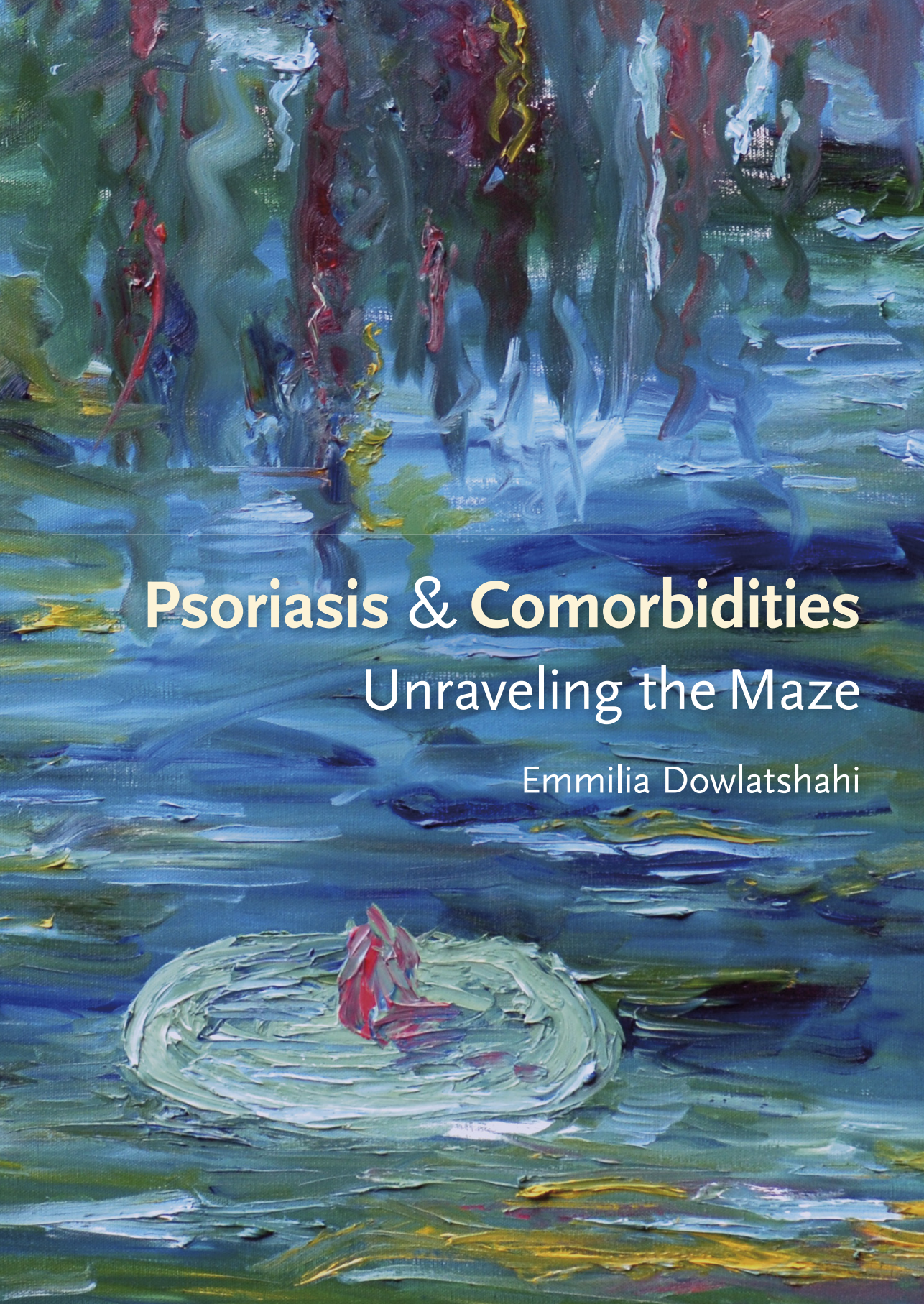

Psoriasis & Comorbidities

Unraveling the Maze

Emmilia Dowlatshahi

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Unraveling the Maze

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Psoriasis & Comorbidities: Unraveling the Maze

Psoriasis en comorbiditeiten: het doolhof ontrafeld

Proefschrift

ter verkrijging van de graad van doctor aan de
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op gezag van de rector magnificus
Prof.dr. H.A.P. Pols
en volgens besluit van het College voor Promoties.

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We must now highly resolve to arise and lay hold of all those instrumentalities that promote the well-being and happiness, the knowledge, culture and industry, the dignity, value and station, of the entire human race.

- Sir 'Abdu'l-Bahá Abbás, 1875

CONTENTS

Appendices

Chapter 1

Introduction & Aims of this Thesis

1. HISTORY OF PSORIASIS

Hippocrates (circa 400 B.C.) was one of the first to describe a group of dry and scaly skin diseases including psoriasis, eczema, red flat lichen, tubercular lupus and leprosy. In the times of Hippocrates, psoriasis was known under the names of lepra and psora, as well as alphos and leichen. Consequently, society believed psoriasis was like leprosy, mange (scabies) and vitiligo and psoriasis patients were isolated, did not receive medical aid, wore specific clothing and had to carry a rattle or a bell.

One of the first historical mentions of psoriasis dates back to the Holy Bible in the Old Testament, in the books of Leviticus ad Deuteronomious where reference is made to the "Tharaath" as a skin condition and leprous disease.

Herodotus and Plato united the group of the skin diseases, characterized by peeling, dryness and itch with the Greek term *psora*. The Greek philosopher Celsus was the first to clinically describe psoriasis (40 A.D.). Around 200 A.D. Roman physician Claudius Galen used the words *psoriasis vulgaris* (common psoriasis) for the first time and from then the term was used to refer to all skin conditions accompanied by itch.

Beginning of the 19th century, the English doctor Robert Willan described psoriasis, its manifestations and complications and distinguished two diseases: discoid psoriasis, called Lepra Graecorum (Lepra Vulgaris, Lepra Willani), and Psora Leprosa. In 1841, Ferdinand Von Hebra and Moritz Kaposi definitely set psoriasis apart from leprosy. Other dermatologists of the 19th Century such as Polotebnov, Pospelov, Gebr and Koebner studied psoriasis in depth and considered it to be a systemic disease. The association between psoriasis and arthritis was described for the first time by Jean Louis Alibert in 1818 and he named psoriasis *Dartre squameuse centrifuge of Alibert*. Pierre Bazin described *psoriasis arthritique* in 1860. In 1937 Seghers and Robinson considered psoriatic arthritis as a clinical entity.

2. EPIDEMIOLOGY

One of the first epidemiological studies on psoriasis was conducted on the Faroe Islands in the 1960s reporting a prevalence of psoriasis of 2.8% in the general population.[1] This prevalence has been confirmed in studies conducted in other western countries.[2-4] A recent systematic review mentioned that a total of 53 studies to date have reported the prevalence and incidence of psoriasis in the general population and concluded that it varied according to age and geographic region (psoriasis being more frequent in areas more distant from the equator), the case definition of psoriasis used in the studies, environmental factors, ultraviolet exposure, genetics, historical migration patterns and regional variations in antigen exposure.[5,6] The prevalence in children ranges from 0% (in Asia) to 8.5% in Norway with an incidence of around 40 per 100.000 person-years in the United States. In adults, the lowest

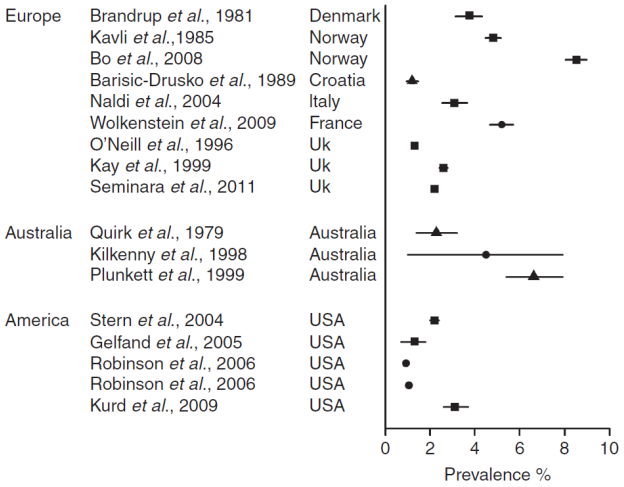

Figure 1. Studies providing information on prevalence of psoriasis in adults.[5]
Circle: period prevalence; square: lifetime prevalence; triangle: point prevalence.

prevalence has been observed in the United Kingdom (1.3%) and the highest values were seen in North-East and Southern Europe (5.2% in France) (Figure 1). Several studies show a first peak at age 30 and a second peak around age 50, suggesting the existence of an early and a late onset form of psoriasis.[5,7-10]

3. PATHOPHYSIOLOGY

Psoriasis is a T-cell mediated inflammatory condition of the skin. A combination of environmental factors such as stress, specific drugs, trauma or smoking and genetic factors trigger a series of cascades in the skin involving the innate and adaptive immunity, which interact together to form the process of inflammation in psoriasis. Plasmacytoid dendritic cells and keratinocytes produce pro-inflammatory cytokines such as interferon-α, interleukin-1, interleukin-6, Tumor necrosis factor-alpha (TNFα) and chemokines. These activate the myeloid dendritic cell, which in turn present antigens and secrete interleukins leading to the differentiations of Th-1 and Th-17 helper cells. The T cells then secrete mediators that activate keratinocytes and induce the production of antimicrobial peptides, proinflammatory cytokines and chemokines. These processes maintain inflammation in psoriasis (Figure 2).[11]

Continuous research on mediators of inflammation in psoriasis, such as IL-12, IL-23, IL-17, Janus kinases (JAK) and phosphodiesterase 4 (PDE4) has become important for the development of new targets for antipsoriatic therapy.[12]

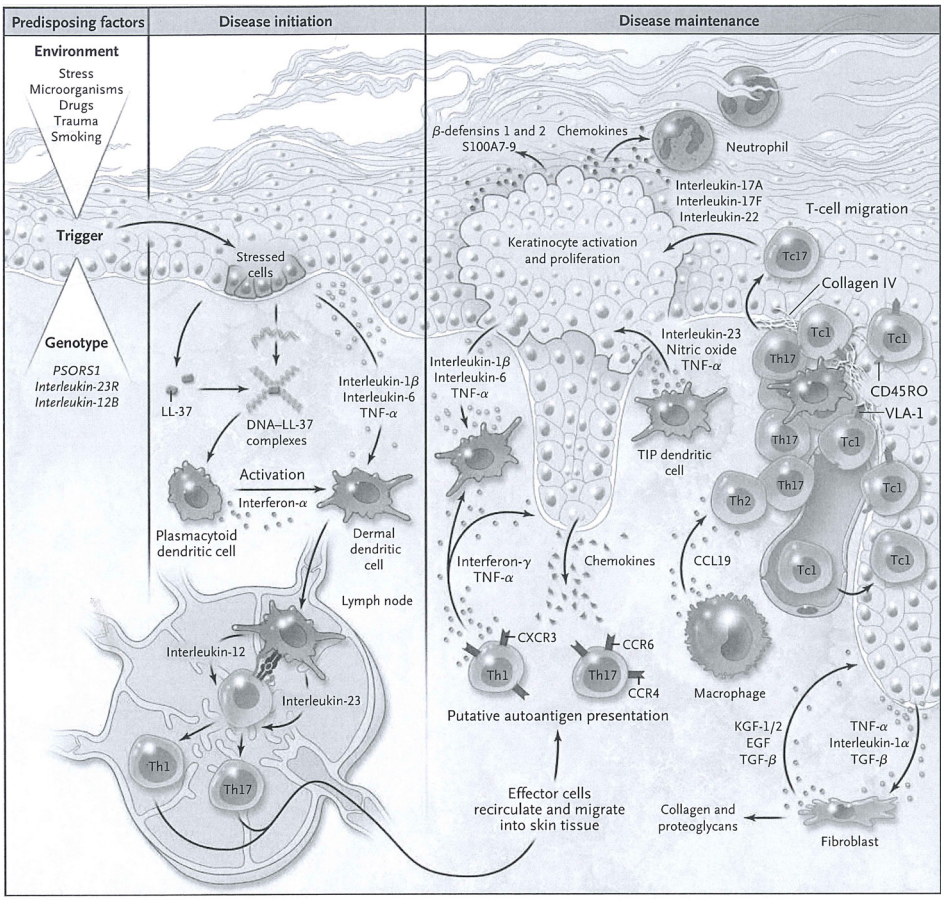

Figure 2. Schema of the evolution of a psoriatic lesion from initiation to maintenance of disease.
Reproduced with permission from Nestle et al[11] Copyright Massachusetts Medical Society.

3.1 Genetics

The fact that genes could be involved in psoriasis was first mentioned by Farber who observed that the incidence of psoriasis is higher amongst relatives of psoriasis patients than among the general population.[13] The lifetime risk of getting psoriasis if no parent, one parent or both parents have psoriasis is 0.04, 0.28 and 0.65, respectively in a questionnaire survey of more than 3000 families in Sweden.[14] Early onset psoriasis has been associated with HLACw allele encoding for a MHS protein.[15] To date, 36 genes have been shown to be associated with psoriasis in European individuals.[16] Many loci overlap with those associated with other autoimmune disease like Crohn's disease and ankylosing spondylitis.

3.2 Microbiome

In the past years much research has been done on skin and gut microbiome and exploring the role of imbalance of bacteria in contributing to skin diseases such as psoriasis.[17-19] Staphylococci and Propionibacteria have shown to be significantly lower in psoriatic skin compared to healthy skin.[20,21] Future psoriasis therapies could include treatments that modify the microbiome.

4. CLINICAL AND HISTOPATHOLOGICAL FEATURES

The most common form is psoriasis vulgaris and accounts for more than 90% of all cases.[23] It is characterized by thick, red plaques with white to silvery colored scales, predominantly on the elbows, knees and lower back (Figure 3). The disease severity can vary from a few plaques to involvement of the entire surface of the skin. The scales on the plaques are a result of hyperproliferation of the epidermis due to multiplication of keratinocytes which multiply so rapidly that they move to the upper epidermis without losing their nucleus (parakeratosis). This results in thickening of the epidermis referred to as acanthosis and also elongation of the rete ridges. The activation of dendritic cells, neutrophils, T cells and macrophages leads to an inflammatory infiltrate in the epidermal and dermal layer. The accumulation of neutrophils in psoriatic epidermis is referred to as Munro microabscesses, named after William Jon Munro (1829-1908) an Australian physician.

The skin of psoriatic patients is prone to develop lesions after local trauma, characterized as Koebner phenomenon, after Herry Koebner (1834-1904), a German dermatologist and a student of Von Hebra. The vessels within the papillae are dilated and tortuous and when psoriasis scaling is scraped off, this leads to bleeding spots, called Auspitz's sign, after Heinrich Auspitz (1835-1886).

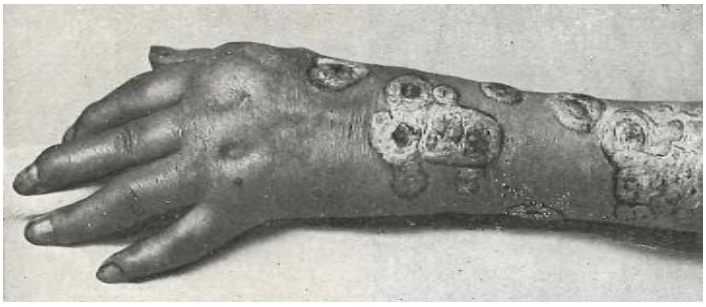

Figure 3. « Psoriasis nummulaire sur le poignet, en nappe sur l'avant-bras, avec arthropathies psoriasiques de la main et des doigts » (original title from Précis de Dermatologie).[22]
The description of psoriasis according to J. Darier, A. Civatte, A. Tzanck:
« L'élément du psoriasis est typique. Sous sa forme moyenne et commune, c'est une tâche d'un rouge vif, bien circonscrite, couverte de squames sèches, nacrées, lamelleuses, friables, abondantes, tache non infiltrée de base, et non prurigineuse. »

The other types of psoriasis are less common and include guttate psoriasis which typically occurs after a streptococcal throat infection, inverse psoriasis involving the body folds, erythrodermic psoriasis and generalized pustular psoriasis including the acute form referred to as Zumbusch and the generalized pustular psoraisis of pregnancy.[23] The localized pustulosis palmoplantaris, which is characterized by sterile pustels on palms and soles can be accompanied with psoriatiform lesions on the body, although this presentation is often considered a separate entity, related to smoking.[24]

Psoriatic arthritis can be considered as its own entity but is also often seen in combination with psoriasis vulgaris. Its prevalence among patients with psoriasis ranges from 6 to 39%.[25,26] The diagnosis was based on criteria established by Moll and Wright, Vasey and Espinoza and Bennett. Moll and Wright described five subgroups of psoriatic arthritis on the basis of clinical observations: distal interphalangeal arthritis, symmetrical polyarthritis, mono- or asymmetrical oligoarthritis, spinal disease and arthritis mutilans. The recent CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria were developed for the purpose of clinical research.[27] In patients with psoriasis, this seronegative arthritis manifests itself as asymmetrical inflammation of the joints, which can become symmetrical when arthritis persists. In more than three-quarter of patients, psoriatic arthritis develops on average 10 years after the onset of psoriasis of the skin.[28] In the remaining patients, psoriatic arthritis occurs prior to or at the time of skin involvement. In psoriatic arthritis, the distal inter-phalangeal joints and nails are often affected, which enables physicians to distinguish this joint disease from rheumatoid arthritis.

Nail involvement is caused by psoriasis lesions in the nail bed and includes pitting, oil spots, onycholysis, subungual keratosis and red spots. The prevalence varies between 10 and 80% but a recent survey among patients of a psoriasis association indicated a prevalence of nail psoriasis of 66%.[29]

5. THERAPY

There are very few skin diseases where the therapy has changed so dramatically during the past 25 years. Psoriasis and other skin diseases were originally treated with arsenic and coal tar. It is only beginning of the 20th century when more tailor made treatments such as the Goeckerman regime (combination of tar and UV) were developed to treat psoriasis patients. However most patients were very much encouraged by their physicians to seek the sun well into the mid-1950s. Figure 4 depicts a timeline of the different psoriasis treatments.

Presently the choices for anti-psoriatic therapy are numerous and depend on several factors:

- Psoriasis related factors: type, disease severity, localization, disease duration, presence of psoriatic arthritis.
- Treatment related factors: previous therapies, effectiveness, side effects, contra-indications.

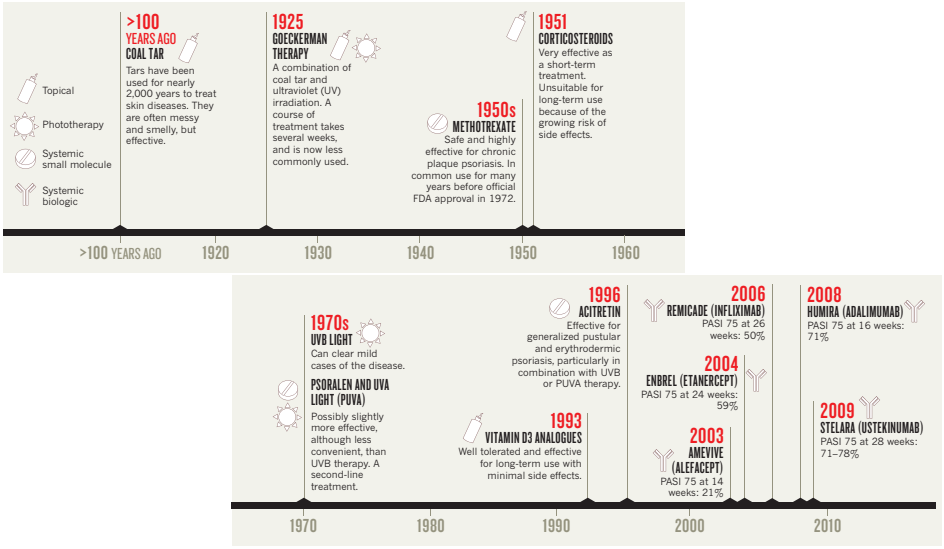

Figure 4. Psoriasis treatment in time.[30]

- Patient related factors: age, gender, comorbidities, physical and mental health, patients' preference and compliance to therapy.

5.1 Topical therapies

Topical corticosteroids have been used for more than half a century in psoriasis patients. They are more effective than placebo, however their long-term use is limited due to the possible side effects such as skin atrophy, hypertrichosis, hypopigmentation and striae.[31] They can be used as monotherapy or in combination with phototherapy and other systemic therapies.

Topical vitamin D3 analogues, developed in the early 1990s, affect keratinocyte growth and differentiation and inhibit T lymphocyte activity.[32] Vitamin D products are more effective than placebo. For body and scalp psoriasis, vitamin D and corticosteroid combination treatment was significantly more effective than vitamin D alone or corticosteroid alone. When applied to the scalp, vitamin D alone was less effective than both potent and very potent topical corticosteroids. Vitamin D derivatives cause local adverse events such as burning and irritation. However the combination with corticosteroids seems to be tolerated as well as potent corticosteroids alone.[33]

Head to head studies with topical corticosteroids have shown that Vitamine D3 analogues such as calcipotriol are as effective,[34,35] except for when calcipotriol is compared to a combination of potent corticosteroids and calciptriol.[36]

Coal tar and anthralin have been used for several decades in psoriasis patients, however they are less commonly used due to side effects such as skin irritation and staining and to the superiority of other topical treatments. They are often used in inpatient setting.

Topical retinoids such as tazarotene modulate keratinocyte proliferation and differentiation[37] and are anti-inflammatory[38] but also cause irritation and erythema at the site of application and are therefore not commonly used (tazaroten is not available in the Netherlands).

5.2 Phototherapy and photochemotherapy

Traditionally patients with psoriasis were encouraged to seek sunny holiday destinations. In some countries, healthcare insurance would remunerate a stay at the dead sea. This was considered as balneotherapy. The use of UV phototherapy was derived from this practice. Narrowband UVB and PUVA cause depletion of cells involved in the pathogenesis of psoriasis, including lymphocytes, macrophages and dendritic cells.[39,40]

Narrowband UVB has proven to be more effective than broadband UVB.[41] The dose depends on the minimal erythema dose (MED) and patients are treated thrice-weekly. PUVA monotherapy refers to the use of 8-methoxypsoralen which sensitizes the cells to the effects of longer-wavelength UV light and can be administered topically or orally.[42] Exposure to more than 350 PUVA treatments greatly increases the risk of squamous cell carcinoma and basal cell carcinoma.[43]

5.3 Systemic therapies

In the Dutch treatment guideline for psoriasis, fumaric acids are the first choice for the treatment of moderate to severe plaque type psoriasis. However methotrexate is more favorable with joint and skin involvement. Ciclosporine can be administered as monotherapy for periods up to 2 years, however long-term treatment is challenging due to adverse events.

Fumaric acids inhibit the proliferation of keratinocytes and mediators of inflammation in psoriasis.[44,45] The treatment is only registered in Germany and used as first choice in patients without joint complaints. Fumaric acids are used off-label in the Netherlands. A randomized controlled trial showed that fumaric acids are as effective as methotrexate in the treatment of moderate to severe plaque psoriasis.[45]

Methotrexate (MTX) inhibits the dihydrofolate reductase enzyme. This results in the inhibition of thymidylates and purine synthesis, leading to the impairment of RNA and DNA synthesis. Originally used in rheumatoid arthritis, it has proven a very effective treatment in psoriasis and psoriatic arthritis with a PASI 75 (reduction in baseline score for the PASI of more than 75%) of 60% and a PASI 90 among 40% of patients after 16 weeks of treatment.[46] Side effects are mostly dose-dependent. The most important adverse drug reactions associated with MTX are hepatotoxicity and myelosuppression and can lead to dose-reduction or discontinuation of the treatment.[42]

Ciclosporine is a calcineurin inhibitor and immune modulator and inhibits the production of interleukins and activity of T lymphocytes. Due to its nephrotoxicity and the possible increase in blood pressure, it should be reserved for short-term therapy (induction therapy)

until satisfactory response is achieved, generally requiring 10 to 16 weeks. The efficacy is dose-dependent and the PASI 75 response is 50% at 8 weeks with a daily dose of 3mg/kg.[42]

Oral retinoids such as acitretin have antiproliferative and anti-inflammatory properties. They have teratogenic properties and therefore cannot be administered in women of child-bearing age. The most common side effects are mucocutaneous dryness and hyperlipidemia. Acitretin is not recommended as first choice monotherapy in plaque psoriasis, however its use in combination with topical calcipotriol or phototherapy (Re-UVB or Re-PUVA) has been proven effective.[47]

The first biological to be approved by the Food and Drug Administration for the treatment of moderate to severe psoriasis was alefacept in 2003. Efalizumab was approved in 2003 and was withdrawn from the market in 2009 due to the increased risk of progressive multifocal leukoencophalopathy. Many other biologicals followed: the TNFα antagonist adalimumab, etanercept and infliximab and the interleukin-12/23 antagonist ustekinumab. These therapies attain PASI 75 response varying from 30 to 80% at 12 weeks. A recent study has been published showing no significant difference in drug survival, mean PASI change and Skindex-29 response between etanercept, adalimumab and ustekinumab at weeks 12 or 52.[48] As these drugs are being administered to patients, new biologic treatments emerge aiming at inhibiting novel and already known pathways involved in psoriasis. Recent examples are the anti-interleukin-17A receptor antibodies secukinumab, brodalumab, and ixekizumab.[49-51] Two small molecule drugs are currently in phase III trials: tofactinib (an inhibitor of the Janus kinases) and apremilast (inhibitor of the phosphodiesterase 4 (PDE4)). These are promising therapies and are cheaper to manufacture than biologic drugs.[52,53]

Biologic therapies are very expensive however studies show promising results. The next step is the approval of biosimilars for psoriasis.[54] A biosimilar is a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components. Approval is based on an assurance that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. The European Medicines Agency (EMA) have approved 20 biosimilar medicines since 2006, based on an abbreviated clinical development programme which includes a thorough assessment of efficacy and safety according to high EMA demands of equivalence criteria but not repeating proof of benefit in every indication.[55,56] Physicians administering biosimilars, will play an important role in contributing to pharmacovigilance of biosimilars by their cooperation in post-marketing surveillance and patient registries. Particularly dermatologists, since use in psoriasis of the first European Union approved biosimilar monoclonal antibody infliximab (Remsima or Inflectra) in October 2013 depends on extrapolation to psoriasis from phase 3 studies in two other indications (rheumatoid arthritis and ankylosing spondylitis).[57]

6. DISEASE SEVERITY AND HEALTH RELATED QUALITY OF LIFE

In the past decades several tools have been developed to measure disease severity in psoriasis. These range from instruments used by physicians to patient administered questionnaires. Some only give an indication of the extent of the lesions (Body Surface Area [BSA]), while others also take into account the character of the lesions (Psoriasis Area and Severity Index [PASI] and the self-administered PASI [SAPASI]). A recent systematic review showed that the Physician's Global Assessment (PGA) was very reliable and correlated well with the PASI.[58] The PASI is the most commonly used clinical measure in research. It's response distribution is low because only half of the scale is used, however due to its widespread use, this severity measure enables to compare outcomes between trials. Newer simplified scores, such as the Simplified Psoriasis Index, attempt to overcome the limitations of the available instruments.[59] Finally, the choice of instrument depends on the nature of the study; an Internet survey would request patients to report the number of palms (BSA) or the SAPASI, whereas a clinical study would more likely require the use of the PASI or the PGA.

In order to address the impact of psoriatic disease on patients, it is inevitable to evaluate patient reported outcome measures (PROMs) such as those measuring the impairment of health related quality of life (HRQoL). Mild disease could have a profound impact on patients' HRQoL.[4] A large number of instruments have been developed to measure HRQoL in psoriasis patients including dermatology specific questionnaires such as the Dermatology Life Quality Index (DLQI),[60] the Skindex-29[61] and the Psoriasis Disability Index (PDI)[62] and generic instruments such as the Short-Form-36 (SF-36)[63] and the Euro QoI 5D.[64] The former instruments allow comparison between skin diseases and the latter generic instruments allow comparison between all diseases. Commonly, the combination of a dermatology specific and a generic instrument is recommended.[65] In psoriasis, PROMs are a cornerstone of systemic treatment, giving treating physicians tools to assess treatment satisfaction and QoL in their patients.

7. PSORIASIS COMORBIDITIES

The first comorbidity to be studied in psoriasis was joint manifestation, described by Jean Louis Alibert in 1818.[66] A large Scandinavian cohort followed more than 150,000 Swedes over a decade (1970-1979) with regard to inpatient hospitalization for all diagnoses, showing that psoriasis patients had higher rates of alcoholism, hypertension, infections, pneumonia, liver cirrhosis, urticaria, and rheumatoid arthritis.[67] In the 1980s a number of landmark studies appeared: the PUVA follow-up study noted a dose-dependent risk of cutaneous squamous-cell carcinoma in 1,380 patients treated for psoriasis with oral methoxsalen (8-methoxypsoralen) and ultraviolet A photochemotherapy (PUVA).[68]

A landmark paper on patients with rheumatoid arthritis showed that cardiovascular deaths were reduced by 70% in individuals treated with methotrexate and that this treatment

decreases systemic inflammation.[69] The mechanisms involved are partly due to traditional cardiovascular risk factors.[70]

An association between cardiovascular disease and psoriasis was found in the early 70's.[10,71,72] In 2004, a Swedish cohort study investigated cardiovascular mortality and showed that inpatients were significantly at a higher risk than outpatients.[73] A study using GPRD data concluded that the risk of myocardial infarction was greatest in young patients with severe psoriasis.[74] The interest in the study of cardiovascular comorbidity in psoriasis patients resulted in multiple research groups investigating this association in population-based cohorts based in different countries.[75-90] The results of these studies are inconsistent, possibly due to difference in case definition of exposure, outcome and psoriasis disease severity, the study setting and design, the methods used to adjust for cardiovascular risk factors, residual confounding and statistical power. The discrepancy in the results obtained in these studies has led to controversial discussion in the literature of the past decade.

Further relatively well-studied possible comorbidities in psoriasis are malignancies,[91-95] infections,[67,96] non-alcoholic fatty liver disease,[97,98] osteoporosis,[99] inflammatory bowel disease[100,101] and COPD.[102]

The concept of comorbidity in psoriasis is based on the hypothesis that psoriasis not only leads to skin inflammation, but also causes systemic inflammation mediated by inflammatory markers such as interleukins and TNFα circulating in the serum.[103] These may alter the function of hepatocytes, endothelial cells, atheroma and thrombus risk, leading to increasing cardiovascular risk factors. This so-called "psoriatic march" can eventually lead to atherosclerosis and finally to cardiovascular events.[104]

Another hypothesis is that components of the metabolic are risk factors for psoriatic disease,[105] This has been confirmed in the Nurses' Health Study, where smoking, obesity and high wait circumference increase the risk of incident psoriasis.[106,107]

Most of the studies investigating the association between psoriasis and other diseases are observational in nature and are based on large secondary or routine databases using different case definitions for exposure and outcome, and it is therefore often a challenge to compare their results. These databases are mostly limited by residual confounding (the datasets were not primarily designed to study the association and many of the potentially relevant confounders are missing or incomplete), or detection bias (patients seek medical aid when visiting their dermatologist, and other medical conditions other than those involving the skin are more likely to be diagnosed). Furthermore, disease severity in psoriasis patients in these studies is often defined using proxies, such as psoriasis medication (topical versus systemic medication).[88,108,109]

However, observational studies can aid in generating a hypothesis and establishing an association between exposure and outcome. This does not necessarily imply a causal association. In 1965 Sir Austin Bradford Hill established a number of criteria describing in what circumstances we can pass from an observed association to causation, some of which were also mentioned in "A treatise of human nature" by the Scottish philosopher David Hume:[110,111]

- Strength of an association.
- Consistency showing that the association has been repeatedly observed by different persons, in different places, circumstances and times.
- Specificity, meaning that the same cause always produces the same effect.
- Temporality, indicating that the cause must be prior to the effect.
- Presence of a biological gradient or dose-response relationship.
- Biological plausibility.
- Coherence of the association with generally known facts of the natural history and biology of the disease.
- Confirmation in experiments.
- Analogy assuming that like effects imply like causes.

8. AIMS OF THIS THESIS

Figure 5 depicts the complexity of the association between psoriasis and its comorbidities. The goal of this thesis is to attempt to explain a number of the links in this chart by using various datasets.

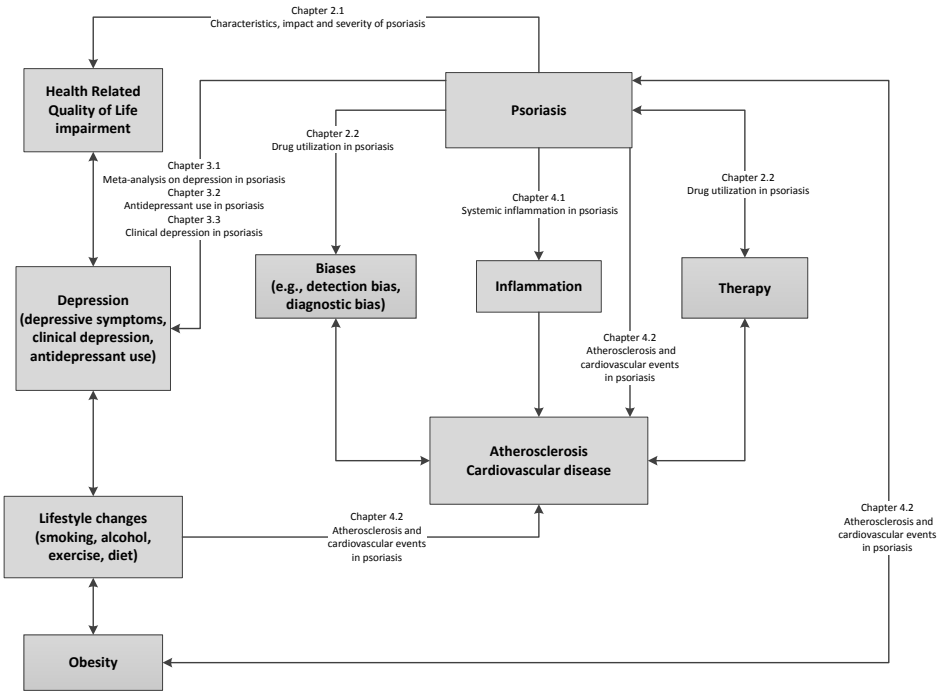

Figure 5. Complexity of the association between psoriasis and comorbidities.
Adapted from commentary by Nijsten and Wakkee.[112]

We addressed the following topics in this thesis:

- Characteristics of psoriasis, disease severity and health related quality of life
- Depressive symptoms, clinical depression and antidepressant use
- Inflammation, atherosclerosis and cardiovascular disease

Firstly, we described the characteristics of psoriasis patients and the impact of this chronic skin condition on their quality of life using a Belgian database with patients diagnosed with psoriasis by a dermatologist (chapter 2.1). We investigated healthcare consumption in psoriasis patients compared to patients without psoriasis by analyzing data on all drug prescriptions in the Dutch General Practitioner database (chapter 2.2).

After concluding that psoriasis has a significant impact on the health related quality of life of patients, we were interested to know whether these patients also experienced more symptoms of depression. We therefore summarized the available data on depression in psoriasis by means of a systematic review and meta-analysis (chapter 3.1) including studies assessing depressive symptoms according to questionnaires, clinical depression according to the International Classification of Disease codes (ICD-codes) and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and also antidepressant use. Estimates were given of the prevalence of depressive symptoms and depression according to the different assessment methods. In this meta-analysis, psoriasis patients showed high prevalence of depressive symptoms according to questionnaires. We were therefore interested to know whether an increased questionnaire score also implies clinical depression as diagnosed by the DSM-IV. We were able to investigate this using data from the population-based Rotterdam Study, where all participants were asked to complete the Center for Epidemiologic Studies Depression score (CES-D) and patients with an elevated score were referred to a psychiatrist for an interview to determine whether they had clinical depression (chapter 3.3). We were also interested whether psoriasis patients use more antidepressants and have more depressive episodes than controls without psoriasis. This was investigated in a population-based study, using the Dutch hospital and pharmacy linked databases (PHARMO RLS) (chapter 3.2).

In recent years there has been a lot of controversial discussion in the literature on whether to consider psoriasis as a systemic disease. Numerous research groups have investigated the presence of markers of inflammation in the serum of psoriasis patients. We therefore conducted a meta-analysis of the available studies to determine whether inflammatory markers are elevated in psoriasis patients compared with healthy controls, taking into account the influence of age, gender and disease severity (chapter 4.1). Finally, we investigated the association between psoriasis and cardiovascular disease in the population-based Rotterdam Study, where atherosclerosis, myocardial infarction, stroke and heart failure were studied in psoriasis patients and controls, adjusting for known cardiovascular risk factors (chapter 4.2).

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Chapter 2

Characteristics of Psoriasis Patients

Chapter 2.1

A descriptive study of psoriasis characteristics, severity and impact among 3,269 patients: results of a Belgian cross-sectional study (BELPSO)

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ABSTRACT

Background: Although several large observational studies have reported on psoriasis characteristics, very few have included severity assessments by dermatologists and validated health related quality of life measures.

Objective: To describe psoriasis characteristics, clinical severity and its impact on quality of life of patients diagnosed with psoriasis by a dermatologist.

Methods: From 2006 to 2007, 192 Belgian dermatologists examined psoriasis patients. Demographics, type of psoriasis, body sites affected, Psoriasis Area and Severity Index (PASI), Body Surface Area (BSA) and Physician's Global Assessment were assessed. Patients answered questions concerning their psoriasis and completed the Dermatology Life Quality Index (DLQI), Skindex-17 and European Quality of Life-5 Dimensions (EQ-5D).

Results: Of the 3,629 psoriasis patients, more than three quarters had plaque psoriasis for more than 16 years. One fifth had nail involvement and 16% had affected genitals. 15% suffered from severe joint pain and 6.4% reported psoriatic arthritis diagnosed by a rheumatologist. Despite therapy in 83% of patients, clinical psoriasis severity was relatively high (mean PASI 8.5 and %BSA12). 40% of patients reported a substantial impact of psoriasis according to the DLQI and Skindex-17 and the mean EQ-5D score was 0.76.

Conclusion: Psoriasis patients consulting dermatologists present with relatively severe disease and often report a high impact on their physical and psychological well-being.

INTRODUCTION

Psoriasis is among the best studied dermatological diseases. Nevertheless, most of the descriptive studies assessing psoriasis prevalence and its clinical characteristics in samples of the general population were published in the 60's and 70's.[1-4] One of the landmark epidemiological studies on psoriasis was conducted on the Faroe Islands where the prevalence of psoriasis at the time of examination was 2.8% among 11,000 subjects.[5,6] These observational studies provided important data on age at onset and prevalence of disease, family history, common sites affected by psoriasis and the influence of climate, stress and pregnancy on the disease. Other studies suggested the existence of different variants of psoriasis based on the age at onset of disease among hospitalized patients in Germany and members of a Swedish psoriasis advocacy group.[4,7] A population based survey in the United States showed that psoriasis occurs in about 2% of the population and that the majority of patients have mild disease that nevertheless may have a profound impact on patients' lives.[8]

A European patient membership survey including 17,990 patients who stated having been diagnosed with psoriasis by a physician showed that 75% of respondents had chronic plaque type psoriasis with a mean age at onset of 30 years. About 60% of the members had more than 3% of BSA involvement and 30% reported psoriatic arthritis (PsA).[9] The basic clinical characteristics of psoriasis of more than 28,000 newly diagnosed Japanese patients who consulted a dermatologist were accurately described in 2003.[10] In this dataset, no information on clinical disease severity and patient reported outcomes was presented. 86% of patients had chronic plaque psoriasis and 1% had PsA. The mean age of onset was about 40 years and two peaks were noted, in the twenties and forties. The scalp, back and extensor sides of the extremities were most commonly affected by psoriasis.

The objective of the present cross-sectional study is to describe clinical characteristics and clinical disease severity assessed by dermatologists and impact of psoriasis on patients' lives using validated questionnaires among a large sample of Belgian psoriasis patients visiting a dermatologist in an open access healthcare system.

MATERIALS AND METHODS

Participating dermatologists and patients

The BELPSO survey is a 1-year open label, cross-sectional epidemiological point prevalence study in psoriasis patients treated in dermatologic clinical practice in Belgium. Of the 518 members of the Royal Belgian Society of Dermatology and Venerology, 192 dermatologists agreed to include patients for this study (response rate 37%). From January 2006 to February 2007 participating dermatologists were asked to screen all psoriasis patients seen at their practice. Patients were eligible if they were 18 years or older, were diagnosed with psoriasis,

had provided written informed consent and were able to complete Dutch or French Health Related Quality of Life (HRQoL) instruments.

Patients who had participated in an interventional clinical trial in the 3 months prior to the study were excluded. The survey targeted to enrol a maximum of 5,000 patients diagnosed with psoriasis or the total number of psoriasis patients enrolled during one year, whichever came first.

The study was approved by the research ethics committee in Belgium and all participants gave written informed consent.

Questionnaire

Patient's and investigator's questionnaire were used to collect patient data. The investigator's case report form (CRF) contained information such as age, gender, age at diagnosis of psoriasis, duration of disease, type of psoriasis (i.e., chronic plaque, guttate, erythrodermic, pustular, palmoplantar and inverse psoriasis) and the localisation of the lesions at the time of clinical examination. The investigators were asked to only report the most dominant form of psoriasis.

Clinical psoriasis severity was assessed using a 5-point static Physician's Global Assessment (sPGA) for all psoriasis patients. The percentage of affected Body Surface Area (%BSA) and the Psoriasis Area and Severity Index (PASI) were also estimated. Joint involvement was evaluated by means of 5 questions derived from existing diagnostic criteria (namely the Moll and Wright, the Vasey and Espinoza and the Bennett criteria),[11-13] but without laboratory and imaging studies. The psoriasis treatment history was assessed by checking medical records of the participating dermatologists for photo(chemo)therapy, topical, systemic and biological treatment.

In the questionnaire given to patients, demographic data, family history of psoriasis, treatment for joint pain (regular intake of non-steroidal anti-inflammatory drugs [NSAIDs]) and consent for participation in a follow-up study were recorded. Patients were asked to score a subject global assessment (SGA) for clinical psoriasis severity, itching and joint pain in the past week on a 6-point Likert scale. The impact of psoriasis on the patient's HRQoL was measured with the SGA, the Dermatology Life Quality Index (DLQI), the Skindex-17 and the generic Euro-Qol 5D (EQ-5D). The scores of the DLQI and Skindex-17 were categorized as previously suggested.[14,15]

Basic data concerning each investigator were recorded: gender, the spoken language (Dutch or French), originally from North or South of Belgium, year of graduation from medical school, university where dermatology training was completed and type of dermatology practice (private and/or [academic] hospital).

Statistics

Results were generally expressed as means ± standard deviations (SD) or median and range for continuous variables as appropriate. Frequency tables were used for describing categorical variables. Mean values from two groups were compared by the Student t-test (corrected for unequal variances if necessary) or by the Mann-Whitney test when the variable was not normally distributed. Analysis of variance (ANOVA) or the non-parametric Kruskal-Wallis test was applied for the comparison of several groups. The classical chi-square test for contingency tables was used for comparing categorical variables.

P-values were two sided and considered significant if <0.05. Calculations were always done on the maximum number of data available and missing data were not replaced. All statistical calculations were performed using the SAS (version 9.1 for Windows) and S-Plus (version 6.2) statistical packages.

RESULTS

Participating dermatologists

Of the 192 participating dermatologists, 61.5% resided in the Northern part of Belgium and 74.5% were female. The mean age was 43.2 years (± 9.98) and they practiced dermatology for an average of 17.3 years (± 9.91). Almost half of the dermatologists combined work in a private practice and hospital, 15.6% was affiliated to a hospital and 35.9% worked exclusively in private practice. On average, each dermatologist included 17 patients (± 30), however half of the investigators included less than 10 patients.

Study population

A total of 3,269 patients were willing and eligible to enter this study. This population is described in Table 1. Of the included patients, 99.3% had used or was currently using topical antipsoriatics, 62.0% phototherapy, 30.3% a conventional systemic drug and 5.9% a biological. The majority of patients (40.6%) received a combination of two types of psoriasis treatment.

Psoriasis type

The most frequent type of psoriasis was plaque psoriasis (77%) followed by guttate (13%), palmoplantar (5%) and inverse psoriasis (3%). Gender differences were more pronounced for pustular and palmoplantar psoriasis than for plaque and guttate psoriasis. Guttate psoriasis affected younger patients more significantly than palmoplantar, inverse and plaque psoriasis (p<0.0001). Patients affected by plaque and guttate psoriasis were diagnosed earlier than palmoplantar and inverse psoriasis patients. Patients with chronic plaque, erythrodermic and guttate psoriasis were affected significantly longer by their disease compared to those with palmoplantar and inverse psoriasis (p<0.0001) (Table 1).

