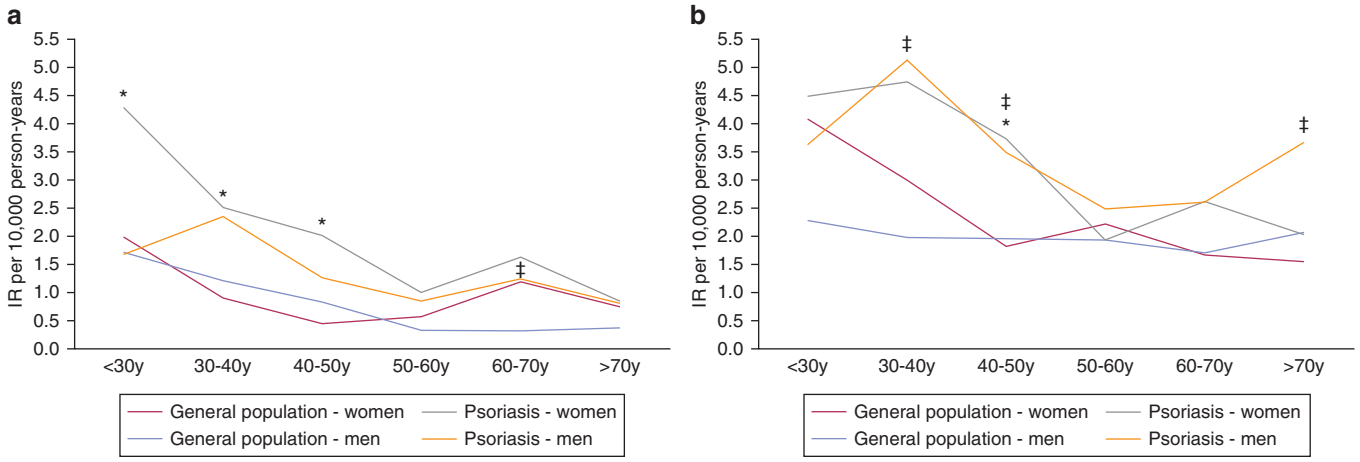

Figure 2. Age-specific incidence of Crohn disease and ulcerative colitis in men and women with psoriasis and in the general population. (**a**) Incidence of definite Crohn disease by sex and age in the general population and patients with psoriasis. (**b**) Incidence of definite ulcerative colitis by sex and age in the general population and patients with psoriasis. *Significantly higher for women with psoriasis compared with women without psoriasis. ‡Significantly higher for men with psoriasis compared with men without psoriasis. IR, incidence rate; y, year.

gastroenterologists (Egeberg et al., 2016). Moreover, that study pooled together use of certain systemic nonbiologic and biologic therapies (i.e., retinoids, psoralens, etanercept, and ustekinumab) but did not assess the relationship with a number of other frequently used treatment modalities (including methotrexate, cyclosporine, apremilast, infliximab, adalimumab, and secukinumab). This study therefore expands the existing literature considerably, not only by using more rigorous criteria for IBD (definite/probable/possible) but also by showing specific risk estimates among patients receiving topical therapy (mild psoriasis), systemic nonbiologic therapy (moderate to severe psoriasis), biologic treatment (most severe psoriasis). However, only relatively few patients (n = 2,187) were treated with biologics, thereby limiting interpretation of IBD risk in these patients. Since their introduction, adalimumab and ustekinumab have been the most frequently used biologics for psoriasis in Denmark (Egeberg et al., 2018a), which may explain the lack of association with IBD in the biologics-treated cohort, because these drugs may also dampen symptoms of IBD. Consequently, patients receiving biologic treatment of their psoriasis would experience fewer IBD symptoms and would therefore be less likely to be diagnosed with IBD. On the other hand, because studies have reported that multiple sclerosis is less severe in patients with concomitant IBD (Zephir et al., 2014), and it is tempting to speculate that milder psoriasis may indeed be more strongly associated with IBD as well. Indeed, one previous study reported that patients with psoriasis and concurrent IBD had a milder psoriasis phenotype compared with psoriasis patients without IBD, whereas patients with CD and concurrent psoriasis had more severe CD compared with patients without psoriasis (Eppinga et al., 2017). Along these lines, it is well-established that although psoriasis is slightly more frequent in women, women tend to have milder psoriasis than men (Hagg et al., 2017). In our study, there were striking sex differences, for example, a noticeably higher incidence of CD among women with psoriasis (Figure 2). Female sex is also a risk factor for complications such as colectomy among IBD patients (Burisch et al., 2017), and a very recent study found a lower CD risk in females than males in childhood but higher female risk after the age of 25 years (Shah et al., 2018), highlighting the importance of these observed sex differences. Although psoriasis patients tend to smoke more than the general population, smoking may aggravate CD while having beneficial effects on UC (van der Heide et al., 2009). The high increased risk of CD and UC among psoriasis patients with concurrent PsA may, at least in part, be explained by shared genetic risk loci such as IL12B, 5q31, IL23R, and IL2/IL21 (Roberson and Bowcock, 2010).

In their respective clinical development programs, the incidence of IBD among patients treated with IL-17 inhibitors has been conspicuously higher than what we observed in our psoriasis population. Between-study comparison of IRs may be challenging, because different diagnostic methods may be applied. For example, during the ixekizumab clinical trial program, adjudication was performed using the methodology

Table 5. Recorded disease manifestations of Crohn disease and ulcerative colitis among the general population and patients with psoriasis

Diagnosis	General Population, %	Psoriasis, %	*P*-Value
Crohn disease			0.340
Small intestine only	36.1	42.8	—
Large intestine only	24.4	23.0	—
Small and large intestines	27.9	28.6	—
Other areas only	11.6	6.6	—
Fistula	12.1	18.2	0.131
Ulcerative colitis[1]			
Pancolitis	60.2	67.4	0.066
Proctitis	34.3	27.8	0.085
Proctosigmoiditis	12.6	9.6	0.239
Left-sided colitis	7.5	9.6	0.351
Left-sided proctocolitis	2.8	1.6	0.395
Other areas	11.0	14.7	0.181

[1]Percentages do not add up to 100, because more locations may be reported in the same patient.

applied in the well-established Registre Epidemiologique des Maladies de l'Appareil Digestif (EPIMAD) registry (Gower-Rousseau et al., 1994), whereas identification of CD and UC in the secukinumab trials was "based on customized broad search criteria" (van de Kerkhof et al., 2016, pp 89). Nonetheless, from their clinical development programs, it was reported that IRs (shown here per 10,000 person-years) of CD were 11 (95% CI = 5−23) for ixekizumab (Reich et al., 2017), 11 (95% CI = 2−32) for secukinumab (van de Kerkhof et al., 2016), and 20 (95% CI not reported) for brodalumab (Lebwohl et al., 2015), with IRs of UC being 19 (95% CI = 11−23) for ixekizumab (Correction, 2017; Reich et al., 2017) and 15 (95% CI = 4−38) for secukinumab (van de Kerkhof et al., 2016). However, although the incidence of CD and UC may be increased with use of antibodies targeting IL-17, the absolute risk associated with these drugs remains low. Although the exact reason for the increased risk remains unclear, inhibition of IL-17 has been shown to weaken the intestinal epithelial barrier, thereby leading to increased gastrointestinal inflammation (Lee et al., 2015; Maxwell et al., 2015). Although this study may help put these clinical trial data into context, we emphasize that this study was not aimed at assessing IBD risk associated with specific drugs.

Several strengths and limitations of this study warrant discussion. Exclusion of confirmed or suspected IBD before the study start enabled a more direct comparison with IRs observed in clinical trials, whereas the inclusion of probable IBD diagnoses enabled comparison with clinical trials in which potential IBD cases that cannot definitively be confirmed to be either CD or UC were included. Moreover, possible IBD may include patients with unspecific gastrointestinal symptoms that may constitute irritable bowel syndrome or other gastroenterological conditions that do not meet the formal diagnostic criteria of CD or UC and may be a more realistic representation of the gastrointestinal complaints that patients report, for example, when consulting a dermatologist. However, although we defined cases of definite CD and UC as patients for whom the diagnosis was ascertained by a gastroenterologist, we lacked information on the specific diagnostic criteria on which the diagnosis was based, including data such as endoscopy findings and gastrointestinal histology samples. Moreover, in the psoriasis clinical trial program for ixekizumab, adjudication was performed in accordance with the EPIMAD definition, whereas our IBD cases were not, and although our IRs may be more appropriate for direct comparison with those from clinical trials, these definitory differences should be kept in mind when interpreting our findings. Furthermore, description of family history of IBD was limited by the fact that information on true biological relatives is not always recorded, for example, in cases of adoption or migration. Finally, we had approximately 8,100 person-years of exposure to biologics during our study (of which 76.4 person-years were for secukinumab), which may limit interpretability of our findings in the biologics-treated group, and especially with regard to IBD risk in patients receiving anti-IL-17 therapy.

In conclusion, we found an increased risk of CD and UC in patients with psoriasis. Patients with concurrent PsA had the highest risk of CD but not UC. Female sex and PsA were noticeable risk factors for IBD. Patients receiving biologic therapy for psoriasis did not have an increased IBD risk compared with the general population, likely because many anti-psoriatic biologics (e.g., adalimumab, infliximab, and ustekinumab) are also effective in treating symptoms of IBD, thereby postponing time to diagnosis. Although timely referral may be appropriate in patients presenting with gastrointestinal complaints consistent with IBD, the absolute psoriasis-associated risk of CD and UC remains low.

MATERIALS AND METHODS

Study approval was obtained from the Danish Data Protection Agency. Register studies do not require ethical approval in Denmark.

Data sources and study population

Routinely collected administrative and health care data in Denmark can be linked at the individual level for research purposes using the unique identification number assigned to all residents at birth or migration (Schmidt et al., 2014). The tax-supported health care system provides unencumbered access to health care, including general practitioners and hospitals, for all Danish residents. All hospital admissions and outpatient consultations are recorded in the Danish National Patient Register according to the Danish modification of the ICD-10 (Andersen et al., 1999). Drugs given during hospital admission, or dispensed from hospital clinics (e.g., biologic therapy) are also recorded in this register, whereas all prescriptions dispensed from pharmacies are registered in the Danish Registry of Medicinal Products Statistics (Gaist et al., 1997). Primary care services, including general practitioner and private clinics, are recorded in the Danish National Health Service Register (Andersen et al., 2011). Data on smoking and alcohol abuse were collected by data retrieval algorithms, as previously described (Egeberg et al., 2018b). Information on tax-reported household income is recorded by Statistics Denmark (Baadsgaard and Quitzau, 2011), and information on age, sex, vital statistics, and migration status is available from the Civil Registration System (Schmidt et al., 2014).

From a source population comprising all Danish adults (≥18 years) between January 1, 1997, and December 31, 2016, we identified all patients with recorded codes consistent with psoriasis, as previously described (Egeberg et al., 2018b). The study start for patients was the date of first recorded occurrence of psoriasis or their 18th birthday, whichever came last. Patients were followed up until the first of either December 31, 2016; death; migration; or the occurrence of an endpoint. Patient were matched (birth date and sex) with general population individuals in a 1:1 ratio. The index date (study start date) for the matched individuals was the same as for the corresponding psoriasis patients. To ensure that we captured only new-onset IBD during follow-up, study subjects were excluded if they had received a diagnosis of either confirmed or suspected IBD any time before the index date. The Strengthening the Reporting of Observational Studies in Epidemiology recommendations were used for conduct and reporting of this study (von Elm et al., 2007).

