Burden of disease in psoriasis and psoriatic arthritis. Occurrence, healthcare use, costs and health outcomes.

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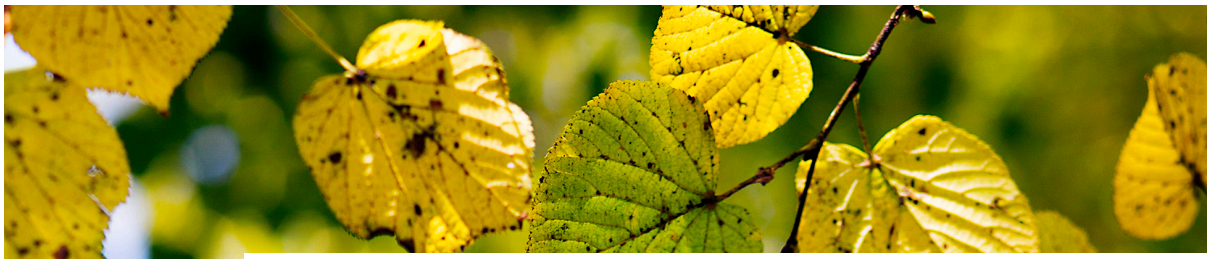

Burden of disease in psoriasis and psoriatic arthritis

Occurrence, healthcare use, costs and health outcomes

SOFIA LÖFVENDAHL | FACULTY OF MEDICINE | LUND UNIVERSITY

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Sofia Löfvendahl

LUNDS UNIVERSITET

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Burden of disease in psoriasis and psoriatic arthritis. Occurrence, healthcare use, costs and health outcomes

Abstract

Psoriasis (PSO) and psoriatic arthritis (PsA) are two related chronic inflammatory diseases. A proportion of people with PSO also develop PsA. PSO and PsA seem to have multiple impacts; from the health and well-being of the individual; to the need for healthcare resources for disease management; to the loss of productivity. Compared with other chronic diseases, such as heart disease and diabetes, population-based observational healthcare research on PSO and PsA is limited.

The overall aim of this thesis was to study the impact of PSO and PsA in terms of occurrence, costs, healthcare use and patient-reported outcomes (PROs), from a population-based perspective. The included studies used data related to residents in the Skåne region, and the study populations were identified in the Skåne Healthcare register (SHR). Information was based mainly on population-based registers but also on surveys and medical records.

The point prevalence of physician-diagnosed PSO with or without PsA in the Skåne region by the end of 2010 was1.2%, corresponding to 12,958 diagnosed individuals. The prevalence for PSO alone and PSO with PsA was 1.0% and 0.2% respectively. The ICD-10 diagnostic codes registered for PSO and PsA in the SHR showed overall good accuracy when compared to information in medical records. The annualized mean societal cost for PSO patients with PsA was 97% higher compared with PSO alone patients (€17,600 vs. €8,900). Only a minor fraction of the costs was identified as attributable to PSO and PsA specifically, indicating increased comorbidity in these patients.

Analyses on healthcare use among PSO and PsA patients, and population-based matched referents, indicated remaining disparities in the socioeconomic pattern of healthcare use, especially related to income. The effect was less accentuated for PSO and PsA compared to referents. Regarding PROs, we showed that, in a cohort of PsA patients, continuous and never users of biological drugs, which were the majority of the patients, reported better PROs and lower societal costs compare to irregular users of biological drugs.

This thesis contributes with knowledge on the impact of PSO and PsA from different perspectives, that can be useful both for researchers and policy makers. In addition, the work also adds information on data quality, and methods for prevalence and cost calculations using register-based data.

Key words

Psoriasis, Psoriatic Arthritis, Occurrence, Costs, Healthcare use, Disparities, Outcomes

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Skäms inte för att du är människa, var stolt!

Inne i dig öppnar sig valv bakom valv oändligt.

Du blir aldrig färdig, och det är som det skall.

TOMAS TRANSTRÖMER

(Ur Romanska Bågar)

Contents

Abstract

Psoriasis (PSO) and psoriatic arthritis (PsA) are two related chronic inflammatory diseases. A proportion of people with PSO also develop PsA. PSO and PsA seem to have multiple impacts; from the health and well-being of the individual; to the need for healthcare resources for disease management; to the loss of productivity. Compared with other chronic diseases, such as heart disease and diabetes, population-based observational healthcare research on PSO and PsA is limited.

The overall aim of this thesis was to study the impact of PSO and PsA in terms of occurrence, costs, healthcare use, and patient-reported outcomes (PROs), from a population-based perspective. The included studies used data related to residents in the Skåne region, and the study populations were identified in the Skåne Healthcare register (SHR). Information was based mainly on population-based registers but also on surveys and medical records.

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Svensk sammanfattning

Psoriasis (PSO) och psoriasisartrit (PsA) är två kroniska inflammatoriska sjukdomar som är relaterade till varandra på så sätt att en andel av dem som har PSO också utvecklar PsA. PSO drabbar främst huden och naglarna, medan PsA, förutom att påverka huden också visar sig som smärta, stelhelhet och svullnad i och runt de perifera lederna samt i ryggen och bäckenet. Länge betraktades PSO och PsA som relativt milda sjukdomar och med god prognos, men senare forskningar har visat att sjukdomarna har betydande inverkan på individen i form av bland annat försämrad funktion och minskad hälsorelaterad livskvalitet. Samhället i stort påverkas också genom behov av hälso- och sjukvårdsresurser samt produktivitetsförluster.

Jämfört med andra kroniska sjukdomar, såsom hjärtsjukdomar och diabetes, finns det tämligen lite dokumentation om PSO och PsA ur ett befolkningsperspektiv. När det gäller Sverige så finns det, så vitt vi vet, inte någon nyligen publicerad information om förekomsten av PSO och PsA samt om socioekonomiska skillnader i utnyttjandet av hälso- och sjukvården. Det finns mer vetenskaplig dokumentation om kostnader och om patienternas hälsostatus, men till stor del bygger denna forskning på mindre, klinikbaserade patientmaterial, vilket ofta innebär att patienter med mindre allvarliga problem, men som likväl söker vård, exkluderas. Dessa luckor i forskningsfältet runt PSO och PsA är grunden för denna avhandling.

Det övergripande syftet har varit att studera PSO och PSA angående förekomst, kostnader, socioekonomiska skillnader i vårdutnyttjande och hälsostatus ur ett befolkningsperspektiv. De fyra studierna som ingår i avhandlingen har baserats på information avseende boende i Region Skåne och studiepopulationerna har identifierats i Region Skånes Vårddatabas (RSVD). Data hämtades från både nationella och regionala register samt från två frågeenkäter och patientjournaler.

I studie I beräknades förekomsten av läkardiagnosticerad PSO och PsA i den allmänna befolkningen (alla åldrar) i Skåne den sista december 2010 till 1.2%, vilket motsvarar 12,958 individer. 1.0% var personer med enbart diagnos för PSO, och 0.2% personer med diagnos både för PSO och för PsA.

Andelen med PsA bland dem med PSO och PsA, var något mer än 17%. Diagnoskoderna registrerade för PSO och PsA i RSVD visade i stort god tillförlitlighet vid jämförelse med information från medicinska journaler. Andelen fall med en korrekt diagnos registrerad i RSVD varierade med antalet gånger individen hade fått diagnosen och på vilken vårdnivå diagnosen hade getts. Högst andel korrekt registrerade diagnoser kunde konstateras för patienter som blivit diagnosticerade mer än en gång i den specialiserade vården. I studie II framkom att den årliga genomsnittliga samhällskostnaden för patienter med diagnos för både PSO och PsA var 97% (17,600 vs. 8,900 euro) högre jämfört med patienter med enbart diagnos för PSO. Endast en mindre del av de identifierade kostnaderna kunde hänföras specifikt till diagnoserna PSO och PsA, vilket indikerar en grad av samsjuklighet bland dessa patienter.

I studie III utgick vi från en studiepopulation av PSO och PsA patienter samt en jämförelsegrupp utan de aktuella sjukdomarna, där vi studerade skillnader i vårdkonsumtion relaterade till socioekonomiska faktorer efter att hänsyn tagits till sjukvårdsbehov. Resultaten visade att det fanns kvarvarande skillnader i vårdkonsumtion relaterade till framförallt inkomst efter beaktande av sjukvårdsbehov. Att ha PSO eller PsA verkade inte medföra någon ytterligare negativ effekt av utbildning och inkomst. Snarare verkade förekomsten av PSO och PsA försvaga effekten av inkomst på vårdutnyttjande.

I studie IV beskrevs patientrapporterade hälsoutfall, i termer av funktionsstatus, hälsorelaterad livskvalitet, smärta och trötthet, samt samhällsekonomiska kostnader för patienter med PsA. Utfallen analyserades för fyra olika patientgrupper klassificerade utifrån mönster för behandling med biologiska läkemedel under en fyraårsperiod. Majoriteten av patienterna verkade adekvat behandlade med stabilt goda patientrapporterade hälsoutfall och förväntade kostnader mellan de olika behandlingsgrupperna. En liten, men inte obetydlig, andel utgjordes av patienter med oregelbunden användning av biologiska läkemedel. Dessa patienter rapporterade genomgående sämre hälsoutfall och de hade också högre kostnader för vårdkonsumtion och sjukfrånvaro jämfört med patienter med stabil biologisk behandling över tid.

Sammantaget tillför denna avhandling kunskap om påverkan av PSO och PsA på samhället och individen utifrån olika perspektiv. Resultaten kan bistå både forskare och beslutsfattare på ett flertal sätt. Information om förekomst och kostnader kan exempelvis utgöra underlag i studier om kostnadseffektivitet av olika insatser i sjukvården. Vidare kan materialet tjäna som

populationsbaserad referens i studier med andra urvalskriterier. Avhandlingen bidrar också med kunskap om registerforskning gällande datakvalitet samt metoder för prevalens- och kostnadsberäkning.

Abbreviations

ATC	Anatomic Therapeutic Chemical Classification
BASFI	Bath Ankylosing Spondylitis Functional Index
CASPAR	Classification Criteria for Psoriatic Arthritis
CI	Confidence interval
DLQI	Dermatology Life Quality Index
EQ-5D	Euroqol- five dimensions
FS	Functional status
GH	General Health
GBD	Global Burden of Disease (project related to WHO)
HAQ	Health assessment questionnaire
HR	Hazard ratio
HRQoL	Health-related quality of life
ICD-10	International Classification of Disease and Related Health Problems, version 10
LISA	Longitudinal integration database for health insurance and labour market studies at Statistics Sweden
NRS	Numerical rating scale
PIN	Personal Identification Number
PASI	Psoriasis Area Severity Index
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
PsA	Psoriatic arthritis
PSO	Psoriasis
PPV	Positive Predicted Value
RCT	Randomized controlled trial
SHR	Skåne Healthcare Register
SD	Standard deviation
SpA	Spondyloarthritis
SPDR	Swedish Prescribed Drug Register
SPR	Swedish Population Register
SSATG	South Swedish Arthritis Treatment Group
SSIA	Swedish Social Insurance Agency
SSQ	SpAScania Questionnaire
WHO	Word Health Organization

List of papers

This thesis is based on the following papers, referred to in the text by their roman numerals I-IV.

I. **Löfvendahl S**, Theander E, Svensson A, Carlsson KS, Englund M, Petersson IF. Validity of diagnostic codes and prevalence of physician-diagnosed psoriasis and psoriatic arthritis in southern Sweden—a population-based register study. PLoS One 2014;9:e98024.

II. **Löfvendahl S**, Petersson IF, Theander E, Svensson Å, Zhou C, Steen Carlsson K. Incremental Costs for Psoriasis and Psoriatic Arthritis in a Population-based Cohort in Southern Sweden: Is It All Psoriasis-attributable Morbidity? J Rheumatol. 2016 Jan 15. pii: jrheum.150406. [Epub ahead of print] PubMed PMID: 26773111.

III. **Löfvendahl S**, Jöud A Petersson IF, Theander E, Svensson Å, Steen Carlsson K. Income disparities in healthcare use remain after controlling for healthcare need. Evidence from Swedish register data on psoriasis and psoriatic arthritis. Submitted.

IV. **Löfvendahl S**, Petersson IF, Theander E, Svensson Å, Steen Carlsson K. Patient-reported outcomes and costs in relation to biological treatment patterns –population-based data on patients with psoriatic arthritis in southern Sweden. Manuscript.

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Paper II is a pre-copy-editing, author produced pdf of the article accepted for publication in The Journal of Rheumatology following peer-review. Due to journal policy the final version cannot be published in the thesis.

Description of contributions

Paper I

Study design:	Sofia Löfvendahl, Ingemar Petersson, Åke Svensson, Elke Theander, Martin Englund
Data collection:	Sofia Löfvendahl, Rebecca Rylance, Liz Lövall, Pernilla Nilsson
Data analysis:	Sofia Löfvendahl, Ingemar Petersson, Åke Svensson, Elke Theander, Liz Lövall
Manuscript writing:	Sofia Löfvendahl
Manuscript revision:	Sofia Löfvendahl, Ingemar Petersson, Åke Svensson, Elke Theander, Martin Englund, Katarina Steen Carlsson

Paper II

Study design:	Sofia Löfvendahl, Katarina Steen Carlsson
Data collection:	Sofia Löfvendahl, Anna Jöud, Caddie Zhou
Data analysis:	Sofia Löfvendahl, Katarina Steen Carlsson
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Paper III

Study design:	Sofia Löfvendahl, Katarina Steen Carlsson
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Data analysis:	Sofia Löfvendahl, Katarina Steen Carlsson
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Manuscript revision:	Sofia Löfvendahl, Ingemar Petersson, Åke Svensson, Katarina Steen Carlsson

Paper IV

Study design:	Sofia Löfvendahl, Katarina Steen Carlsson
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Manuscript writing:	Sofia Löfvendahl
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Introduction

This thesis is about the burden of disease in psoriasis (PSO) and psoriatic arthritis (PsA) and deals with questions such as: how many are affected? what are the costs due to these diseases? do socioeconomic factors play any role for healthcare use among PSO and PsA patients? And how do PsA patients perceive their health status?

PSO and PsA are chronic inflammatory diseases interrelated in that a number of those with PSO also develop PsA. PSO mainly affects the skin and the nails, while PsA, in addition to affecting the skin, is manifested as pain, stiffness and swelling in and around the peripheral joints or the spine.

In the past, PSO and PsA were considered mild diseases, but later studies have challenged this view [1]. Many of those suffering from PSO and PsA experience both reduced health–related quality of life, functional limitation, pain, stigmatization and work disability, not only those with arthritis. Also people with limited PSO may consider the disease to be a large problem in everyday life [2]. As an added burden, there is evidence of an increased occurrence of comorbidities in these patient groups [3, 4]. As these diseases are chronic and often affect individuals of working age, there are implications not only for the individuals, but also for society in terms of healthcare costs and costs due to productivity losses. Treatment with biological drugs, introduced for Swedish patients with PSO in 2004, and for patients with PsA in 2002, have significantly increased the possibility to alleviate severe symptoms in these patients. This change in drug therapy has however also affected the cost structure as these drugs have been considered as highly priced to date. The current introduction of biosimilars, usually less expensive biological drugs, may however once again affect the cost structure. The introduction of biological drugs has also led to an increased demand for patient-reported outcome information by the need of cost-effectiveness analyses for pricing and reimbursement decisions [5, 6].

Compared to many other chronic diseases, such as heart disease and diabetes, little have been done for less prevalent diseases such as PSO and PsA regarding population-based observational scientific research and public

health efforts [7, 8]. From a societal perspective, it is important to also explore such aspects of somewhat less common chronic conditions.

In 2010, the Center for Disease Control and Prevention in the United States decided to address PSO and PsA from a public health perspective as a complement to the pure clinical and biomedical standpoints [8]. Six key areas in the intersection of public health and clinical science were put in focus, of which one was burden of disease with emphasis on use, costs, employment, work, prevalence and health-related quality of life. Two other key areas were validation of diagnosis and disparities. Lately the importance of studying the burden of PSO and PsA has attracted attention also globally and nationally. In 2014 PSO was included in the WHO strategy work on non-communicable chronic diseases [9]. In Sweden, the National Board of Health and Welfare was recently commissioned by the Government to study PSO including PsA, and examine the patient needs, and what efforts could improve the care for these patients [10]

Regarding Sweden, to the best of our knowledge there have been no recent population-based studied on the occurrence of PSO and PsA, healthcare seeking patterns and factors influencing these patterns. There is more scientific evidence on costs and patient-reported outcomes, but to a large extent this research is based on small, highly selected clinical cohorts, which usually exclude patients with less severe disease course. These shortcomings in the research field of PSO and PsA are the basis for this thesis. Epidemiological and health economic methods are applied on the research questions. The studies are observational in design and based mainly on population-based register data but also on survey data and medical records.

Conceptual framework

This chapter is divided in two parts. Part one outlines the conceptual framework for this thesis; central concepts of epidemiology, and the core of economics along with the application of this within health and healthcare are presented. The second part covers the empirical framework, i.e. PSO and PsA are described, and related scientific evidence on occurrence, healthcare use, costs and health outcomes is reviewed.

Epidemiology

Definition

Epidemiology is about measuring health, identifying the causes of ill-health and intervening to improve health [11]. There are a number of different definitions of epidemiology. The early and narrow definition encompassed only the concepts of ill-health and disease [12] while also health in general is included in a latter and broader definition [13]. Epidemiology can be seen as a framework which provide logic and structure for the analysis of health problems.

Study designs

Epidemiological study designs can be classified on the basis of two nodes (Table 1) depending on the study aim. Common descriptive studies are those with data on occurrence of for example disease, comorbidities or smoking. Analytical studies aim mainly at identifying causes of disease and evaluating interventions. The second dividing line goes between experimental and non-experimental studies. The experimental design is often used in studies of treatment effects where one treatment is compared to another and where the choice of treatment between different individuals is randomly assigned, i.e. randomized controlled trials (RCT). In this way biases are reduced. Non-

experimental studies are observational, where a course of events is observed and related data are used for the analyses.

There are different types of non-experimental studies. The main feature of a cohort design is that a group of subjects with a common exposure, e.g. a disease, is followed over time regarding relevant outcomes, such as healthcare use or costs. In contrast, in a case-control design the cases are defined as those individuals that have the outcome of interest and the controls without that particular outcomes are selected. Preferably, both cases and control are selected form the same source population. In real practice, many study designs are combinations of cohort and case-control designs [11].

Table 1. Different types of study designs.

	Experimental	Non-experimental
Descriptive	-	Case-report Incidence Prevalence
Analytic	Randomized clinical trial Intervention study	Cross-sectional Cohort study Case-control study

Sources of error

In epidemiological studies, it is important to be aware of potential sources of error that can influence the results and the internal validity of a study. *Random error* is a random variation in a variable due to biological variation. This type of error can be reduced by increasing the size of the study sample/population. *Non-random errors or bias* refers instead to systematic deviations that are not due to chance alone. Examples of common biases are misclassification of disease and selection bias, where the first refers to when a disease is classified as something it actually is not, and the second refers to differences between those selected for analysis and those eligible. Bias arises to various extent in most epidemiological studies, but to reduce the impact as much as possible, it is important to be careful in the phase of study design. *Confounding (also a type of systematic error)* occurs when a factor, for example sex or age, has an independent influence on both the exposure and the outcome of interest. Common methods to control for confounding are matching and stratification.