Table 1. Demographic and clinical characteristics of patients stratified for psoriasis type.

Variable	N[1]	All psoriasis types	Plaque N (%)	Guttate N (%)	Erythrodermic N (%)	Pustular N (%)	Palmoplantar N (%)	Inverse N (%)	p-value[2]
	3,268	100 %	2,528 (77.4)	419 (12.8)	26 (0.8)	31 (0.95)	166 (5.08)	98 (3.0)	
Male	1,746	53.4 %	1,436 (82.3)	172 (9.85)	18 (1.03)	10 (0.57)	61 (3.49)	49 (2.81)	<0.0001
Female	1,520	46.6 %	1,091 (71.8)	246 (16.2)	8 (0.53)	21 (1.38)	105 (6.91)	49 (3.22)	
Mean age ± SD	3,268	47.7 ± 15.4	48.0 ± 15.3	43.5 ± 15.1	53.3 ± 14.1	50.0 ± 16.2	51.7 ± 14.9	50.1 ± 17.5	<0.0001
Mean age at onset of psoriasis ± SD	2,488	32.1 ± 17.1	31.4 ± 16.7	29.2 ± 16.1	29.2 ± 18.3	38.9 ± 17.7	44.0 ± 16.3	41.5 ± 19.2	<0.0001
Duration of psoriasis disease (years) ± SD	3,220	15.8 ± 14.2	16.5 ± 14.3	14.3 ± 14.4	24.5 ± 13.9	11.1 ± 16.3	7.71 ± 10.2	8.89 ± 10.2	<0.0001

[1] The total number of N does not always represent 100% of the study population because of missing values.

[2] Statistical difference for gender, age, age at onset, and duration of disease across types of psoriasis, calculated using Kruskal-Wallis for gender and ANOVA for mean age at inclusion, mean age at onset of psoriasis and for duration of psoriasis disease.

Localisation of psoriasis

At the time of clinical examination, the most frequent localisation of psoriasis was the elbow followed by the scalp, the lower leg, knee and back (Table 2). On average, 6.3 different body sites were involved. Of the 698 patients with only one localisation of psoriasis, the scalp (56.7%), elbow (47.3%) and lower leg (29.0%) were most commonly affected.

Table 2. The frequency of body sites affected by psoriasis (n=3,269).

Localisation	Number of patients (%)
Elbow	2,152 (65.8)
Scalp	2,027 (62.0)
Lower leg	1,853 (56.7)
Knee	1,621 (49.6)
Back	1,496 (45.8)
Upper leg	1,477 (45.2)
Lower arm	1,442 (44.1)
Chest	1,429 (43.7)
Buttock	1,337 (40.9)
Upper arm	1,328 (40.6)
Back of hand	881 (27.0)
Nail	691 (21.1)
Face	687 (21.0)
Back of foot	612 (18.7)
Genitalia	522 (16.0)
Palm	405 (12.4)
Foot sole	328 (10.0)
Neck	270 (8.26)
Other	98 (3.00)

Clinical psoriasis severity

According to the sPGA scale, approximately one quarter of patients had no lesions or was almost clear of psoriasis, more than one third of the patients had mild psoriasis (36.1%) and 35.6% had moderate to severe disease (Table 3). In 2,528 patients with chronic plaque psoriasis the mean %BSA was 12.3 (SD 14.8; range 0.3-95.0) and the median PASI score was 6.25 (Interquartile Range 9). In patients with plaque psoriasis 31.6% had a PASI >10 and 32.9% had a BSA >10%. Both PASI and %BSA scores were significantly higher in men than in women (9.49 ± 8.08 vs. 7.34 ± 7.48; and 13.3 ± 15.1 vs. 10.8 ± 14.5, respectively; $p<0.001$).

Table 3. Disease severity: distribution of the 6-point physician's global assessment (PGA) scale for all patients and according to the type of psoriasis.

Type of psoriasis[1]	N	Absence of lesions, discoloration (%)	Almost exempt of lesions (%)	Mild (%)	Moderate (%)	Severe (%)	Very severe (%)
All psoriasis types	3269	38 (1.16)	832 (25.5)	1,179 (36.1)	812 (24.8)	353 (10.8)	55 (1.68)
Plaque	2528	29 (1.15)	647 (25.6)	914 (36.2)	638 (25.2)	265 (10.5)	35 (1.38)
Guttate	419	4 (0.95)	98 (23.4)	163 (38.9)	107 (25.5)	43 (10.3)	4 (0.95)
Erythrodermic	26	1 (3.85)	3 (11.5)	2 (7.69)	3 (11.5)	9 (34.6)	8 (30.8)
Pustular	31	2 (6.45)	12 (38.7)	7 (22.6)	5 (16.1)	4 (12.9)	1 (3.23)
Palmoplantar	166	0 (0.00)	38 (22.9)	55 (33.1)	42 (25.3)	24 (14.5)	7 (4.22)
Inverse	98	1 (1.02)	34 (34.7)	38 (38.8)	17 (17.4)	8 (8.16)	0 (0.00)

[1] The distribution of PGA differed significantly ($p<0.0001$) between the various types of psoriasis.

Evaluation of joint involvement

Of the total study population 26.9% patients complained about the presence of joint pain, 7.0% scored their joint pain as (very) severe and 6.4% reported PsA diagnosis confirmed by a rheumatologist. Patients with pustular psoriasis complained significantly more about joint pain than those affected by other types of psoriasis ($p= 0.036$), but only one reported a confirmed diagnosis of psoriatic arthritis.

In this population, 14.1 % of the patients used NSAIDs regularly for joint pain. The use of NSAIDs was more frequent in women than in men (16.1% vs 12.4%, $p = 0.004$) and those with longer duration of psoriasis (18.9 ± 15.4 vs 15.2 ± 14.1; $p<0.0001$), and differed across different types of psoriasis ($p=0.048$); patients with erythrodermic and pustular psoriasis more frequently used NSAIDs (24% and 27%, respectively) compared to patients with plaque type psoriasis (14%).

Family history of psoriasis

Of the 3,166 patients where information on family history of psoriatic disease was available, 36.8% reported a positive family history of psoriasis (Table 4). These patients were slightly younger than those without a family history (46.6 ± 15.0 vs 48.4 ± 15.6; $p=0.002$) and their duration of disease was longer. Patients with early psoriasis onset (< 30 years) or those with erythrodermic or guttate psoriasis were significantly more likely to report a positive family history than others ($p <0.0001$ and $p=0.006$ respectively).

Table 4. A comparison of the distribution of demographic and disease characteristics between patients with and without a family history of psoriasis.

Variable	N	Family history of psoriasis		p-value
		Yes N (%)	No N (%)	
All patients	3,166	1,165 (36.8)	2,001 (63.2)	
Gender	3,164			
Male		592 (35.1)	1,096 (64.9)	0.032
Female		572 (38.8)	904 (61.2)	
Age (years)	3,166	46.6 ± 15.0	48.4 ± 15.6	0.002
Age at time of psoriasis diagnosis (years)	3,121	28.3 ± 15.7	34.2 ± 17.4	0.0002
Age at time of psoriasis diagnosis	3,121			
≤ 30 years		679 (43.0)	902 (57.1)	<0.0001
> 30 years		473 (30.7)	1,067 (69.3)	
Duration of psoriasis disease (years)	3,221	18.4 ± 15.3	14.0 ± 13.5	<0.0001
Type of psoriasis	3,165			
Plaque		911 (37.2)	1,535 (62.8)	0.006
Guttate		166 (40.4)	245 (59.6)	
Erythrodermic		11 (44.0)	14 (56.0)	
Pustular		6 (20.0)	24 (80.0)	
Palmoplantar		41 (25.3)	121 (74.7)	
Inverse		30 (33.0)	61 (67.0)	

Patient reported outcomes

Subject global assessment

Of the 3,269 psoriasis patients, 25.9% self-reported having no disease or mild disease and 28.5% indicated having severe psoriasis (SGA≥4) in the last week prior to consultation (Figure 1).

Of all patients, 39.8% reported little to no itching due to their psoriasis, but almost a quarter reported suffering from a (very) severe itch.

Dermatology specific HRQoL

The mean DLQI was 8.68 (SD 6.73; range 0-30) among all psoriasis patients. For 34.6% of the patients psoriasis had a large effect on their life (DLQI >10). Patients with moderate to severe psoriasis (PGA≥3) reported higher DLQI scores than those with milder disease (10.8 ± 7.2 vs 7.2 ± 6.0; p<0.0001). Women presented slightly higher DLQI-scores than men (9.04 ± 6.71 vs 8.37 ± 6.71; p=0.014). The patients in whom psoriasis was diagnosed before the age of 30 years presented significantly higher DLQI-scores than others (9.54 ± 6.93 vs. 7.70 ± 6.33; p<0.0001), but disease duration did not affect DLQI scores (p=0.34). Erythrodermic patients presented a higher DLQI-score than those with other types of psoriasis (p=0.002).

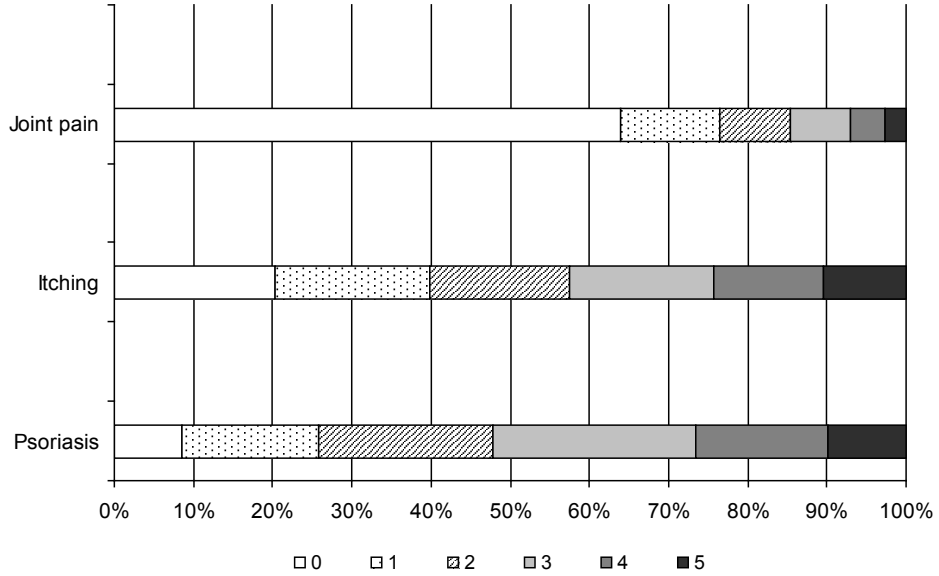

Figure 1. Subject global assessment of joint pain, itching and psoriasis severity in the past week on a 6-point Likert scale (n=3,269).

The mean total Skindex-17 score was 13.2 (±8.32; range 0-34). The impact of psoriasis on the psychological dimension was considered high by 40.1% of the patients. More than half the patients scored the impact of the symptoms on their daily life as high. Patients with moderate to severe psoriasis reported higher Skindex-17 scores than those with milder disease (16.0 ± 8.7 vs 11.3 ± 7.5; $p<0.0001$). For both subscales of the Skindex-17, women presented significantly higher scores than men ($p<0.014$). The patients who were diagnosed with psoriasis before the age of 30 had higher scores of the psychosocial and symptom dimensions of the Skindex-17 compared to the remaining patients ($p<0.0001$). Erythrodermic patients presented the highest Skindex-17 scores.

Generic HRQoL

The mean EQ-5D score was 0.76 (SD 0.61; range -0.59 – 1.0). (A score equal to 1 corresponds to the utility of being completely healthy and 0 corresponds to the utility of being deceased.) This observation was supported by a mean self-related health state (using a Visual Analogue Scale) of 71.3 (SD 18.4). Patients with moderate to severe psoriasis reported higher impact than those with milder disease according to the EQ-5D (0.71 ± 0.30 vs 0.80 ± 0.22; $p<0.0001$). Concerning the five dimensions of the EQ-5D, the majority of patients did not have any real problems, with the exception of moderate to extreme pain and discomfort in 54.1% of the patients and moderate to extreme anxiousness or depression in 45.1% of patients. Men showed slightly, but significantly higher EQ-5D scores than women (0.79 ± 0.24 vs 0.72 ± 0.28; $p <0.0001$). Erythrodermic patients presented significantly lower EQ-5D scores than all

other patients (0.42 ± 0.44; p<0.0001). Patients with inverse and palmoplantar psoriasis had lower scores than those with chronic plaque and guttate psoriasis. No relevant associations were detected with age and disease duration.

DISCUSSION

As expected more than three quarters of the psoriasis patients visiting a dermatologist had plaque psoriasis.[16-18] However, guttate psoriasis affected more than one eighth of Belgian and European psoriasis patients, which is considerably higher than the 2.8% in the study from Japan.[9,10] We observed less inverse psoriasis than in the EUROPSO study (12% vs 3%), possibly explained by the fact that in the latter study the results were self-reported by the patients and they could indicate multiple types of psoriasis, whereas in the present study dermatologists could only indicate the most dominant psoriasis type. This is illustrated by the observation that more than 10% of participants had psoriasis on their palms and soles and only 5.8% were classified as palmoplantar psoriasis. As expected, guttate psoriasis affected relatively younger patients[19,20] and women were twice as likely to have pustular and palmoplantar psoriasis.[20] Other population based studies focussed on studying psoriasis in general, however they did not differentiate between psoriasis types.[1,8]

The distribution of body sites affected by psoriasis was driven by plaque psoriasis that most commonly involves the scalp, extensor sites of the extremities and lower back.[21] In the present study, dermatologists observed nail involvement in more than 20% of patients, which is much higher than that reported by Japanese dermatologists[10] but lower than that observed in a cross-sectional survey.[1] The genitals were affected in 16% of the study population emphasizing the need to examine or discuss the involvement of these sensitive areas and their possible consequences. Three population surveys of patients visiting a dermatologist reported that involvement of the genitals might occur in 29-40% of patients at some time during the course of the disease.[1,2,22] In a recent questionnaire-based survey among members of the Dutch Psoriasis Society, 46% of the responding patients with psoriasis reported genital involvement at some time during the course of their disease.[23]

To our knowledge, this is the first large observational study documenting clinical psoriasis severity assessed in detail by dermatologists. In two studies patients self-reported the extent of BSA involvement assessing the number of palms affected,[8,9] but none of the other observational studies included prospective assessments of psoriasis severity by a physician. Among more than 2,500 Belgian patients with chronic plaque psoriasis of which more than 80% received therapy, the mean BSA involved was 12% and the mean PASI was 8.5. According to the PGA, about a quarter were almost clear of their psoriasis and more than a

third had moderate to severe disease. These observations suggest relatively severe disease among patients visiting a dermatologist, which may be explained by the fact that patients with more severe psoriasis and dermatologists with special interest in psoriasis were more likely to participate in this study. This results in an overrepresentation of patients with moderate to severe psoriasis. These findings may also suggest that a large proportion of patients were not under optimal disease control with their current treatment, which may be related to patients' preferences or physicians' reluctance to treat psoriasis more aggressively as has been postulated previously.[24,25]

Although we did not use validated diagnostic criteria for PsA, this study suggests that approximately 5-15% of patients with cutaneous psoriasis have joint involvement. Of all participating patients, more than a quarter reported joint pain, 15% used NSAIDs to control their joint pain and 6% had a diagnosis of PsA confirmed by a rheumatologist. This is in accordance with other studies.[10,26] Interestingly, patients with pustular psoriasis were more likely to have joint complaints.

Among the included patients, 30-50% reported high levels of HRQoL impairment using the DLQI and Skindex-17, which is comparable to other hospital-based studies[27,28] but as expected higher than that observed in psoriasis patients from the general population.[8] Although clinical disease severity and HRQoL impact are different constructs, patients with more severe psoriasis reported a higher impact of disease on their lives.[29,30] This is confirmed by erythrodermic patients reporting the highest score on the DLQI and Skindex-17. Although male psoriasis patients had more severe disease at the time of enrolment, women with psoriasis reported more impaired HRQoL, suggesting that this latter group of patients may benefit from additional psychological care especially at a younger age. In this study, the mean EQ-5D was 0.76 for all patients and 0.71 for those more severely affected, which is considerably lower than that measured in the general Belgian population suggesting a lower HRQoL in psoriasis patients.[31] The observed level of generic impairment in psoriasis patients is comparable to that observed in other chronic diseases such as asthma, diabetes, rheumatoid arthritis, several types of cancer (e.g., prostate cancer and haematological malignancies) and dermatological diseases such as severe acne and hand eczema.[32-36]

Strengths and limitations

The major strength of this study is that it includes a large study population and that all patients were diagnosed and examined by a dermatologist. This also implies that the results are specific to patients consulting a dermatologist, which may reduce the generalizability of the findings. However, the Belgian medical system allows patients to seek specialised medical care freely (i.e., through an open access healthcare system), at low personal costs and without long delays, suggesting that the results obtained could be generalised to most psoriasis pa-

tients in the general population. In contrast to other observational studies on the presentation of psoriasis, clinical disease severity was assessed in detail (PASI, BSA and sPGA) and several validated HRQoL instruments were used to assess the impact of psoriasis. All patients, regardless of their treatment at the time of the survey, were included, and not only newly diagnosed patients as in the Japanese survey.[10] Therefore, the true clinical and psychosocial impact of the disease may be underestimated. An advantage of these less stringent eligibility criteria is that we could assess the HRQoL impairment among patients who have been dealing with psoriasis for a long time (16 years on average in this study). Comorbidities were not included in the questionnaire and therefore patients with skin diseases other than psoriasis and those with known mental or physical illness, which could interfere with patient's HRQoL, could not be excluded from the study. Dermatologists were asked to indicate the most dominant type of psoriasis and could not indicate different types of psoriasis making these estimates less precise and more difficult to compare with other studies. No complete set of criteria for the diagnosis of PsA was used and laboratory and imaging studies were not performed, introducing diagnostic bias. About one third of all dermatologists in Belgium participated and their demographics and the sites of inclusion (private practice and hospital) varied substantially. These findings suggest a modest selection bias. The cross-sectional design does not enable us to describe the longitudinal course of psoriasis, but informed consent was obtained to contact participants in the future.

CONCLUSION

In the present study, the majority of the included psoriasis patients had plaque psoriasis located at the usual body sites. More than one fifth had nail involvement and 16% had affected genitals. Approximately 10% of patients seem to suffer from PsA. Despite the use of therapies in most patients, the clinical psoriasis severity was relatively high and about 40% of patients reported a substantial impact of psoriasis on their HRQoL.

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Chapter 2.2

Increased overall drug utilization in psoriasis patients: a case-control study based on Dutch general practitioner data.

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Submitted for publication

Chapter 3

Depressive Symptoms & Clinical Depression in Psoriasis

Chapter 3.1

The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis

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ABSTRACT

The reported prevalence of depression in psoriasis varies substantially. This study aims to determine the prevalence and odds of depressive symptoms and clinical depression in psoriasis.

A systematic literature search was conducted. Mean questionnaire values and proportions for depressive symptoms and clinical depression were pooled according to different assessment methods. In controlled studies, standardized mean differences (SMD) and OR compared depression in psoriasis patients with controls using the random effects model.

The majority of the 98 eligible studies were conducted in tertiary centres, without a control group. The prevalence of depressive symptoms was 28% using questionnaires and the prevalence of clinical depression was 12% using International Classification of Diseases (ICD)-codes, 19% using the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and 9% for antidepressant use. Psoriasis patients had significantly more depressive symptoms (SMD 1.16; 95% CI 0.67-1.66) and population-based studies showed that they were at least one and a half times more likely to experience depression (OR 1.57; 95% CI 1.40-1.76) and they used more antidepressants than controls (OR 4.24, 95% CI 1.53-11.76).

More than 10% of psoriasis patients suffer from clinical depression, and twice as many have depressive symptoms. The high prevalence of these symptoms is likely to be affected by the tertiary study populations and differential misclassification using questionnaires, where psoriasis-related symptoms may be detected as depressive symptoms.

INTRODUCTION

Psoriasis is estimated to affect 3% of the Caucasian population and is known to have a major impact on patients' Health Related Quality of Life (HRQoL).[1-3] The latter captures patients' perspectives and may assist in calculating the burden of disease, treatment evaluation, and identifying patients who are in high need of psychological counselling. Psoriasis patients often feel impaired by their physical appearance, leading to stigmatization, avoidance of social interaction and isolation. It has been assumed that this altered behaviour and impaired HRQoL may lead to depression, anxiety, stress-related disorders and even to suicidal ideation.[4-8] A study using a structural equations modeling approach, demonstrated the complex association between psoriatic symptoms, disease severity, depressive symptoms and quality of life, showing that a significant proportion of the variance of depressive symptoms was explained by HRQoL.[9] However, psoriasis patients may also have other comorbidities that increase the risk of developing depression.[10,11]

The prevalence of depression in psoriasis varies from 6 to 62%, depending mainly on study design, study population, sample size, and outcome definition for depression.[12-14] Most studies use validated questionnaires assessing depressive symptoms. Larger population-based studies using secondary databases, assess depression with International Classification of Disease (ICD) codes or measure antidepressant use with Anatomical Therapeutic Classification (ATC) codes. Very few studies define depression based on the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classification of psychiatric diseases. According to this classification, major depression is defined as depressed mood or loss of interest for at least 2 weeks, accompanied by 5 of the following symptoms: weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, diminished concentration, recurrent thoughts of death or suicide.[15]

We were interested to what extent the well-documented impairment of HRQoL in psoriasis translates into depressive symptoms (assessed by questionnaires) and ultimately clinical depression (assessed by antidepressant use, ICD-codes and DSM-IV). We aimed to provide a pooled estimate of the prevalence and odds of depressive symptoms and clinical depression in psoriasis patients.

MATERIALS AND METHODS

Types of studies

No restrictions were made as to the type of study (experimental or observational), publication date or language.

Types of participants

Studies conducted in adults aged 18 years and older were included. Psoriasis patients were defined as those with a confirmed diagnosis of psoriasis by a physician (dermatologist, rheumatologist, general practitioner (GP) or other healthcare provider), a self-report of a physician's diagnosis for psoriasis or according to a diagnostic code (ICD9: 696.0-1/ICD10: L40.0-9, or OXMIS code). No restriction was made as to type of psoriasis, but a distinction was made as to whether studies included patients with cutaneous plaque psoriasis, psoriatic arthritis (PsA) or other types.

Types of outcome measures

Depression was defined using different methods: (1) diagnosis by a psychiatrist, psychologist, GP or other healthcare provider, (2) DSM-IV criteria, (3) self-report of a physician's diagnosis of depression, (4) ICD-codes (ICD-9-CM 296.2-3, 298.0, 300.4, 309.1, 311, ICD10: F32.0-9 and F33.0-9), (5) Mini International Neuropsychiatric Interview (MINI),[16] (6) antidepressant use using ATC codes or self-report, (7) validated questionnaires assessing depressive symptoms such as the Beck Depression Inventory (BDI),[17,18] Center for Epidemiologic Studies Depression Scale (CES-D),[19] Hospital Anxiety and Depression Scale (HADS),[20,21] Hamilton Rating Scale for Depression (Hamilton DS),[22] Carroll Rating Scale for Depression (CRSD),[23,24] Zung Self-rating Depression Scale (Zung-SDS)[25,26] and Montgomery Asberg Depression Rating Scale (MADRS).[27] The General Health Questionnaire (GHQ) measured patient's "general health".[26,28] These questionnaires and their cut-off values are described in the Supplementary Table 3.

Search strategy

The search was performed by a medical librarian in Embase, Medline, PubMed, PsycInfo and the Cochrane Database, from inception to August 2012 (Supplementary Table 1).

Study selection and data extraction

The titles and abstracts were screened and articles were selected based on the inclusion and exclusion criteria. Data was extracted using a standardized form (Supplementary Table 2). Baseline values for proportions or mean values according to questionnaires, and the proportion of patients with a diagnostic code for depression or antidepressant use were registered. Studies where outcome values were reported separately for subgroups were also included (Supplementary Table 2). When several studies reported results from the same population, the study with the most complete data was included in the meta-analysis. Participants from the same studies were only included once per combined analysis. However in one study by Turel Ermertcan et al, the results of psoriasis patients were split into four groups and there were only two control groups. We therefore included information on the control group twice in order to be able to calculate a standardized mean difference (SMD) for the four psoriasis groups.

The quality of the articles was rated using an adapted version of the NOS (range 0-10; Wells et al, 2012)[29] (for the score sheet, see Supplementary Material).

These steps were conducted independently by E.A.D. and F.S.v.L. or E.A.D and M.W. Differences were resolved and consensus was reached through discussion.

Statistical analysis

In controlled and uncontrolled studies, pooled mean values and the prevalence of psoriasis patients with depressive symptoms according to the questionnaires were calculated. Pooled prevalence of clinical depression in psoriasis was calculated according to antidepressant use, ICD, and DSM-IV.

In controlled studies, depressive symptoms were compared between psoriasis patients and controls by calculating the difference in mean questionnaire values, obtaining a SMD and 95% confidence interval (CI). Odds ratio (OR) and 95% CI for depressive symptoms and clinical depression between psoriasis patients and controls were obtained according to questionnaires, antidepressant use, ICD and the DSM-IV .

The analyses were performed using a random-effects model according to the method of DerSimonian and Laird,[30] taking into account within-study and between-study variance.

Heterogeneity between studies was quantified using I^2 statistics.[31] Publication bias was assessed graphically with funnel plots and statistically with Egger's regression.[32] The trim and fill method provided an estimate of the number of missing studies and of the pooled effect size if these studies had been included.

Meta-regression and subgroup analyses

Sources of heterogeneity between studies were explored by performing meta-regression for age, gender, Psoriasis Area and Severity Index (PASI) and Newcastle-Ottawa Scale (NOS) score (all determined a priori). Another method used to address the heterogeneous data was to conduct subgroup analyses. In this study, the primary subgroup analysis consisted of the distinction between the different methods of assessment for depression. In addition, subgroup analyses were performed for variables which were significant in the meta-regression.

The present study was conducted and reported in accordance with the PRISMA guidelines for reporting systematic reviews and meta-analyses.[33]

All statistical analyses were performed using Comprehensive Meta-Analysis Version 2.2 (Biostat, Englewood, NJ, USA).

RESULTS

Study characteristics

The electronic search yielded 1,815 articles, of which 98 were eligible. Twenty-six studies compared psoriasis patients with healthy controls (Figure 1).

In the meta-analysis of the 98 studies, data was pooled on 401,703 psoriasis patients. Two studies included more than 100,000 patients each[5,34] and three studies included more than 20,000 patients each.[35-38] In the 26 controlled studies, data on 264,568 psoriasis patients and 1,174,612 healthy controls was pooled.

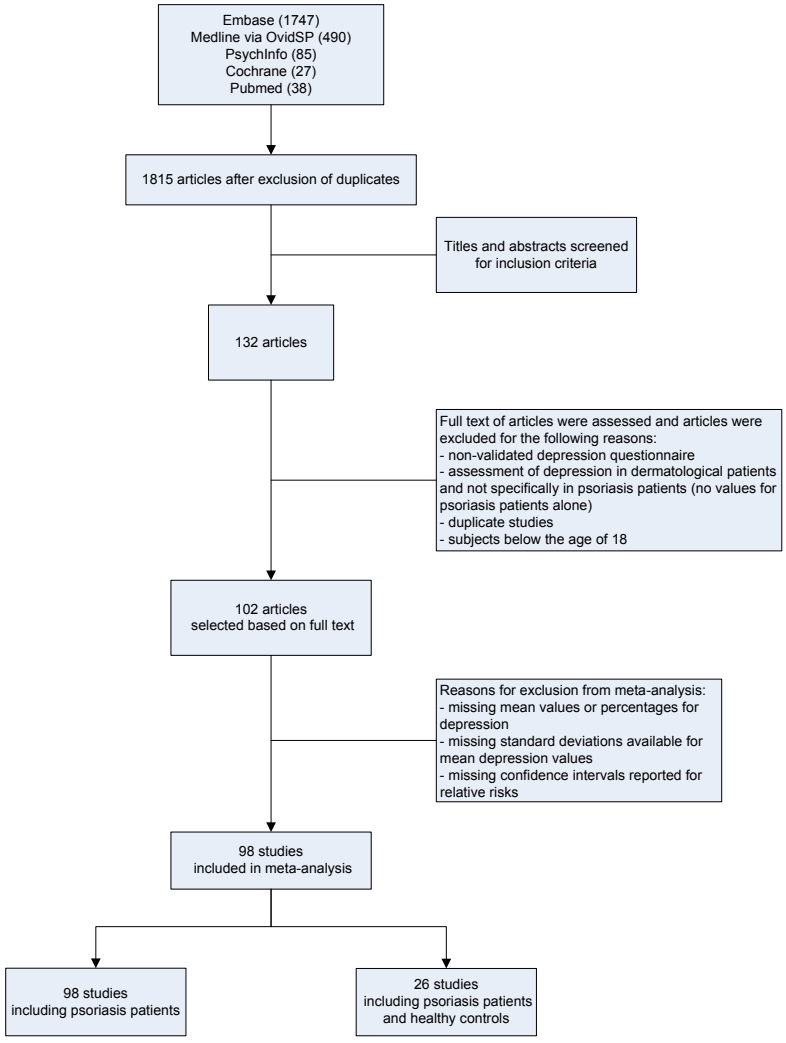

Figure 1. Flow chart of search strategy and study selection.

More than one fourth of studies were conducted in tertiary centres of which 17 were restricted to inpatients and 33 to outpatients (Supplementary Table 2). Six studies assessed depression among members of psoriasis advocacy groups. Eight very large population-based studies derived their data from pharmacy, insurance or administrative databases.[5,7,34-37,39,40]

In more than 60% of studies, psoriasis was diagnosed by a dermatologist. Approximately 40% of studies measured disease severity using the PASI, with a mean PASI of 13. The remaining studies either did not measure the severity or used other measures, or failed to report the obtained mean PASI values.

The majority of studies assessed depressive symptoms using questionnaires. Several studies used ICD-codes and only a few defined depression according to antidepressant use and DSM-IV criteria (Tables 1 and 2). Only 14 studies measured incident depression i.e., excluding patients with a history of psychiatric diseases or those taking psychotropic medication before psoriasis onset.

None of the studies scored the maximum of 10 points on the modified NOS for quality assessment. The highest score was 7 points, which was reached by 6 studies, while the majority of studies scored between 4 and 6 points (n=67) (Supplementary Table 2).

Prevalence of depressive symptoms

Among the 98 studies, the most commonly used questionnaire was the HADS followed by the BDI (Table 1). According to the HADS, the prevalence of depressive symptoms was 23% using the standard cut-off value of 8, with a pooled mean value of 5.86 (95% CI 5.05-6.67). However, the other frequently used instrument, the BDI, showed that 36% (95% CI 26-46%) of psoriasis patients were depressed on using the cut-off value of 10 points, with a pooled mean value of 13.34 (95% CI 11-18-15.51) (Table 1). The other questionnaires Hamilton RS, Zung-SDS, CES-D were only used in two to three studies each. The proportion of depressive symptoms was highest in the studies using the CES-D score (n=3) with a pooled rate of 55% (95% CI 31-77%), and lowest among the studies using the HADS questionnaire (23%). The forest plot in figure 3a shows the prevalence of psoriasis patients with depressive symptoms for the studies using validated questionnaires (n=33), which varies a lot, resulting in a high heterogeneity (I^2=97%, p<0.001). We notice that there are a few studies reporting prevalence estimates higher that 50% for depressive symptoms. The pooled results estimated that more than a quarter of the psoriasis patients showed symptoms of depression (28%, 95% CI 22-34%).

Prevalence of clinical depression

The proportion of depressed patients decreased when measuring clinical outcomes: 19% according to the DSM-IV and 12% according to the ICD (Table 1). Antidepressant use was even lower, with a pooled rate of 9% (95% CI 6-14%) in ten studies (Figure 2a). A total of 49% of patients had an impaired general health according to the five studies using the GHQ, which is remarkably higher than the above mentioned proportions for depression and depressive symptoms (Figure 2a).

Table 1. Depression outcomes in psoriasis patients.

Questionnaires reporting mean values for depressive symptoms	**Number of studies**	**Pooled mean and 95% CI [1]**
HADS	26	5.86 (5.05-6.67)
BDI	21	13.34 (11.18-15.51)
Hamilton DS	6	6.50 (4.37-8.64)
CRSD	6	13.41 (11.99-14.84)
Zung-SDS	2	31.68 (6.28-57.08)
CES-D	2	23.56 (20.39-26.74)
MADRS	1	6.09 (4.17-8.01)
Questionnaires reporting proportion of patients with depressive symptoms	**Number of studies**	**Pooled rate and 95% CI [1]**
HADS, % patients with a score ≥ 8	19	23% (19-27%)
BDI, % patients with a score ≥ 10	10	36% (26-46%)
Hamilton DS, % patients with a score >7	2	25% (22-28%)
Zung-SDS, % patients with a score > 50	2	37% (29-46%)
CES-D, % patients with a score >16	3	55% (31-77%)
All questionnaires [2]	33	28% (22-34%)
Clinical outcome measures for depression	**Number of studies**	**Pooled rate and 95% CI [1]**
ICD	10	12% (8-18%)
DSM-IV	4	19% (12-29%)
Antidepressant use	10	9% (6-14%)
MINI interview	2	21% (12-35%)
General health	**Number of studies**	**Pooled rate and 95% CI [1]**
GHQ, mean value	4	4.93 (3.96-5.89)
GHQ, % patients with a score ≥ 2	5	49% (39-58%)

Abbreviations: BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; Hamilton DS, Hamilton Depression Score; CRSD, Carroll Rating Scale for Depression (CRSD), MADRS, Montgomery Asberg Depression Rating Scale; Zung-SDS, Zung Self-rating Depression Scale; CES-D, Center for Epidemiologic Studies Depression Scale; MINI, Mini International Neuropsychiatric Interview; ICD, International Classification of Diseases; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; GHQ, General Health Questionnaire.

[1] All estimates were calculated using the method of DerSimonian and Laid and the random effects model. See Supplementary Figures 1a, b, c and d and Figure 3a for the individual forest plots.

[2] Meta regression was conducted for this analysis: age: -0.03 (-0.08 to 0.01); gender: -0.004 (-0.02 to 0.01); PASI 0.04 (-0.008 to 0.09); NOS score: -0.09 (-0.28 to 0.10).

Odds of depressive symptoms

Of the 26 controlled studies, 42% used questionnaires. Nine out of eleven questionnaire-based studies reported mean values for the used questionnaires, showing that psoriasis patients were significantly more likely to show depressive symptoms compared with healthy

Table 2. Depression outcomes in psoriasis patients compared with healthy controls.

Questionnaires reporting mean values for depressive symptoms	**Number of studies**	**Pooled SMD and 95% CI [1]**
BDI	4	0.86 (0.36-1.35)
HADS	2	0.48 (0.19-0.77)
Hamilton DS	2	2.08 (0.83-3.34)
MADRS	1	-0.06 (-0.45-0.33)
All questionnaires [2]	9	1.16 (0.67-1.66)
Questionnaires reporting proportion of patients with depressive symptoms	**Number of studies**	**Pooled OR and 95% CI [1]**
HADS, % patients with a score ≥ 8	3	8.00 (1.42-45.17)
MADRS, % patients with a score >10	1	2.13 (0.76-3.27)
All questionnaires	4	6.06 (0.99-37.04)
Clinical outcome measures for depression	**Number of studies**	**Pooled OR and 95% CI [1]**
Antidepressant use, % psoriasis compared with controls	2	4.24 (1.53-11.76)
ICD, % psoriasis compared with controls	5	1.57 (1.40-1.76)
General health	**Number of studies**	**Pooled OR and 95% CI [1]**
GHQ, % patients with a score ≥ 3	1	0.90 (-0.10-1.79)

Abbreviations: BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; Hamilton DS, Hamilton Depression Score; MADRS, Montgomery Asberg Depression Rating Scale; GHQ, General Health Questionnaire; ICD, International Classification of Diseases; SMD, Standardized Mean Difference; OR, Odds Ratio.

[1] Estimates were calculated using the method of DerSimonian and Laid and the random effects model. See Supplementary Figures 2a, b, and c and Figure 3b for the individual forest plots.

[2] Meta regression was conducted for this analysis: age: -0.03 (-0.16 to 0.09); gender: 0.0008 (-0.29 to 2.67); PASI -0.72 (-1.39 to (-0.05)); NOS score -0.51 (-0.88 to (-0.14)).

controls (SMD 1.16; 95% CI 0.67-1.66; Table 2). In the forest plot (Figure 3b), the two groups of individuals with depression confirmed by a psychiatrist from the study by Turel Ermertcan showed the highest SMDs for depression (3.39, 95% CI 2.50-4.29 and 4.00, 95% CI 2.99-5.01).[41] The high heterogeneity, with an I^2 of 91%, decreased to 82% when excluding these two groups, but remained high. The majority of the remaining studies had significant SMDs ranging from 0.47 to 1.97.

According to the HADS and MADRS, psoriasis patients were six times more likely to show depressive symptoms compared with their healthy peers (OR 6.06, 95% CI 0.99-37.04; Figure 2b), however this result was not significant (p=0.051). The difference between psoriasis and controls was greatest when using the HADS questionnaire (n=3 studies) with a pooled OR of 8.00 (95% CI 1.42-45.17). Only one study used the MADRS questionnaire and its primary objective was to compare depressive symptoms in migraine patients with those in psoriasis patients and healthy controls.[42] In this study, depressive symptoms were not significantly

Figure 2. Pooled prevalence and odds ratio of depression according to assessment method.

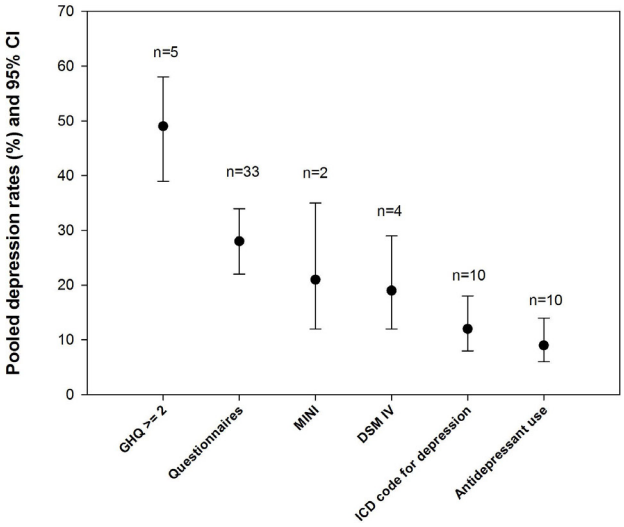

Figure 2a. Prevalence of depressive symptoms and clinical depression in psoriasis.
Abbreviations: CI, Confidence Interval; GHQ, General Health Questionnaire; MINI, Mini International Neuropsychiatric Interview; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; ICD, International Classification of Diseases. Questionnaires include Hospital Anxiety and Depression Scale, Hamilton Depression Score, Beck Depression Inventory, Zung Self-rating Depression Scale and Center for Epidemiologic Studies Depression Scale (see Table 1).
"n" represents the number of studies per assessment method.

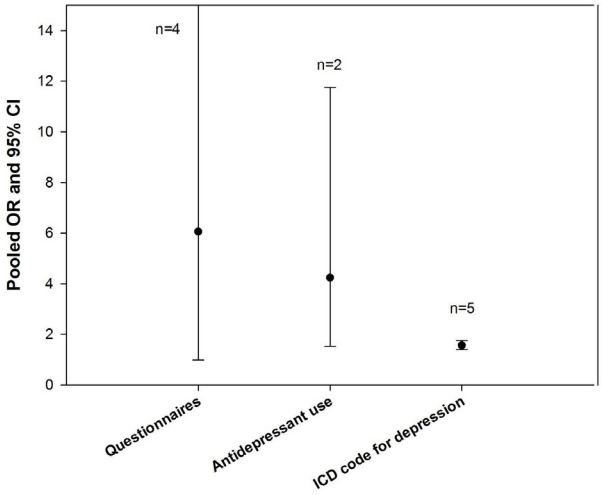

Figure 2b. Odds ratio for depressive symptoms and clinical depression in psoriasis patients compared with healthy controls.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval; International Classification of Diseases. Questionnaires include Hospital Anxiety and Depression Scale and Montgomery Asberg Depression Rating Scale (see Table 2).
"n" represents the number of studies per assessment method.

elevated in the psoriasis group compared with the controls (OR 2.13, 95% CI 0.76-3.27) (Table 2).

Odds of clinical depression

The likelihood of using antidepressant drugs (n=2 studies) was four times higher among psoriasis patients (OR 4.24, 95% CI 1.53-11.76), while five studies that used ICD-codes to assess depression, yielded an OR for depression of 1.57 (95% CI 1.40-1.76). Figure 2b illustrates that the observed OR for depressive symptoms and clinical depression decreases according to the following order, depending on the used instrument: from questionnaires, to antidepressant use, to ICD-codes.

Meta-regression and subgroup analyses

Heterogeneity between the studies was considerable (I^2>90%) when pooling the mean scores of the questionnaires and proportions of patients with depressive symptoms and clinical depression. Meta-regression and subgroup analyses were conducted to determine the possible sources of heterogeneity.

The rate for depressive symptoms in psoriasis patients according to questionnaires was independent of mean age, gender, PASI and the quality assessment score (Table 1). No subgroup analysis was conducted based on study location, because this was already reflected in the analyses including studies using ICD-codes and antidepressants, which were all population-based, versus the studies using questionnaires, which were mostly based in tertiary centres.

The SMD for studies measuring depressive symptoms in psoriasis compared with controls was neither dependent on the weighted mean age, nor on gender distribution in the studies. An increase in PASI and NOS score led to a decrease of the SMD for depressive symptoms (Table 2). We therefore conducted subgroup analyses for these covariates. Twelve groups were included in the subgroup analysis of which the PASI was missing for six groups and was below 10 for the rest; there was no significant difference in SMD between the two groups. The six groups with a NOS score below 5 (of which four groups were from the same study by Turel Ermertcan et al.) had a higher SMD compared with the groups with an NOS score above 5 (respectively 1.91, 95% CI 1.30-2.52 and 0.47, 95% CI -0.09-1.03).

There is possibly some degree of overlap of participants in studies from two research groups. The studies by Gupta and Gupta, which were the only to report mean CRSD, were pooled alone and not included in the combined analysis.[43-48] The studies published by the research group based in Manchester used the HADS, reporting means or proportion of depressive symptoms.[13,14,49-55] The authors could not exclude some degree of overlap of participants between the studies (C.E.M. Griffiths, personal communication). Including all four studies reporting proportions in the combined analysis, resulted in a pooled proportion of depressive symptoms of 28%[13,14,51,55] and only including the largest study,[14] yielded a

Figure 3. Forest plots of studies using questionnaires reporting proportions or mean values for depressive symptoms.

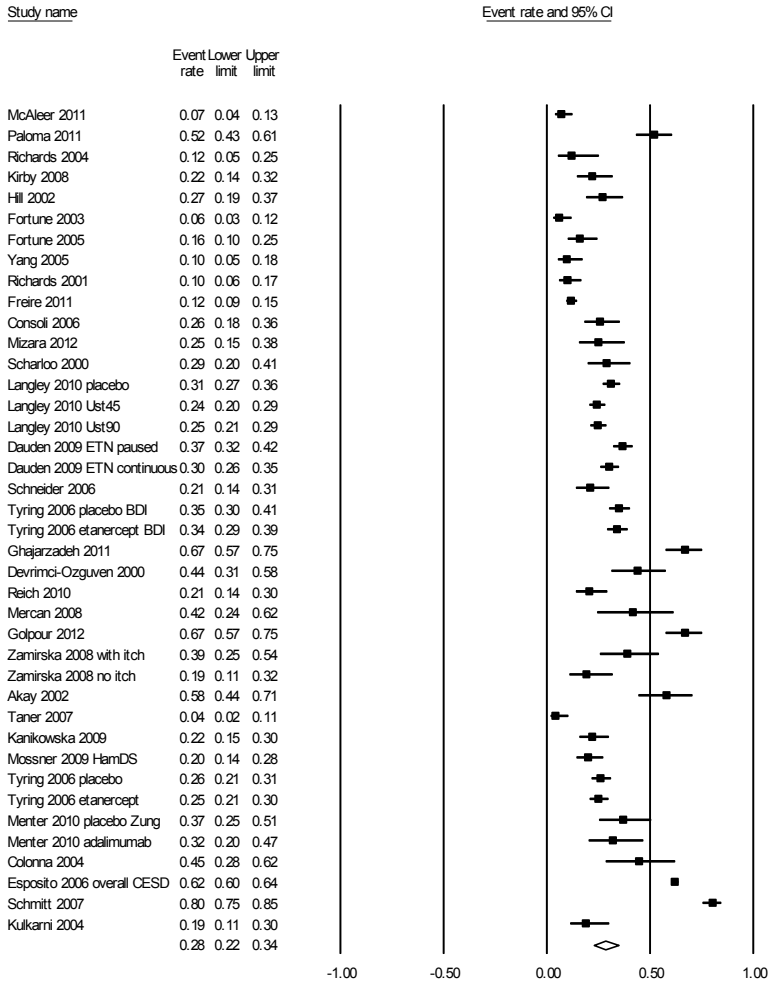

Figure 3a. Proportion of depressive symptoms in psoriasis patients.
The mentioned studies used the Hospital Anxiety and Depression Scale, Hamilton Depression Score, Beck Depression Inventory, Zung Self-rating Depression Scale and Center for Epidemiologic Studies Depression Scale to measure depressive symptoms.

similar proportion of 30% (95% CI 24-37%), suggesting little impact of the possible overlap of participants.

