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# PSORIASIS: OBSERVATIONAL STUDIES ON CLINICAL COURSE, ECONOMIC BURDEN AND TREATMENT

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# PSORIASIS: OBSERVATIONAL STUDIES ON CLINICAL COURSE, ECONOMIC BURDEN AND TREATMENT
THESIS FOR DOCTROAL DEGREE (Ph.D.)

By


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# POPULAR SCIENCE SUMMARY OF THE THESIS

Signs and symptoms of psoriasis at onset can predict the course of the disease and it may be possible to modify the risk of developing severe psoriasis with early systemic intervention. This is important because severe psoriasis is associated with impaired quality of life, increased risk of death, high health care costs, and suboptimal treatment outcomes.

Study 1 in this thesis followed 721 patients from onset of psoriasis and ten years thereafter. The study found that patients with plaque phenotype, more than mild disease activity, and scalp lesions at onset had a probability of 52% to develop severe psoriasis compared to 11% in patients with mild disease activity at onset ($p<0.001$). Furthermore, patients with pain at sites where tendons attach to bone were almost five times more likely to develop psoriatic arthritis, a debilitating joint disease, than patients without joint pain at onset (59% vs 12%, $p<0.001$). Among all patients treated with systemics for psoriasis, patients who were treated within one year of disease onset had lower risk of having severe psoriasis after ten years compared with patients who were treated thereafter (38% vs 65%, $p=0.044$).

Study 2 in this thesis identified 39,074 patients with psoriasis and 154,775 control individuals without psoriasis in regional Swedish health data registers and followed them for up to nine years. The study found that patients with mild and severe psoriasis died on average 0.8, and 2.6 years younger than controls without psoriasis. The cause of death contributing most to the excess mortality was cardiovascular disease, accounting for 48% of the excess mortality in patients with mild disease and 33% in patients with severe disease. Analyzing data from a subset of these patients alive in 2010, Study 3 estimated the economic impact of psoriasis. The economic impact of psoriasis generally increased with disease severity. However, the study also found that effective treatment might reduce costs. Study 4 also used a subset of patients from the study on mortality and explored how patients with psoriasis were treated. Irrespective of whether patients were treated with topicals, systemics, or biologics a majority of patients discontinued, switched, or received add-on therapy within one year of treatment start. Furthermore, within one year of having discontinued treatment, 49% of patients on topicals, 61% of patients on systemics, and 80% on patients on biologics, restarted the same or another treatment.

Study 5 in this thesis analyzed data on 727 treatment episodes with adalimumab, etanercept, and methotrexate in 542 patients. The study found that adalimumab might be a good choice as first line systemic treatment for psoriasis: Patients treated with adalimumab had better drug survival, lower disease activity, and better quality of life than patients treated with methotrexate, the most frequently prescribed first line systemic treatment in psoriasis. Nevertheless, the results indicate that even with adalimumab, mean PASI during maintenance treatment was higher than some recent treatment goals and patients still had impaired quality of life.

Psoriasis is a chronic inflammatory skin disease that affects both body and psyche. It is associated with comorbidities including heart attack, stroke, and cancer. In recent years, advances in medicine have improved treatment of psoriasis. However, much is still unknown about the clinical course of the disease, its impact on mortality, economic burden, and treatment effectiveness in clinical practice. This thesis aims to address these knowledge gaps with the ultimate goal to help improving the care of patients with psoriasis.

Overall findings from these studies reinforce the notion that plaque psoriasis is a chronic disease associated with substantial burden both from economic and clinical perspectives. Identification of subgroups of patients with adverse prognosis may contribute to better and more cost-effective management of the disease. The finding that early systemic intervention may affect the disease course may affect the treatment paradigm in psoriasis, but needs to be confirmed in randomized controlled clinical trials.

# ABSTRACT

Better understanding of long-term prognosis, clinical course, comorbidities, economic burden, and treatment of psoriasis, can improve care of patients with the disease and may inform decisions on resource allocation, benefitting not only patients but also the society in general.

The Stockholm Psoriasis Cohort (SPC), Study 1, was initiated to describe the clinical course or psoriasis. The SPC enrolled 721 patients with onset of psoriasis within the last twelve months. 542 (75%) patients had plaque psoriasis and 174 (24%) had guttate psoriasis. Patients were followed in medical records and registers, and among the 686 participants alive after ten years, 546 (80%) responded to a questionnaire and 509 (74%) were also examined clinically. Plaque psoriasis was strikingly persistent. Forty one percent of the patients with severe disease at onset had severe disease at ten years compared with 9% of participants with mild or moderate disease at onset (Relative Risk [RR]=4.3; $p<0.001$). Guttate onset was associated with a favorable disease course: After ten years, 56/116 (48%) of patients were in remission without treatment and only 1/94 patients with mild or moderate guttate onset had severe psoriasis at ten years. Recursive partitioning analysis identified groups with distinctive risks for severe skin disease and Psoriatic Arthritis (PsA): The cumulative incidence of severe disease in participants with plaque phenotype, at least moderate disease, and scalp psoriasis at onset was 52% (95% Confidence Interval [CI]: 41% to 64%), compared to 11% (95% CI: 8% to 14%) in patients with mild disease at onset. Forty-eight of 82 patients (59%) with peripheral enthesitis at onset had PsA after ten years compared to 37/304 (12%) without arthralgia at onset ($p<0.001$). Systemic treatment at or before enrolment was associated with reduced risk for severe disease at ten years compared to systemic initiation later (Odds Ratio: 0.24; 95% CI: 0.06 to 0.90). Overall, this study indicates that the course of psoriasis can be predicted with good discriminatory power and that it may be modified by early effective intervention. The latter finding should be confirmed in randomized controlled clinical trials.

The second study estimated all-cause and cause-specific mortality in 34,355 patients with mild psoriasis and 4,719 patients with severe psoriasis compared to 154,775 age- sex- and residency matched controls. The study found that patients with mild and severe psoriasis had excess all-cause mortality: Hazard ratio (HR) 1.15 (95% CI: 1.10 to 1.21) for patients with mild psoriasis, and HR 1.56 (95% CI: 1.36 to 1.79) for patients with severe psoriasis. Cardiovascular disease accounted for the largest proportion of excess mortality (48% in mild psoriasis and 33% in severe psoriasis). For patients with mild and severe psoriasis, the causes of death with the highest excess risks were kidney disease (HR: 2.20; 95% CI: 1.36 to 3.56), and liver disease (HR: 4.26; 95% CI: 1.87 to 9.73), respectively. The findings suggest that it may be valuable to screen patients with psoriasis for cardiovascular, kidney, and liver disease.

Economic burden of psoriasis in 2010 and potential cost offsets with biologic treatment were estimated in Study 3, using data on 31,043 patients with psoriasis and 111,645 sex-, age- and residency-matched controls. Patients had higher direct and indirect costs compared to controls after adjusting for the Charlson Comorbidity Index (CCI): USD 3,555 versus USD

2,190 ($p < 0.001$) for direct costs and USD 9,898 versus USD 6,579 ($p < 0.001$) for indirect costs. Both mean direct and mean indirect costs generally increased with disease severity inferred by most potent treatment received, albeit the increase was not monotonic. Disregarding the costs of biologics, initiation of biologic treatment was estimated to generate one-year direct and indirect cost offsets from USD 1,135 (95% CI: 328 to 2,050) to USD 4,422 (95% CI: 2,771 to 6,552), and USD 774 (95% CI: -535 to 2,019) to USD 1,875 (95% CI: 188 to 3,650), respectively. Collectively, these findings show that psoriasis is associated with substantial direct and indirect costs, which may be modifiable with effective treatment.

Study 4 described treatment patterns in 19,103 patients with psoriasis and estimated the one-year cumulative incidences of treatment events (discontinuation, switch, or augmentation) with topicals, systemics, and biologics at 93%, 72%, and 75%, respectively. Within one year of having discontinued treatment, the cumulative incidences of starting a new treatment was 49% for topicals, 61% for systemics, and 80% for biologics. These findings highlight the unmet needs across the disease spectrum and underscore the chronicity of the disease.

Study 5 estimated real-world effectiveness of adalimumab and etanercept compared to methotrexate. After adjusting for confounders, adalimumab had better drug survival (HR: 0.67; 95% CI: 0.51 to 0.88), lower mean predicted PASI (-2.0; 95% CI: -2.6 to -1.5) and DLQI (-0.9; 95% CI: -1.5 to -0.3) during maintenance treatment than methotrexate. The results for the comparison between etanercept and methotrexate were more mixed. These findings support adalimumab as first line systemic treatment for psoriasis, but further data, especially on safety and costs, are needed.

## LIST OF SCIENTIFIC PAPERS

I. Svedbom A, Mallbris M, Larsson P, Nikamo P, Wolk K, Kjellman P, Sonkoly E, Eidsmo L, Lindqvist U, Ståhle M. (2021). Long-term outcomes and prognosis in new-onset psoriasis. Jama Dermatology, [Epub ahead of print].

II. Svedbom, A., Dalen, J., Mamolo, C., Cappelleri, J. C., Mallbris, L., Petersson, I. F., & Ståhle, M. (2015). Increased cause-specific mortality in patients with mild and severe psoriasis: a population-based Swedish register study. Acta dermato-venereologica, 95(7), 809-815.
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III. Svedbom, A., Dalén, J., Mamolo, C., Cappelleri, J. C., Mallbris, L., Petersson, I. F., & Ståhle, M. (2016). Economic burden of psoriasis and potential cost offsets with biologic treatment: a Swedish register analysis. Acta dermato-venereologica, 96(5), 651-657.

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# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADA | Adalimumab |
| BMI | Body Mass Index |
| CASPAR | Classification Criteria for Psoriatic Arthritis |
| CCI | Charlson Comorbidity Index |
| CDC | Centers for Disease Control and Prevention |
| CDR | Cause of Death Register |
| CI | Confidence Interval |
| C-index | Concordance Index |
| CLT | Central Limit Theorem |
| DAG | Directed Acyclic Graph |
| DLQI | Dermatology Life Quality Index |
| DRG | Diagnosis Related Group |
| EMR | Electronic Medical Record |
| EQ-5D 3L | EuroQoL Five Dimensions 3 Levels |
| ETN | Etanercept |
| EUR | Euro |
| GLM | Generalized Linear Model |
| HCRU | Healthcare Resource Utilization |
| HLA | Human Leukocyte Antigen |
| HR | Hazard Ratio |
| HRQoL | Health Related Quality of Life |
| ICD | International Classification of Disease |
| IID | Independent and Identically Distributed |
| IPC | International Psoriasis Council |
| IQR | Interquartile Range |
| LOESS | Locally Weighted Regression |
| MADRS-S | Montgomery-Åsberg Depression Rating Scale-Self Reported |
| MS | Multiple Sclerosis |
| MTX | Methotrexate |
| NA | Not Applicable |
| NPR | National Patient Register |
| OR | Odds ratio |
| PASE | Psoriatic Arthritis Screening and Evaluation |
| PASI | Psoriasis Area and Severity Index |
| PDR | Prescribed Drug Register |
| PGA | Physician Global Assessment |
| PH | Proportional Hazard |
| PRO | Patient Reported Outcome |
| PsA | Psoriatic Arthritis |
| PSOREST | Psoriasis Retrospective Study |
| PUVA | Psoralen and Ultraviolet A |
| RPA | Recursive Partitioning Analysis |
| RR | Relative Risk |
| SD | Standard Deviation |
| SEK | Swedish Krona |
| SHCR | Skåne Health Care Register |

| | |
|---|---|
| SPC | Stockholm Psoriasis Cohort |
| S-PGA | Static Physician Global Assessment |
| TNF | Tumor Necrosis Factor |
| TPR | Total Population Register |
| UK | United Kingdom |
| USD | US Dollar |
| UV | Ultraviolet |

# 1 INTRODUCTION

## 1.1 PSORIASIS

### 1.1.1 Clinical manifestations and diagnosis

Psoriasis is an immune-mediated skin disease with a predisposing genetic component (1). The disease exhibits substantial variability in morphology, distribution, and severity (2). Lesions may occur at any site, but most frequently affect the scalp, elbows, knees, forearms, shins and the trunk (1). The disease course is variable (3). It may be chronic with stable lesions or may fluctuate between periods of substantial disease activity and remissions (3). Episodes of increased disease activity may be associated with growth of existing lesions or appearance of new lesions (4).

Psoriasis is primarily a clinical diagnosis ascertained by a combination of features, morphology and configuration of skin lesions (5). The reference standard for diagnosing the disease is a clinical diagnosis made by a dermatologist (5). The agreement on diagnosis of both typical and atypical psoriasis among dermatologists have been reported at 97% (6), indicating high face validity. Nevertheless, other skin disorders may resemble psoriasis and if the diagnosis is uncertain, histopathological analysis of skin biopsies can aid differential diagnosis (5).

Several disease classification systems exist and in 2006, the International Psoriasis Council (IPC) published a simplified classification comprising four main phenotypes based on morphology: plaque psoriasis, guttate psoriasis, pustular psoriasis, and erythrodermic psoriasis. (7)

Plaque psoriasis (**Figure 1A**) is the most common form, affecting approximately 90% of patients with psoriasis. In plaque psoriasis, lesions are generally clearly demarcated red plaques covered by silvery scales. In terms of distribution, plaques may range from few and limited in size to large and widespread, covering a substantial area of the body. The IPC further divided plaque psoriasis into five phenotypes based on lesion morphology and location: flexural, seborrheic, scalp, palm and sole, and follicular psoriasis. (7)

Guttate psoriasis (**Figure 1B**) is characterized by red droplets which may be widespread. Lesions are often located on the trunk, but may appear all over the body. Guttate psoriasis is most common in children, adolescents, and young adults. It is often preceded by a streptococcal infection. Lesions may resolve over three months but may also develop into plaque psoriasis. Guttate lesions may also present in patients with plaque phenotype. (7)

Pustular psoriasis (**Figure 1C**) presents as blisters of non-infectious pus. Blisters may be localized affecting, for example, palms and soles or generalized with dark red patches, congregating into large areas of pus. Pustular psoriasis may occur in patients with plaque phenotype but may also develop in individuals without a history of psoriasis. (7)

Erythrodermic psoriasis is a serious condition (**Figure 1D**) characterized by extensive (covering ninety percent or more of the skin) erythema with a high degree of inflammation and may result in shedding of the skin. The disease may be preceded by plaque psoriasis but can also occur in individuals without a history of psoriasis. (7)

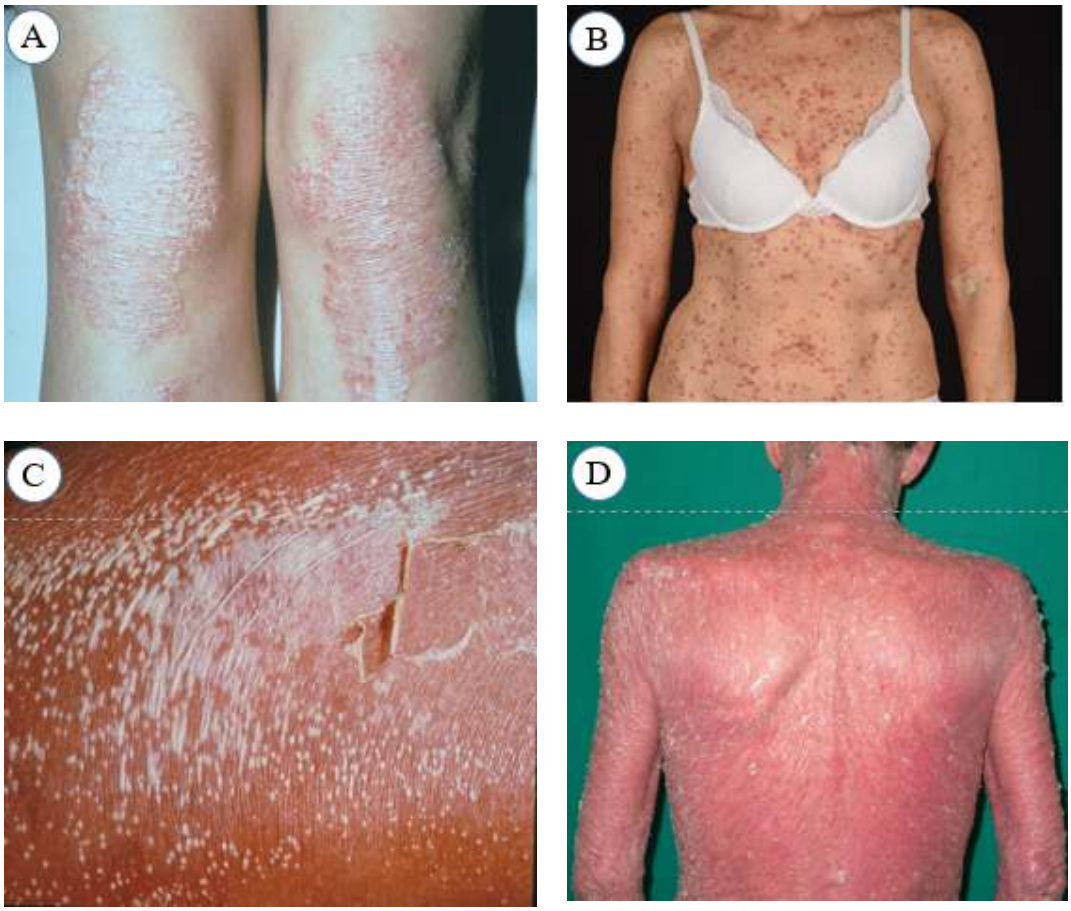


**Figure 1 Main psoriasis phenotypes as defined by the International Psoriasis Council.** Panel A shows plaque psoriasis. Panel B shows guttate psoriasis. Panel C shows pustular psoriasis. Panel D shows erythrodermic psoriasis. Photographs reproduced with permission from the Karolinska University Hospital.

No common pathogenic mechanism for the disease has been established and the different phenotypes are considered variants of the same disease from a morphological point of view. The reason is fourfold: A red and scaly appearance is the most common feature in all manifestations and sponge like pustules is a frequent characteristic; (ii) different manifestations may be contemporaneous; (iii) different manifestations may occur sequentially; and (iv) members of a single family may exhibit different phenotypes. (8)

The manifestations of psoriasis may differ systematically between ethnicities. A survey of American dermatologists indicated that African-American patients had less erythema but more dyspigmentation than white patients (9). Furthermore, small plaques are found be more prevalent in Asian than European patients (10).

Psoriatic arthritis (PsA) is an inflammatory joint disease common in individuals with psoriasis and typically occurs after the onset of skin disease. The features of PsA are clinically diverse and no laboratory test definitively identifies the disease. Inflammation can involve distal interphalangeal joints, be symmetric or asymmetric, involve only single large joints such as the knee, or be axial, affecting the spine. Symptoms of the disease include pain, stiffness, impaired functioning, and progressive degeneration of the affected joints. In addition, PsA is characterized by painful inflammation in the soft tissues surrounding the joints, enthesitis. The most severe and rare phenotype is arthritis mutilans with destructive inflammation typically in fingers and toes. (11)

The course of PsA is heterogeneous, but is frequently progressive and spontaneous remission is rare (11). The disease is heavily linked to psoriasis and psoriasis is a major factor in the diagnosis of PsA (12). Nevertheless, reflecting differences in genetics, clinical course, and impact of treatment; it is debated whether PsA should be defined as a manifestation of psoriasis or a separate disease and therefore a comorbidity (12).