Matching

Matching means that cases and controls are made more comparable with respect to important determinants of the outcome being studied. Controls may

be selected to correspond to the cases on age, sex and other factors, and can be done individually (individual matching) or at group level (frequency matching).

Generalizability

Another aspect of an epidemiological study is the generalizability or the external validity, i.e. to what extent the results of a particular study are applicable to populations other than the study population. Usually a target population is the entire group of people or objects to which a researcher wants to generalize the study results, while a source population is the population from which study patients or objects are drawn. It is mainly the inclusion and exclusion criteria for a study that describe the target population. For example, results from a study with a source population of women with a particular comorbidity may not be valid for women overall. An advantage of observational studies, compared to RCTs is that the external validity is usually higher as the former study to greater extent mirrors un unselected patient population often seen in real clinical practice.

Health economics

Definition

There are a number of different definitions of the discipline health economics and one textbook definition is "*health economics as a discipline can be defined as the application of the theories, tools and concepts of economics to the topics of health and healthcare*"[14]. In an evaluation of the Swedish health economics research field carried out by an international panel of health economist in 2006 a similar definition was used: "*health economics is the application of theoretical or empirical economic analysis of health or healthcare using standard or specifically developed techniques from economics*"[15]. It is worth noting that according to these definitions, the boundaries of health economics stretch beyond the economics of healthcare to encompass the broader social determinants of health and the interactions between health, labour markets and other aspects of economic activity. This means that health economists also contribute to the field of public health [16].

Scarcity and allocation of resources

The fundamental basis of economic science is that resources are limited, which means that more is wanted of goods and services than is available, either to individuals or to populations. From this follows that choices have to be made not only about what to do but also what to leave out. This scarcity issue is highly relevant within healthcare. A demographic shift towards an aging population, and increased focus on chronic diseases, and their remedies are likely factors that may contribute to widen the gap between what can be offered and what people what to receive [17]. Furthermore, the introduction of new, often costly, technology which improves quality and sometimes also offers the possibility to treat additional patient groups and rising expectations has a major impact on this gap. Health economic analyses are tools that may assist policy-makers in their work on allocations of scarce resources to improve health.

Opportunity cost

The concept of opportunity cost is central in economics and hence also in health economics. Opportunity cost is the value of a resource in its most highly valued alternative use. Because the resources are scarce, when we use these resources in a particular way we have to be aware the there is an opportunity forgone to obtain benefits if using the resources in another way. Opportunity cost differs from the accounting concept of costs. In a world of competitive markets, in which all goods are traded and where there are no market imperfections, opportunity cost is revealed by the market prices of resources. Where these stringent conditions are not met, opportunity costs and market prices can diverge and shadow prices may have to be estimated to measure the former [18].

Efficiency and equity

Economics traditionally focus on the efficiency of resource allocations, but policy-makers also place emphasis on equity goals and distributional issues [16]. In general, the term efficiency is used to describe the relationship between inputs and outputs, which can be valued in terms of costs and benefits. Efficiency is about maximizing benefits with the resource available, or minimizing costs for a given level of benefit. Applying this to the healthcare system, the benefits may be interpreted as pain relief, improved functional status or health-related quality of life. As opposed to maximization

of benefits, the term equity is about the distribution of the same. Usually, efficiency and equity are conflicting objectives. The fact that healthcare can be very expensive and that factors beyond individual control may cause bad health, e.g. congenital diseases, genetic predisposition of disease and accidents, has been used as arguments for distributional efforts to increase equity in healthcare. In order to satisfy societal concepts of equity, it may make sense to accept some inefficiency [19].

Classifications of diseases

The term disease is objective in its nature, in contrast to the term health which relates to a subjectively perceived notion about the well-being [20]. A disease is usually assessed by external criteria, for example by a combination of different predefined symptoms, tissue abnormalities or laboratory test [21].

The term disease is closely linked to the term diagnosis [22]. The diagnosis is a type of label that can be used in the communication with the patient and others about a disease. A diagnosis is not necessarily always a disease, but can be a symptom indicating a healthcare need. A diagnosis has mainly two functions. The diagnosis is used in the patient record as a description and summary of the cause of a healthcare contact. It also forms the basis for medical and healthcare statistics at different levels. A common diagnostic classification system is the ICD-10, International Classification of disease, version 10, developed by the WHO [23]. ICD-10 is used worldwide and has been adapted and translated into national versions. The Swedish translation of ICD-10 was introduced by the National Board of Health and Welfare in 1997 [24].

Concepts related to classification of diseases are diagnostic and classification criteria. Diagnostic criteria are based on a specific combination of signs, symptoms and tests that the clinician uses to attempt to determine a correct diagnosis in a clinical setting. Diagnostic criteria are generally broad and reflect different features of a disease, in order to accurately identify as many people with the disease as possible. Classification criteria are standardized definitions that are primarily intended to create well-defined, relatively homogenous cohorts for clinical research; they are not intended to capture all possible patients, but rather the majority of patients with key shared features of the condition [25]. While clinical research often bases the case definitions on classification criteria, research based on administrative healthcare registers often uses ICD-based diagnostic codes.

Burden of disease perspective

The expression burden of disease is closely related to the WHO project on Global Burden of Disease (GBD) with the main purpose to generate a comparable set of estimates of mortality and morbidity by age, sex and regions of the world [26]. This continuous work was partly initiated because of the growing importance of non-communicable diseases and their non-fatal impact on health status of a population, and the conclusion that death and causes of death have become inaccurate measures to describe the overall health status of a population. The work is characterized by the use of summary measures of population health, usually measures combining mortality and disability such as DALY (Disability-Adjusted-Life Years), and the use of ICD diagnostic codes for the classification of diseases.

Still, the term burden of disease is also used in the literature not referring specifically to the WHO project. In a recent Canadian report, which performed a literature research related to the term burden, it was shown that the research literature includes a variety of related terms and phrases covering a number of various areas; some of the phrases were for example treatment burden, medication burden, economic burden, subjective burden and inequitable burden [27, 28].

PSO and PsA (classified among "other musculoskeletal disorders") are included in the WHO GBD work [29] and for PSO there are also other reports using the WHO GBD concept [30]. Inspired by the burden of disease concept, this thesis encompasses an understanding of the impact of PSO and PsA from broader perspective as was exemplified in the Canadian reported mentioned above [28].

Occurrence of disease

Data on disease occurrence and the distribution of a disease is useful information for disease controlling and healthcare planning. Data on disease occurrence may reveal differences over time, between sexes, across age groups and between different geographical populations [31]. In studies of disease occurrence, one distinction is between the incidence approach which measures disease onsets, and the prevalence approach which measures disease states. Another distinction is between register-based and survey-based methods for accessing data on occurrence. The first method uses disease registers or healthcare administrative register, which may be either

population-based or clinical-based, while the latter method uses information directly from population samples via questionnaires or interviews.

In this thesis, the prevalence approach is used, which is preferable when studying diseases with ill-defined onset and/or chronic diseases with relatively stable disease state or requiring long-term therapy as is the case in PSO and PsA. In the following the focus is on describing a register-based prevalence approach as the Skåne healthcare register (SHR) is used to collect data on disease occurrence in this thesis.

The point prevalence of a disease is usually estimated in cross-sectional studies, and is defined as the proportion of individuals with the disease in a specified population at a specific point in time. The numerator is the individuals identified with a disease and the denominator is the individuals in the source population. Studying the point prevalence using longitudinal population-based healthcare administrative registers, a number of prerequisites need to be fulfilled [31]. First, both the target population and source population need to be defined. The source population may be defined by a geographical area or by a healthcare register covering a certain catchment area, i.e. the catchment covers the healthcare facilities that are included in the healthcare register. Second, the register must cover the disease in question so that relevant cases can be ascertained by e.g. diagnostic codes, and it must be likely that the individuals with the disease attend a physician by whom the individual is diagnosed. Third, the time window of healthcare history needs to be long enough to capture all prevalent cases. Fourth, there must also be registers available that cover all individuals in the source population regarding vital status and residence on prevalence day. It should preferably also be possible to verify that all cases that have been ascertained actually have the disease. One approach to check this is to review a sample of medical records to verify the diagnosis.

Cost of illness studies

A cost of illness analysis is a way of measuring the burden of disease incorporating also costs of the disease [27]. It is descriptive in design and gives information about how resources are spent and lost in society due to disease. The main purpose is to inform policy-makers about the economic magnitude of a disease or health problem, or to provide cost data in economic evaluations [32, 33]. The cost of illness studies that we see today began to appear in the 60s and the methodologies of these types of studies have now become well-established [34, 35], but the usefulness of this type of studies

has long been under debate [36, 37]. The reason for this is that cost of illness studies does not sort as economic evaluations as they do not examine clinical outcome. They are therefore considered of minor use in priority setting. However, it has been proposed that cost of illness studies could be of some use as a guide to setting priorities in research and development [38].

Design

Cost of illness studies are usually described according to the epidemiological data used and methods chosen to estimate the economic cost. The prevalence approach refers to the total number of cases in a determined period of time while incidence studies refer to the new number of cases arising in a predefined period of time. The prevalence approach is particularly relevant for chronic diseases and for the study of changes in costs over time. Usually, either a top down or bottom-up method or a combination of the two is used. In the first method, the total cost of illness is divided between different diseases using diagnostic codes as separation. The latter approach usually starts with a subpopulation with the actual disease and all cost related to the disease are estimated [33].

Cost calculation analysis

There are three main steps in the cost calculation analysis. In the first step all relevant costs are *identified* and divided into direct medical costs (visits, inpatient stays, drug), indirect medical costs (transportation, out of pocket expenses) and indirect costs which are costs due to productivity losses such as sick leave, disability pension, reduced productivity at work and informal care. Intangible costs which relate to reduced quality of life, grief and social isolation should be included but due to estimation problems they are usually not. In this first step, also the perspective of the study should be decided. The main recommendation in Sweden is a societal perspective, which means that all costs should be included, both direct and indirect cost [39]. In contrast, from a budget perspective (of a healthcare stakeholder) only direct costs are included, a model used by the National Institute for Health and Care Excellence in the UK for example [40].

In the second step, all identified costs should be *quantified* which means that the magnitude of resource use should be assessed. There are two different approaches in this step; in micro-costing, each single resource component that has contributed in the provision of the service is assessed, while in gross-costing total costs at the service unit are divided by the total number of services produce during a time. Both methods estimate the unit cost, but while

the first method results in the actual cost the latter method ends up in the average cost [33].

In the third step, all resources should be *valued*, i.e. they should be linked to a monetary value. Market prices, provided on perfect markets are assumed to reflect the opportunity cost, but in terms of direct costs, there is rarely any direct market for healthcare. Therefore, usually tariffs and internal price lists for various treatments from counties or hospitals are used to value the resources. The productivity losses are usually valuated with the human capital approach, which is the value of lost earnings [41]. It can also be estimated using the friction cost method, which only includes the short-term productivity loss that arises before a job position is replaced with another individual [42].

Strategies for interpreting healthcare use disparities

Equity in healthcare is recognized as an important policy issue in most western countries [43], and policy goals in Sweden and other European countries state that socioeconomic status should not influence the individuals' opportunity to receive healthcare [44]. Many of these healthcare systems have a guiding principle aiming at distributing healthcare according to need, often coupled with an organization which reduces the impact of the individual's ability to pay for healthcare at the point of use.

In the research literature on equity in healthcare, there is a plethora of perspectives, concepts and methods. Despite the high priority assigned to equity in healthcare by policy-makers, the terminology around equity is not always used in a consistent manner. The terminology can vary geographically and also depending on research field [45-47]. A study on disparities in healthcare use is included in this thesis (Paper III). A number of concepts related to this subject are discussed below.

Equity

Equity, and the negative form inequity, in healthcare is often discussed in terms of fairness or justice, and researchers from different fields have written extensively on this subject [45, 47, 48]. The term can be either related to funding of healthcare, distribution of healthcare, or distribution of health. It may be argued that equity in health is the only equity to be concerned about, since equity in healthcare derives exclusively from a concern about the distribution of health. The economic contribution to the analysis of health equity is considered to be relatively small compared to that of other

disciplines [49], and are not further discussed here. Instead, the focus here is on equity in the distribution of healthcare. A widely used definition of inequity in health/healthcare distribution, proposed by Whitehead [45], refers to differences which are unnecessary and avoidable, but in addition, also considered unfair and unjust.

Equity concepts in the economic literature

Two commonly used definitions of equity in healthcare are equality of 1) access for equal need, and 2) utilization for equal need [46]. The distinction between access (as in 1) and utilization (as in 2) is that the former is a supply side definition and the latter is a function of both supply, demand and need. Here the focus is on the second definition and the terms need and demand.

Vertical and horizontal equity

The principle of distribution according to need is usually divided in two versions: 1) horizontal equity which means that individuals in *equal need receive the equal amount of healthcare* and 2) vertical equity which means that *greater needs are met by greater use* [46, 48, 50]. Horizontal equity mainly examines whether or not people with the same need of healthcare make the same use of healthcare. However, in practice, it is rather difficult to assess what equal need means and how it might be measured. For example, if we look at ethnicity or socioeconomic status, we might agree that these should not in themselves affect the use of health services and are non-need factors. Nevertheless, different socioeconomic and ethnic groups might have different use of health services because they have different levels of ill-health. But if we control for need factors and find that the use of healthcare services is affected by non-need factors, there is evidence of horizontal inequity, because people with the same need consume different amounts of care. Vertical equity in the distribution of healthcare is usually interpreted to mean that individuals with different levels of need use appropriately different amounts of healthcare. This concept is less extensively explored in the research literature due its more normative perspective, which is related to issues about what ought to be considered as "appropriately different amounts".

Disparities or inequalities in healthcare use?

Inequity should be distinguished from the terms disparities and inequalities in healthcare use; terms related to observed differences in healthcare use. Disparities or inequalities refer to differences between people or populations which can be shaped by policy-making pursuing healthcare equity.

In certain papers the terms disparities and inequalities are used interchangeably while others make a distinction between the two terms [51]. In the literature, no clear distinctions between the terms are given but there are nuances. More specifically, healthcare disparities often refer to differences that cannot be explained by variations in healthcare needs, patient preferences, or treatment recommendations while health inequality, used more often in the scientific literature, describes differences associated with specific attributes such as income or race [51]. In this thesis, the term disparities is used and it refers to a general notion of differences in healthcare use. Not all healthcare disparities are *per se* inequitable [52]. Some determinants of health, such as age, cannot be influence by policy. Usually younger people tend to have better health than older people. Furthermore, differences in healthcare use reflecting differences in health status may also be justified as disparities which are not inequitable. This implies some adjustment of need before it is possible to talk about inequity.

Need variables and demand for healthcare

From the above it can be concluded that the term need is crucial in the context of healthcare use disparities. According to the economic theoretical literature, the term need can be employed in many ways [46, 48, 50], e.g. need as initial health or need as capacity to benefit [46]. The difference between these two terms is that the latter one takes into account whether the use of healthcare actually improves a person's health or not which the first term ignores. In a Swedish healthcare policy perspective, need is defined in the Swedish national model for transparent prioritizations in healthcare, aimed to be a guideline for healthcare providers at different levels in the healthcare system. In this model need seems to be defined in terms of capacity to benefit. It is stated that a healthcare need is related to both the severity of the individual's condition as well as expected benefits to be gained by a certain treatment. The severity in turn incorporates the suffering, the functional status and the health-related quality of life, both at present and in the future [53].

In empirical research, need has been operationalized into observable characteristics in various ways. In addition to age and sex, such characteristics used in the literature are presence of indicators of morbidity and self-reported health status but also the presence of disability pension [54-57]. Variables such as education, income, employment status and ethnicity have on the other hand been cited as examples of factors that in themselves should not be related healthcare use. Nevertheless, empirical analyses face challenges of potential unobserved need, [52, 58, 59] as need, in addition to a direct relation to healthcare use also may be mediated by socioeconomic factors [60].

Demand for healthcare is also interrelated to the term need, and what is finally consumed by the patient is influence by both. The demand for healthcare is a derived demand in the sense that it is derived for the demand for health provided that the healthcare system can promote health [52]. People may have different preferences for health and hence also differ in their demand for health despite the same need.

Patient-reported outcomes

The patients' perspective is also of importance when measuring the burden of disease [61]. Patient-reported outcomes (PROs) refer to information about symptom status, physical function, mental health, social function and well-being in relation to a health condition or disease and its treatment, and the patients' responses are without interpretation by health professionals or anyone else. PROs provide patients' perspective on treatment benefit beyond survival, disease, and physical markers; and are often the outcomes of greatest importance to patients [62, 63].

The awareness of the importance of the patient's view of his or her health as a complement to the biomedical evaluation in the treatment of patients have created a need for identifiable, valid, and reliable patient-reported measures (PROMs) [6].

PROMs are either generic or disease-specific. Generic measures usually include general dimensions such as mobility, function in activities of daily living pain and depression and are designed for use with any illness group or population sample. The advantage of this type of instrument is that the outcomes can be compared across different diseases, groups of patients or populations. The disadvantages are primarily conceived irrelevance of the questions, lack of sensitive to change, and that the number of questions can be very extensive.

Disease-specific measures describe severity, symptoms, or functional limitations specific to a particular disease state, condition or diagnostic grouping and such measures are therefore more sensitive to detect small changes in clinically important outcomes than generic measures. The advantage is that specific instruments cover aspects of a particular disease that are relevant to patients and health professionals. The disadvantages include limited utility for comparisons between diseases.

Empirical framework

Psoriasis

PSO is a chronic inflammatory disease that mainly affects the skin and the nails. Family history as well as environmental factors such as tobacco smoking, infections, mental stress and certain medications can contribute to disease susceptibility [64, 65]. The disease has systemic features, and is characterized by a relapsing course that can fluctuates between and remission and severe inflammation.

PSO is a clinical diagnosis usually based on a clinical examination of the patient. There are yet no laboratory tests or other tests to confirm the diagnosis. Rarely, a skin biopsy may be needed to exclude other diseases and to support the clinical diagnosis [9]. No established diagnostic criteria exist for PSO and there is no unified classification for the clinical spectrum of the disease [66]. Severity in PSO is often evaluated using the Psoriasis Area Severity Index (PASI,) which assesses the extent to which different body parts are affected, together with assessment of the patients' health-related quality of life (HRQoL), often measured by the disease-specific instrument Dermatology Life Quality Index (DLQI) [67].

