

# Psoriasis in Sweden

## Observational studies from an epidemiological perspective

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*Vi hade dem i säcken, knöt gaffeln och släppte ketchupen. Allt hände på en gång... och nu är vi i allsvenskan.*

Mika Sankala, tränare för GIF Sundsvall vid uppflyttningen till Allsvenskan 2007



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# Abstract

**Background:** Psoriasis is a heterogeneous disease with several clinical manifestations; the symptoms are characterized by redness, scaliness and thickness of the skin. There are several treatment options available for psoriasis and patients with moderate to severe psoriasis generally need systemic agents. In 2004 biologics were introduced for patients with moderate to severe psoriasis in Sweden.

**Methods:** The Swedish Health Care Registers and the Swedish registry for systemic treatment of psoriasis PsoReg, were used to; estimate the incidence of psoriasis cases in the Swedish specialist care, to examine the treatment allocation and important factors related to the initiation of especially biologic treatment.

**Results:** On average 9000 new psoriasis patients entered specialist care in Sweden each year under study, corresponding to an incidence of 98 patients per 100,000 person-years. In the treatment allocation analysis of the incident psoriasis cases in the Swedish specialist care Patients living in a Metropolitan Area and with a University degree were more likely to initiate a biologic treatment. By analysing biologic-naïve patients enrolled in PsoReg, PASI (the physician's assessment of the psoriasis severity) and Psoriasis Arthropathy were shown to be two important factors associated with the initiation of biologic treatment while sex was not. Furthermore, it was also shown that the decision to initiate biological treatment was more strongly associated with PASI than with DLQI (the patients' assessment of the disease impact Quality of Life).

**Conclusion:** These studies indicate that there are inequalities in the assignments of systemic psoriasis treatments (especially in biologic treatment). Since the allocation of treatments should not depend on sex, education or residency in a Metropolitan Area but rather the need of care, it is important that future studies continue analysing possible factors that could influence the initiation of treatment in clinical practice in Sweden.

**Keywords;** Psoriasis, Systemic treatments, Biologic treatments, PASI, DLQI, Register-based research

# Abbreviations

BMI	Body mass index
BSA	Body Surface Area
CI	Confidence interval
QoL	Quality of Life
DLQI	Dermatology Life Quality Index
HR	Hazard ratio
HRQoL	Health-Related Quality of Life
NPR	The Swedish National Patient Register
OR	Odds ratio
PASI	Psoriasis Area and Severity Index
PDR	Prescribed Drug Register
PIN	Personal Identification Number
PROM	Patient Reported Outcome Measurement
PsA	Psoriasis Arthropathy
PsoReg	the Swedish register for conventional systemic treatment of psoriasis
RCT	Randomized Clinical Trial
SEK	The currency of Sweden, Swedish crowns



# List of papers

The thesis is based on the following papers which will be referred to in the text as papers I-IV.

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<b>Paper I</b>	Hägg D, Eriksson M, Schmitt-Egenolf M, Sundström A. Specialist-treatment of psoriasis in Sweden between 2007 and 2009: incidence and treatment allocation during a two-year follow-up ( <i>Manuscript</i> )
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<b>Paper II</b>	Hägg D, Eriksson M, Sundström A, Schmitt-Egenolf M (2013) The Higher Proportion of Men with Psoriasis Treated with Biologics May Be Explained by More Severe Disease in Men. PLoS ONE 8(5): e63619. doi:10.1371/journal.pone.0063619
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<b>Paper III</b>	Hägg, D., Sundström, A., Eriksson, M. and Schmitt-Egenolf, M. (2015) Decision for biological treatment in real life is more strongly associated with the Psoriasis Area and Severity Index (PASI) than with the Dermatology Life Quality Index (DLQI). Journal of the European Academy of Dermatology and Venereology, 29: 452–456. doi: 10.1111/jdv.12576
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<b>Paper IV</b>	Hägg D, Sundström A, Eriksson M, Schmitt-Egenolf M. Severe psoriasis is less common in women – a registry based study of the clinical outcome measure - Psoriasis Area and Severity Index (PASI) in 4045 patients. ( <i>Submitted</i> )
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# Populärvetenskapligt abstrakt

**Bakgrund:** Psoriasis har länge ansetts som enbart en hudsjukdom men idag vet man att psoriasis är en systemsjukdom som påverkar många av kroppens organ, däribland huden. I Sverige uppskattas det att 200 000-300 000 individer lider av psoriasis, och för de flesta av dessa är mjukgörande salvor tillräckligt för att hålla kontroll på sjukdomen, men när det inte hjälper så finns konventionella systemiska läkemedel att tillgå. I Sverige introducerades biologiska läkemedel under år 2004 som ett behandlingsalternativ till systemiska läkemedel för dem som lider av måttlig till svår psoriasis.

**Varför?** Genom att använda den information som finns tillgängligt i våra stora nationella databaser är det möjligt att analysera vilka faktorer som är viktiga vid start av behandling och hur behandlingarna fördelas i samhället.

**Hur?** I det nationella kvalitetsregistret PsoReg registreras patienter som lider av måttlig till svår psoriasis samt deras konventionella och biologiska behandlingar. Där återfinns även information om svårighetsgraden i form av ett mått där läkaren uppskattar svårighetsgraden - Psoriasis Area and Severity Index (PASI), och ett där patienten svarar på frågor om hur sjukdomen har påverkat vardagen - Dermatology Life Quality Index (DLQI). Genom att länka PsoReg via personnumret med de nationella hälsodataregistren så är det möjligt få tillgång till ytterligare information, som annan läkemedelsbehandling, utbildning och vårdbesök.

**Resultat:** *Studie I:* Antalet psoriasispatienter som kom in i den svenska specialistvården mellan 2007 och 2009 uppskattades till ca 9000 individer årligen (motsvarande 98 patienter per 100,000 personår). Mellan åldrarna 50 och 69 år var det betydligt fler kvinnor som diagnosticerades, medan inga könsskillnader återfanns i övriga åldrar. Efter tidpunkten för första psoriasisdiagnos inom specialistvården genomfördes en två-årsuppföljning av 24 411 psoriatiker, där det visade sig att vara boende i en storstadskommun ökade chanserna att få tillgång till biologisk behandling. Om patienten hade använt en större mängd mjukgörande salvor (mer än 1160 gram) året före diagnostillfället så ökade chanserna att påbörja antingen en konventionell systemisk behandling (icke-biologisk) eller en biologisk behandling. *Studie II:* I PsoReg undersöktes 2294 patienter som aldrig tidigare fått en biologisk behandling. Under uppföljningen så inledde 343 patienter en biologisk behandling. I den statistiska analys som genomfördes var den kroniska inflammatoriska ledsjukdomen psoriasisartrit och svårighetsgrad av psoriasis (PASI) de två främsta faktorerna som förklarade inledandet av biologisk behandling, medan kön och BMI inte verkade ha något

samband. *Studie III:* Vid insättning av biologiska läkemedel är ett av kriterierna att patienten ska ha minst 10 i PASI och minst 10 i DLQI. För att utvärdera om något av de två måtten har ett starkare samband till start av biologisk behandling, genomfördes en analys av 2216 patienter i PsoReg som vid inklusion i registret aldrig tidigare fått en biologisk behandling. Resultatet visade att de patienterna med ett högt PASI och ett lågt DLQI hade en större chans att inleda en biologisk behandling jämfört med dem som hade ett lågt PASI och ett högt DLQI, efter att ha justerat för kön, ålder, BMI (Body Mass Index), psoriasisartrit, rökning, alkoholkonsumtion och sjukdomsduration. *Studie IV:* I en av våra tidigare studier (Studie II) noterades att män hade en svårare psoriasis än kvinnor enligt bedömningsmättet PASI. För att försöka belysa varför män hade en svårare psoriasis granskades skillnaden mellan män och kvinnors PASI-värde inom de olika beståndsdelarna av bedömningsmättet. Analysen visade att män hade en högre grad av rodnad, infiltration och fjällning på bål, armar och ben. Däremot så fanns det ingen skillnad avseende dessa på huvudet.

**Slutsatser** Dessa studier tyder på att det finns ojämlikheter vid initieringen av systemiska psoriasisbehandlingar (särskilt i biologisk behandling). Då behandlingar varken ska påverkas av kön, utbildning eller bostadsort, utan av vårdbehov, är det viktigt att vid framtida studier fortsätter att analysera möjliga faktorer som kan påverka start av behandling i den kliniska verksamheten.

# Introduction

During the past decades there has been a significant progress in the understanding of the disease psoriasis, but several areas have been addressed for further research.<sup>1</sup> There are still research gaps in the basic science that needs to be filled with large epidemiological studies, and with the new biologic treatments, there is an increased need for monitoring factors related to the start of treatment and allocation under “real-world” circumstances. The introduction of biologic treatments in the psoriatic population has provided an additional option of treatments for those who do not respond or have become intolerant to topical or conventional systemic treatment.<sup>2,3</sup> However, compared with conventional systemic treatment, biologics are associated with considerably higher costs and constitute a large part of the health care budgets.<sup>4,5</sup> Thereby, it is important to examine the elements behind the decision to initiate biologic treatment in everyday clinical practice.

The Nordic countries have a long tradition of collecting data in National Administrative Registers, and with the possibility to link the Swedish Health Care Registers with the Swedish Quality Registers by the Personal Identification Number (PIN), a unique research environment is provided.<sup>6</sup> However, in 2008 the Swedish Government stated in a proposition that the register-based research was underutilized which led to an investigation in how to promote register-based research.<sup>7,8</sup> This resulted in a large investment with a series of actions including improving infrastructure, quality of data, research competence and simplifying data linkage. It was also proposed that the use of Patient-Related Outcome Measures (PROM) should continue and be developed in the Quality Registers. By observing decisions that are made in healthcare, it is possible to identify variations in clinical practices that may result in new knowledge that will be beneficial to both clinicians and patients.