Endpoints

The co-primary IBD endpoints were a first-time diagnosis of CD (ICD-10 K50) or UC (ICD-10 K51). The IBD diagnosis was categorized into definite IBD, probable IBD, and possible IBD. Definite IBD included only patients who received an IBD diagnosis (CD or UC) that was verified by a gastroenterologist and did not have any subsequent diagnosis of UC (for patients with definite CD) or CD (for patients with definite UC). Probable IBD included patients who

received an IBD diagnosis either by a gastroenterologist, abdominal surgeon, or internal medicine specialist. Possible IBD included any physician diagnosis of IBD (confirmed or suspected), regardless of specialty.

Statistical analysis

Descriptive characteristics were presented as means and standard deviations for continuous variables and frequencies and as percentages for categorical variables. Patients were divided into groups and categorized according to their use of treatments prescribed specifically for treatment of their psoriasis and divided into the following groups: (i) topical or no treatment, (ii) systemic nonbiologic treatment, and (iii) biologic treatment. Topical treatment included topical corticosteroids and/or topical vitamin D analogs. Systemic nonbiologic treatment included methotrexate, cyclosporine, acitretin, and apremilast. Biologic treatment included adalimumab, etanercept, infliximab, ustekinumab, and secukinumab. To accurately assess the impact of psoriasis treatment, these drugs were included only if they were prescribed specifically for psoriasis. To ensure correct risk-time allocation and to explore the temporal relationship, such psoriasis therapy was included as a time-varying variable, whereby patients could contribute risk-time in the topical treatment group until they received their first systemic nonbiologic or biologic treatment (if appropriate). Similarly, patients were considered exposed in the systemic nonbiologic group only until they were switched to a biologic, at which time they would contribute risk-time in the biologics-treated group. We presented IRs per 10,000 person-years of exposure and calculated aHRs (in which age, sex, socioeconomic status, smoking, and alcohol abuse were considered) through Cox regression models. Socioeconomic status was calculated as an age-standardized index (quintiles) based on the mean annual household income in the last 5 years before the study start. IRs and HRs were presented overall and in strata based on presence or absence of PsA and in age bands. We performed sensitivity analyses with additional adjustment for use of nonsteroidal anti-inflammatory drugs, systemic antibiotics, and oral contraceptives. To ensure that our findings were not solely explained by differences in health care use, we also performed a sensitivity analysis in which the reference population was sampled from people without psoriasis who were seen in the Danish health care system within 30 days of the index date for the respective psoriasis patients. Model assumptions, including the absence of interactions between model covariates, were tested and found to be valid unless otherwise specified. All statistical tests were conducted using a level of significance of 0.05, and results were reported with 95% confidence intervals (CIs), where applicable. All analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC) and STATA software, version 13.0 (StataCorp, College Station, TX).

CONFLICT OF INTEREST

Outside of the submitted work, AE has received research funding from Pfizer, Eli Lilly, the Danish National Psoriasis Foundation, and the Kgl Hofbundtmager Aage Bang Foundation and honoraria as a consultant and/or speaker from Almirall; Leo Pharma; Samsung Bioepis Co., Ltd.; Pfizer; Eli Lilly; Novartis; Galderma; and Janssen Pharmaceuticals. Outside of the submitted work, JPT is supported by an unrestricted grant from the Lundbeck Foundation and has received speaker honoraria from Galderma, Sanofi-Genzyme, LEO Pharma, and MEDA; has attended advisory board meetings for Roche, Eli Lilly, and Sanofi-Genzyme; and is an investigator for LEO Pharma and Eli Lilly. Outside of the submitted work, JB reports personal fees from AbbVie, Janssen-Cilag, Celgene, MSD, Pfizer, and Takeda and nonfinancial support from Calpro. Outside of the submitted work, J-FC has served as a consultant or advisory board member for Abbvie, Amgen, Boehringer-Ingelheim, Celgene Corporation, Celltrion, Enterome, Ferring, Genentech, Janssen and Janssen, Eli Lilly, Medimmune, Merck & Co., Pfizer, Protagonist, Second Genome, Seres, Shire, Takeda, and Theradiag; has been a speaker for Abbvie and Ferring; has been a member of the speaker's bureau for Amgen; and has stock options with Intestinal Biotech Development and Genfit.

AUTHOR CONTRIBUTIONS

AE had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: AE. Acquisition, analysis, and interpretation of data: all authors. Drafting of the manuscript: AE. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: AE. Obtained funding: none. Administrative, technical, or material support: AE. Study supervision: AE.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2018.07.029.

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Risk of first-time and recurrent depression in patients with psoriasis: a population-based cohort study*

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Summary

Background Psoriasis impairs quality of life, but it is unknown whether psoriasis is also an independent risk factor for depression.
Objectives To evaluate the incidence and risk of new and recurrent depression in patients with psoriasis.
Methods We used individual-level linkage of Danish administrative registers. Patients with psoriasis aged ≥ 18 years between 1 January 1997 and 31 December 2016 were matched 1 : 1 with individuals without psoriasis. Incidence rates were calculated and adjusted hazard ratios (HRs) estimated by Cox regression.
Results There were 247 755 patients with psoriasis: 220 721 were treated with topicals (mild psoriasis), 24 771 with systemic nonbiologics (moderate psoriasis) and 2263 with biological therapy (severe psoriasis). The same number of matched referents without psoriasis were also analysed. During a maximum 20 years of follow-up, 45 641 patients with psoriasis and 36 299 referents developed depression. In adjusted models, the HRs (95% confidence interval) of depression were 1·19 (1·17–1·20), 1·19 (1·15–1·23) and 1·50 (1·23–1·84) for mild, moderate and severe psoriasis, respectively. The highest risk was observed among patients with severe psoriasis aged 40–50 years. Concurrent inflammatory bowel disease, but not psoriatic arthritis, was associated with increased risk of depression. The incidence of depression was markedly higher among patients with previous depression.
Conclusions Psoriasis was independently associated with risk of depression. These results may help clinicians identify particularly high-risk individuals.

What's already known about this topic?

- Psoriasis negatively affects quality of life and confers significant morbidity.

What does this study add?

- Patients with psoriasis, especially those qualifying for biological therapy and aged 40–50 years, have a significantly increased risk of depression.

Psoriasis is a chronic, inflammatory and often stigmatizing skin condition affecting more than 125 million people worldwide.[1] The burden of psoriasis is considerable, and the negative impact of psoriasis on patients' functioning has been reported to be greater than for other medical conditions such as diabetes and heart failure.[2]

While psoriasis itself may impact quality of life, for example measured by the Dermatology Life Quality Index (DLQI), numerous studies have also associated psoriasis with the presence of medical comorbidities, including psoriatic arthritis (PsA), inflammatory bowel disease (IBD), diabetes and cardiovascular disease.[3–6]

Patients with psoriasis have an increased incidence and prevalence of depression;[7,8] however, the question of whether psoriasis itself represents an independent risk factor for depression remains controversial.[9–11] We therefore examined

the risk of new and recurrent depression (or symptoms of depression) in patients with psoriasis in a population-based cohort study.

Patients and methods

Data sources and study population

Denmark has a unique network of administrative and healthcare registries.[12] These can be linked at the individual level to provide virtually complete information on the entire population from cradle to grave, including (but not limited to) data on vital statistics, medical conditions and treatment thereof, education and income.[12–16] In Denmark, the tax-supported healthcare system gives all residents equal and universal access to healthcare services, including general practitioners and hospitals.

Among Danish adults (≥ 18 years) alive and resident in Denmark between 1 January 1997 and 31 December 2016 we identified all patients with recorded psoriasis. The patients were followed (study start) from the first recorded occurrence of psoriasis or their 18th birthday, whichever came last, until the first of either 31 December 2016, death, migration or the occurrence of an end point. Each patient was matched on birth date and sex with one individual from the general population. The index date (study start date) for the matched individuals was the same as for the corresponding patient with psoriasis.

Patients were classified as having psoriasis if they had received a diagnosis of psoriasis or had been treated with pharmacotherapy where the reason for the prescription was specified as psoriasis (e.g. if a patient received methotrexate where the indication was listed as 'for treatment of psoriasis'). The primary end point was the first occurrence of depression, defined by either a diagnosis of depression by a physician or psychologist, or by initiation of treatment with antidepressant drugs if the drug was prescribed for treatment of depression. The relevant codes used for this study are available in Table S1 (see Supporting Information). The Strengthening the Reporting of Observational Studies in Epidemiology recommendations were used for the conduct and reporting of this study.[17]

Statistical analysis

Descriptive characteristics were presented as means and SDs for continuous variables and frequencies and percentages for categorical variables. Patients with psoriasis were categorized according to use of psoriasis-specific therapy in the following groups: (i) topical treatment; (ii) systemic nonbiological treatment; and (iii) biological treatment (or apremilast, as use of this drug in Denmark is restricted to patients qualifying for biological treatment). To ensure the accuracy of this severity classification, only treatments prescribed for cutaneous psoriasis were used. Consequently, if patients received treatment with methotrexate for PsA, for example, rather than for cutaneous psoriasis, this was not included.

SAS statistical software version 9·4 (SAS Institute Inc., Cary, NC, U.S.A.) and Stata software version 13·0 (StataCorp, College Station, TX, U.S.A.) were used to summarize incidence rates (IRs) per 1000 person-years, and we used Cox regression models to calculate hazard ratios (HRs) for the risk of depression. This method is generally considered a powerful tool in detecting disease and treatment effects in large cohorts.[18] The incidence of depression during follow-up was calculated for: (i) all individuals; (ii) individuals without a history of depression at any time prior to study start; and (iii) individuals with a history of depression, where the last recorded code was a minimum of 3 years prior to the index date (to ensure that any depression occurring during follow-up was in fact a new case of depression). HRs for depression were calculated as fully adjusted, in which age, sex, socioeconomic status, smoking, alcohol abuse, PsA, IBD, hypertension, diabetes and hyperlipidaemia (defined by use of cholesterol-lowering drugs) were considered. These potential confounders were chosen a priori.

Although it has become more infrequent since the introduction of systemic (in particular biological) treatment modalities, Danish patients still require inpatient hospital admission for treatment of their psoriasis (e.g. with coal tar), in case of severe flares or for treatment of pustular psoriasis. These patients may represent a particular subgroup of patients with different characteristics and risk profiles. Consequently, we performed subanalyses in which we assessed the risk of depression in patients following inpatient hospitalization due to psoriasis, while controlling for age, sex, socioeconomic status, smoking, alcohol abuse, PsA, IBD, hypertension, diabetes and hyperlipidaemia, as well as use of topical, systemic nonbiological and biological therapy.

The model assumptions were tested and found to be valid. All statistical tests were conducted using a level of significance of 0·05, and the results were reported with 95% confidence intervals (CIs), where applicable.

Results

The study cohort comprised a total of 247 755 patients with psoriasis and the same number of matched individuals without psoriasis from the general population. There was a slight female predominance in all groups, except for patients receiving biological therapy, where 65·0% of patients were men (Table 1). At baseline, the mean age was markedly lower among patients who were treated with biologics during the study. Smoking (18·5–24·1% vs. 14·3%) and alcohol abuse (8·4–10·3% vs. 6·6%) were more frequent among patients with psoriasis than in the general population. Medical comorbidity was generally more frequent among patients with psoriasis than in the reference group without psoriasis (Table 1).