### 1.1.2 Nosology

Given the absence of biomarkers and formal diagnostic criteria, presence or absence of psoriasis is arguably a matter of perspective. For example, some researchers have discussed the notion of a preclinical phase of psoriasis (3, 13). In such a perspective, a patient has psoriasis before it has manifested clinically. On the other hand, instances of spontaneous remissions lasting decades have also been reported (14). A key notion may be whether predisposition to clinical manifestations are considered a disease. Such considerations may develop over time (15). For example, osteoporosis, a condition that confers increased risk of fragility fracture, was officially recognized by the WHO as a disease in 2004 and thereby took a large step from being viewed as a natural part of ageing to a recognized pathology (15). For psoriasis, there appears to be no formal agreement on the matter, potentially because risk factors and the clinical course of the disease are insufficiently described, prohibiting development of consensus.

### 1.1.3 Pathogenesis

Psoriatic lesions result from abnormal differentiation and growth of keratinocytes. The pathogenesis for this process is incompletely understood but reflects upregulation of the cellular immune system, dendritic cells, T cells, and immune-related chemokines and cytokines. The disease has a strong genetic component. (16)

The causative model for psoriasis includes genetic and environmental factors and their interaction; with genetic factors explaining 70% of disease susceptibility (17). Several candidate genes have been identified including the human leukocyte antigen (HLA)-C locus on chromosome six (18). A number of environmental triggers for psoriasis have been reported including smoking, excessive alcohol consumptions, obesity, and stressful life events (19). Infections may also play a role and streptococcal infection often precedes onset of guttate psoriasis (20).

Historically, other, now discarded, theories on the pathogenesis of psoriasis existed. For example, psoriasis was hypothesized to be infectious, and a French researcher reportedly developed lesions after scaring the skin over his deltoid and rubbing in psoriatic scales into the scars: Plaques appeared at the elbows two days after the inoculation and lesions were well-marked after two weeks (21). On the basis of the high serum cholesterol, it was also hypothesized that psoriatic lesions resulted from lipid accumulation in the skin (22). Other hypotheses included that the disease originated from the joints, that it was neuropathic in nature, and that psoriasis was a parasitic disease – a notion that explained clustering of the disease in families, and which was popular in the early 20$^{th}$ century (23). James Nevins Hyde, who was among the first to recognize the association between exposure to sunlight and skin cancer, hypothesized that psoriasis was the result of the inverse relationship, i.e. that susceptible individuals developed psoriasis due to lack of light exposure (24).

The strong genetic basis for psoriasis suggests that there is some natural selection to preserve the trait over generations. One hypothesis is that the upregulated innate immunity in patients with psoriasis decreases the risk of certain infections, with scarlet fever (25) and leprosy (26) suggested as candidates.

### 1.1.4 Epidemiology

A systematic review (27) on the incidence and prevalence of psoriasis found that incidence estimates ranged from 79 to 230 cases per 100,000 person-years; and prevalence estimates ranged from 0.9% to 8.5%. No major differences in incidence or prevalence between men and women were observed. However, the incidence of psoriasis with age may follow a bimodal distribution with peaks observed before and after the fifth decade of life. The occurrence of psoriasis appeared to vary by geographic region, with the disease increasing in frequency with the distance from the equator. Differences between ethnic groups have also been reported with low prevalence found in African Americans compared to Caucasians in the United States. The reasons for the geographical and ethnic variation is unknown but likely reflect both genetic and environmental factors. The reported variation across studies may also reflect differences in study methodology, such as case definition, ascertainment procedures, and sampling schemes. (27)

Comparatively few studies have described long-term trends in the incidence of psoriasis. A US study found that the incidence almost doubled between 1970–74 and 1995–1999 (28). Furthermore, a meta-analysis of five population based cohort studies in Norway found that self-reported prevalence of psoriasis increased with each consecutive survey from 4.8% in 1979-1980 to 11.4% in 2007-2008 (29). However, a Danish population based administrative register study found the incidence to be fluctuating between 2003 and 2012 (30), and a UK study observed a slight decline between 1999 and 2013 (31)

### 1.1.5 Comorbidities

Even though the first observed association between psoriasis and another disease – diabetes mellitus – was made in 1897 (32), psoriasis was historically viewed as an affliction in the

healthy (21, 33). Nevertheless, the notion that the disease may be systemic and associated with poor health was also entertained (23). Over the years, psoriasis has increasingly been viewed as a systemic inflammatory disorder and has been associated with numerous comorbidities including cardiometabolic disease, inflammatory bowel disease, kidney disease, cancer, infections and mood disorders (32). The excess risk of comorbidities observed in patients with psoriasis appears to be dose-dependent in the sense that patients with severe disease are at higher risk than patients with mild disease (32). The pathogenic mechanisms for the excess comorbidity burden in psoriasis are unknown but may include genetic susceptibility, shared risk factors, and shared inflammatory pathways (32). The underlying mechanisms may differ between comorbid conditions (32).

### 1.1.6 Impact on patients

Psoriasis is a multifaceted disease. Clinical manifestations reduce health related quality of life (HRQoL), impair the ability to perform daily activities, and affect productivity (2). Furthermore, treatment may be unpleasant, time consuming and carry the risk of severe side effects (34).

The lesions in patients with psoriasis may hurt, itch, bleed, or burn (35). Other manifestations include skin scaling, erythema and swelling (2). These symptoms affect physical HRQoL directly and indirectly through their effect on mobility, vitality, sleep and rest (36).

The visible disfiguration in patients with psoriasis may trigger negative reactions in the patient and others, resulting in impaired emotional functioning, negative body and self-image, psychological distress, and disrupted social relationships (36). In a comparison of the impact on physical and psychological burden of eleven diseases including cancer, ischemic heart disease, and congestive heart failure; only patients with depression or chronic lung disease had lower psychological HRQoL than patients with psoriasis (37).

Psoriasis can affect activities of daily living. For example, clothing, personal hygiene, sporting, and sexual activities were reported to be adversely effected in 27% to 56% of patients with moderate to severe disease (38). In addition, the effects of the disease extend to the professional lives of patients with close to seventy per cent of patients reporting adverse impact in this domain (39).

Psoriasis may affect work productivity. It has been estimated that approximately 35% of absenteeism and 45% of presenteeism in patients with the psoriasis result directly from the disease. (40)

It should also be noted that cultural and socioeconomic factors can influence the experience and even presentation of symptoms (41), potentially making generalization of disease impact between cultures challenging.

### 1.1.7 Treatment

Treatment for psoriasis is as yet non-curative and the objective is to control symptoms (2). In addition to providing recommendations on the management of skin manifestations of the disease, a number of psoriasis treatment guidelines also advice on screening for comorbidities such as cardiovascular disease, metabolic syndrome, and depression (42-45). In fact, it has been suggested that the multifaceted nature of psoriasis requires a holistic approach that is better characterized as management than treatment (46).

Historically, treatment of psoriasis was very heterogeneous and a review from the early 20$^{th}$ century state that "[An] enormous number of medicines … have been used internally or externally for psoriasis" (23). Examples include thyroid glands in minced raw, dried, or liquid extract form (47, 48); subcutaneous injections of arsenic (21), topical mercury (21), and occlusive dressings in the form of vulcanized Indian rubber suits (49).

Today, three treatment modalities exist: topicals; phototherapy; and systemics (2). Treatment choices are individualized and reflect disease severity, lesion characteristics, recalcitrance, comorbidities and preferences of the patient (45). Due to potential serious adverse events, treatment risk-benefit profile is an important factor in clinical decision making (45). Historically, switching, rotating and combining therapies were common as physicians sought to restrict cumulative dose and side effects (50). Frequently used psoriasis treatments are described in terms of mode of administration, frequency of administration, and effectiveness in **Table 1** below.

**Table 1 Characteristics of psoriasis treatments.**

| Treatment | Mode of administration | Frequency of administration during maintenance treatment | Effectiveness |
|---|---|---|---|
| Corticosteroids | Topical | Once or twice per day | 60% |
| Vitamin D derivatives | Topical | Once or twice per day | 45% |
| Calcineurin inhibitors | Topical | Twice per day | 30% |
| UVB | Phototherapy | Three times per week for seven to twelve weeks [b] | 70% |
| PUVA | Phototherapy | Two to three times per week for nine to fifteen weeks [c] | 90% |
| Acitretin | Oral | Once per day | 15% |
| Cyclosporine | Oral | Twice per day | 45% |
| Methotrexate | IV, IM, SC or oral | Once per week | 50% |
| Apremilast | Oral | Twice per day | 30% |
| Adalimumab | Subcutaneous | Every second week | 70% |
| Etanercept | Subcutaneous | Once or twice per week | 50% |
| Infliximab | Intravenous | Every six to eight weeks | 80% |
| Ustekinumab | Subcutaneous | Every twelve weeks | 70% |
| Secukinumab | Subcutaneous | Every month | 80% |
| Ixekizumab | Subcutaneous | Every four weeks | 90%[a] |
| Brodalumab | Subcutaneous | Every two weeks | 90%[a] |
| Tildrakizumab | Subcutaneous | Every twelve weeks | 65%[a] |
| Guselkumab | Subcutaneous | Every eight weeks | 85%[a] |
| Risankizumab | Subcutaneous | Every twelve weeks | 90%[a] |
| Dimethyl fumarate | Oral | Three times per day | 30%[a] |

Note: Efficacy (Proportion of patients who achieve at least 75% reduction in PASI [PASI75]) were adapted from Bohencke and Schon (1) unless otherwise noted. Mode of administration and frequency during maintenance treatment were obtained from FASS (51) unless otherwise noted. [a] From Sawyer et al 2019 (52); [b] from Singh et al (2016) (53); [c] from Farahnik et al. (2016) (54). IV stands for intravenous, IM stands for intramuscular, and SC stands for subcutaneous.

Swedish treatment guidelines were updated in 2019 (45). The guidelines recognize that treatment choices should be customized to the patient, but patients with limited disease may generally be treated with topical agents. If the disease is more severe, the guidelines stipulate treatment with phototherapy or systemics. Methotrexate is recommended in patients with severe disease. Tumor Necrosis Factor (TNF) inhibitors are indicated for the same population, albeit as a slightly lower priority. Interleukin inhibitors are recommended for patients who have failed TNF inhibitors, or in whom TNF inhibitors are not relevant alternatives. Apremilast may also be an alternative for this patient population. (45)

Topical treatments include creams, ointments, and foams that are applied to the areas of skin affected by psoriasis (55). They are often effective with relatively benign side-effects profile, albeit skin atrophy is a theoretical concern with long-term use of topical corticosteroids (55). Topicals may also be used as augmentation to other treatments (56). One disadvantage is that their application may be time consuming and have adverse cosmetic properties, resulting in low adherence (57) and almost 50% of first prescriptions for a previously untried topical medication for psoriasis are never collected from the pharmacy (58). The most frequently used topicals for psoriasis are corticosteroids, vitamin D3 analogues, and fixed dose combinations of vitamin D3 analogues and corticosteroids (55). Other topicals such as

retinoids (tazarotene), coal tar, and dithranol are available, but used less frequently given their comparatively burdensome applications (55).

Phototherapy comprise three main types: Broadband ultraviolet (UV) A, Narrowband UVB, and photochemotherapy UVA (PUVA) (59). UVA and UVB refers to different wavelengths of the light: UVA ranges between 320 and 400 nanometers (nm); UVB ranges between 290 and 320 nm, and narrowband UVB has a wave-length around 311 nm (59). The mechanism of action of phototherapy is not completely understood (60).

UVB light is administered in a light box for a brief duration (seconds to minutes) (53). However, preparations and post administration activities result in appointments lasting fifteen to twenty minutes (53). A UVB treatment course generally consists of three sessions per week, with a minimum of twenty-four hours between sessions (53). Each course consists of twenty to 36 sessions (53). Potential long-term safety concerns with UVB include cosmetic skin ageing and skin cancer. However, UVB appears safe with no excess risk of melanoma and non-melanoma skin cancer observed over five years in 3,867 patients (61).

Psoralens, a group of photosensitizing compounds, increase the sensitivity of the skin to UV light and are therefore used with UV light as therapy for psoriasis (54). Psoralens are available as orals or bath salts and are usually administered prior to UVA exposure. Similarly to UVB, the light is administered for a short duration (seconds to minutes) in a light box. However, preparations differ from UVB. If psoralen is administered orally, the patient should ingest a psoralen 75 minutes before the appointment and if bath PUVA is administered the patient should soak in a bathtub with a mixture of hot water and the psoralen for thirty minutes prior to light exposure. PUVA is very effective (**Table 1**) but is associated with long-term increased risk of skin cancer and short-term side effects including burning, itching and nausea. (54)

Systemic treatments for psoriasis comprise traditional small molecule systemics such as methotrexate, acitretin, and cyclosporine; novel small molecule systemics such as apremilast and dimethyl fumarate; and biologics (45). The distinction between small molecules and biologics is that small molecules are generated using chemical synthesis whereas biologics comprise large and complex molecules, generally antibodies, produced by living cells (hence the term biologic) (45). Administration, and effectiveness differ between systemic treatments (**Table 1**), but one common feature for all systemic treatments, except acitretin, is that they have direct immunosuppressive effects. Whilst efficacy differs between systemic treatments, a meta-analysis of safety found no significant differences between systemic treatments for serious adverse events (62). However, the evidence was generally short-term and of low to moderate quality (62).

## 1.2 OBSERVATIONAL RESEARCH

The studies presented in this thesis are observational and patients are followed over time. This section contextualizes these types of studies and discusses broad methodological issues relevant to them.

### 1.2.1 Study design

The design of a study should reflect the research objective and ethical considerations, but necessarily also reflect resource constraints, and data availability (63). There are numerous categorization schemes for study design (64). For example, studies may be categorized according to objective (e.g. prevention, diagnosis, or treatment), investigative purpose (e.g. descriptive or analytical), use of study results (e.g. basic or applied), data collection (e.g. primary or secondary), or role of investigator (e.g. observational or experimental) (64).

A parsimonious high-level categorization scheme divides studies into three main types: Theoretical, Descriptive, and Analytical (65); with each study type further divided into subcategories (**Figure 2**). Theoretical studies explain or develop understanding of processes that occur for participants; descriptive studies describes outcomes in a group; and analytic studies quantifies the relationship between variables, e.g. treatment and outcome (65). Studies can fall under more than one category (65). For example, baseline characteristics in an observational cohort study may describe the state of a population and therefore have a descriptive purpose, whereas exposure during follow-up may be related to outcomes for an analytic purpose.

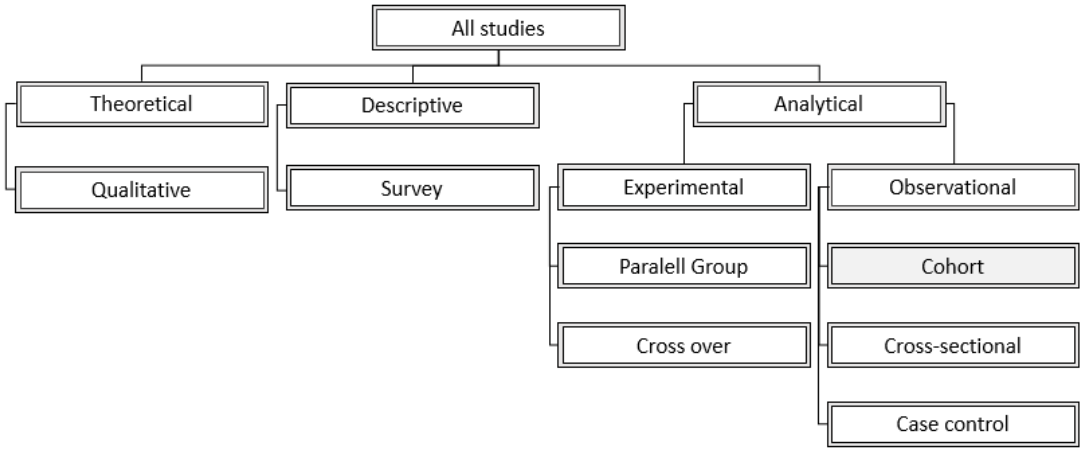


**Figure 2 Parsimonious classification of study design.** Adapted from Glasziou and Heneghan (2009) (65).

The studies in this thesis are observational cohort studies and therefore fall into the highlighted category in **Figure *2***. The studies are observational given that patients are not assigned a specific treatment or exposure as part of the study, and they are cohort studies because patients are identified at one point in time and followed thereafter. However, it should be noted that they have both analytical and descriptive objectives.

Cohort studies may be classified as prospective and retrospective (66). However, whether a cohort study is prospective or retrospective is a question of perspective: Data may be collected prospectively while the analysis of the data (e.g. selection of patients and study design) may be retrospective (66).

### 1.2.2 Populations and sampling

Knowledge of characteristics and associations in a population informs expectations on members of that population. Obtaining data for an entire population is often impracticable and prohibitively expensive. Therefore, data from a sample (a subset of a population) is used to make inferences (draw conclusions) about the population (67): The findings from the sample is generalized to the population.

A framework for sampling in human studies suggested in Hernan (2016) (68) is shown in **Figure *3***. In this framework, the population of interest is called target population; and the characteristic of interest is called parameter. The target sample is a defined subset of the population for which the researcher wishes to make inferences. Ideally, the target sample is identified from the target population using a random process. Under random sampling, the estimate of the population parameter is expected to be correct on average and uncertainty around the estimate can be quantified. (68). True random sampling is often difficult and investigators frequently rely on non-random sampling procedures they believe will generate a sample that is representative of the target population (68). However, the actual sample may deviate from the target sample depending on selection mechanisms that are outside the control of the researcher. For example, women may be more likely than men to participate in a research study. In theory, the representativeness of the actual sample to the target sample may be explored quantitatively to assess and improve generalizability (69). However, important information from non-participants are frequently missing, making an informed quantitative assessment of representativeness difficult (69). Similarly, in the absence of external validation, transportability of the parameter estimate to another target population is also uncertain. Furthermore, generalizability and transportability may be problematic when conditions in a study are dissimilar to conditions outside the study, resulting in that participants alter their behavior or are otherwise affected by the study setting (70, 71).

The terminology used in the framework discussed above is not universal. For example, the terms target population, generalizability, and transportability can be referred to as source population, internal validity, and external validity or generalizability, respectively (72).

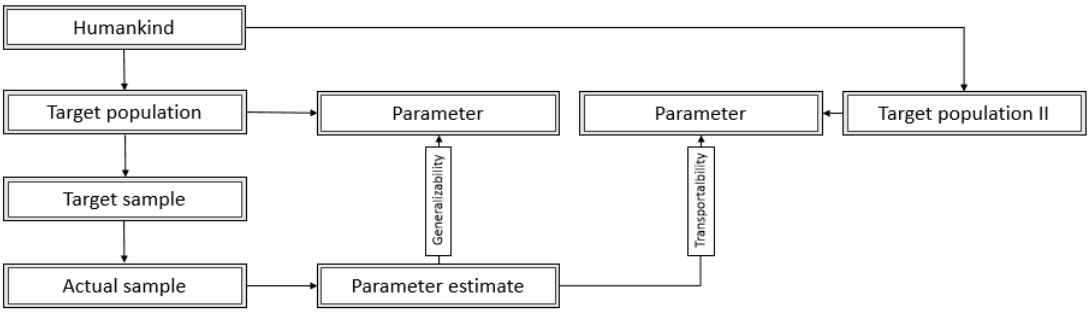


**Figure 3 Framework for participant selection in clinical studies.** Adapted from Hernan (2016) (68).

### 1.2.3 Variables and distributions

Data to estimate population parameters are obtained from a sample in the form of variables. Variable have two defining characteristics: They provide descriptive attributes, and they can vary between observations (73).