Currently there is no cure for PSO, and treatment is directed at reducing signs and symptoms, and modifying the natural progression of the disease. Most people with PSO have mild to moderate symptoms and can be treated with topical emollients or phototherapy. Around 20% of the PSO patients have moderate to severe disease, and are in need of systemic treatments, which are usually prescribed by dermatologists. In 2004 biological drugs were introduced for patients with PSO. Current treatment guidelines suggest that biological treatment should be prescribed when patients do not respond to conventional systemic treatment or in cases with intolerance or contraindications to conventional treatments [68].

Moderate to severe PSO has been associated with a number of comorbidities, in particular cardiovascular disease, Chron's disease and depression [69]. An

increased mortality has been reported in patients with severe PSO defined as users of biological drugs but not in patients with mild PSO [70].

Psoriatic arthritis

A proportion of patients with PSO also develops psoriatic arthritis (PsA). This is thus also a chronic inflammatory disease which, in addition to skin symptoms also manifests as inflammatory peripheral arthritis, enthesitis, dactylitis tenosynovitis or spondyloarthritis, resulting in stiffness and swelling in and around the peripheral joints or spine. While the cause is not known, genetic factors, along with the immune system, are likely to play a role in determining who will develop PsA [71]. Suggested trigger factors are tobacco smoking, stress, trauma.

Skin symptoms can precede onset of joint symptoms by up to ten years [72]. Most people (60-75%) who develop PsA already have been diagnosed with PSO. In 10-15% of the patients, inflammatory arthritis is the first symptom and simultaneous onset of arthritis and skin disease occur with approximately the same frequency [72, 73]

PsA is a clinically diverse disease with various manifestations, and it is recognized that patients can have any combination of the disease features [74, 75]. The diagnosis is based on a clinical examination by a physician where the combination of skin and joint problems is identified. PsA may be difficult to diagnose due to its heterogeneity, lack of consistent diagnostic criteria and the caveat that symptoms may resemble those seen in other rheumatic diseases [75, 76].

There exists no curative treatment for PsA, but modern therapies, in particular treatment with biological drugs may significantly reduce symptoms, improve joint function and prevent complications. The main goals of treatment are to achieve clinical remission, improve patients' HRQoL, and inhibit structural damage. Some PsA patients with mild symptoms can be managed in primary care. Patients with a definitive diagnosis, which does not response to non-steroid anti-inflammatory drugs (NSAIDs) and/or local corticosteroid injections should be referred to a rheumatologist. There are both international and national guidelines for the treatment of patients with PsA [77, 78].

For PsA, there is evidence for an increased occurrence of comorbidities related to metabolic, mental and circulatory disease [4] with an increased prevalence compared to the general population [79, 80]. Clinical studies on

mortality in PsA have shown conflicting results [1], but population-based studies indicate no increased all-cause mortality in these patients compared to the general population [70, 81].

Burden of disease in psoriasis and psoriatic arthritis

Occurrence

Overall

Several studies from different countries across the world have examined the prevalence of PSO and PsA [82-84]. Studies from Europe and the United States have estimated the prevalence of PSO in the range from 0.7% to 4% in the general population (Table 2) and the corresponding estimate for PsA ranges from 0.1% to 0.42% (Table 2). Estimates of the prevalence of PsA among those with PSO vary from 7% to 30% (Table 2). Variation in methodology and applied case ascertainment criteria may have contributed to the differences in prevalence estimates. In general, clinical-based studies and studies based on self-reported information on PSO and PsA have reported higher prevalence rates compared to population-based studies, and studies with ascertainment criteria based on diagnostic codes or classification criteria although there are exceptions [81].

When including populations also from Asia and South America the ranges in prevalence estimates become even wider. Reported estimates from these geographical areas are generally lower compared to Europe and the United States [85-87]. The reasons for these variations are not completely understood, but differences in genetic predispositions between different populations may contribute [82].

Sex and age

PSO can appear at any age but most often in young age. There is a tendency to a bimodal distribution in the age at onset. Based on this, two types of PSO have been proposed: Type I, with early onset and heritability, and type II with onset after 40 years and significantly lower or no heritability [88]. Some studies have reported an equal frequency of PSO between the sexes, while others showed a higher prevalence in men [83].

The average age at PsA onset is about 40 years of age, and slightly lower in men than in women [71]. There are conflicting results on the sex distribution

in PsA patients. Some studies have found an equal occurrence in men and women [89], some have found that it is more frequent in men [90, 91], and others have found that it occurs more frequently in women [81].

Table 2. A selection of European and US studies, mainly from the last decade, estimating the prevalence of PSO, PsA and PsA in patients with PSO.

Type of prevalence study	Study	Country	Year	Source population	Ascertainment method	Prevalence estimate, %
PSO prevalence	Shbeeb [81]	US	2000	G	DC medical records	0.7
	Löfvendahl [92]	Sweden	2014	G	DC in healthcare register	1.23
	Ferrándiz [93]	Spain	2001	G	SR	1.43
	Gelfand [94]	UK	2005	G	Diagnostic code in register	1.52
	Hellgren [95]	Sweden	1967	G	CE	1.9
	Lomholt [96]	Faroe Islands	1964	G	CE	2.5
	Naldi [97]	Italy	2004	G	SR	3.1
	Kurd [98]	US	2009	G	SR and CE	3.15
	Meding [99]	Sweden	1992	G	SR	4
PsA prevalence	Cacir [100]	Turkey	2011	G	SR and CE	0.05
	Hanova [101]	Czech Republic	2010	G	DC in healthcare register	0.05
	Shbeeb [81]	US	2000	G	DC in medical records	0.10
	Nossent [102]	Norway	2009	RC	DC in medical records	0.13
	Love [103]	Iceland	2007	G	CE	0.14
	Ogdie [104]	UK	2013	G	DC in medical records	0.19
	Löfvendahl [92]	Sweden	2014	G	DC in healthcare register	0.21
	Gelfand [105]	US	2005	G	SR	0.25
	Anagnostopoulos [106]	Greece	2010	G	SR and CE	0.35
	Salaffi [107]	Italy	2005	G	SR and CE	0.42
Proportion of PSO with PsA	Gelfand [105]	US	2005	G	SR	11
	Löfvendahl [92]	Sweden	2014	G	DC in healthcare register	17
	Radtke [108]	Germany	2009	DC	Patient and doctor questionnaires	19
	Zachariae [109]	Nordic countries	2002	PO	SR	30
	Mease [110]	7 European and North America countries	2013	DC	DC	30

Source population: DC=Dermatology clinic, RC= Rheumatology clinic, G=General population, PO=Patient organization, Ascertainment method: SR=Self-reported, CE=Clinical examination, DC=Doctor-confirmed

Costs

Because of differences in cost perspective, methodologies and healthcare systems, caution is advised for comparisons between cost studies [111]. In a relatively recent international review, the annual mean cost of PSO and PsA together ranged between €2866 and €11,928 [112]. Unsurprisingly, studies have shown that the economic burden of PSO and PsA increases with disease severity [113, 114]. For PSO it seems that direct costs exceed indirect costs [115, 116], although there are studies reporting differently [117]. PsA seems to incur greater cost compared with PSO alone because of the added burden of joint involvement [118], with estimates of mean annual direct costs of €5,600 and indirect costs of €55,600 [119]. Most studies find that loss of productivity is the largest cost component even when costs for biological treatment are included [120, 121]. Many of the studies to date have been restricted by data availability and limited time frame for observation. This may be a particular problem concerning mild PSO with irregular healthcare needs [122]. Moreover, few studies have considered the relatively high degree of comorbidities among people with psoriasis and PsA [3].

Healthcare use disparities

A number of studies have consistently shown that there seems to be higher use of primary care services among lower income groups and higher use of specialist service among higher income groups in a number of countries in Europe and North America [43, 123]. A Norwegian study supports the pro-rich use of secondary outpatient care but did not find any income-related influence on primary care use [124]. Studies have also indicated that the impact of socioeconomic factors differs between an initial healthcare contact and how much care is consumed [125]. In Sweden, there are studies indicating that there may be PSO healthcare use disparities related to sex in that women to a lesser extent receive ultra-violet (UV) treatment [126], and to age in that there are fewer opportunities to biological treatment in older ages [127]. It has also been shown that the use of UV treatment decreased with increased distance to UV treatment facilities [128]. Furthermore, it has also been reported that there may be differences in the treatment with biological drugs in favor for male PSO patients [129], but this difference could be explained by men being more severely affected by PSO [130]. As far as we know there are no Swedish studies on healthcare use and the influence of socioeconomic factors, such as education and income, in PSO and PsA patients.

Patient-reported outcomes

Patient-reported outcome in psoriatic arthritis

As PsA is a heterogeneous disease with a dual component of joint and skin manifestations a multifactorial assessment of disease aspects should be emphasized [131, 132]. A wide range of PROMs exist for PsA but few of them have been developed specifically for PsA [62]. A commonly used PROMs in PsA patients is the Health Assessment Disability Index (HAQ-DI), which is a disease-specific instrument initially developed for rheumatoid arthritis. The disease-specific PROM Dermatology Life Quality Index (DLQI) is designed for patients with skin disease and is used in clinical trials for PSO and PsA, but to a lesser extent in real clinical practice PsA studies [133, 134].

In the literature, most information on PROs in PsA patients are reported in relation to RCTs and the evaluation of different treatment strategies [135]. The information on PROs from RCT is not always transferable to other patient settings due to low external validity of RCTs. For rheumatoid arthritis, a recent study showed that the mean percentage of patients in two observational clinical practice cohorts that satisfied the entry criteria for biological drug treatment in RCTs was only 3.7% [136]. It is important to investigate PRO levels in broader PsA patient populations seen in real clinical practice when novel treatments become established, in order to identify whether there are unmet needs and what characterizes patients reaching different PRO values. There are real clinical practice studies including measures of PROs for PsA patients but few of them have included the skin aspect of PsA [135, 137-140].

Aims

The overall aim of this thesis was to study the impact of PSO and PsA on the individual and on society.

The specific aims were:

- to validate diagnostic codes for PSO and PsA and to estimate physician-diagnosed prevalence of PSO and PsA in the Skåne region.
- to estimate the incremental societal costs per person for PSO and PsA compared to matched population-based referents free from PSO and PsA.
- to estimate the costs attributable specifically to PSO and PsA problems.
- to investigate the influence of socioeconomic and demographic factors on the probability of healthcare use, and on healthcare costs among a cohort of PSO and PsA patients, and matched population-based referents free from PSO and PsA controlling for healthcare need.
- to investigate patient-reported outcomes and total social costs over time in a population-based cohort of PsA patients. Outcomes were analyzed in four subgroups characterized by type of drug treatment during four consecutive years.

Methods

Settings

Sweden offers good conditions for observational healthcare research [141]. First, there are national and regional population-based registers covering information about healthcare use, socioeconomic and demographic status and civic status for the entire population. Second, the unique personal identification number (PIN), given to each individual residing in Sweden on a permanent basis, allow for linkage across the different registers. Third, financial barriers to healthcare use exist but are considered low. Fourth, there is a standardized procedure for assigning data for research purposes, which ensures that patients' integrity is maintained and that vulnerable patients are protected.

Swedish healthcare is predominately tax-financed (91%) with user fees and private insurance covering 8% and 0.29% of the total healthcare expenditure respectively [142]. A small user fee is paid by the patient until it has reached the sum of approximately €112 for healthcare contacts and €244 for prescription drugs respectively during a 12-month period (1€=9.03 SEK in 2011). After that all out of-pocket payment is waived for the remaining period of the 12 months following the date of the first consultation or prescribed drugs of the period. The responsibility for providing healthcare in Sweden is decentralized to 21 regions of different sizes. The usual path into healthcare is by a visit to a general practitioner but patients can also access secondary care directly.

All studies in this thesis were conducted using data related to residents in the Skåne region. Its population, 1.2 million in 2011, accounts for 13% of the Swedish population and it holds both rural and urban areas. All levels of healthcare, i.e. from primary care to highly specialized care are represented in the region, and the residents are usually listed to a primary care physician in the vicinity of their residence. Healthcare provision at consultant level outside the region normally requires a restricted permission procedure. Thus, we expected there to be a negligible volume of healthcare provided outside

the region for Skåne residents [143]. The Skåne region resembles Sweden as a whole on a number of key socioeconomic variables, such as education and income [144, 145].

Design

Different study designs were used to address the research questions of this thesis. All studies (Papers I-IV) were observational and population-based in design. The study populations were individuals in the Skåne region identified by means of the Skåne Healthcare register (SHR). Paper I was a healthcare register-based prevalence study using the ICD-10 classification for identification of patients with PSO and PsA. Medical records were used in the validation of diagnostic codes.

In Papers II-III we used a cohort of PSO and PsA patients with matched referents without PSO and PsA. Paper II was a prevalence-based bottom-up cost study with longitudinal data on resource use and costs. In Paper III, we used longitudinal resource and cost data in combination with cross-sectional data on socioeconomic and demographic status. Paper IV was a longitudinal study of a cohort of PsA patients. In addition to longitudinal register-based data on resource use and costs we used cross-sectional survey data on patients-reported outcomes, using both generic and disease-specific instruments.

For information on resource use and costs we used national and regional registers on drug use and productivity losses in addition to information from SHR. For information on socioeconomic and demographic status we used cross-sectional data from Statistics Sweden. The information from the different data sources were linked by mean of the individuals' PIN.

Ethics

All studies were conducted according to the Declaration of Helsinki and approved by the Regional Ethical Review Board in Lund, Sweden (Dnr 301/2007, Dnr 406/2008 and supplement to Dnr 2012/359). For the review of the medical records (Paper I), consent was obtained from the medical director/physician responsible for each patient. The data extracted from the medical records were anonymized prior to analysis.

Definitions of psoriasis and psoriatic arthritis

PSO and PsA were defined using diagnostic codes according to the ICD-10 version [23]. Decisions about which codes to use were based on the literature and discussions with professionals in the dermatology and rheumatology field. Selected codes for PSO and PsA are listed in Table 3, and the combination of ICD-10 codes used for different definitions of PSO and PsA in Paper I-IV are listed in Table 4. The Venn diagram in Figure 1 shows the interrelation between the different subgroups of PSO and PsA analyzed in this thesis.

Table 3. ICD-10 diagnostic codes used to identify cases of PSO and PsA.

ICD-10 diagnostic code	Diagosis full text
L40.0	Psoriasis vulgaris
L40.1	Generalized pustular psoriasis
L40.2	Acrodermatitis continua
L40.4	Guttate psoriasis
L40.5	Arthropathic psoriasis
L40.8	Other psoriasis
L40.9	Psoriasis unspecified
M07.0	Distal interphalangeal psoriatic arthropathy
M07.1	Arthritis mutilans
M07.2	Psoriatic spondylitis
M07.3	Psoriatic arthropaties
M09.0	Juvenile arthritis in psoriasis

Table 4. Defintions of PSO and PsA used in Papers I-IV.

Defintions	**Psoriasis patients with or without psoriatic arthritis**	**Patients with psoriasis alone**	**Patients with psoriasis and psoriatic arthritis**	**Patients with psoriatic arthrits**
ICD- 10 diagnostic codes	L40.0 L40.1 L40.2 L40.4 L40.5 L40.8 L40.9	L40.0 L40.1 L40.2 L40.4 L40.8 L40.9	L40.5 alone or any of the codes L40.0, L40.1, L40.2, L40.4, L40.8, L40.9 in combination with any of the codes M07.0, M07.1, M07.2, M07.3, M09.0	L40.5 M07.0 M07.1 M07.2 M07.3
Defintion used in Paper	Papers I-III	Papers I-III	Papers I-III	Paper IV
Phrasing used in text and in Papers*	PSO patients with or without PsA or PSO/PsA patients	Patients with psoriais alone or PSO patients	Patients with PSO and PsA or PsA patients	PsA patients

* A coherent terminology was used throughout all Papers, with deviations because of different journal practice.

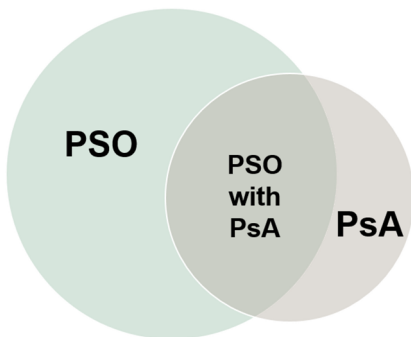

Figure 1. The Venn diagram shows the relationship between the different diagnostic subgroups of PSO and PsA patients presented in this thesis; PSO with or without PsA (Paper I-III), PSO alone (Paper I-III), PSO with PsA (Paper I-III), and PSA with or without PSO (Paper IV).

Study populations

We used three different population-based patient cohorts retrieved from the SHR; two PSO cohorts with the same definitions of PSO and PsA, but with different patient inclusion periods (Papers I-III), and the SpAScania cohort (Paper IV). In Papers II-III, we also used a referent cohort. An outline of Papers I-IV regarding study populations and their characteristics is illustrated in Table 5.

The psoriasis cohorts

From the SHR we identified all individuals who, at any time during the period 1 January 2005 to 31 December 2010 (cohort in Paper I) and during the period 1 January 1998 to 31 December 2007 (cohort in Papers II-III) had been given a physician-confirmed diagnosis of PSO according to our definition as primary or secondary diagnoses (Table 4). From these individuals, we thereafter identified those with a physician-confirmed diagnosis of PsA.

The SpAScania cohort

This SpAScania cohort was established in 2008 by identifying all individuals (age >15 years and living in the Skåne region at the end of 2007) in the SHR who, during the period 2003-2007 had been given a physician-confirmed diagnosis of spondyloarthritis (SpA) as identified by ICD-10 codes. Eligible individuals in the study presented in Paper IV were a subgroup of the SpAScania cohort, namely those with a diagnosis of PsA (Table 4) registered in the SHR. In addition, the diagnosis should have been given at least once by a rheumatologist or internist or at least on two separate occasions by any other physician.

Referent cohort

A population-based referent cohort was created by identifying three referents by means of the Swedish Population Register (SPR) for each included patient matched for year of birth, sex, and municipality. The referents had to be alive and residents in the Skåne region on December 31, 2007, and they were also required to have no history of registered healthcare use consistent with PSO or PsA in the SHR 1998-2011. The referent cohort was used in Papers II-III.

Table 5. Outline of Papers I-IV regarding study populations and their characteristics.

	Paper I Prevalence	Paper II Costs	Paper III Disparities in healthcare use	Paper IV Patient outcomes and drug treatment
Psoriasis cohort	✓	✓	✓	
The SpAScania cohort				✓
Referent cohort		✓	✓	
Patient inclusion period	2005-2010	1998-2007	1998-2007	2003-2007
No. of patients	16171	15283	14450	885
No. of PSO patients	13185	12562	11793	NA
No. of PsA patients	2986	2721	2657	885
No. of referents	NA	45849	43350	NA
Ages included	All ages	All ages	≥19 years of age	≥15 years of age
Mean age (SD) at end of inclusion period	53 (19)	52 (19)	54 (17)	56 (12)
Women, %	49%	50%	51%	57%

NA=Not Applicable
SD=Standard deviation

Data Sources

The data sources used in Papers I-IV are described below, and illustrated in Table 6. Figure 2 shows the study periods for Papers I-IV, and for what purpose and during what period information from the different data sources were used.