During the maximum 20 years of follow-up, 46 641 (18·8%) and 36 299 (14·7%) individuals had a recorded episode of depression, among patients with psoriasis and the general population, respectively. Of these, 17 001 (36·5%)

and 14 605 (40·2%), respectively, did not have a history of depression prior to the start of the study (i.e. first-time depression). Overall, the IRs of depression per 1000 person-years were lowest for patients treated with biologics, although this group was also somewhat younger. The IRs (per 1000 person-years) of first-time depression were 12·6 (95% CI 12·4–12·8), 13·0 (95% CI 12·4–13·6) and 11·5 (95% CI 9·2–14·5) among patients with psoriasis treated with topical therapy, systemic nonbiological therapy and biological therapy, respectively, compared with 10·5 (95% CI 10·3–10·7) in the general population. Across all groups, IRs of depression were markedly higher among patients with a history of previous depression (Table S2; see Supporting Information). Specific IRs for patients with psoriasis without PsA are shown in Table S3 (see Supporting Information).

Risk of any depression

In fully adjusted models, increasing age, female sex, smoking, alcohol abuse, low socioeconomic status and medical comorbidity were associated with a significantly increased risk of depression. Among patients with psoriasis, risk of depression was increased among patients receiving topical (adjusted HR 1·19, 95% CI 1·17–1·20), systemic (adjusted HR 1·19, 95% CI 1·15–1·23) and biological therapy (adjusted HR 1·50, 95% CI 1·23–1·84). Notably, while comorbidities such as IBD (adjusted HR 1·30, 95% CI 1·23–1·37) and diabetes (adjusted HR 1·24, 95% CI 1·21–1·27) were associated with a significant risk of depression, concurrent PsA was not associated with an increased risk of depression (adjusted HR 1·01, 95% CI 0·96–1·06) (Table S4; see Supporting Information). In age-specific strata, the highest risk

Table 1 Characteristics of the study population

		Patients with psoriasis		
	Reference population (n = 247 755)	Topical (n = 220 721)	Systemic nonbiologic (n = 24 771)	Biologic (n = 2263)
Age (years)				
Mean ± SD	51·1 ± 18·6	51·1 ± 18·9	52·6 ± 16·0	37·7 ± 13·2
Median (interquartile range)	52·4 (36·8–65·2)	52·4 (36·4–65·5)	53·9 (41·5–64·2)	36·7 (27·2–47·1)
Sex, n (%)				
Female	132 506 (53·3)	117 716 (53·3)	13 548 (54·7)	792 (35·0)
Male	115 699 (46·7)	103 005 (46·7)	11 223 (45·3)	1471 (65·0)
Smoking, n (%)	35 349 (14·3)	40 861 (18·5)	5961 (24·1)	419 (18·5)
Alcohol abuse, n (%)	16 373 (6·6)	18 588 (8·4)	2210 (8·9)	234 (10·3)
Educational level, n (%)				
Primary school	82 541 (33·3)	75 832 (34·4)	9193 (37·1)	799 (35·3)
Middle school	15 451 (6·2)	17 784 (6·2)	936 (7·8)	175 (7·7)
High school and vocational school	82 540 (33·3)	75 104 (34·0)	9606 (38·8)	835 (36·9)
Short higher education	31 844 (12·9)	27 270 (12·4)	2778 (11·2)	216 (9·5)
Bachelor degree	3187 (1·3)	2577 (1·2)	149 (0·6)	28 (1·1)
Master degree	14 149 (5·7)	11 251 (5·1)	710 (2·9)	80 (3·5)
PhD and research fellowships	752 (0·3)	493 (0·2)	32 (0·1)	4 (0·2)
Other/unregistered	17 291 (7·0)	14 410 (6·5)	1367 (5·5)	130 (5·7)
Income level, n (%)				
Lowest	50 758 (20·5)	44 273 (20·0)	3534 (14·3)	536 (23·7)
Below average	48 278 (19·5)	45 335 (20·5)	5191 (21·0)	300 (13·3)
Average	48 323 (19·5)	44 434 (20·1)	5830 (23·5)	514 (22·7)
Above average	49 714 (20·1)	43 107 (19·5)	5752 (23·2)	529 (23·4)
Highest	50 682 (20·5)	43 572 (19·7)	4464 (18·0)	384 (17·0)
Comorbidity, n (%)				
Diabetes, at baseline	13 461 (5·4)	15 934 (7·2)	1684 (6·8)	56 (2·5)
Diabetes, during follow-up	22 333 (9·0)	26 164 (11·9)	3586 (14·5)	275 (12·2)
Hypertension, at baseline	35 395 (14·3)	38 989 (17·7)	4073 (16·4)	120 (5·3)
Hypertension, during follow-up	52 516 (21·2)	54 748 (24·8)	7458 (30·1)	462 (20·4)
Statin use, at baseline[a]	1951 (0·8)	1984 (0·9)	285 (1·2)	11 (0·5)
Statin use, during follow-up	56 435 (22·8)	58 240 (26·4)	8205 (33·1)	573 (25·3)
Psoriatic arthritis, at baseline	181 (0·1)	3316 (1·5)	2254 (9·1)	195 (8·6)
Psoriatic arthritis, during follow-up	291 (0·1)	7164 (3·3)	5602 (22·6)	969 (42·8)
IBD, at baseline	2342 (1·0)	3216 (1·5)	396 (1·6)	22 (1·0)
IBD, during follow-up	3352 (1·4)	4629 (2·1)	642 (2·6)	48 (2·1)
History of depression	30 942 (12·5)	35 916 (16·3)	3916 (15·8)	226 (10·0)

IBD, inflammatory bowel disease. [a]Prescription within the past 6 months.

of depression was observed among biologic-treated patients aged 40–50 years (adjusted HR 2·25, 95% CI 1·57–3·22) (Fig. 1).

Risk of first-time depression

Patients with psoriasis receiving topical treatment had a slightly increased risk of first-time depression (adjusted HR 1·13, 95% CI 1·11–1·16), as did patients who received systemic nonbiological psoriasis therapy (adjusted HR 1·16, 95% CI 1·10–1·21) and patients on biological therapy (adjusted HR 1·30, 95% CI 1·04–1·64). Among this cohort, the presence of PsA was associated with a slightly increased risk of first-time depression (adjusted HR 1·10, 95% CI 1·02–1·17), whereas the risk associated with other conditions including hypertension, diabetes and IBD was somewhat higher, albeit still lower than for risk factors such as smoking and alcohol abuse (Table S4; see Supporting Information).

Risk of recurrent depression

Among patients with a history of prior depression (i.e. those perceived to be particularly vulnerable), the risk of recurrent depression was not increased among patients treated with topical therapy (adjusted HR 1·00, 95% CI 0·99–1·02), and was only marginally increased in patients receiving systemic nonbiological therapy (adjusted HR 1·06, 95% CI 1·01–1·12). While there was a trend towards an increased risk among patients treated with biologics, this was not statistically significant (adjusted HR 1·62, 95% CI 0·92–2·87). Moreover, among patients with a history of previous depression, risk factors such as IBD and diabetes had very little impact on the risk of recurrent depression (Table S4; see Supporting Information).

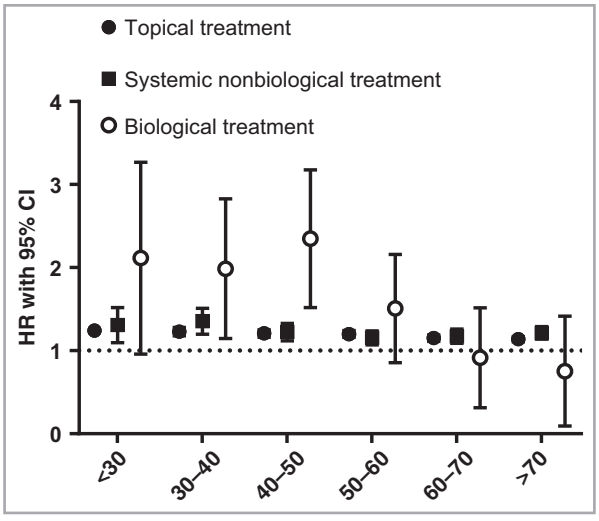

Fig 1. Adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) of depression in patients with psoriasis across age strata.

Risk of depression in patients hospitalized due to psoriasis

In total, 5883 patients had at least one inpatient hospitalization due to psoriasis. At baseline, the mean age was 49·1 ± 18·4 years, and 48·9% were women. Compared with the general population, these patients had lower education and income levels, whereas smoking, alcohol abuse and medical comorbidity occurred markedly more frequently than in the general population (Table S5; see Supporting Information). The IR of first-time depression per 1000 person-years was 15·5 (95% CI 14·5–16·5), while the IR of recurrent depression was 416·3 (95% CI 363·8–476·2). After adjustment for confounding factors, the risk of first-time depression after hospitalization due to psoriasis was slightly increased (HR 1·23, 95% CI 1·14–1·33).

Discussion

In this nationwide registry-based cohort study, psoriasis managed with topical or systemic nonbiological therapy (presumably mild-to-moderate severity) was associated with a marginal increase in risk of depression after controlling for measured confounders. A somewhat higher risk was seen among patients requiring biological therapy – namely those with more severe psoriasis, and especially among patients 40–50 years of age – suggesting that these patients may represent a particularly vulnerable group in which increased awareness may be needed.

The incidence of recurrent depression was increased approximately 10-fold compared with first-time depression; however, the risk of recurrent depression was not increased among patients with psoriasis compared with the general population, and neither was the risk of recurrent depression noticeably associated with severity of psoriasis. While patients qualifying for biological therapy may represent patients with the greatest psoriasis-associated impairment in quality of life, these therapies may potentially reduce this impairment by improving psoriasis. Indeed, conventional systemics and biologics have been associated with reduction in depressive symptoms in some studies, whereas others have shown conflicting results.[19–24]

Nevertheless, very recent data from Denmark suggest that even among patients treated with biologics, only very few patients have achieved a DLQI score ≤ 1 after 1 year of therapy, suggesting that the negative impact on quality of life is not completely ameliorated by use of currently approved biologics.[25] On the other hand, while hospitalized patients predominantly have severe disease, these individuals may often not wish to receive, or have certain contraindications to, systemic therapy. For these patients, hospitalization may be used as a way to achieve stabilization in patients with low adherence to treatment, such as those with a high comorbidity burden (e.g. alcohol abuse), which may be contributing to the risk of depression.

Previous studies have used various definitions to examine the risk of depression in patients with psoriasis. Wu *et al.*[11] examined the risk of depression in patients with psoriasis using electronic medical records based in the U.S.A. After adjustment for potential confounders, the authors reported an adjusted incidence rate ratio (IRR) of 1·14 (95% CI 1·11–1·17), an estimate comparable with the overall findings in our study. Notably, when stratified based on treatment patterns, patients with mild psoriasis (i.e. those receiving no treatment or topical treatment only) had a 14% increased risk of depression (adjusted IRR 1·14, 95% CI 1·12–1·17), whereas patients classified as having severe psoriasis (i.e. those receiving either phototherapy, conventional systemic medication or biological therapy) had only an 8% increased risk of depression (adjusted IRR 1·08, 95% CI 1·01–1·14). A previous study from Denmark[9] studied the risk of first-time depression, defined either by hospitalization for depression or by prescription of antidepressants regardless of the reason these were prescribed. The risk was found to be increased only in patients < 50 years of age with at least three hospital contacts due to psoriasis (adjusted IRR 1·23, 95% CI 1·03–1·46).