This thesis has used the Swedish Health Care Registers and the Swedish Register for conventional systemic treatment of psoriasis (PsoReg) to cover four different aspects in the process of initiating a treatment in the psoriatic population. One of the aspects was to estimate the incidence of psoriasis in the specialist care and the subsequent allocation of conventional systemic- and biologic treatment in Sweden. Today there are many studies made on the prevalence of psoriasis but only a few which are describing the incidence of psoriasis<sup>9</sup>, and further studies on this subject may provide a better insight into the burden of the disease and the premises in the early stage of initiating conventional systemic treatment. The second aspect is to examine whether there are any sex differences in the initiation of biologic treatments. To make a valid evaluation of the treatment allocation, the measure of disease severity

is a crucial factor. Using data from (PsoReg) it was possible to relate the initiation of biologic treatments with the disease severity measured by the Psoriasis Area and Severity Index (PASI). At the initiation of biological therapy the Swedish guidelines states that both the physicians' assessment of the disease severity and the patients' assessment of disease impact on the Health-Related Quality of Life (HRQoL) should be taken in to consideration. The third aspect is to evaluate if any of these two assessments are more related than the other to the initiation of biologic treatment. The final subject that will be addressed in this thesis is the sex differences in the PASI measure that was found in PsoReg. By analysing the separate elements on which the PASI score is based, an attempt was made to elucidate why men have a higher PASI score than women in PsoReg.

This thesis is structured in five chapters. The **Background** contains a short introduction to the disease psoriasis, the variety of treatment options, different tools to assess the severity of disease (Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI)) and strengths and weaknesses of observational studies. The general objectives of this thesis and the specific aims of the four papers are stated in the **Aims of the thesis**. **Material and method** presents the sources of information of this thesis, the linkage of the registers, the study populations and the statistical analysis. The **Results chapter** presents the main findings from the studies which are finally discussed in the **Discussion** chapter.

# Background

## Psoriasis

The term Psoriasis is derived from the Greek word *psōra* which means 'being itchy' and has previously been considered merely a skin disease.<sup>10</sup> However, today it is known to be a chronic autoimmune disease which is manifested in different ways, often with defined red and scaly plaques.<sup>11</sup> Skin psoriasis comes in different forms such as guttate, pustular, inverse psoriasis and the most common form plaque psoriasis. A more uncommon form of psoriasis is Erythroderma, which covers most of the body surface area. The disease activity fluctuates in periods, both in extent and severity and is associated with seasonal variations where exposure to sunlight reduces the disease activity.<sup>11,12</sup> It is a complex disease in which not only the skin is affected, but rather several parts of the body. About 6-42 % of the patients suffering from psoriasis are also affected by psoriasis arthropathy (PsA).<sup>13,14</sup>

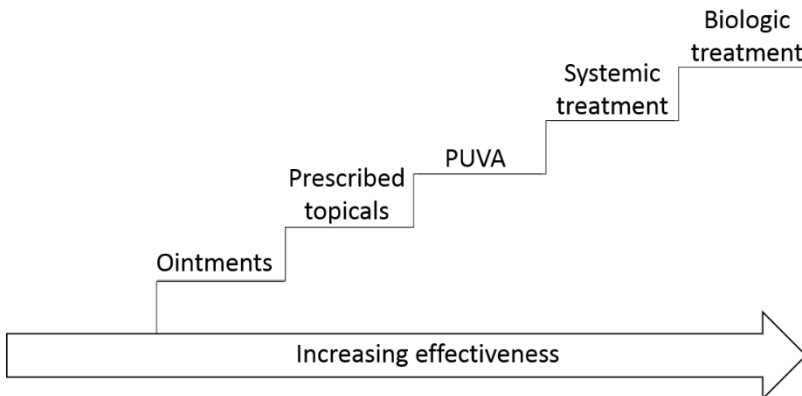
Psoriasis is a common disease with a prevalence that varies geographically.<sup>15</sup> In the Nordic countries, the prevalence is estimated to be about 2-3 percent<sup>16</sup>, which in Sweden equals 200,000–300,000 individuals suffering from psoriasis. The general belief is that the prevalence is the same for men and women<sup>17,18</sup>, but there are studies showing either that men have a higher prevalence<sup>19</sup> or that women have a higher prevalence.<sup>20</sup> The onset of psoriasis can occur at any point in life, but it is clear that heredity has a major role whether psoriasis debuts at a young age, as compared with a late onset.<sup>21</sup> About 50% have their onset before the age of 25, and women tend to debut earlier than men.<sup>22</sup> It has been suggested that the disease onset has two peaks, the first during puberty and the second between the ages 40 and 50.<sup>23,24</sup>

A majority of those who suffer from psoriasis have a mild disease activity, but approximately 25 percent have been estimated to suffer from moderate to severe psoriasis<sup>25</sup>, and may therefore need conventional systemic treatment to control the disease. Moderate to severe psoriasis is also associated with Crohn's disease<sup>26-28</sup>, cardiovascular disease,<sup>29,30</sup> depression<sup>31,32</sup> and an increased risk of death.<sup>33-35</sup>

The causes of psoriasis are not fully understood, but a number of risk factors are recognized, including family history and environmental risk factors, such as smoking, stress, obesity, and high alcohol consumption.<sup>36-39</sup> Patients suffering from psoriasis are stigmatized to such an extent that it causes a considerable psychosocial disability and has a major impact on the Quality of Life (QoL).<sup>40,41</sup>

## Treatments

There is currently no treatment that can cure psoriasis. Depending on disease activity, extent, patient preferences and form of psoriasis, there are a variety of treatment methods.<sup>42</sup> The major part of the patients suffering from psoriasis have mild symptoms and are sufficiently treated with ointments or moisturizers, while topical treatment (calcipotriol with/ without corticosteroids), light therapy and conventional systemic treatments are available for moderate to severe psoriasis. If patients are intolerant or non-responsive to conventional systemic treatments, biological treatments remain as an alternative to control the disease activity.<sup>43</sup> The choice of treatment for a patient with moderate to severe psoriasis is individualized and based on several factors; type of psoriasis, age, health status, previous treatment, the patient's own wishes etc.<sup>44,45</sup> In order to supplement the biologic treatment it is common to combine it with topical treatment or a conventional systemic treatment.<sup>46</sup>



**Figure 1.** Schematic of psoriasis treatment ladder.

Biologic treatments were introduced for psoriasis patients on the Swedish market in 2004. However, there is a big difference in cost between conventional systemic therapy and biological treatment. Methotrexate which is the most common systemic treatment has a total estimated annual cost of about SEK 1000 per patient, while biological treatments can amount to SEK 130,000 per patient and year. Today there are four different biologic substances available Etanercept (Enbrel®), Infliximab (Remicade®), Adalimumab (Humira®) and Ustekinumab (Stelara®). Biologics are designed to target specific components of the immune system and have been proven to be very efficient.<sup>47-49</sup> All systemic- and biologic therapies are associated with long-term side effects.<sup>50</sup> The biologic agent Efalizumab (Raptiva®) was withdrawn from the market due to severe side effects by the European Medicine Agency in 2009.<sup>51</sup>

## **Assessing the severity of psoriasis**

To assess the severity of the disease and evaluate the response to treatment, several instruments have been developed and take different aspects of the disease into account. In this project two common assessment tools have been used, the Psoriasis Area and Severity Index (PASI) and the Dermatology Life Quality Index (DLQI).

### ***Psoriasis Area and Severity Index (PASI)***

PASI was developed 1978 and today it is the most widely used tool to measure the clinical severity of psoriasis and is considered to be the gold standard of assessing the extent of the skin involvement.<sup>52,53</sup> In this assessment, four different body sections are examined; head, arms, trunk and legs. In each body section, the percentage of the skin involvement on a scale from 0 to 6 (0: 0%, 1: 1-9%, 2: 13-29%, 3: 30-49%, 4: 50-69%, 5: 70-89%, 6: 90-100%), and the severity of the skin lesion is estimated and assessed by three clinical signs Erythema, Induration and Desquamation on a scale from 0 (none) to 4 (very severe). The result of the assessment is weighted into a single score ranging from 0 (no disease) to 72 (maximal disease severity).<sup>54</sup>

### ***Dermatology Life Quality Index (DLQI)***

DLQI is a questionnaire made specifically for patients suffering from skin diseases and was developed in 1994.<sup>55</sup> It is the most important Patient Reported Outcome Measure (PROM) in dermatology and is frequently used in studies. The general objective of DLQI is to assess the impact of the skin disease on the Quality of Life in terms of social functioning and psychological well-being. The questionnaire consists of ten questions concerning how daily activities such as leisure, work, personal relationships etc. have been affected by the skin disease during the past week. Each question has four different options "not at all", "a little", "a lot" or "very much", where each question is scored from 0 to 3. The scores are summed, giving a total score ranging from 0 (no impairment of life quality) to 30 (maximum impairment).