Register data

Skåne Healthcare register

The SHR holds information transferred from both computerized medical records and from administrative application sources on all healthcare utilization in the Skåne region from 1998 and onwards. In the register, data on all primary care and specialized outpatient and inpatient care is continuously collected for individuals living in the Skåne region, including personal identification number (PIN), age, sex, health care provider (physician, nurse, physiotherapist and other), date of visit and diagnostic codes according to ICD-10. Private and public care is registered in exactly the same way in the SHR except for the diagnostic codes in private care which are not forwarded to the SHR. The SHR is an administrative healthcare register, which is continuously affected by management and economic

changes in the Skåne region. The completeness of the medical diagnoses in the SHR has increased gradually over the years, from only 15% in the start year of 1998 to over 90% in year 2008. Especially after 2004, the coverage has dramatically changed. This is likely due to the introduction of a direct connection between reporting diagnosis and reimbursement [146].

Swedish Population Register

The Swedish population register (SPR) is the civil registration of vital events (e.g. births, deaths, marriages, residential area) of all Swedish inhabitants, administered by the Swedish Tax Agency. The register is continuously updated and used for a variety of purposes by official authorities, and by healthcare providers. In the register, all citizens are identified by their unique PIN. As Swedish citizens are free to seek healthcare almost wherever they want in the country, we linked data from SHR to SPR to exclude non- Skåne residents from the study populations. We also identified deaths and relocations by use of SPR.

Social Insurance Register

In Sweden, you are entitled to sickness benefit when you are unable to work due to disease or injury. Sickness benefit is generally limited to one year but can be extended. You receive compensation from day two and if you are employed, your employer will pay sick pay for day two to 14, and from day 15 you receive sickness benefit. If your work ability is permanently reduced by at least 25% you can receive a disability pension. All sick leave periods exceeding 14 days, and all disability pension are administered by the Swedish Social Insurance Agency (SSIA). The SSIA register includes dates, type and amount of sick leave and disability pension as well as diagnostic codes according to ICD-10 (one main diagnosis for sick-leave and two main diagnoses for disability pension) For individuals only sick listed seven days or less no data exists in these registers. For those individuals with a work disability lasting 14 days and longer all data, from day one, are included in the register. If you are unemployed you will get compensation from day two from the SSIA. Sick leave and disability pension can be granted for 100, 75, 50 or 25% of a working day depending on the extent to which your work ability is reduced.

Lisa database

The longitudinal integration database for health insurance and labour market studies (LISA-database) is administrated by Statistics Sweden and holds annual registers since 1990, and includes all individuals 16 years of age and

older that were registered in Sweden as of December 31 for each year. The database integrates existing data from the labour market, educational and social sectors and is updated each year with a new annual register.

Swedish Prescribed Drug Register

The Swedish Prescribed Drug register (SPDR) is a national individual level data register where all dispensed prescribed drugs to the entire Swedish population are registered since 1 July 2005, with estimated national coverage close to 100% [147]. The SPDR includes dispensed item according to the Anatomic Therapeutic Chemical Classification (ATC), dispensed amount, personal identification number, age and sex, date of prescribing and dispensing, and costs. Information on the indication for treatment is not collected in the register, and since the register holds data on dispensed drugs it is not known what was actually prescribed or used by the patient.

South Swedish Arthritis Treatment Group Register

The South Swedish Arthritis Treatment Group Register (SSATG) is a clinical protocol for monitoring the performance of biological treatment for patients with rheumatic diseases, involving 12 rheumatology units in southern Sweden. The register was set up in 1999 and constitutes a large, prospective population-based cohort. The coverage for the Skåne region has been estimated to 90-95% for the years when the patients were enrolled [148]. By early 2012 the SSATG register comprised more than 4,900 patients with over 7,600 biological treatments. In 2012 SSATG merged with the Swedish Rheumatology Quality Register holding national data on biological-treated patients at rheumatology units in Sweden.

Medical records

Medical record information was use to validate the diagnostic codes for PSO and PsA registered in the SHR. Information from the primary care medical records was delivered on paper, while information from the specialized care medical records was made available electronically.

Survey data

SpAScania Questionnaire

Information related to the patients in the SpAScania cohort were collected by means of two questionnaire surveys. The first SpAScania questionnaire (2009

SSQ) was sent out between May and August 2009 to all patients in the SpAScania cohort who were ≥18 years of age, still alive and resident in the Skåne region at the time (n=5,771). The second survey (2011 SSQ), a repeat of the first survey, was sent out between November 2011 and January 2012 excluding patients who had declined to participate in the first survey. Reminders were sent on two separate occasions within ten weeks of the first mailing.

The SSQs consisted of a number of well-validated self-reported outcome instruments, in addition to questions on patient characteristics, demographics, and lifestyle issues. Both SSQs had the same content, except for a few questions that were different in the follow-up. The SSQs were drawn up by a panel of three physicians (two specialists in rheumatic diseases and one general practitioner), three physiotherapists (specialists in rheumatic diseases), and one health economist. Before the first survey, the composite SSQ was tested in three focus groups, consisting of 20 patients in total, with different SpA diagnoses, and one patient research partner from the Swedish Rheumatism association in order to improve face and content validity. This resulted in minor corrections to improve patients' understanding. Data from the SSQs has been used in several studies [139, 149].

Table 6. Data sources used in Paper I-IV.

Data sources	Paper I Prevalence	Paper II Costs	Paper III Disparities in healthcare use	Paper IV Patient outcomes and drug treatment
Skåne Healthcare Register (SHR)	✓	✓	✓	✓
Swedish Population register (SPR)	✓	✓	✓	✓
Social insurance register (SSIA)		✓		✓
Longitudinal integration database for health insurance and labour market studies (LISA)			✓	
Swedish Prescribed Drug Register (SPDR)		✓	✓	✓
South Swedish Arthritis Treatment Group Register (SSATG)				✓
Medical records	✓			
SpAScania Questionnaire (SSQ)				✓

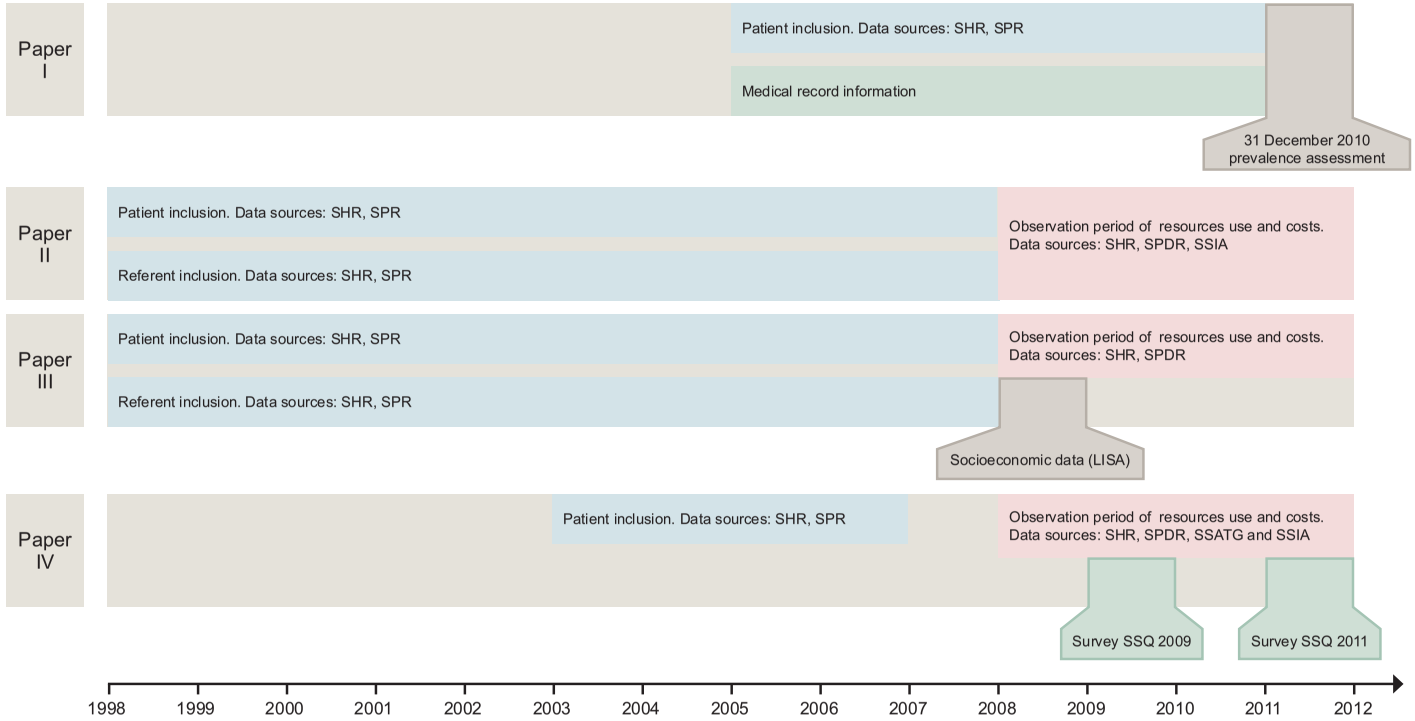

Figure 2: Overview of study periods and data sources used in Papers I-IV
SHR=Skåne Healthcare Register, SSIA=Social insurance register, SPDR=Swedish Prescribed Drug Register, SSATG=South Swedish Arthritis Treatment Group Register, SSQ=SpAScania Questionnaire

Validation of diagnostic codes

In Paper I, we validated the ICD-10 diagnostic codes in SHR for two groups of patients: those with PSO alone (PSO) and those with PSO and PsA (PsA). In the latter group, we validated only the diagnostic codes consistent with PsA (Table 4). The individuals with PSO alone and PsA were divided in five groups respectively according to how frequent the code appeared within the same patient (frequency of diagnostic codes) and level of care during the six-year study time window (2005-2010) (Figure 3).

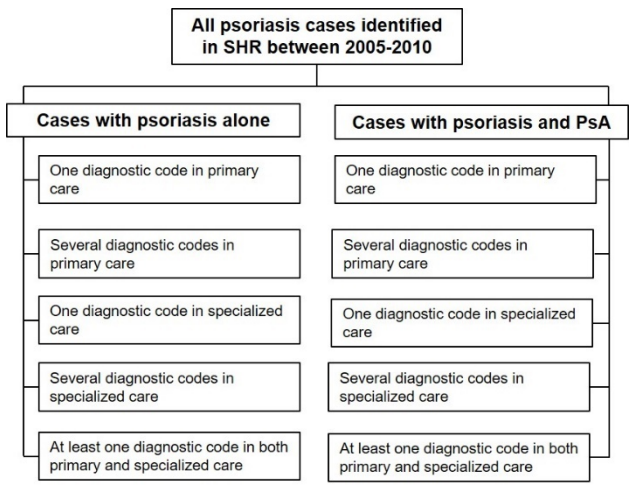

Figure 3. Subgroups according to frequency of diagnostic codes and level of care in diagnostic code validation procedure.

In each subgroup, 20 individuals were selected at random, which in total added up to 100 selected individuals for the validation of the diagnostic codes for PSO alone and PsA, respectively. For all physician visits (any physician) registered in SHR at which the patients had received any diagnostic code consistent with PSO or PsA during the period 2005-2010, the corresponding medical record notes were thoroughly read for validation of whether the diagnostic code captured in the SHR truly reflected PSO and PsA. For individuals with a diagnostic code for PSO alone or PsA both in primary care and specialized care we started by reviewing the specialized care medical records.

For the review of the medical records we used two separate extraction forms, one for the PSO alone and one for PSO (not displayed in thesis). Both forms were developed by one experienced dermatologist and two experienced rheumatologists. The form used for the PSO alone consisted of questions regarding heredity, rash, scaling, nail involvement and localization of skin changes. In addition to this it was possible to include other information, e.g. patient history and pharmaceutical treatment from the medical record with relevance for the verification of the psoriasis diagnosis. Based on this information it was decided whether the PSO diagnosis was 1) verified, 2) unverified due to insufficient information or 3) verified as a non-PSO diagnosis. In the form used for the validation of the diagnostic codes for the PsA patients one common classification criteria for PsA, the classification Criteria for Psoriatic Arthritis (CASPAR) was used as the standard (not displayed in thesis) [150]. For patients not fulfilling the CASPAR criteria it was still possible to qualify as a valid case if the medical records included additional information with relevance for the verification of the PsA diagnosis. Based on the information in the predefined form it was decided whether the PsA diagnosis was 1) verified from an overall assessment of the medical record, 2) not verified due to insufficient information in the medical record, 3) verified as a non-PsA diagnosis. Finally, we applied the CASPAR criteria alone.

The reviews of the medical records and a preliminary completion of the extraction forms were performed by an external physician with experience form both the dermatology and rheumatology field. After this initial phase, one dermatologist and one rheumatologist reviewed all the forms for PSO and PsA and made the final decision regarding the accuracy of the diagnosis. In cases of ambiguity, the specialized physicians reviewed the medical records again.

Occurrence of disease

In paper I, four different prevalence estimates were calculated pre- and post-validation (Table 7). The point prevalence of physician-diagnosed PSO and PsA was estimated by dividing the number of individuals who met our inclusion criteria by the number of residents living in the Skåne region by 31 December 2010. By means of the individuals' PIN, data were linked from the SHR to the SPR to exclude those who were no longer alive or no longer residents in the region by the end of 2010. In the calculation of the prevalence

estimates, the figure used for the number of residents living in Skåne was reduced by 15% to adjust for the uncertainty generated by the loss of patients consulting only private practitioners and whose diagnoses are not forwarded to the register (although the patients PIN and date of consultations are). For a detailed reasoning behind the magnitude of the deduction used, see a previous article from our group [151].

Table 7. Prevalence estiamtions in Paper I.

	Numerator	Denominator
1.	Psoriais patients with or without psoriatic arthritis	Skåne region population
2.	Patients alone	Skåne region population
3.	Patients with psoriais and psoriatic arthrtis	Skåne region poulation
4.	Patients with psoriais and psoriatic arthrtis	Psoriasis poulation

Costs calculations

Cost calculation perspective

Resource use and associated cost data were used in Papers II-IV. We used a prevalence approach and the cost calculations had a societal perspective. All costs were expressed in 2011 Euros (1 Euro=9.03 Swedish krona in 2011). All costs were inflated to the 2011 price level using consumer price index. We calculated the mean annualized total cost per patient over the period 2008-2011, and adjusted the observation time for drop outs due to relocation from the region or death.

Two strategies for analyzing costs between groups were used. First, we calculated the incremental mean annualized cost as the mean difference in costs of all-cause healthcare resource use and productivity losses between the PSO and PsA patients and the individuals in referent cohort. This method is preferred when there is reason to believe that non-disease related costs are present [152]. Second, in Paper II we also estimated the costs specifically attributable to PSO and PsA problems, and analyzed whether these costs were equivalent to the incremental costs [142].

Direct costs

To attach monetary value to each individual's healthcare visits/inpatient stays we used center-specific unit costs from the SHR. Costs are allocated between

different weighted visits and inpatient stays according to the diagnostic related-groups (DRGs) system which classifies healthcare episodes based on diagnoses, medical procedures, sex and age of patient [153]. Due to various administrative database reasons, we were not able to retrieve costs for all healthcare contacts during the observation period. Costs for privately organized healthcare were not covered at all in our SHR dataset. In public primary care, the share of missing cost data increased from zero in 2008 to an average of 34% in 2011. In public specialized care, less than on average 10% of the cost data were missing. The methods used to estimate missing cost data are presented in Table 8.

Table 8. Cost estimation methods for healthcare contacts with missing cost values in the SHR.

	Public healthcare	**Private healthcare**
Primary care	Yearly fixed cost according to regional pricelists [154] for: - Physician vist - Nurse visit - PT/OT visit - Other healthcare provider categories	Yearly fixed cost according to regional pricelists[154] for: - Physician vist - Nurse visit - PT/OT visit - Other healthcare provider categories
Specialized care	Yearly average cost for healthcare provider categories with costs in SHR: - Rheumatologist/Dermatologist/Internist visit - Other physician visit - Nurse visit - PT/OT visit - Other healthcare provider categories visit - Inpatien stay	Yearly average cost within the public specialized care for healthcare provider categories with costs in SHR: - Rheumatologist/Dermatologist/Internist visit - Other physician visit - Nurse visit - PT/OT visit - Other healthcare provider categories visit - Inpatient stay

PT=Physiotherapist
OT=Occupational therapist

To assign monetary value to drug use, the cost variable in SPDR was used. This variable refers to the pharmacy wholesale prices including costs paid by the patient and subsidy paid by the healthcare region. Costs due to drugs given in hospitals are covered in the healthcare costs as the SPDR does not include data on drugs used in hospital, and only partially drugs that are used in ambulatory care but administered in daycare at hospitals (e.g. infusion administered biological drugs). The drug use was classified in four categories (Table 9) based on the ATC classification. For information on which drugs were included in the different categories, see Paper II.

Table 9. Classification of drug use in Paper II.

	Categories of drug use
1.	Biological drugs
2.	Non-biologicla drugs
3.	Topical emollients
4.	All other drug use

Indirect costs

We valued the loss of productivity following the human capital, i.e. we included all accumulated days of sick leave and disability pension [41]. A monetary value was assigned to the productivity losses using information from "Ekonomifakta" about the average gross income (with social fees added) for women and men in the employed workforce in Sweden 2008-2011[155]. A full-time working schedule in Sweden is normally 40h (8 hours for five days a week). However, there are also part-time schedules which means less than 40 hours a week. In our data, we did not have information about the individuals' actual working schedules. We only had information about the extent of the sickness benefit. Therefore, as not to overestimate the cost due to productivity losses on the aggregated level, we assumed a stipulated full-working schedule for all individuals in the study, but we reduced the full-time salary for women by 12.5%. The rational for this reduction was that The Labour Force Survey (LFS) from Statistics Sweden shows that Swedish women 20-65 years of age worked on average 35 hours per week during the period 2008-2011 [156]. The corresponding figure for men was 40 hours per week. Sick leave was defined as net sick days. Net sick days are the total number of days for which sickness benefit or disability pension payment is received from the SSIA, multiplied by the extent of the sick leave or disability pension for each day (e.g., 20 sick days with 25% of a day extent are equal to five net sick days). We multiplied the average day salary by the number of net-sick days.

Psoriasis and psoriatic arthritis attributable costs

We defined healthcare consultations and work loss episodes as attributable to PSO and PsA problems if registered with an ICD-10 diagnostic code associated with these diseases (Table 4). For healthcare costs, the calculation was possible to perform for publicly provided healthcare (physician visits in primary and secondary outpatient care and inpatient care), as we lacked information about ICD-10 diagnostic codes for private healthcare providers.

For filled prescriptions, drugs and associated costs in categories one to three (in Table 9) were defined as related PSO and PsA problems.

Healthcare use, socioeconomic factors and need

In Paper III, we investigated the influence of socioeconomic and demographic factors on the probability of healthcare use and on healthcare costs respectively, controlling for healthcare need using regression analysis.