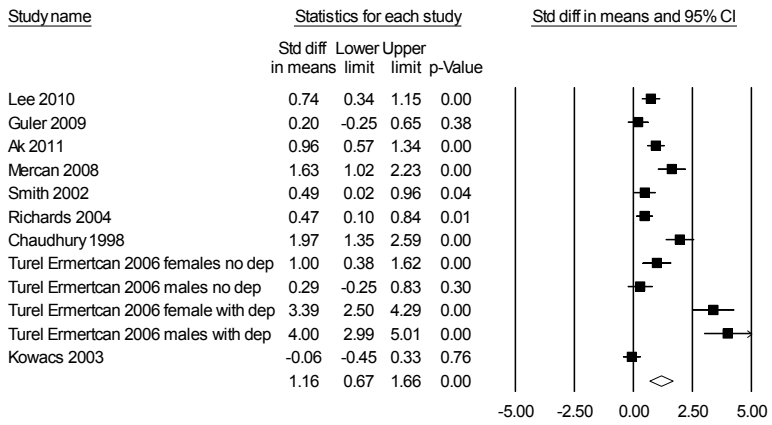

Figure 3b. Standardized mean difference for depressive symptoms in psoriasis patients compared with healthy controls.

The mentioned studies used the Beck Depression Inventory, Hamilton Depression Score, Hospital Anxiety and Depression Scale and Montgomery Asberg Depression Rating Scale to measure depressive symptoms.

Publication bias

In the pooled analysis of depressive symptoms in psoriasis (33 studies), there was no publication bias based on the funnel plot, Eggers regression or the trim and fill method (See Supplementary Figure 1b).

As to the analyses for questionnaire means in controlled studies, there was publication bias according to the Eggers regression (9.67, 95% CI 4.15-15.20, p=0.004). However only one study was trimmed according to the trim and fill method, yielding an adjusted SMD of 1.37 (95% CI 0.71-2.03), slightly higher than the unadjusted SMD of 1.16 (95% CI 0.67-1.66) and still significantly elevated for the psoriasis group.

DISCUSSION

The present study shows that psoriasis patients are at least one and a half times more likely to manifest signs of clinical depression than their healthy peers. More than one quarter of psoriasis patients show symptoms of depression and approximately one tenth have signs of clinical depression.

These results were independent of the mean age and the gender distribution. The majority of the studies included patients with plaque psoriasis, and studies including only patients with PsA did not seem to have a higher prevalence of depression.

Eight of the studies were population-based and most of them investigated ICD diagnoses for depression,[5,7,34,36,37,40] showing a prevalence of depression varying from 2 to 10%. These might

better reflect depression in the general psoriasis population compared with most of the other studies conducted in tertiary centres using questionnaires, which only assess depressive symptoms and are likely to overestimate the prevalence of depression.[56] Questionnaires are case-finding instruments and may capture somatic symptoms that are not necessarily indicative of clinical depression.

Patients from the studies investigating antidepressant use, represented the entire span of the psoriasis population: patients from psoriasis associations, patients recruited through internet advertisements, inpatients, outpatients and patients registered in large pharmacy and healthcare databases. The pooled proportion of 9% therefore reflects antidepressant use in the broad psoriasis population, which is in line with the depression rates obtained using ICD-codes.

The pooled analysis of studies using the DSM-IV criteria, the gold standard for the diagnosis of depression, yielded high rates for depression. This could have several explanations: it could be due to the low number of available studies (n=4), the tertiary study setting, the highly selective psoriasis population with moderate to severe disease, or the fact that patients with an elevated questionnaire score were subjected to the DSM-IV criteria.[57-60] Another explanation could be the discrepancies between ICD-10 and DSM-IV related to mental disorders.[61] A recent study showed that the ICD-10 was more sensitive to the mild range of depressive symptoms, while the DSM-IV was more sensitive to the moderate to severe range.[62] In the case of attention deficit-/hyperactivity disorder, the prevalence was more than twice as high according to the DSM-IV criteria.[63] Finally, diagnosing patients using the DSM-IV is time consuming and necessitates a psychiatrist or psychologist, possibly explaining why it is not commonly used in a dermatology setting.

Chronic diseases affect the psychological health of patients, and higher levels of psychosocial disability decrease treatment adherence, resulting in treatment dissatisfaction which may also contribute to depression.[8] Depression has been proven to be a common co-morbidity in patients with chronic diseases such as diabetes, rheumatoid arthritis and heart failure with comparable differences in proportions of depressive symptoms and clinical depression.[64-68] It is challenging to conduct a head to head comparison of the prevalence of depression in patients with different chronic conditions because the studies do not always use the same case definition for depression.

We observe that the differences between the instruments in the proportion of subjects assessed as having a depression were much larger in patients with psoriasis. In the controls there was only a modest difference between the proportion of subjects with depressive symptoms according to the HADS score, and clinical depression according to antidepressant use and ICD-code. A possible explanation could be that the psychometric properties of

questionnaires assessing depressive symptoms have been extensively studied, but not in a population with skin diseases. Therefore, psoriasis related symptoms and complaints may be falsely detected by the questionnaires as being depressive symptoms, resulting in differential misclassification and an overestimation of the prevalence of depressive symptoms in psoriasis patients compared with healthy controls. Furthermore, studies using questionnaires predominantly include psoriasis patients from tertiary centers, with severe disease, who may therefore also have more symptoms of depression.

A study by Schmitt and Ford demonstrated a high convergent validity of the CES-D in psoriasis patients, hypothesizing that HRQoL impairment leads to depressive symptoms. In this study a significant proportion of the variance of depressive symptoms was explained by HRQoL.[9] The fact that QoL indexes correlate with measures of psychiatric symptoms[69] was also confirmed in a cluster analysis by Sampogna et al. in psoriasis patients, showing two distinct groups: clinical severity measurements and another cluster formed by quality of life (QoL) and psychological indexes.[70]

Strengths and limitations

This is to date the largest study to systematically summarize the available data on depression in psoriasis. The broad inclusion criteria for depression instruments enables the study of these different tools and their effect on the prevalence and odds of depression. We chose to focus on depression as outcome. Nevertheless, antidepressant use may not be necessarily indicative of underlying depressive disease as the frequency of off-label use in medically ill patients is quite high, moreover antidepressant use could reflect other mental disorders as well. Several studies could not be included because they did not use one of the validated instruments, possibly leading to reporting bias. However, there did not seem to be considerable publication bias, neither for controlled, nor for uncontrolled studies.

There were a large number of uncontrolled studies in this meta-analysis, including a very specific psoriasis population, possibly resulting in selection bias. Furthermore, the questionnaires might have been administered in a specific way to individuals from these studies, leading to information bias.

Most of the included questionnaires were primarily designed to assess the intensity of depression in psychiatrically diagnosed patients (BDI, Hamilton RS) and were subsequently used to detect depressive symptoms in normal populations. These instruments were validated for non-dermatological diseases and no validation studies have been conducted in psoriasis. The HADS is the most commonly used depression screening instrument in psoriasis due to its feasibility, however a review noted that the BDI, CES-D and the Zung-SDS were among the most thoroughly evaluated instruments in primary care.[71] Only four studies used the DSM-IV criteria, and therefore no distinction could be made in the studies between patients with major or minor depression and dysthymia. Only two studies used a questionnaire fol-

lowed by a clinical interview,[59,60] in accordance with the case-finding approach to diagnosing depression.[56]

The appraisal of the eligible studies showed that only a small percentage scored high points for the NOS score. One point was allocated to the studies with a healthy control group, representative of the average community. Therefore, more than 70% of all studies, without a control group or with a selected control group (hospital controls or controls with other dermatological conditions), did not get a point for this item.

Determining the prevalence of depression was not always the primary objective of the studies included; several studies were primarily interested in comparing depression in psoriasis patients with depression in patients with other skin conditions, whereas others focussed on the effect of psoriasis therapy on depressive symptoms.

Data from different studies was pooled despite the high degree of heterogeneity, which is partly a result of the varying prevalence and odds of depression according to studies. This, together with the fact that very few studies were available for some of the outcomes, could also explain the large confidence intervals. Meta-regression and subgroup analyses were conducted to attempt to explain this heterogeneity.

The results of this study, particularly those of the questionnaires, may not entirely be extrapolated to the general psoriasis population. The prevalence of depressive symptoms was mainly determined in convenient samples of psoriasis patients from tertiary care populations. On the other hand, the prevalence obtained from population-based studies could be generalized to the psoriasis population.

CONCLUSION

In addition to the impact on HRQoL, psoriasis patients manifest more signs of depression than healthy controls. The prevalence is highest for depressive symptoms in patients consulting tertiary centres. This could be due to misclassification of psoriasis-related symptoms as being depressive symptoms when using questionnaires. Approximately 10% of psoriasis patients from the general population suffer from clinical depression.

Although we did not identify clear risk factors associated with psychological distress, we recommend administering a HRQoL tool or a depression questionnaire to patients that seem to be severely affected by their psoriasis. In patients suspected of depression, physicians should actively ask for signs of clinical depression, as elaborated in the DSM-IV classification, and if necessary refer them to a psychiatrist.

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Supplementary Table 1. Digital search strategy.
(last update performed on 20th of Augustus 2012)

Database	Search string
Embase	(depression/exp OR 'antidepressant agent'/exp OR (depress* OR antidepress*):ab,ti) AND (psoriasis/exp OR (psoria*):ab,ti)
Medline via OvidSP	(exp depressive disorder/ OR depression/ OR exp antidepressive agents/ OR (depress* OR antidepress*).ab,ti.) AND (exp psoriasis/ OR (psoria*).ab,ti.)
PsycInfo	(exp "depression (emotion)"/ OR exp major depression/ OR atypical depression/ OR "Long-term Depression (Neuronal)"/ OR exp antidepressant drugs/ OR (depress* OR antidepress*).ab,ti.) AND ((psoria*).ab,ti.)
Cochrane central	(exp depressive disorder/ OR depression/ OR exp antidepressive agents/ OR (depress* OR antidepress*):ab,ti) AND (exp psoriasis/ OR (psoria*):ab,ti)
PubMed	(Depress*[tiab] OR antidepress*[tiab]) AND psoria*[tiab] NOT medline[sb]

Supplementary Table 2. Characteristics of studies included in the meta-analysis.

Author, year	Country	Center	Psoriasis						Healthy controls			Diagnosis of depression	NOS score
			N	% Male	Mean age	Diagnosis of psoriasis	Type	Mean PASI	N	% Male	Mean age		
Ak 2011 *[72]	-	dermatology clinic	61	100	23.7	dermatologist	-	9.2	55	100	26.1	BDI †	6
Akay 2002 *[73]	Turkey	tertiary	50	60	39.7	dermatologist	plaque, no PsA	7.6	40	65	42.9	BDI ‡	6
Alpsoy 1998 moclobemide[74]	Turkey	-	22	36.4	44.5	dermatologist	plaque	3.6				BDI, Hamilton DS ‡	5
Alpsoy 1998 placebo[74]	Turkey	-	20	35	37.3	dermatologist	plaque	4.4				BDI, Hamilton DS ‡	5
Bashir 2010[75]	Pakistan	outpatient (military hospital)	8	100	-	dermatologist	-	-				GHQ-12, ICD-10 ‡	5
Bharath 1997[76]	India	outpatient	30	-	-	-	-	-				GHQ-12, ICD-9	3
Biljan 2009[57]	Croatia	tertiary	70	51.4	51	dermatologist	-	-				DSM IV	5
Calikoglu 2001[77]	Turkey	-	17	35.3	36.6	-	plaque	-				BDI	1
Campolmi 2012[78]	-	hospital clinic	77	35.1	-	-	-	13.6				Hamilton DS	2
Cauli 2011[79]	10 countries	rheumatology department, multicentre	319 **	58.3	51	rheumatologist	PsA	2.8				HADS	3
Chan 2009 any depressive disorder[58]	China	dermatology clinic	58	0	-	dermatologist	plaque 98.7%, pustular 0.9%, erythrodermic 0.5%, PsA 11%	14.0				Hamilton DS, BDI, DSM IV	6
Chan 2009 no psychiatric diagnosis[58]	China	dermatology clinic	145	0	-	dermatologist	plaque 98.7%, pustular 0.9%, erythrodermic 0.5%, PsA 11%	5.5				Hamilton DS, BDI, DSM IV	6
Chan 2009 overall DSM[58]	China	dermatology clinic	221	49.8	45.8	dermatologist	plaque 98.7%, pustular 0.9%, erythrodermic 0.5%, PsA 11%	7.9				Hamilton DS, BDI, DSM IV	6
Chaudhury 1998 *[80]	-	inpatient	30	93.3	34.1	inpatients	-	-	30	93.3	33.9	Hamilton DS (controls free of psychiatric disorders)	3

Supplementary Table 2. (continued)

Author, year	Country	Center	Psoriasis						Healthy controls			Diagnosis of depression	NOS score
			N	% Male	Mean age	Diagnosis of psoriasis	Type	Mean PASI	N	% Male	Mean age		
Chern 2011 conventional[81]	Taiwan	tertiary	36	91.7	41.9	dermatologist	plaque	18.9				HADS	4
Chern 2011 goeckerman[81]	Taiwan	tertiary	48	68.8	39.5	dermatologist	plaque	27.1				HADS	4
Chromej 2011[82]	Slovakia	outpatient	302	52	45.2	dermatologist	-	-				medical records, patient history, medical exam	2
Colonna 2004[83]	-	inpatient or outpatient	30	0	-	dermatologist	-	-				Zung †	4
Consoli 2006[84]	France	article in local press	93	51.6	47.9	dermatologist	-	7.1				MINI, HADS	5
Crown 2004 *[39]	USA	Database US Marketscan	2489	51.1	50.4	ICD-9-CM 696.1	-	-	7467	49.3	50.5	ICD	5
Dauden 2009 ETN continuous[85]	multicenter Europe	-	352	71.6	44.8	dermatologist	plaque	21.9				HADS	2
Dauden 2009 ETN paused[85]	multicenter Europe	-	359	71.6	45.2	dermatologist	plaque	22.8				HADS	2
Davidsson 2005[86]	nordic countries	pso association, inpatient, outpatient	6451	-	-	dermatologist	-	-				antidepressant use	5
Devrimci-Ozguven 2000 *[87]	Turkey	tertiary, outpatient	50	72	35.4	dermatologist	-	1.8	50	-	matched	BDI †	7
Dowlatshahi 2011 *[35]	The Netherlands	Pharmo database	25691	48.6	42.0	antipsoriatic medication and hospital diagnoses (ICD)	-	-	128573	48.3	33.00	antidepressant use	5
Esposito 2006 female[12]	Italy	postal survey to pat from pso association	863	0	46.0	-	plaque	-				CES-D	3

Supplementary Table 2. (continued)

Author, year	Country	Center	Psoriasis						Healthy controls			Diagnosis of depression	NOS score
			N	% Male	Mean age	Diagnosis of psoriasis	Type	Mean PASI	N	% Male	Mean age		
Esposito 2006 male[12]	Italy	postal survey to pat from pso association	1528	100	49.5	-	plaque	-				CES-D	3
Esposito 2006 overall[12]	Italy	postal survey to pat from pso association	2391	63.9	48.2	-	plaque	-				CES-D	3
Fortune 2002[49]	UK	dermatology clinic	225	52	43.3	dermatologist	PsA not excluded	11.9				HADS	5
Fortune 2002 group1[52]	UK	psoriasis clinic	40	30	42.7	dermatologist	plaque	10.5				HADS	5
Fortune 2002 group2[52]	UK	psoriasis clinic	53	34	43.1	dermatologist	plaque	9.2				HADS	5
Fortune 2002 group3[52]	UK	psoriasis clinic	116	42.2	42.8	dermatologist	plaque	9.9				HADS	5
Fortune 2003[53]	UK and Ireland	dermatology department	112	10.7	43.3	dermatologist	plaque	11.5				HADS ‡	6
Fortune 2003 *[13]	UK	dermatology clinic	60	55	41.4	dermatologist	-	9.8	60	-	matched	HADS	6
Fortune 2005[51]	-	outpatient speciality psoriasis clinic	300	54	43.5	dermatologist	-	9.0				HADS	4
Fortune 2005[50]	UK	psoriasis speciality clinic	95	40	42	dermatologist	plaque	12.3				HADS	5
Freire 2011[88]	Spain	rheumatology clinic	495 **	57.2	50.4	rheumatologist	PsA	-				HADS, antidepressant use	3
Gerdes 2008 *[89]	Germany	academic and non-academic hospital	1131	-	49.7	dermatologist	plaque 87.5%, guttate 5.7%, pustular 4.7%, erythroderm 1.2%, palmoplantar 3.6, inversa 0.7%	26	7099	-	NM	antidepressant use	5

Supplementary Table 2. (continued)

Author, year	Country	Center	Psoriasis						Healthy controls			Diagnosis of depression	NOS score
			N	% Male	Mean age	Diagnosis of psoriasis	Type	Mean PASI	N	% Male	Mean age		
Ghajarzadeh 2011[90]	Razi hospital	outpatient	100	60	36.2	-	plaque 88%, guttate 9%, nail involvment 3%, PsA 18%	-				BDI	1
Gniadecki 2011 BIW[91]	-	multicentre	379 **	64.1	46.1	dermatologist, PsA in 90% of cases diagnosed by rheumatologist	plaque and PsA combined	-				HADS	4
Gniadecki 2011 QQW[91]	-	multicentre	373 **	61.7	46.9	dermatologist, PsA in 90% of cases diagnosed by rheumatologist	plaque and PsA combined	-				HADS	4
Golpour 2012[59]	Iran	dermatology department	100	44	34.3	dermatologist and biopsy confirmed by pathologist	plaque 95%, guttate 3%, inverse 1%, pustular 1%, no PsA	-				BDI, DSM IV	4
Gulec 2009[92]	Turkey	tertiary	105	48.6	33.3	dermatologist	-	7.7	109	48.6	35.4	BDI	4
Guler 2009 *[93]	-	inpatient, outpatient	41	53.7	39.1	dermatologist	-	-	35	42.9	34.9	BDI	6
Gupta 1988[45]	USA	tertiary, inpatient	82	51.2	44.6	dermatology resident/head nurse dermatology	plaque 75.3%, erythrodermic 3.0%, guttate 4.3%, pustular 11%, other 6.4%	-				CRSD	4
Gupta 1989 no nocturnal wakening[44]	Canada	tertiary, inpatient	33	-	44.6	dermatologist	-	-				CRSD	4
Gupta 1989 with nocturnal wakening[44]	Canada	tertiary, inpatient	46	-	49.3	dermatologist	-	-				CRSD	4
Gupta 1993[48]	USA	tertiary, inpatient, outpatient	217	51.2	47.8	dermatologist	-	-				CRSD	4
Gupta 1994[46]	USA	outpatient	77	-	-	dermatologist	-	-				CRSD	4

Supplementary Table 2. (continued)

Author, year	Country	Center	Psoriasis						Healthy controls			Diagnosis of depression	NOS score
			N	% Male	Mean age	Diagnosis of psoriasis	Type	Mean PASI	N	% Male	Mean age		
Gupta 1997 sexually affected[43]	USA	tertiary, inpatient	49	-	46.8	dermatologist	-	-				CRSD	4
Gupta 1997 sexually unaffected[43]	USA	tertiary, inpatient	71	-	46.8	dermatologist	-	-				CRSD	4
Gupta 1998 pso control[47]	USA	tertiary, inpatient	101	-	48.4	dermatologist	-	-				CRSD, BSI	4
Gupta 1998 pso stigmatized[47]	USA	tertiary, inpatient	36	-	43.2	dermatologist	-	-				CRSD, BSI	4
Han 2011 *[40]	USA	PharMetrics Patient centric database	7971	50.5	47.2	ICD-9-CM code 696.1-8 and phototherapy or systemic th	no PsA	-	31884	50.5	47.1	ICD-9-CM, antidepressant use	6
Hardy 1982 *[94]	-	outpatient, one inpatient	11	18.2	40.4	dermatologist	-	-	12	16.7	42.6	BDI	5
Harvima 1996 overall[95]	Finland	tertiary, outpatient, patients from pso association	38	63.2	23 to 69	dermatologist	plaque	6.81				BDI, GHQ-12	4
Harvima 1996 active pso[95]	Finland	tertiary, outpatient, patients from pso association	21	66.7	43.0	dermatologist	plaque					BDI, GHQ-12	4
Harvima 1996 stable pso[95]	Finland	tertiary, outpatient, patients from pso association	17	58.8	49.9	dermatologist	plaque					BDI, GHQ-12	4
Hill 2002[96]	UK	postal survey sent to oupatients and pat from pso association	89	37.1	49.7	-	-	-				HADS	4
Husted 2010 no PsA[97]	-	tertiary	449	57.9	46.6	dermatologist/ rheumatologist	no PsA	-				clinic physicians (standard protocol)	4

Supplementary Table 2. (continued)

Author, year	Country	Center	Psoriasis						Healthy controls			Diagnosis of depression	NOS score
			N	% Male	Mean age	Diagnosis of psoriasis	Type	Mean PASI	N	% Male	Mean age		
Husted 2010 PsA[97]	-	tertiary	611	57.9	50	dermatologist/ rheumatologist	PsA	-				clinic physicians (standard protocol)	4
Kanikowska 2009[98]	-	-	120	-	45	-	plaque	-				BDI	2
Karadag 2010[99]	Turkey	tertiary	10	90	42.3	dermatologist	-	7.5				BDI	2
Karanikas 2009 *[100]	Greece	tertiary, outpatient	24	45.8	51.3	clinicians/ histopathologists	plaque 54.2%; palmoplantar 20.8%; capitis 12.5%; generalized 8.3%; erythrodermic 4.2%	-	24	45.8	43.4	BDI	7
Kilic 2008 *[101]	Turkey	tertiary	105	48.6	35.4	dermatologist	-	7.7	109	48.6	33.3	BDI †	7
Kimball 2011[34]	USA	IMPACT claims database	114512	49.7	46.4	ICD	-	-				ICD	4
Kirby 2008[102]	UK	psoriasis outpatient clinic	83	49.4	42.2	dermatologist	plaque	-				HADS	4
Korsunskaya 2010[103]	-	-	56	-	-	-	local pso	-				HADS	1
Korsunskaya 2010[104]	Russia	-	26	-	-	-	generalized pso	-				HADS	1
Kotrulja 2010 type I pso[105]	Croatia	tertiary	44	56.8	42.0	dermatologist	plaque	-	70		49.7	BDI & GHQ-28	4
Kotrulja 2010 type II pso[105]	Croatia	tertiary	26	96.2	63.1	dermatologist	plaque	-	70		49.7	BDI & GHQ-28	4
Kowacs 2003 *[42]	Brazil	tertiary, outpatient	35	60	43.5	dermatologist	-	-	92	38	39.2	MADRS	5
Kulkarni 2004[106]	Medicare Health Maintenance Organisator	postal survey	63	39.7	72.7	ICD code for psoriasis and top steroids	plaque	-				CES-D	3
Kurd 2010 *[5]	UK	General Practitioner Research Database	149998	47.4	40.2	OXMIS and reading code	-	-	766950	47.8	33	OXMIS and reading code	7
Langley 2010 overall[107]	USA	-	1230	68.3	-	-	-	-				HADS, antidepressant use	2

Supplementary Table 2. (continued)

Author, year	Country	Center	Psoriasis						Healthy controls			Diagnosis of depression	NOS score
			N	% Male	Mean age	Diagnosis of psoriasis	Type	Mean PASI	N	% Male	Mean age		
Langley 2010 placebo[107]	USA	-	410	69	47.0	-	-	20.1				HADS	2
Langley 2010 Ust45[107]	USA	-	409	69.2	45.1	-	-	19.4				HADS	2
Langley 2010 Ust90[107]	USA	-	411	66.7	46.6	-	-	19.4				HADS	2
Lee 2010 *[108]	Korea	tertiary	138	58	43.5	skin biopsy and clinical manifestation	all	9.1	30	50	39.3	BDI	6
Mattoo 2001 *[109]	India	tertiary, outpatient	103	73.8	40.9	dermatologist	-	-	55	63.6	31.6	GHQ-12 (controls free of psychiatric disorders)	7
Maza 2012[110]	France	multicentre, tertiary	142	68.3	48	dermatologist	plaque	18.5				HADS	4
McAleer 2011 all group[111]	Ireland	tertiary	135	68.1	43	dermatologist	plaque, PsA 17%	6.1				HADS	4
McAleer 2011 female[111]	Ireland	tertiary	135	68.1	43	dermatologist	plaque, PsA 17%	6.1				HADS	4
McAleer 2011 male[111]	Ireland	tertiary	135	68.1	43	dermatologist	plaque, PsA 17%	6.1				HADS	4
Mehta 2008[112]	India	outpatient	50	86	38	dermatologist	plaque	-				MINI	4
Menter 2010 adalimumab[113]	-	phase II randomized placebo controlled trial	44	70.5	45.6	-	-	16.7				Zung #	2
Menter 2010 placebo[113]	-	phase II randomized placebo controlled trial	52	65.4	43.3	-	-	16				Zung #	2
Mercan 2008 *[114]	Turkey	tertiary, psycho-dermatology outpatient clinic	24	-	37.3	dermatologist	-	-	33	-	36.1	BDI (controls free of psychiatric disorders)	4

Supplementary Table 2. (continued)

Author, year	Country	Center	Psoriasis						Healthy controls			Diagnosis of depression	NOS score
			N	% Male	Mean age	Diagnosis of psoriasis	Type	Mean PASI	N	% Male	Mean age		
Meyer/Feneron 2009[115]	multicenter France	members of pso association and dermatologists	590	51.4	55.8	GP or specialist	plaque	-				antidepressant use (self report)	4
Mizara 2012 *[116]	UK	tertiary	55	52.7	42.2	dermatologist	PsA 25%	-	53	39.6	31.4	HADS †	7
Mossner 2009[117]	Germany	tertiary	137	-	from 18 to 60	dermatologist	plaque	-				Hamilton DS	3
Mossner 2009[118]	Germany	tertiary, outpatient	135	-	-	dermatologist	plaque, PsA 28%	-				Hamilton DS, antidepressant use	4
Okubo 2011[119]	Japan	tertiary	41	78	44.2	dermatologist	plaque	18.7				GHQ-28	5
O'Leary 2004[120]	UK	outpatients (skin clinic), patients from pso association	141	41.1	45.2	dermatologist (self-report and outpatients)	-	-				HADS	6
Pacan 2003[121]	Poland	inpatient	77	58.4	42.8	dermatologist	plaque	19.3				BDI, ICD	5
Paloma 2011 *[122]	-	-	58	56.9	49.6	-	-	-	58	56.9	49.6	HADS	3
Pearce 2006[123]	USA	-	90	60	50.5	-	plaque	9.8				HADS	2
Reich 2009[124]	-	PHOENIX 2 study	1154	-	18 to 64	-	-	-				HADS	2
Reich 2010[125]	Poland	inpatient and outpatient	102	62.7	45.2	dermatologist	plaque, 23 had PsA in the past	12.5				BDI	4
Richards 2001[14]	UK	psoriasis clinic	115	53	41.5	dermatologist	PsA not excluded	9.1				HADS †	5
Richards 2004[55]	UK	outpatient	43	48.8	50	dermatologist	plaque	-				HADS #	4
Richards 2004 *[54]	-	pso speciality clinic, outpatient, inpatient	58	48.3	44	dermatologist	plaque	-	58	51.7	47	HADS	6
Sampogna 2006 pso<65yrs[6]	Italy	inpatient	792	59.3	-	dermatologist	palmoplantar 7.4%, pustular 2.7%, gutatte 13.7%, plaque 66.5%, other 2.3%, PsA 7.4%	8.3				GHQ-12 †	6

Supplementary Table 2. (continued)

Author, year	Country	Center	Psoriasis						Healthy controls			Diagnosis of depression	NOS score
			N	% Male	Mean age	Diagnosis of psoriasis	Type	Mean PASI	N	% Male	Mean age		
Sampogna 2006 pso≥65yrs[6]	Italy	inpatient	144	59	-	dermatologist	palmoplantar 7.9%, pustular 5.7%, gutatte 7.9%, plaque 64.2%, other 5%, PsA 9.3%	8.7				GHQ-12 †	6
Schaaf 2009[126]	Germany	inpatient	105	58.1	49.9	-	-	-				HADS	3
Scharloo 2000[127]	The Netherlands	tertiary, outpatient	69	55.1	48.3	dermatologist	no PsA	-				HADS †	6
Schmitt 2007[9]	USA	internet advertisements	265	36.6	42.6	Self-report of physicians diagnosis	PsA 21.1%	-				CES-D, antidepressant use (self-report) #	5
Schmitt 2010 *[7]	Germany	administrative outpatient database (GKV Database)	3147	44.7	57.1	ICD code and psoriasis medication	-	-	3147	44.7	57.1	2 times ICD and ATC codes	5
Schneider 2006[128]	Germany	tertiary, inpatient	91	51.6	52.2	dermatologist	plaque	-				HADS	4
Sharma 2001[60]	India	dermatology department	30	60	18 to 60	dermatologist	plaque 66.6%, erythrodermic 13.3%, PsA 3.3%	-				GHQ-H Hindi version, DSM IV	5
Sharma 2011[129]	India	outpatient	162	69.1	44.6	dermatologist	plaque, no PsA	-				Zung	4
Smith 2002 *[130]	UK	PsA: rheumatology outpatient; healthy co: volunteers from a factory	28 **	-	42	rheumatologist	PsA	-	50	46	40	HADS †	6
Taner 2007[131]	Turkey	tertiary, outpatient	95	45.3	n=18 in age grp 18-25, n=59 in age grp 26-39, n=18 in age grp>40	dermatologist	plaque	-				BDI †	4

Supplementary Table 2. (continued)

Author, year	Country	Center	Psoriasis						Healthy controls			Diagnosis of depression	NOS score
			N	% Male	Mean age	Diagnosis of psoriasis	Type	Mean PASI	N	% Male	Mean age		
Tee 2010[132]	Singapore	outpatient	100	-	21 to 60	-	-	-				HADS	2
Tsai 2011 *[36]	Taiwan	national health insurance claims database	51800	61.6	46.4	ICD-9-CM code 696.0 (PsA) or 696.1 other pso	PsA not excluded	-	207200	-	-	ICD-9-CM	6
Turel Ermertcan 2006 females pso with dep *[41]	Turkey	-	20	0	35.9	-	-	6.5	27	0	39.9	Hamilton DS	3
Turel Ermertcan 2006 females pso without dep *[41]	Turkey	-	19	0	34.7	-	-	6.5	27	0	39.9	Hamilton DS	3
Turel Ermertcan 2006 males pso with dep *[41]	Turkey	-	16	100	37.9	-	-	7.3	31	100	41.8	Hamilton DS	3
Turel Ermertcan 2006 males pso without dep *[41]	Turkey	-	23	100	44.9	-	-	9.3	31	100	41.8	Hamilton DS	3
Tyring 2006 etanercept[133]	USA, Canada	multicenter	311	65.3	45.8	dermatologist	-	18.3				BDI, Hamilton DS	3
Tyring 2006 placebo[133]	USA, Canada	multicenter	307	70.4	45.6	dermatologist	-	18.1				BDI, Hamilton DS	3
Williamson 2004 PNSS <16[134]	UK	outpatient rheumotology clinics	-**	-	-	dermatologist	PsA	-				HADS	5
Williamson 2004 PNSS ≥16[134]	UK	outpatient rheumotology clinics	-**	-	-	dermatologist	PsA	-				HADS	5
Yang 2005[135]	Singapore	National Skin Center	93	82.8	42.5	dermatologist	-	10				HADS	5
Zachariae 2008 BDI-13[136]	Denmark	outpatient	40	60	53.8	dermatologist	-	12.9				BDI-13	5

Supplementary Table 2. (continued)

Author, year	Country	Center	Psoriasis						Healthy controls			Diagnosis of depression	NOS score
			N	% Male	Mean age	Diagnosis of psoriasis	Type	Mean PASI	N	% Male	Mean age		
Zamirska 2008 no vulvar itch[137]	Poland	inpatient	52	0	44.4	dermatologist	plaque 83.9%, PsA 16.1%	14.7				BDI	5
Zamirska 2008 with vulvar itch[137]	Poland	inpatient	41	0	46.8	dermatologist	plaque 83.9%, PsA 16.1%	17.9				BDI	5
Zhang 2011 *[37]	USA	administrative claims database	21332	47	52	ICD-9≥ 696.0 or PsA free without 696.1	-	-	21332	47	52	ICD	6

Abbreviations: Pso, Psoriasis; PsA, Psoriatic arthritis; dep, depression; pat, patients; PNSS, psoriasis nail severity score; BDI, Beck's Depression Inventory; HADS, Hospital Anxiety and Depression Scale; Hamilton DS, Hamilton Depression Score; CRSD, Carroll Rating Scale for Depression (CRSD), MADRS, Montgomery Asberg Depression Rating Scale; Zung-SDS, Zung Self-rating Depression Scale; CES-D, Center for Epidemiologic Studies Depression Scale; MINI, Mini International Neuropsychiatric Interview; ICD, International Classification of Diseases; DSMIV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; GHQ, General Health Questionnaire; NOS, Newcastle-Ottawa Scale.

"-" indicates that the outcome was not mentioned.

* Studies with a healthy control group.

** Studies including 100% patients with PsA.

Some studies reported outcomes per subgroups of patients; these subgroups are presented in the table above.

Incident versus prevalent depression:

† indicates that incident depression was measured and that patients with a history of psychiatric diseases (including depression were excluded).

‡ indicates that all patients taking psychotropic medication were excluded.

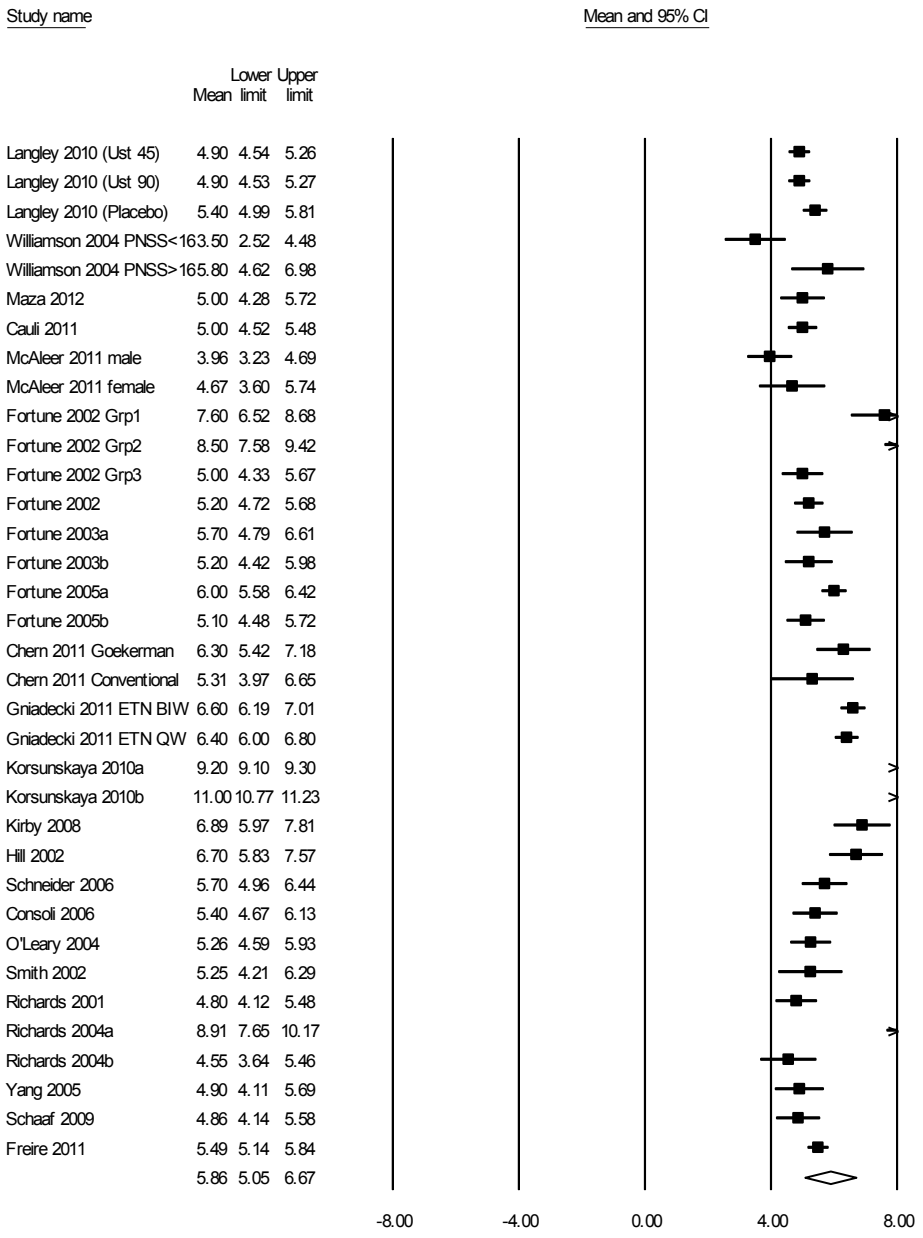
# indicates that the number of patients with a history of psychiatric disease or taking psychotropic medication was known at the beginning of the study, but these patients were not excluded.

All other studies either did not measure incident depression or did not mention it in the methods' section.

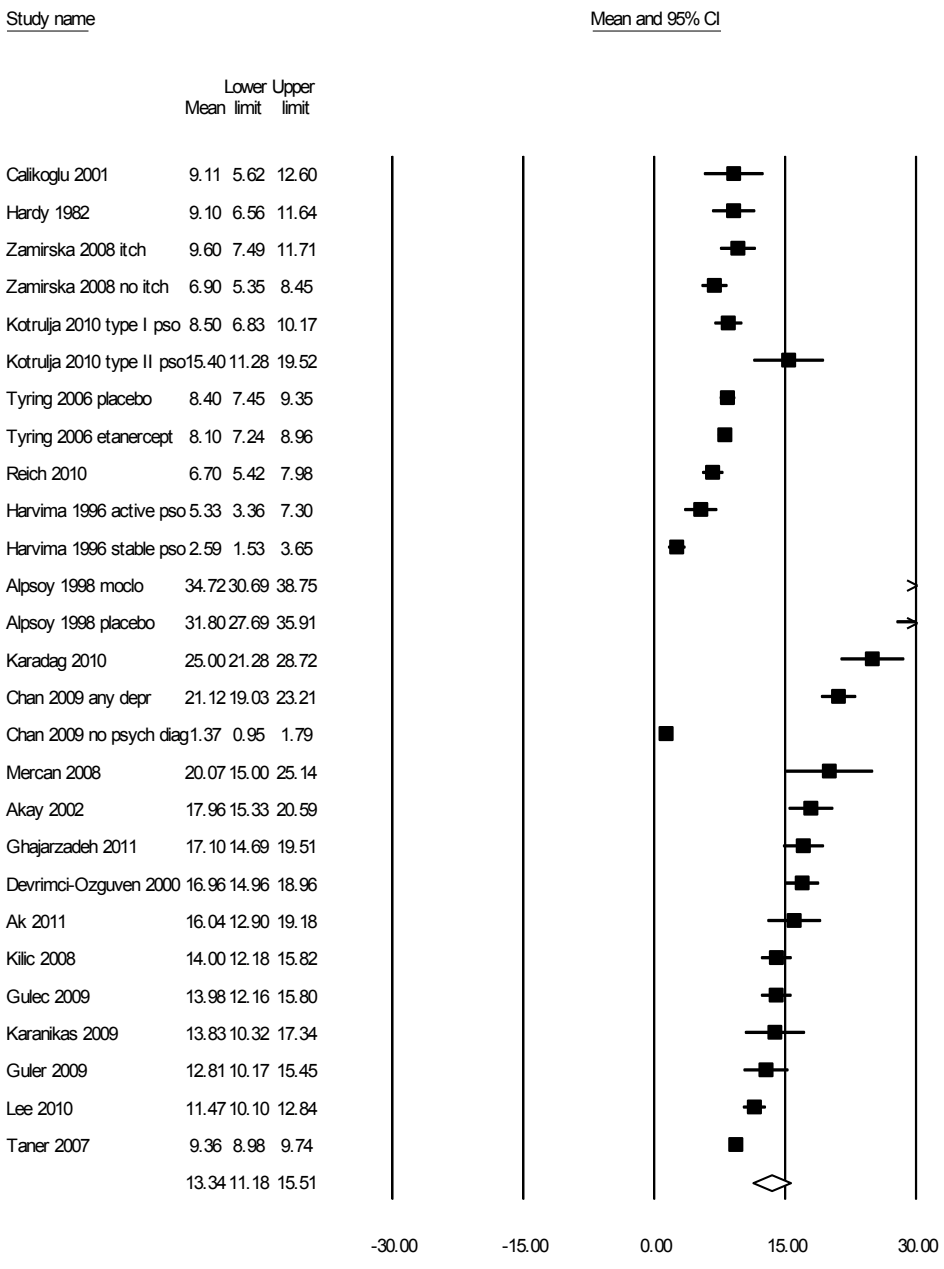
Supplementary Table 3. Depression questionnaires and their cut-off values.

