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ECONOMIC BURDEN OF PSORIASIS

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ABSTRACT

Psoriasis may cause a substantial economic burden to patients, health service providers, third parties, and the society as a whole. However, all of these costs may not be adequately considered when assessing the treatment costs for psoriasis. Psoriasis may negatively affect work productivity as psoriasis has a relatively high incidence in working age people that lead to possible costs because of lost productivity.

The aims of this thesis were to estimate the economic burden of psoriasis particularly from patients' and health service providers' perspectives and to estimate the background factors (e.g., severity of psoriasis) that may have led to high costs. Another aim was to estimate the total medication costs and to estimate psoriasis' proportion of health-related productivity losses.

The patient sample was based on patients with psoriasis who visited the Department of Dermatology in Turku University Hospital during a one-year study period. These patients were sent a questionnaire. From the patients who gave consent, medication information, clinical information, and number of visits to Turku University Hospital were collected. This data was linked to the information from the questionnaire.

Overall psoriasis was estimated to cause a substantial economic burden for the patient, health service provider, health insurance system, employer, and the society as a whole. The direct costs represented only a small proportion of the overall financial burden of psoriasis, whereas indirect costs were significant. The estimated annual costs for patients and employers were almost twice the costs to health service providers or the Social Insurance Institution of Finland.

In conclusion, the cost contribution of patients and employers should be considered when assessing the costs of different treatments, in addition to commonly studied direct costs of medications and costs to health service providers. Methods used to assess these costs should be well justified and be described clearly to allow comparisons between studies and to evaluate the quality of the results.

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TIIVISTELMÄ

Psoriaasi saattaa aiheuttaa merkittävän taloudellisen taakan potilaille, sairaalapalvelujen tuottajalle, kolmansille osapuolille ja yhteiskunnalle. Näitä kuluja ei kuitenkaan ole otettu aina huomioon, kun psoriaasin kustannuksia on arvioitu aiemmissa tutkimuksissa. Psoriaasi saattaa vaikuttaa negatiivisesti potilaan työkykyyn, sillä psoriaasilla on korkeahko esiintyvyys työikäisissä ihmisissä, aiheuttaen mahdollisesti tuottavuuden madaltumista.

Tutkimuksen tavoitteena oli selvittää psoriaasin taloudellinen kokonaistaakkaa erityisesti potilaiden ja sairaalapalvelujen tuottajan näkökulmasta ja arvioida mahdollisten taustatekijöiden (esim. psoriaasin vaikeusaste) vaikutusta kustannuksiin. Tavoitteena oli myös lääkityksen kokonaiskustannusten arviointi ja arvioida psoriaasin aiheuttamaa osuutta terveyteen liittyvästä työkyvyn menetyksestä.

Tutkimusten aineistoksi valittiin psoriaasia sairastavat potilaat, jotka kävivät Turun yliopistollisessa keskussairaalassa ihotautiklinikalla vuoden tutkimusjakson aikana. Näille potilaille lähetettiin kyselylomake. Suostumuksen antaneilta potilaita kerättiin tiedot käytetyistä lääkkeistä, kliinisiä tietoja ja käynnit Turun yliopistollisessa keskussairaalassa. Nämä tiedot yhdistettiin kyselylomakkeen tietoihin.

Psoriaasin arvioitiin aiheuttavan merkittävän taloudellisen taakan potilaalle, sairaalapalvelujen tuottajalle, sairausvakuutukselle, työnantajalle ja yhteiskunnalle. Suorat kustannukset muodostivat pienen osan kokonaiskustannuksista epäsuorien kustannusten ollessa merkittäviä. Psoriaasin aiheuttamat vuosittaiset kustannukset potilaille ja työnantajille olivat lähes kaksinkertaiset verrattuna sen aiheuttamiin kustannuksiin Kansaneläkelaitokselle tai sairaalanpalvelujen tuottajalle.

Johtopäätöksenä totean, että psoriaasin aiheuttama taakka potilaille ja työnantajille tulisi ottaa huomioon, kun arvioidaan psoriaasin hoitomuotojen kustannuksia ja seurauksia, tyypillisesti huomioitujen suorien lääkityskustannusten ja sairaalapalveluiden tuottajille koituvien kustannusten lisäksi. Näiden kustannusten määrittelemiseen käytettyjen menetelmien tulisi olla hyvin perusteltuja ja selkeästi kuvailtuja, jotta tuloksia voidaan vertailla ja niiden laatua arvioida.