Outcome variables

First, we analyzed factors affecting the risk of use of five types of healthcare services during the period 2008-2011 (Table 10). Second, we analyzed the mean annualized costs due healthcare use including costs of drugs for people with at least some service at all during the period 2008-2011.

Table 10. Types of healthcare services as outcome variables in Paper III.

Leve of care	Healthcare provider categories
Primary care	Physician visitis
Primary care	Non-physician visits*
Specialized care	Physician visitis
Specialized care	Non-physician visits*
Inpatient care	NA

* Nurse, physiotherapist, occupational therapist etc
NA=Not applicable

Explanatory variables

Information related to 2008, the first year of the study period, on education, income, country of birth was retrieved from the LISA-database at Statistics Sweden.

Education

Level of education was defined as the highest achieved level of education and three groups were defined: 'Low' = 0–9 years, 'Medium' = 10–12 years, 'High' = 13 or more years. The group "Medium" was used as reference category.

Income

Individualized disposable household incomes (including wage, transfers and taxes) was categorized into five income quintiles for all individual groups in the study population. The third income quintile ("median") was used as reference category.

Country of birth

The variable country of birth was split into two groups: "Nordic origin"= subject and both parents born in the Nordic countries (Sweden, Denmark, Norway, Island and Finland), and "non-Nordic origin"=the subject or at least one parent born outside the Nordic Countries. Born within the Nordic countries was used as reference category.

PSO, PsA and additional morbidities

We used the presence of PSO and PsA respectively as the primary healthcare need variables. We also used additional morbidity variables to control for need. Presence of the following morbidities (no/yes) in any individual were identified as: at least one healthcare contact during the study period in SHR with a physician confirmed diagnosis (main or secondary) of a metabolic (ICD-10 codes E00-E90), mental (ICD-10 codes F00-F99) or circulatory (ICD-10 codes I00-I99) disease. Table 1, in Paper III presents proportions of individuals with a contact within the three disease chapters but also within well-known subgroups within these broader groups. The reason for controlling for entire ICD-10 diagnostic chapters and not specific diagnostic codes was that we wanted to encompass as much as possible of the underlying morbidity.

Regression models

Equation [1] presents a linear version of our empirical model of the form variable (coefficient): PSO/PsA diseases ($\beta 1$) metabolic disease ($\beta 2$), mental disorder ($\beta 3$), circulatory disease ($\beta 4$), education ($\beta 5$), income ($\beta 6$), born within/outside a Nordic country ($\beta 7$) and error term (ε). The same set of variables were included in 1) Cox-regressions of the decision to use healthcare or not in any given time time-point (y=0/1); and 2) semi-logarithmic linear regressions of the mean annualized healthcare costs (y=ln(cost)).

$$y=\alpha + \beta_1 PSO/PsA + \beta_2 Metabolic + \beta_3 Mental + \beta_4 Circulatory + \beta_5 Edu + \beta_6 Income + \beta_7 CountryofBirth + \varepsilon \quad [1]$$

We modified the equation [1] by separately adding alternative interaction terms with PSO and PsA. The rationale for including interactions between PSO and PsA respectively and the other explanatory variables was to explore the potential variability of the size of the estimated effects within different strata of these variables for the PSO and PsA patients in addition to the direct effect of each variable. Combinations of base and interaction effects were explored in 6 different models as shown in Table 11. We did not use the interaction Models (Models 3-6) in the analysis of the probability of healthcare use. As the material was stratified in many levels and few individuals had zero healthcare use (see Paper III) there were too few values in different data cells for analysis.

Table 11. Versions of equation 1 used in Paper III.

Model	Included explanatory variables
Model 1	PSO PsA Education Income Country of birth
Model 2	PSO PsA Metabolic disease Mental disorders Circulatory disease Education Income Country of birth
Model 3	Model 2 PSO*morbidities (metalbolic disease, mental disorders, circulatory diesease) PSA*morbidities (metalbolic disease, mental disorders, circulatory diesease)
Model 4	Model 2 PSO*Education PSA*Education
Model 5	Model 2 PSO *Income PSA*Income
Model 6	Model 2 PSO*Country of Birth PSA*Country of Birth

Patient-reported outcomes and drug use

Patient-reported outcome measures

In paper IV, four valid, and reliable PROMs, and global health, pain and fatigue from the 2009 and 2011 SSQs were used (described below). Self-reported data on year of symptom start, year of diagnosis, highest level of education, smoking status (never/ever), weight and height were also patients-reported information from the SSQ questionnaire. Information about sex, age and comorbidities was retrieved from SHR.

EQ-5D

The EuroQol five-dimension (EQ-5D) is a health-related quality of life (HRQoL) instrument from which a single-index value of the respondent's health status can be derived, based on a health profile of three levels in five dimensions including mobility, self-care, pain/discomfort and anxiety/depression. [157]. In determining values for the 243 health states defined by the EQ-5D, we used the UK tariff which is widely used [158]. We truncated all the negative values in the tariff to 0. Lower EQ-5D-values reflect decreased HRQoL.

DLQI

The Dermatology Life Quality Index (DLQI) is a non-preference-based PROM developed to measure HRQoL in adults (18+ years) with skin conditions [159]. The DLQI has been validated for people with PSO [160] and has been used for people with PsA [133, 161]. Higher scores reflect a decreased HRQoL.

HAQ

The Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) is a measure of function. HAQ-DI consists of questions about pain and ability to perform activities of daily living and the derived score range from 0 to 3 (best to worst). The HAQ-DI was originally developed for patients with rheumatoid arthritis [162], but has been shown to work well also for patients with PsA [163].

BASFI

Bath Ankylosing Spondylitis Functional Index (BASFI) is a physical function measure consisting of 10 questions related to body function, activity,

participation and environmental factors. The total score range between 0 and 10 (best to worst) and the final score is expressed by calculating the mean [164]. Although the index was primarily constructed and validated for patients with ankylosing spondylitis it has also been used in studies evaluating health status in PsA patients [165].

Additional outcome measures

Global health, related to the joints (GH-joints) and to the skin (GH-skin), pain and fatigue were measured with a numerical rating scale ranging from 0 to 10 (best to worst). Global health has been found a reliable tool for assessing skin and joint activity in PsA patients and is also recommended to be divided into separate measures due to the dual component of PsA [166, 167]. In DLQI, HAQ, BASFI, pain and fatigue the questions related to last week, in EQ-5D to the present day and in GH no time interval was stated.

Classification of drug treatment groups

In Paper IV, outcomes were analyzed in four subgroups characterized by type of drug treatment during four consecutive years (2008-2011). The four drug treatment subgroups were classified according to biological treatment given in real clinical practice during 2008-2011 (Table 12). The focus was on biological drug use overall as a binary outcome variable and not with specific agents (for information on which drugs were included, see Paper IV).

Table 12. Definition of subgroups with different biological drug use schemes during the period 2008-2011.

Subgroup	Biological drug use scheme
Non- biological drug users*	No biological drug use during the period 2008-2011
Continuous biological drug users	Biological use during each year during the period 2008-2011
Beginners	Biological drug use in 2011 but less the four times (years) during the entire period 2008-2011
Irregular users	Biological drug use one or more times (years) during 2008-2010, but not in 2011

* Called never users in text

Statistical analyses

The proportion of correct diagnostic codes (the positive predicate value PPV), was calculated by dividing the number of patients fulfilling the criteria for PSO and PsA by the number of patients in the validation study sample (Paper I). Between-group comparison for fulfilling the criteria were performed using Chi-squared test (only presented in thesis text).

The point prevalence of PSO and PsA in the general population was calculated by dividing the number of identified PSO and PsA patients respectively in the SHR on 31 December 2010 by the Skåne region population on 31 December 2010. 95% confidence intervals around the prevalence estimates were calculated using a binomial distribution. Both the pre-and post-validation estimates were calculated. The post-validation estimates were based on the most conservative estimate of the PPV of the diagnostic codes for PSO and PsA. We also assumed no misclassification of PSO and PsA in the other direction in SHR.

In the cost analysis, the data was pooled over the four-year observational period and expressed as mean annualized cost during the period. Hence, the costs were analyzed as cross-sectional data in the Papers II-IV. In the calculation of the annualized cost the observation time was adjusted for drop outs due to relocation from the Skåne region or death. Arithmetic mean and standard deviation (SD) of cost were reported for the cost data. Two-sample t-test was used to test for differences in normally distributed variables and a Chi-squared test was used for categorical variables.

In Paper III we used Cox proportional hazards regression, with days to first contact as the time variable, to analyze factors affecting the probability of healthcare use. This regression was used as it accounts for differences in observation time due to censoring from relocation and death. The results were presented as hazard ratios (HR) with 95% confidence interval (CI). Observations were censored at the date of death, relocation out of the Skåne region or end of the study period (31 December 2011). To verify the proportional hazard assumption in the Cox model, we plotted the relative hazards over time for each categorical variable. By visual inspection, all of the variables were considered to meet the proportional hazard assumption. In the analysis of the mean annualized healthcare costs we used a semi-logarithmic linear regression to handle the skewed distribution of healthcare costs. Coefficients for categorical variables are interpreted as the percentage difference compared to the reference category.

Both types of regressions in Paper III accounted for the matching variables. The Cox model was stratified by each "pair" of person with PSO and PsA and his/her matched referents [168]. The baseline hazard was accordingly allowed to vary between strata which captured age, sex and residential area. The semi-logarithmic model treated "pairs" of persons with PSO and PsA and referents as a fixed number of strata and included them in the regression as an absorbing categorical factor [169].

Analysis of variance was used to compare differences in mean PROs and costs across the four different drug treatment groups in Paper IV. The analysis was adjusted for sex, age and disease duration for those PROs where these variables seemed to influence the outcome (see Paper IV). In pairwise comparisons of PRO values and costs, the Bonferroni correction method was used. Differences in median PRO and cost values were tested using the Kruskal-Wallis test. Paired t-test was used to test differences in outcomes reported in SSQ 2009 compared to SSQ 2011.

P-values <0.05 were considered statistically significant. We used STATA software v13.0 (Stata, College Station, Texas, USA) for all the statistical analyses.

Results

Validation of diagnostic codes

Psoriasis alone

In Paper I, there were 37,888 physician visits consistent with a PSO diagnostic code registered in the SHR for the cases with PSO alone during the study period 2005-2010. This corresponds to a mean (SD) of 0.47 (0.58) physician-visits per year and patient. A diagnostic code for PSO as primary code were registered for 10,005 (75.9%) of the patients and 7,703 (58.4%) had at least one PSO diagnostic code given by a dermatologist, rheumatologist or internist.

Overall, it was shown that at least 79 of 97[1] (81%) of the validated PSO cases were registered with a correct diagnostic code in SHR (Figure 4). For the rest of the 18 cases (19%), description of lesions and patient history were not sufficient for assessing whether it was PSO or not. Thus, the PPV of an ICD-10 PSO diagnostic code was within the range of 81% to 100%. The number of dermatologist confirmed PSO cases increased in the presence of more than one diagnostic code in both primary and secondary care (Figure 4). There was a significant difference in PPV values between the different groups ($p=0.012$).

Psoriatic arthritis

There were 28,143 physician visits consistent with PsA registered in the SHR for this group of patients. This corresponds to a mean (SD) of 1.57 (1.73) physician-visits per year and case. A diagnostic code for PsA as primary code was registered for 2,719 (91.8%) of the patients and 2,634 (88.2%) had at

[1] We selected 100 cased for validation but medical records for three cases were impossible to obtain due to administrative reasons.

least one PsA diagnostic code given by a dermatologist, rheumatologist or internist.

The minimal number of correctly recorded cases with PSO and PsA according to the overall assessment of the medical records was found to be 59 of 93[2] (63%) (Figure 4). For an additional 27 cases (29%), the information in the medical record was not sufficient to ascertain whether it was PsA or not. Thus, the PPV of an ICD-10 PsA diagnostic code was within the range of 63% to 92%. Seven cases (8%) had probably another diagnosis, e.g. rheumatoid arthritis, gout or osteoarthritis with PSO. The number of patients that strictly fulfilled the classification CASPAR classification criteria (solely based on information in medical records) was 36 (39%). The proportion of confirmed cases increased with at least one code in both primary care and specialized (Figure 4). The increase was even more accentuated for cases with several diagnostic codes rendered in specialized care. There was a significant difference between the groups when using the CASPAR criteria (p=0.046) but not when using the overall medical assessment criteria (p=0.266).

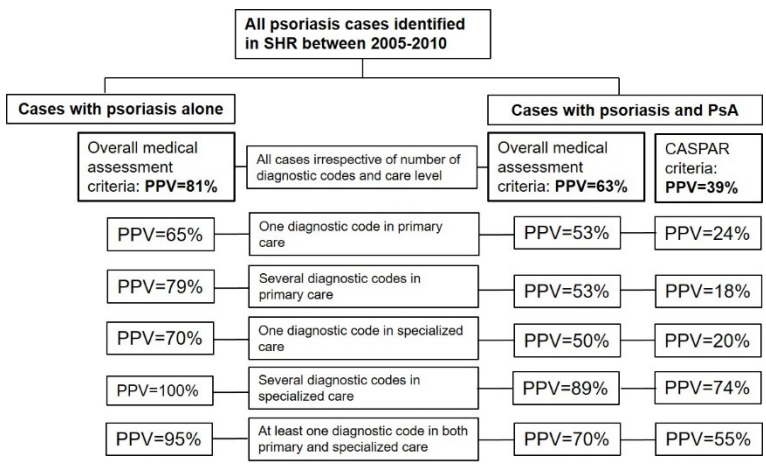

Figure 4. PPV for PSO and PsA cases overall and subdivided according to the frequency of diagnostic codes and level of care. For PsA both overall medical assessment criteria and CASPAR criteria were used.

[2] We selected 100 cases for validation but medical records for seven cases were impossible to obtain due to administrative reasons.

Occurrence

In Paper I, the pre-validation overall prevalence of PSO (with or without PsA) was estimated to 1.53% among 1,055,766 residents of all ages in the Skåne region by the end of 2010 (Table 13). The corresponding figures for PSO alone, PSO with PsA and PsA within patients with PSO were 1.25%, 0.28% and 18.5% respectively. Using the most conservative estimates of the positive predicted value, 81% and 64% for PSO and PsA respectively, the post-validation overall prevalence of PSO and PSO with PsA was 1.23% (Table 14). The corresponding figure for cases with PSO alone was 1.02%. The adjusted prevalence figure for cases with PSO and PsA was 0.21%. The prevalence of PsA cases in the PSO population was adjusted slightly downwards to 17.3% (Table 14). The validation did not change the relative magnitude of the prevalence estimates across sexes.

Table 13. Pre-validation prevalence estimates of physician-diagnosed PSO and PsA by sex in the Skåne region by December 31, 2010.

	Prevalence % of PSO and PsA in the Skåne region population (95% CI)			**Prevalence of PsA in the PSO cohort**
	All PSO cases (n=16,171) in the Skåne region pop. (N=1,055,766)	PSO alone (n=13,185) in the Skåne region pop. (N=1,055,766)	PSO with PsA (n= 2,986) in the Skåne region pop. (N=1,055,766)	PSO with PsA (n= 2,986) in the PSO cohort (N=16,171)
Women	1.54 (1.50-1.57)	1.22 (1.19-1.25)	0.32 (0.31-0.34)	20.8 (19.95-21.72)
Men	1.53 (1.49-1.56)	1.28 (1.25-1.31)	0.24 (0.23-0.26)	16.0 (15.25-16.87)
All cases	1.53 (1.51-1.56)	1.25 (1.23-1.27)	0.28 (0.27-0.29)	18.5 (17.87-19.07)

Table 14. Post-validation prevalence estimates of physician-diagnosed PSO and PsA by sex in the Skåne region by December 31, 2010. Use of the most conservative positive predictive value.

	Prevalence % of PSO and PsA in the Skåne region population (95% CI)			**Prevalence of PsA in the psoriasis cohort**
	All PSO cases (n=12,958) in the Skåne region pop. (N=1,055,766)	PSO alone (n=10,717) in the Skåne region pop. (N=1,055,766)	PSO with PsA (n= 2,241) in the Skåne region pop. (N=1,055,766)	PSO with PsA (n= 2,241) in the PSO cohort (N=12,958)
Women	1.23 (1.20-1.26)	0.99 (0.96-1.02)	0.24 (0.23-0.25)	19.5 (18.54-20.47)
Men	1.22 (1.19-1.25)	1.04 (1.01-1.07)	0.18 (0.17-0-20)	15.0 (14.17-15.93)
All cases	1.23 (1.21-1.25)	1.02 (1.00-1.03)	0.21 (0.20-0.22)	17.3 (16.65-17.96)

Costs

Cost comparisons

Paper II showed that the incremental mean annualized societal cost was 55% higher for PSO and PsA patients compared to referents (€10,500 vs. €6700, p<0.001) (Figure 5), and the costs were significantly higher for PSO/PsA patients through all cost components (all p<0.001) (see Paper II). A higher cost for PSO/PsA patients was identified regardless of sex and age with the greatest absolute difference compared to referents observed among people aged 20-64 years (Figure 6, panel A).

Compared to the PSO group, the PsA group had 97% higher mean annualized societal cost per patient (€17,600 vs. €8,900, p<0.001) during the observation period (Figure 5). This difference was driven by higher costs in all cost components but inpatient care. The difference in costs within primary care was due significantly to more physiotherapist/occupational therapist contacts for PsA patients. The use was tenfold higher for biological drugs and sixfold for non-biological drugs among PsA patients (see Paper II). The difference between PsA and PSO was present in all age groups for both sexes. However, it was most pronounced among women (Figure 6, panel B).

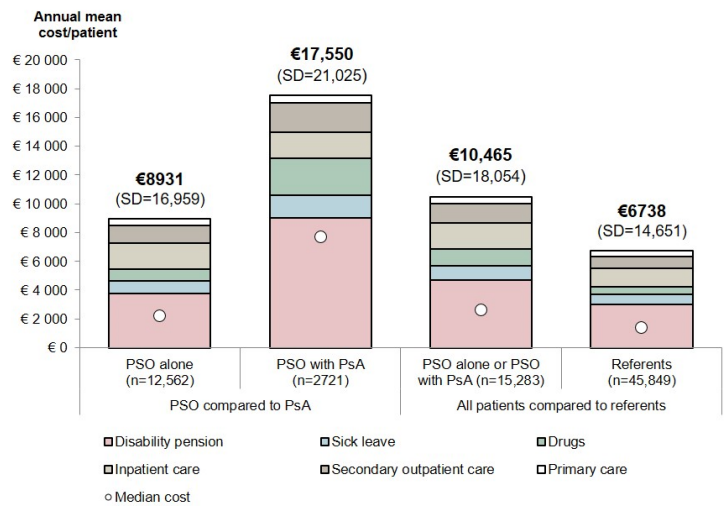

Figure 5. Mean annualized (2008-2011) societal cost over different cost components for patients with PSO and PsA compared to referents, and patients with PSO compared to patients with PsA. The white bullet represent median annualized cost per patient.