Questionnaire	Description	Cut-off value
Center for Epidemiologic Studies Depression Scale (CES-D)	Twenty items with questions on six dimensions of depression: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite and sleep disturbance. This scale is one of the most widely used instruments in psychiatric epidemiology.	16[19,138]
Hospital Anxiety and Depression Scale (HADS)	A fourteen-item scale with seven items related to anxiety and seven items related to depression.	8[58,59]
Beck Depression Inventory (BDI)	Multiple choice survey with 21 questions on depression symptoms and also physical symptoms during the past 1 to 2 weeks. It is one of the most widely used instruments for measuring the severity of depression.	10[17,18]
Zung Self-rating Depression Scale (Zung-SDS)	Twenty-item self-report questionnaire that rates the affective, psychological and somatic symptoms associated with depression. The scale contains ten positively worded and ten negatively worded questions.	50[25,26]
Hamilton Rating Scale for Depression (Hamilton DS)	A 21-item questionnaire used to rate the severity of depression with questions on mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss and somatic symptoms. The Hamilton DS was not designed to diagnose depression but is very commonly used as a screening scale for depression.	7[22]
Carroll Rating Scale for Depression (CRSD)	This scale was developed as a self-rating instrument for depression, closely matching the items of the Hamilton rating scale. The CRSD assess the same 17 symptoms as the Hamilton RS. It consists of 52 statements which have to be answered by yes or no.	10[23]
Montgomery Asberg Depression Rating Scale (MADRS)	Based on a clinical interview that moves from broad questions to more detailed ones. It contains 10 questions, and each question has 6 possible ratings and covers symptoms of depression such as sadness, sleep difficulties, changes in appetite and concentration and pessimistic and suicidal thoughts. It does not assess somatic symptoms.	10[27]

Supplementary Figures 1. Depression outcomes in psoriasis patients.
a. Questionnaires reporting mean values.
HADS



BDI


Study name
Mean and 95% CI
Mean
Lower limit
Upper limit
Calikoglu 2001 9.11 5.62 12.60
Hardy 1982 9.10 6.56 11.64
Zamirska 2008 itch 9.60 7.49 11.71
Zamirska 2008 no itch 6.90 5.35 8.45
Kotrulja 2010 type I pso 8.50 6.83 10.17
Kotrulja 2010 type II pso 15.40 11.28 19.52
Tyring 2006 placebo 8.40 7.45 9.35
Tyring 2006 etanercept 8.10 7.24 8.96
Reich 2010 6.70 5.42 7.98
Harvima 1996 active pso 5.33 3.36 7.30
Harvima 1996 stable pso 2.59 1.53 3.65
Alpsoy 1998 moclo 34.72 30.69 38.75
Alpsoy 1998 placebo 31.80 27.69 35.91
Karadag 2010 25.00 21.28 28.72
Chan 2009 any depr 21.12 19.03 23.21
Chan 2009 no psych diag 1.37 0.95 1.79
Mercan 2008 20.07 15.00 25.14
Akay 2002 17.96 15.33 20.59
Ghajarzadeh 2011 17.10 14.69 19.51
Devrimci-Ozguven 2000 16.96 14.96 18.96
Ak 2011 16.04 12.90 19.18
Kilic 2008 14.00 12.18 15.82
Gulec 2009 13.98 12.16 15.80
Karanikas 2009 13.83 10.32 17.34
Guler 2009 12.81 10.17 15.45
Lee 2010 11.47 10.10 12.84
Taner 2007 9.36 8.98 9.74
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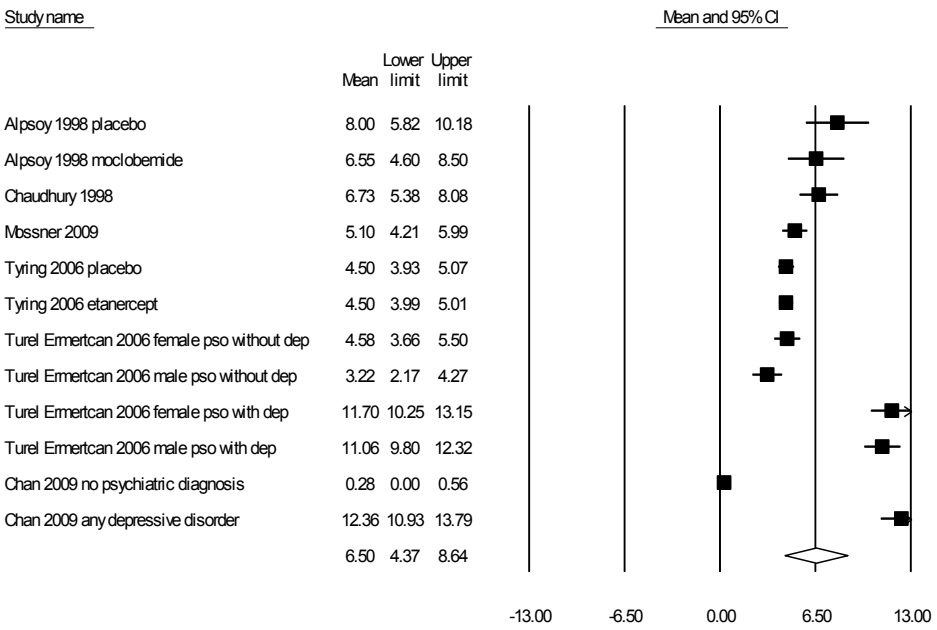
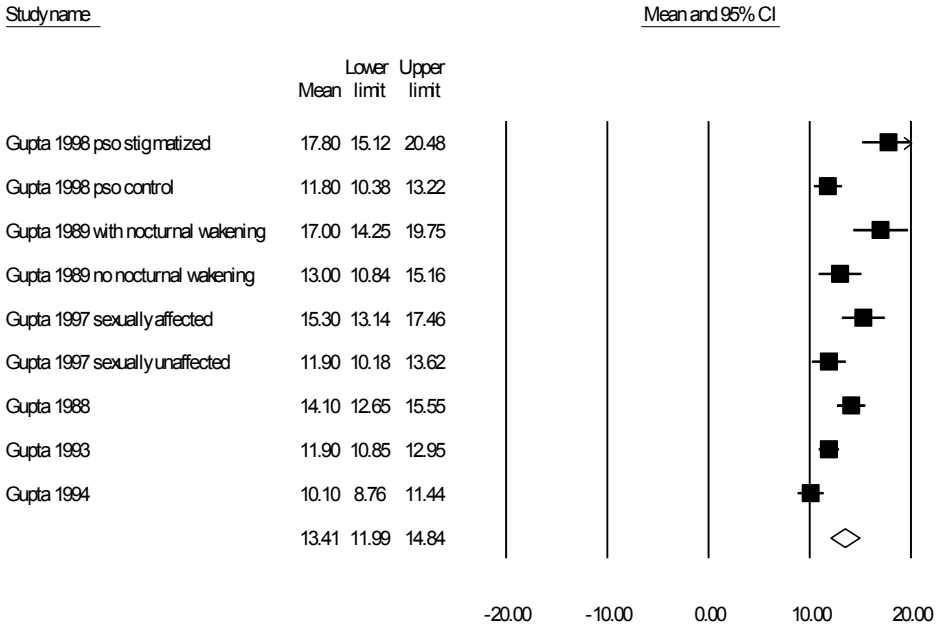
0.00
15.00
30.00

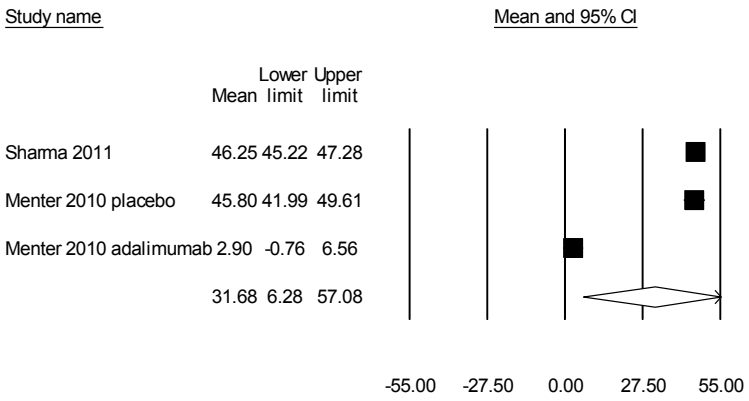
Hamilton DS



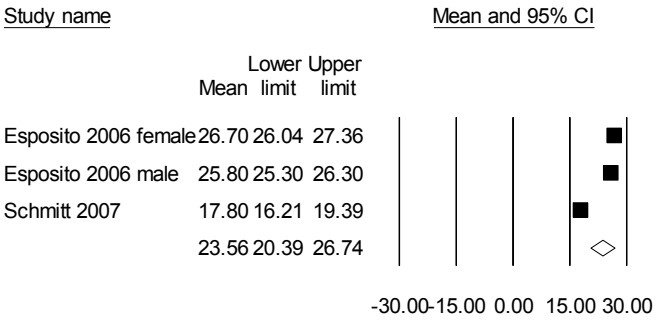
CRSD



Zung-SDS



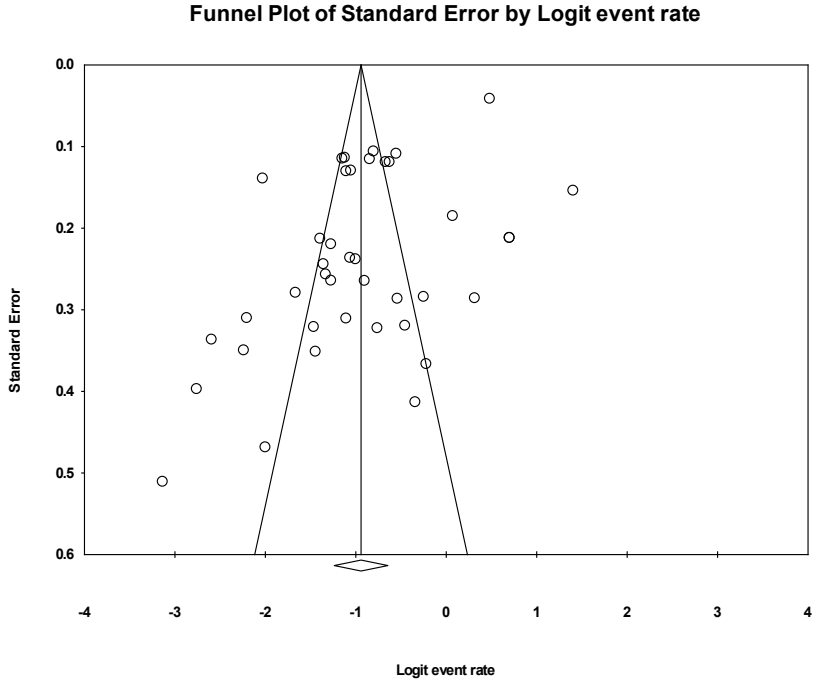
CES-D



b. Questionnaires reporting proportion of patients with depressive symptoms (HADS, BDI, Hamilton DS, Zung-SDS, CES-D).

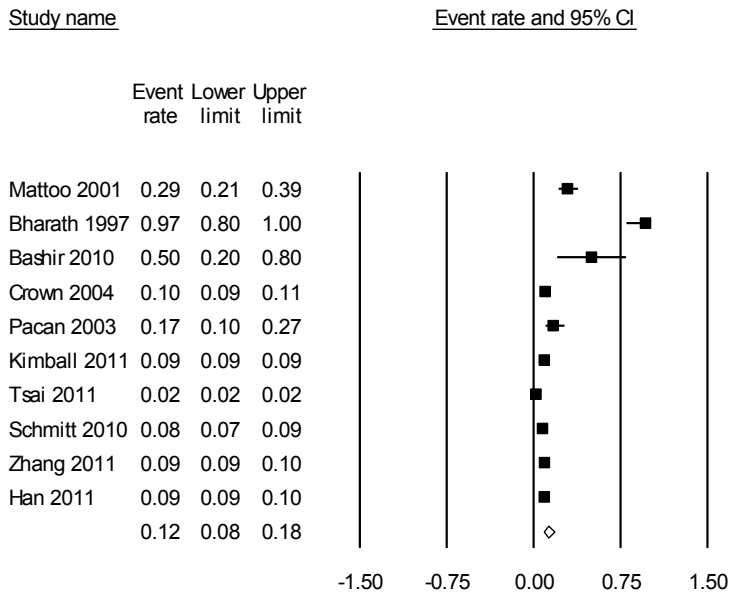
See Figure 3a of manuscript for forest plot.

Publication bias

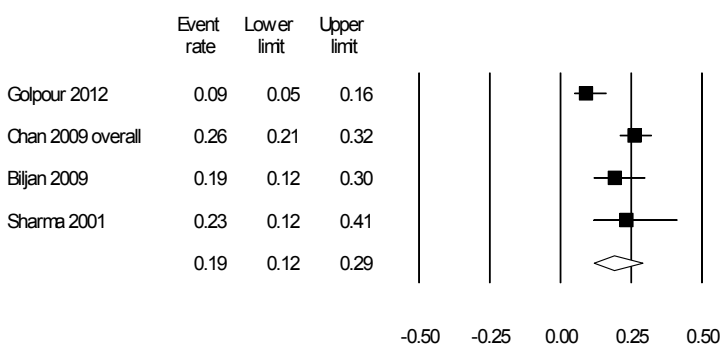


c. Clinical outcome measures for depression.

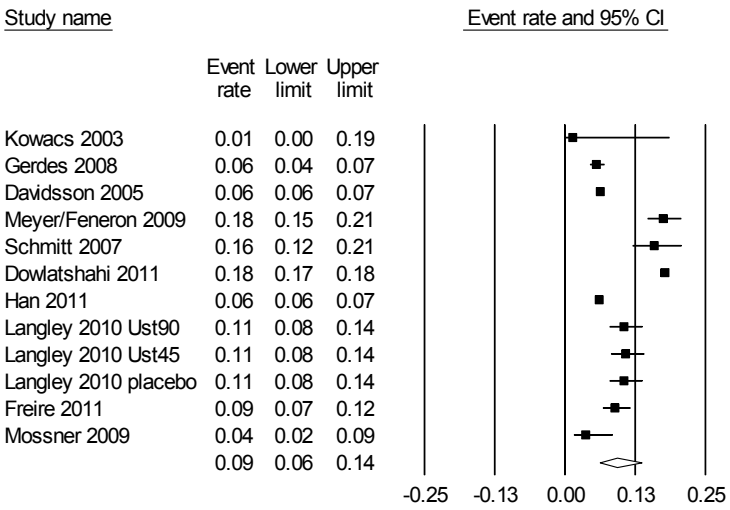
ICD



DSM-IV

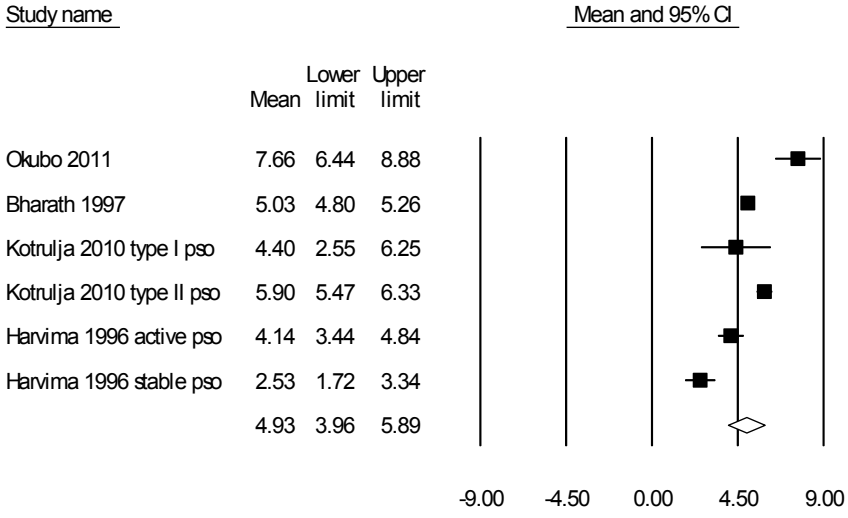


Antidepressant use

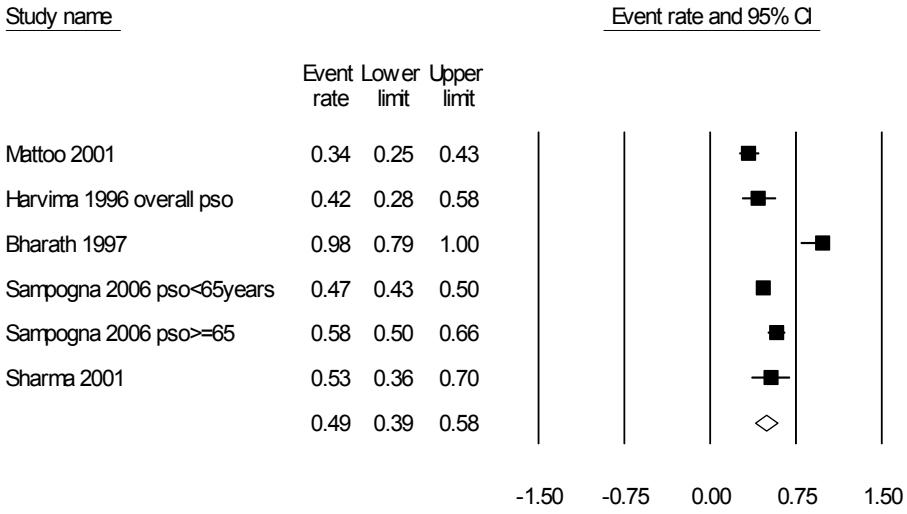


d. General Health

GHQ means



GHQ ≥2

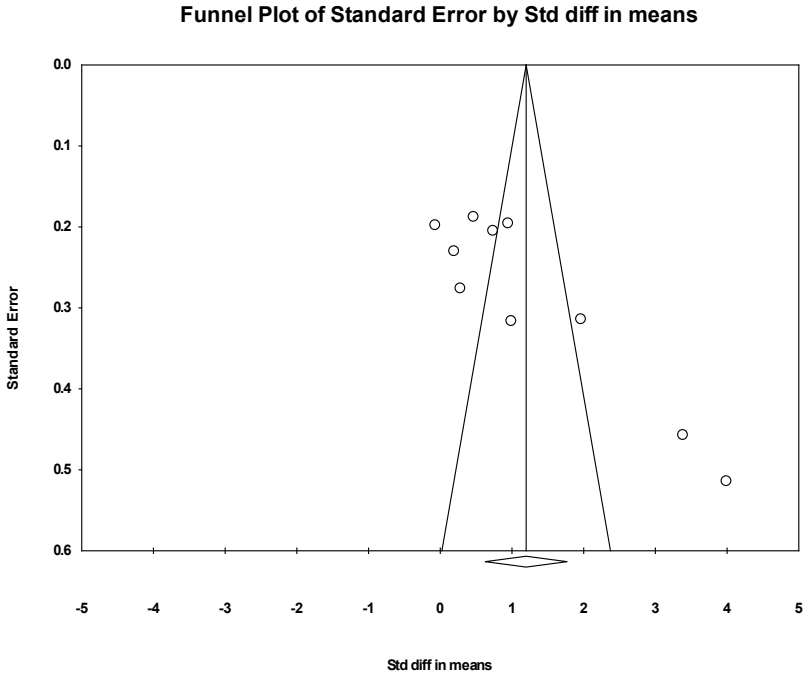


Supplementary Figures 2. Depression outcomes in psoriasis patients compared with healthy controls.

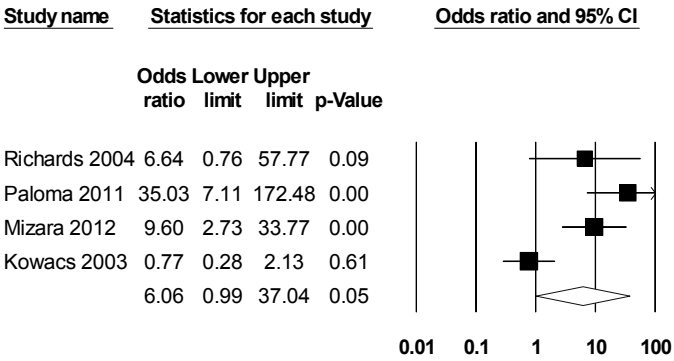
a. Questionnaires reporting mean values for depressive symptoms (BDI, HADS, Hamilton DS, MADRS).

See Figure 3b of manuscript for forest plot.

Publication bias

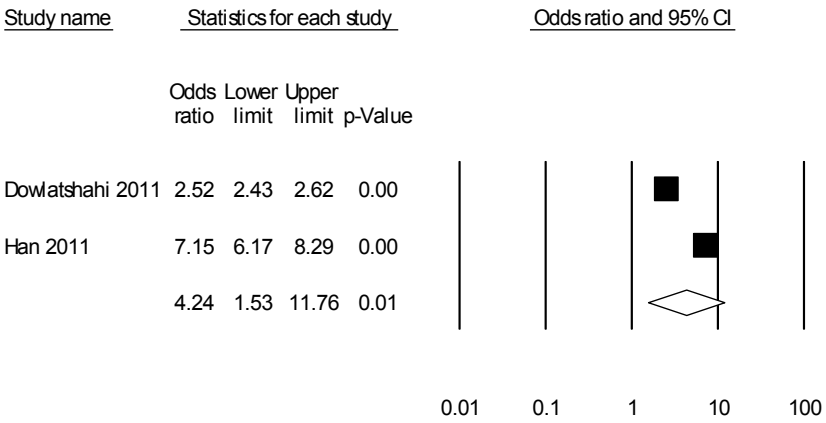


b. Questionnaires reporting proportion of patients with depressive symptoms (HADS and MADRS).

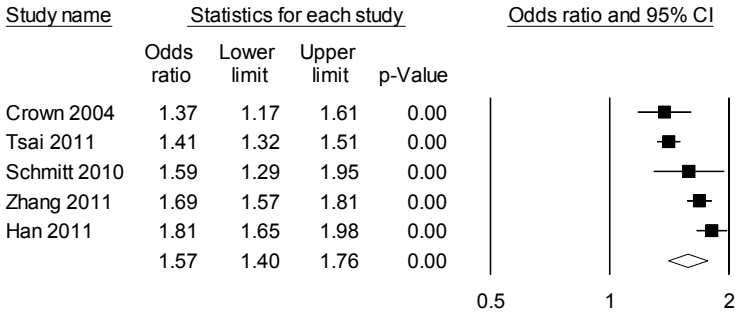


c. Clinical outcome measures for depression.

Antidepressant use



ICD



SUPPLEMENTARY MATERIAL: QUALITY ASSESSMENT SCORE

MODIFIED NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

COHORT or CROSS SECTIONAL STUDIES

Stars indicate the number of points allocated if the item criterion is met. A maximum of 10 points can be allocated to each article.

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the general psoriasis population ❋
   b) somewhat representative of the general psoriasis population ❋
   c) selected group of psoriasis patients: hospital based, tertiary centre, inpatients, outpatients
   d) no description of the derivation of the cohort
2) Selection of the non-exposed cohort
   a) representative of the average community (healthy control, community control) ❋
   b) selected group of controls (hospital controls, other dermatological condition)
   c) no control group or no description of control group
3) Ascertainment of psoriasis or psoriatic arthritis
   a) diagnosed by dermatologist/rheumatologist ❋❋
   b) diagnosis by physician other than dermatologist/rheumatologist (GP) or use of diagnosis-code in database (ICD, OXMIS) ❋
   c) based on self-report
   d) no description of psoriasis case definition
4) Assessment of disease severity
   a) disease severity was assessed with PASI, PGA, BSA SAPASI (self-report) ❋
   b) disease severity was assessed with or using psoriasis treatments (topical vs. systemic) ❋
   c) no disease severity assessed or reported
5) Demonstration that outcome of interest (depression) was not present at start of study
   Were patients with prevalent depression excluded at the start of the study?
   a) yes, only incident depression was measured ❋
   b) no, patients with prevalent depression were not excluded
   c) no description: it was not mentioned whether patients with depression at the start of the study were excluded

Comparability (Confounding)

1) Comparability of psoriasis and healthy controls on the basis of design or analysis
   a) study controls for confounding using a multivariate model ❋
   b) psoriasis patients and healthy controls are matched (for age/gender…) ❋
   c) no controlling for confounding or matching

Outcome

1) Assessment of outcome depression
   a) clinical diagnosis: psychiatrist (DSM IV), psychologist ❋ ❋
   b) diagnosis by GP, ICD code, other healthcare provider, questionnaire ❋
   c) antidepressant use
   d) not mentioned or self-reported by patients
2) Non-response rate
   a) difference between responders and non-responders described ❋
   b) only non-response rate mentioned without further description ❋
   c) no information

Chapter 3.2

Increased antidepressant drug exposure in psoriasis patients: a longitudinal population-based cohort study.

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ABSTRACT

Psoriasis has a major impact on health related quality of life. The present cohort study investigated the use of antidepressant drugs between psoriasis patients and a reference population, using pharmacy and hospitalization data from 1998 to 2008 covering more than 2,5 million Dutch residents. Multivariate Cox regression compared the risk of first antidepressant use and Poisson regression compared the number of episodes of antidepressant use. 25,691 psoriasis cases and 128,573 reference subjects were followed for more than 9 years with an incidence of first antidepressant use of 21 and 9 per 1,000 person years respectively and an adjusted hazard ratio (HR) of 1.55 (95% confidence interval (CI) 1.50-1.61). Within the psoriasis group, the HR of receiving an antidepressant was significantly higher after the first antipsoriatic treatment (HR 1.07, 95% CI 1.02-1.12). Psoriasis patients have a twofold increased antidepressant use, the period beyond antipsoriatic treatment being characterized by a further increase in antidepressant drug dispenses.

INTRODUCTION

In recent years much attention has been drawn towards psychiatric disorders among patients with dermatologic conditions, often referred to as "psychodermatology".[1] Reports of suicidal ideation among patients with skin disease lead to rising concerns.[2,3] In psoriasis, studies have demonstrated a significant impairment of health related quality of life (HRQoL) and a higher likelihood of developing depression.[4] Although the correlation between psoriasis severity and impact on the HRQoL is weak,[5] the chance of having psychiatric comorbidity seems to increase with psoriasis severity.[6] Two previous large healthcare-database studies focussing on major psychiatric disorders confirmed a significant and positive association with psoriasis.[6,7] Remarkably, the practical implications of actual antidepressant drug dispenses have only received limited attention. Two studies investigated drug prescriptions in general, including antidepressants in psoriasis patients, during a restricted time period: one cross-sectional study showed that at the time of hospital admission, psoriasis patients had a 1.4 times higher risk of using an antidepressant drug compared to healthy individuals,[8] while another case-control study focusing on the period three years before the date of psoriasis diagnosis observed no increased use of antidepressants.[9] Furthermore, other studies investigated self-reported assessment of depressive symptoms, which can bias the outcome definition.[4,10-12] These studies had a cross-sectional study design, a limited sample size or lacked a comparative control group.

The objective of this study was to longitudinally compare antidepressant use and episodes in psoriasis patients from 1997 to 2008 to a non-psoriatic reference group from a large sample of the general population, specifically focusing on the time before, during and after treatment initiation for psoriasis.

MATERIALS AND METHODS

Data source

Data was retrieved from the Pharmo Record Linkage system, a large patient-centric data network linking multiple observational databases, including drug dispensing and hospitalization data for approximately 2,5 million residents in the Netherlands.[13,14] Information on each prescription includes product name, Anatomical Therapeutic Chemical (ATC) classification of the drug, date of dispense, quantity dispensed, dosage and regimen.

Study population

Psoriasis patients were identified using a previously described algorithm based on dispensed drugs and hospitalizations for psoriasis and psoriatic arthropathy.[15-17] The index date for psoriasis patients was the date of the first available active treatment for psoriasis, varying

from topical corticosteroids to systemic antipsoriatic therapies. The reference population consisted of subjects without psoriasis, who were assigned a random index date. Five reference subjects were randomly selected for every psoriasis patient using frequency matching for the index date.

The eligibility date represents the date of first registration in a pharmacy linked to the Pharmo system. Between 1997 and 2008 all subjects were followed from the eligibility date to the year of last available prescription, the date when registered subjects moved away or the date of death, whichever came first.

Drug exposure

Antidepressants (ATC code N06A) were Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic antidepressants (TCAs) or other antidepressants. The start of an episode of antidepressant use was defined as the date of dispensing of the first prescription for any antidepressant. The length was the number of days for which the prescribed quantity and prescribed dosage would suffice and the end of an episode was defined as no new prescription within four months after the end date of the last antidepressant prescription. According to the American College of Neuropsychopharmacology and other guidelines, recovery from a Major Depressive Episode can be ascribed after at least 4 months of remission have been ascertained.[18,19] An episode of antidepressant use is not equivalent to a Major Depressive Episode, which is based on assessment of depressive symptoms, however according to the available recommendations, this seemed the most appropriate way to define an episode.

Covariates

The covariates gender and age at eligibility date included in the multivariate models were determined *a priori*. In order to adjust for comorbidities, we calculated the number of unique prescriptions at ATC second level (number of unique therapeutic main groups) during the 6 months before the index date. This method has been described previously.[16] To avoid overadjustment, we excluded antidepressants from this count.

Statistical analyses

Student's t-test was used to test for differences between continuous variables and Chi-square test for categorical variables. To quantify first antidepressant use we calculated incidence rates (IR) per 1000 person years with 95% confidence interval (CI). Multivariable Cox proportional-hazards analyses compared hazards for the first antidepressant use between the two groups. We verified that the hazards for categorical variables were proportional using the log minus log function. Poisson regression model compared IRs of number of episodes of antidepressant use, where observation time from eligibility date until the end of follow-up was used as an offset. To investigate the pattern of antidepressant use, we calculated cumulative IRs and incidence rate ratios (IRR) of episodes of antidepressant use in both groups for the entire

follow-up using time windows of 6 months and plotted these rates with their respective 95% CI against time since diagnosis of psoriasis (+/- 10 years).

We conducted an internal comparison within the psoriasis group using psoriasis patients as their own controls and calculated the hazard ratio (HR) of antidepressant use before and after index date using Cox proportional hazards model with robust standard errors.[20] We report the mean number of episodes before and after the index date and the IRR using Generalized estimating equations (GEE) for counts with unstructured correlation matrix, robust standard errors and exposure time as an offset.[21]

Sensitivity analyses

We analyzed antidepressant use 7 months before and after the index date (4 months is the maximum duration between two prescriptions in the same episode and 3 months is the common maximum duration of a prescription in The Netherlands) and also in an analysis excluding the time around the index date.

The effect of disease severity was studied, where dispensing of topical antipsoriatic medication served as a proxy for mild disease and systemic psoriasis medication and hospitalization for psoriasis as a proxy for moderate to severe disease.

Statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and SPSS version 17.0 (SPSS inc., Chicago, IL, USA).

The present study was conducted and reported according to the guidelines elaborated in the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology).[22]

RESULTS

Study population

In this study we included 25,691 psoriasis patients and 128,573 reference subjects. Gender distribution was similar in the two groups, while the mean age was six years higher in the psoriasis group (Table 1). In both groups the mean follow-up time was approximately 9.5 years. Antidepressant use was more than twice as frequent in psoriasis subjects as in the reference population (17.8% versus 7.9%, $p<0.001$). In particular, SSRIs were the most commonly prescribed antidepressants in both populations (Table 1). Multiple episodes of antidepressant use were observed in 7.6% of the psoriasis and 2.9% of the reference population ($p<0.001$).

Table 1. Baseline characteristics of the reference and psoriasis population.

	Reference N=128,573	Psoriasis N=25,691	p-value
Gender, male, n (%)	62,141 (48.3)	12,494 (48.6)	0.38
Age at eligibility date, years, median (IQR)	33 (18; 50)	42 (28; 56)	<0.001
Years of follow-up, mean[1]	9.38	9.46	
Antidepressant use, n (%)			
Any antidepressant	10,137 (7.88)	4,576 (17.81)	<0.001
Selective serotonin reuptake inhibitor[2]	6,630 (5.16)	3,014 (11.73)	<0.001
Tricyclic antidepressant[2]	3,336 (2.59)	1,650 (6.42)	<0.001
Other antidepressants[2]	2,784 (2.16)	1,359 (5.29)	<0.001
Episodes of antidepressant use, n (%)			
1	6,326 (4.92)	2,593 (10.09)	<0.001
2	2,020 (1.57)	959 (3.73)	
3	803 (0.62)	471 (1.83)	
4	435 (0.34)	239 (0.93)	
5	234 (0.18)	127 (0.49)	
≥6	300 (0.23)	167 (0.65)	

Abbreviation: IQR, Interquartile Range.

[1] Years of follow-up from eligibility date to end of follow-up in Pharmo database.

[2] Values do not add up to sum of all antidepressants because patients could have more than one type of antidepressant.

Antidepressant use in the psoriasis group compared to the reference population

First antidepressant use. The unadjusted IR of antidepressant use per 1000 person years was significantly increased in psoriasis patients (21.2, 95% CI 20.6-21.8) compared to the reference population (8.8, 95% CI 8.7-9.0). The crude HR was 2.37 (95% CI 2.29-2.45), demonstrating that psoriasis patients were about 2.4 times more likely to use antidepressant drugs without adjusting for factors that may confound this association (Table 2).

Adjusting for age and gender only had a limited effect on the HR (adjusted HR 2.19, 95% CI 2.11-2.27), while adjusting for unique prescriptions dispensed 6 months before index date had a remarkable effect since the HR decreased to 1.55 (95% CI 1.50-1.61), but remained significant.

Episodes of antidepressant use. Psoriasis patients had more than twice as many episodes of antidepressant use than the reference population, 37 versus 15 per 1000 person years (IRR 2.54, 95% CI 2.48-2.61) (Table 3). After Poisson regression, the adjusted HR of 1.47 (95% CI 1.43-1.51) was comparable to the adjusted HR of the analysis on first antidepressant use.

Table 2. First antidepressant use in reference and psoriasis groups.

	Reference	Psoriasis
First antidepressant use, n	10,137	4,576
Person years[1]	1,148,051	215,562
Incidence rate per 1,000 person years (95% CI)	8.83 (8.66-9.00)	21.23 (20.61-21.84)
Crude HR (95% CI)	1	2.37 (2.29-2.45)
Adjusted HR (95% CI)[2,3]	1	1.55 (1.50-1.61)

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval.
[1] Sum of number of person years from eligibility date to date of first prescription for an antidepressant or to the end of follow-up in Pharmo.
[2] Adjusted for age, gender and number unique prescriptions 6 months before index date.
[3] COX regression.

Table 3. Episodes of antidepressant use in reference and psoriasis groups.

	Reference	Psoriasis
Episodes of antidepressant use, n	18,070	8,961
Person years[1]	1,206,416	242,934
Incidence rate per 1,000 person years (95% CI)	14.98 (14.76-15.20)	36.89 (36.12-37.65)
Crude IRR (95% CI)	1	2.54 (2.48-2.61)
Adjusted IRR (95% CI)[2,3]	1	1.47 (1.43-1.51)

Abbreviations: CI, Confidence Interval; IRR, Incidence Rate Ratio.
[1] Sum of number of person years from eligibility date to the end of follow-up in Pharmo.
[2] Adjusted for age, gender and number unique prescriptions 6 months before index date.
[3] Poisson regression using entire follow-up time of each patient as offset.

We compared IRs of episodes of antidepressant use in the psoriasis group with those of the reference population during 10 years before and after first treatment for psoriasis (index date) (Figure 1) and also plotted the cumulative IRRs (Figure 2). The IRRs gradually increased from 2.17 ten years before to 2.48 one and a half years before first antipsoriatic treatment. The IRRs were highest within the first 6 months after psoriasis treatment, namely 2.79 and slowly decreased in the 5 years hereafter to reach a plateau at an IRR of around 2.64 until the end of follow-up after 10 years. Looking at the entire period before and after the index date and hereby excluding the year around the index date, the IRR for episodes of antidepressant use is higher in the years after index date than in the years before. If we adjusted these crude rates for age, gender and comorbidity, the risk of dispensing an antidepressant was reduced but still remained 50% higher in the psoriasis population. The adjusted risk of antidepressant use followed the pattern of the crude data, by peaking around the index date (adjusted HR seven months before index date 1.54, 95% CI 1.39-1.71, adjusted HR seven months after index date 1.89, 95% CI 1.70-2.09) and when excluding the seven months before and after index date, the adjusted HR were higher in the years after (adjusted HR 1.73, 95% CI 1.65-1.81) than before the index date (adjusted HR 1.33, 95% CI 1.25-1.42).

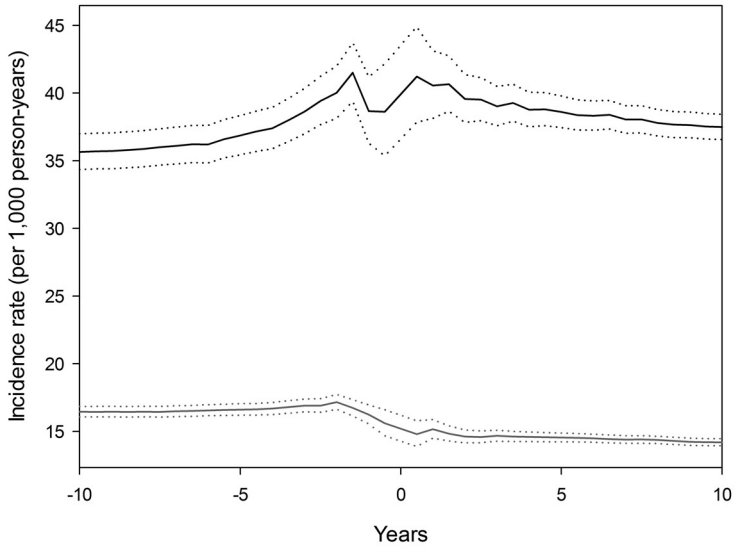

Figure 1. Incidence rates of antidepressant use in psoriasis and reference group.
Black straight and dotted line: Incidence rates and 95% confidence interval in psoriasis group.
Grey straight and dotted line: Incidence rates and 95% confidence interval in reference group.
Year "0" represents the index date.

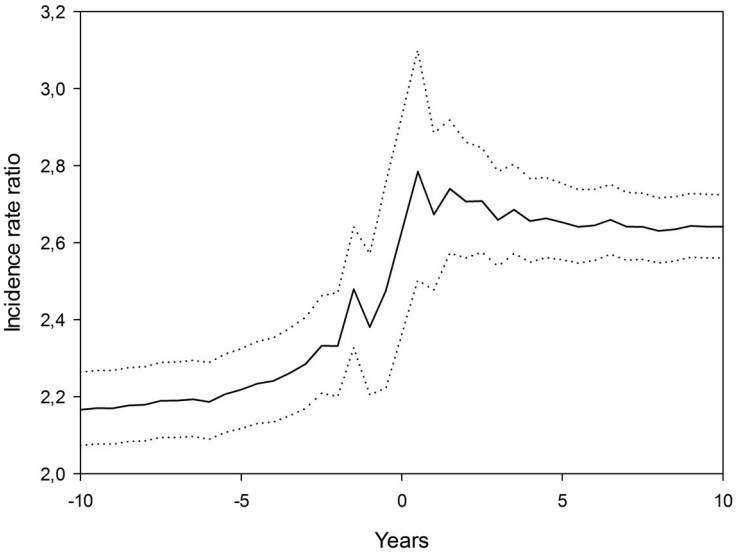

Figure 2. Incidence rate ratio of antidepressant use in psoriasis compared to reference population.
The dotted line represents the 95% confidence interval.
Year "0" represents the index date.

Internal comparison of antidepressant use within the psoriasis group

When restricting the analysis to the psoriasis population and comparing antidepressant use before and after the index date, psoriasis patients were about 7% more likely to receive antidepressant drugs after the index date, when controlling for within patient variation using the GEE model (HR 1.07, 95% CI 1.02-1.12) (Table 4). However, there was no significant difference in the mean number of episodes before and after index date, 0.035 and 0.037 respectively (IRR 1.03, 95% CI 0.98-1.09, p=0.26).

Table 4. Analysis of antidepressant use within the psoriasis group before and after index date (n=25,691).

	Before index date	After index date
First antidepressant use in psoriasis patients		
Antidepressant users, n	1,977	3,480
Person years[1]	74,369	148,241
Incidence rate per 1,000 person years (95% CI)	26.58 (25.41-27.76)	23.48 (22.70-24.26)
Hazard Ratio (95% CI)[2]	1	1.07 (1.02-1.12)
Episodes of antidepressant use in psoriasis patients		
Episodes of antidepressant use, n	2,810	6,151
Person years[3]	78,871	164,064
Incidence rate per 1,000 person years (95% CI)	35.63 (34.31-36.95)	37.49 (36.55-38.43)
Mean number of episodes (95% CI)	0.035 (0.033-0.037)	0.037 (0.033-0.041)
Incidence Rate Ratio (95% CI)[4]	1	1.032 (0.977-1.090)

Abbreviations: CI, Confidence Interval.

[1] Sum of number of person years from eligibility date to date of first antidepressant or to index date (for analysis before the index date) and from index date to first antidepressant after index date or to end of follow up in Pharmo (for analysis after the index date).

[2] Cox proportional hazard model with robust standard errors.

[3] Sum of number of person years from eligibility date to index date (for analysis before the index date) and from index date to end of follow up in Pharmo (for analysis after the index date).

[4] Poisson regression model using generalized estimating equations with unstructured correlation matrix and robust standard errors.

Effect of psoriasis severity on antidepressant drug use

Patients with mild psoriasis had a 2.3-times higher risk (95% CI 2.23-2.40) of using antidepressant drugs compared to reference subjects. In a multivariate COX regression model, the age, gender and comorbidity adjusted HR for antidepressant use remained significant (adjusted HR 1.55, 95% CI 1.49-1.61) in this subgroup of patients. Patients with more severe psoriasis had a crude HR of 2.81 (95% CI 2.59-3.04) and an adjusted HR of 1.57 (95% CI 1.44-1.70) compared to the non-psoriasis population. Psoriasis patients with severe disease were at a higher risk of having a first antidepressant than patients with mild disease, with an overall p-value of p<0.001.

DISCUSSION

Our study shows that dispensing of antidepressants is twofold higher in psoriasis patients and that they have twice as many episodes of antidepressant use than the reference population. The longitudinal study design enabled us to demonstrate that antidepressant use is already increased before psoriasis patients seek medical treatment for their skin and that it peaks around the time of treatment initiation but also remains increased hereafter.

Our outcomes are in line with prescription data from German hospitalized psoriasis patients showing a 1.4 times higher risk of using an antidepressant[8] and are also comparable to the 1.4 to 1.5 times higher risk of major psychiatric disorders in psoriasis observed in the General Practice Database from the United Kingdom and an interdisciplinary administrative outpatient database from Germany.[6,7]

Adjusting for unique number of prescription drugs 6 months prior to the index date, as a proxy for the general healthcare consumption pattern, resulted in a considerable decrease of the risk of using an antidepressant. This effect could be explained by detection bias, i.e. patients with psoriasis visit their physician more often, which equally increases their risk of diagnosis and treatment of other diseases including depression.[23] This effect was also confirmed by other studies, showing that the likelihood of being diagnosed with depression increases with the number of physician visits due to psoriasis[6] and that on average, psoriasis patients with severe disease receive more different systemic drugs than the general population.[8]

The increased risk of antidepressant use after adjustment may be explained by the effect of psoriasis on the HRQoL, leading to stigmatization, shame, difficulties in daily activities and coping problems,[11,24-26] which may result in depressive symptoms.[27] An alternative explanation may be reverse causality; depression may lead to self-neglecting behaviour, isolation and therefore induces lifestyle changes such as smoking, alcoholism and obesity, which in turn can lead to increased inflammation and eventually to psoriasis. However, since the effects of generalized inflammation mostly become apparent after a long induction period, the association between depression, lifestyle changes and psoriasis would take years to manifest itself.[28,29] Genetics could play a role in the association between psoriasis and depression. Genome wide association studies on psoriasis susceptibility loci[30-34] and on genes for major depressive disorder[35] showed no common genes. However, a recent study on inflammation-related genes in depression identified that the gene PSMB4, critical for T-cell function, was associated with susceptibility to Major Depressive Disorder.[36] Susceptibility to psoriasis has also been associated to the area of chromosome 1q21 (PSORS4) that encodes for the PSMB4 gene.[34]

The pattern of antidepressant use in this study shows three discernable periods (Figure 2): First, during the years before the index date, antidepressant use gradually increases and reaches a maximum in the proximity of the index date. Hereafter, antidepressant use does

not decline to its level from before the index date but remains constantly high and reaches a plateau until the end of follow-up. The use of antidepressant drugs remained increased after the index date, also when adjusting for confounders. Assuming that the index date represents the date of first diagnosis of psoriasis, the period of more than one year before the index date would represent a period without active psoriasis or where psoriatic disease has not yet manifested itself. The risk difference of antidepressant use between the two groups in this first period may, therefore, be explained by intrinsic factors at work such as unhealthy lifestyle factors, different healthcare consumption attitudes and genetic factors leading to higher use of antidepressants than in subjects that do not develop psoriasis. Interestingly, other studies have shown that psoriasis patients are already more obese before the manifestation of psoriatic disease,[28] which may also lead to depression.[37] We then observed a deviation of antidepressant use starting one and a half years prior to the first dispensing of antipsoriatic medication until one and a half years thereafter in the psoriasis population and in the analyses comparing the psoriasis group to the reference population. This increase in antidepressant use may not merely be explained by increased healthcare consumption in psoriasis patients. Antidepressant use attains a maximum around the index date, whereupon the patient seeks medical care due to psoriasis de novo or exacerbation of disease and thus the severity of disease in this acute phase may have a more pronounced impact on the psychological condition of the patient.

If there is a causal relationship between psoriasis and depression, then this may be reflected in the risk difference of 0.5 comparing the period before and after the index date (Figure 2) where the IRR of antidepressant use increases from 2.2 to 2.7. The observation that, beyond the index date, the risk of antidepressant use does not return to its level of before the index date suggests that it remains difficult to control psoriasis on the long term and that disease severity remains relatively stable in time.[38] Therefore, the significant increase in risk of antidepressant dispensing beyond the index date could be attributed to the impact of chronic skin disease on patients' HRQoL. On the other hand, a study comparing QoL scores in a 11 year period demonstrated a significant decrease of approximately 25% in the overall psychosocial impact of psoriasis on patients' HRQoL, suggesting that this group of patients accommodate to the impact of their disease over time.[39]

Strengths and limitations

The present study is the largest population based longitudinal study comparing antidepressant prescriptions during an almost 10 year observation period in psoriasis patients to a reference population. It is based on prescription data from 2,5 million Dutch residents, and is therefore well representative of the Dutch population. The longitudinal study design enabled us to focus in detail on drug prescriptions around the time of initiation of psoriasis therapy. Besides analyzing unique prescriptions, we also investigated multiple episodes of antidepressant use, which resulted in comparable outcomes. The obtained risk estimates

confirm the estimates found in studies on the association between psoriasis and major psychiatric disorders,[6,7] also strengthening our definition of depressive episodes based on antidepressant prescription data. We are aware that antidepressant drug use does not imply the diagnosis of a depression but may also represent other psychiatric morbidities. In the Dutch general practice, 45% of antidepressant users had depression, 17% had anxiety and panic disorders, and 9% had sleeping disorders.[40]

Our definition of psoriasis was based on a drug and hospitalization algorithm; nevertheless it had a 98.2% sensitivity and a 80.2% specificity.[16] This could result in non-differential misclassification of psoriasis cases, which might lead to underestimation of the effect of psoriasis on antidepressant use. As also the case in other secondary database studies, residual confounding was likely because data on potential confounders such as weight, smoking, alcohol consumption, physical activity or socioeconomic status were not available. However, the risk estimates were stable across the different analyses including the within patient analysis, in which the effect from unmeasured confounding factors between psoriasis cases and reference subjects was attenuated. We calculated the exposure to antidepressants from dispensed pharmacy prescriptions assuming good drug compliance. However, the rate of non-adherence to antidepressant treatment can vary from 40 to 75%,[41] especially among long term users, which was not the objective of this study. Although the average follow-up was almost a decade, it is possible that patients had a depression before they were registered in the database, resulting in non-differential misclassification. To minimize the impact of this bias, prevalent antidepressant users (n=143) who had changed pharmacists and who had an antidepressant drug dispensed in the first pharmacy where they were registered, were excluded from the analysis.