Certain limitations apply to the interpretation of the present findings. Depression is a complex and multifactorial condition, and while observational studies may provide evidence of associations, such data cannot establish a causal link. Consequently, whether the slightly increased risk of depression associated with psoriasis in our study was in fact due to psoriasis itself, or whether this was due to unmeasured lifestyle factors remains unclear. Indeed, the magnitude of the association especially among patients with mild and moderate psoriasis was relatively small, and we cannot refute that this finding may be due to increased awareness of depressive symptoms among physicians.

Moreover, we lacked information on objective measures of psoriasis severity such as Psoriasis Area and Severity Index scores. Furthermore, although the severity assessment based on treatment of psoriasis has previously been validated with high accuracy, it is likely that treatment of psoriasis may have reduced the signs and symptoms of psoriasis, and any psoriasis severity-correlated risk would have been reduced as a consequence. Even patients with relatively mild psoriasis may have psoriasis in visible or highly bothersome locations (e.g. the face or genitals), which may considerably impair quality of life and, in turn, lead to depression.[26,27] Such information would not be captured by use of pharmacotherapy, and the results should be interpreted accordingly.

Lastly, the end point of depression is highly heterogeneous and may range from severe major depressive disorders requiring specialist psychiatric care to milder symptoms of depression that may be managed by general practitioners alone, and the results should be interpreted accordingly. Important strengths of the study include the sheer number of patients in the nationwide cohort, and the well-established high quality of the Danish registries whereby recall bias and loss to follow-up are virtually nonexistent.

In conclusion, we found an overall modest increased risk of depression in patients with psoriasis, with the highest risk occurring among middle-aged patients with severe psoriasis and the highest incidence among those with a prior history of depression. These results may help clinicians identify which patients are at particularly high risk of depression, in whom pre-emptive measures may be needed to reduce the future risk of depression.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Administrative codes used in the study.

Table S2 Summary of the number of events, follow-up time and incidence rates per 1000 person-years.

Table S3 Incidence rates per 1000 person-years of depression among patients with psoriasis without psoriatic arthritis.

Table S4 Hazard ratios estimating the risk of depression in patients with psoriasis compared with the general population.

Table S5 Characteristics of patients hospitalized due to psoriasis.

Powerpoint S1 Journal Club Slide Set.

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Risk of self-harm and nonfatal suicide attempts, and completed suicide in patients with psoriasis: a population-based cohort study*

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Linked Comment: Sbidian. *Br J Dermatol* 2016; **175**:456–457.

Summary

Background Psoriasis is a common inflammatory skin disease, and inflammation may affect suicidal behaviour. Current data on the incidence and risk of suicidal behaviour in patients with psoriasis are scarce.

Objectives We investigated the association between psoriasis and the risk of self-harm and suicide attempts and suicides.

Methods All Danish patients aged ≥ 18 years with mild or severe psoriasis (cases) from 1 January 1997 to 31 December 2011 were matched on age, sex and calendar time 1 : 5 with healthy controls. The outcome was a diagnosis of self-harm or a nonfatal suicide attempt, or completed suicide. Incidence rates per 10 000 person-years were calculated, and incidence rate ratios (IRRs) and confidence intervals (CIs) were estimated by Poisson regression models.

Results The study cohort comprised 408 663 individuals, including 57 502 and 11 009 patients with mild and severe psoriasis, respectively. In total 280 cases of self-harm or suicide attempts, and 574 suicides occurred during follow-up. There was no increased risk of self-harm or suicide attempts in patients with mild psoriasis (IRR 1·01, 95% CI 0·17–2·01), but this risk was significantly increased in severe psoriasis (IRR 1·69, 95% CI 1·00–2·84). There was no increased risk of suicides in mild (IRR 1·05, 95% CI 0·84–1·32) or severe psoriasis (IRR 0·78, 95% CI 0·45–1·36). Similar results were found when suicides were confirmed by official forensic investigations, and when psoriasis was compared with atopic dermatitis.

Conclusions We found limited evidence to suggest an increased risk of self-harm and nonfatal suicide attempts in patients with psoriasis. Importantly, after adjustment for psoriatic arthritis this risk was no longer significantly increased. The risk of completed suicide was also not increased, regardless of psoriasis severity.

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Conflicts of interest
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What's already known about this topic?

- Psoriasis is an inflammatory disease with severe impact on quality of life, and inflicts a substantial psychosocial burden on patients.

What does this study add?

- Psoriasis may be associated with a small increased risk of self-harm and nonfatal suicide attempts, but the risk of completed suicide is not increased.
- Importantly, after adjustment for psoriatic arthritis, the risk of self-harm and nonfatal suicide attempts was no longer significantly increased.

Psoriasis and atopic dermatitis (AD) are the two most common chronic immune-mediated inflammatory skin diseases. Both diseases have severe impact on quality of life and inflict a substantial psychosocial burden on patients.[1] The inflammatory response in psoriasis is considered to be promoted mainly by T helper (Th)17 cells, with proinflammatory mediators such as interleukin (IL)-17, IL-22 and IL-23, although Th1 cells and Th1 cytokines such as IL-12 and tumour necrosis factor (TNF)-α also play a role.[2] In contrast, AD is thought to be mediated mainly by a Th2 response, with exaggerated IgE responses to allergens and a lesser influence of Th17 cells.[3]

Evidence has highlighted the substantial effects that these diseases have on the psychosocial well-being of patients. Health-related quality of life in psoriasis and AD is similar to that of other major disorders such as diabetes.[4,5] Furthermore, adults with psoriasis and AD are more likely to have depression than healthy individuals.[6] Interestingly, research in neuroinflammation associated with diseases of the central nervous system, including depression, has in recent years increasingly also focused on the role of the same proinflammatory cytokines that are involved in psoriasis and AD.[7] Levels of several Th1 and Th2 cytokines such as IL-1, IL-4, IL-6 and TNF-α have been shown to be increased in cerebrospinal fluid and post mortem brains of suicide victims, and may affect suicidal behaviour.[8]

Data on the risk of self-harm and suicide attempts, and suicide in patients with these common immune-mediated inflammatory skin disorders are limited, and although an increased risk of 'suicidality' in patients with psoriasis has been suggested, no study has separately examined the risk of self-harm and nonfatal suicide attempts, and completed suicides, in patients with psoriasis. We investigated this clinically important issue in a population-based cohort study.

Materials and methods

Data sources and study population

Study approval was obtained from the Danish Data Protection Agency (reference 2007-58-0015; internal reference GEH-2014-018, I-Suite 02736). Approval from an ethics committee is not required for register studies in Denmark. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations were used for the conduct and reporting of this study.[9]

All Danish citizens receive free and equal healthcare services, which ensure unencumbered access to general practitioners and hospitals. At birth or immigration, each individual receives a unique and permanent 10-digit personal identification number, which allows for unambiguous linkage across the nationwide administrative registers in Denmark. All inpatient and outpatient hospital consultations (including consultations at psychiatric hospitals) are recorded in the Danish National Patient Register.[10] The register was established in 1978, and used codes from the International Classification of Diseases, Eighth Revision (ICD-8) until 1994, and from ICD-10 thereafter. For administrative reasons, the ninth revision (ICD-9) was never used in Denmark.

Hospital procedures, including hospital-based pharmacological treatment, for example therapy with biological agents, are coded in the register as treatment procedure codes. Since 1994, detailed and accurate information on all pharmacy-dispensed medications has been registered according to the international Anatomical Therapeutic Chemical (ATC) classification in the Danish Registry of Medicinal Products Statistics.[11] Information on tax-reported household income is recorded by Statistics Denmark, and information on age, sex and vital and migration status are available from the Civil Registration System.[12,13] Within 14 days of death, all deaths and causes of deaths are registered in the National Causes of Death Registry.[14]

Identification of cases and controls

For cases, we identified all Danish patients aged ≥ 18 years with either mild or severe psoriasis between 1 January 1997 and 31 December 2011. Patients were classified with severe disease when they received systemic antipsoriatic therapy (biological drugs, ciclosporin, psoralens, retinoids or methotrexate). Patients with psoriasis who did not receive systemic therapy were classified as having mild disease. We have previously described and validated the method for identification of psoriasis and classification of severity, with a sensitivity of 98%.[15] The index date for cases was the first occurrence of mild or severe psoriasis, and each patient was matched (on age, sex and calendar time) with five controls from the general population. The index date for controls was the index date for the corresponding case, and the cohort was followed until migration, death from any cause or the occurrence of an end point, whichever came first. We excluded individuals with a history of self-harm (e.g. cutting or burning oneself with cigarettes) or suicide attempts (ICD-8 codes 950–959 and ICD-10 codes X60–X84, Y87·0) prior to study inclusion.

Outcomes

All unnatural deaths in Denmark are reported to the police, who perform an inquest involving specialized forensic doctors. The police and forensic doctors contact hospitals where the deceased was treated, the deceased's physician, the person who found the deceased, and the deceased's relatives and close friends, and obtain information about the method of death, place of death and presence of a suicide note. A forensic autopsy is conducted following this inquest if the cause of death remains uncertain. The final classification of death due to suicide is made by the independent forensic doctor based on the combined information from these sources.[16]

The coprimary end points were the first diagnosis of self-harm or nonfatal suicide attempt (ICD-10 codes X60–X84) recorded in the National Patient Register, or a recorded suicide in the national Causes of Death Registry.

Two sets of analyses were performed examining the risk of suicide. In the first set of analyses, the end point was a

physician-reported suicide, and in the second set of analyses we included only those suicides that were confirmed by a police forensic investigation. The risks of self-harm and suicide were estimated in separate analyses, and the occurrence of self-harm or a nonfatal suicide attempt did not result in censoring in analyses of the risk of suicide. Importantly, specific diagnostic codes of suicide ideation are not used in Denmark.

Pharmacological treatment, medical comorbidities and socioeconomic status

Baseline treatment up to 6 months before study inclusion was defined for antidepressants (ATC code N06A), psycholeptics (ATC code N05) and cholesterol-lowering agents (ATC code C10A). Baseline comorbidity was described by ICD codes up to 5 years prior to study inclusion for mental disorders (ICD-8 codes 290–316 and ICD-10 codes F00–F99) and cancer (ICD-8 codes 140–209 and ICD-10 codes C00–C96). Hypertension was defined either by a hospital diagnosis or if a patient within 90 days received treatment with at least two of the following classes of antihypertensive drugs: α-adrenergic blockers, nonloop diuretics, vasodilators, β-blockers, calcium channel blockers and renin–angiotensin system inhibitors, as previously described and validated, with a positive predictive value of 80% and a specificity of 95%.[17] Diabetes was defined by either a hospital diagnosis (ICD-8 code 250 and ICD-10 codes E10–E14) or use of glucose-lowering drugs (ATC code A10). We tracked smoking history through an algorithm as previously described.[15] Alcohol abuse was defined by diagnoses of alcohol abuse or conditions strongly related to alcohol abuse (e.g. alcoholic liver disease), pharmacological treatment with drugs used in alcohol dependence, and treatment interventions for alcohol dependence (Table S1). We calculated an age-standardized index of socioeconomic status between 0 (lowest) and 4 (highest) based on the average gross annual income during a 5-year period before study inclusion.