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ABBREVIATIONS AND TERMINOLOGY

Absenteeism	A patient unable to work due to health-related reasons (e.g., sick leave)
ATC-code	The anatomical therapeutic chemical code
Biologics	Infusible or injectable biological medications
BSA	Body surface area
Direct costs	Represent the costs associated with medical resource utilization (e.g., medication costs) and possible expenditures as the result of an illness (e.g., travel costs)
DLQI	Dermatology life quality index
DRG	Diagnosis-related group
FCA	Friction cost approach
Final payer	The party that covers the costs no matter how the party in question is funded (e.g., tertiary level hospital costs' final payers are the municipalities)
FPA	Finnish Psoriasis Association
GP	General Practitioner
HCA	Human capital approach
Health service provider	Includes parties that directly provide health care services, no matter how they are funded (e.g., hospital, health care centre). Costs to health service providers are the costs that are needed to provide the treatments. These costs may afterwards be charged from final payers
ICD-10	International classification of diseases version 10
Indirect costs	Represent the costs of work loss and reduced productivity from illness and disease
Kela	Social Insurance Institution of Finland
NCD	Non-communicable disease
NHI	National Health Insurance

NS	Statistically non-significant
$p<0.05$	Results with P values less than 0.05 were considered to be statistically significant
PASI	Psoriasis Area and Severity Index
PDI	Psoriasis Disability Index
Presenteeism	A patient with lowered working performance due to health related reasons but not off work
PsA	Psoriatic arthritis
Psoriasis	Refers to all types of psoriasis patients who have skin symptoms, unless otherwise mentioned (patients may also have psoriatic arthritis)
PUVA	Ultraviolet-A phototherapy with psoralen
QALY	Quality Adjusted Life Years
QOL	Quality of Life
SF-36	Short form - 36
Societal costs	Costs to all possible parties, includes both direct and possible indirect costs
Third party	Other than patients or the health service provider, e.g., health insurance
TUH	Turku University Hospital
UV-Phototherapy	Refers to all types of ultraviolet-phototherapy unless otherwise mentioned
UVB	Ultraviolet-B phototherapy
WHO	World Health Organization
WLQ	Work limitations questionnaire
WPAI	Work productivity and activity impairment

LIST OF ORIGINAL PAPERS

This thesis is based on the following original papers, which will be referred to in the text by their Roman numerals.

I Mustonen A, Leino M, Mattila K, Koulu L, Tuominen R. Treatment costs of psoriasis in a tertiary-level clinic. BMC Health Serv Res 2014 Aug 15;14:344-6963-14-344.

II Mustonen A, Mattila K, Leino M, Koulu L, Tuominen R. Psoriasis causes significant economic burden to patients. Dermatol Ther (Heidelb) 2014 Jun;4(1):115-124.

III Mustonen A, Mattila K, Leino M, Koulu L, Tuominen R. The costs of psoriasis medications. Dermatol Ther (Heidelb) 2013 Dec;3(2):169-177.

IV Mustonen A, Mattila K, Leino M, Koulu L, Tuominen R. How much of the productivity losses among psoriasis patients are due to psoriasis. BMC Health Serv Res 2015 Mar 4;15:87.

1. INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that has no known cure. A third of patients with psoriasis suffer from joint pains and are also diagnosed to have psoriatic arthritis (PsA). Psoriasis may have a negative influence on a patient's life in many ways and may lower the quality of life (QOL). Psoriasis may cause substantial economic burden to the patients, health service providers, third parties, and the society as a whole. However, all of these costs may not be adequately considered when assessing the treatment costs for psoriasis.

Treatments for psoriasis aim at increasing the QOL of patients and reduce symptoms. Psoriasis is an inflammatory disease that can fluctuate from flares to remission. As a chronic disease, the treatment costs are also continuous and span over the patient's lifetime.

Psoriasis can be treated in many different ways. Patients with mild psoriasis are mainly treated with topical ointments and topical medications. UV-phototherapy and traditional systemic medications are mainly used for the treatment of moderate to severe psoriasis. Biological drugs are usually used only after other treatments have failed or the patient has very severe symptoms. The therapy for psoriasis is interesting from a cost perspective in Finland, as the costs of different treatments are reimbursed and managed by different parties. UV-phototherapy is also interesting from a cost perspective, as it is given in series in a hospital setting and thus, may generate a large burden for the patient and the employer as well as the treatment provider.