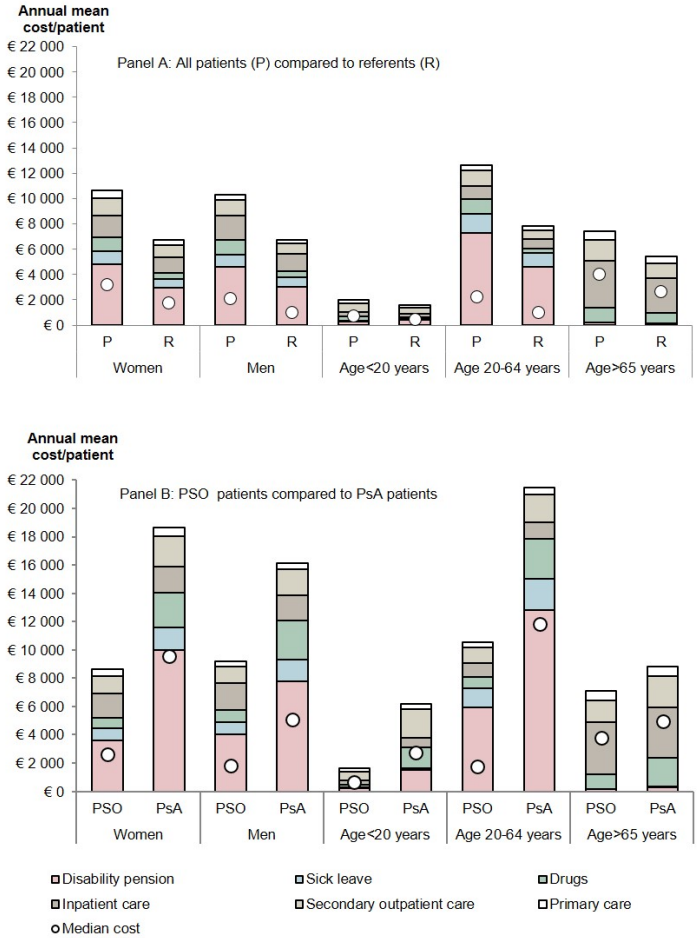

Figure 6. Mean annualized (2008-2011) cost per patient over different cost component. A: Comparison between all patients (P) and referents (R). B: Comparison between patients with PSO and patients with PsA. The white bullet represent median annualized cost per patient.

Distribution of cost sources

Costs due to productivity losses represented the largest share of the total societal costs in all groups with the highest share for PsA (60%) (Paper II). Annualized mean drug cost represented 15% (biological drugs 10%) of the costs for PsA. The corresponding figures for PSO was 9% (biological drugs 1.6%) and for referents 7% (biological drugs <1%).

Costs attributable to morbidity associated with PSO and PsA

The overall proportion of costs identified as attributable to PSO and PsA problems was greatest among the PsA patients (Table 14). For both PSO and PsA, cost due to work loss accounted for the highest proportion of costs attributable to PSO/PsA problems (82% for PSO and 89% for PsA). The proportion of healthcare costs and drug costs attributable to PSO and PsA was highest for PsA patients, 31% and 71% compared to 7% and 26% for PSO patients.

Table 14. Mean annualized cost per patient due to all-resource use and cost attributable to resource use associated specifically with PSO and PsA diagnoses contacts (first and secondary diagnoses) or pharmaceuticals. In Euros.

	PSO patients (N=12,562)			PsA patients (N=2,721)		
	Mean cost due to all resource use[a]	Mean cost due to resource use[b]	Mean cost due to skin and joint problems (% of all costs)	Mean cost due to all resource use[a]	Mean cost due to resource use[b]	Mean cost due to skin and joint problems (% of all costs)
HEALTHCARE						
Primary care physician	271	214	15 (7)	286	225	25 (11)
Secondary outpatient care*	217	155	31 (20)	714	598	395 (66)
Secondary outpatient care**	635	499	3 (0.6)	760	589	31 (5)
Inpatient care	1,778	1,778	135 (8)	1,841	1,841	571 (31)
Total	*2,901*	*2646*	*184 (7)*	*3,601*	*3,253*	*1,022 (31)*
DRUGS	816	816	216 (26)	2,585	2,585	1,844 (71)
PRODUCTIVITY LOSSES***	4,666	4,666	3,803 (82)	10,566	10,566	9,390 (89)

[a] Mean costs in this column include all resource use i.e both public and private healthcare.

[b] For healthcare; mean cost due to resource use (both primary and secondary diagnoses) within only public healthcare providers (approximately 70% of all outpatient physician consultations) as we do not have information about ICD-10 diagnostic codes for private healthcare providers. All inpatient care is within public healthcare providers. For drugs and productivity losses, the mean cost is the same as presentented in the column "All resourse use".

* Outpatient care with dermatologist, rheumatologist or internist.

** Outpatient care with other specialist than dermatologist, rheumatologist or internist.

*** Productivity losses include both sick leave and disability pension.

Healthcare use, socioeconomic factors and need

Study population characteristics

In Paper III, a total of 14,450 patients fulfilled the inclusion criteria for PSO (n=11,793) or PsA (n=2,657) and we had 43,350 referents. The PSO/PsA patients had marginally lower education and were to a greater extent born in the Nordic countries compared to the referents. The PSO and PsA groups, respectively, differed slightly; PsA had a higher percentage of women and young people and individuals born in a Nordic country. The majority of the individuals had at least one outpatient healthcare contact during the four-year study period. Also, as much as 38% and 32% in PSO/PsA and referent groups, respectively, registered at least one inpatient episode. As expected, PSO/PsA patients incurred higher mean annualized healthcare costs during the study period compared to the referents and PsA patients incurred higher costs than PSO patients. For detailed description on characteristics, se Paper III.

Healthcare use

Model 1 in Tables 15a to 15c shows the hazard ratios (HR) and 95% confidence intervals (CI) for primary care, secondary care, and inpatient care use across PSO and PsA and socioeconomic/demographic variables. In Model 2 we also controlled for additional morbidity, i.e. metabolic, mental and circulatory diseases.

In Model 1 the probability of visiting a physician or non-physician professional was significantly associated with PSO and PsA across all healthcare levels with the most pronounced HR for physician visits in secondary care for those with PsA (HR 2.22) (Table 15a). When including additional morbidity (Model 2) PSO/PsA remained significantly associated with healthcare use but to a lesser extent compared to Model 1. Metabolic, mental and circulatory morbidities were highly associated, sometimes even more than PSO/PsA, with a healthcare visit across all healthcare levels. Overall the association was most pronounced for circulatory disease. In Model 1, low education (0-9 year) was consistently associated with higher probability of primary care (Table 15a) and inpatient care (Table 15c) use while the reversed was observed for secondary outpatient care (Table 15b), although the association was only significant for physician visits. When adding the additional morbidity (Model 2), the significant effect of low education disappeared for physician primary care use. High education (>12 years) was associated with lower probability of primary care use both without and with the additional need variables added (Table 15a).

The income gradient worked in two directions. Both those with income below and above the median were less likely to use primary care, secondary outpatient care, and inpatient care with two exceptions; Income quintile 2 had higher probability of use of non-physician professionals in secondary outpatient care (Model 1 in Table 15b) and use of inpatient care (Model 1 in Table 15c). Overall, these results were valid both without and with additional morbidity variables but is noteworthy that in model 2 the significant association between probability of physician use in secondary care and incomes in quintile 4 and 5 disappeared (Table 15b). So did the significant association between non-physician use in secondary outpatient care and income quintile 2. Individuals born outside a Nordic country were significantly more likely to use other non-physician professionals in primary care (Table 15a) and the reverse was observed for inpatient care (Table 15c).

Table 15a. Hazard ratios (HR) and 95% confidence intervals (CI) for the association of primary care use (at least one visit) and presence of PSO/PsA, comorbidities socioeconomic and demographic factors during follow-up 2008-2011. **Primary care use**

Variable[#]	Primary care – physician				Primary care – other healthcare personnel[$]			
	Model 1		Model 2		Model 1		Model 2	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Presence of PSO/PsA[¤]								
No presence (Ref)								
PSO	1.25***	1.22-1.29	1.19***	1.16-1.22	1.20***	1.17-1.23	1.14***	1.11-1.17
PsA	1.29***	1.22-1.36	1.20***	1.14-1.27	1.33***	1.25-1.41	1.23***	1.16-1.31
Metabolic disease[¤, £]			1.33***	1.29-1.37			1.40***	1.35-1.45
Mental disorders[¤, £]			1.49***	1.44-1.54			1.24***	1.20-1.28
Circulatory disease[¤, £]			1.53***	1.49-1.59			1.55***	1.50-1.60
Education[¤]								
0-9 years	1.04***	1.01-1.07	1.02	0.99-1.05	1.00	0.97-1.04	0.98	0.95-1.01
10-12 years (Ref)								
>12 years	0.83***	0.81-0.86	0.86***	0.83-0.89	0.92***	0.88-0.95	0.95***	0.91-0.98
Income[¤]								
Quintile 1 (Low)	0.81***	0.78-0.85	0.81***	0.77-0.84	0.84***	0.81-0.88	0.84***	0.81-0.88
Quintile 2	0.95**	0.92-0.99	0.92***	0.89-0.96	0.98	0.94-1.02	0.96*	0.92-1.10
Quintile 3 (Ref)								
Quintile 4	0.89***	0.86-0.93	0.93***	0.90-0.97	0.93***	0.89-0.96	0.97	0.93-1.01
Quintile 5 (High)	0.84***	0.81-0.88	0.90***	0.86-0.94	0.86***	0.82-0.89	0.91***	0.87-0.95
Born outside a Nordic country[¤]	1.01	0.98-1.06	1.02	0.98-1.06	1.04**	1.00-1.09	1.04**	1.00-1.09
Observations[§]	55,771		55,771		55,783		55,783	

[#] The Cox model was stratified by each "pair" of person with PSO/PsA and his/her matched referents The baseline hazard was accordingly allowed to vary between strata which captured age, sex and residential area. The matching variables are therefore omitted from the explanatory variable list.

[$]Other=nurse, physiotherapist, occupational therapist etc.

[¤]Reference categories are referents, no morbidity, education 10-12 years, income quintile 3 and born in a Nordic country. Ref=1

[£]Metabolic disease =ICD10 group E00-E90. Mental disorders=ICD-10 group F00-F99. Circulatory disease=ICD-10 group I00-I99

[§]Observations with entry and exit on the same day are not included in the analysis.

***p<0.001, **p<0.05, *p<0.1

Table 15b. Hazard ratios (HR) and 95% confidence intervals (CI) for the association of secondary care use (at least one visit) and presence of PSO/PsA, comorbidities socioeconomic and demographic factors during follow-up 2008-2011. **Secondary care use**

Variable[#]	**Secondary care – physician**				**Secondary care – other healthcare personnel**[$]			
	Model 1		Model 2		Model 1		Model 2	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Presence of PSO/PsA[¤]								
No presence (Ref)								
PSO	1.41***	1.37-1.45	1.35***	1.31-1.39	1.41***	1.36-1.45	1.33***	1.28-1.37
PsA	2.22***	2.09-2.36	2.12***	2.00-2.25	2.07***	1.95-2.21	1.93***	1.81-2.06
Metabolic disease[¤, £]			1.26***	1.22-1.30			1.68***	1.62-1.75
Mental disorders[¤, £]			1.50***	1.46-1.56			1.50***	1.44-1.55
Circulatory disease[¤, £]			1.42***	1.38-1.47			1.56***	1.51-1.62
Education[¤]								
0-9 years	0.96**	0.93-0.99	0.94***	0.91-0.97	0.98	0.94-1.01	0.95***	0.91-0.98
10-12 years (Ref)								
>12 years	0.97	0.93-1.00	1.00	0.97-1.04	1.01	0.96-1.05	1.05**	1.01-1.10
Income[¤]								
Quintile 1 (Low)	0.87***	0.83-0.91	0.86***	0.83-0.90	0.94***	0.89-0.98	0.94***	0.89-0.98
Quintile 2	0.99	0.95-1.03	0.96*	0.92-1.00	1.06***	1.02-1.11	1.04	0.99-1.09
Quintile 3 (Ref)								
Quintile 4	0.93***	0.90-0.97	0.97	0.93-1.01	0.86***	0.82-0.90	0.91***	0.87-0.96
Quintile 5 (High)	0.92***	0.88-0.96	0.97	0.93-1.01	0.82***	0.78-0.86	0.89***	0.85-0.94
Born outside a Nordic country[¤]	1.03	0.99-1.07	1.03	0.98-1.06	1.04*	1.00-1.09	1.03	0.98-1.08
Observations[§]	55,744		55,744		55,785		55,785	

[#] The Cox model was stratified by each "pair" of person with PSO/PsA and his/her matched referents. The baseline hazard was accordingly allowed to vary between strata which captured age, sex and residential area. The matching variables are therefore omitted from the explanatory variable list.

[$]Other=nurse, physiotherapist, occupational therapist etc.

[¤]Reference categories are referents, no morbidity, education 10-12 years, income quintile 3 and born in a Nordic country. Ref=1

[£]Metabolic disease =ICD10 group E00-E90. Mental disorders=ICD-10 group F00-F99. Circulatory disease=ICD-10 group I00-I99.

[§]Observations with entry and exit on the same day are not included in the analysis.

***p<0.001, **p<0.05, *p<0.1

Table 15c. Hazard ratios (HR) and 95% confidence intervals (CI) for the association of inpatient care (at least one day) and presence of PSO/PsA, comorbidities socioeconomic and demographic factors during follow-up 2008-2011.
Inpatient care

Variable[#]	Inpatient care			
	Model 1		Model 2	
	HR	95% CI	HR	95% CI
Presence of PSO/PsA[¤]				
No presence (Ref)				
PSO	1.23***	1.18-1.28	1.12***	1.08-1.17
PsA	1.49***	1.38-1.61	1.33***	1.22-1.44
Metabolic disease[¤, £]			1.49***	1.43-1.56
Mental disorders[¤, £]			1.71***	1.63-1.78
Circulatory disease[¤, £]			2.52***	1.38-1.47
Education[¤]				
0-9 years	1.09***	1.04-1.13	1.05**	1.00-1.10
10-12 years (Ref)				
>12 years	0.95**	0.90-1.00	1.03	0.97-1.09
Income[¤]				
Quintile 1 (Low)	0.99	0.94-1.05	0.98	0.92-1.04
Quintile 2	1.10***	1.04-1.16	1.05*	0.99-1.12
Quintile 3 (Ref)				
Quintile 4	0.81***	0.76-0.86	0.86***	0.81-0.92
Quintile 5 (High)	0.75***	0.71-0.80	0.84***	0.78-0.89
Born outside a Nordic country[¤]	0.94**	0.88-1.00	0.91***	0.86-0.97
Observations[§]	55,744		55,744	

[#] The Cox model was stratified by each "pair" of person with PSO/PsA and his/her matched referents The baseline hazard was accordingly allowed to vary between strata which captured age, sex and residential area. The matching variables are therefore omitted from the explanatory variable list.
[§]Other=nurse, physiotherapist, occupational therapist etc.
[¤]Reference categories are referents, no morbidity, education 10-12 years, income quintile 3 and born in a Nordic country. Ref=1
[£]Metabolic disease =ICD10 group E00-E90. Mental disorders=ICD-10 group F00-F99. Circulatory disease=ICD-10 group I00-I99.
[§]Observations with entry and exit on the same day are not included in the analysis.
***p<0.001, **p<0.05, *p<0.1

Healthcare costs

Table 15 shows the β-coefficients and 95% confidence intervals (CI) for the annualized mean healthcare cost across PSO, PsA, additional morbidity variables, and socioeconomic/demographic variables conditional on positive healthcare use at least once during the four-year study period (99% of the PSO/PsA patients and 96% of the referents). Model 1 shows that PSO and PsA were pronouncedly positively associated with healthcare costs: +106% for PsA (β =1.06) and +46% for PSO (β =0.46) compared to the referents. From Model 2 is seen that the presence of other morbidities was positively association with healthcare costs. The most distinct association was noted for the presence of circulatory disease: +77% (β =0.77).

In Model 1, low education (0-9 years) was significantly associated with higher healthcare costs compared to those with medium education (10-12 years) while the reversed was observed for those with high education. The significant associations disappeared when we added additional morbidity variables (Model 2 in Table 16).

Overall, income showed a bell-shaped relationship to healthcare costs with the quintiles 2 and 3 having the highest mean annualized cost (Models 1-6 in Table 16). Higher income (quintiles 4 and 5) was highly associated with lower healthcare cost, as was the low income (quintile 1).

Some heterogeneity with respect to education and income was seen among PSO and PsA, respectively, (Models 4 and 5 in Table 16). While low education overall was associated with higher costs, the marginal effect of PSO and PsA in interaction with low education was negative (–0.12; –0.22) (Model 4). The resulting total effect of PSO and PsA on the mean annualized healthcare costs showed significantly lower costs among those with low education compared to those with medium education (PSO: p=0.04, PsA:p=0.01). The total effect of PSO and PsA and low education was 0.32 (95% CI 0.27-0.37) and 0.82 (0.71-0.92) respectively which is less the effect only of PSO and PsA in Model 2. For PsA, that is almost double costs compared to the reference category (referents with 10-12 years of education). For total effect of education for each stratum within the PSO and PsA groups, see Paper III.

The bell-shaped pattern of income quintiles was preserved, but to a lesser extent when accounting for interactions of presence of PSO, PsA and income (Model 5 in Table 16). The "top of the bell" was found in income quintile 2. Including the interaction terms for PSO, PsA and income increased the base effect of disease in income quintiles 4 and 5 for PSO and in income quintile 5 for PsA. However, this increase was counteracted by the negative effect found in income quintiles 4 and 5. The resulting total effect of PSO and PsA on the mean annualized healthcare costs preserved a tendency for lower healthcare costs among those with low and high incomes, particularly in the PsA group (see Paper III).

Table 16. Linear regression of factors influencing mean annual healthcare costs during the period 2008-2011 (costs are in logarithm form).