Statistical analysis

We described baseline characteristics with means and SDs for continuous variables and frequencies and percentages for categorical variables. We used SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, U.S.A.) and Stata software version 11.0 (StataCorp, College Station, TX, U.S.A.) to summarize incidence rates per 10 000 person-years, and we performed Poisson regression analyses to obtain incidence rate ratios (IRRs) for self-harm and suicide attempts. In adjusted analyses, information on antidepressant use and alcohol abuse was continuously updated during follow-up. In the adjusted analyses, we used antidepressant therapy rather than hospital diagnoses of depression, as this enabled capture of patients treated for depression by their general practitioners who might not have sought hospital treatment.

We performed sensitivity analyses with exclusion of patients treated with retinoids (ATC code D05BB), as these drugs may increase the risk of depression and suicide.[18] In addition, to compare our findings with another common skin disease, we identified all Danish adults (age ≥ 18 years) with a hospital dermatologist diagnosis of AD (ICD-8 code 691, ICD-10 code L20) between 1 January 1997 and 31 December 2011. Consequently, each patient with AD was matched (age, sex and calendar time) with five controls from the general population, to estimate their risk of self-harm and suicide attempts, and suicide, when compared with healthy controls.

All statistical tests were conducted using a level of significance of 0·05, and the results are reported with 95% confidence intervals (CIs), where applicable.

Results

After exclusion of 390 individuals with a history of self-harm or suicide attempts prior to study start, the study comprised a total of 68 511 patients with psoriasis as cases. Of these, there were 57 502 mild and 11 009 severe cases of psoriasis. These cases were matched with 342 555 controls from the general population. After exclusion of 1254 controls with a history of self-harm or suicide attempts, and 1149 controls with incomplete follow-up due to migration, the final control population comprised 340 152 individuals. The baseline characteristics are shown in Table 1.

During the study period, there were 280 cases of self-harm or suicide attempts and 574 physician-reported suicides. Of the physician-reported suicides, forensic police investigations concluded that 445 were in fact confirmed suicides. The characteristics of these patients are described in Table 2, and the incidence rates per 10 000 person-years for cases and controls are shown in Table 3.

In analyses of psoriasis regardless of its severity (henceforth named 'overall psoriasis'), the risk of self-harm or suicide attempts was significantly increased (IRR 1·42, 95% CI 1·08–1·88, P = 0·014) in the crude (unadjusted) analysis, but not in the fully adjusted analysis (IRR 1·17, 95% CI 0·88–1·55, P = 0·28) (Table 4). While there was no increased risk in patients with mild psoriasis (adjusted IRR 1·01, 95% CI 1·17–2·01, P = 0·96), the risk was significantly increased in patients with severe psoriasis in both the crude (IRR 2·23, 95% CI 1·33–3·74, P = 0·002) and adjusted (IRR 1·69, 95% CI 1·00–2·84, P = 0·049) analyses. The crude analyses showed no increased risk of physician-reported completed suicides in overall (IRR 1·12, 95% CI 0·91–1·39, P = 0·28), mild (IRR 1·17, 95% CI 0·92–1·46, P = 0·18) or severe psoriasis (IRR 0·92, 95% CI 0·53–1·59, P = 0·74), and no significant changes were observed in the adjusted analyses. Similarly, there was no increased risk of police-confirmed completed suicides, as shown in Table 4.

Sensitivity analyses

For mild and severe psoriasis, when patients were stratified based on age (< 30, 30–59, ≥ 60 years), the highest incidence of self-harm and suicide attempts occurred in

Table 1 Baseline characteristics of the entire study population

	Overall psoriasis		Mild psoriasis		Severe psoriasis	
	Controls	Patients	Controls	Patients	Controls	Patients
Total number	340 152	68 511	285 544	57 502	54 608	11 009
Age (years), mean ± SD	51·2 ± 16·7	51·2 ± 16·7	51·8 ± 16·9	51·7 ± 16·9	48·4 ± 15·3	48·4 ± 15·3
Women, n (%)	175 587 (51·6)	35 304 (51·5)	147 495 (51·7)	29 654 (51·6)	28 092 (51·4)	5650 (51·3)
Men, n (%)	164 565 (48·4)	33 207 (48·5)	138 049 (48·3)	27 848 (48·4)	26 516 (48·6)	5359 (48·7)
Socioeconomic status, mean ± SD	2·0 ± 1·4	2·0 ± 1·4	2·0 ± 1·4	2·0 ± 1·4	2·1 ± 1·4	2·1 ± 1·4
Smoking, n (%)	32 426 (9·5)	8733 (12·8)	27 169 (9·5)	7126 (12·4)	5257 (9·6)	1607 (14·6)
Comorbidity, n (%)						
Alcohol abuse	5440 (1·6)	1583 (2·3)	4503 (1·6)	1343 (2·3)	937 (1·7)	240 (2·2)
Cancers	8431 (2·5)	1757 (2·6)	7263 (2·5)	1544 (2·7)	1168 (2·1)	213 (1·9)
Diabetes	11 920 (3·5)	3314 (4·8)	10 256 (3·6)	2910 (5·1)	1664 (3·1)	404 (3·7)
Hypertension	37 550 (11·0)	9597 (14·0)	32 738 (11·5)	8348 (14·5)	4812 (8·8)	1249 (11·4)
Mental disorders	7497 (2·2)	2150 (3·1)	6400 (2·2)	1859 (3·2)	1097 (2·0)	291 (2·6)
Medication, n (%)						
Antidepressants	23 083 (6·8)	6181 (9·0)	19 778 (6·9)	5245 (9·1)	3305 (6·1)	936 (8·5)
Antipsychotics	7376 (2·2)	1915 (2·8)	6263 (2·2)	1678 (2·9)	1113 (2·0)	237 (2·2)
Anxiolytics	17 637 (5·2)	4691 (6·9)	14 994 (5·3)	4002 (7·0)	2643 (4·8)	689 (6·3)
Cholesterol-lowering drugs	23 745 (7·0)	5824 (8·5)	20 810 (7·3)	5130 (8·9)	2935 (5·4)	694 (6·3)
Hypnotics and sedatives	19 037 (5·6)	5005 (7·3)	16 334 (5·7)	4261 (7·4)	2703 (5·0)	744 (6·8)

individuals aged < 30 years, and the incidence of completed suicides was highest in individuals 30–59 years of age. However, in age-stratified estimates, the risk of self-harm and suicide attempts was increased only in 'overall psoriasis' (age < 30 years; IRR 1·81, 95% CI 1·02–3·20, P = 0·043), and there was no increased risk of completed suicide (either physician-reported or police-confirmed suicide) in any age group, regardless of psoriasis severity (data not shown).

Exclusion of patients treated with retinoids had no significant bearing on any of the reported results (Table S2). After exclusion of individuals with psoriatic arthritis the risk of self-harm and suicide attempts in severe psoriasis was no longer statistically significant (P = 0·078); however, there was still no increased risk in analyses of physician-reported completed suicide (mild psoriasis, n = 89, P = 0·15; severe psoriasis, n = 11, P = 0·90) or police-confirmed completed suicide (mild psoriasis, n = 74, P = 0·058; severe psoriasis, n = 10, P = 0·42).

When patients with severe psoriasis (cases) were compared with those with mild psoriasis (controls), the risk of self-harm and suicide attempts was significantly increased (age- and sex-adjusted IRR 2·04, 95% CI 1·21–3·44, P = 0·008), but the risk of physician-reported completed suicide (age- and sex-adjusted IRR 0·72, 95% CI 0·42–1·25, P = 0·24) or police-confirmed completed suicide (age- and sex-adjusted IRR 0·81, 95% CI 0·46–1·43, P = 0·47) was not significantly increased. In analyses where patients with AD (n = 7663) were compared with matched controls (n = 37 924), there were eight (incidence rate 1·48, 95% CI 0·74–2·96) and 23 (incidence rate 0·86, 95% CI 0·57–1·30) occurrences of self-harm or suicide attempts among cases (AD) and controls, respectively. Similarly, there were 11 (incidence rate 2·03, 95% CI 1·13–3·67) and 26 (incidence rate 0·98, 95% CI 0·66–1·43) physician-reported completed suicides, respectively. Of these, 24 and nine, respectively, were confirmed by forensic investigations.

The IRR of self-harm and suicide attempts was 1·71 (95% CI 0·77–3·83, P = 0·19), and the risk of physician-reported completed suicide was significantly increased (IRR 2·08, 95% CI 1·03–4·21, P = 0·041) in patients with AD. In analyses of police-confirmed completed suicide in patients with AD, the risk was increased only in individuals aged > 45 years (IRR 3·68, 95% CI 1·17–11·59, P = 0·026). In fully adjusted analyses comparing psoriasis (cases) with AD (controls), the risk of self-harm and suicide attempts was not increased in mild psoriasis (IRR 1·37, 95% CI 0·62–3·06, P = 0·44), but patients with severe psoriasis had a significantly increased risk of self-harm and suicide attempts (IRR 2·45, 95% CI 1·02–5·93, P = 0·045). Compared with AD, patients with psoriasis did not have an increased risk of completed suicide, regardless of psoriasis severity (Table S3).

Discussion

We found a slightly increased risk of self-harm and suicide attempts in patients with severe psoriasis, but after adjustment for psoriatic arthritis this risk was no longer significantly increased. However, perhaps most importantly, the risk of suicide was not increased in patients with either mild or severe psoriasis. To our knowledge, this is the first study to examine separately the risk of self-harm and suicide attempts, and completed suicide, and our results suggest that patients with psoriasis are not at increased risk of completed suicide, and that the risk of self-harm and nonfatal suicide attempts in these patients is limited.

Table 2 Characteristics of cases and controls at time of event

	Self-harm or suicide attempt				Suicide (physician reported)				Suicide (police/forensic confirmed)			
	Controls	Mild psoriasis	Controls	Severe psoriasis	Controls	Mild psoriasis	Controls	Severe psoriasis	Controls	Mild psoriasis	Controls	Severe psoriasis
Number	172	42	45	21	389	92	78	15	299	76	56	14
Age (years), median	46·8	43·5	48·9	43·9	57·4	53·6	54·6	50·4	58·5	55·8	57·7	51·5
Comorbidity, n (%)												
Alcohol abuse	165 (93·9)	38 (90)	44 (98)	20 (95)	75 (19·3)	27 (29)	14 (18)	4 (27)	57 (19·1)	22 (29)	10 (18)	4 (29)
Mental disorders	86 (50·0)	23 (55)	21 (47)	10 (48)	114 (29·3)	36 (39)	17 (22)	5 (33)	95 (32·8)	28 (37)	13 (23)	5 (36)
Medication, n (%)												
Antidepressants	122 (70·9)	37 (88)	31 (69)	18 (86)	207 (53·2)	50 (54)	45 (58)	5 (33)	169 (56·5)	41 (54)	34 (61)	5 (36)
Antipsychotics	66 (38·4)	20 (48)	18 (40)	8 (38)	94 (24·2)	28 (30)	18 (23)	4 (27)	75 (25·1)	22 (29)	14 (25)	4 (29)
Anxiolytics	95 (55·2)	26 (62)	30 (67)	10 (48)	171 (44·0)	45 (49)	36 (46)	5 (33)	138 (46·2)	34 (45)	26 (46)	5 (36)
Hypnotics and sedatives	91 (52·9)	27 (64)	21 (47)	14 (67)	168 (43·2)	47 (51)	34 (44)	5 (33)	128 (42·8)	38 (50)	22 (39)	5 (36)