## ***Definitions of disease severity***

To define the severity of psoriasis is complex since there are many dimensions in the disease that should be taken into consideration and there is no clear definition for distinguishing between mild, moderate and severe psoriasis. Suggestions have been made that the measure Body Surface Area (BSA) should be used to define the disease severity. BSA is an estimation of the percentage of the area of skin involvement, where a palm of the hand should be equivalent to about 1% of the body surface. One of the proposals has been to categorize the severity into mild (less than 3% of the skin surface), moderate (3-10% of the skin surface area) and severe (>10% of the skin surface are).<sup>56</sup> However, it is not an optimal solution since there are patients with a high BSA involvement but still with a mild psoriasis and conversely severe psoriasis with a low BSA.<sup>57,58</sup>

Another proposal is the 'Rule of tens', where mild psoriasis is defined as:  $BSA \leq 10$  and  $PASI \leq 10$  and  $DLQI \leq 10$ , and moderate to severe psoriasis: as ( $BSA > 10$  or  $PASI > 10$ ) and  $DLQI > 10$ .<sup>57</sup> This approach, with a slight modification, has also been discussed in a Delphi process as a suitable method for evaluating treatment results and to define severe psoriasis:  $BSA > 10\%$  or  $PASI > 10$  and  $DLQI > 10$ .<sup>59,60</sup> The combination of the dermatologist's assessment of the disease activity (PASI) and the patient's experience of the impact of the disease on daily life (DLQI) provides an overall picture of the disease severity.<sup>61,62</sup> Swedish guidelines define severe psoriasis as  $PASI \geq 10$  and  $DLQI \geq 10$  and as a threshold for initiating biologic treatment when other conventional systemic treatment has not been adequate.<sup>63</sup>

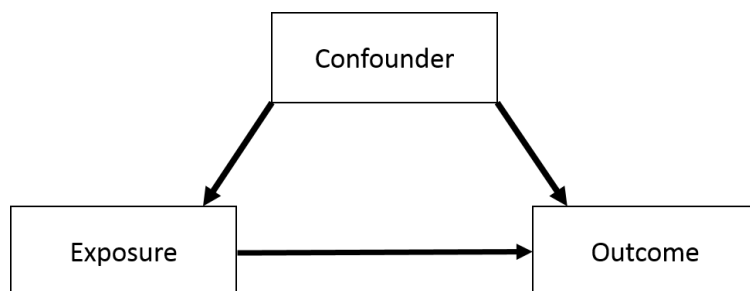
# Register-based studies

Most designs available in observational epidemiological studies could be used when analysing register-based data. The study designs that have been used in this thesis are cross-sectional and cohort studies. In a cross-sectional study the data used is collected at a specific point of time. It is commonly used to assess the prevalence of a disease or analysing the associations between variables. The cohort study is a longitudinal study, where a group of people who share a common characteristic is followed in a well-defined time period. Cohort studies are often used to evaluate associations between exposures and outcome, or to study the incidence of a disease.<sup>64</sup>

An advantage with register-based observational studies is that the data has already been collected (such as register-based studies using Health-Care registers), and they often result in a large sample sizes. Observational studies are non-experimental since the researcher is not controlling any of the aspects in assigning the treatments to the patients. Instead the patients' actual use of the treatments and occurrence of events are merely observed. In contrast to observational studies, in randomized clinical trials (RCT), the patients are randomly assigned to a treatment group or to a control group. This randomization ideally makes the potential differences between the patients at baseline evenly distributed between the treatment group and the control group, and the effect of treatment on the outcome can be estimated by directly comparing the outcomes between patients in the two groups. However, in the observational studies the initiation of treatment is often influenced by the characteristics of the patient (and indeed of the prescribing physician). This may result in a systematical difference in the baseline characteristics among the patients in the groups of treated and untreated, or groups with different treatments.<sup>65</sup> Therefore, it is important to adjust for any potential difference that is associated with the exposure and the outcome of interest when estimating the effect of treatment on outcomes.

## Confounding and selection bias

One of the biggest challenges in observational research is the problem of confounding. The issue of confounding arises when a factor is associated both with the exposure and the outcome of interest. There are various ways to try to prevent or minimize the effects of confounding. One possibility is in the study design by matching the treated patients with the untreated patients by the potential confounders, or by adjusting for the confounders in the statistical analyses, e.g. stratification or multiple regressions analysis. Selection bias occurs when the individuals selected to the study is not a representative sample of the population the conclusions are going to be drawn to. If the selection bias is disregarded the conclusions of the study can be inaccurate.



**Figure 2.** Definition of confounding.

# Aims of thesis

The overall aim of this thesis was, by using Swedish Health Care Registers and PsoReg, to examine the treatment allocation and important factors related to the initiation of especially biologic treatment.

Specific aims of the papers:

- I                      To estimate the number of incident cases in the Swedish specialist care of psoriasis, and to examine the treatment allocation of conventional systemic- and biologic treatment in a two-year follow-up.
- II                     To identify important factors linked to the initiation of biologic treatment in PsoReg.
- III                    Treatment guidelines suggest the values  $\text{PASI} \geq 10$  and  $\text{DLQI} \geq 10$  should be present before initiation of biological treatment. The aim of paper III was to evaluate if either of the two measures, PASI or DLQI, was more strongly associated with the initiation of biological treatment.
- IV                    To investigate differences in severity of psoriasis between men and women by analysing the specific PASI elements.

# Material and Methods

The data sources that formed the base of this study were the Swedish registry for conventional systemic treatment of psoriasis (PsoReg) and Swedish National Healthcare registers including the Swedish Prescribed Drug Register (PDR), the National Patient Register (NPR) and the Longitudinal Population Register on Education, Income and Work (LISA). In Sweden all residents are issued a unique Personal Identification Number (PIN) upon birth or immigration that will be used throughout the life.<sup>66</sup>

## Prescribed Drug Register (PDR)

Information about the patients' drug prescriptions is obtained from the PDR. This register has been up and running since July 2005 and contains all drugs dispensed by prescriptions, with information on e.g. the date of prescribing and dispensing, name, strength and quantity of the dispensed drug, place of residence of the patient (county, municipality), and some characteristics of the work-place of the prescriber.<sup>67</sup> There is an on-going work to reduce the number of incorrect registrations, and the percentage of missing data for the variables sex, age and county is estimated to be 0.02-0.6%.<sup>68</sup>

## National Patient Register (NPR)

Since 2001 there is a complete national coverage of all out-patient visits to hospital in the specialist care. The register contains information about the main and secondary diagnoses and dates for the visits.<sup>69</sup> A quality check of the data was done 2006 and it showed that only 1% of the main diagnoses were missing.<sup>69</sup>

## Statistics Sweden

From Statistics Sweden it is possible to retrieve the socioeconomic characteristics on an individual level from the Longitudinal integration database for health insurance and labour market studies (LISA). The socioeconomic factor that has been used in this thesis was educational level, categorised as: Primary and lower secondary education, less than 9 years, Primary and lower secondary education, 9 (or 10) years, Upper secondary education, Post-secondary education, less than two years, Post-secondary education, two years or longer and Postgraduate education.<sup>70</sup>

## **PsoReg**

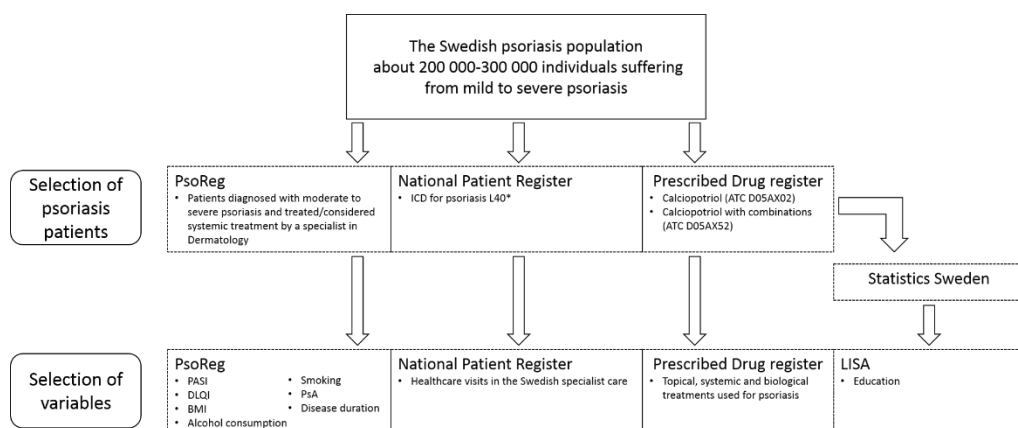
In 2006 PsoReg was established as the Swedish register for conventional systemic treatment of psoriasis. Patients suffering from moderate to severe psoriasis, treated with or considered to be treated with conventional systemic treatment by a specialist in dermatology are eligible to be included in PsoReg. Enrolment of patients can occur when a patient visits a dermatological clinic at local, regional or University Hospitals as an outpatient, at treatment centres operated by the Swedish Psoriasis Association or at private dermatological practices. The main objectives of the registry are to monitor the effectiveness and long-term safety of conventional systemic psoriasis treatments and to optimize the treatments for the patients.<sup>71,72</sup>

At enrolment, patient characteristics such as age at disease onset, type of psoriasis, Psoriasis Arthropathy (PsA), treatments used prior to registration, previous diseases, tobacco and alcohol habits and family history of psoriasis are registered in PsoReg. At each visit to the health care facility, the height, weight, age, use of conventional systemic treatment, clinical (PASI) and HRQOL outcome measures (DLQI) are updated. The coverage in PsoReg is estimated to be about 65% of the biologic treatments in the psoriatic population, and a 40% of the psoriasis patients treated with conventional systemic treatments in Sweden.<sup>73</sup>

## **Linkage between the registers**

From the Swedish population, patients suffering from psoriasis were identified in 1) the NPR by the ICD-10 code for psoriasis (L40\*), 2) the PDR by the unique psoriasis treatments calcipotriol (ATC: D05AX02) and calcipotriol in combination with a corticosteroid (ATC: D05AX52), and finally 3) all patients registered in PsoReg in October 2011 (n=3128). In total 156 504 individuals were identified with psoriasis.