Variables vary. Therefore, they may be described by mathematical functions known as probability distributions (74). Probability distribution assigns probabilities for each possible value that a variable may take (74). Based on subject matter knowledge and the observed data for a variable in a sample, the shape and form of the probability distribution may be assumed (75). A probability distribution is defined by its parameters and the observed data on a variable in an actual sample can be used to estimate the parameters of a distribution in the target population (68).

Estimates of target population parameters may be interesting in themselves. In addition, they are often used to make comparisons. For example, one can estimate the probability that the mean of one distribution is equal or larger than a given value, or that the observed probability distributions in two samples are generated by the same underlying probability distribution, e.g. to assess whether the expected outcome observed in one group is different from the expected outcome observed in a second group.

In addition to representativeness of the target population, a key assumption for many procedures for inferential statistics is that the variable of interest is independent and identically distributed. In this context, independent means that observations do not affect each other; and identically distributed means that all values should come from the same distribution (76) – there should be no trends in the data, e.g. patients recruited late in a study should not be systematically different from those recruited early in a study.

Regardless of the probability distribution of the variable in the population, the central limit theorem (CLT) posits that the sampling distribution of the mean (the distribution of means from repeated samples from the population) will be approximately normal, assuming that the sample size is sufficiently large (77). A rule of thumb is that a sample of thirty is sufficiently large for the sampling distribution of the mean to be approximately normal (78). However, this rule of thumb is debated and larger sample sizes may be required for heavily skewed distributions (78).

### 1.2.4 Precision and bias

An important consideration for many descriptive and analytical studies is to estimate the relevant population parameter(s) with as little error as possible (72). Errors in estimation can be classified into two groups: Random and systematic errors (72). Random error affects the precision of the estimate whereas systematic error affects the generalizability from the actual sample to the target population (72).

#### *1.2.4.1 Random errors*

Conceptually, random error may reflect (i) chance, or (ii) insufficient knowledge of causes and effects. For example, if an observer knew all the physical forces that affect a coin toss, she should be able to perfectly predict the outcome of the toss. However, in most circumstances, she does not know those forces and therefore the outcome appears random to her. A synthesis of the two views is that random variation is the part of reality we cannot predict. (72)

Given the random variation in a variable, the precision of a parameter estimate is uncertain (72). Assuming that the sample is randomly drawn from the population, statistics can be used to derive measures of this uncertainty. Confidence intervals is a frequently used measure of uncertainty for the parameter estimate. A confidence interval for a mean can be defined as: "If a series of samples are drawn and the mean of each calculated, 95% of the means would be expected to fall within the range of two standard errors above and two below the mean of these means" (79). However, it may be noted that even if the notion of random sampling is correct, confidence intervals may be inaccurate given that other sources of uncertainty, such as measurement error, affect precision (80).

#### *1.2.4.2 Systematic errors*

In the Merriam-Webster dictionary, bias is defined as any "tendency which prevents unprejudiced consideration of a question". In research, bias arise when "systematic error [is] introduced into sampling … by selecting or encouraging one outcome … over others" (81). Bias is problematic because it may lead to false associations or failure to identify true relationships (82), distorting our understanding and potentially misdirecting our actions (83). Biases are numerous and a review from 2004 provide an explicitly non-exhaustive list of more than sixty biases (84). The terminology used to describe bias differ by fields. For example, the term "confounding by indication" frequently used by epidemiologists refers to the same concept as the term "selection bias", more frequently used by statisticians (85). Several classification systems for biases exist (84). The discussion below adopts a frequently used classification system that groups biases into three categories: Selection bias, information bias and cofounding (86).

Selection bias arises when the actual sample is not representative of the target population on relevant factors (84). Therefore, in descriptive studies, selection bias affects the generalizability of the actual sample to the target population reflecting that the parameter estimates from the actual sample differs from the true parameter in the target population (68). In analytical studies where the objective is to obtain unbiased estimates of relationships between exposure and outcome, selection bias may occur when sample selection is affected by both exposure (or a cause of the exposure) and the outcome (or a cause of the outcome), resulting in absence of comparability between groups being studied (85). Even if groups are comparable, selection bias may affect the estimates of analytical studies for the same reason it

impacts descriptive studies: the actual sample may not be representative of the target population (87).

Information bias can occur when information used in the analysis is measured or recorded erroneously (72). The impact of information bias depends on whether the measurement or classification error is the same or different across exposure and/or outcome. In a descriptive study, systematic measurement errors will result in lack of generalizability from the actual sample to the target population. For analytic studies, the impact of information bias is more complex and depends on whether the measurement errors affect the exposure and/or the outcome and whether it is the same in all study groups (non-differential misclassification) or differs between study groups (differential misclassification). In the common case of two exposure groups and an outcome without measurement error, the expected bias from non-differential misclassification of exposure is towards the null, i.e. the relationship between exposure and outcome will be underestimated. When misclassification is worse than would be expected of a random process, e.g. through inverse coding of a variable during data entry, the bias may be away from the null, but in the opposite direction. (72)

Confounding bias affect analytical studies. Confounding has been defined as the existence of common causes of exposure and outcome (85) and may result in erroneously estimated associations between exposure and outcome (72). However, it is not sufficient that a variable is associated with both exposure and outcome to be a confounder (72). For example, when exposure has an effect on an outcome, a variable that correlates with exposure will also be associated with outcome, even though it does not confound the relationship between exposure and outcome. Therefore, it is important to carefully consider the causal mechanisms when evaluating whether a factor confounds a relationship or not (72).

# 2 LITERATURE REVIEW

## 2.1 CLINICAL COURSE OF PSORIASIS

Textbooks in dermatology and psoriasis describe the clinical course of psoriasis as varying and unpredictable: It is frequently chronic, but may also wax and wane, and spontaneous remissions of varying lengths occur (8, 88-91). Several textbooks also state that understanding of the course is limited due to absence of prospective observational studies that describe the course from onset (8, 88, 90). This notion is also supported by three position papers on the research agenda in psoriasis, which state that prospective observational studies on the course of psoriasis from onset should be a research priority (92, 93).

A review of the literature demonstrate that a number of studies have described the course of psoriasis using cross-sectional or retrospective designs. Outcomes measures, perspectives, and information provided differ among studies, making a coherent overview difficult. Furthermore, the signs and symptoms of psoriasis are affected by treatment and given developments in medicine over time, the validity of old data to the present may be questionable[1]. Another challenge is that the course may be confounded by age. For example, if symptoms improve with age, the disease course will appear benign even though it is driven by ageing rather than disease duration. However, for the individual patient, such as distinction may be of limited consequence.

**Table 2** presents on overview of 14 studies published the last one hundred years that explicitly aimed to describe the course or prognosis of psoriasis. The studies indicate that a minority of patients may achieve sustained remission, even without treatment. For the majority of patients, symptoms are constant, and for a minority severe.

[1] Romanus (1945) also noted this point, but did not consider it problematic reflecting his view that treatment was standardized and had changed little since 1878 when chyrsarobin (dithranol/anthralin) was introduced. Thereafter the treatment armamentarium in psoriasis has expanded more rapidly, arguably rendering comparisons with historic data increasingly challenging.

**Table 2 Summary of studies describing the clinical course of prognosis of psoriasis.**

| Study | Country | Pheno-type | Method | Index year(s) | From onset | Follow-up (years) | Pat-ients | Outcome |
|---|---|---|---|---|---|---|---|---|
| Hippler (1932) (94) | Germany | Na | Chart review and survey | 1925-1931 | Na | 1-7 | 442 | Complete remission for 1-3 years: 5%<br>Intermittent complete remission: 8%<br>No remission: 88% |
| Hallam (1934) (95)[a] | England | Na | Chart review and survey | 1919-1925 | No | 9-15 | 43 | Complete remission since index: 9% |
| Weinsheimer (1937) (96)[a] | Germany | Na | Chart review and survey | 1928-1934 | Na | 2-9 | 321 | Complete remission since index: 16% |
| Romanus (1945) (14) | Sweden | Na | Chart review and examination | 1892-1922 | Subgroup | 20+ | 232 | Complete remission since index: 21%<br>Intermittent complete remission: 19%<br>No remission: 60% |
| Diedy (1951) (97) | Switzerland | Na | Chart review and examination | 1906-1935 | Na | 15-45 | 49 | No symptoms: 17%<br>Mild symptoms: 38%<br>Moderate symptoms: 24%<br>Severe symptoms: 21% |
| Dorn (1957) (98) | Germany | Na | Chart review and survey | 1953-1955 | No | 2-5 | 312 | Complete remission since discharge: 7%<br>Intermittent mild symptoms: 4%<br>Intermittent moderate symptoms: 30%<br>Intermittent severe symptoms: 14%<br>Constant mild symptoms: 6%<br>Constant moderate symptoms: 25%<br>Constant severe symptoms: 14% |
| Lomholt (1963) (99) | Faroe Islands | Na | Examination and survey | Na | No | Na | 207 | Complete remission: 4%<br>Mild symptoms: 32%<br>Minor spread: 37%<br>Major spread:16%<br>Severe onset followed by minor eruptions: 11% |
| Molin (1973) (100) | Sweden | Na | Chart review and survey | 1957-1966 | No | 4-13 | 300 | Complete remission: 5%<br>Mild: 56%<br>Moderate: 29%<br>Severe: 7%<br>Very severe: 2% |
| Farber (1974) (101) | USA | Na | Survey | Na | Na | Na | 5,355 | Ever complete remission without treatment: 39% |
| Martin (1996) (102) | USA | Guttate | Prospective study | 1982 | Yes | 10+ | 15 | Chronic plaque psoriasis: 33% |
| Kaur (1997) (103) | India | Na | Survey | Na | Na | Na | 1,220 | Ever complete remission during a year: 35%<br>Improved with treatment: 61%<br>Never free of disease: 4% |
| Ferrandiz (2001) (104) | Spain | Na | Survey and clinical examination | Na | Na | Na | 1,774 | Variable course: 39%<br>Consistent course: 61% |
| Ko (2006) (105) | South Korea | Guttate | Chart review and survey | 1980-2004 | Yes | 1.5-19 | 36 | Complete remission: 61%<br>Chronic plaque psoriasis: 39% |
| Sakai (2007) (106) | Japan | Na | Chart review and examination | 1991-1996 | First diagnosis | 5+ | 169 | Improved: 73%<br>Unchanged/Deteriorated: 27% |

Note: [a]Quoted from Romanus (1945) (14).

It has been argued that placebo arms in RCTs provide some information on the short-term course of psoriasis without treatment (107). The majority of patients in placebo arms in RCTs experience minor change (107). However, a minority of patients improve drastically: For example, Ambikaibalan (2020) estimated the proportion of placebo treated patients who experienced 75% and 90% improvement in disease severity (measured using the Psoriasis Area and Severity Index [PASI]) at 5%, and 2%, respectively (108). However, it is uncertain whether those improvements would have taken place outside the trial setting. Siemens (1954)[2] had a similar approach and withheld treatment from 19 hospitalized patients with psoriasis for one month (109). Six of the 19 patients showed pronounced improvement by the end of the month (109).

In terms of prognostic factors for the disease course, early onset has been associated with severe disease course (110). However, this finding has not been replicated in all studies (111). Male sex (106), major eruption at onset (99), and high BMI (106) have also been associated severe course. Short disease duration (14), early treatment (33), and limited initial spread (99) have been associated with mild disease course.

## 2.2 CAUSE-SPECIFIC MORTALITY

The direct mortality impact from psoriasis is practically zero (8). However, a recent systematic review and meta-analysis of observational studies found that psoriasis was associated with excess all-cause mortality (RR: 1.21; 95% CI: 1.14 to 1.28) (112). The excess mortality was dose dependent in the sense that severe psoriasis carried higher risk than mild psoriasis: RR: 1.13 (95% CI: 1.09 to 1.16) for mild disease and RR 1.52 (95% CI: 1.35 to 1.71) for severe disease (112). A number of studies have also explored specific causes of death including cardiovascular mortality (113-117) deaths related to alcohol (118, 119) and smoking (118, 119), suicidality (120), and infection (121).

Studies that systematically explore the components of all-cause mortality in patients with psoriasis compared to the general population have two benefits. Firstly, they can identify the causes of death with the highest absolute and relative risks, informing prevention efforts. Secondly, they may identify hitherto unknown causes of deaths with risks that differ between patients with psoriasis and the general population. However, they are exploratory in nature and multiple testing may result in chance findings.

In addition to the study in this thesis, five studies that systematically estimated the components of all-cause excess mortality in psoriasis were found in the literature (122-126). However, two Danish studies (125, 126) partially included the same population. Therefore, four studies are described in **Table 3**. The studies have some important differences. Firstly, the grouping of causes of death differ. They are grouped either by ICD-10 chapters or by classifications from agencies, such as the US Centers of Disease Control and Prevention

[2] Quoted from Lomholt (1963).

(CDC). Furthermore, the studies differ in definition of psoriasis, and severity grouping. Nevertheless, commonalities exist: All studies were performed on secondary data assets, using either administrative data or electronic medical records databases, and mean age at study cohort entry was similar across studies, ranging from 47 to 53.

**Table 3 Overview of studies that systematically estimated cause specific excess mortality in patients with psoriasis.**

| Study | Country | Data source | Psoriasis definition | Severity strata | Severity definition | Mortality Grouping | Patients/ Controls (n) | Deaths patients/ controls (n) | Study years | Mean age (SD) | Confounding control |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Abuabra (2010) (122) | UK | EMR database | >=1 diagnosis | No | Treatment | CDC categories | 3,603/ 14,330 | 321/ 862 | 1987-2002 | 52 (17) | Age and sex |
| Lee (2017) (124) | Taiwan | Secondary database | >=3 diagnoses with at least 1 from a dermatologist | No[b] | Na | ICD-10 chapters | 80,167/[a] | 7,198/[a] | 2001-2012 | 47 (18) | Age and sex |
| Skov (2019) (126) | Denmark | Secondary database | >=1 hospital-based diagnosis | No | Na | Sundheds-styrelsen categories | 12,160/ 23,936 | 1,982/ 2,554 | 1998-2014 | 48 (19) | Age and sex |
| Colacon (2020) (123) | Canada | Secondary database | >=1 inpatient or >= 3 outpatient diagnoses | No | Na | ICD-10 chapters | 176,858[a] | 2,524/[a] | 2016 | NA | Age and sex |

Note: Salaheden et al (2015) (125) also reported cause-specific mortality for Denmark, However, Skov et al (2019) (126) is presented here given that it provides more recent data. [a] No specific control population: age and sex standardized mortality ratios used to estimate excess risk. [b]Only for all-cause mortality, not for specific causes of death.

**Table 4** presents the direction and statistical significance of the associations between psoriasis and specific causes of death presented in the studies. Given that the causes of death were grouped differently between the studies, estimates are difficult to compare directly. However, it may be noted that all cohorts reported statistically significant increases in cardiovascular mortality, diabetes and metabolic mortality, and cancer mortality.

**Table 4 Summary of results in four studies that systematically estimated cause specific excess mortality in patients with psoriasis.**

| Cause of death | Abuabra (2010) (122) | Lee (2017) (124) | Skov (2019) (126) | Colaco (2020) (123) |
|---|---|---|---|---|
| Infection | **+*** | **+*** | +* | + |
| Cancer | **+*** | **+** | +* | +* |
| Diabetes and metabolic disease | **+*** | **+*** | +* | +* |
| Mental and behavioral disorder | . | **-*** | +* | +* |
| Neurological disease | **+*** | + | +* | + |
| Cardiovascular disease | **+*** | **+*** | +* | +* |
| Respiratory disease | **+*** | + | +* | +* |
| Diseases of the digestive systems / liver disease | + | **+*** | +* | +* |
| Kidney / genitourinary disease | **+*** | **+*** | +* | + |
| Injury, poisoning and other external causes | + | **-*** | +* | . |
| Suicide / Intentional self-harm | + | **+*** | +* | . |
| Unknown/Missing | **+*** | . | +* | . |
| **All-cause** | . | **+*** | **+*** | +* |

Note: *<0.05; "." Indicates that the cause-specific excess mortality was not estimated in the study.

## 2.3 TREATMENT PATTERNS

Treatment patterns is a broad term. For example, it may describe treatment uptake in a population, drug survival or persistence, switching, or adherence. In the current study, it is used as an umbrella term for five events that describe aspects of effectiveness and treatment outcomes: Persistence, switching, augmentation, restart after discontinuation, and insufficient treatment result.

A systematic review on endpoints in real-world effectiveness studies on biologic treatment in psoriasis (127) showed that most real-world studies used either clinical end-points or persistence to estimate effectiveness, but a handful of studies also incorporated switching, dose increase, augmentation, and restarts into outcome definitions (127). Especially persistence, defined as time from start to discontinuation of treatment has been extensively studied, primarily for novel systemics and biologics (128), but also for traditional systemics (129). Most data, especially from Europe, have been derived from clinical registers and retrospective chart reviews, but studies on administrative data using refill patterns have also been published, e.g. in Sbidian et al (2019) (130); and the relative merits of the different approaches have been debated (131, 132).

Data on real-world effectiveness of topicals are scarce, potentially reflecting challenges in operationalizing treatment events given the on-demand nature of topicals. However, the data that do exist indicate that primary persistence is poor with nearly half of new prescriptions never redeemed (58).

## 2.4 ECONOMIC BURDEN

We identified four studies that estimated aspects of economic burden of psoriasis in Sweden.