Previously, Kurd *et al.* described the risk of 'suicidality' (defined as a composite of suicidal ideation, suicide attempt or suicide) in patients with psoriasis.[19] Their main finding was a significantly (hazard ratio 1·44, 95% CI 1·32–1·57) increased risk of suicidality in patients with psoriasis compared with matched controls. However, an important limitation was their use of a composite end point, whereby the risks of suicide attempts and completed suicides were not analysed separately. Singhal *et al.* examined hospital episodes of self-harm, and found a rate ratio of 1·6 (95% CI 1·5–1·7) for the association with psoriasis, and a rate ratio of 1·4 (95% CI 1·3–1·5) for the association with eczema.[20] Notably, rates of self-harm and suicide attempts, and completed suicides in our healthy control populations appear to correspond with those previously reported in Denmark.[21] Similarly, a questionnaire-based study ranging across 13 countries, including Denmark, found a significantly increased risk of suicidal ideation (odds ratio 1·94) in patients with psoriasis.[1]

While the vast impact of psoriasis on quality of life has been proposed to be a mechanism for development of depression, inflammatory cytokine production may be a contributory factor.[22,23] Indeed, studies have shown strong associations between IL-17A and depression, suggesting potential beneficial effects of IL-17A inhibition in depressive disorders.[7] Similarly, a role of inflammation in suicide and suicidal ideation has been proposed.[8,24] In fact, studies have found increased levels of proinflammatory cytokines such as IL-6 and TNF-α in suicide and suicide attempt subjects, and it is tempting to speculate that treatment with TNF inhibitors may favourably affect suicidal behaviour.[8] Along this line, IL-6 is elevated in the cerebrospinal fluid of suicide attempt subjects, and peripheral blood levels of IL-6 have been put forward as a potential biological suicide marker.[8]

While IL-17A may be important for development of depression, IL-17E may indirectly have a role in suicidal behaviour. Specifically, IL-6 is regulated by upstream cytokines that include IL-25 (IL-17E).[25] In our study, we did not find any increased risk of completed suicide in patients with psoriasis, but the risk of suicide in patients with AD was significantly increased. In potential support of the latter finding, significantly increased levels of IL-4 and IL-13 were found in post mortem brains of suicide victims.[8,26] Indeed, IL-4 and IL-13 are pleiotropic Th2 cytokines produced by a wide variety of different cell types that are involved in the pathogenesis of AD, although their exact functions in depression and suicidal behaviour are still unclear.[27,28]

While suicide is a large public health problem, and although it is possible to identify groups at particularly high risk of suicide, the rate of suicide is low even in high-risk groups.[21] Suicide rates in Denmark have been declining in the last decades, and preventive interventions have been directed at the general population to lower the risk of suicide.[29] For example, the availability of methods for suicide has been limited, for example by limiting access to purchase of firearms and restrictions concerning storage of weapons.[30] Moreover, since 2013, packs containing more than 4 g of ibuprofen or

Table 3 Summary of number of events, follow-up time and incidence rates per 10 000 person-years

	Overall psoriasis		Mild psoriasis		Severe psoriasis	
	Controls	Patients	Controls	Patients	Controls	Patients
Self-harm and unsuccessful suicide attempts						
Number of events	217	63	172	42	45	21
Person-years	2 164 529·6	441 528·4	1 768 372·5	358 444·7	396 157·1	83 083·6
Incidence rate	1·00	1·43	0·97	1·17	1·14	2·52
95% CI	0·88–1·15	1·11–1·83	0·84–1·13	0·87–1·59	0·85–1·52	1·65–3·88
Completed suicides (physician reported)						
Number of events	467	107	389	92	78	15
Person-years	2 165 221·8	441 753·4	1 768 919·2	358 585·9	396 302·7	83 167·4
Incidence rate	2·16	2·42	2·20	2·57	1·97	1·80
95% CI	1·97–2·36	2·00–2·93	1·99–2·43	2·09–3·15	1·58–2·46	1·09–2·99
Completed suicides (police/forensic confirmed)						
Number of events	355	90	299	76	56	14
Person-years	2 165 221·8	441 753·4	1 768 919·2	358 585·9	396 302·7	83 167·4
Incidence rate	1·64	2·03	1·69	2·12	1·41	1·68
95% CI	1·48–1·82	1·66–2·50	1·51–1·90	1·69–2·65	1·09–1·84	1·00–2·84

CI, confidence interval.

Table 4 Risk of self-harm and suicide attempts, and completed suicide in patients with psoriasis

	Unadjusted			Adjusted[a]			Additional PsA adjustment[b]		
	IRR	95% CI	P-value	IRR	95% CI	P-value	IRR	95% CI	P-value
Self-harm and unsuccessful suicide attempts									
Overall	1·42	1·08–1·88	0·014	1·17	0·88–1·55	0·28	1·15	0·86–1·53	0·34
Mild psoriasis	1·20	0·86–1·69	0·28	1·01	0·17–2·01	0·96	1·02	0·73–1·43	0·91
Severe psoriasis	2·23	1·33–3·74	0·002	1·69	1·00–2·84	0·049	1·62	0·94–2·81	0·083
Completed suicides (physician reported)									
Overall	1·12	0·91–1·39	0·28	1·00	0·81–1·24	0·99	1·02	0·82–1·26	0·88
Mild psoriasis	1·17	0·92–1·46	0·18	1·05	0·84–1·32	0·67	1·06	0·84–1·33	0·62
Severe psoriasis	0·92	0·53–1·59	0·74	0·78	0·45–1·36	0·38	0·81	0·46–1·43	0·45
Completed suicides (police/forensic confirmed)									
Overall	1·24	0·98–1·66	0·066	1·04	0·83–1·32	0·73	1·11	0·88–1·40	0·37
Mild psoriasis	1·25	0·97–1·61	0·078	1·05	0·81–1·35	0·71	1·13	0·88–1·45	0·35
Severe psoriasis	1·19	0·66–2·14	0·56	1·02	0·57–1·84	0·95	1·03	0·56–1·89	0·91

IRR, incidence rate ratio; CI, confidence interval. [a]Adjusted for age, sex, socioeconomic status, alcohol abuse and antidepressants. [b]Adjusted for age, sex, socioeconomic status, alcohol abuse, antidepressants and psoriatic arthritis (PsA).

10 g of paracetamol, acetylsalicylic acid or phenazone can no longer be purchased over the counter in Denmark. It is well established that in addition to depression, alcohol abuse and unemployment are associated with increased risk of suicide.[31,32] Also, associations between sales figures for antidepressant drugs and suicide rates have demonstrated a strong inverse association.[21]

Importantly, in our study, analyses adjusted for alcohol abuse, socioeconomic status (calculated from tax-reported income) and antidepressant use yielded results similar to those of our primary analyses. While the numbers of physician-reported suicides and those confirmed by forensic investigations were similar, some suspected suicides could not be confirmed by forensic investigations. For example, if the death was caused by a drug overdose, investigations cannot determine whether the person intended suicide or not, if there was no suicide note. In such cases, the physician may report the death as a suicide, whereas the forensic investigator will not.

Certain limitations and strengths apply to the present study. Diagnoses of suicidal ideation are not used in Denmark, but thoughts of suicide are likely to be under-reported in the registries and are subject to severe detection bias. Also, it is likely that self-harm and nonfatal suicide attempts are under-reported, as patients may not seek medical attention, if no or only minor injuries are sustained, or if they choose not to disclose the self-inflicted nature (and aborted purpose) of their injuries due to embarrassment and perceived risk of stigmatization. Moreover, it is possible that the slightly increased risk of self-harm and nonfatal suicide attempts may, in part, be

explained by residual confounding due to the presence of subjective markers such as itch, pain and stress, as well as untreated depression, for which data were not available. However, as the risk of completed suicide was not increased in patients with psoriasis, lack of such information is unlikely to have markedly confounded our results.

An important finding in our study is that after correcting for the presence or absence of psoriatic arthritis, the risks of self-harm and suicide attempts were no longer significantly increased. It is possible that negative effects of psoriatic arthritis on quality of life in patients with psoriasis may, in part, contribute to suicidal risk. For example, sleep quality is significantly diminished in these patients, and is associated with generalized pain and anxiety.[33] Moreover, the Danish population is predominantly white, which may limit the extrapolation of our results to other ethnicities.

Important strengths of the study include the high accuracy of the nationwide registries and the available information on household income, which minimized bias due to sex, age and socioeconomic status. Also, confirmations of suicides by forensic investigation; the statistical adjustments for antidepressant use and alcohol abuse, for which data were continuously updated during follow-up; the length and accuracy of follow-up; the results of the sensitivity analysis; and the large number of individuals add credibility to our findings.

In conclusion, we found a modestly increased risk of self-harm and nonfatal suicide attempts in patients with severe psoriasis, which was nonsignificant after controlling for psoriatic arthritis. We also found no evidence that psoriasis is associated with increased risk of completed suicide. However, the risk of suicide was significantly increased in patients with AD.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Identification of patients with alcohol abuse.

Table S2. Risk of self-harm and nonfatal suicide attempts, and completed suicides in patients with psoriasis, after exclusion of patients treated with retinoids.

Table S3. Risk of self-harm and nonfatal suicide attempts, and completed suicides in patients with psoriasis compared with atopic dermatitis.

Factors associated with patient-reported importance of skin clearance among adults with psoriasis and atopic dermatitis

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Background: Factors that are associated with patient-reported importance of obtaining complete or almost complete clearance of psoriasis and atopic dermatitis (AD) are unknown.

Objectives: To investigate the importance of and factors associated with obtaining complete or almost complete clearance of psoriasis or AD.

Methods: A cross-sectional study of 4016 and 3842 adults with psoriasis and AD.

Results: Patients with AD reported significantly greater importance of almost complete or complete skin clearance compared with patients with psoriasis. For both patient groups, almost complete was more important that complete skin clearance. Increasing disease severity and itch and skin pain were significantly associated with perceived importance of skin clearance for patients with both diseases. AD and psoriasis located on the face or neck and psoriasis located on the palms, soles, or genitals were significantly associated with patient-perceived importance of almost complete skin clearance. Only 7% and 27% of patients with severe AD and psoriasis, respectively, were currently receiving a systemic therapy.

Limitations: Specific reasons for infrequent use of systemic treatments was not examined.

Conclusion: Patients with psoriasis or AD expressed a strong request for almost complete or complete skin clearance. Patient education and effective therapies should be used to reduce disease severity. (J Am Acad Dermatol 2019;81:943-9.)

Key words: atopic dermatitis; Danish Skin Cohort; epidemiology; psoriasis; treatment goals.

Psoriasis and atopic dermatitis (AD) are common chronic inflammatory skin diseases in children and adults. With the advent of novel systemic therapies, including biologics, the management of these diseases has radically improved. This has been most evident for psoriasis, but with the introduction of dupilumab to treat adults with moderate to severe AD, new hope has emerged for these patients as well.

Physicians' expectations for higher levels of drug efficacy have increased overall.[1,2] However, although clinical trials of newer biologics for psoriasis have shown complete skin clearance in more than half of patients,[3] expectations of a satisfactory

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treatment response appear to differ between patients and their physicians.[4] This is also evident from observational registry data, where, for example, the Dermatology Life Quality Index (DLQI) has differed markedly from what was expected based on clinical trial data.[5,6]

As higher levels of skin clearance become the benchmark in psoriasis and eventually in AD, the impact of other factors such as convenience (eg, frequency of injections), differences in safety profile, effects on comorbid conditions, and cost of treatment may need to be rebalanced when deciding the most appropriate treatment. Moreover, dermatologists need insight into factors that are associated with patient-reported importance of complete or almost complete skin clearance because this may affect treatment strategies.