Psoriasis may have a negative impact on working ability. These factors make psoriasis important to society as psoriasis has a relatively high prevalence in people of working age and thus, may result in substantial productivity loss. In the past decade, productivity loss has been included in cost calculations and found to constitute a considerable burden. Health-related productivity loss may occur when a patient has to take sick leave or when productivity at work is reduced due to a health condition. The latter has not been sufficiently studied in patients with psoriasis.

Comparing the economic burden of psoriasis between countries is difficult because of the different types of social and private insurances, and the considerable variety of methods used in studies of the cost of treatment add to this challenge. When assessing treatment protocols, it would be helpful to have cost assessments from all feasible perspectives. It would also be useful to have economic evaluations to facilitate objective comparison between the treatment burdens of different diseases. These comparisons are gaining importance due to limited resources for health care and expensive novel treatments that are becoming available. Consequently, health care resources should be

used as efficiently as possible in order to gain the most health benefit. From the Finnish perspective, there is currently little information regarding the treatment costs or the overall economic burden of psoriasis.

This thesis and the original papers were designed to discover how the economic burden of psoriasis is spread over different parties. The study was based on patients visiting the dermatological clinic in a university hospital during a one-year study-period, composing a cross-sectional sample. Three data sources were used for information: a questionnaire, medical records, and medication records. This design allowed estimations of the economic burden from different aspects of the same study sample, which has not been reported in this level of detail priory.

The aim of this thesis and of the original papers was to estimate the economic burden of psoriasis from a medical perspective. Experts working in medicine should be more aware of the distribution and the components of treatment costs. While also taking into account the costs of under treatment and the costs from possible productivity losses. To make economically sustainable choices when treating a patient or when making health policy decisions, knowledge about the economic burden may be of more value in the future, as treatment opportunities and costs have been rising. When the medical perspective was chosen as an aim of this thesis, the financing of health services and who the final payer was had to be somewhat omitted.

2. FRAME OF REFERENCE

In previous literature regarding the costs of psoriasis, the costs have been estimated from many different perspectives. Typically, these studies estimate the total burden from a final payer's point-of-view or from a societal perspective. There are also studies estimating the economic burden to the patient or the employer. It is not uncommon that the perspective has not been reported at all or has been reported somewhat ambiguously. Societal costs may be used as a term to describe the overall costs. Doing a comprehensive study on the societal costs is demanding and some not so obvious costs may be dismissed, such as indirect costs from lost time or productivity loss.

The Review of Literature of this thesis was divided in parts according to the original articles. This type of approach allowed reviewing of the literature from many perspectives. First general information of psoriasis and its costs are provided. Then the costs from a health provider's perspective are reviewed. Different treatment options were reviewed separately, which allowed specific assessments of the unique costs of each treatment. This section of the Review of Literature overlaps costs from the health service provider as well as the patients' perspectives due to costs to these parties. Patients' perspective and productivity loss costs were reviewed and especially the pitfalls and possibilities of studying these costs were estimated.

The methodology in prior studies also varies from observational prospective cost-of-illness studies, to retrospective case-control studies or cost analyses that use mathematical models to estimate the costs of treatments. The variety in methods and perspectives used in previous literature frequently inhibits direct comparisons between studies, diseases and countries. Thus, indirect comparisons have been essential when assessing previous literature. These indirect comparisons can be done from many perspectives and some studies have been re-assessed from different perspectives in the review of literature and in the original papers.

Comprising this thesis, the first original study (I) estimated the costs of a tertiary level clinic from a final payer's perspective, which in the Finnish health care setting, were the municipalities. The second original study (II) estimated the economic burden from a patient's perspective, which aimed to make a comprehensive picture of this burden in a Nordic state. The third original study (III) estimated the medication costs from a societal perspective, including shares from both the health insurance and the patient. The final original study (IV) estimated the productivity loss costs from an employer's perspective and aimed to specify the proportion of the total health-related productivity loss that was due to psoriasis. All of these original studies combined allowed comparisons of the relative proportions of different aspects as well as estimating the total economic burden of psoriasis.