For the identified psoriasis patients, all dispensed topical-, conventional systemic- and biological treatments was extracted from the PDR for the years 2005 to 2011. The variables selected from PsoReg were PASI, DLQI, Body Mass Index (BMI), alcohol and tobacco habits, PsA and disease duration. In NPR, all visits in the specialist care with the corresponding diagnosis codes were selected (ICD-10), and from Statistics Sweden the educational level was retrieved from the LISA-register.



**Figure 3.** Schematic illustration of the data linkage between PsoReg, the National Patient Register (NPR), the Patient Drug Register (PDR) and Longitudinal integration database for health insurance and labour market studies (LISA).

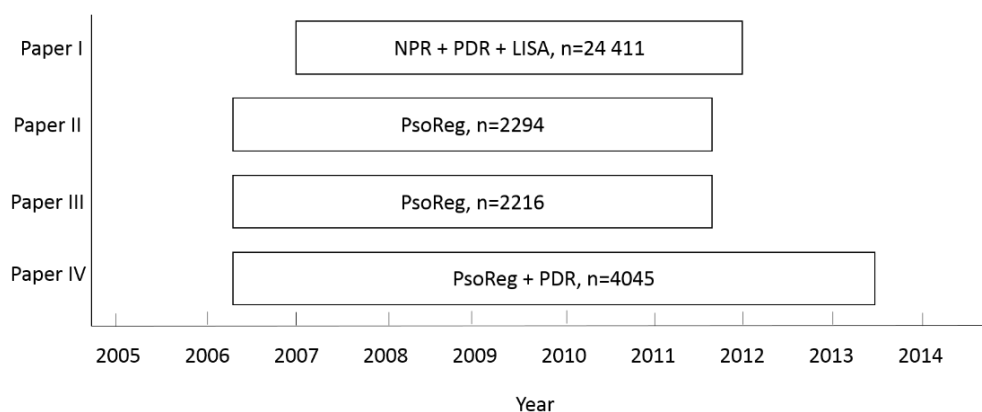
## Study population

In paper I, all patients with a main diagnosis of psoriasis between 2001 and 2009 in the NPR was selected. To estimate the number of incident cases in the Swedish specialist care of psoriasis, those with a psoriasis diagnosis registered between 2001 and 2006 was identified as prevalent cases ( $n=54\ 913$ ). Thereby, all the patients with a first psoriasis diagnosis between 2007 and 2009 were considered as incident ( $n=27\ 211$ ). In a following analysis, the allocation of psoriasis treatment was examined among the incident cases. In total 24 411 patients were identified in the two-year follow-up (in PDR) after removing those with experience of conventional systemic- and biologic treatment prior to the psoriasis diagnosis. Patients diagnosed with other autoimmune disease with similar treatment as psoriasis were also excluded.

Paper II was based on 2294 biologic-naïve patients (i.e. never treated with biologics) extracted from PsoReg in October 2011.

Paper III used the same data as paper II. However, to be able to compare if any of PASI or DLQI were more strongly associated with the biologic initiation, both measures needed to be registered at the same visit. The study population in paper III consisted of 2216 patients who fulfilled that criterion.

The study population in paper IV was retrieved from PsoReg in May 2013 when 4045 patients suffering from moderate to severe psoriasis were registered.



**Figure 4.** *The sources that were used in the four studies and the size of the study population.*

## Ethical concerns

The project is approved by the Umeå Ethical Review Board, and the research was done in adherence to the declaration of Helsinki guidelines. The patients registered in PsoReg have given their informed consent to participate in the research conducted in this thesis.



## Definitions of variables

### *Treatments used in the studies*

The treatments used in this thesis were **topicals** (Emollients and protectives, Calcipotriol (with and without combinations) and Corticosteroids), **conventional systemics** (Methotrexate (oral and injections), Ciclosporin and Acitretin) and **biologics** (Etanercept, Infliximab, Ustekinumab and Adalimumab), see table 3.

### *Main outcomes*

#### **Paper I:**

*Incidence rates:* were calculated by the incident cases in the Swedish specialist care of psoriasis identified with a main diagnosis of psoriasis (ICD-10: L40) in the NPR between 2007 and 2009, with no history of a psoriasis diagnosis between 2001 and 2006.

*Conventional systemic treatments:* Retrieved from the PDR and included Methotrexate oral and injections (ATC: L01BA01 and L04AX03), Ciclosporin (ATC: L04AD01) and Acitretin (ATC: D05BB02).

*Biologic treatments:* The information about biologic treatments were retrieved from the PDR and included Etanercept (ATC: L04AB01), Infliximab (ATC: L04AB02), Ustekinumab (ATC: L04AC05) and Adalimumab (ATC: L04AB04). However, the PDR does not include drugs purchased by clinics that are subsequently administered as infusions at hospitals.

#### **Paper II-III:**

*Biologic treatments:* Information were retrieved from PsoReg and included Etanercept (ATC: L04AB01), Infliximab (L04AB02), Ustekinumab (L04AC05) and Adalimumab (L04AB04).

#### **Paper IV:**

For each body area, four different regressions were fitted, where the score of the plaque characteristics (*Erythema*, *Induration* and *Desquamation*) and degree of skin involvement (*Area*) were outcomes.

**Table 1.** Definition of the treatments that were included in this thesis.

\* In Paper I the registration of Infliximab was incomplete since the PDR does not include drugs received as infusions at hospital or purchased by clinics.

	<b>Treatment</b>	<b>ATC</b>	<b>Used in study</b>
<b>Topicals</b>	Emollients and protectives	D02	Paper I and Paper IV
	Calcipotriol	D05AX02	Paper and Paper IV
	Calcipotriol with combinations	D05AX52	Paper I and Paper IV
	Corticosteroids	D07	Paper I and Paper IV
<b>Conventional systemics</b>	Methotrexate (oral and injections)	L01BA01, L04AX03	Paper I and Paper IV
	Ciclosporin	L04AD01	Paper I and Paper IV
	Acitretin	D05BB02	Paper I and Paper IV
<b>Biologics</b>	Etanercept	L04AB01	Paper I to Paper IV
	Infliximab	L04AB02	Paper I to Paper IV*
	Ustekinumab	L04AC05	Paper I to Paper IV
	Adalimumab	L04AB04	Paper I to Paper IV

## Covariates

**Sex:** Used in all four papers as a dichotomous variable (man or woman).

**Age:** Established at baseline in all four papers. It was used as a continuous variable except in the statistical models in paper I and paper II. In paper III age was categorized into ten years' intervals; '10-20', '21-30', '31-40', '41-50', '51-60', '61-70' and '70 and above', while in paper II age was used as a continuous variable transposed to ten-year intervals.

**PASI:** Used as a measure of the psoriasis severity, retrieved from PsoReg. In paper II PASI was categorized by the 33<sup>rd</sup> and the 66<sup>th</sup> percentile at enrolment which created three groups used as a time-varying covariate.

**PASI and DLQI:** In paper III, a combination of PASI and DLQI was categorised using the thresholds of  $PASI \geq 10$  and  $DLQI \geq 10$  as suggested by the Swedish guidelines, see table 2. In this way four mutually exclusive groups could be created, with a combination of the physician's assessment of the psoriasis severity (PASI) and the patients' assessment of the disease impact Quality of Life (DLQI).

**Table 2.** The categorization of the combined PASI and DLQI.

	Low PASI (<10)	High PASI ( $\geq 10$ )
Low DLQI (<10)	↓PASI/↓ DLQI	↑PASI/↓ DLQI
High DLQI ( $\geq 10$ )	↓PASI/↑ DLQI	↑PASI/↑DLQI

**Psoriatic Arthritis (PsA):** Retrieved from PsoReg and was defined as a dichotomous variable, with either a present active psoriatic arthritis or not.

**Disease duration:** Estimated by patient-reported information of the disease onset from PsoReg.

**BMI:** Retrieved from PsoReg and used in paper II-paper IV. It was calculated by the height and weight according to:  $\frac{Weight(kg)}{Height^2(m)}$ . In paper II BMI was categorized according to the definition of the World Health Organization, where a BMI below 18.5 was classified as: underweight, 18.5-24.9 as normal range, 25.0-29.9 as overweight and 30 and above as obese.<sup>74</sup>

**Smoking:** Retrieved from PsoReg and was defined as a dichotomous variable for either a current non-smoker or smoker.

**Alcohol consumption:** Constructed by using the patient-reported information on frequency and the normal alcohol consumption for each occasion. A high intake of alcohol was defined as 12 standard glasses per week or more.

**Season of PASI assessment:** Used as variable in paper IV since season is influencing the disease activity. It was defined when the PASI assessment was carried out and then categorised into four different seasons: 'summer' (June, July and August), 'autumn' (September, October and November), 'winter' (December, January and February) and 'spring' (March, April and May).

**Treatments before index date:** By data from the PDR, the total quantity of topical treatment dispensed (in grams) one year before the diagnosis of psoriasis were calculated for each patient. The quantity was then categorised by the 85<sup>th</sup> percentile (1160 gram) into; 'none' (0 gram), 'less than' ( $\leq 1160$  grams) and 'more than' ( $> 1160$  grams).

The total quantity of topical treatment dispensed (in grams) one year before enrolment in PsoReg were calculated for a subgroup of the patients included in paper IV.