Variabels[#]	Model 1		Model 2	
	β	95% CI	β	95% CI
Presence of PSO/PsA[¤]				
No presence (Ref)				
PSO	0.46***	0.43-0.49	0.36***	0.33-0.38
PsA	1.06***	1.00-1.12	0.92***	0.87-0.98
Metabolic disease[¤, £]			0.53***	0.50-0.56
Mental disorders[¤, £]			0.71***	0.68-0.74
Circulatory disease[¤, £]			0.77***	0.74-0.80
PSO/PsA and additional morbidities				
PSO and metabolic				
PsA and metabolic				
PSO and mental				
PsA and mental				
PSO and circulatory				
PsA and circulatory				
Education[¤]				
0-9 years	0.06***	0.03 - 0.10	0.01	-0.02 - 0.04
10-12 years (Ref)				
>12 years	-0.09***	-0.12 - -0.05	-0.02	-0.06 - -0.01
PSO/PsA and education[¤¤¤]				
PSO and 0-9 years				
PSO and >12 years				
PsA and 0-9 years				
PsA and >12 years				
Income [¤]				
Quintile 1 (Low)	-0.05**	-0.09 - -0.01	-0.07***	-0.11 - -0.03
Quintile 2	0.12***	0.07-0.16	0.06***	0.02-0.10
Quintile 3 (Ref)				
Quintile 4	-0.19***	-0.23 - -0.15	-0.10***	-0.13 - -0.06
Quintile 5 (High)	-0.32***	-0.37 - -0.28	-0.19***	-0.23 - -0.15
PSO/PsA and income[¤¤¤¤]				
PSO and income Q1				
PSO and income Q2				
PSO and income Q4				
PSO and income Q5				
PsA and income Q1				
PsA and income Q2				
PsA and income Q4				
PsA and income Q5				
Born outside a Nordic country[¤]	-0.03	-0.07 - 0.01	-0.04**	-0.07 - 0.01
PSO/PsA and country of birth[¤¤¤¤¤]				
PSO and born outside the Nordic countries				
PsA and born outside the Nordic countries				
Observations	54,313		54,313	
R-squared	0.44		0.53	

[#]The dataset is matched for sex, age and residential area and each matched pair is handled as a dummy-variable and absorbed in the model.
[¤]Reference categories are referents, no morbidity education 10-12 years, income level 3 and born in a Nordic country. Ref=0
[£]Metabolic disease =ICD10 group E00-E90. Mental disorders=ICD-10 group F00-F99. Circulatory disease=ICD-10 group I00-I99
[¤¤¤]Reference category is referents with 10-12 years of education. Ref=0
[¤¤¤¤]Reference category is referents with income quintile (Q3). Ref=0
[¤¤¤¤¤]Reference category is referents born in a Nordic country. Ref=0
***p<0.001, **p<0.05, *p<0.1

	Model 3		Model 4		Model 5		Model 6	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
	0.48***	0.45-0.52	0.39***	0.35-0.43	0.26***	0.20 - 0.32	0.35***	0.32 - 0.38
	1.26 ***	1.18-1.34	0.98***	0.91-1.06	0.87***	0.75 – 0.99	0.93***	0.87-0.99
	0.57***	0.53-0.60	0.53***	0.50-0.56	0.53***	0.50-0.57	0.53***	0.50-0.56
	0.76***	0.72-0.80	0.71***	0.68-0.74	0.71***	0.68-0.74	0.71***	0.68-0.74
	0.84***	0.80-0-87	0.77***	0.74-0.80	0.77***	0.74-0.80	0.77***	0.74-0.80
	-0.08**	-0.15—0.00						
	-0.26***	-0.39—0.12						
	-0.14***	-0.21—0.06						
	-0.32***	-0.46—0.19						
	-0.20***	-0.27—0.14						
	-0.44***	-0.57—0.32						
	0.01	-0.02-0.07	0.05***	0.02-0.09	0.01	-0.02 - -0.04	0.02	-0.01 - -0.05
	-0.02	-0.05-0.02	-0.02	-0.06- -0.02	-0.02	-0.06 - 0.06	-0.02	-0.06 - 0.01
			-0.12***	-0.18- -0.05				
			0.00	-0.08- 0.09				
			-0.22***	-0.39- -0.10				
			-0.01	-0.35- -0.09				
	-0.07***	-0.11—0.03	-0.07***	-0.11 - -0.03	-0.09***	-0.14 - -0.05	-0.07***	-0.11 - -0.03
	0.06***	0.02-0.10	0.06***	0.02-0.10	0.06***	0.01-0.10	0.06***	0.02-0.10
	-0.10***	-0.13—0.06	-0.09***	-0.13 - -0.06	-0.14***	-0.19 - -0.10	-0.10***	-0.13 - -0.06
	-0.18***	-0.22—0.14	-0.18***	-0.22 - -0.14	-0.24***	-0.28 - -0.19	-0.19***	-0.23 - -0.15
					0.11**	0.02 – 0.21		
					-0.00	-0.09 – 0.09		
					0.20***	0.11 – 0.29		
					0.20***	0.11 – 0.29		
					-0.03	-0.21 – 0.15		
					-0.04	-0.21 – 0.13		
					0.13	-0.05 – 0.30		
					0.20**	0.02 – 0.38		
	-0.04**	-0.08—0.00	-0.04**	-0.08 - -0.01	-0.04**	-0.08 - 0.01	-0.05**	-0.10 - 0.01
							0.09*	-0.01 - 0.19
							-0.16	-0.40 – 0.08
	54,313		54,313		54,313		54,313	
	0.54		0.53		0.53		0.53	

Patient-reported outcomes in psoriatic arthritis patients

PsA patients in the SpAScania cohort - characteristics

In the SpAScania cohort 2,237 patients were identified as having PsA. Out of those, 1,289 (58%) returned the SSQ 2009 and 1,181 (53%) meet the strict inclusion criteria. Of those covered by the strict criteria, 885 (75%) also answered the SSQ 2011. For flowchart of inclusion, see Paper IV.

Out of the 885 patients included for analysis, 240 (27%) used any biological drug during the study period 2008-2011 according to the SPDR and SSATG registries. 190 patients were registered in both SPDR and SSATG, 43 only in SPDR and 7 only in SSATG. 154 patients (17%) was classified as continuous users, 54 (6%) as beginners and 32 (3.6%) as irregular users (see Table 12 subgroup definitions). Reasons for not being in SSATG but in SPDR were that the drug may have been prescribed by another physician than a rheumatologist or that a registration in SSATG did not occur for some reason.

The overall percentage of women was 57% and the mean age (±SD) was 58 (13). There were no overall differences in the characteristics between the four different biological use groups except for the higher percentage of women (69%) and ever smokers (72%) among the irregular users.

Patient-reported outcomes in SSQ 2009 and SSQ 2011

Table 17 shows PROs in SSQ 2009 and SSQ 2011 across the different biological drug subgroups. Irrespective of PROM used, there were differences in mean PRO values between the four groups both in SSQ 2009 and 2011 ($p<0.001$ across all measures). We found similar results when we compared differences in median PRO values between the groups (data not shown). Patients who did not use biological drugs at all and those who used biological drugs during the entire study period reported overall better PRO values compared to beginners and irregular users.

Table 17. Patient-reported outcomes in SSQ 2009 and SSQ 2011 across biological drug use during the period 2008-2011 for PsA patient (N=885) in the SpAScania cohort. Patients who answered both SSQ 2009 and 2011. Values are given as mean and 95% CI.

	SSQ 2009					SSQ 2011				
	Never¤ n=645	Continuous¤¤ n=154	Beginners¤¤¤ n=54	Irregular¤¤¤¤ n=32	p*	Never¤ n=645	Continuous¤¤ n=154	Beginners¤¤¤ n=54	Irregular¤¤¤¤ n=32	p*
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)		Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
EQ-5D[1]	0.69 (0.67-0.71)	0.62 (0.58-0.66)	0.62 (0.55-0.68)	0.41 (0.31-0.53)	<0.001	0.68 (0.67-0.70)	0.63 (0.59-0.68)	0.61 (0.53-0.69)	0.54 (0.42-0.65)	<0.001
DLQI[1]	3.3 (2.9-3.6)	3.2 (2.5-4.0)	6.3 (4.4-8.4)	6.0 (3.7-8.9)	<0.001	3.5 (3.2-3.9)	3.3 (2.6-4.0)	3.6 (2.2-5.2)	6.5 (4.2-9.0)	<0.001
HAQ[2]	0.52 (0.48-0.56)	0.83 (0.73-0.92)	0.69 (0.52-0.87)	1.10 (0.81-1.30)	<0.001	0.54 (0.49-0.57)	0.86 (0.76-0.96)	0.81 (0.65-0.99)	0.95 (0.71-1.18)	<0.001
BASFI[2]	2.68 (2.50-2.87)	3.65 (3.28-4.09)	3.65 (2.94-4.38)	5.37 (4.44-6.40)	<0.001	2.94 (2.74-3.12)	3.92 (3.51-4.30)	4.32 (3.54-5.06)	4.58 (3.67-5.54)	<0.001
GH (joint)[1]	3.84 (3.69-4.02)	4.07 (3.73-4.43)	4.91 (4.35-5.43)	5.93 (5.17-6.64)	<0.001	4.12 (3.93-4.31)	4.26 (3.87-4.64)	4.57 (3.90-5.56)	5.43 (4.62-6.21)	<0.001
GH (skin)[3]	2.97 (2.79-3.17)	2.65 (2.28-3.03)	4.01 (3.14-4.82)	4.32 (3.15-5.48)	<0.001	2.94 (2.77-3.12)	2.52 (2.19-2.87)	3.16 (2.41-3.96)	4.71 (3.81-5.76)	<0.001
Pain[1]	3.88 (3.71-4.06)	4.11 (3.74-4.51)	5.03 (4.35-5.67)	5.75 (4.99-6.55)	<0.001	4.07 (3.89-4.26)	4.37 (3.97-4.75)	4.52 (3.82-5.20)	5.49 (4.58-6.28)	<0.001
Fatigue[1]	4.39 (4.18-4.60)	4.75 (4.35-5.14)	5.79 (5.14-6.40)	6.05 (5.11-6.92)	<0.001	4.66 (4.46-4.88)	4.98 (4.59-5.41)	5.70 (4.93-6.39)	5.91 (4.90-6.77)	<0.001

¤ Never use=no use during the period 2008-2011
¤¤ Continuous=use during the entire period 2008-2011
¤¤¤ Beginners= use in 2011 but less the four times during the entire period 2008-2011
¤¤¤¤ Irregular use=use one or more times during 2008-2010, but not in 2011
* p-value for differences in mean values across biological drug scheme groups.
1 Adjusted for sex
2 Adjusted for sex, age and disease duration
3 Adjusted for age
EQ-5D range 0-1, where 1 indicates better health
DLQI range 0-30, where 0 indicates better health
HAQ range 0-3, where 0 indicates better health
BASFI, GH (joints), GH (skin), Pain, Fatigue: range 0-10, where 0 indicates better health

Pairwise comparisons of PROs across the subgroups showed that never users, both in SSQ 2009 and 2011, reported significantly better mean values compared to continuous users in EQ-5D, HAQ and BASFI. In SSQ 2009, irregular users showed significantly worse values in EQ-5D (0.41 vs 0.62, $p<0.001$), HAQ (1.10 vs 0.69, $p=0.013$), BASFI (5.37 vs 3.65, $p=0.003$) and GH-joint (5.93 vs 4.91, $p=0.023$) compared to beginners. These differences did not remain in SSQ 2011, where instead the reported values for DLQI (6.5 vs 3.6, $p=0.041$) and GH-skin (4.71 vs 3.16, $p=0.016$) were significantly worse for the irregular users compared to beginners.

Changes in PROs between SSQ 2009 and SSQ 2011

Comparison of the reported values between the two surveys for each biological drug use group showed that the never users reported significantly worse outcomes in BASFI, GH-joints, pain and fatigue in 2011 compared to 2009, while the beginners and irregular users reported improved values regarding the skin (DLQI and GH-skin) and functional status (HAQ and BASFI) respectively (Figure 7). The continuous users remained stable across all PROs between the two surveys.

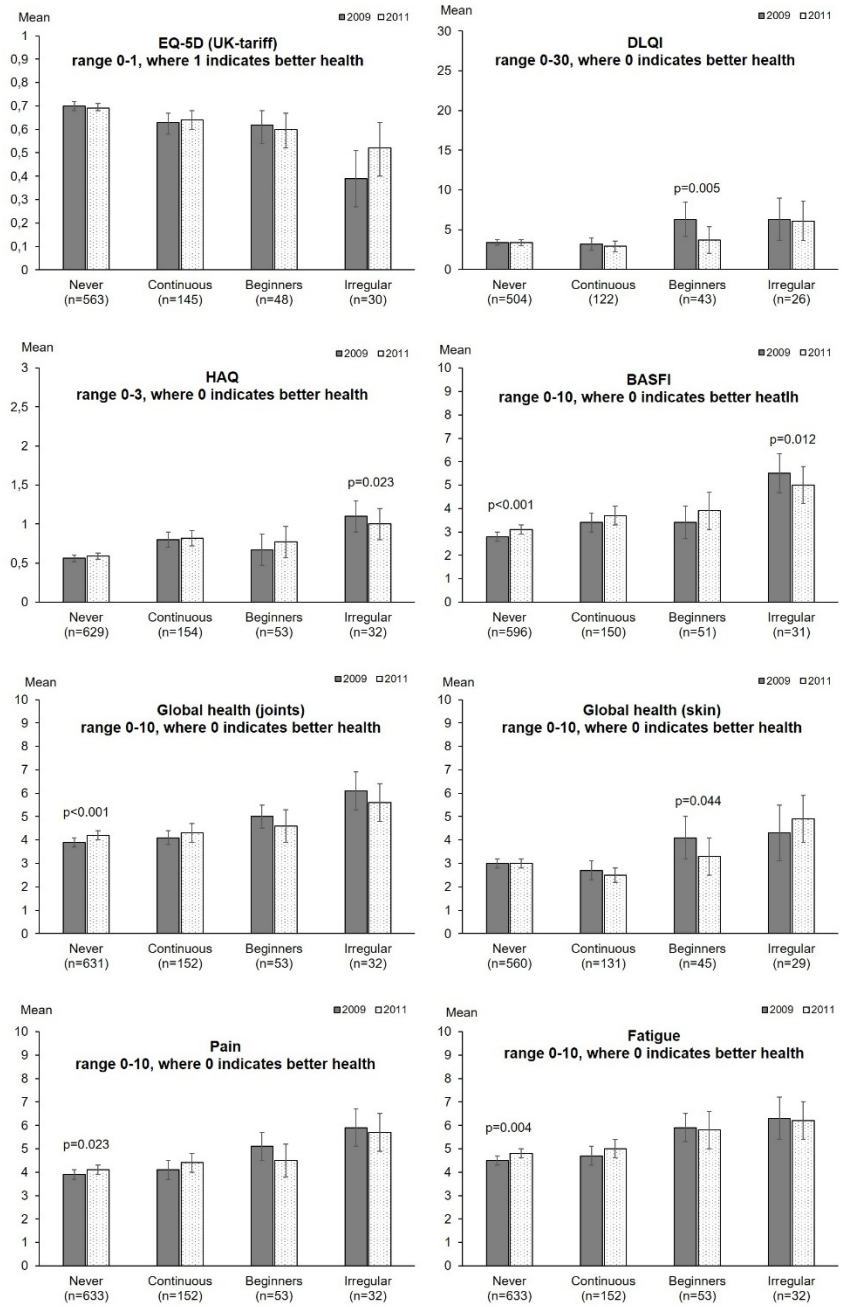

Figure 7. Mean values of PROs in SSQ 2009 and SSQ 2011 across subgroups of biological drug users.

Costs and biological drug use scheme

All cost components varied significantly between the different biological drug use subgroups (Table 18). The overall mean annualized total societal costs were highest for the irregular users. Continuous and irregular users had higher healthcare costs compared to both never users and beginners, but the difference between irregular users and beginner was not significant. The continuous users had higher drug costs compared with all the other groups. There were significantly higher costs due to productivity losses in the irregular users compared to the other groups.

The relative impact of the different cost components differed between the groups. Costs due to productivity losses presented the largest share of the total societal costs in all groups, with the highest share for never and irregular users (68%). Among the continuous users, cost due to drugs and productivity losses accounted for an equal share (40%) of the total costs.

Comparison responders versus non-responders

The responders (n=885) included the patients who answered to both SSQ 2009 and SSQ 2011. The non-responders (n=1,352) included those who responded to only one of the surveys or did not respond at all (see Paper IV). The mean age (SD) was higher for the responders (58 (12)) compared to the non-responders (55(16)). There was a greater proportion of biological drug users among the responders (17%) compared to non-responders (11%). There was no significant difference in mean annualized total societal costs between the two groups, but the responders had significantly higher drug costs.

Table 18 Mean annualized cost per patient for healthcare use, drug use and productivity losses across biological drug use scheme during 2008-2011. Patients who answered to both SSQ 2009 and SSQ 2011. Analysis of variance with adjustment for sex and age.

	Never¤ n=645		**Continuous ¤¤** n=154		**Beginners¤¤¤** n=54		**Irregular¤¤¤¤** n=32		p*
	Mean cost	95% CI	Mean cost	95% CI	Mean cost	95% CI	Mean cost	95% CI	
Annualized mean healthcare costs#	3224	2879-3544	6402	5318-7792	4410	3677-5172	6477	4754-8493	p<0.001
Annualized mean drug costs#, of which	739	655-820	13395	12540-14157	5613	4702-6510	4818	3337-6493	p<0.001
Biological drug	*0%*		*93%*		*84%*		*69%*		
Non-biological drug	*11%*		*1%*		*2%*		*3%*		
Topicals	*6%*		*0%*		*1%*		*3%*		
Other	*83%*		*5%*		*13%*		*24%*		
Annualized mean costs - productivity losses	8599	7311-9856	13510	10678-18527	10905	6939-15419	24555	17110-31874	p<0.001
Annualized mean total societal costs	12562	11177-13840	33309	30240-36541	20928	16604-25327	35850	27843-44384	p<0.001

¤ Never =no use during the period 2008-2011.

¤¤ Continuous=use during the entire period 2008-2011.

¤¤¤ Beginners= use in 2011 but less the four times (years) during the entire period 2008-2011.

¤¤¤¤ Irregular use=use one or more times (years) during 2008-2010, but not in 2011.

Cost for infusion of infliximab is included in the healthcare costs due to registration reasons

* p-value for differences in mean values across biological drug scheme groups.

All costs are expressed in 2011 Euros.

Cost and cost calculations have been described in detail in the method section of the thesis.

Discussion

Main findings

Validation of diagnostic codes

Our results of the diagnostic codes validation analysis (Paper I) suggested that the proportion of correct diagnostic codes varies with frequency of the diagnostic codes and level of care both for PSO and PsA. Similar patterns have been seen in other validation studies on PSO [122, 170, 171] and PsA [104, 171].

Out of those who had received a diagnostic code consistent with PsA at least once in both primary care and specialized care 70% were verified as correct diagnoses in our study. The corresponding figure for a diagnostic code given on several occasions in specialized care was 89%. At the same time, only 45% of the cases with a diagnostic code for PsA in primary care could be verified. These results support the clinical notion that PsA can be difficult to diagnose [104, 172], and indicates that PsA seems to be a disease that needs to be confirmed at least two times, including one time in specialized care. One problem in the validation process was the sometimes limited information given in the medical records, which was especially true for the PSO cases. From this followed that for a number of the patients included in the validation, it was not possible to confirm or regret the diagnosis, and this is the reason why we supposed the calculated PPV-values to be a lower limit for potential confirmed diagnosis.