CAPSULE SUMMARY

- New effective drugs have become available to treat adults with psoriasis and atopic dermatitis, but many patients remain undertreated or have uncontrolled disease with their current therapy.
- We identified factors that are associated with patient-reported importance of obtaining complete or almost complete skin clearance.

In this study, we examined patient-reported treatment goals in a population-based cohort of Danish adults with either psoriasis or AD and identified factors associated with patient-perceived importance of complete and almost complete clearance.

MATERIALS AND METHODS

All appropriate study approvals were obtained (reference 2012-58-0004, journal number VD-2018-286, I-Suite no. 6528).

The Danish Skin Cohort is a prospective cohort comprising data on adults with psoriasis and AD seen and diagnostically verified by dermatologists in hospital centers and a number of private clinics in Denmark. This cohort has been described in detail elsewhere.[7] Briefly, patient disease severity was categorized based on the proportion of body surface area (BSA) that was affected by psoriasis (for patients with psoriasis). BSA data were also available for AD, but patients' current Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD) scores were used for patients with AD, as this is a more well-established severity measure in AD. Consequently, patients were classified as having minimal disease (psoriasis with a BSA of 0 or AD with a PO-SCORAD of 0), having mild disease (psoriasis with a BSA <3 or AD with a PO-SCORAD <25), moderate disease (psoriasis with a BSA of 3-10 or AD with a PO-SCORAD of 25-50), and severe disease (psoriasis with a BSA of ≥10 or AD with a PO-SCORAD >50).

Between May 15, 2018, and July 15, 2018, all patients with psoriasis were asked the following questions in a structured manner: "How important is it to you that your skin becomes almost clear of psoriasis (ie, almost unaffected skin)?" and "How important is it to you that your skin becomes completely clear of psoriasis (ie, completely unaffected skin)?" Patients with AD were asked identical questions during the same time period, with the word *psoriasis* replaced by *AD*. The questions were asked in the native language in Denmark, Danish, in which the phrase *almost clear* corresponds to "becomes clear of most-but-not-all" and *completely clear* corresponds to "becomes completely clear of all." Patients answered these questions using a numeric rating scale (NRS) from 0 (*not important*) to 10 (*most important*). Similarly, patients were asked to rate their current itch (within the last 3 days) and skin pain (within the last 7 days) using the NRS. Data on asthma, rhinitis, and psoriatic arthritis are also recorded for all individuals in the Danish Skin Cohort. Through individual-level linkage with the Danish National Patient Register and the Register of Medicinal Products Statistics, complete information on pharmacologic treatments was obtained for all study participants.[8,9]

Statistical analysis

Summary statistics were created and presented as frequencies with percentages for categoric variables and means with standard deviations for continuous variables. Furthermore, interquartile ranges were estimated for nonnormally distributed continuous outcome variables. Associations between disease severity and treatment goals were assessed using linear regression models adjusted for age, sex, and socioeconomic status. Analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc. Cary, NC), and Stata software, version 13.0 (StataCorp, College Station, TX).

RESULTS

The cohorts comprised 3842 and 4016 adult patients with dermatologist-verified AD and psoriasis, respectively (Table I). There was a strong female

Abbreviations used:

AD: atopic dermatitis
BSA: body surface area
DLQI: Dermatology Life Quality Index
NRS: numeric rating scale
PO-SCORAD: Patient-Oriented SCORing Atopic Dermatitis

predominance, particularly among patients with AD. Patients with psoriasis were slightly older than patients with AD (59.4 vs 48.8 years, respectively; $P < .0001$). Patients with psoriasis had a higher mean body mass index (27.5 vs 25.9 kg/m^2, respectively; $P < .0001$), and a higher prevalence of smoking compared with patients with AD (25.5% vs 16.9%, respectively). Overall, 71.7% and 81.5% of patients with psoriasis and AD, respectively, reported an NRS score of 8 or higher for importance of almost complete skin clearance, whereas 60.0% and 65.9%, respectively, reported this for importance of obtaining complete skin clearance.

Table I. Characteristics of the study population

Characteristics	Atopic dermatitis (n = 3842)	Psoriasis (n = 4016)
Age in years, mean (SD)	48.8 (14.5)	59.4 (14.4)
Women, n (%)	2648 (68.9)	2240 (55.8)
BMI in kg/m^2, mean (SD)	25.9 (5.6)	27.5 (6.5)
Weight in kg, mean (SD)	76.0 (17.5)	81.6 (19.3)
Current smoker, n (%)	650 (16.9)	1022 (25.5)
Psoriatic arthritis, n (%)	—	847 (21.1)
Rheumatologist verified	—	660 (16.4)
Asthma, n (%)	1470 (38.3)	503 (12.5)
BSA, mean (SD)	11.9 (21.4)	10.0 (18.0)
PO-SCORAD, mean (SD)	20.2 (15.6)	—
Total IgE in 10^3 IU/L, median (IQR)	215 (41-1420)	39 (12-192)

BMI, Body mass index; *BSA*, body surface area; *IgE*, immunoglobulin E; *IQR*, interquartile range; *PO-SCORAD*, Patient-Oriented SCORing Atopic Dermatitis; *SD*, standard deviation.

Association between disease severity and treatment goals

Atopic dermatitis. The mean (standard deviation) score (NRS from 0-10) was 8.6 (2.3) for almost complete and 7.7 (2.8) for complete skin clearance in patients with AD (Fig 1). A higher PO-SCORAD was significantly associated with higher patient-perceived importance of almost complete (β = 0.018; 95% confidence interval [CI], 0.012-0.023; $P < .0001$) and complete skin clearance (β = 0.018; 95% CI, 0.011-0.025; $P < .0001$) (Table II). There was no significant difference in patients with or without concurrent asthma or rhinitis in patients with AD. After adjustment for age, sex, and BSA, severity of itch was significantly associated with importance of almost complete (β = 0.07; 95% CI, 0.04-0.10; $P < .0001$) and complete skin clearance (β = 0.08; 95% CI, 0.04-0.12; $P < .0001$) in AD. Similarly, increasing skin pain displayed significant associations with importance of almost complete (β = 0.07; 95% CI, 0.04-0.10; $P < .0001$) and complete skin clearance (β = 0.10; 95% CI, 0.06-0.13; $P < .0001$) in AD.

Psoriasis. For patients with psoriasis, mean NRS scores were 8.0 (2.7) for almost complete and 7.2 (3.1) for complete skin clearance. Increasing BSA was significantly associated with higher patient-perceived importance of almost complete (β = 0.018; 95% CI, 0.011-0.021; $P < .0001$) and complete skin clearance (β = 0.022; 95% CI, 0.016-0.028; $P < .0001$) respectively. When comparing patients across severity strata (ie, mild psoriasis vs mild AD, moderate psoriasis vs moderate AD, and severe psoriasis vs severe AD), patients with AD in all strata reported significantly greater importance of obtaining almost complete ($P < .0001$) and complete ($P < .01$) skin clearance compared with patients with psoriasis. There was no significant difference in patients with psoriasis with or without concurrent psoriatic arthritis. After adjustment for age, sex, and BSA, severity of itch was significantly associated with importance of almost complete (β = 0.14; 95% CI, 0.10-0.17; $P < .0001$) and complete skin clearance (β = 0.17; 95% CI, 0.13-0.21; $P < .0001$) in psoriasis, and increasing skin pain was associated with importance of almost complete (β = 0.14; 95% CI, 0.10-0.17; $P < .0001$) and complete skin clearance (β = 0.17; 95% CI, 0.13-0.21; $P < .0001$).

Association between affected body locations and treatment goals

Atopic dermatitis. After adjusting for differences in BSA, involvement of AD in the face or neck was significantly associated with patient-perceived importance of almost complete skin clearance in patients with AD, whereas involvement of the scalp, palms, soles, genitals, or nails was not. None of the investigated body locations displayed significant associations with importance of complete skin clearance in AD (Table III).

Psoriasis. For psoriasis, BSA-adjusted analyses showed that involvement of the face, neck, palms, soles, and genitals was significantly associated with patient-perceived importance of almost complete skin clearance, whereas scalp involvement was not. In analyses assessing the patient-perceived

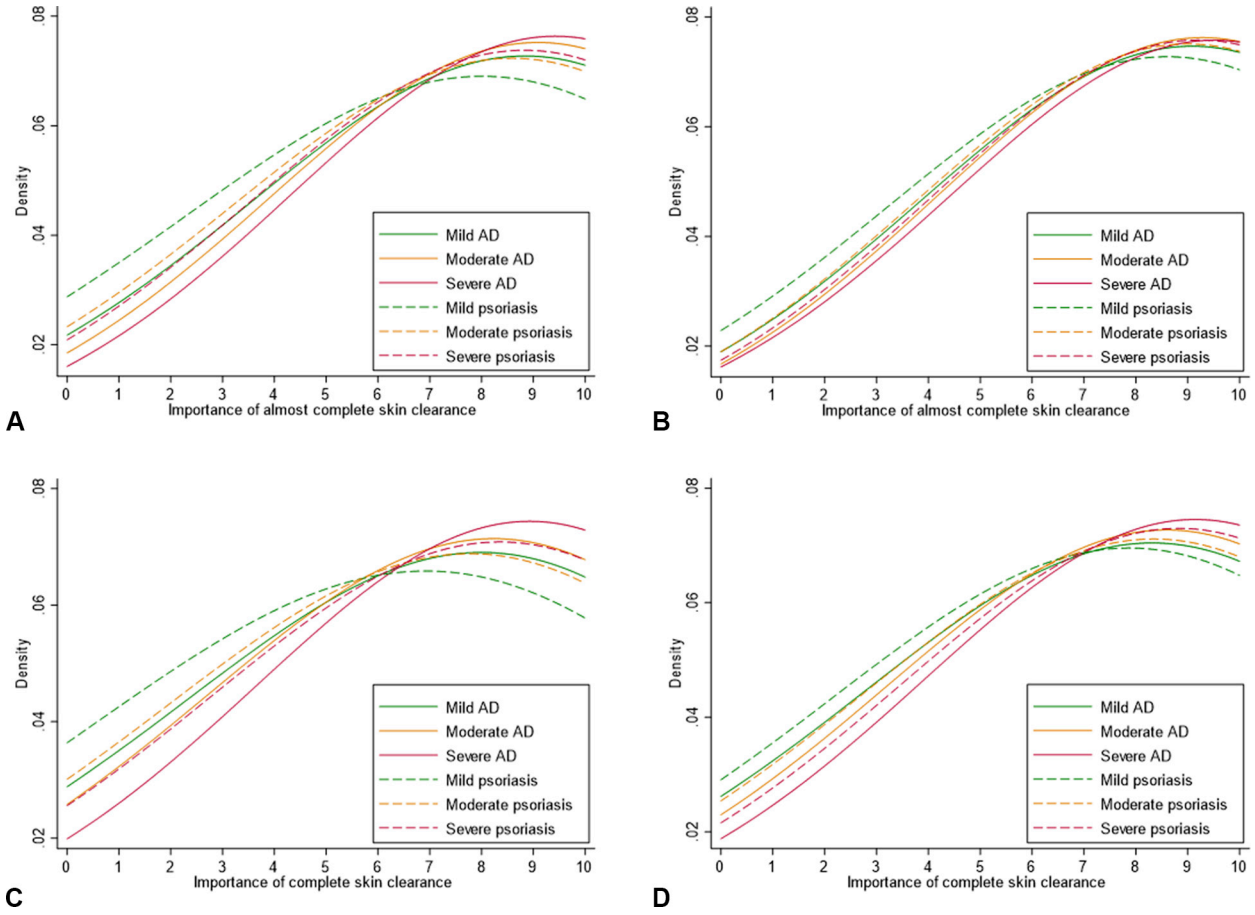

Fig 1. Patient-reported importance of obtaining almost complete and complete skin clearance among patients with psoriasis and atopic dermatitis. **A**, Importance of almost complete clearance (unweighted). **B**, Importance of almost complete clearance (weighted by DLQI). **C**, Importance of complete clearance (unweighted). **D**, Importance of complete clearance (weighted by DLQI). Results are on a numeric rating scale where 0 is least important and 10 is most important. *AD*, Atopic dermatitis; *DLQI*, Dermatology Life Quality Index.

importance of complete skin clearance, only involvement of palms and soles remained statistically significant.