**Metropolitan Area:** Used in paper I and was defined according to Statistics Sweden, where the categorization of the municipalities into Metropolitan Areas is based on statistics for commuting and migration between the surrounding municipalities and the central municipality.<sup>75</sup> The municipality where the patients were registered at the time of psoriasis diagnosis was then used as their home municipality

**Education:** Used in paper I and was retrieved from LISA. The educational variable was aggregated into four different levels 'Primary school', 'Secondary school', 'University' and 'Missing information'. The highest education achieved before the index-date was used for each patient.

**Table 3.** Overview of the studies included in the thesis.

	Design	Analysis	Outcome	Covariates used in the analysis
<b>Paper I</b>	Population-based cohort study	- Cox proportional hazard regressions	Sex and age specific incidence rates (source NPR)  Time to initiation of conventional systemic- or biologic treatment (source PDR)	- Age (continuous in ten-year intervals) - Sex (dichotomous) - PsA (dichotomous) - Education (categorical) - Metropolitan Area (dichotomous) - Quantity of dispensed topical treatment (categorical)
<b>Paper II</b>	Register-based cohort study	- Cox proportional hazard regression	Time to initiation of biologic treatment (source PsoReg)	- PASI (categorical) - PsA (dichotomous) - Sex (dichotomous) - Age (categorical, ten years' intervals) - BMI (categorical)
<b>Paper III</b>	Register-based cohort study	- Logistic regression - Cox proportional hazard regression	Logistic regression: Patients initiated biologic treatment at enrolment vs. patients who remained on systemic treatment (source PsoReg)  Cox proportional hazard regression: Time to initiation of biologic treatment (source PsoReg)	- PASI and DLQI in combination (categorical) - Sex (dichotomous) - Age (continuous) - BMI (continuous) - PsA (dichotomous) - Smoking (dichotomous) - Alcohol consumption (dichotomous) - Disease duration (continues)
<b>Paper IV</b>	Cross-sectional	- Ordinal logistic regressions	Ordinal logistic regressions: The severity (Erythema, Induration and Desquamation) and the affected area in each body section (head, arms, trunk and legs) in PASI (source PsoReg)	- Sex (dichotomous) - Age (continuous) - BMI (continuous) - Disease duration (continuous) - PsA (dichotomous) - Smoking status (dichotomous) - Season (categorical)

## ***Statistical analysis***

### *Incidence rate*

The incidence is a measure of the number of events in a given population within a defined period of time.<sup>76</sup> The incidence rates were calculated by:

$$\frac{\text{Number of new cases}}{\text{Person} - \text{Time at Risk in years}}$$

, where the numerator is the count of new cases, and the denominator is calculated by the amount of time each person is contributing with (in years) in the defined period. The ratio was multiplied by 100,000 to obtain incidence rates per 100,000 person years.

### *Logistic regression*

Logistic regression is useful when the dependent variable only has two possible outcomes, usually denoted as 1 or 0. In multivariable logistic regression it is possible to adjust for potential confounders by including more than one predictors.

### *Ordinal logistic regression*

Ordinal logistic regression is an extension of logistic regression models which allows several outcome categories.<sup>77</sup> In paper IV, the assumption of proportional odds were tested by computing the odds ratios in logistic regressions to verify that the estimates did not vary between the ordinal logistic regressions and the logistic regressions.

### *Cox proportional hazard regression*

Cox proportional hazard regression is a method within survival analysis and is one of the most widely used methods to analyse the time to an event. The assumption of proportional hazard were checked graphically (in paper I-III) by Kaplan-Meier curves and were found to be valid.

**Paper I:** The incidence of psoriasis in the Swedish specialist care was presented by frequencies and sex-and age-specific incidence rates per 100,000 person-year between 2007 and 2009. In the treatment allocation analysis time to initiating conventional systemic- or biologic treatment was analysed by Cox proportional hazard regressions.

**Paper II-Paper III:** The time to initiation of biologic treatment was analyzed by Cox proportional hazard regression in both paper II and III. Days until treatment was calculated from enrolment in PsoReg until the first occurrence of death, end of study or initiation of biologic treatment. This allowed the patients start and end the study at different points, hence contribute with different amounts of time into the study. In Paper II the assessment of PASI, and in paper II the combination of PASI and DLQI, were assumed to be constant between the visits.

In paper III the patients who initiated a biologic treatment in relation to enrolment (defined as start of treatment within 7 days of enrolment) were analyzed with a logistic regression, while the patients who did not start a biologic treatment at enrolment were analyzed by a Cox proportional hazard regression.

**Paper IV** At enrolment the differences in the PASI, and the PASI elements were analyzed by Mann-Whitney-Wilcoxon tests and multivariable ordinal logistic regressions. Four different ordinal regressions were fitted for each body section (head, arms, trunk and legs) with the outcomes; Degree of skin involvement (Area) and plaque characteristics (Erythema, Induration and Desquamation).

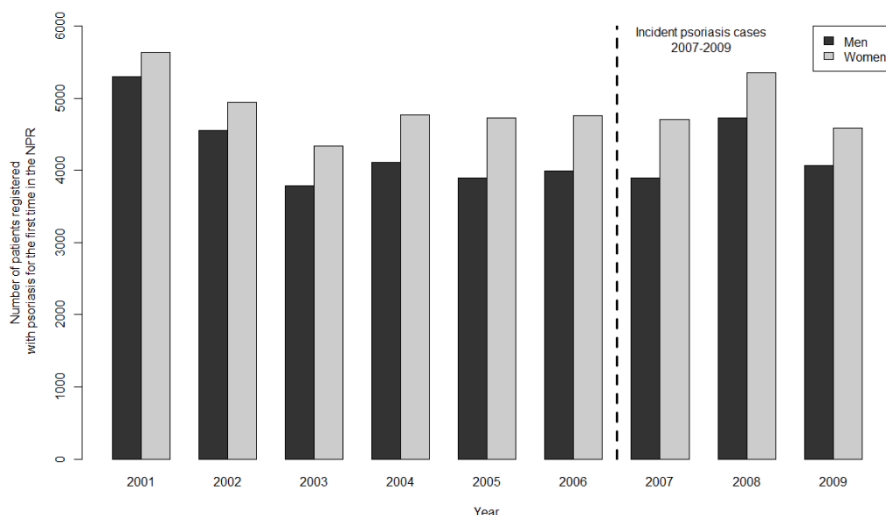
To be able to test for differences in PASI between men and women the non-parametric statistical Wilcoxon Two-Sample test had to be used because of the non-normal distribution of the measure. Differences in proportions were tested by Chi-square tests, while normally distributed continuous variables were tested by Student's t-test. To test differences in medians Wilcoxon median two-sample test was used. In all papers the statistical software that was used for analyses was the Statistical Analysis System (SAS) version 9.3 (SAS Institute Inc., Cary, NC, USA), while graphics was created both in SAS and in the statistical program R (3.2.2). Throughout the studies, p-values below 0.05, and hazard ratios (HR) as well as odds ratios (OR) with 95% confidence interval were considered as statistical significant.

# Main results

## Paper I

### *Incidence of psoriasis in Swedish specialist care*

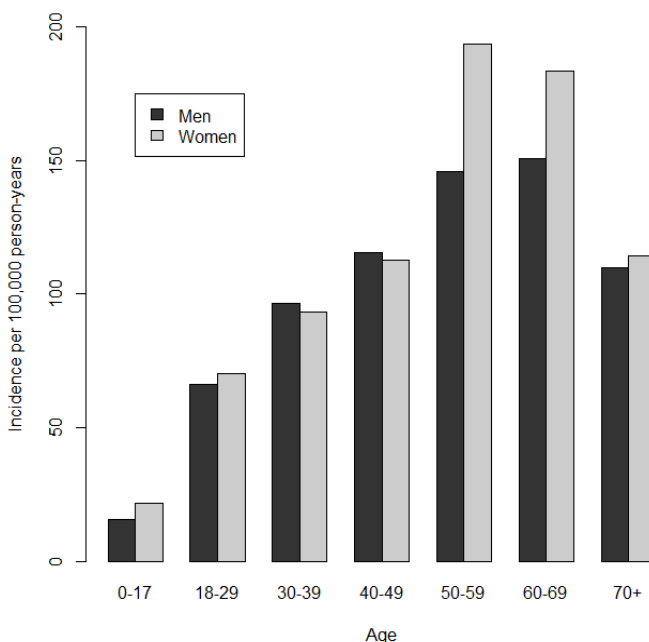
Between the years 2001 and 2009, 82 124 patients were identified with a main diagnosis of psoriasis (ICD 10-code L40) in the NPR. The 54 913 patients with a main diagnosis between the years 2001 and 2006 were defined as prevalent psoriasis cases. The remaining 27 211 patients diagnosed with psoriasis for the first time between 2007 and 2009 were considered to be incident in the Swedish specialist care of psoriasis (women: 53.6% and men: 46.4%), see figure 5. This corresponds to an annual average of 9070 new psoriasis patients in Swedish specialist care.



**Figure 5.** The number of men and women registered with a main diagnosis of psoriasis in NPR for the first time between 2001 and 2009. The patients diagnosed with psoriasis between 2007 and 2009 were considered to be incident in Swedish specialist care of psoriasis.

The estimated incidence of psoriasis in specialist care between 2007 and 2009 was 98 per 100,000 person-years. It increased by age from 18.6 in the age 0-17 up to 169.6 among the patients aged 50-59. In the sex- and age-specific incidence it was shown that between the ages 50-69, women (ages 50-59: 193.6 and ages 60-69: 183.5) had a higher incidence than men (ages 50-59: 145.9 and ages 60-69: 150.8), see fig 6.