Ghatnekar et al 2012 (133) presented a cross-sectional survey of societal costs during one month in 164 patients with psoriasis recruited in two Swedish dermatology clinics between September and December 2009. Mean total costs per patient were estimated at EUR 994. Costs were presented stratified by most potent treatment received: For patients whose most potent treatment was topicals, phototherapy, traditional systemics, and biologics, mean costs were estimated at EUR 369, EUR 1,274, EUR 1,085 and EUR 1,709 respectively  The study did not observe a clear relationship between costs and clinical severity, measured by PASI, or costs and HRQoL measured by DLQI. (133)

Ekelund et al (2013) (134) enrolled 443 patients with psoriasis based on PASI criteria: 153 with PASI<8, 128 with 8 ≤ PASI ≤ 12, and 162 with PASI>12. Mean costs were estimated using a questionnaire with a one year look-back period. The mean annual direct and indirect costs were estimated at EUR 2,169 and 1,230, respectively. Whilst PASI was not a significant cost driver in the study, DLQI, PsA, and systemic treatment were positively and significantly associated with mean annual costs. (134)

Direct and indirect costs for psoriasis in Sweden 2006 and 2009 were presented in Norlin (2015) (135). The study identified patients who had a specialist outpatient visit or inpatient

episode with psoriasis as primary or secondary diagnosis; or dispensed a prescription of a medication with calcipotriol in the relevant years. Direct costs in the study comprised specialist outpatient visits to a Medical Doctor and inpatient treatment of psoriasis (both with a primary diagnosis of psoriasis), and topicals, traditional systemics, and biologics used to treat psoriasis. Indirect costs were estimated with the human capital approach and the proportion of indirect costs attributable to psoriasis estimated by comparing patients with psoriasis to age, sex, and residency matched controls. Total mean direct cost per patient in 2006 and 2009 were estimated at EUR 743, and EUR 855, respectively. Total mean indirect cost per patient in 2006 and 2009 were estimated at EUR 3,509, and EUR 3,010, respectively. In 2009, total mean direct (indirect) costs for patients who were treated with topicals, systemics, and biologics as most potent treatment were estimated at EUR 315 (EUR 2,238), EUR 801 (EUR 5,380), and 12,786 (EUR 10,035), respectively. (135)

Lövendahl et al (2016) (136) estimated mean direct and indirect annual costs in patients with psoriasis and PsA from 2008 to 2011 using the Skåne Health Care Register (SHCR), a population based health care register in the Skåne Region (~1.3 million inhabitants) in Southern Sweden. Patients with psoriasis or PsA were identified using ICD-10 codes in any type of care (primary, specialist outpatient, and inpatient care) between 1998 and 2007. Mean annual costs due to psoriasis and PsA were estimated using two approaches. In the first approach, the mean difference in costs between patients with psoriasis or PsA and age, sex, and residency matched controls without psoriasis or PsA was estimated. In the second approach, only health care resource use and sickness episodes with an ICD-10 code for psoriasis or PsA, and treatments used for the two conditions were considered. Among the 12,562 patients with psoriasis and 2,721 patients with PsA, mean health care costs were estimated at EUR 3,717 and EUR 6,186, respectively. The mean annual incremental direct costs in patients with psoriasis or PsA compared with the controls were estimated at EUR 1,724. Using the second approach, the mean disease specific costs were estimated at EUR 400 for psoriasis and EUR 2,866 for PsA. The mean annual indirect costs were estimated at EUR 4,666 in patients with psoriasis and EUR 10,566 in patients with PsA. The proportions of indirect costs directly attributable to the diseases was estimated at 82% for patients with psoriasis, and 89% for patients with PsA. (136)

## 2.5 RELATIVE EFFECTIVENESS OF ADALIMUMAB, ETANERCEPT, AND METHOTREXATE

The advent of biosimilar adalimumab and etanercept may render biologics viable first line systemic treatment in psoriasis (137). Relative effectiveness of adalimumab and etanercept compared to methotrexate, the most common systemic treatment in current clinical practice, is an important consideration for such a change in treatment paradigm.

Two clinical trials have demonstrated that adalimumab is more effective than methotrexate. The CHAMPION study was a double-blind RCT on 108 patients treated with adalimumab, 110 patients treated with methotrexate, and 53 patients treated with placebo (138). After 16 weeks, the proportion of patients who reached the primary end-point, at least seventy-five

percent reduction in PASI from baseline (PASI75), was estimated at 80% for adalimumab. 36% for methotrexate ($p<0.001$ vs adalimumab), and 20% for placebo ($p<0.001$ vs adalimumab) (138). In pediatric psoriasis, adalimumab and methotrexate were compared in a double-blind RCT on 75 patients (139). After 16 weeks, a higher proportion of patients treated with adalimumab achieved the co-primary end-point PASI75 compared with patients treated with methotrexate (58% vs 32%; $p=0.027$) (139). No RCTs have directly compared etanercept to methotrexate. A Cochrane Collaboration Systematic Review and meta-analysis of RCTs comprising 140 studies on a total of 51,749 randomized participants showed that adalimumab and etanercept were more effective than methotrexate in achieving at least ninety percent reduction in PASI from baseline (PASI90) (62).

In terms of real-world data, three studies have estimated and compared the drug survival of adalimumab, etanercept, and methotrexate. A Spanish study using the BIOBADERM register estimated median drug survival for adalimumab at 1.68 years, etanercept at 1.21 years, and methotrexate at 1.01 years (140). The differences in drug survival between adalimumab and methotrexate, but not between etanercept and methotrexate, were significant at the five percent level (140). Another Spanish prospective observational study, the SAHARAH, enrolled patients with moderate to severe psoriasis treated with systemics (141). Among the 87, 90, and 97 patients treated with adalimumab, etanercept and methotrexate, the 12 (24 months) drug survival was estimated at 68.4% (53.9%), 79.3% (66.3%), and 69.5% (51.6%), respectively (141). No statistical tests were conducted for differences, but the confidence intervals for the drug survival rates were overlapping (141). A retrospective chart review from a single German center comprising 357 patients estimated one year drug survival for adalimumab, etanercept, and methotrexate at 70%, 60%, and 43% ,respectively (142). No statistical significance tests for these differences were conducted (142).

Three real-world studies have estimated effectiveness of the three treatments using s-PGA and PASI as outcomes. In a US cross-sectional study on patients with plaque psoriasis, the proportion of patients who were clear or almost clear from lesions on adalimumab (n=152), etanercept (n=191) and methotrexate (n=174) were 47.7%, 34.2%, and 23.8%, respectively (143). Both before and after adjusting for confounders, the differences between adalimumab and methotrexate, and etanercept and methotrexate were statistically significant at the five percent level (143). An Italian prospective register study estimated outcomes in patients aged 65 or more treated with adalimumab (n=18), etanercept (n=83), or methotrexate (n=74) (144). At week 12 after treatment initiation, the proportions of patients on adalimumab, etanercept, and methotrexate who achieved PASI75 were 65%, 64%, and 49%, respectively (144). No tests for the statistical significance of the observed differences were conducted (144). In an Italian prospective study including 43 patients on methotrexate and 58 patients on etanercept, the mean percentage improvements at six months with etanercept and methotrexate were estimated at 75% and 48%, respectively (145).

# 3 RESEARCH AIMS

There has been considerable advances in the treatment of psoriasis and our understanding of its pathogenesis has improved. Nevertheless, knowledge of the clinical course of psoriasis is limited and comes from retrospective and cross-sectional studies. Therefore, prospectively collected data on the disease course and its predictors holds substantial interest to the medical community at large, especially to clinicians whom patients are likely to see at disease onset. Such data can help practitioners to communicate more accurate expectations of the long-term prognosis and disease impact; and can also help to identify patients who may have the most to gain from frequent follow-up.

Information on cause-specific mortality in psoriasis may identify the most lethal comorbidities in both absolute and relative terms. Furthermore, data on cause-specific mortality stratified by severity may improve our knowledge on the relative importance of comorbidities in the two populations and inform discussion on factors associated with the onset and severity of psoriasis.

Understanding the economic burden of the disease may provide information on subgroups with unmet need, areas for potential improvement, and may contribute with information relevant to setting research agenda and allocating resources. Data on the economic burden of psoriasis in a Swedish setting are scarce and the data that do exist do not include all relevant costs, or do not stratify patients by disease severity.

Many studies have reported on persistence of novel systemic treatment and biologics in psoriasis in Europe. However, other aspects of treatment patterns such as switching and augmentation are less frequently reported. Data on topicals and traditional systemics are also scarce. In addition, few studies have described treatment patterns using population based administrative registers in a European setting. More comprehensive data on treatment patterns, especially for topicals and traditional systemics, may improve accuracy of expectations on treatment and can inform clinical decision-making. With the advent of biosimilars, biologics may be feasible alternatives as first line systemic treatment in moderate-to-severe psoriasis. Improved understanding of the relative effectiveness of adalimumab, etanercept, and methotrexate is therefore an important step in evaluating the relative merits of biosimilars as first line systemic treatment.

To these ends, the specific objectives of this thesis are to:

1. Describe the clinical course of psoriasis and its predictors.
2. Estimate cause-specific excess mortality in patients with psoriasis.
3. Estimate the healthcare and societal economic burden of psoriasis.
4. Describe the real-world treatment patterns in psoriasis.
5. Estimate the relative effectiveness of adalimumab, etanercept, and methotrexate in psoriasis.

# 4 MATERIALS AND METHODS

## 4.1 STUDY SETTING

Healthcare in Sweden is predominately funded through taxes with universal access and limited co-payment (maximum of SEK 2,250 [approximately EUR 244] for medication per year; and EUR 112 for health care visits) (146, 147). Healthcare provision is decentralized to 21 regions and predominately publically funded (84%) with user fees and private insurance financing 15% and 0.6%, respectively (146). Some health care is provided by the municipalities such as care in special housing and home care (146).

Medical doctors have free prescribing rights and clinical thresholds or applications do not hinder access to psoriasis treatments (148). Systemic treatment of psoriasis is predominately provided by dermatologists (45).

## 4.2 DATA SOURCES

This thesis comprises manuscripts from three studies using different data sources: The Stockholm Psoriasis Cohort (SPC) (Manuscript 1), the Psoriasis REtrospective STudy (PSOREST) (Manuscripts 2, 3, and 4), and DermaReg-Pso (Manuscript 5).

The SPC was a prospective observational study enrolling patients with recent onset psoriasis and controls; PSOREST identified all patients with a diagnosis of psoriasis in Region Skåne and Västra Götaland using administrative databases; and DermaReg-Pso is a register following patients on systemic treatment for psoriasis in Stockholm. Both SPC and PSOREST comprised linkages to other databases.

### 4.2.1 Stockholm Psoriasis Cohort

The Stockholm Psoriasis Cohort (SPC) is a prospective observational study on patients with recent onset psoriasis and population matched controls. Patients above 15 years of age with first onset of psoriasis lesions on non-hairy skin within the last 12 months were eligible for study inclusion.

Patients were mainly recruited from the Stockholm area, Sweden, between 2000 and 2005. Patients were referred from dermatology clinics, general practitioners, school nurses, sexual health centers, and youth clinics. The study was also advertised in daily newspapers and in the magazine and website of the Swedish Psoriasis Association. Individuals were screened via a telephone interview conducted by a dermatologist or a study nurse. Patients who were deemed to fulfil the study inclusion criteria were examined clinically by one of two dermatologists and patients with a convincing diagnosis of psoriasis were included. Individuals with a history of skin symptoms suggesting prior psoriasis were excluded.

Clinical examinations were performed using standardized forms at enrollment and at ten years. The data collected comprised phenotypes and clinical manifestations – both classified according to established terminology (149) – history of psoriasis and potential precipitating

factors including infection, defined as acute symptoms requiring anti-infective treatment within ten days of onset of psoriasis, and stressful life events, defined as events with profound effect on the patients within two months of disease onset. A small number of patients were in remission at the time of the enrollment examination. For these patients, medical records were requested and evaluated to validate the initial diagnosis. Fingernails and toenails were examined to assess nail lesions on all patients, albeit only fingernails were included in the analysis reflecting that the evaluation of toenails may be complicated by fungal infections.

Patients with subjective joint problems were seen by a rheumatologist for comprehensive joint examination. Relevant patients were also seen by a rheumatologist at ten years for a similar joint examination. The rheumatological examinations included evaluation of the presence of arthrosynovitis, tenosynovitis, axial enthesitis, peripheral enthesitis, dactylitis, and tender and swollen joint counts.

Genomic DNA was extracted by standard procedures using peripheral blood samples. Information from the examinations, interviews, and laboratory analyses were complemented with data from medical records, the National Patient Register (NPR), the Prescribed Drug Register (PDR), the Causes of Death Register (CDR), and the Total Population Register (TPR).

### 4.2.2 Prescribed Drug Register

The PDR contains national prescription data since 2005. Data are available on date of filling, ATC-code, name of the drug, and dosage. The register covers all prescription drugs that are dispensed at pharmacies. (150)

### 4.2.3 National Patient Register

The NPR contains data since the 1960s on hospital admissions in Sweden. Available variables include date and length of stay, diagnoses, surgical procedures, and DRG codes. Since 2001, the register also contains data on specialized outpatient care provided by medical doctors but with regional differences in quality. (151)

### 4.2.4 Cause of Death Register

The CDR has data on date of death, underlying, and contributing causes of death for individuals who were registered in Sweden when they died (152). Practically all deaths in Sweden are recorded and 96% of those have a recorded cause of death (152). Using data for death in 1995, a study found 77% agreement between the death certificates and case summaries for the deceased individuals (153).

### 4.2.5 Total Population Register

The Total Population Register (TPR) is an administrative register held by Statistics Sweden with information on sex, birth, death (if applicable), and residency for all subjects resident in Sweden from 1961 (154).

### 4.2.6 Skåne Health Care Register

The SHCR is a regional database with population wide coverage for Region Skåne, (total population of 1.3 million) with information derived from electronic medical records and administrative procedures since 1998 (146). The data transferred to the SHCR constitute the basis for reimbursement and therefore the register should include the vast majority of health care contacts across all types of health care reimbursed by the regions. The proportion of health care contacts assigned a diagnosis differ between levels of care and types of care provider. For physician visits, the proportion of visits in primary care with diagnoses has fluctuated between 80% and 100% since 2005 whereas the corresponding proportion for specialist outpatient care exceeded 90% over the same period. Registered variables include department (e.g. orthopedics, infection, or dermatology), contact type (visit, phone call, e-mail, or letter), type of caregiver, emergency visit (yes/no), procedure codes, DRG codes and reimbursement amount. (146)

### 4.2.7 The Vega register

Similar to SHCR, the Vega register is a regional database with total population coverage (155). For reimbursement purposes, all health care visits in the Region Västra Götaland (1.7 million inhabitants) are registered in VEGA since 2005, with ICD and procedure codes prerequisites for reimbursement. Coverage is practically complete for inpatient, outpatient, and primary care. (155)

### 4.2.8 MIDAS

Mikrodata för Analys av Socialförsäkringen (MiDAS) is a database with information on social insurance payments and is held by the Social Insurance Agency (156). Whilst data are available from 1994, changes to the social insurance system have resulted in changes in definitions of variables over time (156).

MiDAS comprise data relating to episodes of social insurance payments. Payment types include sick leave (sickness benefit) and disability pension (sickness compensation, activity compensation, and early retirement pension). If the type of payment or the degree of absence from work changes during an on-going episode, a new episode is registered (156).

Individuals who cannot work due to an illness or symptoms of a temporary character may be paid sickness benefit from the sickness insurance. Eligible for sickness benefit are those who are employed or runs a business, actively looks for a job (registered unemployed), or looks after a child (on parental leave). Sickness benefit can be paid at the level of 25%, 50%, 75% or 100% of a fulltime employment pay (up to a ceiling), depending on the extent of the sick leave. For registered unemployed individuals, business owners, and individuals on parental leave, sickness benefit can be paid from day two of the sick leave. In contrast, employed individuals will first receive sick pay from their employer for a period before receiving sickness benefit. The length of this period is 14 days. (156)

Activity compensation (under 30 years of age) and sickness compensation (over 30 years of age) can be provided to individuals who cannot work full-time due to injury, sickness, or disability. Both sickness and activity compensation are re-evaluated at least every third year, but individuals who receive sickness compensation should be unlikely to return to full-time employment. (156)

### 4.2.9 DermaReg-Pso

DermaReg-Pso is a register enrolling patients who are candidates for systemic treatment in the Stockholm region, Sweden. The register started in 2009 and predominately enrolls patients from the Karolinska University Hospital and a treatment center in Sundbyberg run by the Swedish Psoriasis Association. Clinician and patient reported outcomes (PROs) are collected when the patients visit the clinic and stored in a database. Furthermore, at enrolment, background variables including age at onset, and heredity are captured. All patients provide informed consent prior to enrollment and may opt out from the register at any time. Data collected include the Psoriasis Area and Severity Index (PASI) (157), the Psoriatic Arthritis Screening and Evaluation questionnaire (PASE) (158), the Dermatology Life Quality Index (DLQI) (159), the EuroQol 5 Dimension 3 Level questionnaire (EQ-5D 3L) (160), the Montgomery–Åsberg Depression Rating Scale - Self-Rating (MADRS-S) (161), and clinical and laboratory values. Start and stop dates for treatments are reported by the clinician. Discontinuations of a non-permanent nature are also registered.

### 4.2.10 Data linkage

Sweden registries can be linked using personal identification numbers (PINs) specific to each Swedish resident (162).

Both SPC and PSOREST comprise data linkage. For PSOREST, the personal identification numbers for all individuals with at least one diagnosis of psoriasis (L40.X) were extracted from the SHCR and the Vega register. The PINs of the identified patients were sent to Statistics Sweden, which identified controls for each patient based on sex, residency (municipality), and birth year (+/- one year). Statistics Sweden also generated Study IDs (SIDs) linked to the PINs. Subsequently, Statistics Sweden communicated the PINs and SIDs to the participating registries that – based on the PINs – extracted the relevant data, removed the PINs and sent the data to the research group with the SIDs. Consequently, the research group obtained de-identified but linkable patient-level data from all registries. Furthermore, Statistics Sweden provided the research group with a dataset detailing the link between the patient and referents.

For the SPC the process for data linkage was similar to PSOREST. Statistics Sweden identified up to six controls for each study participant based on age (+/-1), sex, and postcode. The matching date was set to the date of enrolment for the patient in the SPC. Data on health care visits were extracted from the NPR instead of SHCR and VEGA.

## 4.3 PATIENTS

The SPC target population was individuals with recent onset psoriasis in Sweden. The target sample comprised individuals, aged 15 years or more, with first onset of psoriasis lesions on non-hairy skin within the last 12 months from the Stockholm Region, Sweden. The actual sample comprised patients from the target sample who volunteered to participate in the study.

The PSOREST identified patients with a diagnosis (primary or subsequent) of psoriasis in primary care, specialist outpatient care, or inpatient care. The target population comprised all individuals with psoriasis in Region Skåne or Västra Götaland. The target sample was patients with a diagnosis of psoriasis from 2001 to 2010 in Region Skåne and from 2005 to 2010 in Region Västra Götaland. The actual sample comprised all patients with a registered diagnosis of psoriasis in the SHCR and VEGA databases during these periods.

The DermaReg-Pso enrolls individuals who are candidates for systemic treatment for psoriasis in Stockholm, Sweden. The majority of patients are treated at two centers: The Karolinska University Hospital and a clinic run by the Swedish Psoriasis Association in Sundbyberg. Patients in DermaReg-Pso may have concomitant PSA, but are predominately treated for the skin component of the disease. The target population in the DermaReg-Pso are patients who are treated with systemics for psoriasis in the Stockholm area Sweden; the target sample includes patients treated at the two participating clinics; and the actual sample comprises patients from the two clinics who agreed to participate in the register.

## 4.4 OUTCOMES AND COVARIATES

### 4.4.1 Disease severity

There are more than  forty instruments for assessing the severity of psoriasis (2). The most frequently used severity measure in clinical trials is the PASI, which rates severity on a score ranging from 0 to 72, based on assessment of erythema, infiltration, thickness, scaling and extent of lesions over four body regions (head, trunk, upper limb, and lower limb) (157). The PASI has been criticized for being complicated, non-linear, and having low sensitivity and accuracy (163). Nevertheless , it is frequently used as for validation of other instruments and generally shows good correlation with other physician reported instruments, albeit not with patient reported HRQoL (163).