CONCLUSION

Psoriasis patients use more antidepressant medication than the general population, especially at the time when they seek medical care for their psoriasis and thereafter. Physicians should be aware that patients who seek care for chronic dermatological conditions such as psoriasis may have an increased risk of experiencing psychological or psychiatric disorders.

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Chapter 3.3

No increased risk of clinical depression in psoriasis patients from the population-based Rotterdam Study

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Chapter 4

Atherosclerosis, Inflammation & Cardiovascular Disease in Psoriasis

Chapter 4.1

Markers of systemic inflammation in psoriasis: a systematic review and meta-analysis

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ABSTRACT

Background: Studies investigating systemic inflammation in psoriasis use different serum markers and report discrepant results.

Objective: To determine whether systemic inflammation is elevated in psoriasis patients compared to healthy controls and to measure the extent of this elevation, by summarizing available data on serum inflammatory markers.

Methods: PubMed, Embase and Web of Science were searched from inception to March 2011. We included studies comparing the serum inflammatory markers Interleukin (IL)1-beta, IL-6, IL-10, C-reactive-protein (CRP), Intracellular adhesion molecule-1 (ICAM-1), E-selectin or Tumor necrosis factor-alpha (TNFα) in psoriasis with healthy controls. Difference in serum marker levels between patients and controls were pooled as standardized mean differences (SMD) (Cohen's d) using random-effects model.

Results: Seventy-eight studies were eligible. Of the 7,852 individuals 3,085 had (severe plaque) psoriasis. The pooled SMDs were higher in psoriasis compared to healthy controls for IL-6 (d=1.32, 95% CI 0.83-1.81), CRP (d=1.83, 95% CI 0.76-2.90), TNFα (d=1.32, 95% CI 0.86-1.79), E-selectin (d=1.78, 95% CI 1.32-2.25) and ICAM-1 (d=1.77, 95% CI 1.15-2.39). The SMD between cases and controls for IL-1β and IL-10 was not significant. Age had a significant effect on the SMD for IL-6 and TNFα. For IL-6 the effect size was higher for plaque psoriasis studies (d=1.98). The effect size was not influenced by the PASI, measurement method or quality assessment.

Conclusion: The pooled analyses suggest modest, but significantly elevated levels of the pro-inflammatory cytokines in the serum of psoriasis patients with predominantly severe disease. To what extent this modest increment is clinically relevant could be investigated in a synthesis of all studies measuring inflammation before and after antipsoriatic therapy.

INTRODUCTION

Psoriasis is a chronic, relapsing, inflammatory skin disease that affects 2% of the Caucasian population.[1] This skin condition is histologically characterized by abnormal proliferation of keratinocytes and infiltration of immune cells, predominantly T-cells and dendritic cells in psoriatic lesions.[2] The majority of inflammatory cells and cytokines remain in the tissue and a relatively small proportion can be measured in the peripheral blood, such as interleukins (ILs)[3] which have shown to be elevated in patients with cardiovascular disease, metabolic syndrome and diabetes.[4,5]

The search for markers in psoriasis was revived as these were not only found in the skin, but researchers also identified a spillover of inflammatory markers into the systemic circulation, using them to measure disease severity, to objectively monitor treatment response, find new targets for therapy and to explain comorbidities in psoriatic patients.[6,7]

Much attention has been drawn towards "upgrading" psoriasis from a skin condition to a systemic disease as serum biomarkers for inflammation are raised in psoriasis[8] and patients could therefore have a higher risk of developing systemic comorbidities.[6] Data on serum levels of pro- and anti- inflammatory cytokines in psoriasis patients compared to controls are controversial, with some authors not observing any difference, while others report elevated or decreased levels in psoriasis.[3] The studies to date have small sample sizes, investigate different markers and techniques to assess inflammation; moreover measurement of serum inflammation is often not their primary objective.

We conducted the first systematic review and meta-analysis to determine whether six well-known pro-inflammatory serum markers IL-1β, IL-6, C-reactive protein (CRP), Tumor necrosis factor-alpha (TNFα), Intracellular adhesion molecule-1 (ICAM-1), E-selectin are elevated and anti-inflammatory IL-10 decreased in treatment naïve psoriatic patients compared to controls.

MATERIALS AND METHODS

Background to literature search

We investigated whether certain markers of inflammation were elevated in psoriasis patients compared to controls and were interested in the role of inflammatory markers in the development of comorbidities. We therefore conducted an open literature search listing inflammatory markers most commonly mentioned in psoriasis and cardiovascular disease (CVD) (Supplementary Figure 1). This is the case for IL-1β, IL-6 and TNFα which are produced in adipose tissue, are known to be pro-atherogenic but are also involved in skin inflammation in psoriasis as they are produced by the keratinocytes.[2,6] CRP is often used to measure suspected inflammatory state in psoriasis patients, whereas high sensitivity CRP is used in the prediction of CVD.[9-11] The type of CRP measured depended on the objective of the study. We

included all studies measuring CRP, regardless of the type. The adhesion molecules E-selectin and ICAM-1 expressed on endothelial cells are equally known as mediators of inflammation in the prediction of CVD.[12]

Other than the six above-mentioned pro-inflammatory markers, we chose IL-10 as anti-inflammatory cytokine to confirm the hypothesis that IL-10 is below detectable levels in psoriasis patients or at the same level as in healthy controls.[3,6]

Eligibility criteria

Inclusion and exclusion criteria were determined before the search was conducted. We included human studies comparing psoriasis patients with 'healthy' controls, in which one or more of the following inflammatory markers were measured in the serum: IL-1β, IL-6, IL-10, CRP, TNFα, E-selectin and ICAM-1. Studies were excluded if psoriatic arthritis (PsA) was the main exposure. Case reports and letters were excluded. If several studies reported results from the same study population, the most complete report was included.

Search strategy

The systematic search was performed by a medical librarian (L.V.) in PubMed, Embase and Web of Science from 1988 to March 2011. The search strategy is presented in Supplementary Table 1.

Data extraction and quality assessment

Data was collected using a standard data extraction form (Table 1). Information from articles in a language other than English, Dutch, French or German was extracted if an English abstract and comprehensive tables were available.

The quality of the articles was assessed using a checklist based on the REMARK guidelines, also used in other meta-analyses.[13,14] The definition of each checklist item was discussed; two points were allocated to each positive item, one point to a partially fulfilled item and no points were given if the item criterion was not met. The sum of these points was divided by the maximum number of points an article could score.

Study selection

Two reviewers (E.A.D. and E.A.M.V.) independently screened all titles, abstracts and full texts of selected articles and conducted the data extraction and the quality assessment. Disagreements were resolved by consensus.

Data synthesis and analysis

The primary outcome was the difference in mean serum inflammatory marker levels between psoriasis patients and healthy controls for each study. The effect size representing this difference was calculated using the standardized mean difference (SMD), also referred to as

Table 1. Characteristics of included studies.

Author, Year	Country	Psoriasis					Healthy controls			Markers and measurement methods[1]							Quality score[2]
		N	Mean age	% Male	% Plaque psoriasis	Mean PASI	N	Mean age	% Male	IL-1β	IL-6	IL-10	TNFα	(hs) CRP	E-selectin	ICAM-1	
Abdel-Hamid *et al,*[43] 2010	Egypt	60	40	48	83.3	11.8	21	43	48	·	·	·	1	·	·	·	27/52
Abe *et al,*[44] 2002	USA	13	44	77	100	18.9	40	-	-	1	·	·	·	·	·	·	23/56
Ameglio *et al,*[45] 1994	Italy	14	41	7	85.7	-	14	43	14	·	·	·	·	·	·	1	10/52
Anderson *et al,*[46] 2010	Sweden	14	47	29	100	8.5	14	47	29	5	5	5	5	·	·	·	32/56
Ardic *et al,*[47] 2010	Turkey	58	36	47	-	13.0	36	40	47	·	·	·	·	9	·	·	19/53
Arican *et al,*[48] 2005	Turkey	30	35	60	100	9.3	23	35	61	·	1	·	1	·	·	·	22/52
Asadullah *et al,*[49] 1999	Germany	29	-	-	-	-	28	-	-	·	·	·	1	·	·	·	24/52
Balci *et al,*[50] 2009	Turkey	51	40	47	100	6.6	32	42	47	·	·	·	·	4	·	·	17/56
Bevelacqua *et al,*[51] 2006 (mild pso)	Italy	18	36	56	100	-	25	40	56	1	1	·	1	4	·	·	23/52
Bevelacqua *et al,*[51] 2006 (severe pso)	Italy	26	46	62	100	-	25	40	56	1	1	·	1	4	·	·	23/52
Bonifati *et al,*[52] 1994	Italy	20	53	5	90	11.4	10	42	60	·	9	·	1	·	·	·	26/52
Bonifati *et al,*[53] 1995	Italy	19	53	32	100	-	22	57	36	·	·	·	·	·	1	·	22/52
Borghi *et al,*[54] 2008	Italy	65	54	80	100	21.2	114	54	80	·	·	5	·	·	·	·	28/56
Borska *et al,*[55] 2006	Czech	56	48	63	-	22.2	40	48	-	·	·	·	1	·	1	1	29/56
Borska *et al,*[56] 2008	Czech	55	38	64	-	21.7	47	31	57	·	·	1	·	·	·	·	26/56
Bubl *et al,*[57] 1994	Germany	41	-	-	100	-	31	-	-	·	·	·	·	·	·	1	15/55
Carducci *et al,*[58] 1994	Italy	25	51	24	92	11.4	50	48	40	·	·	·	·	·	·	5	15/52
Chandran *et al,*[59] 2010	Canada	26	45	46	100	4.9	26	43	46	·	·	·	·	1	·	·	26/53
Chodorowska,[60] 1998	Poland	27	35	100	-	25.8	20	35	100	·	·	·	1	·	·	·	28/56
Chodorowska *et al,*[61] 2004	Poland	175	38	100	-	29.0	30	40	100	·	·	·	·	1	·	·	22/56
Coimbra *et al,*[62] 2009	Portugal	56	44	55	100	19.3	37	47	57	·	·	·	·	3	·	·	23/56

Table 1. (continued)

Author, Year	Country	Psoriasis					Healthy controls			Markers and measurement methods[1]							Quality score[2]
		N	Mean age	% Male	% Plaque psoriasis	Mean PASI	N	Mean age	% Male	IL-1β	IL-6	IL-10	TNFα	(hs) CRP	E-selectin	ICAM-1	
Coimbra *et al*,[63] 2010a	Portugal	73	45	55	100	18.0	38	47	45	·	·	·	·	3	·	·	29/56
Coimbra *et al*,[64] 2010b	Portugal	66	43	53	100	18.8	37	50	57	·	1	·	1	3	·	·	32/56
Coimbra *et al*,[65] 2010c	Portugal	34	45	41	100	22.6	20	44	45	·	·	·	1	·	·	·	31/56
Coimbra *et al*,[66] 2010d	Portugal	34	43	47	100	14.8	37	47	57	·	·	·	·	3	·	·	34/56
Corbetta *et al*,[67] 2006	Italy	10	41	100	100	13.0	10	41	100	·	·	·	1	·	·	·	29/56
Ctirad *et al*,[68] 2008	Czech	49	38	53	100	20.9	48	30	-	·	·	·	·	3	·	·	28/56
Czech *et al*,[69] 1996	Germany	16	31	56	100	-	16	28	50	·	·	·	·	·	1	·	27/56
De Pita *et al*,[70] 1996	Italy	30	50	77	90	21.3	11	50	73	·	·	·	·	·	·	1	29/56
De Pita *et al*,[71] 1999	Italy	24	52	63	100	8.8	20	52	60	·	·	·	·	·	·	1	26/56
Deeva *et al*,[72] 2010 (severe plaque pso)	Italy	10	33	50	100	44.2	10	37	50	·	9	9	·	·	·	·	23/52
Deeva *et al*,[72] 2010 (mild plaque pso)	Italy	35	50	57	100	8.7	10	37	50	·	9	9	·	·	·	·	23/52
Deeva *et al*,[72] 2010 (erythrodermic pso)	Italy	10	38	50	0[3]	64.6	10	37	50	·	9	·	·	·	·	·	23/52
Fazio *et al*,[73] 1994	Italy	20	53	5	90	11.4	10	42	60	·	·	·	·	·	·	5	21/53
Galadari and Sheriff,[17] 2005 (mild pso)	Abu Dhabi	24	-	67	-	6.6	10	-	70	·	1	·	·	·	·	·	22/53
Galadari and Sheriff,[17] 2005 (moderate pso)	Abu Dhabi	9	-	78	-	22.5	10	-	70	·	1	·	·	·	·	·	22/53
Galadari and Sheriff,[17] 2005 (severe pso)	Abu Dhabi	5	-	40	-	44.4	10	-	70	·	1	·	·	·	·	·	22/53
Gangemi *et al*,[74] 2003	Italy	16	41	63	-	35.8	16	40	56	·	·	·	·	·	·	1	19/53
Gonul *et al*,[75] 2009	Turkey	54	39	65	-	8.9	50	38	66	1	1	·	1	·	·	.	14/56
Griffiths *et al*,[76] 1996	Germany	32	42	59	-	15.0	99	28	56	·	·	·	·	·	·	1	22/52

Table 1. (continued)

Author, Year	Country	Psoriasis					Healthy controls			Markers and measurement methods[1]							Quality score[2]
		N	Mean age	% Male	% Plaque psoriasis	Mean PASI	N	Mean age	% Male	IL-1β	IL-6	IL-10	TNFα	(hs) CRP	E-selectin	ICAM-1	
Groves *et al*,[18] 1995	UK	9	-	-	0[3]	-	17	53	41	·	·	·	·	·	1	1	23/52
Jacob *et al*,[77] 2003	USA	12	48	58	75	-	5	35	20	5	5	5	5	·	·	·	15/52
Jadali *et al*,[78] 2007	Iran	40	38	55	52.5	6.3	40	39	55	·	·	1	·	·	·	·	23/52
Johnston *et al*,[37] 2008	Iceland	30	53	53	100	15.3	29	47	45	5	5	·	·	·	·	·	29/56
Kagami *et al*,[79] 2010	USA	21	42	-	-	22.2	17	34	0	·	·	·	1	·	·	·	22/56
Kanda *et al*,[80] 2010	Japan	61	52	74	100	8.1	31	46	65	1	1	1	1	·	·	·	24/56
Karabudak *et al*,[81] 2008	Turkey	20	23	100	-	13.0	20	21	100	·	·	·	·	4	·	·	20/52
Kaur *et al*,[82] 2008 (BMI<25)	Estonia	10	50	60	100	14.5	22	-	-	·	1	·	·	·	·	·	21/52
Kaur *et al*,[82] 2008 (BMI>30)	Estonia	12	47	58	100	12.4	22	-	-	·	1	·	·	·	·	·	17/52
Kaya *et al*,[83] 2010	Turkey	58	36	47	-	-	36	40	47	·	·	·	·	9	·	·	6/52
Kitamura *et al*,[84] 1999	Japan	30	49	50	0[4]	-	20	47	50	·	·	·	1	·	1	1	19/56
Kowalzick *et al*,[85] 1993	Germany	10	46	100	100	18.6	17	33	53	·	·	·	·	·	·	1	24/56
Krasowska *et al*,[86] 1998a	Poland	59	-	41	100	23.8	10	-	40	·	1	·	·	·	·	·	13/52
Krasowska *et al*,[87] 1998b	Poland	23	-	-	-	-	20	-	-	·	·	·	·	·	·	9	8/56
Krasowska *et al*,[88] 2000	Poland	23	39	65	-	25.4	11	36	45	·	·	·	·	·	·	1	22/56
Laurent *et al*,[89] 1981	UK	15	-	-	-	-	21	-	-	·	·	·	·	5	·	·	20/52
Lecewicz-Torun *et al*,[90] 1997	Poland	19	35	47	78.9	-	14	38	50	·	·	·	·	·	·	1	18/52
Long *et al*,[91] 2010	China	58	36	62	62.1	23.7	50	36	62	·	·	·	·	·	1	1	32/56
Love *et al*,[92] 2010	USA	71	42	46	-	-	2385	39	50	·	·	·	·	9	·	·	26/52
Martinez-Sales *et al*,[93] 2010	Spain	20	-	-	-	-	20	-	-	·	1	·	·	·	1	·	8/52

Table 1. (continued)

Author, Year	Country	Psoriasis					Healthy controls			Markers and measurement methods[1]							Quality score[2]
		N	Mean age	% Male	% Plaque psoriasis	Mean PASI	N	Mean age	% Male	IL-1β	IL-6	IL-10	TNFα	(hs) CRP	E-selectin	ICAM-1	
Martyn-Simmons *et al*,[94] 2011	UK	60	51	77	100	9.2	117	49	42	·	·	·	·	3	·	·	25/53
McLoone *et al*,[95] 2004	UK	5	43	100	-	-	15	43	100	·	·	1	1	·	·	·	21/56
Mizutani *et al*,[96] 1997	Japan	63	47	56	100	-	20	47	55	1	1	·	1	·	·	·	17/52
Mussi *et al*,[97] 1997	Italy	37	53	32	100	11.4	30	49	30	·	·	·	1	·	·	·	23/56
Ohtsuka,[98] 2008	Japan	52	54	62	100	12.8	147	54	62	·	·	·	·	4	·	·	15/52
Park and Kim,[99] 2004	Korea	15	-	-	-	-	15	-	-	·	·	·	·	·	1	·	12/52
Qiu *et al*,[100] 2005	China	33	32	55	-	12.9	30	32	57	·	1	·	1	·	·	·	29/56
Reddy *et al*,[19] 2010	Worldwide	105	45	70	100	17.0	30	-	-	·	·	1	1	·	·	1	31/56
Rocha-Pereira *et al*,[101] 2004	Portugal	60	47	57	100	-	40	47	55	·	·	·	·	4	·	.	20/52
Roussaki-Schulze *et al*,[102] 2005	Greece	45	-	69	100	-	45	-	-	·	1	1	1	·	·	.	23/56
Schopf *et al*,[103] 1993	Germany	17	42	-	94.1	-	17	42	-	·	·	·	·	·	·	1	23/52
Seishima *et al*,[104] 1998 (pso)	Japan	31	55	61	-	-	53	53	57	·	5	·	1	·	·	·	15/52
Seishima *et al*,[104] 1998 (active GPP)	Japan	9	23	56	0[5]	-	53	53	57	·	5	·	1	·	·	·	15/52
Serwin *et al*,[105] 2006	Poland	37	31	62	100	12.7	20	37	-	·	·	·	·	4	·	·	36/56
Szegedi *et al*,[106] 2003	Hungary	18	47	78	100	20.1	10	34	60	·	·	1	·	·	·	·	18/52
Szepietowski *et al*,[107] 1999	Poland	33	38	64	100	20.7	10	38	60	·	·	·	·	·	1	·	24/56
Szepietowski *et al*,[108] 2000	Poland	40	47	70	100	26.0	18	43	67	·	1	·	·	·	·	·	26/56
Szepietowski *et al*,[109] 2002	Poland	20	25	55	100	23.7	20	25	55	·	·	·	·	·	1	·	19/52

Table 1. (continued)

Author, Year	Country	Psoriasis					Healthy controls			Markers and measurement methods[1]							Quality score[2]
		N	Mean age	% Male	% Plaque psoriasis	Mean PASI	N	Mean age	% Male	IL-1β	IL-6	IL-10	TNFα	(hs) CRP	E-selectin	ICAM-1	
Takahashi *et al*,[20] 2010	Japan	122	48	66	83.6	7.3	78	39	69	·	1	1	1	·	·	1	24/56
Toruniowa *et al*,[110] 1995	Poland	20	-	-	-	-	14	-	-	·	1	·	·	·	·	·	15/52
Vanizor Kural *et al*,[111] 2003a	Turkey	30	34	43	-	5.5	30	37	50	·	·	·	·	4	·	1	22/52
Vanizor Kural *et al*,[112] 2003b	Turkey	35	35	49	-	5.8	35	36	54	·	·	·	·	4	·	·	22/52
Yamamoto *et al*,[113] 1997 (plaque pso)	Japan	4	-	-	100	25.4	6	58	-	·	·	·	·	·	1	1	20/52
Yamamoto *et al*,[113] 1997 (GPP)	Japan	6	58	50	0[5]	-	6	58	50	·	·	·	·	·	1	1	20/52
Yiu *et al*,[114] 2010	China	52	44	73	100	14.7	50	43	76	·	·	·	·	9	·	·	31/52
Zalewska *et al*,[115] 2006	Poland	106	45	72	100	16.7	40	46	58	·	1	·	·	.	·	·	9/52
Total	·	**3085**	**43±7.6**	**57%**	·	**17.7±10.5**	**4913**	**42±7.8**	**49%**	**9**	**29**	**13**	**26**	**22**	**12**	**22**	·

Abbreviations: PASI, Psoriasis Area and Severity Index; IL, Interleukin; TNF, Tumor Necrosis Factor; (hs)CRP, (high sensitivity) C-reactive protein; ICAM, Intracellular Adhesion Molecule; pso, psoriasis; GPP, Generalized Pustular Psoriasis.

Areas marked with "-" indicate missing data and "·" indicates not applicable.

[1] The following measurement methods were used: 1=Enzyme Linked Immuno Sorbant Assay (ELISA), 2= Radio immunoassay, 3=Immunoturbidimetry, 4=Nephelometry, 5=other measurement method, 9=method not specified.

[2] Quality assessment score: study score / maximum possible score for the article.

[3] 100% erythrodermic psoriasis.

[4] 100% palmoplantar psoriasis.

[5] 100% pustular psoriasis.

Cohen's d and we reported its respective 95% confidence interval (CI). In studies where the mean was not reported, the median was used. If the standard deviation (SD) was not available, we assumed that the values lay within three SDs from the mean. SMDs were pooled using a random effects-model according to the method of DerSimonian and Laird, where within-study variance and between-study variance were taken into account. Heterogeneity between studies was quantified using I^2 statistics. In six studies the serum levels were given separately according to psoriasis type, severity or Body Mass Index (BMI), instead of reporting an overall mean. These were included as such in the meta-analysis; however, the control group remained the same for the studied outcome measures.

Publication bias was investigated graphically by funnel plots and was statistically assessed via Egger's regression. The trim and fill method provided an estimate of the number of missing studies and an estimate of the pooled effect size if these studies were to be included in the meta-analysis.

All statistical analyses were performed using Comprehensive Meta-Analysis Version 2.2 (Biostat, Englewood, NJ, USA).

Meta-regression and subgroup analyses

Sources of heterogeneity between studies were explored by performing meta-regression analyses for age, gender and psoriasis severity. Subgroup analyses were performed based on psoriasis type (only plaque psoriasis versus different or non-specified types), laboratory measurements (Enzyme Linked Immuno Sorbant Assay (ELISA) versus other techniques or when the measurement method was not specified, and for CRP: ELISA versus immunoturbidimetry versus nephelometry versus other or missing method). Subgroups were analyzed for quality assessment scores whereby studies above and below the upper quartile were compared to each other. For each subgroup the pooled SMD and 95% CI was presented.

We excluded all studies with PsA, however we did not exclude studies with a small number of PsA patients alongside other psoriasis patients. In order to ascertain that the impact of PsA was limited in the meta-analysis, we conducted subgroup analyses comparing studies where PsA patients were excluded to the rest of the studies, showing no significant difference in point estimates between these two categories. The interpretation of this analysis was limited due to the small number of studies explicitly mentioning that PsA patients were excluded. We therefore decided to refrain from further discussing this subgroup analysis in the manuscript.

The present study was conducted and reported according to the PRISMA and MOOSE guidelines.[15,16]

RESULTS

The search yielded 8447 articles (5385 after exclusion of duplicates), of which 78 were included in the meta-analysis. Figure 1 depicts the study selection process.

A total of 7852 individuals (3085 psoriasis patients) were included. Psoriasis patients and healthy controls were comparable as to age (Table 1). The psoriasis type was known in 69% of patients. Of these, 94% (n=1971) had plaque psoriasis and 3.4% (n=71) had erythrodermic psoriasis. A total of 70% of the studies reported a Psoriasis Area and Severity Index (PASI). Within this group, 75% of the patients were from studies reporting a mean PASI >10, indicating that the majority of the studies included patients with severe disease (overall mean PASI 17.7±10.5).

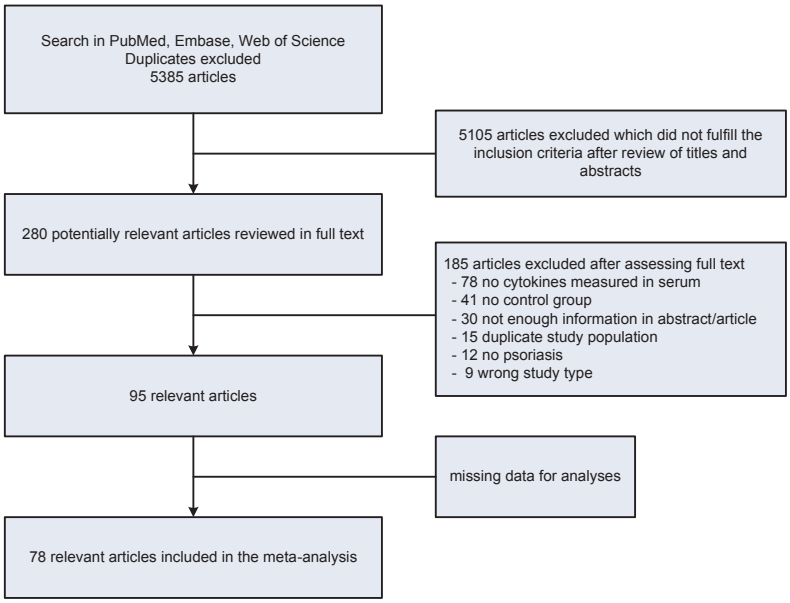


Figure 1. Flow diagram of study selection.

Interleukin-1β

The SMD for studies analyzing IL-1β was -0.32 (95% confidence interval [CI] -1.05-0.41) indicating that there was no significant difference in serum IL-1β between psoriasis patients and controls (Figure 2a). Age and psoriasis severity did not explain the high degree of heterogeneity between the studies (I^2=93%). When adjusting for gender in the meta-regression, we noticed that the higher the percentage of women in the study, the larger the difference in IL-1β between psoriasis patients and controls in the study (p=0.001). Regarding the subgroup analyses, no significant differences were observed between studies including plaque psoriasis only and other studies (p=0.90) (Table 2).

Table 2. Summary of pooled standardized mean differences, meta-regression and subgroup analyses for all studied serum markers.

Markers (Number of Studies)	Pooled Effect Size SMD[1] (95% CI)	Meta-regression analyses[2] Regression coefficient (95% CI)			Subgroup analyses[1,3] SMD for each subgroup (95% CI)					
		Age	Gender	PASI	Psoriasis type		Measurement method		Quality assessment	
					Plaque psoriasis	Other[4]	ELISA	Other[5]	Lower quartile	Upper quartile
IL-1β (8)	-0.32 (-1.05–0.41)	0.02 (-0.21–0.25)	**0.04 (0.02–0.07)**	-0.26 (-0.56–0.05)	-0.36 (-1.27–0.55)	-0.23 (-1.96–1.49)	-0.75 (-1.59–0.10)	0.59 (-0.65–1.82)	-0.15 (-1.54–1.23)	-0.42 (-1.40–0.56)
IL-6 (22)	**1.32 (0.83–1.81)**	**-0.08 (-0.16 to -0.003)**	-0.22 (-0.49–0.04)	0.06 (-0.20–0.33)	**0.92 (0.29–1.54)**	**1.98 (1.19–2.77)**	1.38 (0.76–2.01)	1.25 (0.43–2.08)	0.80 (0.05–1.55)	1.71 (1.06–2.35)
IL-10 (12)	0.25 (-0.90–1.40)	-0.36 (-0.87–0.16)	-0.01 (-0.18–0.17)	0.10 (-0.19–0.39)	0.19 (-1.29–1.66)	0.37 (-1.59–2.34)	0.98 (-0.63–2.59)	-0.89 (-2.94–1.16)	**-2.06 (-4.57–0.45)**	**0.89 (-0.43–2.22)**
(hs)CRP (20)	**1.83 (0.76–2.90)**	0.01 (-0.13–0.14)	0.01 (-0.05–0.07)	0.07 (-0.002–0.14)	1.67 (0.34–3.01)	2.11 (0.34–3.87)	0.64 (-3.00–4.27)	2.30 (0.20–4.40)[6] 1.38 (-0.34–3.10)[7] 2.55 (0.25–4.85)[8]	1.10 (-0.63–2.82)	2.25 (0.95–3.55)
TNFα (24)	**1.32 (0.86–1.79)**	**-0.13 (-0.23 to -0.03)**	-0.01 (-0.04–0.03)	-0.01 (-0.09–0.07)	1.17 (0.47–1.87)	1.47 (0.82–2.12)	1.37 (0.88–1.86)	0.72 (-1.03–2.47)	1.06 (0.21–1.92)	1.44 (0.88–2.00)
E-selectin (11)	**1.78 (1.32–2.25)**	0.01 (-0.04–0.05)	-0.01 (-0.07–0.04)	0.31 (-0.05–0.66)	1.65 (0.89–2.41)	1.89 (1.26–2.52)	NA	NA	1.68 (0.97–2.39)	1.89 (1.22–2.56)
ICAM-1 (21)	**1.77 (1.15–2.39)**	0.04 (-0.06–0.14)	-0.04 (-0.09–0.004)	-0.02 (-0.13–0.09)	1.84 (0.50–3.18)	1.75 (1.04–2.46)	1.88 (1.19–2.57)	1.07 (-0.63–2.78)	1.28 (0.39–2.17)	2.24 (1.36–3.11)

Abbreviations: SMD, Standardized mean difference; CI, Confidence Interval; PASI, Psoriasis Area and Severity Index; ELISA, Enzyme Linked Immuno Sorbant Assay; IL, Interleukin; TNF, Tumor Necrosis Factor; (hs)CRP, (high sensitivity) C-reactive protein; ICAM, Intracellular Adhesion Molecule; NA not applicable.
Values in bold are significant ($p<0.05$).

[1] Random-effects model.

[2] Mixed effects regression. The regression coefficient represents the slope of the regression line.

[3] Comparison of two groups using random effects analysis, except for measurement method for CRP, where four groups are compared.

[4] Other psoriasis types, mix of types or type not specified.

[5] Measurement method other than ELISA or not specified. With the exception of CRP, where the subgroup of other measurements is split into immunoturbidimetry[6], nephelometry[7] and a fourth group with other or not specified measurement[8].

Interleukin-6

Twenty two studies provided plasma IL-6 levels in 994 psoriasis patients and 594 controls (Table 1). Figure 2b shows a significantly higher level of IL-6 in psoriasis patients, with a pooled SMD of 1.32 (95% CI 0.83-1.81). In the forest plot, the study by Galadari et al showed high SMDs ranging from 25 to 36 for the three subgroups of psoriasis severity.[17] However, the point estimate remained significantly higher for psoriasis when excluding this study (d=1.07, 95% CI 0.65-1.49). Meta-regression for age indicates that the older the age of the patients in the study, the smaller the SMD between psoriasis patients and controls across studies (β=-0.08, p=0.04). Gender and PASI had no effect on the SMD in IL-6 (p=0.08 and p=0.66, respectively). The SMD for IL-6 was significantly lower in studies including only plaque psoriasis (n=13) compared to other studies (n=9) (Table 2), indicating that the difference in IL-6 levels between psoriasis patients and controls was larger in studies not restricted to plaque psoriasis. These studies did not have a higher PASI score, nor did they include more erythrodermic patients (Table 1).

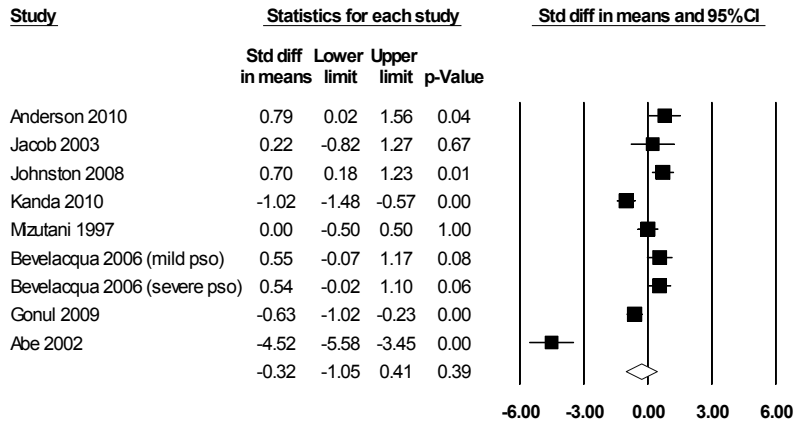
Interleukin-10

Pooling of IL-10 levels resulted in a small, positive but not statistically significant SMD between psoriasis patients and healthy controls (d=0.25; 95% CI -0.90-1.40) (Figure 2c), which could not be explained by age, gender or PASI in the meta-regression, or by psoriasis type in the subgroup analyses.

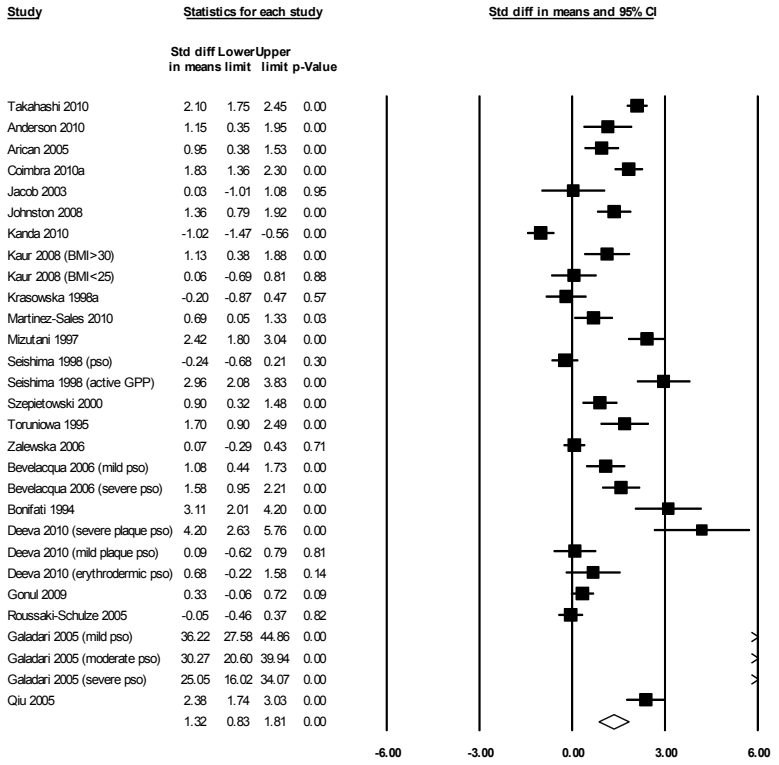
Figure 2 a to g. Forest plots showing standardized mean difference and 95% CI of individual studies and pooled standardized mean difference and 95% CI in psoriasis patients and healthy controls using random effects model.

Abbreviations: Std diff in means, Standardized mean difference; CI, Confidence Interval; pso, psoriasis; BMI, Body Mass Index; GPP, Generalized Pustular Psoriasis.

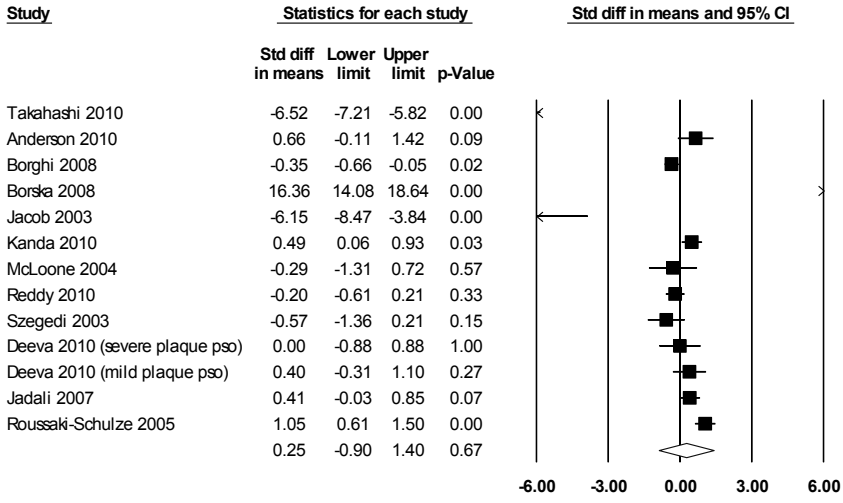
a. Interleukin-1β



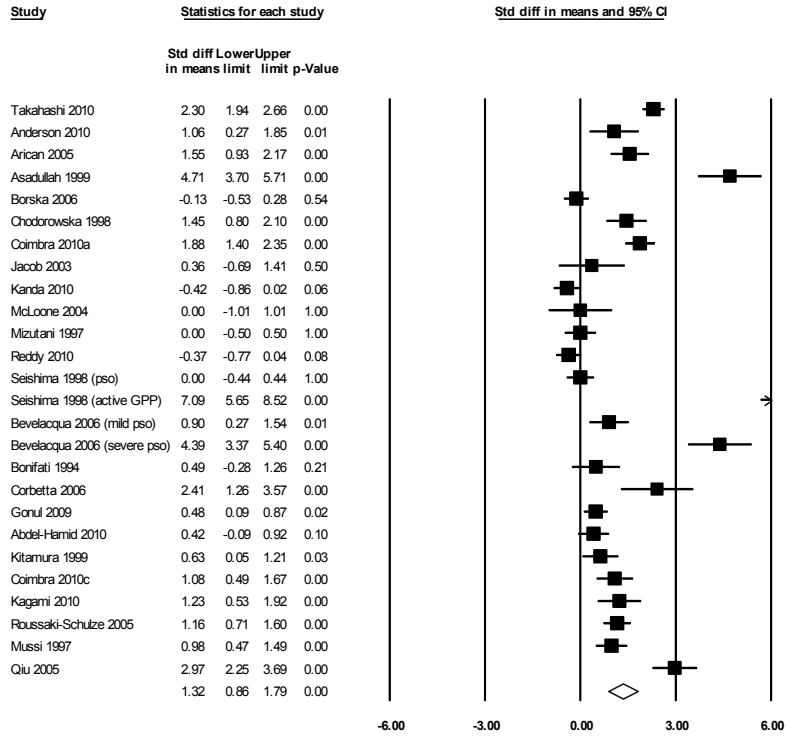
b. Interleukin-6



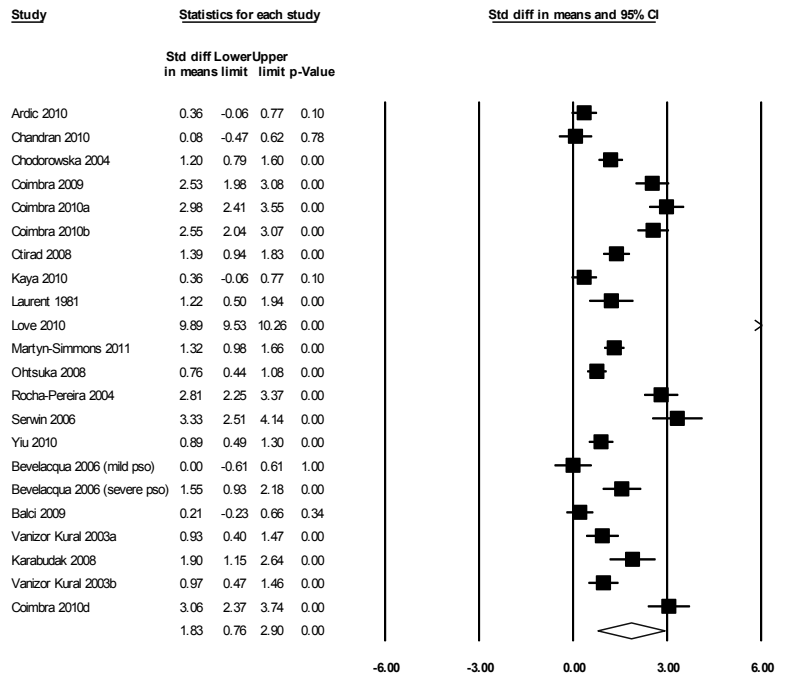
c. Interleukin-10



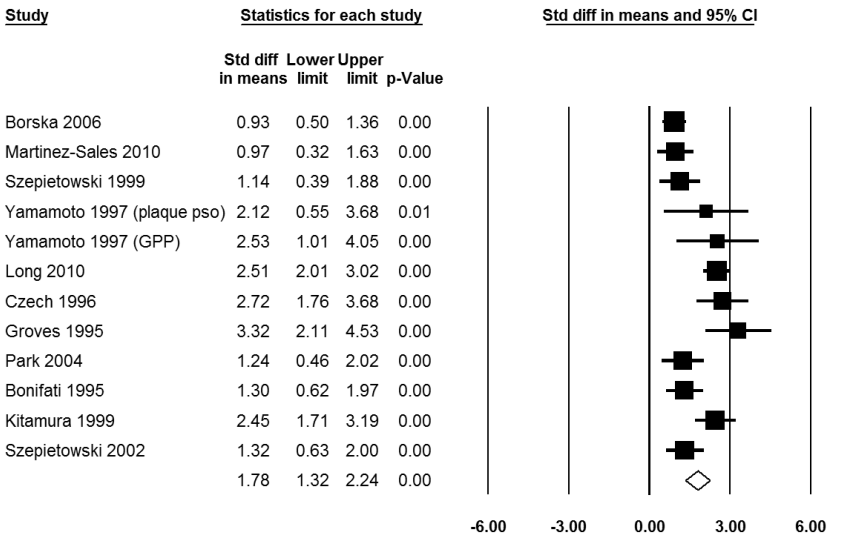
d. Tumor Necrosis Factor-α



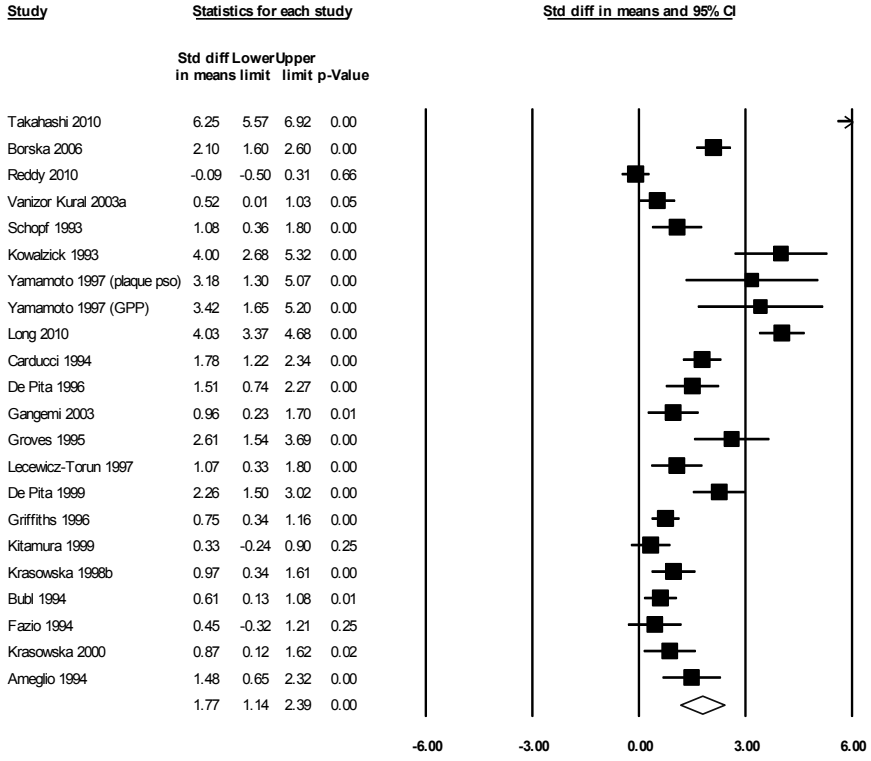
e. C-Reactive Protein



f. E-Selectin



g. Intracellular Adhesion Molecule-1



Tumor Necrosis Factor-α

The search yielded 24 studies showing an elevated SMD for TNFα of 1.32 (95% CI 0.86-1.79) (Figure 2d). Meta-regression showed that the older the age of patients within the studies, the smaller the difference in TNFα between psoriasis patients and controls (β=-0.13, p=0.002). Gender and PASI do not explain the difference in effect size between the studies.