Occurrence

To our knowledge, Paper I is the first Swedish study in recent years to address population-based estimates of physician-diagnosed PSO, with or without physician-diagnosed PsA, using both primary care and specialized care data, and a proper validation process against medical records. A Swedish study from 1967, using clinical examination as case ascertainment method, reported a PSO prevalence of 1.9% [95] which is slightly higher compared to the PSO (post validation) prevalence of 1.2% estimated in this study. One speculation from these figures is that the prevalence of PSO seems not to have change much over time in Sweden, a thought

supported by a Swedish study on military conscripts [173]. In contrast, a recent study indicated that the prevalence of self-reported PSO has increased during a period of 30 years in Norway [174]. Suggested reasons for this change were lifestyle and environmental factors or an increased awareness of the disease. Compared to PSO, there is less information on the prevalence of PsA in Sweden. We found one other study in addition to the one presented here, also using the SHR, estimating the prevalence of PsA in the population of the Skåne region. This study reported a prevalence of 0.25% which is close to our post validation prevalence of 0.21%. However, that study took a starting point in the SpAScania cohort, where PsA is one of the subtype conditions. The inclusion criteria and time period differed somewhat compared with the present study where the PSO population was the basis [151].

Cost of psoriasis and psoriatic arthritis

The distinguishing feature of our cost study was that we compared several different groups of individuals. First, PSO patients with or without PsA were compared with population-based referents without diagnosis for PSO and PsA. Second, patients with PSO alone were compared with PsA patients. Other Swedish studies have focused on PSO patients with or without PsA. There are three recent Swedish studies estimating the mean annual cost for PSO and PsA patients using data from years 2009-2011. Two register-based studies, Paper II in this thesis and Norlin et al. [117, 175], found lower annual direct costs of PSO and PsA compared to direct costs reported in two dermatology-clinic based questionnaire studies by Ekelund et al. and by Ghatnekar et al. [114, 176]. These differences may be explained by case-mix differences, where register-based studies include a larger proportion of patients with milder disease; different cost components; the data collection period (the latter study was conducted during fall/winter when psoriasis tends to flare). One advantaged of our study is that we also included costs due to primary care use. We found that this accounted for a limited, but non-negligible proportion of societal costs – 5% and 3% for PSO and PsA, respectively. Our study reported lower indirect cost compared to Norlin et al. and Ghatnekar et al. These cost differences may be explained by use of different data sources for collection of data on productivity losses.

Only a minor part of the healthcare costs was attributable to PSO/PsA using primary and secondary diagnoses. In addition, our estimated incremental healthcare costs exceeded those with the narrower diagnosis-based definition. There are a number of studies on the prevalence of different comorbidities, and associated costs in PSO/PsA patients [3, 69, 118] and as we did not want to ignore costs due to comorbidity on the causal pathway, often defined via the secondary diagnoses, we also included these diagnoses. The greater proportion of costs due to work loss, 80%, attributable to PSO/PsA problems may be overestimated as a consequence of

the infrequent updating of the ICD-10 diagnostic codes for new work loss episodes in the SSIA register [177].

One limitation of our cost study is that the data did not allow for analysis of costs across different degrees of clinical severity, an aspect of usual interest in cost studies.

Disparities in healthcare use

By combining a study population of people with specific chronic diseases and a matched population-based referent cohort we were able to explore the effect of non-need variables within the PSO and PsA groups in addition to discern the impact of socioeconomic and demographic variable on healthcare use and cost for the overall study population.

One notable finding in Paper III was that PSO and PsA patients with low education had lower healthcare costs compared to patients with middle and high education, although confidence intervals were overlapping to some extent. Furthermore, the effect of income was bell-shaped, i.e. those with mid income (quintiles 2 and 3) had higher use compared to both those with low and high income. This pattern was also found in the PSO and PsA group but to a lesser extent. Our interpretation of this finding is that mechanism driving costs are distinct in individuals diagnosed with a chronic disease in specialized care. In their case, decisions by a physician and by other personnel govern costs whereas demand-side individual socioeconomic and demographic factors play a less important role for the healthcare use. In contrast, patient groups without a diagnosed chronic disease may not have a regular healthcare contact facilitating access.

In contrast to some previous studies [43, 54, 59, 123] indicating pro-rich use of secondary outpatient care, our results showed that, both for PSO and PsA and across all healthcare service types, people in income quintiles 2 and 3 were more likely to use healthcare and they had higher cost compared to those with lower or higher income. To what extent the results are linked to financial barriers in quintile 1 or have other causes is beyond the scope of this study, but such barriers do not seem to impact on observed use or costs in quintiles 2 and 3. A priori, we assumed low financial barriers as the co-payment paid by the patient in Sweden is low and subject to high cost ceiling. However, a recent Swedish study found some evidence for self-reported refraining from healthcare due to financial reasons among more vulnerable socioeconomic groups [178]. It is worth noting that, in our material, a number of those in income quintile 1 were registered with very low income. Other explanations for our findings may be that those with lower and higher income perceive their health status to be better compared to those with median income or that their preferences for healthcare are different. Socioeconomic and demographic variables

could be correlated with differences in the individuals' preferences for healthcare use, but other data would be needed to address such underlying factors. Usually sex and age are factors included in the study of healthcare use. One shortcoming of our study on disparities is that we could not investigate whether these factors had any influence on healthcare use and costs, as we used a patient cohort with a referent cohort matched for age, sex and residential area.

Observed socioeconomic disparities are not necessary signs of inequity, but a possible interpretation of our results from an equity perspective would be that the principle of horizontal equity, with a definition e.g. as individuals in equal need receive the equal amount of healthcare is violated in our study population. After controlling for the presence of PSO and PsA, and additional morbidity, there was still some effect of socioeconomic variables on both the probability of healthcare use and healthcare costs. There were also some differences related to type of healthcare service level and type of healthcare provider. This implies that simple categorical conclusions as regards presence or not of horizontal inequity in healthcare use opens up further questions, e.g. how to aggregate inequity observed at different healthcare service levels and how different components of inequity should be ranked.

Patient-reported outcomes, drug use and costs

Paper IV indicates that the majority of the PsA patients in the SpAScania cohort seems to be adequately treated. Previous studies on long-term outcomes in PsA patients undergoing biological treatment have shown that improvements in PROs are seen relatively shortly after the initiation of biological treatment and stable thereafter for patients remaining on therapy [135, 138, 140]. The continuous users reported stable PROs but they did not seem to be able to reach the same health status as for the general population. A mean EQ-5D for a defined general population in the Skåne region has been estimated to 0.82 [179]. This compares to a mean EQ-5D value of 0.63 for the continuous users in SSQ 2009. The corresponding value for the never users was higher (mean 0.69) but still lower compared to the general population. Our results also suggest that there is a group of PsA patients with an unmet healthcare need. The irregular users presented overall low PROs and high societal costs. The continuous users had higher costs than never users as expected, but our data also shows sustained functional status and HRQoL values in clinical practice over the study time While earlier studies, using clinical trial and observational data, respectively, found similar differences between continuous and irregular users of biologics in samples of PSO including subgroups of PsA [180, 181], we have focused specifically on patients with a physician-confirmed diagnosis of PsA. Our study population appears to represent a broad group of people with PsA,

which means that the results may constitute a reference to studies applying other selection criteria.

Methodological considerations

Ascertainment criteria

A main criticism towards population-based studies using administrative database sources is the reliance on diagnostic codes for case ascertainment, as these may not reflect the patients' true conditions, i.e. misclassification of disease [8]. The validity of chronic diseases and other disorders in the SHR has been tested in several studies, including Paper I in this thesis [92], and presented PPVs have so far proven to be high [143, 182].

A common case ascertainment method for PSO cases is to rely on dermatologist confirmed diagnosis which means that cases included are mostly those given a diagnosis in specialized care. Our study showed that there is a risk of excluding true PSO cases from a study population relying on these case ascertainment criteria only as many patients actually consult only primary care and also get a correct diagnosis there. We showed that in the Skåne region, nearly one third of those with PSO consulted only primary care physicians and received a correct diagnosis. An American study based on self-reported data described that 78% of the PSO patients consulted a specialist and 22% received care from primary care physicians [183].

As case ascertainment criteria for PsA, we used different combinations of ICD-10 diagnostic codes in the different studies. Papers I-III shared one set of code combinations while another set of codes was adopted for Paper IV. The main difference between these sets of code combinations is that in Paper I-III, a code associated with PSO needed to precede a code for PsA (Table 4). To be included as a patient in Paper IV the diagnosis should have been given once by a rheumatologist or internist or at least twice by any other physician. As this restriction was not used in Paper I-III, it is likely that study populations in these studies included also patients with milder symptoms.

Underestimation of costs using register-based data

The total societal cost for patients with PSO and PsA may be underestimated due to the register-based design. First, our register-based approach did not include direct costs, such as the patients' out-of-pocket payment for OTC-drugs and transportation. In two studies on costs from the patient's perspective, the mean

annual cost per person associated with patient and family ranged from about €500 to €2,100, indicating that such costs may be non-negligible [184, 185]. Also, time spent on skin care at home and performing household chores are important factors to take into account when studying the overall burden of PSO and PsA [186]. It is difficult to know to what extent these estimates can be transferred to a Swedish context. For example, it differs between countries which drugs are subsidized, and travel costs are dependent on the density of healthcare facilities.

Second, we did not capture short-term sick leave as the SSIA-register does not include sick leave periods shorter than 14 days. In a study of physician-prescribed sick leave in the Skåne region during 2009-2010, the short term sick leave (8-14 days) within all musculoskeletal disorders and skin disorders accounted for 15% and 13% of the total number of sick leave periods respectively [187]. In a Finnish questionnaire study, PSO patients reported an average sick leave period of 4.5 hours per month [188]. These studies show that short-term sick leave is present among PSO and PsA patients, but the magnitude of the occurrence is still uncertain. We believe there is a strong need for more research on short-term sick leave using a population-based perspective. Costs due to reduced productivity while at work were also not included. Haglund et al. reported a mean productivity reduction of 20% while at work due to disease related problems for PsA patients [189]. Reduced productivity at work has also been reported for PSO and PsA patients; Mustonen et al. [190] reported a mean productivity reduction of 45%.

Use of the cost variable in the SHR

The use of the cost variable in the SHR is associated with challenges as the variable content for different types of healthcare is dependent on the way the internal healthcare accounting system in the Skåne region works, i.e. some of the data were missing. The costs used for estimating missing data were considered a reasonable approximation, although we probably overestimated the costs for private specialized care. There reason for this is that we based costs in private care on the average costs in the public specialized care where costs usually are higher. However, private specialized healthcare accounted for a small part of total healthcare use during the study period.

Need variables

In the study on healthcare disparities (Paper III), we included morbidity related to metabolic diseases, mental disorders and circulatory diseases in addition to the presence of PSO and PsA as need variables in the regression analyses. Not including total morbidity or self-reported perceived health, the models may have compensated the missing information by over- or underestimating the effect of the socioeconomic

factors on healthcare use and costs due to differences in health across different socioeconomic gradients. The previous literature has pointed to the difficulties associated with defining and measuring need in studies analyzing impact of socioeconomic variables on healthcare use controlling for need [191].

In this context, it is important to note that need can be directly associated with healthcare use, but need can also be indirectly associated healthcare use, mediated by socioeconomic status. These two different pathways are empirically difficult to separate. In the cross-sectional dataset in Paper III, it was possible to study correlations, but it was not possible to decide whether need variables impacts socioeconomic status or not. Due to these difficulties, we have presented equations (Models 1-6) both with a narrow need definition (only PSO and PsA) and with additional need variables with and without interactions with different socioeconomic variables.

Statistical considerations

In the presentation of the main results on costs in Papers II-IV we used mean and not median, as is usually done in the medical research when data are skewed. The reason was that the mean value provides information about the cost for all patients which is the basis for healthcare policy decisions. What happens when using the median value is that the skewness is disregarded in that the effect of seldom, but regularly occurring, costly cases on total costs are underestimated [192, 193].

In contrast to the frequent one-year follow-up of costs in cost studies, we used pooled costs over a four-year period, expressed as annualized mean costs. The advantage of our choice of method is that it generates robust cost estimations with reduced effects of outliers. Furthermore, this method also means that resource use among rare healthcare consumers is included in the calculations.

In Paper III, we used a Cox proportional hazard model to analyze factors affecting the probability of healthcare use, and a semi-logarithmic linear regression to analyze factors affecting the mean annualized healthcare costs. There are plenty of methods suggested for analyzing healthcare resources and costs [194]. The Cox regression is not the most commonly used method but it has been used [195]. We preferred the Cox regression as it accounts for differences in observation time due to censoring in contrast to a logit/probit model. We studied healthcare use during a four-year period of time, and during this period around 10% of the subjects died or moved to another healthcare region and were lost to follow during the entire study period (see Paper III).

An alternative to our strategy to analyze factors affecting healthcare use would for example have been a count data model which is sometime used to describe volumes of healthcare use [194]. We did not use a count data model, as we wanted to analyze

the overall burden of healthcare use and not volume of each type of healthcare service separately. The reason for this is that the impact of various factors can differ depending on the initial treatment contact, and how much care is consumed, However, our results did not indicate any clear patterns in the impact of different factors between the first treatment contact and volume. Furthermore, the count data model does not take into account the overall burden of healthcare use, a dimension that is covered in the semi-logarithmic linear regression model of the mean annualized healthcare costs that we use in the study.

Generalizability

All studies in this thesis were observational and population-based, which is an advantage compared with experimental and or clinic-based studies regarding generalizability beyond the source population. In Papers I-II (all ages) and III (ages above 19 years of age), the study populations included patients with a diagnosis of PSO and PsA given by a physician at any level in the healthcare system as registered in SHR during extensive inclusion periods (Figure 2). This together with the fact that the Skåne region resembles Sweden as a whole on key socioeconomic and demographic variables [144] suggests that the results of the studies also apply to the corresponding populations outside the Skåne region. Concerning the matched population-based referents, it is worth saying these individuals do not mirrors the general population, instead the emphasis is on people at higher ages.

In Paper IV, patients from the SpAScania cohort, given a PsA diagnosis at least once by a rheumatologist, dermatologist or internist alternatively twice by any other physician during the inclusion period, and who answered to the SSQs 2011 and 2011 were used as study population. The non-responders to the questionnaires, and additional missing values for certain PROMs in the questionnaires are limitations, and may have introduced both response bias and information bias affecting the generalizability.

Strenghts

The main strength of the studies included in this thesis is the longitudinal population-based design, with investigation of a large unselected population (approximately 1.3 million inhabitants) in a well-defined geographic region. By using extensive inclusion periods, we also included patients with less-frequent healthcare needs. Furthermore, in contrast to many other studies that are largely based on self-reported data, we exclusively used individual level longitudinal data from regional and national registers to collect information about healthcare use, drug

use and productivity losses. This approach overcomes the risk of recall bias, and also permitted information about drugs use and costs for the non-responders in the survey (Paper IV). Regarding the cross-sectional information, we collected survey data at two different points in time for the patients in the SpAScania cohort. This made it possible to study changes in PROs over time and also to relate this information to different longitudinal drug use patterns.

Limitations

Private healthcare providers (approximately 30% of all physician consultations were within private care during 2008-2011) are registered in the SHR but without diagnostic codes. This means that there may be referents misclassified as free from PSO and PsA if they received a PSO and PsA diagnosis only at private healthcare providers during the inclusion period.

There may also be an underestimation of the costs attributable specifically to PSO and PsA problems in Paper II if the patients were more likely to seek private healthcare providers for their PSO and PsA problems compared to other morbidities. The magnitude of this shortcoming is difficult to estimate but is presumable small. The reason for this is that physician healthcare contacts are not a main cost driver for total costs in PSO and PsA patients. An underestimation of the cost attributable specifically to PSO and PsA problems may also depend on the less complete coverage of ICD-10 diagnostic codes for non-physician consultations (e.g. nurse, physiotherapists etc.) in the SHR. Concerning drug cost, we may have overestimated the proportion of cost attributable to PSO and PsA, as the included drugs could have been prescribed for other indications than PSO and PsA.

Conclusions

A number of conclusions can be drawn from the results presented in this thesis.

- The SHR is a valid register for studies on PSO and PsA, with an overall high PPV for diagnostic codes registered for these diseases.
- It may be useful to perform sensitivity analyses using different case ascertainment criteria, since the proportion of correct diagnostic codes varies with frequency of diagnostic codes and level of care.
- Whenever possible, primary care data should be included in epidemiological and economic studies. Studies on PSO and PsA not including primary care data may underestimate costs by up to 5%.
- The prevalence of PSO and PsA in the Skåne region are comparable with results from previous Swedish population-based studies.
- Compared to matched referents, PSO and PsA patients had higher societal costs with the highest costs for PsA patients. The PsA patients had 97% higher costs compared to PSO alone patients.
- Only a minor part of the costs was attributable to PSO and PsA specifically, indicating an increased comorbidity in these patients. Hence, it would be useful to allocate costs based on other diagnoses registered for these patients.
- For PSO and PsA patients, decisions by healthcare personnel seem to govern costs, while demand-side individual socioeconomic and demographic factors play a less important role for the healthcare use. In contrast, patient groups without a diagnosed chronic disease may not have a regular healthcare contact facilitating access.
- In an unselected population of PsA patients seen in real clinical practice over a period of four years, continuity of biological treatment played to role for PROs and costs. There seems to be an unmet healthcare need in certain PsA patients which ought to be addressed more thoroughly.

Final comments

Overall, by means of observational, population-based studies, this thesis contributes to an increased understanding of the burden of disease in PSO and PsA. This information can be used by researchers and policy-makers within the healthcare sector for the benefit of both patients and society as a whole.

Updated information related to PSO and PsA is highly relevant in a Swedish context, as policy makers have prioritized efforts for improvements in healthcare for these patients. This shows in the recently started work on national guidelines for healthcare related to PSO and PsA, guided by the Swedish National Board of Health and Welfare [10].

While Papers I-II primarily provide basic and methodological information, Papers III-IV have a more analytical approach. The studies on occurrence and costs describe the strengths and limitations of using register-based healthcare data. In addition, these studies also provide updated information on the number of individual seeking healthcare for PSO and PsA, and the costs due to these diseases. We estimated mean annualized pooled cost over a period of four years which generated robust cost estimations. However, it is important also with repeat studies for comparing how the current development in drug treatment alternatives for these patients affects the healthcare use patterns, and what the implications for societal costs are.

Besides increasing the knowledge specifically related to PSO and PsA, the study on healthcare use disparities contributes to the existing empirical literature in the field in general. The information about which disparities of healthcare use exist, and in what way they are systematically related to socioeconomic variables may assist in work with designing adequate policies for improving healthcare services, not only for patients with PSO and PsA, but for patients overall.

We provide information on PROs, measured by several instruments, for PsA patients seen in clinical practice. There seems to be advantages in using standardized PROMs in a systematic way in routine practice for PsA, and today, it is possible to register such information by means of the Swedish rheumatology quality register (SRQ) [196]. However, attempts to embed measurements of PRO systematically in routine practice has revealed many barriers, e.g. logistical, legal and social [197]. From a policy perspective, these issues seem to need further elaboration.

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