The Physician Global Assessment (PGA) is an instrument for assessing psoriasis disease severity. There is no standard PGA (164) and the PGA may be used to measure disease severity at given point in time (static) or as change over time (dynamic). There is no agreed formulation of the static PGA (s-PGA), but it generally measures disease severity on a four to seven point ordinal scale, ranging from “clear” to “very severe” (163). The s-PGA correlates well with other physician and patient reported instruments used to assess psoriasis (163). The formulation of the instrument used in the SPC can be found in **Table 5** below.

**Table 5 Static Physician Global Assessment version used in the SPC.**

| S-PGA score | Interpretation |
|---|---|
| 1 | Clear |
| 2 | Almost clear |
| 3 | Mild |
| 4 | Mild to moderate |
| 5 | Moderate |
| 6 | Severe |
| 7 | Very severe |

When patients are treated for psoriasis, the underlying disease severity cannot be measured directly using an instrument such as PASI given that the score of the instrument is affected by treatment. Furthermore, in many studies clinical data are missing and therefore treatment (topicals, phototherapy, and systemic treatment) is used to infer disease severity (165). Hospitalization with psoriasis as a main diagnosis has also been used as an indicator of severe disease; e.g. in Ahlehoff et al (2011) (117). The construct underlying this concept is that psoriasis treatment corresponds to the severity of the disease. A patient with mild disease can manage the disease without prescriptions or with topicals only; if the disease is moderate, phototherapy will suffice, and if the disease is severe, systemic treatment or hospitalization are needed to control the disease. This concept assumes that patients are managed optimally, which is not always the case (166). Nevertheless, it has been shown that treatment with topicals and systemics are valid markers for disease severity in psoriasis; with sensitivity and positive predictive values consistent with commonly accepted thresholds for observational research (165).

### 4.4.2 Health related quality of life

The impact of the disease on HRQoL is also a central outcome in psoriasis and has been measured using psoriasis specific, skin specific, and generic HRQoL instruments (167). In clinical trials, the DLQI is the most frequently used HRQoL instrument (167). The DLQI consists of ten domains, nine of them have four alternatives (“Not at all” to “Very much”) (159). The tenth domain pertains to impact of skin on work and studying and is rated as a dichotomous domain; with affirmative answers directed to a question with three levels (“Not at all” to “A lot”) (159). Eight domains may also be marked as non-relevant (159). The total score ranges from zero to thirty (159). Total DLQI score may be collapsed into five categories to facilitate interpretation (168), see **Table 6**.

**Table 6 DLQI categories.**

| Total score | Effect on patient's life |
|---|---|
| 0 – 1 | None |
| 2 – 5 | Small |
| 6 – 10 | Moderate |
| 11 – 20 | Very large |
| 21 – 30 | Extremely large |

Note: Adapted from Hongbo et al (2005) (168).

### 4.4.3 Psoriatic arthritis

In PSOREST PsA was defined by a registered diagnosis of the disease and in DermaReg, patients classified as having PsA had been diagnosed by a rheumatologist. In SPC, at inclusion, the study dermatologist assessed each patient for PsA by taking a medical history and asking for joint or back pain. If the dermatologists reported joint pain, the patient was seen by a rheumatologist and diagnosed according to the criteria presented in Moll and Wright (1973) (169). At the ten year follow-up, relevant patients were also assessed by a rheumatologist according to the Classification for psoriatic arthritis (CASPAR) criteria (170), the current gold standard for classification of PsA. The CASPAR criteria were not developed when SPC was initiated. For statistical analysis, the CASPAR was applied retrospectively for validation of the diagnosis of PsA. The CASPAR criteria include a radiological assessment but x-rays were not available in the SPC. Nevertheless, patients still needed three points on the CASPAR to be classified as having PsA. Not all relevant patients saw the rheumatologist and in some patients the rheumatologist could not make a conclusive diagnosis. In those patients, the dermatologist assessment, medical records, and register data were used to determine PsA status.

### 4.4.4 Attrition and loss to follow-up

To explore the potential impact of loss-to-follow up in Study 1, we compared baseline characteristics between patients who participated in the ten-year clinical examination and those who did not, stratified by onset phenotype. We also compared uptake of topical psoriasis treatment in the two groups. Treatment with topical medication for psoriasis was defined as a dispensed prescription of the following medications within one year of the ten year clinical examination: topical tars (ATC Code: D05AA), antracen derivaties (D05AC), other antipsoriatics for topical use (D05AX), topical corticosteroids (D07), and emollients (D02). Patients who died during follow-up were excluded from these analyses.

### 4.4.5 Cause-specific mortality

When relevant for assessment, all-cause mortality is the most unbiased end-point in clinical research (171). Cause-specific mortality allows for identification of the conditions resulting in death and provides a metric on the comorbidity burden in a patient population. For the study on cause-specific mortality, we identified the 15 leading causes of death according in the US CDC (172) and collapsed those into eight groups and four additional categories (suicide,

accidents, missing causes of death, and all other causes). The resulting categories along with ICD-10 diagnosis codes are presented in **Table 7**.

**Table 7 ICD-10 codes for the causes of death groups.**

| Cause of death | ICD codes |
|---|---|
| Cardiovascular disease | I00–I09, I11-I13, I15, I20–I51, I60–I69, I10, G45, G46, F01 |
| Neoplasms | C00–C97, D00-D47 |
| Diabetes | E10–E14 |
| Chronic lower respiratory disease | J40–J47 |
| Neurological disease | F00, F02, F03, G00-G44, G47 |
| Kidney disease | N00–N19, N25–N37 |
| Infection | A00-A99, B00-B14, B20-B99, J09–J18 |
| Liver disease | B15-B19, K70-K77 |
| Suicide | U03, X60–X84, Y87.0 |
| Accidents | V01–X59, Y85–Y86 |
| Other causes | Residual (excluding missing causes of death) |

### 4.4.6 Resources and costs

In society, resources are scare and demand for resources needs to be prioritized. This is also true for the health care sector: Available health care resources are insufficient to address all health needs and we have to decide which health needs to prioritize. This scarcity underlies a key concept in economics: The opportunity cost (173). The opportunity cost is the highest benefit foregone by committing a resource to a specific good or service. In other words, the opportunity cost of a specific resource is the benefit that would have been derived from the best alternative use of that resource. This concept of costs differs from financial costs: the price of goods and services. In theory, in a perfect market, the unit cost (price) for a product or service should equate opportunity costs (173). In practice, markets are imperfect but unit costs are used to approximate the opportunity cost (173).

In economics, the concept of costs may be extended beyond goods and services and in health economics, three cost categories are frequently used: Direct, indirect, and intangible costs (174). Direct costs reflect healthcare services and goods; indirect costs reflect to lost production; and intangible costs reflect lost health (174).

Another important aspect of costs is the perspective (175). For example, from the perspective of a patient covered by a health insurance, the costs for an operation may be limited to the co-payment. On the other hand, from the insurer perspective, the cost may include not only the operation, but also rehabilitation.

Whilst, costs are difficult to measure and depend on perspective, they are integral to decision-making as they inform choices we have to make (173). Costs can also be informative in other ways as they can describe and contextualize the burden of a disease (176). For example, it has been argued that knowledge of the costs of a disease in a population provides important information to decision makers on research funding (176). Arguably, for society as a whole, diseases with higher burden merit more attention than diseases with lower burden.

In this thesis, direct costs were estimated for outpatient care, inpatient care, and prescriptions dispensed from pharmacy. Outpatient care costs were estimated by applying unit costs obtained from public payers to outpatient healthcare contacts; costs for inpatient care were derived using Diagnoses Related Group (DRG) points and a cost per DRG point; and costs for medication were estimated using the cost to the patient and payer combined, obtained from the PDR. Indirect costs were estimated using the human capital approach: The observed number of days on sick leave, activity compensation, and sickness compensation were costed at the mean daily gross salary (including employer's contribution) in Sweden.

Given that psoriasis is associated with comorbidities, estimating costs for psoriasis related resource use only would underestimate the costs of the disease. Comparing costs between patients with and without psoriasis may provide a more accurate reflection of the cost burden of the disease. Therefore, the costs of psoriasis in this thesis were estimated as the difference between patients with psoriasis and age- sex-, and residency matched controls.

### 4.4.7 Treatment events

Drug survival and persistence are two terms for the same concept: The length of time from initiation to discontinuation of therapy. In chronic symptomatic disease drug survival is a proxy for successful treatment (177). The underlying notion is that treatment discontinuation results from lack of effectiveness, adverse events, or treatment dissatisfaction. Therefore, longer treatment duration should be associated with better outcomes.

Drug survival is a frequently studied outcome (127), but it is a crude proxy and arguably other treatment events such as dose titration above the label dose, and initiation of augmentation treatment should be added to drug survival to better measure effectiveness. Furthermore, to the extent data on signs and symptoms of the disease are available, these would also give important information on the effectiveness of treatment, and end-points combining drug survival and HRQoL have been explored in psoriasis (178).

Switching is linked to drug survival in the sense that patients who switch treatment will discontinue the original treatment. However, the timing of the switch may reflect the reason for treatment discontinuation: If a treatment switch occurs in close proximity to the treatment discontinuation it is arguably more likely that the original treatment was discontinued due to lack of effectiveness or side effects.

Time from treatment discontinuation to start of new therapy may also be a proxy of unmet need: A short duration between treatment discontinuation and start of a subsequent treatment may indicate that the original treatment was not sufficient or that the disease flared rapidly after treatment discontinuation.

## 4.5 STATISTICAL METHODOLOGY

### 4.5.1 Descriptive statistics

In general, numerical variables that had an approximately normal distribution were described using mean and standard deviation (SD); numerical variables with another distribution were described using median and percentiles (e.g. interquartile range [IQR]); and categorical variables were reported using frequencies and percentages.

### 4.5.2 Univariable analysis

When data could be assumed to be IID and the patient count was sufficiently high, comparisons of means between groups were conducted using t-tests (179) by virtue of the CLT (180). However, in analyses on costs involving groups with fewer than 1,000 subjects, p-values were derived using the bootstrap methods (181).

For categorical variables, comparisons between groups were conducted using chi-square tests (182) or McNemar's test (183) as applicable. Confidence intervals for proportions were derived using the exact method (184).

For time-to-event analysis, we used the Kaplan-Meier product limit estimator (185) to estimate the proportion of patients who had experienced (or had not experienced) an event at a given observation time.

Relative risks of a dichotomous outcome given a covariate were derived using binomial generalized linear models (GLM) with a log-link (186).

Locally weighted regression (LOESS) is a non-parametric regression model (187). LOESS was used to fit smooth curves of PASI and DLQI by treatment and years since treatment initiation.

### 4.5.3 Multivariable analysis

The form of regression model was chosen by selecting models with appropriate family and link functions: Binomial family and logistic link (logistic regression) for binary outcomes; gamma family and identity link for costs; and Gaussian family and identity link (linear regression) for DLQI and PASI. For time-to-event data, Cox proportional hazard models (PH) (188) were fit and the PH assumption tested using at least one of three methods: visual inspection of LOESS curves for Schoenfeld residuals, visual inspection of log(–log) plot of the survival distribution functions, or inclusion of interactions between observation time and covariates in the models. (189) The PH assumption was valid unless otherwise noted.

In Study 1, Firth type penalization (190) was implemented to reduce sparse data bias (191) in Cox PH and logistic regression when there were fewer than ten events per covariate.

### 4.5.4 Marginal effects estimation

In Study 5, we estimated the marginal effect of each treatment (192). The marginal effect of a treatment is the average outcome expected if all patients had received that treatment (192). The marginal effects were estimated using the predictions from the multivariable regression models.

### 4.5.5 Multilevel analysis

For univariable and multivariable analysis, when the same patients had multiple observations in the same model, data were not considered IID and therefore random intercept regression models (193) were fit. Linear regression was implemented for continuous outcomes; logistic regression for binomial outcomes, ordinal logistic regression for ordered categorical outcomes with more than two levels; and shared frailty models for time-to-event data (193).

### 4.5.6 Covariate selection

The objectives of regression modelling can be descriptive, predictive or exploratory (194). In this thesis, the regression models were mainly fit for explanatory purposes. Therefore, we included covariates that could be assumed to be causally related to both the main covariate of interest and the outcome. In Study 1, the multivariable models were more descriptive in nature and predominately fitted to complement the recursive partitioning analysis. In Studies 2 and 3, the variable selection was conducted informally. In Study 5, variable selection was formalized using Directed Acyclic Graphs (DAGs) (195).

### 4.5.7 Recursive partitioning

Recursive partitioning was implemented using a conditional inference framework with adjustments for multiple testing (196). Variables that have previously been associated with the outcomes were included in the recursive portioning analysis. The apparent discriminative ability of models was estimated using c-indices (197, 198) excluding ties on predictor groups (199).

### 4.5.8 Bootstrapping

Health care cost data may be heavily skewed with many observations at zero and few observations with very high values (200). Therefore, the CLT may not be applicable for modest sample sizes and we implemented bootstrapping to perform inferential tests and derive confidence intervals for strata with fewer than 1,000 patients, as recommended by Desgagné et al (201). P-values were derived using the bootstrap t-statistic and the bias corrected percentile method (181) was implemented to derive 95% confidence intervals.

### 4.5.9 Sensitivity analysis of unmeasured confounders

We explored the potential impact of unmeasured confounders in Study 2 using the approach described in Lin et al (1998) (202). We estimated the relative risks of an unobserved risk factor required to nullify the observed associations given assumptions on prevalence of the

unobserved risk factor in the two groups. We performed this analysis both for the point estimate and for the lower bound of the 95% CI.

## 4.6 ETHICAL CONSIDERATIONS

All studies obtained ethics approval (DNR: 00-448 for SPC, DNR 20101954-315 for PSOREST, and DNR 2018-1080-31 for DermaReg) and each registry holder also approved the study. Hence, the study design, conduct, and plan fulfilled formal ethical requirements.

A common approach to consider ethical matters in biomedical research is grounded in four core principles: beneficence (doing good), non-maleficence (avoiding harm), autonomy, and justice (203). The discussion below focuses on the four principles in the context of the three studies presented in the five constituent papers.

For all studies, one source of beneficence is the knowledge generated by the research. In addition, the SPC and DermaReg-Pso may have benefitted study participants directly. The SPC included a survey, a clinical examination and laboratory analyses. Findings from these may have been used to optimize treatment of psoriasis, or refer study participants to other health care providers as necessary. DermaReg-Pso includes a visualization tool and is used by clinicians and patients to follow disease activity, treatment, and outcomes over time, informing clinical decision-making, thereby benefitting study participants directly. PSOREST is based on secondary data and there were no direct benefits to the participants in the study.

The most direct potential maleficence for the three studies is integrity breach. To address this harm, data were pseudonymized and stored safely with access only to relevant members of the study team in accordance with laws and regulations. Furthermore, no patient identifiable data were published. Another potential harm from the studies is that patients may feel discomfort or distress from the findings. For example, knowing that one’s risk of death may be elevated compared to the general population can be disquieting. Therefore, care needs to be taken when communicating the data to patients. Furthermore, it may be argued that the questions asked in SPC and DermaReg could cause distress for patients. In SPC, this challenge was addressed by consulting three patients in the development of the CRFs. In SPC, a blood sample was collected from participants, resulting in physical discomfort and risk of infection. The blood was drawn by trained professionals in a hospital setting using best practices, minimizing discomfort and other risks.

In the SPC and DermaReg, participants provided informed consent that may be withdrawn at any time, arguably fulfilling the principle of autonomy. However, no informed consent was obtained in PSOREST, as this type of research do not require informed consent, partially to avoid identification of participants. However, the vast majority of individuals in Sweden support the use of their medical data for research purposes (204) , and it could be argued that data generated from health care consumption belongs to the entity that finances the health care, i.e. the tax payers as a collective.

In SPC and DermaReg, it appears that the probability of benefits and harms of the study are equally distributed among study participants and that the principle of justice is therefore fulfilled. For PSOREST, potential benefits of the study would likely accrue disproportionally in patients with psoriasis relative to the control population. However, the control population may still benefit from improved resource allocation that may result from the study findings.

Following from the discussion above, I consider that potential benefits with the studies outweigh potential harms and that problems with autonomy and justice are limited. Therefore, the studies in this thesis are in good agreement with the four core principles of biomedical research.

# 5 RESULTS

## 5.1 CLINICAL COURSE OF PSORIASIS (STUDY 1)

### 5.1.1 Cohort and patients characteristics

In the SPC, 721 patients were enrolled and eligible for analysis. After ten years, 546 of 686 patients alive completed a questionnaire and 509 (74%) were examined clinically. On average patients were examined six months after disease onset (Median 6 months, IQR: 3-10 months) and the median time from enrollment to the follow-up examination was 9.6 years (IQR: 8.8-10.4).

At onset 542 (75%) had plaque phenotype, 174 (24%) had guttate phenotype, and five (1%) had other phenotypes.

### 5.1.2 Disease course

At the ten year clinical examination, 346 of 389 patients with plaque onset (89%) retained plaque phenotype, 13/389 (3%) had non-plaque phenotype, and 30/389 (8%) were in complete remission. In patients with guttate phenotype at onset, 75/116 (65%) had developed plaque psoriasis, 4/116 (3%) had non-plaque phenotype, and 37 (32%) were in complete remission.

**Figure 4A** and **Figure 4B** present the distribution of disease severity at enrollment (mild, moderate, and severe) and ten-year clinical examination (minimal disease activity, mild, moderate, and severe), along with transitions between strata. Patients with severe plaque psoriasis at onset were more likely than patients with mild or moderate plaque psoriasis to have severe psoriasis at ten years (11/27 [41%] vs 34/362 [9%]; RR=4.3; $p<0.001$). Similarly, patients with mild plaque psoriasis at onset were more likely than patients with moderate or severe psoriasis to have minimal disease activity at the ten years (59/253 [23%] vs 18/136 [13%]; RR=1.8; $p<0.001$). A minority of patients with severe guttate psoriasis at onset had severe psoriasis at ten years (4/22 [18%]), albeit a higher proportion than among those with mild or moderate guttate psoriasis at onset (1/94 [1%]).