**Figure 6.** The incidence per 100,000 person-years in Swedish specialist care of psoriasis between 2007 and 2009.

### **Treatment allocation**

27 211 patients were defined as incident patients in Swedish specialist care of psoriasis. Out of these there were 24 411 patients, with no history of a systemic- or biologic psoriasis treatment, or with other autoimmune diseases with treatments similar to psoriasis. The study population constituted of these 24 411 patients whose had no previous experience of systemic- or biologic treatment in the analysis of treatment allocation among the incident cases in Swedish specialist care.

In the two-year follow-up in the PDR men were more likely to conventional systemic treatments ( $p<.001$ ) compared to women, but no difference were found between men and women in the initiation of biologic treatment ( $p=0.186$ ). A diagnosis of PsA was an important factor in starting a conventional systemic treatment ( $p<.001$ ), and starting a biological treatment ( $p<.001$ ). Older psoriasis patients were more likely to initiate conventional systemic treatment ( $p=0.002$ ), while younger patients had a higher chance of biologic treatment ( $p<.001$ ). The higher dispensed quantity of topical treatment the year before, the more likely the patients were to initiate a

biological treatment ('1-1160gram':  $p=0.178$ , 'more than 1160gram':  $p<.001$  compared to the reference 'no topical treatment') or a conventional systemic treatment ('1-1160gram':  $p<.001$ , 'more than 1160gram':  $p<.001$  compared to the reference 'no topical treatment').

To live in a Metropolitan Area at the date of the psoriasis diagnosis did not have any relevance regarding the initiation of a conventional systemic treatment ( $p=0.622$ ), however it showed to increase the probability to initiate a biologic treatment ( $p<.001$ ). A University degree increased the chances of initiating a biological treatment during the two-year follow-up (HR 1.56 (1.00-2.44,  $p=0.050$ ), but the opposite was seen when the conventional systemic treatment was the outcome (HR 0.77, 0.69-0.87,  $p<.001$ ).

**Table 4.** The hazard ratios (HR) computed by the Cox proportional hazard regressions with the corresponding 95% confidence interval.

		Conventional systemic treatment, n=2582			Biological treatment, n=197		
Sex		n	HR	95% CI	n	HR	95% CI
Reference	Women	1247	0.80	0.74-0.87	99	0.82	0.63-1.10
Men							
Educational level							
Reference	Secondary school	1268	1.00	0.91-1.10	96	1.41	0.93-2.14
Primary school	University	532	0.77	0.69-0.87	60	1.56	1.00-2.44
Living Area							
Reference	Metropolitan Area	789	0.98	0.90-1.07	94	1.88	1.42-2.50
Non-Metropolitan Area							
Age	Age in years	2528	1.04	1.01-1.07	197	0.76	0.69-0.84
PsA							
Reference	Diagnosed with PsA	1190	8.14	7.51-8.83	145	21.11	15.16-29.40
No PsA							
Quantity topical treatment							
Reference	1-1160 gram	1381	1.20	1.08-1.32	83	0.80	0.58-1.11
No topical treatment	More than 1160 gram	558	2.15	1.91-2.42	41	2.18	1.47-3.23

## **Paper II**

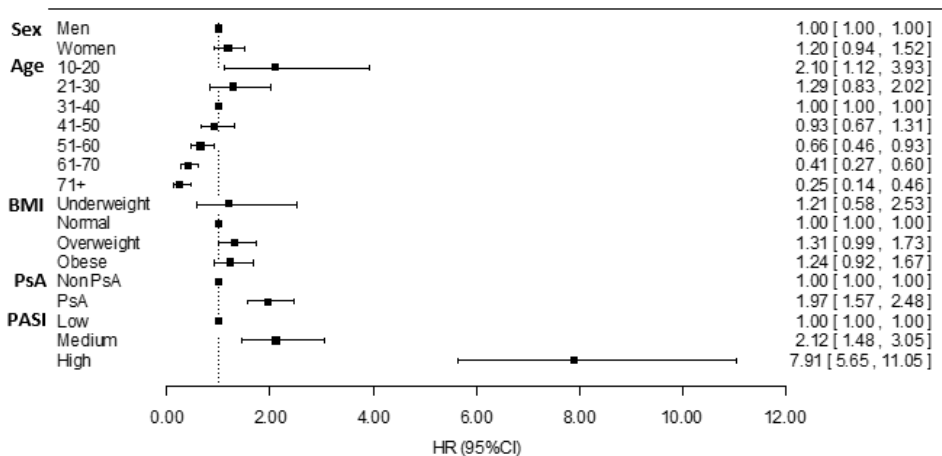
### ***At enrolment***

In the data extraction from PsoReg made in October 2011, n=2294 patients was identified as biologic naïve patients (had not been treated with a biologic treatment before the enrolment in the register). At enrolment men (mean: 52.2 years) were younger than women (mean: 56.0),  $p < 0.001$ . Women had a lower PASI (5.1) compared to men (7.3),  $p < 0.001$ . Men had a higher median PASI than women in all age groups. During the follow-up the PASI-score decreased but men had still a higher median PASI compared to women. Furthermore, men had on average a higher BMI (27.8) than women (27.1),  $p = 0.002$ . No statistical difference could be found between women and men in obesity ( $\text{BMI} \geq 30$ ) ( $p = 0.48$ ) or disease duration ( $p = 0.09$ ) at the enrolment. The categorization of the variable PASI by the 33<sup>rd</sup> and the 66<sup>th</sup> percentiles created the threshold for three groups with different levels of severity; (0.0-4.0), medium (4.1-9.3) and high (9.4 and above).

### ***Time to biological initiation***

During the follow-up 343 patients (women: 13.6% and men: 15.9%) initiated a biologic therapy and 1951 patients remained on conventional treatment. At the time of biologic initiation no difference were found between men and women regarding age ( $p = 0.13$ ), time of follow-up ( $p = 0.48$ ), disease duration ( $p = 0.09$ ) and BMI ( $p = 0.31$ ). However, women (median: 9.8, IQR: 4.8–14.6) had lower PASI than men (median: 12.3, IQR: 7.2–18.4),  $p = 0.001$ .

The results from the Cox proportional hazard regression model showed that patient located in the group of medium PASI (HR: 2.12 (CI 95%: 1.48-3.05)) and high PASI (OR: 7.91 (CI 95%: 5.65-11.05)) were more likely to initiate a biologic treatment compared to the reference low PASI. Patients with PsA (HR: 1.97 (1.57-2.48)) also had a greater chance of initiating a biologic treatment. Younger patients were also more likely to be treated with a biologic treatment; The HR for age group 10–20 years was 2.10 (CI 95% 1.12-3.93), age group 21–30 1.29 (CI 95% 0.83-2.02), age group 41–50 0.93 (CI 95% 0.67-1.31), age group 51–60 0.66 (CI 95% 0.46-0.93), age group 61–70 0.25 (CI 95% 0.14-0.46), age group 71+ 0.25 (CI 95% 0.14-0.46), compared to the reference age group of 31–40. However, BMI and sex showed to be not significant in the initiation of a biologic treatment in PsoReg, see fig 7.



**Figure 7.** Hazard ratios with corresponding 95% CI from the Cox proportional hazard regression model in paper II.

## Paper III

### At enrolment

Using data extracted from PsoReg in October 2011, out of 2294 biologic-naïve patients there were in total 2216 patients who had both a PASI and a DLQI registered at least one visit. The PASI and DLQI at each visit was categorized by the thresholds  $\text{PASI} \geq 10$  and  $\text{DLQI} \geq 10$ , and four mutually exclusive groups could be categorized into a time-varying variable, see table 2. At enrolment most of the patients were located in the group of  $\downarrow\text{PASI}/\downarrow\text{DLQI}$  (54.3%) followed by  $\uparrow\text{PASI}/\uparrow\text{DLQI}$  (15.9%),  $\downarrow\text{PASI}/\uparrow\text{DLQI}$  (15.5%) and  $\uparrow\text{PASI}/\downarrow\text{DLQI}$  (14.4%). Most of the women were classified into the  $\downarrow\text{PASI}/\uparrow\text{DLQI}$  (57.1%), while men were mostly categorized into the group  $\uparrow\text{PASI}/\downarrow\text{DLQI}$  (76.1%) at the time of inclusion.

### ***Time to biological initiation***

There were 159 patients who initiated a biologic treatment within 7 days of the enrolment (analyzed by Logistic regression) and 169 patients did so during the follow-up (analyzed by Cox proportional hazard regression). After adjusting for sex, age, BMI, PsA, smoking, alcohol consumption and disease duration the results from the logistic regression and the Cox proportional hazard regression were quite similar. The group which had the highest chance of initiating a biologic treatment were those with ↑PASI/↑DLQI followed by ↑PASI/↓DLQI, ↓PASI/↑DLQI compared to the reference group ↓PASI and ↓DLQI, see table 4. It was found that even the patients in ↑PASI/↓DLQI had higher chance to initiate a biologic treatment compared to the patients in the group ↓PASI/↑DLQI both in the logistic regression ( $p < 0.001$ ), as well in the Cox proportional hazard regression ( $p < 0.001$ ).

**Table 5.** *The odds ratios (OR) from the logistic regression and the hazard ratios (HR) from the Cox proportional hazard regression for the combined variable of PASI and DLQI, adjusted for sex, age, BMI, PsA, smoking, alcohol consumption and disease duration with the corresponding 95% Confidence interval.*

	<b>OR</b>	<b>95% CI</b>	<b>HR</b>	<b>95% CI</b>
<b>↓PASI and ↓DLQI</b>	Reference	Reference	Reference	Reference
<b>↓PASI and ↑DLQI</b>	2.32	1.14-4.70	1.55	0.95-2.53
<b>↑PASI and ↓DLQI</b>	8.60	4.94-14.95	5.14	3.45-7.68
<b>↑PASI and ↑DLQI</b>	11.48	6.74-19.55	5.22	3.31-8.24

## **Paper IV**

In paper II it had previously been observed that women had a lower disease severity, measured by PASI, than men. In order to analyse if the difference could be explained by one or several specific elements in the PASI measurement, all patients (n=4045 patients) registered in May 2013 were used.