C-Reactive Protein

The mean CRP across studies was significantly elevated in psoriasis compared to controls (d=1.83, 95% CI 0.76-2.90) (Figure 2e). The meta-regression for PASI showed a slope of 0.07 with a p=0.057, demonstrating a trend that an increase in PASI is associated with an increase in difference in mean CRP between psoriasis patients and controls. Regarding the subgroup analyses, no statistically significant differences were observed between subgroups for psoriasis type (Table 2).

E-selectin

The combined SMD for E-selectin was nearly twice as high in psoriasis compared to controls (d=1.78, 95% CI 1.32-2.25). Neither age, nor gender or psoriasis severity explained the high heterogeneity (I^2=78%) between the studies. The measurement method had no influence on the heterogeneity because all 11 studies used the ELISA technique. Analyzing the forest plot, the study by Groves et al including 9 patients with erythrodermic psoriasis appears to have the highest SMD, indicating that patients in this study with severe disease have higher levels of E-selectin than healthy controls[18] (Figure 2f).

Intracellular-Adhesion-Molecule-1

A total of 21 articles including 714 psoriasis patients and 601 controls yielded a significant positive association between psoriasis and ICAM-1 (d=1.77, 95% CI 1.15-2.39). Meta-regression and subgroup analyses did not show significant results. Interestingly the two largest studies including more than 100 therapy naïve psoriasis patients show SMDs varying from -0.09 (95% CI -0.50-0.31) to 6.25 (95% CI 5.57-6.92).[19,20] The remaining studies have SMDs which lie in between (Figure 2g).

Negative subgroups findings

The high level of heterogeneity between studies (all I^2>75%), could not be explained by the subgroup analyses. These showed that the measurement method did not have a significant impact on the SMD for any of the studied markers of inflammation. There was also no significant difference between studies with a higher and those with a lower quality assessment score, with the exception of IL-10, where nine studies with a higher score had a larger pooled effect size than the three studies with a lower score (Table 2).

Publication bias

The funnel plots for IL-1β, TNFα, CRP and ICAM-1 showed evidence of asymmetry (Supplementary Figures 2a, d, e, g). The addition of the "missing" studies imputed using the trim and fill method shifted the effect size for IL-1β and IL-10 towards significance with adjusted point estimates of -0.84 (-1.60-(-0.08)) and 1.96 (0.50-3.43) respectively. For CRP, TNFα, E-selectin and ICAM-1, the addition of the "missing" studies only increased the magnitude of the pooled effect sizes, which remained significant.

The Egger's test confirmed the presence of publication bias for TNFα (6.09, 95% CI 1.42-10.76) and ICAM-1 (5.58, 95% CI 0.003-11.17), however there also appeared to be publication bias for IL-6 (p=0.002).

DISCUSSION

The current meta-analysis shows mild systemic inflammation in psoriasis patients compared to healthy controls with five of the six investigated pro-inflammatory serum markers being increased in psoriasis. The difference is nearly two points at the most and is overall independent of age, gender, disease severity, psoriasis type, measurement methods and quality assessment for the different studies.

Contrary to expected, pooled anti-inflammatory IL-10 was not significantly decreased in psoriasis patients; of the 13 studies on IL-10, only 3 showed a significantly lower IL-10 in psoriasis. The literature on psoriasis suggests that IL-10 deficiency might play a role in its pathogenesis[21] and a study even showed that antipsoriatic treatment lead to normalization of IL-10 values.[20]

The cytokines IL-1β, IL-6 and TNFα produced by the keratinocytes are key in the activation of innate immunity through activation of dendritic and T-cells (Figure 3 and Table 3).[2] These pro-inflammatory cytokines are also produced in adipose tissue, hereby linking inflammation of the skin with obesity.[6] In this meta-analysis, pooled serum IL-1β was the only marker to not be significantly elevated in psoriasis patients compared to healthy controls. This was contrary to expected because IL-1 triggers the production of IL-6 and TNFα in the molecular cascade and should therefore also be elevated.[3] This result could be due to a limited number of studies on serum IL-1β. Age explained part of the heterogeneity between the studies for IL-6 and TNFα, indicating that the older the patients in the study, the smaller the SMD between the psoriasis patients and the controls. This could possibly be explained by decreasing immunity with increasing age.[22]

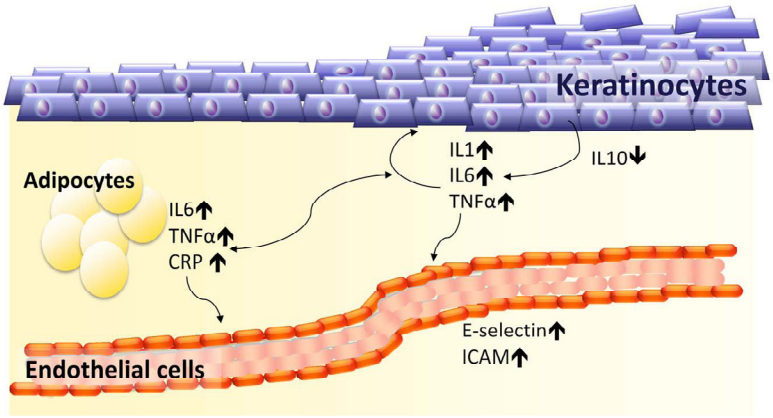


Figure 3. A simplified model, depicting the role of the inflammatory markers in this meta-analysis.

IL-1β and IL-6 act together to enhance CRP.[23] IL-6 was elevated in our analyses and can therefore explain the increased CRP obtained in psoriasis patients. In search of a novel biomarker to monitor disease progression and severity and improve cardiovascular risk prediction, CRP is also being used in other comorbidities.[9,24,25] In the past decade, numerous meta-analyses have investigated the use of CRP in the prediction of CVD, concluding that CRP is at the most a moderate predictor of CVD compared to major established risk factors.[9-11]

Table 3. Role of the selected inflammatory markers.

IL-1β	IL-1 is a pro-inflammatory cytokine which activates neutrophils, monocytes, eosinophils and basophils and triggers production of TNFα, IL-6 by macrophages. Keratinocytes are the main source of IL-1β in the skin.
IL-6	IL-6 is a pro-inflammatory cytokine and is involved in the growth and differentiation of dermal and epidermal cells and can directly stimulate T-cell migration to the epidermis. IL-1 and TNFα activate keratinocytes to produce IL-6.
IL-10	IL-10 acts as an anti-inflammatory cytokine and can be produced by different cell populations, including keratinocytes, T-cell subsets, macrophages and monocytes and is capable of inhibiting synthesis of pro-inflammatory cytokines.
TNFα	TNFα influences the proliferation, activation and differentiation of many cells and enhances the synthesis of IL-1, IL-6 and expression of adhesion molecules such as E-selectin and ICAM-1.
(hs)CRP	CRP is a pro-inflammatory acute phase protein produced by the liver and a sensitive marker of systemic inflammation. Traditional assays for CRP are insufficiently sensitive for measuring the lower serum values associated with atherosclerotic disease. These can be measured by the newer hsCRP assays.
E-selectin	E-selectin is a pro-inflammatory soluble cell adhesion molecule expressed on endothelial cells activated by cytokines. It is enhanced by TNFα and CRP through endothelial cells. During inflammation, E-selectin recruits leucocytes to the site of injury.
ICAM-1	The soluble intracellular adhesion molecule ICAM-1 is induced by TNFα, IL1 and CRP through endothelial cells. It is expressed by the vascular endothelium, macrophages and lymphocytes. It causes leucocytes to bind to endothelial cells and then to migrate into tissues.

Abbreviations: IL, Interleukin; TNF, Tumor Necrosis Factor; (hs)CRP, (high sensitivity) C-reactive protein; ICAM, Intracellular Adhesion Molecule.

The soluble adhesion molecules E-selectin and ICAM-1, located at the end of the inflammatory cascade, are enhanced by TNFα and CRP through endothelial cells.[26,27] Of the inflammatory markers studied in this meta-analysis, the SMD between psoriasis and controls was the highest for E-selectin and ICAM-1. These adhesion molecules have been available for several decades; however their clinical relevance is yet unclear. They can be involved in various conditions, from infections, vasculitis, cancer to atherosclerosis and CVD.[27,28] However, the evidence on adhesion molecules is contradictory, even within the same condition such as CVD.[12,29]

In other inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, there seems to be a general consensus that inflammatory markers are elevated in patients compared to healthy controls.[30-32] This consensus is based on convenient individual studies rather than on meta-analysis. The concept that the elevation of inflammatory markers leads to systemic inflammation and comorbidities such as CVD seems to be logical, however there is a large gap between measuring systemic inflammation in the blood and the registration of events, and it is a further challenge to determine whether these events have a causal relationship to the exposure.[26] This gap should be filled with hard evidence in order to prove a possible relationship between exposure and outcome. The present study confirms the elevation of markers in psoriasis, however does not investigate the link between this modest elevation and eventual metabolic diseases or cardiovascular events.

As to the clinical relevance of these markers of inflammation based on the results of this meta-analysis, we believe that they cannot be considered as markers of disease severity because they were only modestly increased in psoriasis patients compared to controls and the increase was independent of the PASI. However this does not exclude the fact that markers of inflammation could be important targets for therapy, such as is the case with TNFα, and recently IL-17.[33]

Strengths and limitations

This is the first and largest meta-analysis on markers of inflammation in psoriasis combining 78 studies with a psoriasis and comparative group of healthy subjects to pool information on seven different serum markers. We performed an extensive systematic search using three databases to retrieve articles. We limited selection bias of the articles by not restricting the language of the search and included foreign articles if the abstract and full text provided sufficient data. We included a considerably large number of studies, which were mainly observational in nature and consisted of small numbers of psoriasis patients. We not only investigated pro-inflammatory markers but also anti-inflammatory IL-10.

We analyzed baseline values of markers in treatment-naïve psoriasis patients and therefore could not draw conclusions on the use of serum markers in measuring disease progression.

Approximately two studies per outcome did not report the mean marker values completely and therefore could not be included in the meta-analysis, however we do not expect this to have influenced the obtained effect size because these studies showed varying results.[34-42]

We assume that most patients had moderate to severe disease (75% of studies had a PASI>10), possibly limiting the generalizability of our findings. On the other hand, the analyses showed that that the effect size for the serum markers was independent of disease severity.

In order to explain the high degree of heterogeneity between the studies, we conducted several meta-regression and subgroup analyses. The results should be interpreted cautiously because they were based on covariates at the level of the study in contrast to covariates from individual patient data, possibly leading to aggregation bias.

We used three different methods to assess publication bias and depending on the method used there seemed to be publication bias or not. This bias however did not change the direction of the association for any of the markers when using the trim and fill method.

The quality assessment scores were not high due to incomplete data on several items, the latter also influencing our selection of subgroup analyses. We acknowledge that REMARK is more a reporting device; nevertheless we did not expect the study quality to influence the studied outcomes because we compared objective measurements (serum marker levels) which are not dependent on factors such as blinding or allocation concealment. This was confirmed in the subgroup analysis showing no difference in pooled estimate between studies with a high and those with a low quality assessment score.

CONCLUSION

Psoriasis patients show at the most mild systemic inflammation compared to controls. The elevation of the inflammatory markers is independent of psoriasis type and severity, questioning their use as biomarkers. In order to investigate the clinical relevance of this modest increase in inflammation, it would be interesting to conduct a review summarizing the evidence on the effect of antipsoriatic therapy on markers of inflammation.

ACKNOWLEDGMENTS

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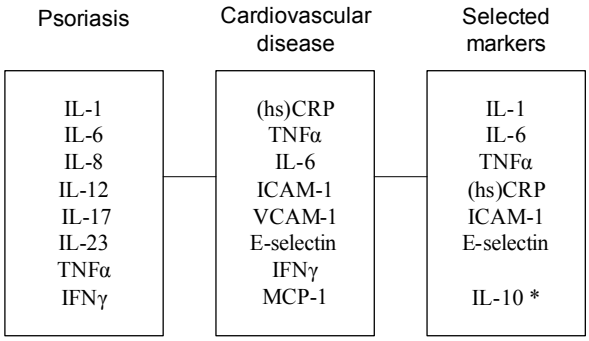
Supplementary Table 1. Search strategy.

Database	Search string
PubMed	psoriasis[tw] AND (interleukin-1[tw] OR il-1[tw] OR interleukin-10[tw] OR il-10[tw] OR interleukin-6[tw] OR il-6[tw] OR tumor necrosis factor*[tw] OR tnf[tw] OR c-reactive protein*[tw] OR crp[tw] OR icam[tw] OR sicam[tw] OR intercellular adhesion molecule*[tw] OR e-selectin*[tw] OR se-selectin*[tw] OR endothelial leukocyte adhesion molecule*[tw] OR elam[tw] OR selam[tw]) NOT (animals[mesh] NOT humans[mesh]) NOT (case reports[pt] OR letter[pt])
Embase	(psoriasis/syn AND (((interleukin OR il) NEAR/1 (1 OR 6 OR 10 OR 1a* OR 1α OR 1b* OR 1β)):ti,ab,de OR ('tumor necrosis' NEAR/1 factor*):ti,ab,de OR tnf:ti,ab,de OR ('c-reactive' NEAR/1 protein*):ti,ab,de OR crp:ti,ab,de OR icam:ti,ab,de OR sicam:ti,ab,de OR ('intercellular adhesion' NEAR/1 molecule*):ti,ab,de OR ((e OR se) NEAR/1 selectin*):ti,ab,de OR ('endothelial leukocyte adhesion' NEAR/1 molecule*):ti,ab,de OR elam:ti,ab,de OR selam:ti,ab,de) NOT ([animals]/lim NOT [humans]/lim)) NOT ('case reports' OR 'case report'):ti,ab,de NOT [letter]/lim
Web of Science	psoriasis AND (((interleukin OR il) SAME (1 OR 6 OR 10 OR 1a OR 1alpha OR 1alfa OR 1b OR 1beta)) OR "tumor necrosis factor" OR tnf OR "c reactive protein" OR crp OR icam OR sicam OR "intercellular adhesion molecule*" OR "e selectin*" OR "se selectin*" OR "endothelial leukocyte adhesion molecule*" OR elam OR selam) NOT (animal* NOT human*) NOT "case report" NOT "case reports"

Supplementary Figure 1. Selected inflammatory serum markers based on a selection of markers analyzed in psoriasis and cardiovascular disease.

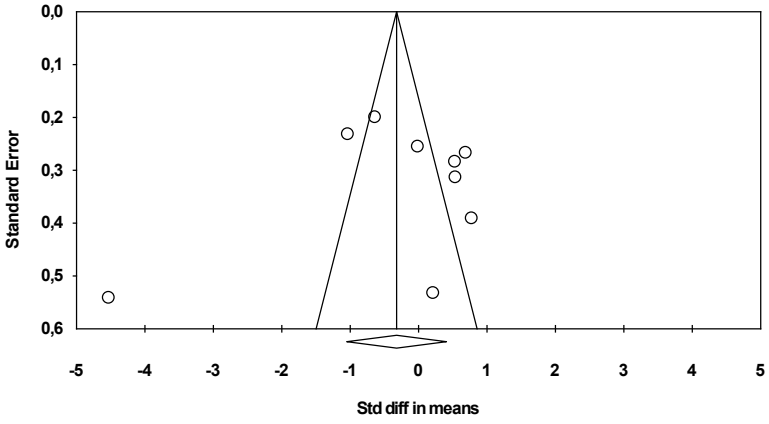


Abbreviations: IL, Interleukin; hsCRP, high sensitivity C-Reactive Protein; TNFα, Tumor Necrosis Factor alpha; ICAM-1, Intracellular Adhesion Molecule 1; IFNγ, Interferon gamma; MCP-1, Monocyte Chemoattractant Protein-1.

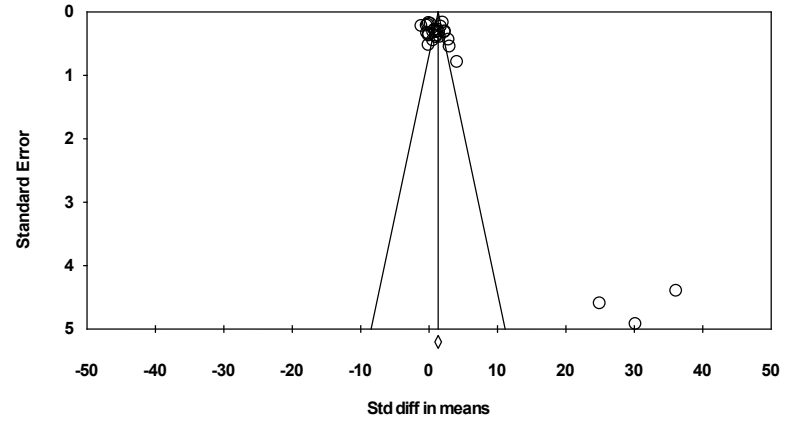
* Il-10 was deliberately chosen as an anti-inflammatory serum marker.

Supplementary Figures 2a to g. Funnel plots identifying publication bias for all studied outcomes.
Abbreviations: Std diff in means, Standardized mean difference.

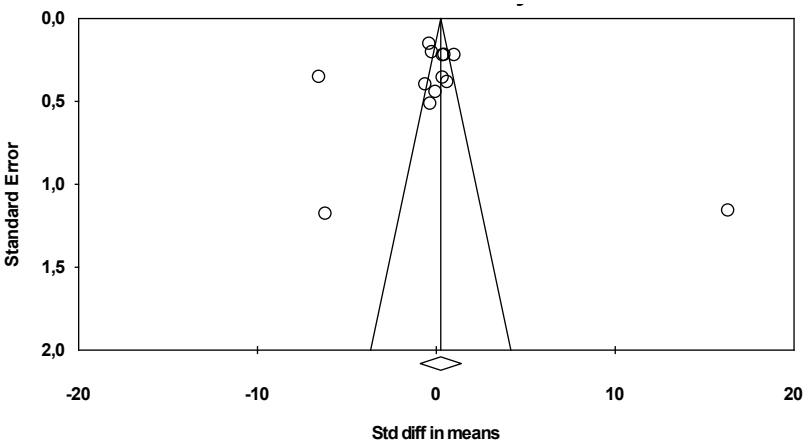
a. Interleukin-1β



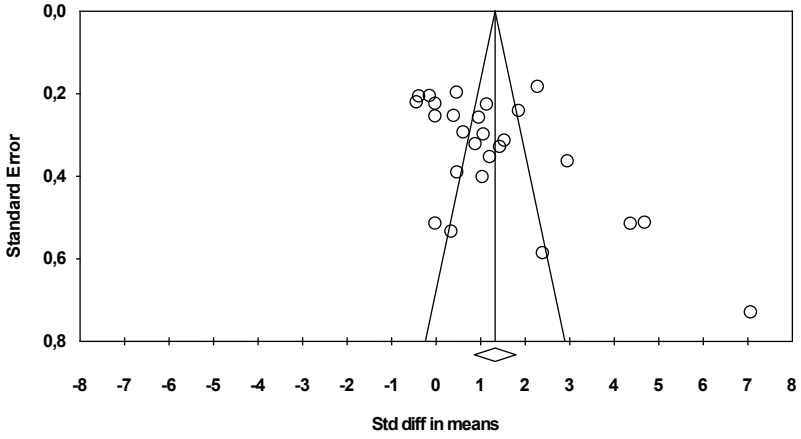
b. Interleukin-6



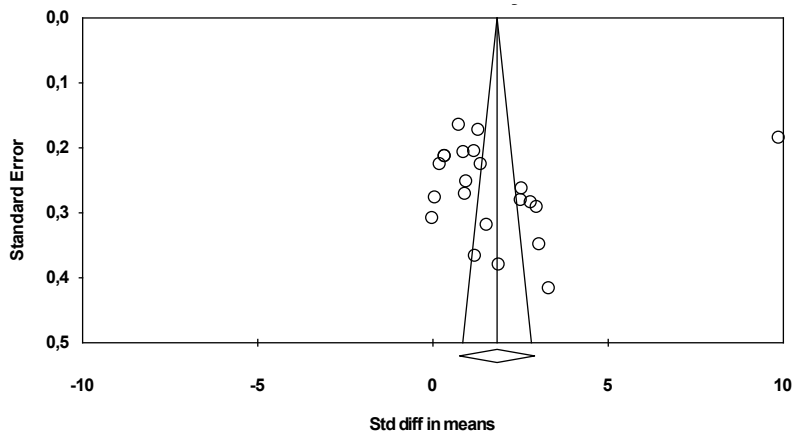
c. Interleukin-10



d. Tumor Necrosis Factor-α

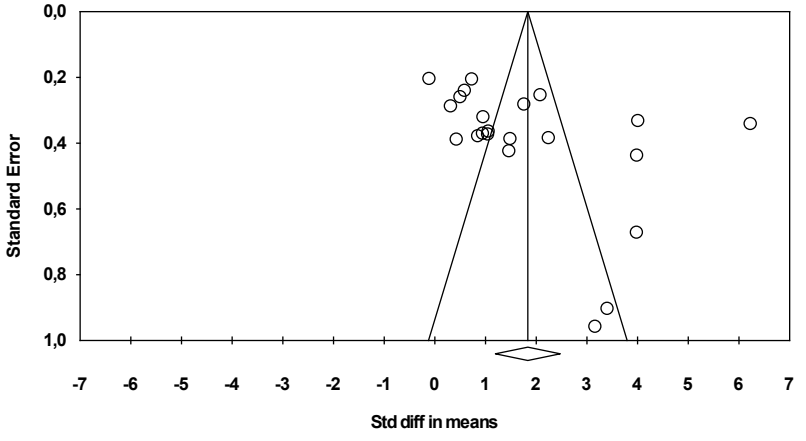


e. C-Reactive Protein



f. E-Selectin

g. Intracellular Adhesion Molecule-1



Chapter 4.2

Psoriasis is not associated with atherosclerosis and incident cardiovascular events: the Rotterdam Study

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ABSTRACT

Psoriasis has been suggested to be an independent risk factor for cardiovascular disease, however available studies have shown inconsistent results. In this study, embedded within the population-based Rotterdam Study, we aimed to assess the association between psoriasis and cardiovascular outcomes.

Adjusted means were calculated for subclinical atherosclerosis using general linear models. Using Cox regression, the hazards of cardiovascular events for psoriasis, as a time dependant variable, were calculated.

A total of 262 psoriasis (of which 24% had systemic or UV treatment) and 8,009 reference subjects were followed for a mean of 11 years. Psoriasis patients were significantly younger, smoked more and had higher diastolic blood-pressure and BMI levels. The adjusted carotid intima-media-thickness was 1.02±0.18mm for psoriasis and 1.02±0.16mm for reference subjects. Similarly, crude and adjusted ankle-brachial index, pulse wave velocity and coronary artery calcium scores did not differ between the two groups. The risk of incident cardiovascular disease was not increased in psoriasis (adjusted HR 0.73, 95% CI 0.50-1.06). The results were similar when coronary heart disease, stroke and heart failure were analyzed separately.

Psoriasis patients with predominantly mild disease from the general population are as likely to develop atherosclerosis and cardiovascular events as subjects without psoriasis.

INTRODUCTION

Psoriasis is an inflammatory condition affecting the skin and, in approximately 10% of the patients, the joints.[1,2] In the last decade, most observational studies on psoriasis have suggested that the chronic inflammation in psoriasis is more than skin deep and results in a 'psoriatic march' that can lead to endothelial dysfunction, atherosclerosis and eventually to cardiovascular disease.[3] Case-control studies assessing the association between psoriasis and atherosclerosis are often based on patients from tertiary clinics with more severe and recalcitrant disease and a higher degree of impairment and are therefore not necessarily representative of the general psoriasis population.[4-6] Studies based on routine databases or selected groups have shown an elevated risk of myocardial infarction (MI) in a specific subgroup, namely young psoriasis patients treated with systemic medication.[7-10] Emerging research on cardiovascular disease in psoriasis in large population-based cohorts using research and routine databases, report inconsistent results.[7-27] Differences across studies can be explained by discrepancies in case ascertainment and definition of exposure and outcome, study-setting and design, adjustment for cardiovascular risk factors, inadequate statistical power and residual confounding.

There is no population-based study thus far, where all subjects receive the same examinations independent of their health status, focussing simultaneously on atherosclerosis and hard cardiovascular outcomes, adjusting for several risk factors. Therefore the present study was designed to address subclinical atherosclerosis, coronary heart disease (CHD), stroke and heart failure in subjects diagnosed with psoriasis by a physician and reference subjects in the population-based Rotterdam Study, where detailed information on cardiovascular risk factors is available.[28]

MATERIALS AND METHODS

Study population

This study is embedded within the prospective population-based Rotterdam Study, described elsewhere.[28] All inhabitants of a suburb of Rotterdam aged 45 years and older were invited to participate. The baseline examination was completed between 1990 and 1993. In 2000, the cohort was extended to include inhabitants who reached the age of 55 years or migrated to the research area. In 2005, a second expansion included all persons aged 45 and older. Participants have been followed since inclusion and examined every 4 years. The current study using data from the original and first extended cohort comprised 10,994 subjects (participation rate of 75%). Information on non-participants was not available because they had not consented to participate in the study.

The Rotterdam Study was approved by the Medical Ethics Committee of Erasmus University, Rotterdam, the Netherlands and adhered to the Helsinki Guidelines. All participants gave written informed consent.

Assessment of psoriasis

Psoriasis subjects in the Rotterdam Study were identified on a continuous basis. Medical record review was performed after a digital search for subjects with a diagnostic code for psoriasis by the GP (S91) and for participants with psoriasis medication according to the Anatomical Therapeutic Chemical Classification System.[29] The GP records were searched for diagnosis of psoriasis in the GP notes, medical specialist reports and hospital discharge letters, registering the medical provider who diagnosed psoriasis. Patients were defined as having "possible" psoriasis if they had a prescription for one of the following medications: psoralens, dithranol, calcipotriol, calcitriol, coal tar, tacrolimus, pimecrolimus, fumaric acid, acitretin, methotrexate, ciclosporin, or biologicals. Definite psoriasis cases (n=277) were patients with a diagnosis of psoriasis by a dermatologist or rheumatologist, patients whose disease was mentioned twice or more by the GP, patients with a diagnosis of psoriasis based on psoriasis specific medication, and patients with psoriasis at the time of skin examination (Supplementary Figure 1). The latter was available in a subgroup of 1,551 of the 10,994 subjects who were screened for dermatological conditions between August 2010 and November 2011. For psoriasis patients from this group (n=47), the date of onset and Psoriasis Area and Severity Index (PASI) were recorded. The PASI was available in 14% of patients and ranged from 0.4-12.7.

We validated our algorithm using skin examination conducted in 1,551 subjects as the golden standard. The sensitivity and specificity were both 98%, with a positive predictive value (PPV) of 62% and negative predictive value of 99.9%. Accounting for patients who did not have psoriasis at skin examination, but during the interview reported having red, scaly plaques in the past, yielded a PPV value of 82%.

The date of psoriasis onset was the date of first diagnosis in the medical record (by the dermatologist, other medical specialist or the GP), the date of first antipsoriatic medication, or the self-reported date of onset (n=18), whichever came first. For the analyses, the "index date" for psoriasis was determined based on the date of psoriasis onset: this was the study entrance date for prevalent cases (with psoriasis onset before study inclusion) or a later date corresponding to the date of psoriasis onset for patients who developed psoriasis after inclusion to the study.

Patients had mild psoriasis if they had only used topical treatment, had a PASI<10 at skin examination, or if they had not been treated at all, during follow-up. Patients with moderate to severe disease had been treated with UV therapy or systemic medication during follow-up[10,27] or had a PASI>10.

Reference population

The reference population consisted of 9,023 participants in the Rotterdam Study who did not use any of the above mentioned antipsoriatic medications during the follow-up and did not have a GP code for psoriasis. Their "index date" was the date of inclusion in the study.

Subclinical measures of atherosclerosis

Atherosclerosis measurements were repeated at center visits. For psoriasis patients, the first available measurement after the date of onset was used in our analyses. If this was not available, measurements up to 6 months prior to the date of onset were included and otherwise psoriasis patients were excluded from the analyses. For reference subjects, the first available measurements after inclusion in the study were used. Carotid atherosclerosis and lower extremity atherosclerosis were assessed by measuring carotid intima-media thickness (IMT) and plaques and ankle-brachial index (ABI). Peripheral artery disease (PAD) was defined as ABI values of 0.9 or less.[30] Coronary artery calcium (CAC) was assessed in the epicardial coronary arteries on CT scans. Carotid-femoral pulse wave velocity (PWV) measured aortic stiffness. The methods for these measurements are described in Supplementary Material and Methods and Supplementary Figure 2 depicts when they were performed. The measurements were not available for the entire population due to various reasons: no consent obtained, measurements conducted after patients left follow-up and limited availability of ultrasonographers. Additionally, for psoriasis patients we only included measures of atherosclerosis after psoriasis onset in our analyses.

Cardiovascular outcomes

The clinical outcomes of this study are incident cardiovascular morbidity and mortality, described in detail previously.[31] The medical records of all study participants were continuously assessed for events. In brief, we investigated incident "hard" CHD defined as MI (fatal or non-fatal) and fatal CHD, excluding subjects with a history of MI or revascularization.[32] Stroke was defined as cerebral infarction diagnosed by CT scan, excluding stroke by intracerebral haemorrhage, possibly caused by trauma and therefore not a cardiovascular event.[33,34] Heart failure was defined according to the European Society of Cardiology.[35] Methods on assignment of prevalent and incident heart failure cases in the Rotterdam Study have been elaborated elsewhere.[36,37]

The primary outcome was incident cardiovascular disease (CVD); the secondary outcomes were the components of CVD, namely CHD, cerebral infarction diagnosed by CT, and heart failure. Median interquartile range (IQR) for follow-up was 9.11 (7.55, 16.03) years.

Cardiovascular risk factors

Information on traditional cardiovascular risk factors was collected: age, gender, smoking, body mass index (BMI), total and high-density lipoprotein (HDL) cholesterol, systolic and

diastolic blood pressure, use of lipid-lowering drugs, diabetes mellitus defined as the use of oral blood-glucose-lowering drugs or insulin or non-fasting glucose >11mmol/L or fasting glucose > 7mmol/L. Hypertension was defined as systolic pressure ≥140mm Hg or diastolic pressure ≥90mm Hg (mean of 2 measurements) or use of blood-pressure-lowering medication for the indication of hypertension.[28]

Statistical analysis

The distribution of baseline characteristics was compared using t-test for continuous variables and Chi-Square for proportions. For atherosclerosis, we compared crude and adjusted means (± standard deviation [SD]) for IMT, ABI, and PWV and proportions for PAD and carotid plaques across the groups using general linear model analysis of variance. Two adjusted models were performed; once for age and gender, and the second model adjusting additionally for BMI, systolic blood pressure, treatment of hypertension, total and HDL cholesterol, current smoking and diabetes mellitus.[38,39] Due to the skewed distribution of CAC and to handle CAC scores of zero, we used the natural logarithm of (CAC+1) and back-transformed the results to obtain the geometric mean (95% confidence interval [CI]). We calculated crude and adjusted hazard ratio (HR) and 95% CI for developing incident CHD, stroke and heart failure using a time-dependant Cox regression analysis where psoriasis was treated as a time-dependent variable using the index date. In this analysis the follow-up in years started from the date of inclusion to the Rotterdam Study until the first cardiovascular event, until death or the end of the follow-up period predetermined for the analyses, whichever came first. We adjusted these analyses according to the two above-mentioned models.

For all analyses, subjects with more than four missing covariates were excluded. For subjects with less than four missing values, the covariates were imputed using multiple imputation (maximum missing values were 2.8%, for BMI).

Sensitivity analysis

To assess the impact of psoriasis severity, the analyses were repeated for patients with mild and moderate to severe disease. In a Cox regression analysis we investigated whether patients with psoriasis onset prior to study inclusion (and therefore a longer duration of psoriasis) had an increased risk of CVD.

All analyses were conducted with SPSS version 17.0. (SPSS inc., Chicago, IL, USA).

RESULTS

A total of 262 psoriasis patients and 8,009 reference subjects were followed for a median (IQR) of 11.1 (8.2; 16.5) and 9.1 (7.5; 16.0) years respectively. Of the 262 psoriasis patients, 44% were

Table 1. Characteristics of psoriasis patients and reference population in the Rotterdam Study.

Variable	Psoriasis N=262	Reference N=8,009	p-value[1]
Age	64.32 ± 6.82	68.78 ± 9.47	<0.001
Male, n (%)	115 (43.9)	3,377 (42.2)	0.56
Psoriasis therapy[2]			
Topical therapy only, n (%)	158 (56.1)	N/A	
UV therapy, n (%)	31 (14.8)	N/A	
Systemic therapy, n (%)	46 (17.6)	N/A	
No therapy, n (%)	52 (19.8)	N/A	
Systolic blood pressure, mm Hg	141 ± 21.92	140.7 ± 22.2	0.85
Diastolic blood pressure, mm Hg	76.7 ± 10.6	75.2 ± 11.8	0.05
Antihypertensive treatment, n (%)	85 (32.4)	2,515 (31.4)	0.72
Hypertension, n (%)[3]	157 (59.9)	5,036 (62.9)	0.33
Body mass index, kg/m^2	27.1 ± 3.9	26.5 ± 3.8	0.007
Waist to hip ratio	0.91 ± 0.08	0.91 ± 0.09	0.32
Total cholesterol, mmol/L	6.27 ± 1.24	6.37 ± 1.21	0.20
HDL cholesterol, mmol/L	1.34 ± 0.35	1.35 ± 0.36	0.63
Cholesterol-lowering medication, n (%)	23 (8.8)	403 (5.0)	0.007
Diabetes mellitus, n (%)	18 (6.9)	698 (8.7)	0.30
Current smoking, n (%)	85 (32.4)	1,773 (22.1)	<0.001

Abbreviations: UV, Ultraviolet; HDL, High density lipoprotein; mmol/l, millimole per liter.
Data are mean ± standard deviation for continuous variables and proportions for dichotomous variables.
[1] P-values were calculated with the t-test for continuous variables and with the Chi-square test for proportions.
[2] Percentages do not add up to 100% because some patients had UV and systemic therapy.
[3] Hypertension: blood pressure ≥140/90 and/or antihypertensive medication.

diagnosed by the dermatologist, 2% by the rheumatologist, 32% by the GP, 16% based on antipsoriatic medication and 6% were diagnosed with psoriasis during skin examination. The gender distribution was comparable in both groups, but the psoriasis subjects were slightly younger (p<0.001) (Table 1). Almost a quarter of patients had received systemic medication or ultraviolet (UV) therapy. At study entry, psoriasis patients smoked significantly more (32% versus 22%), had a slightly higher BMI (27.1kg/m^2 versus 26.5kg/m^2) and diastolic blood pressure and used more cholesterol-lowering medication. There were no significant differences in total and HDL cholesterol, systolic blood pressure, antihypertensive treatment or diabetes mellitus between the two groups (Table 1).

Subclinical measures of atherosclerosis

The crude mean carotid IMT for psoriasis was 1.00±0.20mm and 1.02±0.21mm for reference subjects (p=0.47; Table 2). Neither adjusting for age and gender alone nor adjusting

Table 2. Subclinical measures of atherosclerosis in psoriasis patients after psoriasis diagnosis, compared with the reference population.

Measure of atherosclerosis	N	Crude mean ± SD[1]	p-value	Age and gender adjusted mean ± SD[1]	p-value	Fully adjusted mean ± SD[1,2]	p-value
Carotid intima-media thickness, mm							
Psoriasis	143	1.00 ± 0.20	0.47	1.03 ± 0.19	0.49	1.02 ± 0.18	0.62
Reference	6,525	1.02 ± 0.21		1.02 ± 0.16		1.02 ± 0.16	
Carotid plaque, %							
Psoriasis	165	71.5%	0.09	75.5%	0.004	73.9%	0.01
Reference	6,519	65.1%		65.0%		65.0%	
Ankle-brachial index							
Psoriasis	139	1.06 ± 0.17	0.40	1.03 ± 0.19	0.21	1.04 ± 0.18	0.51
Reference	7,022	1.04 ± 0.20		1.05 ± 0.17		1.05 ± 0.17	
Peripheral artery disease, %[3]							
Psoriasis	139	14.4%	0.26	20.1%	0.48	19.0%	0.73
Reference	7,022	18.1%		18.0%		18.0%	
Coronary artery calcium score[4]							
Psoriasis	106	53.51 (32.99 – 86.42)	0.86	59.64 (38.50 – 92.04)	0.77	51.40 (33.59 - 78.41)	0.69
Reference	3,168	55.98 (51.26 – 61.12)		55.77 (51.50 – 60.41)		56.05 (51.89 - 60.55)	
Pulse-wave velocity, m/s							
Psoriasis	117	13.39 ± 3.14	0.54	13.61 ± 2.81	0.11	13.49 ± 2.60	0.24
Reference	4,551	13.21 ± 3.17		13.20 ± 2.77		13.20 ± 2.56	

Abbreviations: SD, standard deviation; CI, Confidence Interval.

[1] Means are estimated marginal means using general linear model analysis of variance.

[2] Adjusted for age, gender, current smoking, body mass index, total cholesterol, HDL-cholesterol, systolic blood pressure, antihypertensive medication and diabetes mellitus.

[3] Peripheral artery disease was defined as ankle-brachial values of 0.9 or less.

[4] Coronary artery calcium score data were log transformed; we present back-transformed geometric means and 95% CI.

for all cardiovascular risk factors at the time of the IMT measurement, changed the mean IMT considerably for the two groups (fully adjusted mean 1.02±0.18mm for psoriasis and 1.02±0.16mm for the reference population, p=0.62). Of the psoriasis patients, 72% had a carotid plaque compared to 65% of the reference population (p=0.09). When adjusting for age, gender and cardiovascular risk factors, psoriasis patients had 9% more plaques than the reference population (p=0.01). The mean ABI was not significantly different with a fully adjusted mean of 1.04±0.18 for psoriasis and 1.05±0.17 for reference subjects. There was no significant difference in presence of PAD between the two groups (p=0.26).

The crude geometric mean CAC score was 53.51 (95% CI 32.99-86.42) in psoriasis compared to 55.98 (95% CI 51.26-61.12) in the reference group (p=0.86). The adjusted CAC scores

did not change considerably and the difference between the two cohorts remained non-significant. Carotid-femoral PWV was also not significantly different in the crude and fully adjusted models, with an adjusted PWV of 13.49±2.60m/s for psoriasis and 13.20±2.56m/s for the reference population (Table 2).

Cardiovascular disease

We followed 259 psoriasis patients and 7,931 reference subjects for incident cardiovascular events. There were a total of 1,613 cardiovascular events during more than 89,000 person years of follow-up, of which 28 occurred among psoriasis patients. The crude HR for psoriasis in developing the composite outcome CVD, treating psoriasis as a time-dependant variable, was borderline significant with a HR of 0.69 (95% CI 0.48-1.00) suggesting that psoriasis was protective for CVD. However, after adjusting for age and gender the association was no longer significant (HR 0.83, 95% CI 0.57-1.21) and this was comparable to the fully adjusted HR of 0.73 (95% CI 0.50-1.06). When separating CVD into its components, the crude risk for incident CHD was not significantly different in psoriasis patients and reference subjects (HR 0.69, 95% CI 0.40-1.16) and remained similar after adjusting for age and gender and cardiovascular risk factors (Table 3). The fully adjusted risk of developing incident cerebral infarction was not significantly elevated in psoriasis (HR 0.69, 95% CI 0.36-1.34) nor was the risk for incident heart failure (HR 0.80, 95% CI 0.51-1.25).

Sensitivity analysis

For subclinical measures of atherosclerosis, the subgroup analyses in mild psoriasis patients and in those with moderate to severe disease, each compared to the reference subjects showed no significant difference between the groups (data not shown). Patients with mild psoriasis (n=197), representing 76% of psoriasis cohort, showed no elevated adjusted risk of developing CHD (HR 0.85, 95% CI 0.49-1.47), cerebral infarction (HR 0.62, 95% CI 0.28-1.38) or heart failure (HR 1.01, 95% CI 0.64-1.59). The 62 patients with moderate to severe psoriasis had a fully adjusted HR for CHD of 0.21 (95% CI 0.03-1.50). The significantly decreased risk of heart failure of 0.12 (95% CI 0.02-0.83) and CVD of 0.37 (95% CI 0.15-0.89) for the subgroup of moderate to severe psoriasis was no longer significant after adjusting for age and gender (Table 3).

The fully adjusted risk of developing CVD was not elevated in patients with prevalent psoriasis at inclusion to the study compared to incident psoriasis cases and reference subjects (HR 0.64, 95% CI 0.37-1.10), indicating that patients with longer duration of psoriatic disease in our study did not have an increased risk of developing a cardiovascular event.

Table 3. Psoriasis and risk of cardiovascular disease and its components.

Event	Total psoriasis N=259		Mild psoriasis N=197		Moderate to severe psoriasis N=62	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Cardiovascular disease[1]						
N_{pso}=28 N_{ref}=1,585						
Crude	0.69 (0.48-1.00)	0.05	0.85 (0.57-1.29)	0.45	0.37 (0.15-0.89)	0.03
Age and gender adjusted	0.83 (0.57-1.21)	0.15	0.98 (0.65-1.48)	0.92	0.49 (0.21-1.19)	0.11
Fully adjusted[2]	0.73 (0.50-1.06)	0.10	0.84 (0.56-1.27)	0.41	0.46 (0.19-1.10)	0.08
Coronary heart disease						
N_{pso}=14 N_{ref}=812						
Crude	0.69 (0.40-1.16)	0.16	0.94 (0.54-1.62)	0.81	0.15 (0.02-1.08)	0.06
Age and gender adjusted	0.80 (0.47-1.36)	0.41	1.02 (0.59-1.76)	0.96	0.21 (0.03-1.50)	0.12
Fully adjusted[2]	0.70 (0.41-1.19)	0.18	0.85 (0.49-1.47)	0.56	0.21 (0.03-1.50)	0.12
Cerebral infarction						
N_{pso}=9 N_{ref}=467						
Crude	0.73 (0.37-1.42)	0.36	0.69 (0.31-1.55)	0.37	0.82 (0.27-2.56)	0.74
Age and gender adjusted	0.79 (0.41-1.52)	0.48	0.71 (0.32-1.59)	0.41	1.01 (0.32-3.13)	0.99
Fully adjusted[2]	0.69 (0.36-1.34)	0.28	0.62 (0.28-1.38)	0.24	0.93 (0.30-2.90)	0.90
Heart failure						
N_{pso}=20 N_{ref}=1,091						
Crude	0.74 (0.47-1.15)	0.17	1.02 (0.65-1.60)	0.94	0.12 (0.02-0.83)	0.03
Age and gender adjusted	0.91 (0.58-1.41)	0.67	1.17 (0.74-1.84)	0.50	0.17 (0.02-1.22)	0.08
Fully adjusted[2]	0.80 (0.51-1.25)	0.33	1.01 (0.64-1.59)	0.97	0.16 (0.02-1.15)	0.07

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; N_{pso} and N_{ref}, number of events in psoriasis and reference group, respectively.

N psoriasis=259, N reference=7,931

All HRs were calculated using time dependant Cox regression with psoriasis as time dependant variable using the index date.

[1] Cardiovascular disease includes coronary heart disease, cerebral infarction confirmed by computed tomography, and heart failure.

[2] Adjusted for age, gender, current smoking, body mass index, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, antihypertensive medication, diabetes mellitus.

DISCUSSION

The present prospective population-based study with more than 10 years of follow-up, showed similar risk factor profile for CVD among subjects with psoriasis compared to those without psoriasis. Extensively examined psoriasis patients diagnosed by the dermatologist or the GP were not at a higher risk for subclinical atherosclerosis compared to the reference population and psoriasis was not an independent risk factor for incident cardiovascular events.