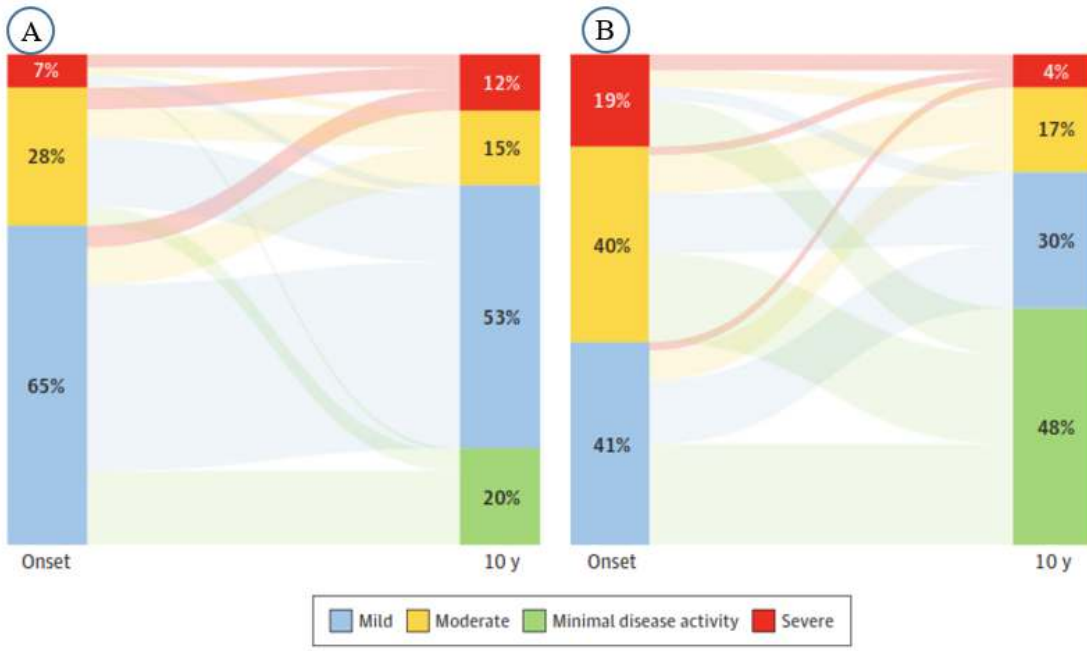


**Figure 4 Phenotype and disease severity from onset to ten years.** Panels A and B show the distriubtion of disease severity at onset and ten years in patients with plaque onset (Panel A) and guttate onset (Panel B). Minimal disease activity was defined as a PASI below one without treatment. Mild disease was defined as topical therapy or PASI between one and five, moderate disease was defined as treatment with phototherapy or PASI between five and ten, and severe disease was defined as PASI exceeding ten or treatment with systemics.

### 5.1.3 Psoriatic arthritis

In patients with plaque phenotype at onset, the proportion of patients with PsA grew from 69/389 (18%) at enrolment to 102/389 (26%) at ten years ($p<0.001$). In patients, with guttate phenotype at onset, the proportion of patients with PsA grew from 5/116 (4%) to 16/116 (14%) ($p=0.02$).

### 5.1.4 Subgroups and prognostic factors

We identified subgroups with distinctive risks for developing severe psoriasis, clinical remission, and PsA (**Figure 5**). Regarding development of severe disease, patients with non-guttate phenotype whose s-PGA exceeded 3 (mild disease) and had scalp lesions, had the highest cumulative incidence of severe psoriasis 52% (95% CI: 41% to 64%) over 12 years compared to 11% (95% CI: 8% to 14%) in patients with s-PGA at three or less. The probability of clinical remission was 57/116 (49%) in patients with guttate onset psoriasis, 59/177 (33%) in patients with non-guttate psoriasis who were also free from scalp lesions; and 23/216 (11%) in patients with non-guttate onset and scalp lesions. The risk of PsA at ten years was highest among patients with peripheral enthesitis at enrollment 48/82 (59%), compared to 24/97 (25%) in patients with arthralgia but no enthesitis, and 37/304 (12%) in patients without arthralgia. The RPA derived algorithm for severe disease and mild disease both had c-indices of 0.794, and the algorithm for PsA had a c-index of 0.821.

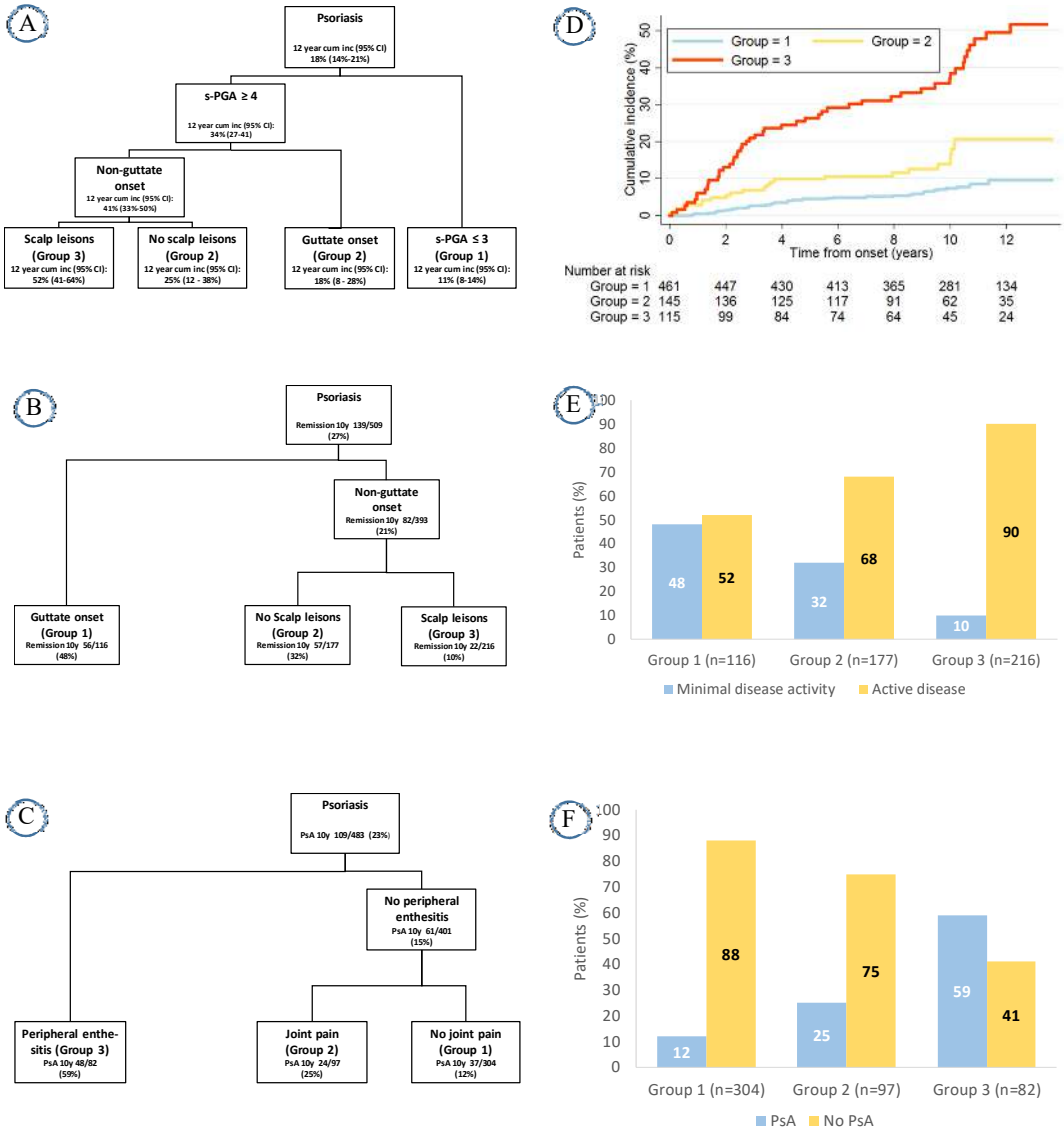


**Figure 5 Classification trees and outcomes for the identified groups for severe psoriasis, minimal disease activity at ten years, and psoriatic arthritis.** Each node in the classification trees shows the identified splitting factor along with respective outcome: Cumulative incidence of severe psoriasis over 12 years (Panel A); proportions of patients with minimal disease activity at ten years (Panel B); and proportion of patients with Psoriatic Arthritis (PsA) at ten years (Panel C). Panel D (cumulative incidence of severe disease), Panel E (proportion of patients with minimal disease activity at ten years), and Panel F (proportion of patients with PsA at ten years) show outcomes in the groups identified in the recursive partitioning. Please note that in Panel A, two leaf nodes were combined (into Group 2) given that the outcomes in the two node groups were not significantly different; furthermore, 26 patients in Cohort B did not have data on peripheral enthesitis and therefore the number of patients in the classification tree for PsA was 483 (Panel E). Note: Cum. Inc. in panel A stands for cumulative incidence; CI stands for confidence interval; PsA stands for Psoriatic Arthritis.

In addition to the characteristics identified as predictors of severity in the RPA, a number of variables were associated with disease severity. In patients with plaque onset, smoking increased the risk for developing severe disease (HR: 1.70; 95% CI: 1.10 to 2.63) and reduced the probability of achieving minimal disease activity at ten years (OR: 0.41; 95% CI: 0.22 to 0.77). Similarly, male sex was significantly associated with both severe disease (increased risk) and clinical remission at ten years (reduced probability) in univariate

analyses. Furthermore, in multivariate analyses, PsA was significantly associated with severe disease and infection triggered disease was significantly associated with clinical remission at ten years.

### 5.1.5 Attrition bias

There were no marked differences in baseline characteristics between participants and non-participants in the ten year clinical examination irrespective of phenotype at onset (**Table 8** and **Table 9**).

**Table 8 Comparison of baseline characteristics in patients with plaque onset who participated in the ten year clinical examination versus patients with plaque onset who were lost to follow-up.**

| Characteristic | CC | LF | p-value |
|---|---|---|---|
| Age – yr median [range] | 42 [30-55] | 47 [26-59] | 0.144 |
| Female sex - no. (%) | 209/389 (54) | 68/121 (56) | 0.634 |
| BMI – mean (SD) | 25.4 (4.4) | 24.7 (4.5) | 0.097 |
| Smoking - no. (%) | 144/389 (37) | 39/116 (34) | 0.504 |
| Comorbidity profile - no. (%) | | | |
| Diabetes | 13/389 (3) | 5/121 (3) | 0.681 |
| Hypercholesterolemia | 101/389 (26) | 29/121 (24) | 0.660 |
| Hypertension | 123/389 (32) | 51/121 (42) | 0.033 |
| Obesity | 52/389 (13) | 14/121 (12) | 0.607 |
| Depression | 15/389 (4) | 7/121 (6) | 0.362 |
| Potential precipitating factors - no. (%) | | | |
| Infection | 52/389 (13) | 21/121 (17) | 0.274 |
| Life crisis | 191/389 (49) | 52/121 (43) | 0.239 |
| Genetic weight - no. (%) | | | |
| First degree | 124/389 (32) | 48/121 (40) | 0.281 |
| Second degree | 59/389 (15) | 17/121 (14) | |
| Higher degree, none, or unknown | 206/389 (53) | 56/121 (46) | |
| Disease severity | | | |
| PASI – median [range] | 2.8 [1.5-4.5] | 2.9 [1.4-4.9] | 0.780 |
| s-PGA – median [range] | 3 [2-4] | 3 [2-4] | 0.571 |
| Joint problems - no. (%) | | | |
| Self-reported joint pain | 172/389 (44) | 50/121 (41) | 0.575 |
| Peripheral enthesitis | 73/370 (20) | 17/116 (15) | 0.220 |

Note: CC – Complete Cases; LF – Lost to Follow-up; PASI – Psoriasis Area and Severity Index; BMI – Body Mass Index; s-PGA – Static Physician Global Assessment. Higher scores on PASI and s-PGA denotes greater disease severity.

**Table 9 Comparison of baseline characteristics in patients with plaque onset who participated in the ten year clinical examination versus patients with guttate onset who were lost to follow-up.**

| Characteristic | CC | LF | p-value |
|---|---|---|---|
| Age – yr median [range] | 32.5 [23-41] | 28 [20-38] | 0.302 |
| Female sex - no. (%) | 73/116 (63) | 33/55 (60) | 0.712 |
| BMI – mean (SD) | 24.4 (4.8) | 23.3 (3.7) | 0.129 |
| Smoking - no. (%) | 45/115 (39) | 17/53 (32) | 0.379 |
| Comorbidity profile - no. (%) | | | |
| Diabetes | 1/116 (1) | 1/55 (2) | 0.587 |
| Hypercholesterolemia | 12/116 (10) | 6/55 (11) | 0.911 |
| Hypertension | 18/116 (16) | 7/55 (13) | 0.630 |
| Obesity | 9/116 (8) | 2/55 (4) | 0.305 |
| Depression | 3/116 (3) | 2/55 (4) | 0.703 |
| Potential precipitating factors- no. (%) | | | |
| Infection | 90/116 (78) | 35/55 (64) | 0.055 |
| Life crisis | 34/116 (29) | 22/55 (40) | 0.164 |
| Genetic weight - no. (%) | | | |
| First degree | 40 (34) | 24 (44) | 0.312 |
| Second degree | 13 (11) | 8 (15) | |
| Higher degree, none, or unknown | 63 (54) | 23 (42) | |
| Disease severity | | | |
| PASI – median [range] | 4.1 [2.6-7.3] | 4.1 [2.9-5.2] | 0.106 |
| s-PGA – median [range] | 3.5 [3-4] | 3 [3-4] | 0.216 |
| Joint problems - no. (%) | | | |
| Self-reported joint pain | 31/116 (27) | 16/55 (29) | 0.746 |
| Peripheral enthesitis | 8/109 (7) | 8/54 (15) | 0.131 |

Note: CC – Complete Cases; LF – Lost to Follow-up; PASI – Psoriasis Area and Severity Index; BMI – Body Mass Index; s-PGA – Static Physician Global Assessment. Higher scores on PASI and s-PGA denotes greater disease severity.

There was no statistically significant difference in topical treatment the year before the clinical examination in patients who participated in the follow up compared to those who did not (41% vs 35%; p=0.145, Figure 6).

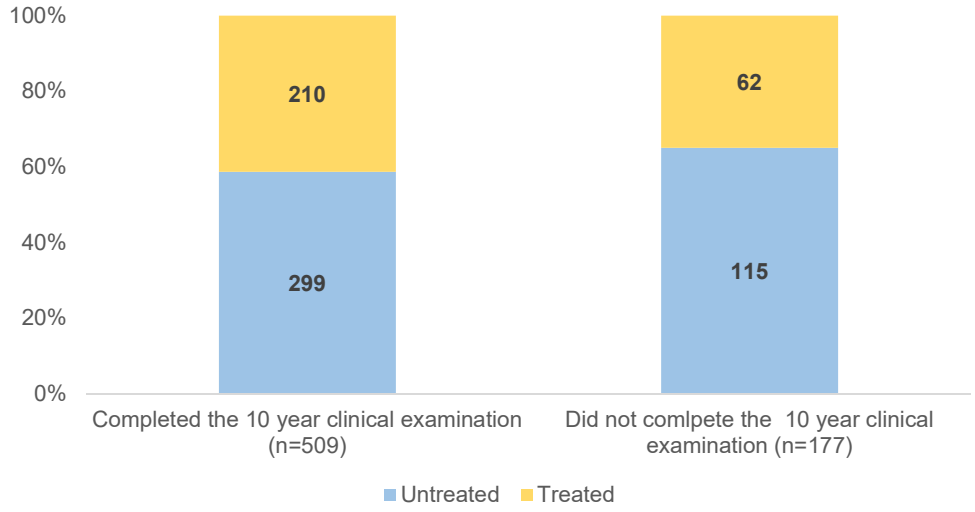


**Figure 6 Uptake of topical treatment stratified by participation status in the ten-year clinical examination.**

### 5.1.6 Impact of early systemic treatment

Among the 66 patients who started systemic treatment before the clinical examination at ten years, patients who initiated treatment at or before the enrolment examination had lower probability of severe disease at ten years compared to patients who started systemics subsequently (6/16) [38%] vs 33/50 [65%]) (p=0.044) (**Figure 7**). After adjustment for factors associated with development of severe disease (s-PGA, smoking, PsA, and scalp psoriasis) early systemic intervention was still associated with decreased risk of severe disease at ten years (OR: 0.24; 95% CI: 0.06 to 0.90).

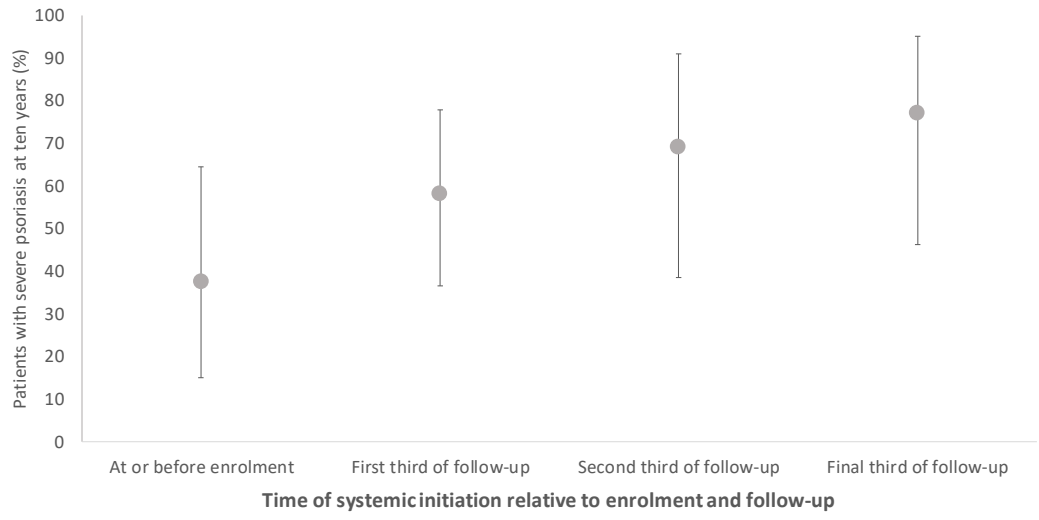


**Figure 7 Proportion of patients with severe psoriasis at the 10-year clinical examination stratified by time to systemic initiation**. The figure shows the proportion of patients with severe disease at the ten year clinical examination and exact binomial 95% confidence limits among patients ever treated with systemics for psoriasis stratified by time to systemic initiation: At or before study enrolment, and during first, second, or third tertile of follow-up.

## 5.2 CAUSE-SPECIFIC MORTALITY (STUDY 2)

There were no statistically significant differences in mean age or sex distribution between the patient and control cohorts, reflecting the study design. However, mean CCI was higher in patients than controls: 0.26 in patients with mild disease vs 0.21 in their controls (p<0.001) and 0.36 in patients with severe disease vs 0.25 in their controls (p<0.001).

The estimated number of excess deaths per 1,000 person years was 1.77 in patients with mild disease and 6.76 in patients with severe disease. Among subjects who died, patients with mild psoriasis were on average 0.8 years younger and patients with severe psoriasis 2.6 years younger than corresponding controls. Cardiovascular disease was the most common cause of death in both patients and controls. The proportion of excess all-cause mortality attributable to cardiovascular disease was 48% in patients with mild psoriasis and 33% in patients with severe psoriasis.

The estimated HRs and 95% CIs for all-cause and cause-specific mortality after adjusting for the CCI are presented in Figure 2. After adjusting for CCI, the HRs for patients with mild and

severe psoriasis for all-cause mortality were estimated at 1.15 (95% CI: 1.10 to 1.21), and 1.56 (95% CI: 1.36 to 1.79), respectively. For patients with mild disease, the causes of death with the highest excess point estimates were kidney disease (HR: 2.20, 95% CI: 1.36 to 3.56), and liver disease (HR: 2.00; 95% CI: 1.34 to 2.99). For patients with severe disease, the highest HR point estimates were observed for liver disease 4.26 (95% CI: 1.87 to 9.73), and missing causes of death 3.42 (95% CI: 1.24 to 9.44). The risk of death from neurological disease was statistically significantly lower in patients with mild disease than controls (HR: 0.64; 95% CI: 0.50 to 0.83) and similar in patients with severe disease compared with controls (HR: 0.51; 95% CI: 0.21 to 1.23).