### ***At enrolment***

Of 4045 patients in PsoReg, 59.1% were men and 40.9% were women. As in the previous data extraction women showed to have a lower median PASI (5.5, IQR 2.7-10) than men (7.4, IQR: 3.6-12.5),  $p < 0.001$ . Men had a higher BMI compared to women ( $p = 0.003$ ). Women had a larger proportion of an active PsA ( $p = 0.015$ ), were older ( $p < 0.001$ ), smoked more frequently ( $p = 0.003$ ), compared to men. The disease duration was longer for women compared to men ( $p = 0.002$ ). There were no seasonal difference between men and women when looking at what time of the year the PASI scores were measured ( $p = 0.296$ ).

### ***Treatments one year before enrolment in PsoReg***

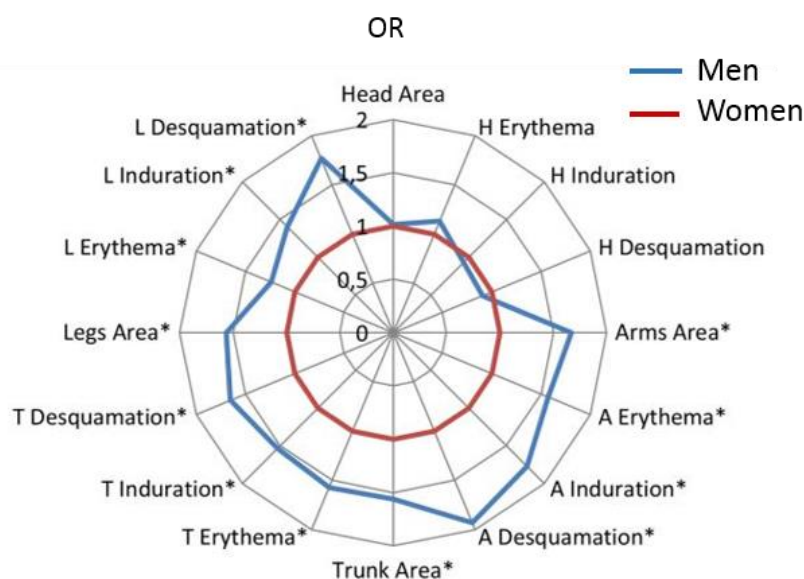
For a subset (n=3125) of the study population, it was possible to estimate the quantity of topical- and conventional systemic treatments (in the PDR) one year before the enrolment in PsoReg. A slightly higher proportion of the women (92.8%) had at least on prescription of topical treatment compared to men (89.8%),  $p = 0.004$ . However, a higher proportion of men (16.7%) had a filled a prescription of a biological treatment compared to women (13.1%),  $p = 0.004$ . No difference was found in the proportion of men and women who had at least one prescription of a conventional systemic treatment.

Women had a higher quantity of prescribed emollients (1,400 grams) compared to men (1,180 grams),  $p = 0.038$ . No difference was found in the prescription of calcipotriol (calcipotriol in combination with corticosteroids or corticosteroids), since men and women were dispensed the same median total quantity in grams,  $p = 0.965$ .

## Multiple ordinal logistic regressions

The results from the multiple ordinal logistic regressions were consistent with the univariate Mann-Whitney-Wilcoxon tests. Men had in general a higher scores in all plaque characteristics (Erythema, Induration and Desquamation) and the degree of skin involvement (Area) in the body regions trunk, arms and legs, while no difference could be identified on the head.

The biggest differences between men and women were observed in the induration at the *arms*; OR: 1.77, CI 95%: 1.52-2.06 and *desquamation*; legs (OR: 1.77, CI 95%: 1.53-2.05), trunk (OR: 1.65, CI 95%: 1.43-1.92), and (arms (OR: 1.93, CI 95%: 1.66-2.24), see fig 8.



**Figure 8.** The odds ratios from the ordinal logistic regressions for the plaque characteristics (Erythema, Induration and Desquamation) and the degree of skin involvement (Area) in each body region (head, arms, trunk and legs) presented in a radar chart. Odds ratios for men adjusted by age, BMI, disease duration, PsA, smoking status and season. Women are used as reference (=1) and \* indicates a statistical significant OR.

# Discussion

The studies in this thesis are all limited to patients with psoriasis treated in specialist care. In paper I the study population was based on patients with visits in specialist, out-patient care registered in the NPR. The study populations in paper II-IV were selected from PsoReg where the inclusion criteria is a diagnosis of moderate to severe psoriasis and treatment with, or consideration of treatment with, conventional systemic- or biologic treatment by a specialist in dermatology.

## General findings

### *Paper I*

Due to probable difficulties in documenting and finding truly new psoriasis cases there are only a few studies on the incidence of psoriasis available.<sup>78</sup> The results from this study are limited to patients diagnosed with psoriasis for the first time in specialist care during the years 2007 to 2009. The first diagnosis of psoriasis ever is probably given in primary care, a level of care that is not available in the Swedish Health Care registers. However, the National Healthcare Registers make it possible to follow the entire Swedish population in all their visits to specialist health care over time, and thereby we can - with a fairly good precision - identify incident cases of psoriasis requiring specialist care, at least in the eyes of the referring physician. A weakness in the study is that the patients identified as an “incident” psoriasis cases between 2007 and 2009 may well have been diagnosed with this condition in specialist care before 2001 (before start of our observation period and the first year when diagnoses in out-patient care were registered). However, this seems quite unlikely since it would mean that a return visit should not have been carried out within a five year period (2001-2006). This scenario – that no return visit to a specialist has been necessary for six years – can be indicative of a long period of remission of the disease, when treatments prescribed by primary care physicians have sufficed. This would mean that the “incident” population we identify, is at least “incident” regarding requirement of specialist care for the past six years. Further, in the analysis of treatment allocation, we refine this population even more by not including those who have been prescribed “specialist treatment”, i.e. conventional systemics or biologics, since start of the PDR in July 2005.

Our definition of newly diagnosed psoriasis patients in specialist care allowed sex-and age specific incidences per 100,000 person-years to be estimated. During the period 2007 to 2009, the general incidence were estimated to 98



cases per 100,000 person-years. Among the incident cases there was a higher percentage of women (53.6%) compared to men (46.4%). We have not been able to find a comparable study, since the available incidence studies are designed exclusively using the onset of psoriasis. Several of these studies have been able to identify two peaks in the onset of psoriasis, between the ages 30 to 39 and a second between the ages between 50 and 69.<sup>36,79</sup> This pattern was not observed in our study, instead the incidence rates showed to continually increase with age.

Patients with a University degree (compared to patients with Primary school as highest achieved educational level) as well as those living in a Metropolitan Area (compared to non-Metropolitan Area) were more likely to initiate a biologic treatment. These results are in line with another study of biologic use.<sup>80</sup> They found, as we did, that residents in urban areas were more likely to receive biologic treatment compared to those residing in non-urban areas. Furthermore, a previous study has shown that highly educated have quicker access to new drugs.<sup>81</sup>

## ***Paper II and IV***

The major part of the patients enrolled in PsoReg are men (paper II: 59.2%, paper III: 59.5% and paper IV: 59.1%). This preponderance of men have also been observed in other European registries for systemic psoriasis treatment, ranging from 68% in the Netherlands to 60% in Germany.<sup>82</sup> Previous studies have identified men receiving UV treatments and conventional systemic treatment in greater extent compared to women, this despite the fact that women made more visits at the clinics.<sup>83,84</sup> Furthermore, several studies of biologics have shown a predominance of men<sup>85,86</sup>, which have been suggested to be due to a more severe psoriasis.<sup>87</sup> This raised the question if any sex difference could be identified in the initiation of biological treatments in PsoReg. The strongest advantage in performing this study with data from PsoReg was the availability of a measure of severity of psoriasis, the PASI. At enrolment, men had a higher PASI compared to women (paper II-paper IV), and that men had a higher score in all the specific elements in the PASI measure except in the head (paper IV). During follow-up, the PASI scores decreased over time for both men and women, but men had still a higher median PASI score than women in each time period (paper II). The results from the Cox proportional hazard regression showed that the most important factors in the decision to initiate a biologic treatment were PASI, PsA and age, while sex and BMI were not statistically significant factors. The results from the ordinal logistic regressions did not show any specific difference in the clinical severity (Erythema, Induration and Desquamation) or degree of skin involvement, but a generally more severe psoriasis in men (except on the

head); this did not provide any distinguishing characterisation as to why men have a more severe psoriasis in PsoReg.

By linking PsoReg with PDR it was possible to analyse the treatments by prescription during the year before enrolment. A higher proportion of men had filled at least one prescription of biologic treatment compared to women, while no sex difference were found among those who had filled at least one prescription of conventional systemic treatment. Furthermore, women showed to have a higher total quantity of prescribed emollients compared to men (paper IV). These differences regarding treatment prior to enrolment, are probably not large enough to explain the difference presented in PASI, since they were quite small in absolute numbers, even if they were statistically significant.