Treatment goals in patients with AD and psoriasis with or without systemic treatment

Modest proportions of patients with psoriasis and AD were currently treated with systemic medication or biologics.

AD. The most frequently used systemic treatment was methotrexate, which was used in 1% to 4% of patients with AD (those with minimal and with mild, moderate, or severe disease, respectively) (Fig 2). Among patients with currently severe AD, only 7% were receiving any systemic therapy. For AD, the NRS for almost complete skin clearance was 9.0 (2.0) and 8.6 (2.3) among patients that did and did not receive systemic treatment, respectively ($P < .05$). For AD, the NRS of compete skin clearance was 8.3 (2.4) in patients treated with systemic therapies and 7.6 (2.8) among patients not currently receiving any systemic therapy ($P < .01$).

Psoriasis. Similar to AD, methotrexate was the most frequently used systemic treatment and was used in 11% to 14% of patients with psoriasis. Among patients with severe psoriasis, 27% were currently receiving a systemic treatment. The mean NRS for importance of almost complete skin clearance was 8.2 (2.6) among patients currently receiving a systemic therapy and 7.9 (2.8) among those who did not currently receive any systemic treatment ($P < .05$). For complete skin clearance, the NRS was 7.4 (3.0) among patients with psoriasis receiving systemic treatment and 7.1 (3.1) among those not currently receiving any systemic treatment ($P < .05$).

Table II. Association between disease severity and treatment goals

	Almost complete skin clearance			Complete skin clearance		
Characteristics	β	**95% CI**	***P* value**	β	**95% CI**	***P* value**
Atopic dermatitis						
PO-SCORAD	0.018	0.012 to 0.023	<.0001	0.018	0.011 to 0.025	<.0001
Age	−0.014	−0.020 to −0.007	<.0001	0.003	−0.004 to 0.011	.4019
Male sex	−0.273	−0.451 to −0.095	.0027	−0.215	−0.433 to 0.003	.0534
Socioeconomic status						
Lowest group	−0.2654	−0.544 to 0.013	.0617	−0.082	−0.422 to 0.257	.6341
Below average	−0.2015	−0.476 to 0.073	.1506	0.025	−0.311 to 0.361	.8836
Average	(reference)			(reference)		
Above average	−0.1631	−0.412 to 0.086	.1993	−0.231	−0.536 to 0.073	.1360
Highest group	−0.2355	−0.478 to 0.006	.0564	−0.718	−1.014 to −0.423	<.0001
Psoriasis						
Body surface area	0.016	0.011 to 0.021	<.0001	0.022	0.016 to 0.028	<.0001
Age	−0.028	−0.035 to −0.022	<.0001	−0.012	−0.020 to −0.005	.0011
Male sex	−0.507	−0.688 to −0.326	<.0001	−0.615	−0.823 to −0.406	<.0001
Socioeconomic status						
Lowest group	0.006	−0.282 to 0.293	.9697	0.069	−0.261 to 0.399	.6803
Below average	−0.073	−0.346 to 0.201	.6024	0.084	−0.231 to 0.399	.6001
Average	(reference)			(reference)		
Above average	0.010	−0.267 to 0.288	.9434	−0.329	−0.649 to −0.010	.0435
Highest group	−0.178	−0.468 to 0.113	.2313	−0.732	−1.067 to −0.397	<.0001

CI, Confidence interval; *PO-SCORAD*, Patient-Oriented SCORing Atopic Dermatitis.

Table III. Association between affected location and treatment goals*

	Almost complete skin clearance			Complete skin clearance		
Location	β	**95% CI**	***P* value**	β	**95% CI**	***P* value**
Atopic dermatitis						
Scalp	0.140	−0.045 to 0.324	.1384	0.056	−0.169 to 0.280	.6274
Face	0.402	0.234 to 0.570	<.0001	0.115	−0.090 to 0.320	.2718
Neck	0.456	0.228 to 0.634	<.0001	0.207	−0.010 to 0.424	.0617
Palms	0.035	−0.169 to 0.239	.7377	0.159	0.089 to 0.406	.2100
Soles	−0.031	−0.375 to 0.313	.8584	−0.205	−0.623 to 0.213	.3356
Genitals	0.247	−0.056 to 0.549	.1097	0.080	−0.288 to 0.448	.6700
Nails	0.080	−0.229 to 0.388	.6121	0.083	−0.292 to 0.457	.6652
Psoriasis						
Scalp	0.123	−0.061 to 0.308	.1909	−0.118	−0.330 to 0.093	.2729
Face	0.287	0.053 to 0.521	.0164	0.125	−0.143 to 0.394	.3601
Neck	0.313	0.017 to 0.609	.0381	0.165	−0.174 to 0.504	.3402
Palms	0.481	0.235 to 0.728	.0001	0.737	0.455 to 1.018	<.0001
Soles	0.492	0.289 to 0.724	<.0001	0.643	0.376 to 0.909	<.0001
Genitals	0.434	0.188 to 0.681	.0005	0.150	−0.133 to 0.432	.2985
Nails	0.238	0.035 to 0.441	.0216	0.015	−0.217 to 0.248	.8984

CI, Confidence interval.
*Estimates are adjusted for percentage of affected body surface area.

DISCUSSION

Main findings

In this study of almost 8000 adult patients, we identified important factors that are associated with patient-reported importance of obtaining complete or almost complete clearance of psoriasis or AD. Patients with AD reported overall greater patient-perceived importance of almost complete and

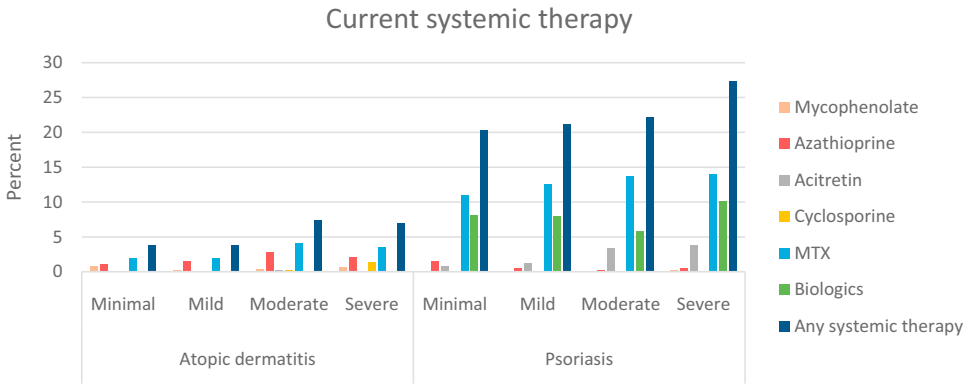

Fig 2. Current treatments among patients with psoriasis and atopic dermatitis. MTX, Methotrexate.

complete skin clearance compared with patients with psoriasis, although this was deemed important by patients with either of these conditions.

Strengths and limitations

Several strengths and limitations apply to the interpretation of these findings. By using nationwide prescription data, we captured all relevant systemic therapies and biologics given to patients participating in the study, thus limiting recall bias. Our study is further strengthened by the sheer number of patients. However, whether the limited use of systemic therapy for patients with psoriasis or AD is due to patients' reluctance to initiate systemic therapy, medical considerations (eg, contraindications), or other causes remains speculative. Similarly, the Danish health care system provides tax-supported health care, and patients receive biologics directly from the dermatologists without the need for special insurance or copay, which may decrease patients' subjective need for greater levels of skin clearance compared with if they had to pay out of pocket. Thus, it is possible that the importance of almost complete and complete skin clearance would be even higher in such patients.

Interpretation

Previous studies have shown positive associations between complete or almost complete clearance of skin disease and patient-reported outcomes.[10-12] Moreover, patients with AD who did not achieve high skin clearance during dupilumab therapy still experienced clinically meaningful reductions in AD severity and symptoms.[13]

However, to our knowledge, no previous studies have addressed the relative importance for patients with psoriasis and AD regarding complete or almost complete skin clearance. Our study not only fills this research gap but further identified specific factors that may affect patients' subjective need for greater skin clearance. We showed that disease severity, itch, and certain anatomic locations were associated with perceived importance of obtaining complete or almost complete skin clearance. Our results indicate that patients who have psoriasis or AD in visible areas, such as the face and neck, may experience cosmetic concerns. Although dupilumab treatment seems to be effective across different body locations, it appears to be less potent on the face.[14] Patients with psoriasis with involvement of the nails, palms, and soles may experience pain and functional complaints, explaining the observed association with self-reported importance of skin clearance. Surprisingly, itch was more strongly associated with importance of skin clearance in patients with psoriasis than in those with AD. Although speculative, pruritus is experienced in nearly all patients with AD, whereas this is seen in greater variation among patients with psoriasis, possibly explaining the difference in pruritus impact between these diseases. Patients receiving systemic therapy or biologics expressed greater importance of skin clearance than patients who were not receiving systemic therapy. This could be an indicator that these patients may be more affected by their disease but also that they may be more motivated to obtain skin clearance because they are willing to take systemic medications (including biologics) and accept the risk of potentially serious adverse effects. Unlike in countries such as the United States, it is against the law for pharmaceutical companies to advertise for prescription-based drugs to patients and other non–health care providers. Consequently, advertisements, for example, for biologics, are not shown in magazines or on television in Denmark. Although patients may readily obtain such information from the Internet, it is possible that their knowledge about novel treatment options are lower than, for example,

in the United States, which may affect patients' subjective need for skin clearance. The very small proportions of patients receiving systemic therapy also show the presence of undertreatment in patients who are candidates for systemic therapy; however, whether this low proportion is due to medical contraindication or to hesitation from patients or physicians remains unclear.

Compared with clinical trials, the use of potent systemic therapies (ie, biologics) for the treatment of psoriasis has yielded lower levels of skin clearance and, as a consequence, also a lower proportion of patients reporting a DLQI of 0 or 1 over time.[5] However, in recent years, hitherto unseen levels of skin clearance have been reported in clinical trials of novel biologics for psoriasis and AD.[3] For psoriasis, there has been a shift toward considering a 90% reduction in Psoriasis Area and Severity Index, or obtaining almost complete skin clearance, as the new criterion standard. This move is in line with findings from this study, which suggest that almost complete skin clearance is of greater importance to patients than complete skin clearance. Nonetheless, our findings emphasize the considerable undertreatment among patients with psoriasis and AD and the apparent disconnect between the use of systemic treatments and patients' needs for complete or almost complete skin clearance.

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