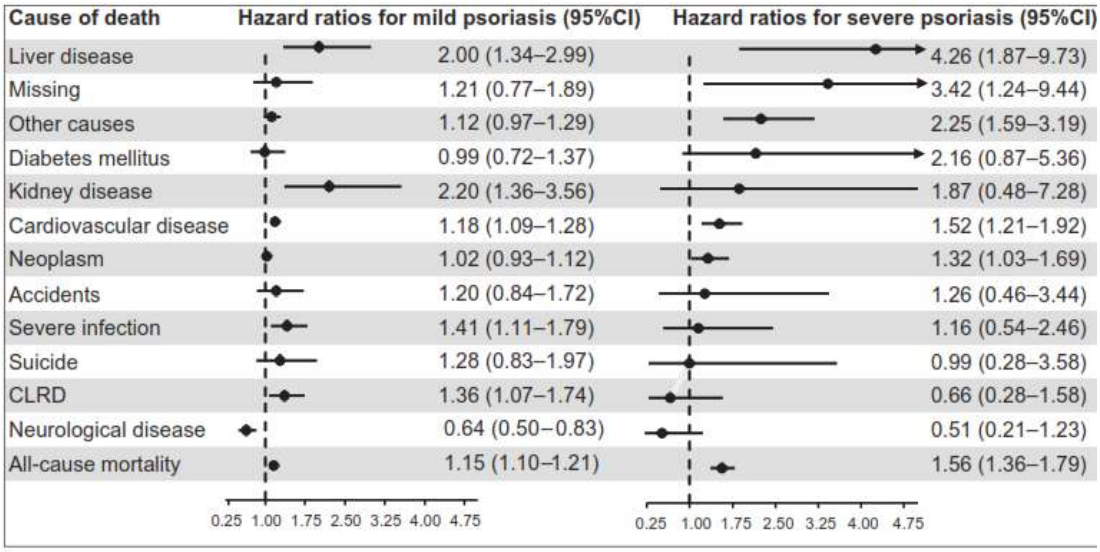


**Figure 8 Estimated hazard ratios for specific causes of death and all-cause mortality among patients with mild and severe psoriasis compared with controls controlling for comorbidities.**

## 5.3 ECONOMIC BURDEN (STUDY 3)

Reflecting the matched study design, differences in sex and age between patients and controls were small. However, comorbidity burden measured using CCI was higher in all severity strata ($p<0.01$).

Patients had higher total HCRU costs than controls after adjusting for CCI: USD 3,555 versus USD 2,190 ($p<0.001$). The mean difference in total HCRU costs (USD) adjusted for CCI between patients stratified by most potent treatment class (none, topical, phototherapy, systemic, biologic, and hospitalization) and controls were estimated at 326 (95% CI: 243 to 409), 1,203 (95% CI: 1,031 to 1,375), 2,816 (95% CI: 2,222 to 3,410), 1,845 (95% CI: 1,422 to 2,269), 17,246 (95% CI: 16,416 to 18,076), and 16,947 (95% CI: 13,813 to 20,082), respectively.

Patients also had higher indirect costs than controls after adjusting for the CCI: USD 9,898 versus USD 6,579 ($p < 0.001$). The difference in mean total indirect costs (USD) adjusted for the CCI between patients stratified by most potent treatment class (none, topical,

phototherapy, systemic, biologic, and hospitalization) and controls were estimated at 1,781 (95% CI: 1,395 to 2,168), 3,697 (95% CI: 2,973 to 4,421), 1,844 (95% CI: 424 to 3,264), 4,523 (95% CI: 2,912 to 6,133), 7,874 (95% CI: 5,482 to 10,265), and 18,935 (95% CI: 2,494 to 35,376), respectively.

Among the 121 patients persistent with biologic treatment for at least 12 months, mean costs of the biologics during the 12 months period were estimated at USD 23,293 (95% CI 22,372 to 24,199). To estimate potential cost offsets with biologics, three counterfactual scenarios on the cost development in the absence of biologic initiation were explored. The first scenario was that costs would been the same as the 12 month period prior to treatment initiation. The second scenario was that costs would have been constant at the level observed the penultimate month before treatment start. The third scenario was that costs would have been constant at the level observed the final month before treatment start. In the first scenario the 12 months direct and indirect costs offsets were estimated at USD 1,135 (95% CI 328 to 2,050) and 774 (95% CI: -535 to 2,019), respectively. In the second scenario the direct and indirect costs offsets were estimated at USD 1,944 (95% CI: 587 to 3,749) and 1,875 (95% CI: 188 to 3,650), respectively. In the third scenario the direct and indirect cost offsets were estimated at USD 4,422 (95% CI: 2,771 to 6,552) and 1,794 (95% CI 537 to 3,377), respectively.

## 5.4 TREATMENT PATTERNS (STUDY 4)

The cumulative incidences of treatment discontinuation at one year with topicals, systemics, and biologics were estimated at 88%, 48%, and 43%, respectively (**Figure 9, Panel A**). The cumulative incidence of any treatment event (discontinuation, switch, or augmentation) at one year with topicals, systemics, and biologics were estimated at 93%, 72%, and 75%, respectively (**Figure 9, Panel B**). Over the observation period, the rate of treatment discontinuation was lower with biologics than systemics (p=0.044), whereas overall treatment event rate was higher with biologics than systemics (p=0.003).

For biologics, the cumulative incidences of insufficient treatment results within twelve and 24 months of treatment start were estimated at 29% and 41% respectively (**Figure 9, Panel C)**.

Within one year of having discontinued treatment, the cumulative incidence of starting a new treatment was 49% for topicals, 61% for systemics, and 80% biologics (**Figure 9, Panel D)**. The proportion who restarted the same treatments they discounted was estimated at 53% for topicals, 35% for systemics, and 39% for biologics, respectively.

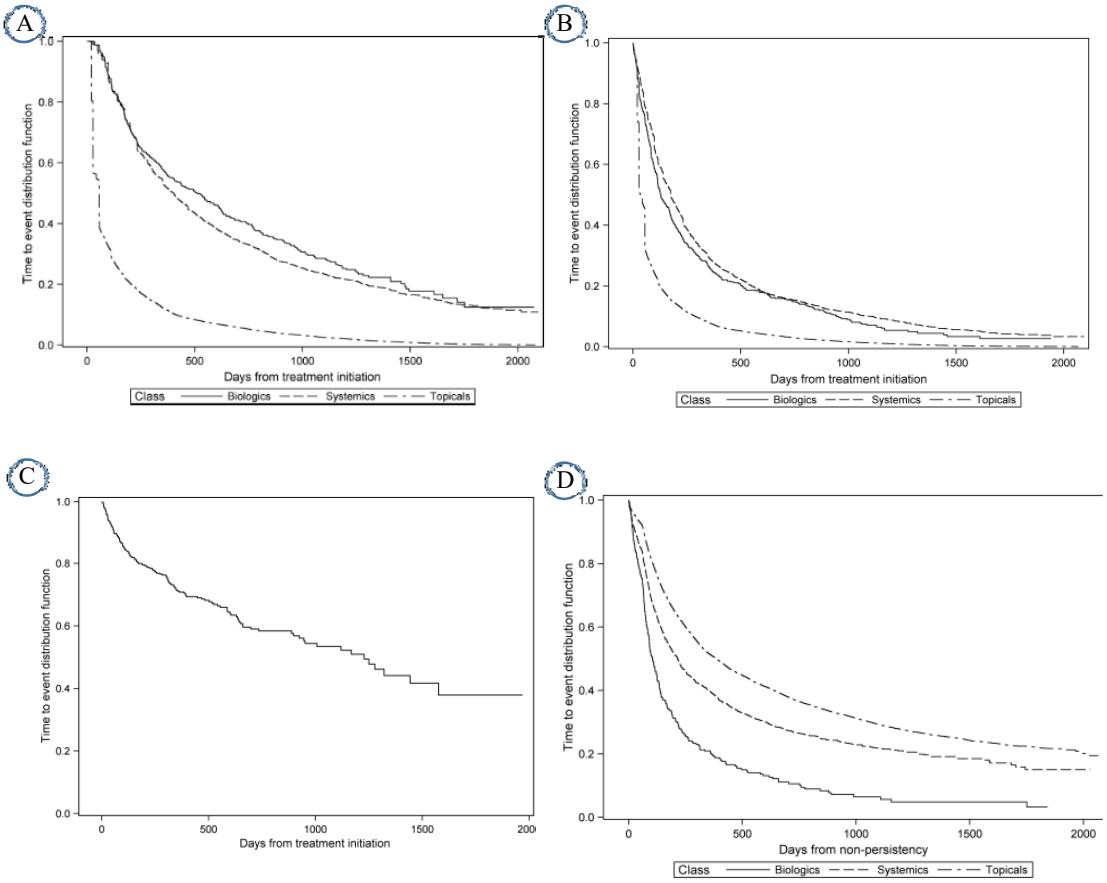


**Figure 9 Kaplan Meier Product Limit Estimators Plots.** Panel A presents estimated time to treatment discontinuation. Panel B presents estimated time to first treatment event (discontinuation, switch, and augmentation). Panel C presents estimated time to insufficient treatment result with biologics; and panel D presents estimated time to restart after treatment discontinuation.

## 5.5 REAL-WORLD EFFECTIVENESS OF ADALIMUMAB, ETANERCEPT, AND METHOTREXATE (STUDY 5)

In total, 727 treatment episodes with adalimumab, etanercept, and methotrexate in 524 patients were analyzed. Mean age (SD) in the cohort was 48.3 (15.6) years, mean BMI was 27.4 (5.1), 326 patients (62%) were male, 180 (34%) had PsA, and 159/516 (31%) smoked.

The drug survival for ADA, ETN, and MTX are presented in **Figure 10**. In the unadjusted model, no statistically significant difference between ADA and MTX was found (HR: 0.80; 95% CI: 0.62 to 1.04), whereas ETN had worse drug survival than MTX (HR: 1.56; 95% CI: 1.25 to 1.95). In the analyses adjusted for covariates, ADA had higher drug survival than MTX (HR: 0.67; 95% CI: 0.51 to 0.88), whereas no statistically significant difference between ETN and MTX was found (HR 1.23; 95% CI: 0.97 to 1.56).

**Figure 11** presents LOESS plots of disease severity measured as PASI and DLQI during treatment with ADA, ETN and MTX. In regression models adjusting for confounders, ADA had lower mean PASI (-2.0; 95% CI: -2.6 to -1.5) and lower mean DLQI (-0.9; 95% CI: -1.5 to -0.3) than patients on MTX during maintenance treatment. Using the same regression framework to compare ETN to MTX, ETN had lower mean PASI during maintenance treatment (-0.7; 95% CI: -1.2 to -0.2) whereas there was no statistically significant difference in mean DLQI between the treatments (- 0.5; 95% CI:  -1.1 to 0.1).

In analysis of marginal mean PASI and DLQI, predicted mean PASI during maintenance treatment with ADA, ETN, and MTX were 2.9 (95% CI: 2.5 to 3.3), 4.2 (95% CI: 3.8 to 4.6), and 4.9 (95% CI: 4.6 to 5.3), respectively. The predicted mean DLQI with ADA, ETN, and MTX were 3.8 (95% CI: 3.3 to 4.4), 4.3 (95% CI: 3.7 to 4.8), and 4.8 (95% CI: 4.3 to 5.2), respectively.

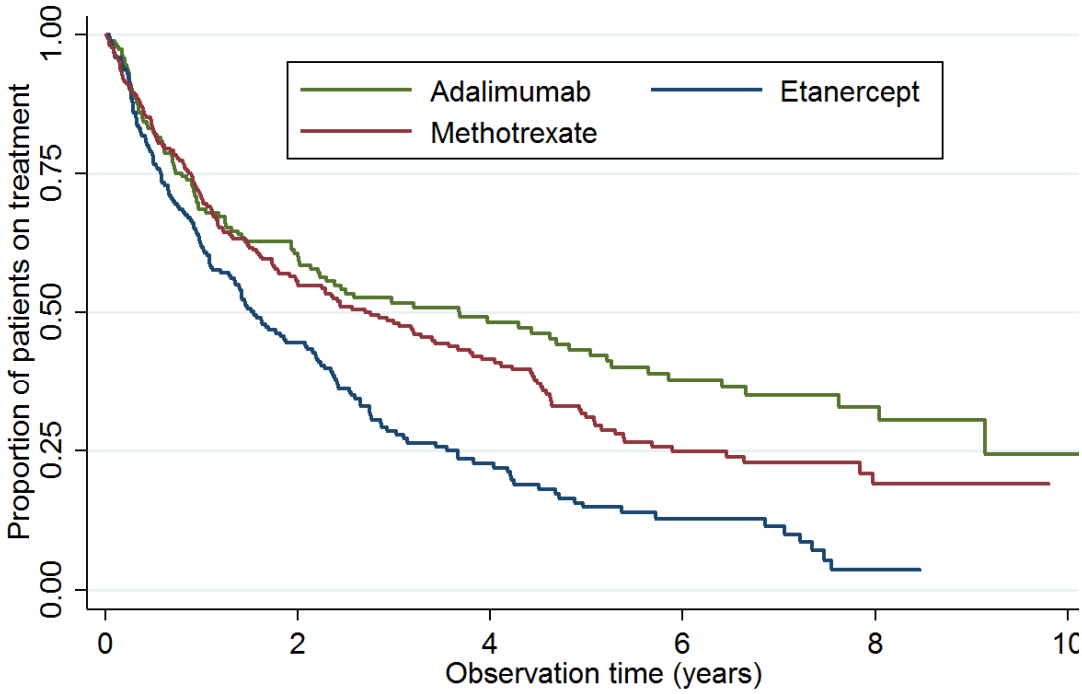


**Figure 10 Drug survival in patients with moderate to severe psoriasis.** The figure shows time to treatment discontinuation with methotrexate, etanercept, and adalimumab in DermaReg.

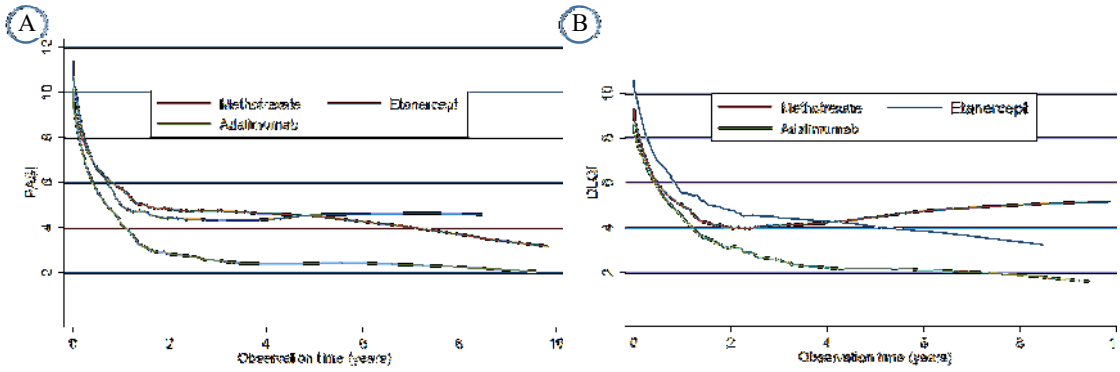


**Figure 11 LOESS curves for PASI and DLQI.** The figures present LOESS curves for PASI (Panel A) and DLQI (Panel B) from treatment initiation to treatment discontinuation stratfied by treatment.

# 6 DISCUSSION

## 6.1 METHODOLOGICAL CONSIDERATIONS

### 6.1.1 Stockholm Psoriasis Cohort (Study 1)

#### *6.1.1.1 Selection bias*

The target population in the SPC was patients with incident psoriasis in Sweden. The target sample was patients fifteen years or older with first onset of psoriasis within the last twelve months on non-hairy skin. The actual sample was the 721 patients, predominately from the Stockholm area, Sweden, with first recalled onset of psoriasis within the last twelve months on non-hairy skin who enrolled in the study. Furthermore, sex-, age-, and postcode-matched controls were enrolled into the study.

The SPC had a broad recruitment strategy to obtain a representative sample of patients with new onset psoriasis. However, the actual sample was not randomly selected and patients were required to provide informed consent, therefore the actual sample is likely systematically different from the target sample. In particular, patients with limited lesions and frail patients may be underrepresented in the study.

The SPC was a long-term prospective observational study and is susceptible to attrition bias – a type of selection bias in which those who complete the study are systematically different from those who do not. Among the 686 patients alive at ten years, 546 (80%) completed a questionnaire and 509 (74%) were also examined clinically. Registry data allowed for virtually complete follow-up of all patients in terms of filled prescriptions, specialist outpatient visits, and inpatient care. A comparison of filled prescriptions for topicals used to treat psoriasis in patients who participated in the ten year clinical examination compared to those who did not, found that treatment uptake was similar between the two groups. Finally, baseline characteristics were similar between those who completed the study and those who did not. Taken together these data suggest that attrition bias should be limited. However, it is impossible to rule out the risk of attrition bias completely as full data were not observed for those who did not complete the study.

#### *6.1.1.2 Information bias:*

Two dermatologists specializing in psoriasis diagnosed all patients in the SPC at enrollment, minimizing misclassification of exposure. History of skin lesions were elicited from the patients and it is possible that some patients may have forgotten about prior lesions or failed to notice the lesions when they occurred. Therefore, some patients defined as having recent onset psoriasis may have had prevalent disease. Patients were enrolled within one year of disease onset. Therefore, recall bias for factors associated with disease onset may exist. Furthermore, the majority of patients were treated between onset and the enrollment, making direct assessment of underlying disease severity using instruments such as PASI or s-PGA challenging. For Study 1, the only information related to the onset elicited from patients were

stressful life events and infections requiring antibacterial or antiviral treatment; two types of events that should be easy to recall.

The two main outcomes were skin disease severity and PsA. The true disease severity of skin psoriasis is confounded by treatment. Therefore, we defined disease severity as a composite end-point comprising PASI and treatment. The composite end-point is unlikely to be a perfect measure of actual disease severity. Furthermore, PASI was measured at up to three examinations and it is possible that some patients had severe disease that was not observed during clinical examination and was not treated with systemics. Some treatments for psoriasis may also be used in other indications, most notably PsA. To mitigate this potential misclassification bias, medical records were screened, and register data examined when medical records were inconclusive.

Psoriatic arthritis may be susceptible to misclassification bias. It is a clinical diagnosis and the CASPAR criteria, developed for classification of PsA in patients in a rheumatology setting, may be less appropriate in a dermatology setting. In addition, one of the CASPAR criteria – juxtaarticular new bone formation on a radiograph – was not available in the SPC. However, in patients with inflammatory articular joint disease, current psoriasis and lack of rheumatoid factor are sufficient to classify patients as having PsA. At enrollment examination, all patients with inflammatory joint disease had current psoriasis lesions, and few were rheumatoid factor positive, indicating that radiographic data would have limited impact on the prevalence of PsA. At the ten year clinical examination, the PsA classification was also made using the CASPAR criteria and for patients in which the examination was inconclusive, medical records and registry data were consulted for classification.