Subclinical measures of atherosclerosis

Among approximately 140 psoriasis cases, none of the adjusted subclinical measures of atherosclerosis were higher compared to the reference population, with the exception of the binary outcome carotid plaque which was significantly elevated in psoriasis after adjustment. Carotid plaques could be actually increased in psoriasis patients compared to controls. However other reasons are likely to explain this finding. Because of the number of tests in our study (n=8), chance findings due to multiple testing may occur: the p-value for the fully adjusted model for plaque exceeded the Bonferroni corrected p-value of 0.006 (0.05/8). Furthermore, using a dichotomous variable might have affected our findings; when IMT was used as a continuous variable, no significant difference was seen between the two groups. Our findings are in line with a study observing no difference in endothelial dysfunction between psoriasis patients and healthy controls after exclusion of CVD and traditional cardiovascular risk factors.[40] Other studies analyzing IMT, ABI, CAC and PWV in psoriasis patients compared to controls are few, are relatively small case-control studies with a suboptimal selection of controls and are conducted in selected groups such as patients recruited from hospital dermatology outpatient clinics[5,41-45] and dermatology inpatients with relatively severe disease.[46,47] These factors could explain the discrepancy between the elevated measures of atherosclerosis in psoriasis patients compared to the controls in these studies and the absence of a significant difference in our study. The mean values for IMT in the Rotterdam Study are in the range of the mean IMT among psoriasis outpatients without cardiovascular risk factors or history of CVD in two studies.[42,43] The control groups in these studies were much smaller, consisted of healthy individuals and had significantly lower IMT values, compared to the psoriasis group. The IMT studies and the only two other studies measuring PWV[41,44] included patients who were 20 years younger on average than the Rotterdam Study population possibly explaining the lower IMT and PWV values obtained.

Only one other study analyzed CAC score in 32 patients with a long history of severe psoriasis, showing a higher mean CAC score (78±140) than in the Rotterdam Study, but with a CAC score range similar to our study. The controls, matched for cardiovascular risk factors, had a considerably lower CAC score than psoriasis patients, possibly because they were enrolled from a different source.[47]

Coronary heart disease

Our results, based on hard endpoints of MI and CHD mortality, are in line with studies confirming the absence of association between psoriasis and MI.[7,23,24,27] A German case-control study showed that psoriasis was associated with cardiovascular risk factors, but not with MI and stroke, with ORs of 1.14 (95% CI 0.81-1.62) and 0.97 (95% CI 0.61-1.54) respectively.[23] A large Dutch cohort demonstrated that the adjusted risk of ischemic heart disease was comparable between the psoriasis and reference population (HR 1.05, 95% CI 0.95-1.17).[27] Another case-control study among Israeli inpatients showed that the association between CVD and psoriasis was no longer significant after adjusting for risk factors.[24] In the PUVA Follow Up Study, psoriasis patients were not at an increased risk of CVD deaths (standardized mortality ratio 1.02, 95% CI 0.90-1.60), with the exception of patients with extremely severe disease.[25]

Of more than 20 original studies on the association between MI, CHD and psoriasis, the majority were based on secondary databases, limited by detection bias and where information on cardiovascular confounders was not always available. Although most studies have demonstrated increased, but varying risks of cardiovascular events, a recent systematic review concluded that there was no consistency in the literature as to elevated cardiovascular risk factors in psoriasis patients.[48] Even the studies investigating these outcomes using the same database (GPRD) resulted in varying risks owing to differences in study design, exposure and outcome definitions and depending on whether incident or prevalent cases of CVD were investigated.[7,10,14,18,31] Initially, all psoriasis patients seemed to be at an increased risk of developing CVD, but now it is considered to be limited to young patients with severe disease.[7-11] Interestingly, in our study the risk estimates obtained for CVD in psoriasis patients, albeit not statistically significant, were consistently below one, suggesting a possible protective effect for which we have no explanation.

Stroke

The risk of stroke in psoriasis has been investigated in several studies, but with different outcome definitions: ischemic, hemorrhagic, unspecified stroke, stroke confirmed or not by computed tomography (CT) to including all subtypes. In studies assessing CVD, stroke should be restricted to ischemic stroke excluding non-cardiovascular related subtypes to avoid overestimation of cardiovascular events. The impact of this outcome definition is nicely illustrated in two publications using the Taiwanese Health Insurance database: in one study psoriasis is not associated with stroke (OR 1.04, 95% CI 0.82-1.33)[26] and in another psoriasis is associated with ischemic stroke (HR 1.27, 95% CI 1.05-1.52).[12] A Danish population-based study showed that the adjusted risk for ischemic stroke was significantly higher in mild and severe psoriasis patients compared to the reference population.[11] The disparity with our results may be explained by the difference in degree of adjustment for cardiovascular risk factors, measuring study outcomes independent of patients' health status, the use of a narrow definition of stroke and assessment of incident versus prevalent stroke.[13,14]

Heart failure

Only one other study analyzed heart failure using data from the Taiwan National Health Insurance, adjusting for income, geographical region and level of urbanization of the patients' community with an OR for psoriasis of 1.63 (95% CI 1.22-2.19).[26] In this same study mild psoriasis patients did not have an elevated risk for heart failure, however a significant association was found with psoriasis patients exposed to photo- or systemic therapy (OR 1.69, 95% CI 1.24-2.30). The discrepancy with our results can be explained by missing adjustment for cardiovascular risk factors.

Strengths and limitations

The Rotterdam Study is a detailed population-based study with a follow-up of more than 10 years and a very high participation rate among the inhabitants of the same district in Rotterdam.[28] Psoriasis subjects underwent the same examinations as the reference population every 4 years, irrespective of disease severity, health status and overall healthcare utilization, minimizing selection and detection bias. Epidemiology of CVD being one of the main study objectives of the Rotterdam Study, this therefore reduces residual confounding on cardiovascular predictors and disease. In this study the standardized measures of atherosclerosis are state-of-the-art and the identification of cardiovascular events (using clinical data, symptoms, ECG changes, echocardiography, X-rays, CT, diagnoses by medical specialists and not only ICD codes)[31] limits possible non-differential misclassification bias. The present study used hard endpoints, such as hard CHD and CT-confirmed stroke, to minimize the effect of over-detection of softer endpoints, such as angina or transient ischemic attack, and therefore the outcomes are less likely to be affected by subject status or psoriatic disease. Psoriasis patients were identified using medical files, pharmacy data and, in a subset, clinical examinations, resulting in the expected prevalence of 3% (of which 24% had moderate to severe disease), confirming the validity of the exposure definition.[49,50] For all psoriasis patients a reliable date of onset of disease was available. To explore the cause-effect relationship of whether chronic psoriasis-related-inflammation would lead to atherosclerosis and CVD, we restricted the analyses to measurements and events occurring after psoriasis onset during an observation period of more than 10 years.

Subjects were only included in the Rotterdam Study if they were 55 years and older. This limits the generalizability of our findings to younger or non-Caucasian populations. In the studies that document increased risk of CVD, the greatest relative risk is in the younger population with severe disease; however due to the design of the Rotterdam Study, we were unable to investigate this risk in younger patients. Moreover the majority of the patients in our study had mild disease. We acknowledge the limited sample size of the psoriasis group; however this is inherent to a population-based-approach. We found no significant difference in risk of CVD between psoriasis and reference subjects. Although our study may have been underpowered for some of the endpoints, a larger sample size would most likely

lead to a narrower 95% CI but not alter the HR substantially. Moreover, for the subclinical measures of atherosclerosis, post hoc power analyses showed that our study had very high power to show a difference between the two groups (data not shown). The case definition of psoriasis may have resulted in the identification of false positive psoriasis cases, which could have diluted the effect of psoriasis on CVD, resulting in risk estimates closer to one (i.e. differential misclassification bias). This is the largest study to concurrently assess subclinical atherosclerosis and incident cardiovascular events adjusting for cardiovascular risk factors in the same population-based sample of psoriasis patients and reference subjects. The case definition of psoriasis was predominantly based on healthcare utilization (i.e., diagnoses by physicians and drug dispenses), not taking into account patients who had not sought care for their psoriasis. These would have most probably been mild psoriasis cases and we expect that including them would not have influenced our results considerably. In order to capture the entire range of psoriasis patients in the future, screening for skin conditions in Rotterdam Study participants is ongoing, independent of whether participants seek medical care from their GP or take antipsoriatic medication.

CONCLUSION

Psoriasis patients from the general population with predominantly mild disease have a comparable cardiovascular risk profile to subjects without psoriasis and do not have a higher prevalence of subclinical atherosclerosis. In the present cohort, psoriasis did not appear to be an independent risk factor for incident cardiovascular events. Ultimately, a prospective cohort of incident psoriasis cases of substantial size, varying in age and disease severity could clarify the relationship between psoriasis, atherosclerosis and CVD.

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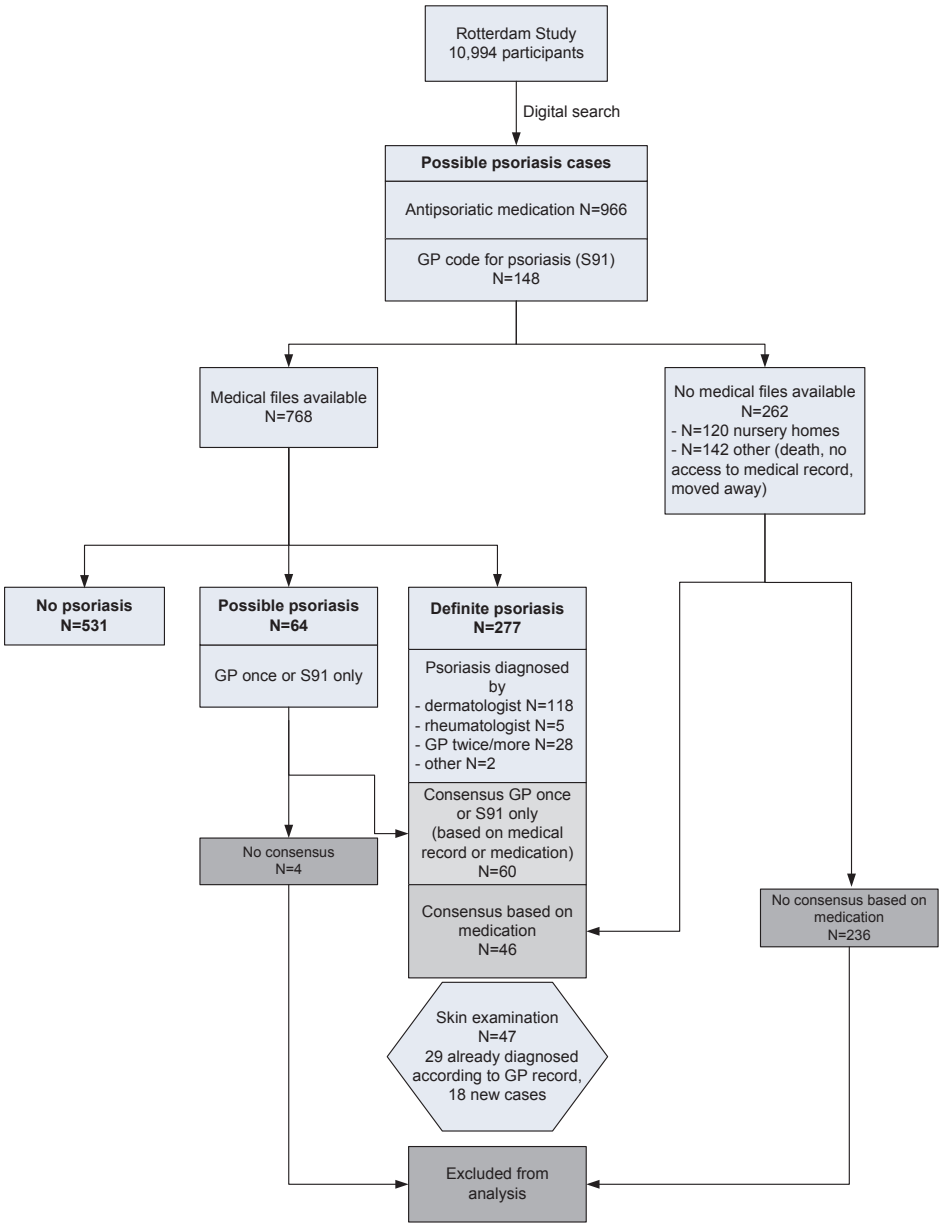
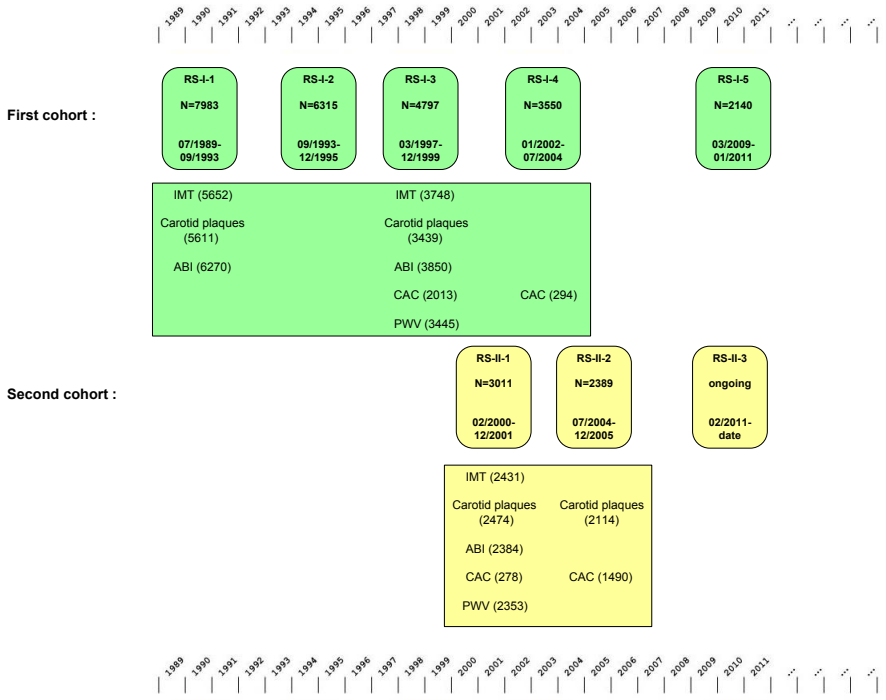
Supplementary Figure 1. Psoriasis case identification.



Supplementary Figure 2. Flowchart of the Rotterdam Study depicting measurements conducted at subsequent visits to the research center.



Abbreviations: IMT, Intima media thickness; ABI, Ankle brachial index; CAC, Coronary artery calcium; PWV, Pulse wave velocity.
The number of available measurements per outcome, per visit to the research center is indicated in parentheses.

SUPPLEMENTARY MATERIALS AND METHODS: MEASUREMENTS OF ATHEROSCLEROSIS.

Carotid atherosclerosis was assessed using the maximum common carotid intima-media thickness summarized as the average of the maximal measurements from the near and far walls of the left and right carotid arteries. Carotid plaques were defined as a focal widening relative to adjacent segments, with protrusion into the lumen composed either of only calcified deposits or a combination of calcification and non-calcified material and assessed in the common carotid, bifurcation, and internal carotid arteries.[1] Ultrasonography of the carotid arteries was performed with a 7.5 MHz linear array transducer (ATL UltraMark IV; Advanced Technology Laboratories, Bethel, Washington).

Lower extremity atherosclerosis was measured using the ankle-brachial index (ABI) by computing the ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm. ABI was calculated for each leg and the lowest ABI in either leg was used in the analysis.[2,3] Values greater than 1.4 were excluded because high ABI may represent a different underlying pathology related to calcified, non-compressible arterial vessels.

Coronary artery calcium was assessed in the epicardial coronary arteries on scans obtained with either a C-150 electron beam computed tomography scanner (Imatron, South San Francisco, California) or a 16 or 64 slice multidetector computed tomography scanner (Somatom Sensation 16 or 64; Siemens, Forchheim, Germany) and quantified using the Agatson method.[4,5]

Carotid-femoral pulse wave velocity was assessed with an automatic device (Complior; Artech Medical, Pantin, France) that measures the time delay between the rapid upstroke of the feet of simultaneously recorded pulse waves in the carotid and the femoral arteries in meters per second.[6]

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Chapter 5

General Discussion & Perspectives

1. From Health Related Quality of Life to clinical depression: the disease spectrum evaluated.
   1.1 The link between Health Related Quality of Life and depression
   1.2 Influence of psoriasis severity
   1.3 Patient reported outcome measures in treatment evaluation
   1.4 Clinical implications
   1.5 Educational interventions
   1.6 The inflammation hypothesis in depression
   Conclusion 1

2. Inflammation and cardiovascular disease: the psoriatic march decomposed.
   2.1 Cardiovascular risk factors
   2.2 Markers of inflammation
   2.3 Subclinical measures of atherosclerosis
   2.4 Cardiovascular events
   2.5 Surveillance bias
   2.6 The choice of systemic therapies to prevent cardiovascular outcomes
   Conclusion 2

1. FROM HEALTH RELATED QUALITY OF LIFE TO CLINICAL DEPRESSION: THE DISEASE SPECTRUM EVALUATED.

In this thesis we used a multifaceted approach to analyzing depression in psoriasis, by investigating Health Related Quality of Life (HRQoL), depressive symptoms, clinical depression and antidepressant use, using various data sources and statistical methods. These include a cross-sectional study, two population-based cohorts and a systematic review of the literature incorporated into a meta-analysis.

A total of 40% of psoriasis patients from dermatological outpatient clinics in Belgium reported a substantial impact of psoriasis on their lives according to dermatology specific questionnaires (Chapter 2.1). The level of generic impairment of the quality of life was comparable to the level observed in other chronic diseases such as asthma, diabetes and rheumatoid arthritis and also comparable to the level found in prostate cancer patients and patients with hematological malignancies. Patients with moderate to severe disease reported higher quality of life scores than those with milder disease, regardless of whether dermatology specific or generic instruments were used.

According to a systematic review and meta-analysis of the literature on depression in psoriasis, one quarter of psoriasis patients manifest depressive symptoms and 12% are diagnosed with clinical depression (Chapter 3.1). Psoriasis patients are one and a half times more likely to manifest signs of clinical depression compared with their healthy peers. Depressive symptoms in psoriasis were assessed in mostly small studies based in tertiary centers. The relationship between psoriasis and clinical depression was investigated in large population-based studies using administrative databases. The actual prevalence of depression according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria is hard to estimate due to the scarcity of available studies. However it is definitely lower than the prevalence of depressive symptoms. This difference was also noted in the population-based Rotterdam Study, where we demonstrated that symptoms of depression assessed according to the Center for Epidemiologic Studies Depression Scale (CES-D) >16 were manifest in 8.5% of 236 psoriasis patients, however when the patients with an elevated CES-D score underwent clinical examination by the psychiatrist, only 3 patients were diagnosed with a major or minor depression according to the DSM-IV (Chapter 3.3).

According to the meta-analysis we conducted in chapter 3.1, the overall pooled proportion for antidepressant use in psoriasis in the literature was 9% (6-14%). Data on drug dispenses from the Dutch pharmacy database showed that psoriasis patients were one and a half times more likely to use an antidepressant compared to the reference group (after adjustment for age, gender and general healthcare consumption). The use of antidepressant medication peaked when patients sought medical care for their psoriasis and thereafter (Chapter 3.2).

The effect of this increased healthcare seeking behavior was also reflected in the results from the Dutch General Practitioner (GP) database which show that psoriasis patients use significantly more medication of all therapeutic groups than patients without psoriasis of the same gender, age and GP practice (Chapter 2.2). Patients with moderate to severe psoriasis had more prescriptions for medication compared to patients with mild disease. In the Dutch GP database the odds of antidepressant use was 1.35, 95% confidence interval (CI) 1.26-1.45 in psoriasis patients compared to controls without psoriasis, which is in in the range of the results from the data we obtained from the Dutch pharmacy database (odds ratio [OR] 1.47, 95% CI 1.43-1.51), with a dose-response relationship for patients with moderate to severe disease in both studies.

The results of the studies conducted in this thesis lead to the chart in Figure 1, depicting the association between psoriasis, health related quality of life, depressive symptoms, clinical depression and antidepressant use. In the following, an attempt will be made to comment on the steps delineated in this figure.

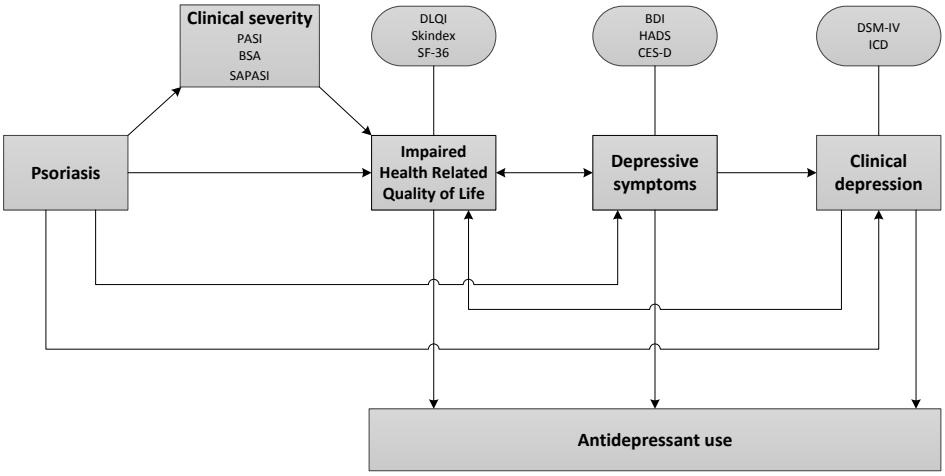

Figure 1. Potential pathways underlying the association between psoriasis and clinical depression. Abbreviations: PASI, Psoriasis Area and Severity Index; BSA, Body Surface Area; SAPASI, Self-administered PASI; DLQI, Dermatology Life Quality Index; SF-36, Short Form-36; BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; CES-D, Center for Epidemiologic Studies Depression Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; ICD, International Classification of Diseases.

1.1 The link between Health Related Quality of Life and depression

A structural equations modeling approach to test and estimate causal relations between objective disease severity, psoriasis symptoms, HRQoL and depressive symptoms, confirmed that psoriasis might first lead to problems in everyday life measured by a HRQoL instru-

ment. One of the models showed that a very high proportion of the variability of depressive symptoms is explained by HRQoL impairment, demonstrating that it is directly related to the development of depressive symptoms.[1]

Although further studies in dermatological patients are lacking, an observational study in outpatients with depression showed that they had substantial and long-lasting decrements in multiple domains of functioning and well-being of the Short form 36 (SF-36).[2] There is increasing interest in HRQoL as a measure of response to antidepressant treatment because it evaluates not only symptoms, but also physical, mental and social functioning and role performance. The Factors influencing Depression Endpoints Research (FINDER) study was designed to estimate HRQoL using the SF-36 and European Quality of Life-5 Dimensions (EQ-5D) in more than 3,000 patients with a clinically diagnosed episode of depression at baseline and after commencing antidepressant treatment.[3] A higher number of previous depressive episodes and a longer duration of the current depressive episode were associated with a poorer HRQoL outcome. Further, severity of depression measured by the Hospital Anxiety and Depression Score (HADS) at baseline was significantly associated with a worse SF-36 Mental component summary. Outpatients with an untreated episode of depression experienced improvements in HRQoL after starting antidepressant medication. We can conclude that there is a reciprocal relationship between HRQoL and depression: impairment of HRQoL due to psoriasis can lead to depressive symptoms, and depression also impairs HRQoL.

1.2 Influence of psoriasis severity

In chapter 2.1, Belgian psoriasis patients with more severe disease reported a higher impact of psoriasis on their lives. This was also confirmed by the fact that erythrodermic patients had the highest scores on the Dermatology Life Quality Index (DLQI) and Skindex-17 scales. However other studies have shown that the correlation between severity of psoriasis and impact on HRQoL is weak[4] and that psoriasis caries a substantial burden even when disease severity is not extensive.[5] According to an internet survey among psoriasis patients in the United States, lower self-administered Psoriasis Area and Severity Index (SAPASI) scores were associated with higher CES-D scores, after adjustment for HRQoL using the DLQI.[1] An 11 year prospective study demonstrated a 25% decrease in the psychosocial impact of psoriasis on patients' HRQoL. This suggests that patients either accommodate to the impact of their disease over time, or that they are adequately treated and the impact decreases when clinical disease severity is also reduced.[6]

1.3 Patient reported outcome measures in treatment evaluation

Treatment dissatisfaction in psoriasis patients. More than 45% of patients with psoriasis and psoriatic arthritis participating in a survey from the National Psoriasis Foundation in the United States were dissatisfied with their treatment.[7] At the time of the survey 50% of patients with mild, 24% with moderate and 9% with severe disease, were not receiving treat-

ment for their psoriasis. 20% of patients with severe disease were using topical medication alone. The dissatisfaction was highest in the group of patients with moderate disease (Body Surface Area [BSA] of 3-10%), supporting the evidence that disease severity is not a good indicator to measure patient satisfaction. Some patients consider their psoriasis to be very debilitating despite low disease severity scores.[5] Setting clear treatment goals in psoriasis can help to overcome impairment in HRQoL, high disease burden and treatment dissatisfaction that can lead to low treatment compliance.[8] A review of generic and dermatology specific HRQoL instruments recommended the combination of SF-36 and Skindex-29 as instruments of choice.[9] Involving psoriasis patients in the process of the choice of treatment is likely to improve their satisfaction with treatment and also clinical outcome.[10]

The question arises about the role patient reported outcome measures (PROMs) should play in daily practice and which instrument should be used. The choice of instrument depends on the study setting, the disease and the purpose of its use. It is essential to distinguish between a clinical setting primarily benefiting the patient and a clinical trial setting. In the former setting (primary, secondary or tertiary), time constraint, practicality and the consequences for treatment should be taken into consideration. In the context of a clinical trial investigating a new antipsoriatic therapy for example, it is essential to use a standardized instrument that enables to compare the results with studies on other treatments, to evaluate the impact of a treatment and to compare treatments costs. Standardized instruments are also used to compare HRQoL between different conditions.

HRQoL instruments for psoriasis. In the case of psoriasis, several instruments have been used: dermatology specific, disease specific and generic instruments measuring the HRQoL, but also conceptual questionnaires such as those assessing depressive symptoms. The DLQI was developed by Finlay and colleagues for use in clinical daily practice and was designed as a generic HRQoL tool.[11] It was derived from answers to questions posed to dermatology patients on how their skin disease affected them. It is presently the most commonly used PROM in dermatology. In the United Kingdom, it is even required to use the DLQI to determine whether psoriasis patients are eligible to receive biological drugs, and in the European S3 guidelines, treatment goals are defined using the DLQI. However this questionnaire has several content and methodological limitations and does not meet the recent psychometric requirements for instruments assessing the HRQoL. It focusses more on physical limitations of skin disease and very few items address the psychological impact of the skin disease, which is important in psoriasis. It failed to fit the Rasch analysis and suffers from item bias because more than half of the questions are affected by external factors such as age, gender and diagnosis.[12,13] The disease specific Psoriasis Disability Index (PDI) was developed to quantify the impact of psoriasis on patients' lives, however with suboptimal subscales and psychometric properties.[14,15]

Which questionnaire to use? We suggest the use of an alternative dermatology-specific instrument such as the Skindex-29 or the Skindex-17, a Rasch reduced version of the Skindex-29.[16] This instrument has been extensively studied and refined in different population-based samples and has been validated for psoriasis.[17-19] It also contains more questions on the psychological impact of skin disease. Nevertheless, a disadvantage of dermatology specific instruments is that, due to the large number of dermatological diseases and their varying impact on HRQoL, it is unlikely that one single dermatology specific instrument could capture the variation of complaints for different dermatological conditions.

The generic SF-36 is the most commonly used instrument to assess HRQoL for all diseases and is very useful if physicians are interested in comparing QoL between different conditions. Because psoriasis has an impact on the psychological well-being of patients, questionnaires assessing depressive symptoms such as the Beck Depression Inventory (BDI) and the HADS are also commonly used.

Overlap between HRQoL and depression questionnaires. HRQoL instruments partly measure concepts that are also contained in depression instruments. The mental component of the generic SF-36 includes questions on emotional well-being, social functioning, energy and fatigue.[20] Of the dermatology specific questionnaires, the Skindex focuses the most on elements that are also part of the depression questionnaires such as sleep, tiredness and depression and also addresses feelings of embarrassment, humiliation and frustration. Symptom severity and impact on everyday life seem closely correlated, which explains much of the correlation between HRQoL instruments and depression instruments in patients with psoriasis, and partly explains the overestimation of the prevalence of depressive symptoms based on depression questionnaires.

1.4 Clinical implications

It is a challenge to administer a questionnaire to psoriasis patients visiting the outpatient clinic, specifically due to shortage in time to administer it, and also to interpret the results. However addressing the impact of psoriasis on patients in everyday clinical practice is essential; it is an efficient way of assessing how patients feel about their skin condition which may aid to measure treatment success, to make therapeutic choices such as switching to another treatment or to determine the usefulness of starting a systemic treatment. An example of the usefulness of determining QoL is suggesting a more aggressive treatment for a patient with active psoriasis and signs of depression, but also patients with “only” nail psoriasis and no skin involvement may benefit from systemic treatment if they experience strong impairment of their QoL.

Physicians should use an empathic approach and not only address the physical aspects but also the psychosocial aspects of psoriasis. In practice, this could be accomplished by asking a general question such as how psoriasis affects their daily life, social activities or

relationships, which could be quantified using a visual analogue score. If there is a significant impact of psoriasis on daily life, a validated instrument could be used. This would preferably be a disease specific instrument of which only one has been developed for psoriasis.[15] In this thesis we show that more than 25% of psoriasis patients from predominantly tertiary centers manifest signs of depressive symptoms, therefore these symptoms need to be addressed in the questionnaires. However, questions on sleeping pattern, changes in appetite, sadness and interest in life are not incorporated in the dermatology specific questionnaires. Until then, we recommend the use of the Skindex to measure the impact of psoriasis on patients' QoL and if depression is suspected during medical consultation, we recommend the use of a depression questionnaire such as the BDI or HADS. The advantage of using for example the SF-36 or the Skindex is that these instruments have been validated for psoriasis,[16,21,22] while validation studies for depression questionnaires such as the BDI, HADS or CES-D in psoriasis have yet to be conducted. On the other hand, we could consider the routine use of the Skindex questionnaire at baseline and during treatment, to monitor the effect of treatment and treatment satisfaction in combination with disease severity. The S3 guidelines propose a minimum efficacy goal at 10-16 weeks after initiation of systemic therapy, consisting of a PASI 50 and a DLQI of less than 5 points (no effect to moderate effect on patients' life). The treatment should be regarded as inefficient and stopped if these goals are not met and an alternative treatment initiated.[23] Although recommended in the S3 guidelines, presently, disease severity and QoL are mainly measured in the context of clinical trials, but seldom in regular patient care. If QoL instruments are to be used in outpatient clinics to monitor systemic treatment, the frequency of their administration and the influence of their outcome on the choice or modification of treatment should be clarified.

1.5 Educational interventions

The impact of psoriasis on the QoL of patients and the fact that it can lead to depressive symptoms and clinical depression, make it inevitable to address these aspects of this chronic and debilitating skin disease. Personalized antipsoriatic treatment for improvement of psoriasis clinical outcomes must go hand in hand with coping strategies and interventions to improve QoL, ascertain and treat possible depression. Several concepts of educational and behavioral interventions have been described for psoriasis and psychological interventions enhance the effectiveness of standard treatments.[24-27] Physicians in Ghent (Belgium) launched an educational program for patients with chronic diseases combining cognitive educational sessions, stress-reduction techniques and skin workshops facilitated by experts, with a significant improvement of QoL after the intervention.[28] An internet survey showed that dissatisfaction with antipsoriatic treatment was higher in patients who had a higher likelihood of depression according to the CES-D score and less than half of the patients with psoriasis and depressive symptoms was receiving treatment for depression.[1] Increasing patient's knowledge about their skin disease and treatment can encourage participation in the

choice of treatment and can contribute towards patients satisfaction, treatment compliance and improvement of clinical outcome.[29]

1.6 The inflammation hypothesis in depression

Another hypothesis underlying the relationship between psoriasis and clinical depression could be chronic inflammation. Clinical studies have demonstrated that depression is associated with increased levels of serum cytokines.[30-32] In the population-based Rotterdam Study, subjects with increased levels of interleukin 6 (IL-6) were more likely to have a depressive disorder.[33] In a meta-analysis a significant association was seen between clinical depression and C-reactive protein (CRP), IL-1 and IL-6. The association was much higher when clinical interviews were used compared to using questionnaires assessing depressive symptoms.[32] The pro-inflammatory cytokine Tumor necrosis factor-alpha (TNFα) is also believed to be involved in depression.[34] A randomized trial showed that 12 weeks of treatment of psoriasis with a TNFα inhibitor, reduces the symptoms of depression. However we should take into account the fact that in this study the majority of participants either did not have depressive symptoms or had predominantly mild depressive symptoms.[35,36] This could be attributed to the improvement of clinical severity but also due to the anti-inflammatory effect of the drug. A concept finding (phase O) clinical study is being conducted to detect systemic inflammation and abnormality of cerebral glucose metabolism using PET/CT to determine the association with metabolic syndrome and major depressive symptoms in patients with psoriasis (ClinicalTrials.gov identifier: NCT01661127). We do not know whether the relationship between depression and inflammation is causal in nature and the biological plausibility is questionable. We doubt that the relationship between psoriasis and depression is mediated by systemic inflammation. It seems more logical to believe that psoriasis leads to depression through its impact on the emotional, social and physical aspects of an individual's life, thus the HRQoL.

CONCLUSION 1

Assessing the impact of psoriasis on a patients' quality of life, setting treatment goals and expectations prior to initiation of therapy and evaluation of treatment using patient reported outcomes are indispensable in the care of psoriasis, regardless of whether they are outpatients or participating in clinical trials. A holistic approach to psoriasis characterized by personalized treatment and the use of interventions to address the well-being of patients should become a pillar of antipsoriatic therapy.

2. INFLAMMATION AND CARDIOVASCULAR DISEASE: THE PSORIATIC MARCH DECOMPOSED.

There is evidence in the literature that psoriasis could be triggered by risk factors such as smoking, obesity and weight gain.[37-39] Inflammation of the skin or inflammation caused by risk factors leads to increased inflammatory serum markers. Systemic inflammation subsequently causes atherosclerosis and eventually leads to cardiovascular events such as myocardial infarction and stroke. This "psoriatic march"[40] seems biologically plausible, however it is not that straightforward.[41] In this thesis we attempted to investigate and clarify the different steps depicted in Figure 2.

2.1 Cardiovascular risk factors

In the population-based Rotterdam Study, the risk factors smoking, body mass index, diastolic blood pressure and the use of lipid lowering agents, were significantly more elevated in the psoriasis group. There were no significant differences in total cholesterol and high-density lipoprotein (HDL) cholesterol, systolic blood pressure or diabetes between the psoriasis patients and the reference population (Chapter 4.2). These results are partly in line with those from a general-practice database from the United Kingdom, (The Health Improvement Network [THIN]), where obesity, raised triglyceride levels, hypertension and raised glucose levels were more common in psoriasis patients than in controls. Psoriasis was associated with the metabolic syndrome after adjustment for age, gender and follow-up, also in a "dose-response" manner.[42] In chapter 2.2, based on prescription data from the Dutch GP database, we found similar results: psoriasis patients used more medication associated with the metabolic syndrome, namely lipid lowering agents, antihypertensive drugs and blood thinning agents, with higher prescriptions for moderate to severe than for mild psoriasis. However we noticed that psoriasis patients have an increased use of medication from all therapeutic classes, including medication we expected to be unrelated to psoriasis, such as antiemetics, spasmolytics, ophthalmologicals or antivertigo preparations. Based on these results, we conclude that psoriasis patients have increased overall drug utilization, regardless of whether the medication is associated with the metabolic syndrome or not. It is therefore uncertain if the presence of metabolic syndrome in psoriasis is real or a result of the increased health care utilization in this group of patients with chronic skin disease. Physicians should not screen these patients more than they would others, unless it is medically indicated.

2.2 Markers of inflammation

The hypothesis of a causal link between psoriasis and comorbidities based on systemic inflammation or common genetic predisposition has been suggested.[40,43] Due to the vast amount of literature available on the subject of psoriasis, inflammation, metabolic syndrome and cardiovascular disease, it is always possible to find a logical explanation linking these

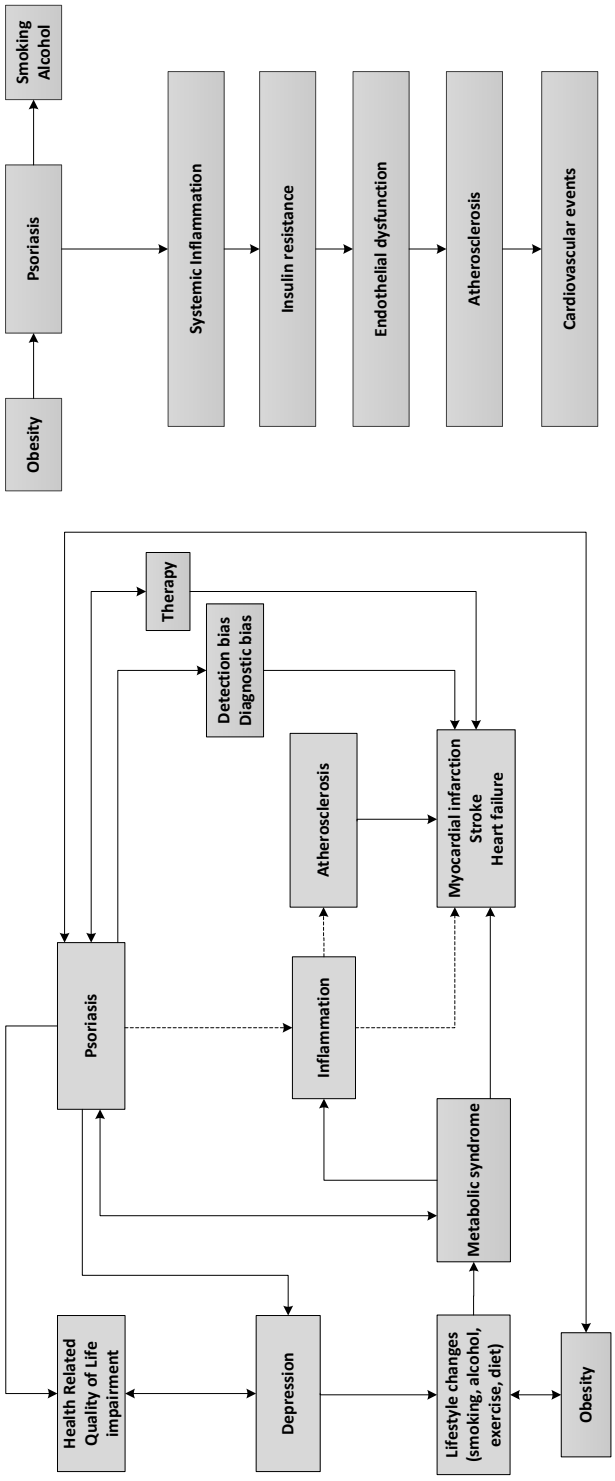

Figure 2. The "psoriatic maze" versus the "psoriatic march":
Left is adapted from Nijsten and Wakkee.[41] Right is adapted from Boehncke et al.[40]

elements. However, when screening the available literature on serum markers of systemic inflammation in psoriasis, we noticed that the results were not consistent: some studies reported no difference in serum levels of markers between psoriasis patients and controls, while others showed an increase or decrease. We conducted a meta-analysis on the available translational research on serum markers of inflammation in psoriasis, just as has commonly been done in the case of research on CRP in cardiovascular disease.[44-46] The studies were mainly laboratory research, their sample sizes were not based on a power calculation, the outcomes were hardly ever adjusted for confounders and often the most important outcome was whether the results were significant or not. Based on the nature of the studies and the modest difference in serum levels between psoriasis patients and controls ranging from 1,5 to 2, it remains uncertain how clinically relevant this slight elevation could be.

Does inflammation lead to atherosclerosis? Would the chronic increase in serum inflammatory markers lead to atherosclerosis, then we would be interested to know, as from which marker levels the risk of developing atherosclerosis would increase. In the Framingham Heart Study, no significant association was found between a large selection of biomarkers of inflammation (including CRP, IL-6, Intercellular Adhesion Molecule 1 [ICAM-1]) and aortic atherosclerosis, in contrast to other studies conducted in the same Framingham cohort finding associations between similar markers and carotid atherosclerosis,[47,48] which are thought to represent a later stage of plaque burden. A systematic review of studies assessing the relationship of biomarkers with coronary calcium showed that the associations were no longer significant after adjustment for traditional risk factors.[49] These results highlight that biomarkers are not necessarily useful in the identification of subclinical atherosclerosis and emphasize the importance of traditional risk factors.[50] However, is also possible that markers of serum inflammation, such as shown for IL-18 in a large prospective study, are not associated with atherosclerotic burden, but directly associated with cardiovascular events.[51]

An interesting study to follow is the cardiovascular inflammation reduction trial (CIRT) which aims to test the inflammatory hypothesis in conditions associated with systemic inflammation. More than 7,000 patients with prior myocardial infarction and type 2 diabetes or metabolic syndrome will be randomized to receive low-dose methotrexate or placebo for a period of 3 to 5 years. This is the first clinical trial to investigate whether targeting inflammation alone will reduce cardiovascular risk.[52]

2.3 Subclinical measures of atherosclerosis

Measures of atherosclerosis such as intima media thickness (IMT), ankle-brachial index (ABI) and pulse wave velocity (PWV) have been shown to be strong predictors of coronary heart disease (CHD).[53] Among 12 newer coronary heart disease risk markers, the addition of the coronary artery calcium (CAC) score provided the most statistically and clinically significant

improvement in Framingham risk predictions.[54] In psoriasis many investigations have been conducted on the presence of subclinical measures of atherosclerosis. These are small case control studies on IMT, ABI, CAC and PWV, conducted in selected groups.[55-62] In the population-based Rotterdam Study with a follow up of more than 10 years, where psoriasis subjects (n=262) underwent the same examinations as the reference population (n=8,009) irrespective of psoriasis severity or healthcare utilization, the IMT, ABI, CAC and PWV were not significantly different between the two groups after adjustment for age, gender and cardiovascular (CV) risk factors. This could be due to the predominantly mild severity of psoriasis in this population (76%). However a subgroup analysis in patients with moderate to severe disease from our study population also did not show significant differences between the groups (Chapter 4.2). This was the largest study to date where detailed information on standardized measures of atherosclerosis was available after diagnosis of psoriasis and adjustment for cardiovascular risk factors was possible. According to our data, psoriasis patients do not have elevated measures of atherosclerosis compared to the general population, independent of disease severity. Based on these results, we cannot conclude psoriasis that patients are at increased risk of developing atherosclerosis, and therefore cardiovascular events. Moreover the traditional risk factors are more important predictors of cardiovascular disease.

2.4 Cardiovascular events

In the past decade, numerous articles have been published on the association between psoriasis and cardiovascular disease showing inconsistent results, which could be explained by the different databases used, the study design, case definition of exposure and outcome and residual confounding. Most of the studies were based on data from secondary databases, which were not designed for the study outcome, in this case cardiovascular disease (CVD), and therefore had limited information on important confounders such as CV risk factors.[63,64] The authors of these studies often listed residual confounding as one of their main limitations.

Cardiovascular disease in the Rotterdam Study. We therefore decided to investigate the association between psoriasis and CVD in the Rotterdam Study, which was specially designed to investigate the epidemiology of CVD[65] and represents a unique study population due to the fact that the examinations were conducted in all patients at the same period, limiting the effects of detection and surveillance bias. We studied incident hard cardiovascular endpoints such as hard CHD, computer tomography (CT) confirmed stroke and heart failure and the analyses were conducted on measurements occurring after psoriasis onset. These restrictions were not always made in other studies on this topic. We were able to dynamically adjust the analyses for cardiovascular risk factors determined at the examination rounds and not just once during the entire follow up of 10 years. Moreover, there have been very few publications on the risk of stroke and heart failure in psoriasis, which are also components of CVD. A total of 259 psoriasis patients and 7,931 reference subjects were followed for a mean of 11 years;

after adjustment for age, gender and CV risk, psoriasis was not associated with coronary heart disease, stroke or heart failure. All the hazard ratios were below 1 and not significant. In the stratified analyses for disease severity, psoriasis was also not associated with incident cardiovascular events (Chapter 4.2). We therefore conclude, based on the results from The Rotterdam Study, that psoriasis is not an independent risk factor for CVD. Other studies on this subject have shown at most a modest increment in CV risk in psoriasis, with significant ORs ranging around 1.5. The higher risk was found in a small subpopulation of mostly young patients with severe psoriasis.[64] The results were based on routine care databases (General Practitioner Research Database and THIN), which have more limitations than data from a prospective cohort. In the Rotterdam Study we show that in a random selection of psoriasis patients from the general population it is unlikely that psoriasis represents an independent risk factor for subclinical atherosclerosis and incident hard cardiovascular events.