A possible explanation of a higher PASI score in men compared to women, could be due to men seeking care at a later stage than women, which could increase the severity of psoriasis by lack of proper treatment. This scenario is not unreasonable, as several studies have shown that men seek medical care later than women.<sup>88,89</sup>

### ***Paper III***

In accordance with the treatment guidelines, to initiate a biologic treatment the criteria  $PASI \geq 10$  and  $DLQI \geq 10$  should be fulfilled. By combining high and low PASI with high and low DLQI and use the four combinations as time-varying variables, it was possible to explore its relation to the start of biologic treatment. It was found that the highest proportion of women in PsoReg were classified to have high disease impact on the HRQoL ( $DLQI \geq 10$ ) but low on the disease activity ( $PASI < 10$ ), while men had the opposite status, high on the disease activity ( $PASI \geq 10$ ) but low disease impact on the HRQoL ( $DLQI < 10$ ).

The patients with high the disease activity ( $PASI \geq 10$ ) and high disease impact on the HRQoL ( $DLQI \geq 10$ ) were most likely to initiate a biologic. Additionally, the patients with high the disease activity ( $PASI \geq 10$ ) but low disease impact on the HRQoL ( $DLQI < 10$ ) were more likely to initiate a biologic treatment compared to high disease impact on the HRQoL ( $DLQI \geq 10$ ) but low the disease activity ( $PASI < 10$ ). Hence, the decision to initiate biologic treatment is more strongly associated with PASI than with DLQI.

PASI and DLQI are two measures assessing different aspects of the psoriasis severity, where DLQI are more associated to the patients suffering and socio-economic costs.<sup>62</sup> As the PASI was more associated to the start of biologic treatment, it means that the relevance of the DLQI may be underestimated in

clinical practice. In a study of patients suffering from rheumatoid arthritis, it was found that women initiated biologic treatments at the same level as men in the clinician's assessment of the disease activity, but at a higher level of self-reported subjective disease activity than men.<sup>90</sup> Furthermore, other studies (one based on data from PsoReg) have showed that women had a significantly higher score on DLQI compare to men.<sup>91-93</sup> These results are in line with our findings; that patients' subjective disease activity might be more or less disregarded, where the relevance of DLQI may be underutilized, and thus contrary to the Swedish treatment guidelines.

### ***Methodological challenges***

In register-based studies a limitation is the insecurity uncertainty if whether the selected patients truly are reflecting the population of interest, i.e. the generalizability must always be considered. Approximately 65% of the patients with a biologic treatment and about 40% of the with conventional systemic treated patients treatment are estimated to be included in PsoReg. If there is a process of selection selecting a special set of patients to problem in PsoReg, the 65% of the biologically treated patients in PsoReg would not correspond (regarding relevant patient characteristics) with the remaining patients (35%) with moderate to severe psoriasis treated with biologic treatments, but outside of the register. To assess whether the population in PsoReg differs from the psoriasis-population outside the register, it is necessary to perform a specific study of differences in the patient characteristics. However, this was not within the scope of this thesis.

The validity of the PDR is considered to be high, and in contrast to other registers it contains information about dispensed medication and not only the prescribed medication. However, there is a risk that the patients does not take the medication according to the instructions (or at all), which might a possible source of error. In paper I, the patients with a main diagnosis of psoriasis in the NPR between 2007 and 2009 (and no history of psoriasis between 2001 and 2006) were considered to be incident psoriasis patients in the Swedish specialist care. The validity in NPR is considered to be regarded high, and it is likely that we managed to capture the greater part of those who received a main diagnosis of psoriasis for the first time in specialist care during this period. However, private clinics that does not report to NPR could cause an underestimation of the incidence.

High validity and high reliability are important if the assessment tools such as PASI and DLQI should be regarded as providing data of good quality. High reliability should in repeated trials yield consistent results under the same conditions, and high validity means that assessments truly estimate what it

intends to estimate. The measures used in these studies, PASI and DLQI focuses on different aspects of the assessment of the disease impact on the patient <sup>62,94</sup>. DLQI is a dermatology specific HRQoL focusing on how the quality of life is affected by the skin disease and it has been shown to be a valid and reliable measure in psoriasis.<sup>93,95-97</sup> PASI is the most widely used measure and has been considered to be the gold standard to assess psoriasis severity.<sup>98,99</sup> The validity and reliability in PASI are considered as high.<sup>53,100</sup>

Even if DLQI is considered to be the standard measures to estimate the HRQoL in dermatology, some weaknesses had been discussed.<sup>97,101,102</sup> Not only the HRQoL impairment is affecting the response in the DLQI, but also external factors such as sex, age and country of birth.<sup>103,104</sup> Weaknesses found in the PASI measure are; it is not correlated with QoL, it is affected by humidity and recent use of emollients.<sup>94,105,106</sup>

In most drug trials there are some time without active treatment to let the effects from the previous treatments to be eliminated from the body. Once a new therapy is initiated, the effect could with certainty be determined to be due to the new treatment. However, the patients in PsoReg have no wash out period before the enrolment. This makes it important to try to adjust for any differences at baseline between the groups that you want to compare, for example by looking at previous treatments, both in PsoReg and in PDR.

The variables used in the studies of this thesis all have low percentages of missing data. However, one important part in the decision to start a treatment, is the dialogue between the clinician and the patient. This dialogue is not documented or measured in the register, and it is not implausible that there are e.g. gender, as well as socio-economic differences in the care seeking behaviour. Furthermore, an analysis was made of the patients that were prescribed any of the two psoriasis specific treatments calcipotriol (without or with corticosteroid) and Ustekinumab. It was shown that between the years 2010 and 2014 more men (60.4%) than women had filled at least one prescription of Ustekinumab. Further, between 2006 and 2014 the proportion of men that filled at least one prescription of calcipotriol was 56.7%, see paper IV. This indicates that the higher proportion of men registered in PsoReg may reflect also the population outside the register.

## ***General discussion***

Observational studies are valuable sources to monitor the treatment allocation and factors related to the initiation of treatments in the real world process of decision making. There are many factors that need be taken into consideration when initiating a treatment. One crucial factor in the decision

process is the patient's severity of disease. PsoReg provides the most frequently used measure to assess the disease activity, PASI.

Women who are planning pregnancy or who are pregnant are recommended to avoid conventional systemic treatment.<sup>107,108</sup> Regarding biologic treatment, there is a limited number of studies on the safety for women in child bearing age. However, European guidelines and the British Association of Dermatologists' are recommend avoiding treatment with biologics.<sup>44,109</sup> This could also be a possible explanation to why women are older when entering the specialist care of psoriasis. Another suggestion could be the lowered estrogen levels in women above 50. Studies have shown that the level of sex hormones has a positive impact in the disease severity of psoriasis.<sup>110-112</sup>

The possibility to link Swedish Health Care Registers with the Swedish Quality Registers provides a unique environment to analyse allocation of treatments in combination with tools measuring the severity of the disease such as PASI and PROM:s like DLQI.<sup>113</sup> An advantage of register-based studies is that over time, the information in the registers will increase and the follow-up will be become longer. This also implies that the registries should be considered as a living data source.

It is likely that new biologics and also less expensive biosimilars will be available for patients with moderate to severe psoriasis in a near future. The introduction of new treatment options will probably result in lower treatment costs and broader use of biologic treatment.<sup>114-116</sup> As a result, the psoriasis population as it has been defined in this thesis will not look the same in the future, both when it comes to demographic composition or the drug use.

Therefore, it is crucial that future longitudinal studies on psoriasis treatment always take the calendar time into careful consideration.

### ***Future perspectives***

The studies in this thesis have identified determinants associated with the initiation of systemic psoriasis treatments, and an unequal assignment of treatments seems present. The start of a treatment should be guided by the need for care, and not be influenced by either sex, residence or education. Register-based studies are an important tool for monitoring the treatment allocation in the Swedish clinical practice. Since registers are constantly in change, and with the development of new drugs, more studies are needed to explore the determinants associated to the decision of initiating systemic treatments. When examining factors related to the initiation of such treatments it is essential to take the severity of the disease into consideration.

In the future, the history of dispensed topical treatment at baseline may be used as a proxy for disease severity, however more studies are needed to evaluate the validity of this estimation.

## ***Conclusions***

By linking Swedish Health Care Registers and Swedish Quality Registers it is possible to retrieve important characteristics related to the initiation of treatments of a population suffering from a specific disease in the real world clinical practice.

- Between the years 2007 and 2009 there about 9000 new psoriasis patients entered specialist care in Sweden each year, corresponding to an incidence of 98 patients per 100,000 person-years.
- Psoriasis patients who lived in a Metropolitan Area, had a University degree or a diagnosis of Psoriasis Arthropathy were more likely start a biologic treatment during the two-year follow-up.
- A high quantity of dispensed topical treatment the year before the first psoriasis diagnosis increased the chances of initiating a systemic or biologic treatment.
- The severity of the psoriasis (assessed by PASI), an on-going Psoriasis Arthropathy and age were associated with an initiation of a biologic treatment, whereas sex and BMI were not.
- The initiation of biologic treatment was more strongly associated with PASI than with DLQI.
- Women, at enrolment in PsoReg, had in general lower scores than men in all plaque characteristics (Erythema, Induration and Desquamation) and the degree of skin involvement (Area) in the body regions trunk, arms and legs, while no difference could be identified on the head.

These studies indicate that there are inequalities in the assignment of systemic psoriasis treatments (especially in biologic treatment). We have been able to show that the initiation of biologic treatment are associated with education and residency in a Metropolitan Area, whereas the patients' subjective disease activity (DLQI) might be more or less disregarded, and thus contrary to the Swedish treatment guidelines. Since the allocation of treatment should depend on the need of care it is important that future studies continue analysing possible factors that influence the initiation of treatment in the clinical practice in Sweden.

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