#### *6.1.1.3 Confounding*

Study 1 was mainly descriptive in nature and multivariable regression was used to isolate potential predictors, rather than establish causality. However, the analysis of the impact of systemic treatment on disease severity at ten years was analytical and there may be residual confounding in the analysis.

#### *6.1.1.4 Statistical considerations.*

We evaluated the discriminatory power of the subgroups with differential risks for severe disease, minimal disease activity, and PsA using c-indices (197, 198). The c-indices were estimated based on the sample used to develop the algorithms and therefore likely overestimates the discriminative power of the subgroups (205). Internal validation using bootstrap techniques or external validation in another cohort would be more informative (205).

### 6.1.2 PSOREST (Studies 2, 3 and 4)

#### *6.1.2.1 Selection bias*

The target population in the PSOREST study was all individuals with psoriasis in Region Skåne and Västra Götaland. The target sample comprised all patients with diagnosed psoriasis between 2001 and 2010 in Region Skåne and between 2005 and 2010 in Västra Götaland. The actual sample comprised all patients with a registered diagnosis of psoriasis in the two regions during the relevant periods. The study also included sex-, age-, and residency matched controls without a diagnosis of psoriasis.

One strength of PSOREST is the population based approach: All patients with a registered diagnosis of psoriasis in the Skåne and Västra Götaland regions within the relevant periods were included in the study. Therefore, the actual sample should be close to the target sample. Furthermore, healthcare in Sweden has universal access and is mainly funded with taxes. Patients are generally able to consume the health care they perceive they need and the target sample should be close to the target population. However, three caveats on patient selection should be noted. First, patients with psoriasis that did not come to clinical attention were not identified in the study. Second, visits to some private practitioners in Region Skåne did not have a diagnosis code (146). Third, we had a prevalent cohort design, only enrolling patients who survived and had a psoriasis diagnosis from 2001 in Region Skåne and from 2005 in Västra Götaland.

Among the three limitations, the most problematic from a selection perspective is probably the exclusion of patients who have not sought clinical attention for their disease. It seems reasonable that the majority of individuals with psoriasis who do not have health care contacts have mild disease. Hence, the target sample may be biased towards severe patients.

The underreporting of diagnoses from private practitioners in Region Skåne may also bias the sample towards severe patients, reflecting that patients treated exclusively in a primary care setting may have comparatively mild disease on average.

The prevalent cohort design may be problematic in the study on cause-specific mortality. If patients with incident disease have a spike in mortality, we would not capture that spike as some of the most vulnerable patients would have died before study start. However, psoriasis is hypothesized to be associated with cumulative inflammatory burden (206), arguably resulting in increased relative risk of mortality with disease duration. A related source of selection bias is that that severely ill patients may not get a diagnosis of psoriasis even though they have the disease, biasing the psoriasis cohort to a comparatively healthy population, at least close to first registered diagnosis.

For Study 4, treatment is the exposure of interest. Medications administered at a clinic may be obtained directly by the hospital and therefore not be registered in the PDR (150). This selection bias should be limited as 98-99% of ETN and ADA doses are channeled to

pharmacies (207). It is unlikely that other subcutaneous injections, orals, or topicals would be handled differently.

#### *6.1.2.2 Information bias: Measurement error in exposure*

The main source of misclassification bias for patient selection in PSOREST is that all patients in the study were not diagnosed by dermatologists, the gold-standard for a psoriasis diagnosis (5). However, primary care physicians have a diagnostic accuracy of 80% for typical and atypical psoriasis (6). Given that most patients by definition are typical, diagnostic accuracy should be higher on average. Furthermore, the SHCR has good positive predictive value for a psoriasis diagnosis with EMRs used as gold-standard (208). Misclassification of psoriasis is likely to be limited and mainly affect patients with mild disease.

The problem of misclassification of patients with psoriasis as controls is likely limited reflecting that controls are sampled from the general population, and misclassified patients with psoriasis would be included pro rata from the general population.

In Study 4, the exposure is treatment. The PDR does not have a structured variable (e.g. ICD-10 code) for the indication of the prescription (150) and the relevant medications may have been used for other indications. This potential bias is likely largest for topicals, as we did not implement any restrictions and therefore some patients may have used the treatments for other indications. For traditional systemics and biologics, we implemented an algorithm based on diagnoses, clinic, and prescriber specialty. Even after application of the algorithm, misclassification may still exist. Theoretically, the algorithm should decrease sensitivity and increase specificity. To the extent outcomes are less variable within an indication than between indications, the algorithms should improve overall precision of the estimates.

#### *6.1.2.3 Information bias: Measurement error in outcome*

In terms of measurement error, a strength is that the data used for outcomes in Studies 2 to 4, i.e. filled prescribed drugs, procedure codes, health care contacts, and cause-specific mortality are available for practically all patients. However, a number of important limitations need to be noted in terms of outcome assessment.

Study 4 considered four outcomes: persistence, any treatment event (composite of persistence, switch, and augmentation), treatment restart, and failure of biologic treatment. All outcomes were derived using prescriptions and procedure codes and contextual data are very limited. For example, the reason for treatment discontinuation is not noted. Therefore, patients who take a treatment holiday may be classified as having discontinued treatment. Furthermore, we do not know if patients actually consumed the filled prescriptions or not. In addition, not all relevant outcomes may be included. For example, treatment with infliximab or phototherapy that is not reimbursed would not be covered in the registers. The net effect on persistence from measurement error in outcome is difficult to assess: Treatment holidays may result in underestimation of persistence, whereas filled – but not consumed – prescriptions would overestimate persistence. Augmentation, switching, and failure of biologic treatment

may be biased downwards, reflecting missing outcome data on infliximab and home phototherapy.

For Study 2, the outcome is cause-specific mortality. Virtually all deaths are captured in the CDR (152) but the identification of the underlying cause is a complex and partially subjective process. The quality of the causes of deaths in the CDR have not been systematically reviewed on deaths occurring later than 1995 (152). The misclassification between patients and controls is likely non-differential, biasing estimates toward the null.

For Study 3, the outcomes were direct and indirect costs and a number of limitations should be noted. Firstly, it is uncertain whether the costs used in the analysis reflect the economic value of the products and services. Secondly, some relevant resource use may not have been captured, e.g. over the counter prescriptions and home-based phototherapy. Thirdly, we compared costs in individuals with and without psoriasis and some of the observed differences may not result from psoriasis or attributable comorbidities, but may reflect increased detection of comorbid diseases during health care contacts for psoriasis. In terms of indirect costs, the human capital approach was used to estimate the value of lost production and this method has been criticized for overestimating indirect costs (209). Another consideration for indirect costs is that most sick leave episodes shorter than 14 days are not recorded in MiDAS (156), potentially resulting in biased cost estimates: For example, a reduction of a sick leave episode by one day from 14 to 13 would be estimated as a reduction of 14 days. The net impact of measurement error in costs is difficult to assess. However, the estimated cost difference between patients with and without psoriasis is difficult to attribute directly to psoriasis. Using data from SHCR, Löfvendahl et al (2017) (136) found that psoriasis accounted for 7% of the difference in health care costs, 26% of the difference in drug costs, and 82% of the difference in indirect costs observed between patients with psoriasis and controls.

#### *6.1.2.4 Confounding*

The treatment patterns study was mainly descriptive whereas the studies on cause-specific mortality and economic burden were analytical. Therefore, confounding is a potential source of bias is the two latter studies. Two main limitations exist. Firstly, we did not use a formal framework to identify relevant confounders, such as DAGs. Secondly, we did not have information on possible confounders including obesity, smoking, excessive alcohol consumption, and exercise; factors that may be causally related to psoriasis, excess mortality, and increased health care consumption.

The prevalent cohort design may also be problematic in terms of blocking of the causal pathway: psoriasis may impair health (for which CCI is a proxy in this study) and the CCI may therefore block the causal pathway from psoriasis to death. For example, psoriasis has been linked to myocardial infarction (32). Therefore, if a patient suffers a myocardial infarction causally linked to her psoriasis prior to study inclusion, adjusting for the CCI

(which includes myocardial infarction) would falsely attenuate the association between psoriasis and death.

#### *6.1.2.5 Statistical considerations.*

A number of statistical considerations should also be noted.

In Study 4, the same patients were included multiple times in the same cohort, violating the assumption of independence between observations. Therefore, the confidence intervals presented in the analysis may not have the stated coverage and p-values may be erroneous.

For Study 2, three limitations may be noted. The non-proportionality of the PH assumption may be problematic, but the impact should be limited given that the point estimates of HR in models starting one year into the follow-up were similar to the HRs in the base case models. Furthermore, given that we evaluated specific causes of death we censored patients who died from other causes. Whilst this assumption disregards competing risks, it is still valid when the objective is to evaluate whether a factor, such as a disease, is relevant from a biological perspective (210, 211). Finally, there were few deaths from some causes in the analysis of patients with severe disease, resulting in a potential spare data bias for certain outcomes, biasing the HR point estimate from the null (191).

In the analysis of costs in Study 3, we fitted GLMs with an identify link. Therefore, the coefficients in the in the models are additive and it has been argued that costs should be modelled using a log-link instead (212) and, in theory, the identify link may produce predictions of costs below zero. However, the difference between identify link and log-link in GLM models of costs are minor in models with few covariates (213) and we chose the identify link for ease of interpretation.

#### *6.1.2.6 Transportability*

Transportability of the findings are uncertain. Firstly, the data come from two regions in Sweden and there may be significant variation in treatment within (214) and between countries (215). Secondly, the treatment armamentarium for moderate-to-severe psoriasis have expanded substantially in recent years and treatment goals have changed (216).Thirdly, the health care delivery and practice may differ between settings. Furthermore, relative measures have better transportability than absolute measures (217). Therefore, the findings on the impact of psoriasis on relative cause-specific mortality arguably have higher transportability than the findings on treatment patterns and economic burden; both which may be more difficult to extrapolate in time and space.

### 6.1.3 DermaReg-Pso (Study 5)

#### *6.1.3.1 Selection bias*

The target population was all individuals treated with systemics for psoriasis in Region Stockholm. The target sample comprised all patients treated with systemics for psoriasis at

the Karolinska Sjukhuset and a treatment center in Sundbyberg, Stockholm run by the Swedish Psoriasis Association; and the actual sample comprised all patients registered in DermaReg-Pso at the two treatment centers.

DermaReg-Pso enrolls patients from the two treatment centers with the highest volume of patients treated with systemics for psoriasis in Sweden. Whilst this may be considered a strength given that clinicians in these clinics should be experienced in diagnosis, treatment, and evaluation of psoriasis, it may systematically bias the target sample to more difficult patients. Furthermore, the register requires informed consent, and some patients opt out from the register, resulting in potential for systematic differences between the actual sample and the target sample. The impact of this potential bias is difficult to examine without data on the non-participating patients.

#### *6.1.3.2 Information bias*

There may be information bias in exposure, outcome and covariates. Firstly, the clinician reports treatment and it is not certain that patients take their medications; therefore, there may be misclassification in exposure. Secondly, effectiveness in psoriasis is a multi-faceted concept comprising clinical effectiveness, adverse events, HRQoL, and treatment satisfaction; and it is not certain that the end-points in the study adequately measure these constructs, resulting in potential misclassification of outcome. Thirdly, covariates may be measured with imprecision. For example, given the lack of washout prior to treatment initiation, disease severity prior to treatment initiation may not be an adequate marker for disease severity. Fourthly, bias may arise if follow-up differs systematically among the three treatments. We addressed the first two limitations by using multiple end-points: Treatment discontinuation arguably reflects treatment dissatisfaction, and drug survival, DLQI and PASI collectively captures broad aspects of psoriasis that are important to patients. We addressed the third limitation by evaluating disease severity over the entire period of data availability prior to initiation with the relevant treatment episode; and assessed the fourth limitation by examining the data and found no evidence of systematically differential follow-up among the three treatments.

#### *6.1.3.3 Confounding*

The study compared two treatments, adalimumab and etanercept to methotrexate, and the distribution of patient characteristics among the three treatments were uneven, suggesting potential confounding bias. We developed three DAGs to make underlying assumptions on causality explicit. It is possible that the DAGs are incorrect or omit important variables; and that residual confounding exists after controlling for variables as indicated in the DAGs. One example may be comorbidities such as inflammatory bowel disease for which ADA, and MTX, but not ETN are indicated.

#### *6.1.3.4 Transportability*

Differences in treatment targets, clinical practice, and patient selection may limit the transportability of the findings in space and time. Even within the study setting, changing treatment practice necessitated control for calendar year to address confounding. Furthermore, as evidenced by the analysis of PASI and DLQI during maintenance treatment, a number of patients had inadequately controlled psoriasis given current treatment targets and therefore drug survival estimates would likely differ in the current environment. Adherence to more strict treatment targets would reduce drug survival for all three treatments, but less for adalimumab than methotrexate.

#### *6.1.3.5 Statistical considerations.*

We fitted linear random intercept models with normally distributed errors and an identity link. PASI ranges between 0 and 72 and DLQI ranges between 0 and 30. During maintenance treatment, both PASI and DLQI are heavily skewed towards zero and it is possible that another error distribution would have suited the residuals better.

# 7 CONCLUSIONS

Psoriasis is a chronic inflammatory disorder affecting both body and psyche. The studies in this thesis aimed to expand our knowledge of its clinical course, comorbidities, economic impact, and treatment.

Study 1 demonstrates that plaque psoriasis has a comparatively stable course. Patients with severe disease at onset were more than four times more likely to have severe disease after ten years than patients with mild or moderate disease (41% vs 9%; $p<0.001$). The study on treatment patterns also underscores the recalcitrance of psoriasis. A high proportion of patients restarted treatment within one year of discontinuation; with the probability increasing with potency of discontinued treatment: 49% for topicals, 61% for systemics, and 80% for biologics. The SPC also found that the course of psoriasis may be predicted with good discriminatory power. Patients with plaque phenotype, more than mild symptoms (s-PGA>3), and scalp involvement were more likely to develop severe psoriasis than patients with mild symptoms (s-PGA≤3), irrespective of phenotype at enrolment (52% vs 11%, $p<0.001$). For PsA, patients with peripheral enthesitis at enrollment were more likely to have PsA at ten years than patients who reported no arthralgia at onset (59% vs 12%, $p<0.001$). Therefore, patients with these characteristics at onset may merit comparatively close follow-up or referral to specialists; especially since undertreatment of both psoriasis and PsA appear common (166). In general, patients with guttate onset had a good prognosis with 48% having minimal disease activity after ten years. Furthermore, only 1/94 (one per cent) of patients with guttate phenotype of mild or moderate disease severity at onset had severe psoriasis at ten years.

In terms of treatment, Study 5 found that ADA was superior to MTX whereas the findings for ETN versus MTX were more mixed. In line with results from clinical trials, these results suggest that ADA is more effective than MTX for treating skin manifestations of psoriasis, and may be a good option as a first line systemic treatment; albeit more data, especially on safety and costs are needed. In addition, even though ADA was comparatively effective, mean PASI was estimated at 2.9 during maintenance, reasonably in line with current treatment goals (45). However, the notion that psoriasis treatments may be insufficient is supported by the findings from Study 4 where more than 70% of patients on systemic and biologics augmented, switched, or discontinued treatment within one year from treatment start. Finally Study 1 found that early systemic treatment associated with reduced risk of severe disease at ten years: Six of 16 patients (38%) who initiated systemic treatment at or before enrolment had severe disease at ten years compared to 33 of 50 patients (65%) who started systemic treatment later in the disease course ($p=0.044$), a finding that was statistically significant after controlling for covariates. Given the non-randomized nature of the analysis, this finding should be viewed with a very high degree of caution and new studies, preferably randomized controlled clinical trials, are needed to determine the impact of early systemic treatment.

Study 2 found that all-cause mortality was increased in both mild and moderate to severe psoriasis. Whilst cardiovascular deaths accounted for most excess deaths, the highest relative risks of death for patients with mild psoriasis and severe psoriasis were kidney disease, and liver disease, respectively. The reasons for the elevated risks of deaths due to cardiovascular, kidney and liver disease are unclear. However, these organs are interdependent; and all three are adversely impacted by systemic inflammation, smoking, and excess alcohol consumption; factors also are associated with psoriasis (218-220). Liver disease and kidney disease are less frequent causes of death than cardiovascular disease and are therefore arguably less important to screen. However, liver and kidney function tests are recommended to monitor systemic treatment in psoriasis (221) and could potentially be used to identify patients with elevated risks for kidney and liver disease.

The study on the economic burden with psoriasis support the notion that psoriasis is associated with substantial direct and indirect costs and that the economic burden generally increases with disease severity. The analysis also demonstrates that treatment with biologics have the potential to decrease both direct and indirect costs, with the net impact on direct costs depending on the cost of biologics. This finding could inform economic evaluation of treatments in psoriasis and therefore improve resource allocation in the health care system.

Overall findings from these studies reinforce the notion that plaque psoriasis is a chronic disease associated with substantial burden both from clinical and economic perspectives. Identification of subgroups of patients with adverse disease course may contribute to better and more cost-effective management of the disease. The finding that early systemic intervention may affect the disease course may affect the treatment paradigm in psoriasis, but needs to be confirmed in sufficiently powered randomized controlled clinical trials.

# 8 POINTS OF PERSPECTIVE

This thesis attempts to enhance our knowledge of clinical, epidemiologic and economic aspects of psoriasis. Even though new knowledge has been gained, new questions have also arisen due to results and limitations.

The estimated effectiveness of novel systemics in psoriasis systematically differs between clinical trials and clinical practice (222). The reasons for these differences are debated (223) and may include patient characteristics, adherence, and treatment setting. Understanding the reasons for these differences may facilitate improved treatment outcomes in clinical practice. To this end, a study linking DermaReg to Swedish Health Registers may be valuable given the depth and breadth of data such a study would have. Furthermore, the observation that early systemic intervention may be disease modifying should be tested in a clinical trial; and such a trial is currently under way (224).

The studies in this thesis support a large body of evidence showing that some patients do not respond to or lose response to novel systemics. Identifying genotypes/other biomarkers or phenotypes with differential response rates to given treatments would enable clinicians to better tailor treatment to patients. Given the depth of the data in DermaReg, a study systematically exploring predictors of treatment response on these data may be valuable.

In terms of comorbidities and cause-specific mortality, all studies following patients over time rely on prevalent cohorts, albeit at least one study has implemented a wash-out period (225). Therefore, survivorship bias is a potential problem, and one that the SPC largely is free from. Therefore, even though SPC is limited in size, it may provide important information on comorbidities. Furthermore, detailed data on patients and controls from onset may enable identification of subgroups or patients with especially elevated risk of comorbidities.

The data in SPC may also be used to describe development of disease severity with disease duration and age, and disentangle the impact of the two factors. The study is also well equipped to examine the hypothesized existence of two types of psoriasis: One with early onset and adverse prognosis (Type 1), and one with later onset and better prognosis (Type 2). It could also beneficially be used to examine drivers of disease severity in comparatively mild population, not frequently seen in a dermatological setting.

One important limitation with SPC is that patients were not seen frequently and therefore the description of the clinical course of psoriasis has important limitations. New technology and the growth of investment in dermatology since the advent of SPC may facilitate a larger study with more frequent examinations and longer follow-up.

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