Identifying a new risk factor for heart disease. In an editorial, Stern applies five criteria used by the US Preventative Task force for evaluating potential new risk factors for heart disease, showing that psoriasis is unlikely to be a clinically useful independent risk factor for CVD.[66,67] A new risk factor should be easily and reliably measured. It should be an independent predictor of major CHD events in persons of intermediate risk who have no history of CHD (most of the studies to date did not look at incident CVD). When assessed in intermediate risk persons, the risk factor should reclassify a substantial proportion as high risk. Reclassified persons should be managed differently. If two or more risk factors provide similar prognostic information, then convenience, costs and safety may be important in choosing among them.

United States recommendations on screening for cardiovascular risk factors in psoriasis. Nevertheless, the American Journal of Cardiology in the United States advises that psoriasis patients with moderate to severe psoriasis and patients with mild psoriasis and increased CV risk factors should be informed that they may be at risk for coronary artery disease and should therefore undergo appropriate evaluation screening for CV risk factors.[68] We believe that these measures are not justified and are based on studies which are not population-based, and where surveillance bias is an important limitation. These measures will lead psoriasis patients with moderate to severe disease to believe that their psoriasis increases their risk of metabolic syndrome or CVD, whereas it is possible that the real cause of their risk increase is either impairment of QoL leading to stigmatization, isolation and depressive symptoms, resulting in risk factors such as obesity and smoking, or even positive family history for CVD.

Risk factors and antipsoriatic treatment. The increased risk for CVD in moderate to severe psoriasis could also be confounded by antipsoriatic treatment such as cyclosporine, which can lead to hypertension or acitretine, which can cause hyperlipidemia, both risk factors for

CVD. Therefore the choice of an antipsoriatic treatment should take into account the presence of pre-existent risk factors. On the other hand, addressing risk factors might also contribute to better treatment responses. In a recent trial, overweight mild to moderate psoriasis patients randomized to a hypocaloric diet achieved significant weight loss after 16 weeks and a higher mean PASI change compared to the group with a normal diet.[69] According to data from the Psocare study in Italy, psoriasis patients with lower BMIs responded better to systemic therapy than obese patients.[70] These results suggest that life-style change could lead to a better control of psoriasis and response to antipsoriatic therapy.

Framingham risk score in psoriasis. The present guidelines for the prevention of coronary heart disease recommend the use of risk scores such as the most widely used Framingham risk score (FRS) to identify adults at higher risk of CHD, who would benefit from preventive therapy.[71] This has led to publications on the 10-year FRS in psoriasis patients, most of them were small studies conducted in tertiary centers[72-75] and one study assessing the 10 year risk was a phase III study with more than 2,800 patients.[76] They show that approx. 3-10% of psoriasis patients with moderate to severe disease are at high risk. Interestingly, in the article by Fernandez Torrez, the risk was independent of disease severity measured by the PASI. However we should be cautious when interpreting FRS in psoriasis because the risk depends on the presence of risk factors and not on the presence of psoriasis. As previously mentioned, psoriasis patients seem to have more risk factors for the metabolic syndrome, and therefore their FRS is higher than in controls.

2.5 Surveillance bias

Chapter 2.2 demonstrates that overall drug utilization is elevated in psoriasis patients compared with controls, also for drugs unrelated to psoriasis, independent of psoriasis disease severity. Moreover, there have been innumerable publications on comorbidities of psoriasis, other than CVD, associating psoriasis with several, not always obviously related, chronic diseases such as chronic obstructive pulmonary disease, osteoporosis and Crohn's disease.[77-79] It is likely that increased healthcare utilization by psoriasis patients, also affects their risk of being diagnosed with other comorbidities. Possibly, the reason why we found that psoriasis was not associated with CVD in the Rotterdam Study, was because there was a minimal amount detection bias in this population and because all patients of a suburb of Rotterdam were invited to participate regardless of comorbidities with a high participation rate of approximately 75%.

2.6 The choice of systemic therapies to prevent cardiovascular outcomes

We are concerned about the continuing trend of upgrading psoriasis to a systemic inflammatory disease and therewith introducing a compelling reason for more aggressive treatment. Plaque psoriasis does not cause irreversible organ damage and while psoriatic arthritis can

lead to destructive joint damage, there is no evidence available that it affects the organs. We should acknowledge that the management of psoriasis patients could be influenced by the claim that psoriasis is a dangerous disease due to increased CVD and mortality, and the emphasis on the severe HRQoL impairment. This could lead to overtreatment of psoriasis and consequently push health insurance companies to reimburse costly treatments. Physicians should be cautious when wanting to treat psoriasis more aggressively in order to prevent possible cardiovascular events. Especially after one of the recent biological drugs, the IL-12/23 antagonist briakinumab, was withdrawn from the market due to concerns about the increased incidence of major adverse cardiac events.[80] Moreover, TNFα inhibitors are contraindicated in patients with stages III to IV heart failure according to the New-York Heart Association.

Effect of antipsoriatic therapy on cardiovascular events. Several studies have looked at the effect of systemic psoriasis therapies on the incidence of myocardial infarction but did not find consistent results. A cohort study using administrative and pharmacy claims data from a large insurance company in the United States, found no difference in MI risk in the systemic treatment group compared with psoriasis patients receiving UVB phototherapy.[81] Data from more than 8,000 psoriasis or psoriatic arthritis patients enrolled in the Kaiser Permanente Southern California (KPSC) health plan, among which more than 1,600 patients were treated with TNFα inhibitors adalimumab, etanercept or infliximab, showed that the risk of developing MI halved in patients using TNFα inhibitors compared to patients on topical treatment (adjusted for age and gender HR 0.50, 95% CI 0.32-0.81). This could be due to selection bias of healthy patients in the TNFα group, leading to confounding by indication. However, longer duration of TNF inhibitor therapy (>685 days) was not associated with significantly lower risk of MI with a HR of 1.36, 95% CI 0.64-2.90.[82] In a Danish psoriasis cohort, results varied between the composite outcome death, MI and stroke (lower risk in patients with systemic treatment) and the composite outcome cardiovascular death, MI and stroke (no significant reduction of risk).[83] A recent meta-analysis of short term randomized clinical trials evaluated the effect of anti-IL12 and IL23 on CVD, noticing no significant difference in the rate of a composite CVD endpoint in patients treated with biologics compared with those treated with standard care or placebo therapies.[84] There are more studies on their way assessing intermediary cardiovascular outcomes in patients with moderate to severe disease treated with biologic agents measuring coronary calcium score, serum cytokines and traditional risk factors (ClinicalTrials.gov identifier: NCT01356758). A head to head comparison of a biological agent and fumaric acid for cardiovascular and metabolic risk factors is on its way (ClinicalTrials.gov identifier: NCT01088165). In the meantime, psoriasis registries such as the PSONET,[85] the industry funded PSOLAR[86] and long term post marketing studies will provide valuable information on efficacy and adverse events of antipsoriatic treatments. Presently there is no convincing evidence supporting the use of systemic therapies in psoriasis for other reasons than treating psoriasis itself.

CONCLUSION 2

The results presented in this thesis support the multifactorial nature of the association between psoriasis, cardiovascular risk factors, atherosclerosis and cardiovascular events, refuting the hypothesis of a straight march. There is a need for a large prospective cohort of incident psoriasis cases, varying in age and disease severity, with a long follow-up to clarify the relationship between psoriasis, atherosclerosis and cardiovascular disease. Until then, caution is warranted when interpreting results from large database studies with limitations inherent to their design. Nevertheless, physicians and specifically dermatologists are not only expected to treat a skin condition, but also have a responsibility towards safeguarding the general health of their patients.

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Chapter 6

Summary/Samenvatting

1. INTRODUCTION AND AIMS OF THIS THESIS

We gave a general introduction to this thesis in **chapter 1**. Psoriasis is a chronic skin condition that affects approximately 2% of the European population. Environmental factors such as stress, medication, trauma or smoking and genetic factors trigger the production of pro-inflammatory cytokines and chemokines and maintain inflammatory processes in the skin. The most common form is plaque psoriasis and can be present in combination with psoriatic arthritis, which can also be considered as its own entity. The treatment options for psoriasis are vast and range from topical treatment, phototherapy to systemic therapy and the more recent biological drugs. Apart from assessing the success of antipsoriatic treatment using severity scores, measuring and addressing the health related quality of life (HRQoL) using patient reported outcome measures has become an important part of treatment evaluation. In the introduction, we give an insight on psoriasis comorbidities. Observational studies in the past decade have focused on the investigation of the metabolic syndrome and cardiovascular disease in psoriasis, mainly in routine and secondary databases often developed for other purposes. The question remains whether the association between psoriasis and these comorbidities is causal in nature. In this thesis, we show the complexity of this association and mainly focus on the study of HRQoL, depression and cardiovascular disease in psoriasis patients using various data sources: pharmacy and general practitioner databases and data from a prospective population-based cohort.

2. CHARACTERISTICS OF PSORIASIS PATIENTS

In **chapter 2.1**, we describe psoriasis characteristics, clinical severity and their impact on quality of life (QoL) of patients diagnosed with psoriasis by more than 190 Belgian dermatologists. Of the 3,629 psoriasis patients, more than three quarters had plaque psoriasis for more than 16 years. Plaque psoriasis involved most commonly the scalp, extensor sites of the extremities and lower back. One fifth of patients had nail involvement, 16% had affected genitals, 15% suffered from severe joint pain, 6.4% reported psoriatic arthritis diagnosed by a rheumatologist. Despite the fact that 80% of patients were receiving current therapy, the clinical psoriasis severity was relatively high with a mean Psoriasis Area and Severity Index (PASI) of 8.5, Body Surface Area (BSA) of 12% and 37% of patients with moderate to very severe disease according to the Physician's Global Assessment (PGA). 40% of patients reported a substantial impact of psoriasis, according to the Dermatology Life Quality Index (DLQI) and Skindex-17. The mean European Quality of Life-5 Dimensions (EQ-5D) score was comparable to the level of impairment observed in other chronic diseases such as asthma, diabetes and rheumatoid arthritis. Patients with moderate to severe disease reported a higher impact of psoriasis on their QoL than patients with mild disease. Based on these results we concluded

that psoriasis patients consulting dermatologists have relatively severe disease and often report a high impact of psoriasis on their QoL.

In **chapter 2.2** we investigated drug utilization in psoriasis patients compared with controls in the Dutch General Practitioner (GP) database. We followed 17,627 psoriasis patients and 17,627 controls matched for age, gender, GP and follow-up for a mean duration of more than 4 years. We investigated all drug prescriptions (therapeutic groups and chemical substances) and categorized the prescriptions into groups: (1) drugs for psoriasis symptom relief (painkillers and emollients), (2) drugs for psoriasis treatment (topical and systemic), (3) drugs associated to comorbidities such as metabolic syndrome, and (4) drugs which we expected to be unrelated to psoriasis. Approximately 20% of psoriasis patients received no treatment for psoriasis and 8% had moderate to severe disease. The rest only used topical antipsoriatic drugs. During the follow-up, a mean of 9 unique drugs was prescribed in psoriasis patients; this was significantly higher than in controls (mean of 7). The number of annually prescribed drugs did not vary over time and was stable in the period up to a decade after psoriasis diagnosis. All of the most commonly prescribed therapeutic groups were significantly more often prescribed in psoriasis patients than in controls. Drugs related to symptoms of psoriasis were significantly higher in psoriasis patients compared with controls (odds ratio (OR) 2.17, 95% confidence interval [CI] 2.07-2.28), with higher ORs in patients with moderate to severe disease compared with those with mild disease. The OR of medication related to psoriasis comorbidities was 1.46 (95% CI 1.39-1.53) and was similar to the OR of drugs, which were *a priori* not expected to be associated with psoriasis (OR 1.49, 95% CI 1.42-1.57), such as ophthalmologicals (OR 1.33, 95% CI 1.26-1.40), nasal preparations (OR 1.29, 95% CI 1.22-1.36) and laxatives (OR 1.29, 95% CI 1.14-1.45). This study shows that all types of medication are more often prescribed in psoriasis patients and this increased drug use is not limited to medication associated with psoriasis comorbidities, indicating an increased healthcare utilization in psoriasis patients compared with controls.

3. DEPRESSIVE SYMPTOMS AND CLINICAL DEPRESSION IN PSORIASIS

In **chapter 3.1** we give a systematic overview of the literature on depression in psoriasis. Our goal was to determine the pooled prevalence and odds of depressive symptoms and clinical depression in psoriasis in controlled and uncontrolled studies. The majority of the eligible studies were conducted in tertiary centres, without a control group. The prevalence of depressive symptoms was 28% using questionnaires and the prevalence of clinical depression was 12% using International Classification of Diseases (ICD) codes, 19% using Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria and 9% of psoriasis patients used antidepressants. Psoriasis patients had significantly more depressive symptoms

(standardized mean difference [SMD] 1.16, 95% CI 0.67-1.66) and population-based studies showed that they were at least one and a half times more likely to experience depression and used four times more antidepressants than controls. Based on the meta-analysis we conducted, we can say that psoriasis patients not only suffer from impaired HRQoL, but more than 10% suffer from clinical depression, and more than a quarter have depressive symptoms. The high prevalence of depressive symptoms in this meta-analysis is likely to be affected by the tertiary study populations and the use of questionnaires, where psoriasis-related symptoms may be detected as depressive symptoms.

Chapter 3.2 represents a cohort study where we used pharmacy and hospitalization data from 1998 to 2008 for more than 2.5 million Dutch residents to investigate the use of antidepressant drugs in psoriasis patients and a reference population. A total of 25,691 psoriasis and 128,573 reference subjects were followed for more than 9 years. The incidence of antidepressant use was more than twice as high in the psoriasis group, and the hazard ratio (HR) adjusted for age, gender and healthcare consumption was 1.55 (95% CI 1.50-1.61). Psoriasis patients had more than twice as many episodes of antidepressant use than the reference population, with an adjusted HR of 1.47 (95% CI 1.43-1.51). Antidepressant use was already increased before psoriasis patients sought medical treatment for their skin and peaked around the time of treatment initiation and remained increased thereafter. Within the psoriasis cohort, psoriasis patients were 7% more likely to receive antidepressant drugs after the initiation of antipsoriatic therapy. This study shows that psoriasis patients use more antidepressant drugs than the general population, specifically at the time when they seek medical care for their psoriasis and in the period after antipsoriatic treatment.

In **chapter 3.3** we evaluate whether psoriasis patients have more depressive symptoms and signs of a clinical depression compared to reference subjects in a population-based sample. Participants of the Rotterdam Study were screened for depressive symptoms using the Centre for Epidemiological Studies-Depression scale (CES-D), independent of other comorbidities. Subjects with a score above 16 (cut off for depressive symptoms according to the questionnaire), were interviewed, and depression was categorized according to the DSM-IV. A total of 296 psoriasis and 7,733 reference subjects were included. Psoriasis patients had predominantly mild disease and approximately one quarter had used systemic medication or UV-therapy. The median CES-D score and number of subjects with a score above 16 did not differ significantly between the groups. Psoriasis was not associated with a CES-D≥16 (OR 0.99, 95% CI 0.62-1.58). A total of 20 psoriasis subjects had a CES-D≥16 and 15 underwent a clinical interview. A total of 3 subjects had a major or minor depression and 6 subjects had depressive symptoms according to the DSM-IV criteria. Psoriasis patients with depressive symptoms assessed by the CES-D tool were not significantly more likely to develop a clinical depression compared to subjects from the reference group. In this population-based sample,

psoriasis subjects with predominantly mild disease manifest as much depressive symptoms and clinical depression as patients without psoriasis.

4. ATHEROSCLEROSIS, INFLAMMATION AND CARDIOVASCULAR DISEASE IN PSORIASIS

In **chapter 4.1** we performed a systematic review of the literature and a meta-analysis to determine the extent to which systemic inflammation is elevated in patients with psoriasis compared with healthy controls. We included studies comparing the serum inflammatory markers interleukin (IL)-1β, IL-6, IL-10, C-reactive protein (CRP), intracellular adhesion molecule (ICAM)-1, E-selectin and Tumour necrosis factor-alpha (TNFα) in patients with psoriasis and healthy controls. Differences in serum marker levels between patients and controls were pooled as SMD using a random-effects model. We included 78 studies, comprising a total of 7,852 individuals of which 3,085 had psoriasis. 64% of psoriasis patients had plaque psoriasis. The overall mean PASI was 17.7, indicating that the majority of the studies included patients with severe psoriasis. The pooled SMDs were higher in patients with psoriasis than in healthy controls for IL-6 (1.32), CRP (1.83), TNFα (1.32), E-selectin (1.78) and ICAM-1 (1.77). The SMD between cases and controls for IL-1β and IL-10 was not significant. Age had a significant effect on the SMD for IL-6 and TNFα; the older the patients in the study, the smaller the SMD between psoriasis patients and controls, possibly explained by decreasing immunity with increasing age. For IL-6 the effect size was higher for plaque psoriasis studies (1.98). The effect size was not influenced by the PASI. This meta-analysis suggests modest but significantly elevated levels of the proinflammatory cytokines in the serum of psoriasis patients with predominantly severe disease compared with controls. The difference is two points at the most and is overall independent of age, gender, disease severity and psoriasis type.

In **chapter 4.2** we investigated whether psoriasis is associated with cardiovascular outcomes using data from the population-based Rotterdam Study. In this study, risk factors for cardiovascular disease (CVD) and subclinical measures of atherosclerosis were regularly assessed and hard cardiovascular outcomes were registered for all participants, regardless of comorbidities. A total of 262 psoriasis and 8,009 reference subjects were followed for a mean of 11 years. 24% of psoriasis patients had used systemic treatment or phototherapy for their psoriasis. Psoriasis patients were significantly younger, smoked more, and had higher diastolic blood pressure and body mass index (BMI) levels compared with the reference subjects. All analyses were adjusted for age, gender, current smoking, BMI, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, antihypertensive medication and diabetes mellitus. The crude and adjusted carotid intima-media thickness, ankle-brachial index, pulse-wave velocity, and coronary artery calcium scores did not differ between psoriasis patients

and reference subjects. The risk of incident CVD was not increased in psoriasis (adjusted HR 0.73, 95% CI 0.50-1.06) in the Cox regression analysis where psoriasis was the time-dependent variable. When analysed separately, the risk of coronary heart disease, cerebral infarction and heart failure was also not elevated in psoriasis patients compared to controls. The results of this population-based study suggest that psoriasis patients with predominantly mild disease are not at a higher risk for subclinical atherosclerosis and psoriasis is not an independent risk factor for cardiovascular disease.

5. GENERAL DISCUSSION AND PERSPECTIVES

In **chapter 5** we discuss the findings of this thesis and offer our insights on clinical implications and future perspectives.

Firstly we analysed the relationship between psoriasis, health related quality of life, depressive symptoms and clinical depression and conclude that addressing psoriasis patients' well-being should become a part of psoriasis treatment.

The second part of the discussion is dedicated to the complexity of the association between cardiovascular risk factors, systemic inflammation, subclinical atherosclerosis and cardiovascular events, showing the need of a well-designed large prospective cohort in order to investigate the multifactorial nature of this association. We conclude that it is unnecessary that psoriasis patients undergo standard screening for cardiovascular risk factors and cardiovascular disease. Nevertheless, it is important that medical practitioners and dermatologists not only address the skin, but also the general health, comorbidities and well-being of their patients.

1. INLEIDING EN DOELEN VAN DIT PROEFSCHRIFT

In **hoofdstuk 1**, beginnen we een met een algemene introductie van dit proefschrift. Psoriasis is een chronische huidaandoening die bij ongeveer 2% van de Europese bevolking voorkomt. Naast genetische factoren, beïnvloeden ook omgevingsfactoren waaronder stress, medicatie, trauma's en roken de productie van pro-inflammatoire cytokines en chemokines en zo ook de inflammatoire processen in de huid. De meest voorkomende presentatie is plaque psoriasis en kan ook gepaard gaan met arthritis psoriatica, welke soms ook beschouwd wordt als een aparte entiteit. Er zijn verschillende therapieën voor psoriasis; variërend van topicale behandeling, lichtbehandeling tot systemische middelen waaraan de biologicals als laatste zijn toegevoegd. Het bepalen van de kwaliteit van leven van patiënten is, naast het effect van een behandeling op de ziekte-ernst, een belangrijke uitkomstmaat geworden bij de evaluatie van een therapie. In de introductie, geven we een overzicht van de comorbiditeiten van psoriasis. De afgelopen tien jaar is observationeel onderzoek bij psoriasis voornamelijk gericht geweest op het onderzoeken van comorbiditeiten zoals het metaboolsyndroom en hart- en vaatziekten met name in secundaire databases die vaak voor andere doeleinden zijn ontwikkeld. De vraag of het verband tussen psoriasis en deze comorbiditeiten causaal is, is echter nog niet beantwoord. In dit proefschrift laten we de complexiteit van deze associatie zien en richten onze aandacht met name op het onderzoeken van de kwaliteit van leven, depressie en hart- en vaatziekten bij psoriasis patiënten met data van verschillende bronnen: apothekersdata, huisartsendata en data van een prospectieve populatie-gebaseerde studie.

2. KENMERKEN VAN PSORIASISPATIËNTEN

In **hoofdstuk 2.1** beschrijven we de kenmerken van psoriasis, de ziekte-ernst en de invloed hiervan op de kwaliteit van leven van psoriasispatiënten op basis van gegevens van meer dan 190 Belgische dermatologen. Meer dan driekwart van de 3,629 psoriasispatiënten had plaque psoriasis gedurende meer dan 16 jaar. Bij een vijfde van de patiënten waren de nagels aangedaan, bij 16% waren de genitaliën aangedaan, 15% had gewrichtsklachten en 6.4% van de patiënten rapporteerde arthritis psoriatica, gediagnosticeerd door een reumatoloog. Ongeveer 80% van de patiënten werd ten tijde van de studie behandeld voor psoriasis, en toch was de ziekte-ernst relatief hoog met een gemiddelde Psoriasis Area and Severity Index (PASI) van 8.5, een Body Surface Area (BSA) van 12% en matig tot zeer ernstige ziekte volgens de Physician's Global Assessment (PGA) in 37% van de patiënten. Een wezenlijke impact van psoriasis op de kwaliteit van leven, volgens de Dermatology Life Quality Index (DLQI) en de Skindex-17 werd door 40% van de patiënten gerapporteerd. De gemiddelde European Quality of Life-5 Dimensions (EQ-5D) score was vergelijkbaar met de score van patiënten

met chronische aandoeningen zoals astma, diabetes en reumatoïde artritis. Patiënten met matig tot ernstige ziekte rapporteerden een hogere impact van psoriasis op hun kwaliteit van leven vergeleken met patiënten met milde ziekte. Op basis van deze resultaten, kunnen we concluderen dat psoriasispatiënten die bij de dermatoloog komen, relatief ernstige ziekte hebben en een hoge impact op hun kwaliteit van leven rapporteren.

In **hoofdstuk 2.2** hebben we medicatiegebruik vergeleken tussen psoriasispatiënten en controles zonder psoriasis in het Databestand van Nederlandse Huisartsen. We hebben 17,627 psoriasispatiënten en 17,627 controles gematched voor leeftijd, geslacht en follow-up tijd, gevolgd voor een gemiddelde duur van meer dan 4 jaar. We hebben alle medicatievoorschriften (therapeutische groepen en chemische stoffen) onderzocht en hebben de voorschriften in categorieën ingedeeld: (1) medicatie voor symptomen van psoriasis (pijnstillers en emollientia), (2) medicatie voor de behandeling van psoriasis (topicale en systemische middelen), (3) medicatie met een verband tot de comorbiditeiten zoals het metaboolsyndroom en depressie, en (4) een groep met geneesmiddelen die *a priori* ongerelateerd zijn aan psoriasis.

Ongeveer 20% van de psoriasispatiënten werd er niet voor behandeld en 8% had matig tot ernstige ziekte. De resterende patiënten gebruikten alleen topicale middelen voor psoriasis. Psoriasispatiënten kregen gemiddeld 9 verschillende geneesmiddelen voorgeschreven gedurende de follow-up; dit was significant hoger dan het gemiddelde aantal voorschriften bij de controles, namelijk 7. Het aantal jaarlijks voorgeschreven middelen veranderde niet in de tijd en was stabiel tot 10 jaar na de psoriasis diagnose. De meest voorgeschreven therapeutische hoofdgroepen werden significant vaker voorgeschreven aan psoriasispatiënten. Middelen die gerelateerd zijn aan symptomen van psoriasis waren significant hoger bij psoriasispatiënten dan bij de controles (odds ratio [OR] 2.17, 95% betrouwbaarheidsinterval [BI] 2.07-2.28), met een hogere OR voor psoriasispatiënten met matige tot ernstige ziekte vergeleken met patiënten met milde ziekte. De OR van geneesmiddelen gerelateerd aan psoriasis comorbiditeiten was 1.46 (95% BI 1.39-1.53) en kwam overeen met de OR van geneesmiddelen waarvan a priori verwacht werd dat ze niet geassocieerd zouden worden met psoriasis (OR 1.49, 95% BI 1.42-1.57), zoals ophthalmologica (OR 1.33, 95% BI 1.26-1.40), neuspreparaten (OR 1.29, 95% BI 1.22-1.36) en laxeermiddelen (OR 1.29, 95% BI 1.14-1.45). Deze studie laat zien dat de voorschriften voor heel veel geneesmiddelen verhoogd zijn bij psoriasispatiënten. Het verhoogde geneesmiddelgebruik beperkt zich niet tot geneesmiddelen dit te maken hebben met de behandeling van psoriasis en eventuele comorbiditeiten. Dit wijst op een algeheel verhoogde gezondheidsconsumptie bij psoriasispatiënten vergeleken met controles.

3. DEPRESSIEVE SYMPTOMEN EN KLINISCHE DEPRESSIE BIJ PSORIASIS

In **hoofdstuk 3.1** geven we een systematisch overzicht van de literatuur over depressie bij psoriasis. Het doel van dit hoofdstuk is om de prevalentie en odds van depressieve symptomen en klinische depressie in psoriasis te bepalen in studies met en zonder een controlegroep. De meerderheid van de geschikte studies werd uitgevoerd in tertiaire centra, zonder een controle groep. Uit de vragenlijsten bleek dat depressieve symptomen voorkomen bij 28% van de psoriasispatiënten. De prevalentie van klinische depressie was 12% volgens de International Classification of Diseases (ICD) codes, 19% volgens de Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) en 9% van de psoriasispatiënten gebruikte antidepressiva. In studies met een controle groep, hadden psoriasispatiënten significant meer depressieve symptomen (standardized mean difference [SMD] 1.16, 95% BI 0.67-1.66) en populatie-gebaseerde studies toonden aan dat psoriasispatiënten anderhalf keer waarschijnlijker te maken krijgen met depressie en vier keer zo vaak antidepressiva gebruiken dan controles. Op basis van de uitgevoerde meta-analyse kunnen we concluderen dat psoriasis niet alleen invloed heeft op de kwaliteit van leven van patiënten, maar dat 10% van de psoriasispatiënten aan een klinische depressie lijdt en meer dan een kwart aan depressieve symptomen. De hoge prevalentie van depressieve symptomen in deze meta-analyse kan beïnvloed zijn door de tertiaire studiepopulaties en het gebruik van vraaglijsten, waarmee psoriasis gerelateerde symptomen als depressieve symptomen worden gedetecteerd.

Hoofdstuk 3.2 is een cohortstudie waarin we apothekersdata en data van ziekenhuisopnames van meer dan 2.5 miljoen Nederlanders van 1998 tot 2008 hebben gebruikt om antidepressivagebruik bij psoriasispatiënten en een referentiepopulatie te onderzoeken. 25,691 psoriasispatiënten en 128,573 referentiepatiënten werden gevolgd gedurende meer dan 9 jaar. De incidentie van antidepressivagebruik was meer dan twee keer zo hoog in de psoriasisgroep en de hazard ratio (HR) aangepast voor leeftijd, geslacht en gezondheidszorgconsumptie was 1.55 (95% BI 1.50-1.61). Psoriasispatiënten hadden twee keer zoveel episodes van antidepressivagebruik vergeleken met de referentiepopulatie, met een aangepaste HR van 1.47 (95% BI 1.43-1.51). Antidepressivagebruik was reeds verhoogd voordat psoriasispatiënten medische hulp zochten voor de behandeling van de huid, en bereikte een piek rondom de tijd van aanvang van de behandeling van psoriasis. Nadien bleef antidepressivagebruik verhoogd. Binnen het psoriasiscohort hadden psoriasispatiënten 7% meer kans om een antidepressivum te krijgen na hun eerste behandeling voor psoriasis. Deze studie laat zien dat psoriasispatiënten meer antidepressiva gebruiken dan de algemene bevolking, met name rondom de tijd waar zij medische zorg zoeken voor psoriasis en de periode na start van de psoriasisbehandeling.

In **hoofdstuk 3.3** onderzoeken we of psoriasispatiënten meer depressieve symptomen en klinische depressie hebben vergeleken met controles afkomstig uit een populatie-gebaseerde studie. Deelnemers van de Rotterdam Study werden onafhankelijk van comorbiditeiten gescreend voor depressieve symptomen met de Centre for Epidemiological Studies-Depression vraaglijst (CES-D). Deelnemers met een score hoger dan 16 (afkapwaarde voor depressieve symptomen volgens de vraaglijst), werden geïnterviewd, en depressie werd gecategoriseerd volgens de DSM-IV. In totaal werden 296 psoriasis en 7,733 referentiepatiënten geïncludeerd. De psoriasispatiënten hadden overwegend milde ziekte en ongeveer een kwart had systemische- of lichtbehandeling. De mediaan CES-D score en het aantal deelnemers met een score boven de 16 was niet verschillend tussen de twee groepen. Er was geen associatie tussen psoriasis en een CES-D≥16 (OR 0.99, 95% BI 0.62-1.58). In totaal hadden 20 psoriasispatiënten een CES-D≥16 en daarvan ondergingen 15 een interview. Uiteindelijk hadden 3 deelnemers een "major" of "minor depressive disorder" en 6 deelnemers hadden depressieve symptomen volgens de DSM-IV criteria. Psoriasispatiënten met depressieve symptomen volgens de CES-D ontwikkelden niet significant meer klinische depressie vergeleken met deelnemers van de referentie groep. In deze populatie-gebaseerde studie, hebben psoriasispatiënten met overwegend milde ziekte net zo vaak depressieve symptomen en klinische depressie als patiënten zonder psoriasis.

4. ARTERIOSCLEROSE, INFLAMMATIE EN CARDIOVASCULAIRE ZIEKTE BIJ PSORIASIS

In **hoofdstuk 4.1** hebben we de literatuur systematisch doorzocht en een meta-analyse uitgevoerd om te bepalen in welke mate systemische inflammatie verhoogd is bij psoriasispatiënten vergeleken met gezonde controles. We hebben studies geïncludeerd die de inflammatoire serum markers interleukin (IL)-1β, IL-6, IL-10, C-reactive protein (CRP), intracellular adhesion molecule (ICAM)-1, E-selectin en Tumour necrosis factor-alpha (TNFα) hebben onderzocht bij psoriasispatiënten en gezonde controles. Het verschil in gemiddelde concentratie van serum markers tussen patiënten en controles, ook standardized mean difference (SMD) genoemd, werd gepooled voor alle studies volgens het random-effects model. 78 studies met 7,852 individuen werden geïncludeerd, waarvan 3,085 met psoriasis. 64% van de psoriasispatiënten had plaque psoriasis. De geincludeerde patiënten hadden een gemiddelde PASI van 17.7, en betreft dus een subgroep met ernstig psoriasis. De gepoolde SMDs waren hoger in psoriasispatiënten dan in gezonde controles voor IL-6 (1.32), CRP (1.83), TNFα (1.32), E-selectin (1.78) en ICAM-1 (1.77). De SMD tussen psoriasis en controles voor IL-1β en IL-10 waren niet significant. Leeftijd had een significant effect op de SMD voor IL-6 en TNFα; hoe ouder de patiënten in de studie, hoe kleiner de SMD tussen psoriasis en controles, mogelijk te verklaren door vermindering van immuniteit met de leeftijd. Bij IL-6, was de SMD

hoger voor studies met plaque psoriasis (1.98). De SMD was onafhankelijk van de PASI. Deze meta-analyse laat zien dat de proinflammatoire cytokines in de serum van psoriasispatiënten met voornamelijk ernstige ziekte, significant, maar alleen licht verhoogd zijn vergeleken met controles. Het verschil tussen de serumwaarden bij psoriasis en controles bedraagt hooguit 2 punten, en is over het algemeen onafhankelijk van leeftijd, geslacht, ziekte-ernst en type psoriasis.

In **hoofdstuk 4.2** hebben we onderzocht of psoriasis geassocieerd is met hart- en vaatziekten in de populatie-gebaseerde Rotterdam Study. In deze studie worden regelmatig cardiovasculaire risicofactoren en maten van subklinische atherosclerose gemeten en hart- en vaatziekten geregistreerd, onafhankelijk van comorbiditeiten. In totaal werden 262 psoriasispatiënten en 8,009 referentiepersonen gevolgd gedurende gemiddeld 11 jaar. Van de geïncludeerde psoriasispatiënten had 24% een systemische- of lichtbehandeling. Psoriasispatiënten waren significant jonger, rookten meer en hadden hogere diastolische bloeddruk en Body Mass Index (BMI) dan de controles. Alle analyses werden aangepast voor leeftijd, geslacht, roken, BMI, cholesterol, high-density lipoproteïne, cholesterol, systolische bloeddruk, antihypertensiva en diabetes mellitus. De ruwe en aangepaste intima-media dikte van de arteria carotis communis, enkel-arm-index, polsgolfsnelheid, en scores voor coronaire calcium waren niet verschillend tussen psoriasispatiënten en referentiepersonen. Het risico voor incidente hart- en vaatziekte was niet verhoogd voor psoriasis (aangepaste HR 0.73, 95% BI 0.50-1.06) volgens de Cox regressie analyse met psoriasis als tijd-afhankelijke variabele. Ook het risico van verschillende manifestaties van hart- en vaatziekten, namelijk coronaire hartziekte, beroertes, en hartfalen, was niet verhoogd in psoriasispatiënten vergeleken met controles. De uitkomsten van deze populatie-gebaseerde studie suggereren dat psoriasispatiënten met een overwegend milde ziekten geen verhoogd risico hebben op het krijgen van subklinische atherosclerose, en dat psoriasis geen onafhankelijke risicofactor is voor hart- en vaatziekten.

5. ALGEMENE DISCUSSIE EN TOEKOMST

In **hoofdstuk 5** worden de bevindingen van dit proefschrift besproken en wordt er inzicht gegeven in klinische implicaties en toekomstig onderzoek.

In het eerste deel hebben we de relatie tussen psoriasis, kwaliteit van leven, depressieve symptomen en klinische depressie onderzocht en concluderen we dat het welzijn van patienten deel moet uitmaken van de behandeling van patiënten met psoriasis.

Het tweede deel van de discussie is gewijd aan de complexiteit van de associatie tussen cardiovasculaire risicofactoren, systemische inflammatie, subklinische atherosclerose en cardiovasculaire aandoeningen, en laat zien dat we een grote prospectieve cohort studie

nodig hebben om de multifactoriële natuur van deze associatie te kunnen doorgronden. We concluderen dat het niet noodzakelijk is dat psoriasispatiënten standaard gescreend worden op cardiovasculaire risicofactoren en hart- en vaatziekten. Het is echter wel van belang dat behandelaars en dermatologen naast aandacht voor de huid, zich bewust zijn van de algemene gezondheid, comorbiditeiten en het welbevinden van hun patiënten.

Appendices

ABBREVIATIONS

ABI, Ankle-brachial index
ATC code, Anatomical Therapeutic Chemical code
BDI, Beck Depression Inventory
BMI, Body Mass Index
BSA, Body Surface Area
CAC, Coronary artery calcium
CES-D, Center for Epidemiologic Studies Depression Scale
CHD, Coronary heart disease
CRP, C-reactive protein
CRSD, Carroll Rating Scale for Depression
CVD, Cardiovascular disease
DLQI, Dermatology Life Quality Index
DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition
EQ-5D or Euro-QoL, European Quality of Life-5 Dimensions
GHQ, General Health Questionnaire
GP, General Practitioner
HADS, Hospital Anxiety and Depression Scale
Hamilton DS, Hamilton Rating Scale for Depression
HRQoL, Health Related Quality of Life
ICAM-1, Intracellular adhesion molecule-1
ICD, International Classification of Diseases
IL-1β, Interleukin-1 beta
IL-6, Interleukin-6
IL-10, Interleukin-10
IMT, Intima-media thickness
MADRS, Montgomery Asberg Depression Rating Scale
MINI, Mini International Neuropsychiatric Interview
PASI, Psoriasis Area and Severity Index
PDI, Psoriasis Disability Index
PGA, Physician's Global Assessment
PROM, Patient Reported Outcome Measures
PWV, Pulse wave velocity
SAPASI, Self-administered Psoriasis Area and Severity Index
SF-36, Short Form with 36 questions
SSRI, Selective Serotonin Reuptake Inhibitor
TCA, Tricyclic antidepressant
TNFα, Tumor necrosis factor-alpha
Zung-SDS, Zung Self-rating Depression Scale

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PUBLICATIONS IN THIS THESIS

The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis.
Dowlatshahi EA, Wakkee M, Arends LR, Nijsten T.
J Invest Dermatol. 2014 Jun;134(6):1542-51.

Markers of systemic inflammation in psoriasis: a systematic review and meta-analysis.
Dowlatshahi EA, van der Voort EA, Arends LR, Nijsten T.
Br J Dermatol. 2013 Aug;169(2):266-82.

Increased antidepressant drug exposure in psoriasis patients: a longitudinal population-based cohort study.
Dowlatshahi EA, Wakkee M, Herings RM, Hollestein LM, Nijsten T.
Acta Derm Venereol. 2013 Sep 4;93(5):544-50.

Psoriasis is not associated with atherosclerosis and incident cardiovascular events: the Rotterdam Study.
Dowlatshahi EA, Kavousi M, Nijsten T, Ikram MA, Hofman A, Franco OH, Wakkee M.
J Invest Dermatol. 2013 Oct;133(10):2347-54.

A descriptive study of psoriasis characteristics, severity and impact among 3,269 patients: results of a Belgian cross sectional study (BELPSO).
Lambert J, **Dowlatshahi EA**, de la Brassinne M, Nijsten T.
Eur J Dermatol. 2012 Mar-Apr;22(2):231-7.

OTHER PUBLICATIONS

Psoriasis is independently associated with nonalcoholic fatty liver disease in patients 55 years old or older: Results from a population-based study.
van der Voort EA, Koehler EM, **Dowlatshahi EA**, Hofman A, Stricker BH, Janssen HL, Schouten JN, Nijsten T.
J Am Acad Dermatol. 2014 Mar;70(3):517-24.

Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study.
Flohil SC, van der Leest RJ, **Dowlatshahi EA**, Hofman A, de Vries E, Nijsten T.
J Invest Dermatol. 2013 Aug;133(8):1971-8.

Etanercept: an overview of dermatologic adverse events.
Lecluse LL, **Dowlatshahi EA**, Limpens CE, de Rie MA, Bos JD, Spuls PI.
Arch Dermatol. 2011 Jan;147(1):79-94.

Prevalence and associated factors of viral hepatitis and transferrin elevations in 5036 patients admitted to the emergency room of a Swiss university hospital: cross-sectional study.
Russmann S, **Dowlatshahi EA**, Printzen G, Habicht S, Reichen J, Zimmermann H.
BMC Gastroenterol. 2007 Feb 5;7:5.

PhD PORTFOLIO

Name PhD student:	Emmilia Assal Dowlatshahi
Erasmus Medical Centre Department:	Dermatology
PhD period:	2010-2014
Promotor:	Prof. Dr. T. Nijsten
Supervisor:	Dr. M. Wakkee

	Year	Workload Hours/ECTS
1. PhD Training		
Research skills		
Workshop on literature search, Erasmus MC	2010	6 hours
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers	2010	22 hours
NIHES course: Principles of Research in Medicine – Prof. A. Hofman	2010	0.7 ECTS
NIHES course: Introduction to Data-analysis – Prof A. Albert	2010	0.7 ECTS
NIHES course: Pharmaco-epidemiology and Drug Safety – Prof. M. Sturkenboom	2011	1.9 ECTS
NIHES course: Case-Control studies – Prof. M. Szklo	2011	0.7 ECTS
NIHES course: Cohort studies – Dr J. Nieto	2011	0.7 ECTS
Discipline Overstijgend Onderwijs: Samenwerking	2014	8 hours
Specific courses		
Systematic review and meta-analysis, Vrije Universiteit Medisch Centrum	2011	0.6 ECTS
Meta-analysis online course, Comprehensive meta-analysis	2012	0.5 ECTS
Conferences		
3rd Congress of the Psoriasis International Network, Paris, France	2010	1 ECTS
Dermatologendagen, Papendal, The Netherlands	2011	1 ECTS
41st meeting of the European Society for Dermatological Research (ESDR), Barcelona, Spain	2011	1 ECTS
6th International Dermato-Epidemiology Association Congress (IDEA), Malmo, Sweden	2012	1 ECTS
21st Congress of the European Academy of Dermatology and Venereology (EADV), Prague, Czech Republic	2012	1 ECTS
14th Annual scientific meeting of the Nederlandse Vereniging voor Experimentele Dermatologie (NVED), Lunteren, The Netherlands	2013	1 ECTS
International Investigative Dermatology, Edinburgh, United Kingdom	2013	1 ECTS
4th Congress of the Psoriasis International Network, Paris, France	2013	1 ECTS
23rd Congress of the EADV, Amsterdam, The Netherlands	2014	1 ECTS

Oral presentations

Antidepressant drug use in patients with psoriasis: a population-based cohort study. ESDR, Barcelona, Spain	2011	1 ECTS
Atherosclerosis and cardiovascular disease in psoriasis: the Rotterdam Study. IDEA, Malmö, Sweden	2012	1 ECTS
Atherosclerosis and cardiovascular disease in psoriasis: the Rotterdam Study. Dermatology conference, Erasmus MC, Rotterdam, The Netherlands	2012	1 ECTS
Atherosclerosis and cardiovascular disease in psoriasis: the Rotterdam Study. 4th Congress of the Psoriasis International Network, Paris, France	2013	1 ECTS
Depressive symptoms and clinical depression in psoriasis: a systematic review and meta-analysis. Dermatology conference, Erasmus MC, Rotterdam, The Netherlands	2014	1 ECTS

Poster presentations

A descriptive study of psoriasis characteristics, severity and impact among 3,269 patients: results of a Belgian cross sectional study. NVED, Lunteren, The Netherlands	2011	1 ECTS
Antidepressant drug use in patients with psoriasis: a population-based cohort study. ESDR Barcelona, Spain	2011	1 ECTS
Markers of systemic inflammation in psoriasis: a systematic review and meta-analysis. ESDR Venice, Italy	2012	1 ECTS
Markers of systemic inflammation in psoriasis: a systematic review and meta-analysis. NVED, Lunteren, The Netherlands	2013	1 ECTS
Varying prevalence of depression according to assessment method: a systematic review and meta-analysis. International Investigative Dermatology, Edinburgh, United Kingdom	2013	1 ECTS
Atherosclerosis and cardiovascular disease in psoriasis: the Rotterdam Study. 4th Congress of the Psoriasis International Network, Paris, France	2013	1 ECTS
Increased overall drug utilization in psoriasis patients: a case-control study based on Dutch general practitioner data. EADV, Amsterdam, The Netherlands	2014	1 ECTS

Seminars, workshops and master classes

Quantifying unobserved confounding – Dr. R.H.H. Groenwold	2010	1 hour
Drug use as a time varying variable – Prof. B. Stricker	2010	1 hour
Interaction and effect modification – Prof. F. Dekker	2010	1 hour
Ruysch Minisymposium, Publication bias in clinical and laboratory animal research, Academic Medical Center Amsterdam	2010	3 hours
Dermoscopy Boerhaave course, Leiden	2010	8 hours
NIHES masterclass: Improving forensic analysis with human genomics – Prof. M. Kayser	2010	2 hours
NIHES masterclass: From 'data analysis' to model fitting – Prof. O. Miettinen	2011	2 hours
NIHES masterclass: Spurious precision? Meta-analysis of observational studies – Prof. M. Egger	2011	2 hours
NIHES masterclass: Causal mediation analysis – Prof. T. van de Weele	2011	2 hours
PhD Day, Erasmus MC, Rotterdam	2011	8 hours
Dermoscopy course, Antwerp University, Belgium	2011	7 hours

Dermatologen in Opleiding dagen, Zeist	2012	16 hours
Breakthroughs in immune mediated diseases, Amsterdam	2013	8 hours

Occasional reviewer for the following journals

Acta Dermato-Venereologica
British Journal of Dermatology
Journal of the European Academy of Dermatology and Venereology
Journal of Investigative Dermatology

2. Teaching activities

Frank van Leersum, supervision of master's thesis	2011
Organization of dermatology conferences for residents and dermatologists, Erasmus MC, Department of Dermatology	2012 - present

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