These perspectives were chosen because they were estimated to be relevant to decision makers and specialists working in dermatological care. The aim was not to study the financing of social and health services, and thus, the final payer of the costs was not studied.

3. REVIEW OF LITERATURE

3.1. Psoriasis

Psoriasis is a chronic inflammatory disease primarily affecting the skin (1). Recently, the World Health Organization (WHO) listed psoriasis as a non-communicable disease (NCD), alongside diseases such as stroke, heart attack, diabetes, and pulmonary diseases, which indicates the significance of psoriasis. It is one of the most common chronic skin disorders with estimated prevalence varying from 0.5–8.5% in European countries (2-4) with most studies in Europe and the U.S. reporting prevalence varying between 0.5% and 4.6% (2,3,5,6). In a large cross-sectional study, the prevalence of psoriasis in Finland was estimated to be around 2.6% (7). Although psoriasis may occur at any age, the majority of patients report onset before the age of 40 years (8). There have also been suggestions of a bimodal distribution with a second peak of onset at around 50 to 59 years (2,8). Psoriasis has been associated with genetic inheritance, and multiple genes have been associated with psoriasis (1). Especially patients with early onset psoriasis have been associated with genetic inheritance (1).

Psoriasis is caused by the proliferation of keratinocytes, which are activated by cytokines released by activated T-lymphocytes (5). However, the primary trigger of the disease has remained unclear (1,9). Chronic plaque psoriasis or psoriasis vulgaris is the most common form of the disease, affecting 80 to 90% of patients (1,5,9). Other types of psoriasis include inverse psoriasis, guttate psoriasis, generalized pustular psoriasis, pustular psoriasis of palms and soles, and erythroderma (9). Around 5 to 35% of patients with psoriasis also have psoriatic arthritis (PsA) (9-15). PsA has been stated to be an under-reported and under-diagnosed disease (13). PsA usually affects intraphalangeal joints, sacroiliac joints, and/or apophyseal joints of the spine (13).

Severe psoriasis has been associated with several comorbidities including cardiovascular diseases, metabolic syndrome, and depression (8,16-19). Patients with severe psoriasis have been estimate to have higher risk of mortality than age-matched patients without the disease (20,21).

3.1.1. Measurement of psoriasis severity

There are a variety of methods to measure the severity of psoriasis (8). It can be measured by the magnitude and severity of clinical symptoms of skin, e.g., using the psoriasis area and severity index (PASI) and/or assessing the affected body surface area (BSA) (22). PASI values range from 0 to 72, with higher values indicating greater disease activity. PASI values are based on the assessment of the patient's lesions by a

health care professional (23). PASI is calculated from values of four body areas (upper limbs, head, trunk, and lower limbs), which are assessed for the proportion of skin affected (from 0–6) and the severity of the lesions (from 0–4) (23,24). Patients may be considered to have severe disease if PASI is above 10 (25) or above 20 in some sources (24).

The effects of psoriasis on QOL have been measured with many types of questionnaires, including generic instruments, such as short form-36 (SF-36) and dermatology specific instruments such as Skindex and Dermatology Life Quality Index (DLQI) (8,23,26,27). The latter has been commonly used to determine the QOL patients with skin disorders, and the instrument is considered well-validated but has had some defects such as minimal important clinical difference (27,28). DLQI is also the measure used by the current care guidelines in Finland and the Social Insurance Institution of Finland (Kela) to determine the effect that psoriasis has on the QOL (29). There are also psoriasis-specific QOL instruments such as Psoriasis Disability Index (PDI) (27). Although use of a generic instrument allows the impact of psoriasis on QOL to be compared with other diseases, more specific questionnaires may provide more accurate and specific results of psoriasis. DLQI is most commonly used dermatology specific measure (28), in which values range from 0 (QOL not affected at all) to 30 (QOL severely affected). Patients with DLQI above 10 may be considered to have severe disease (25).

In a study (30) performed in the Nordic countries and Faroe Islands, the mean PASI of psoriasis patients was estimated to be 9. However, PASI values were only available for the patients recruited by dermatologists or managed in dermatology departments. These patients had higher self-reported severity scores and lower QOL than the majority of patients recruited by membership of a psoriasis association (30). In a recent large descriptive Belgian study (14) from 2012, mean PASI values were estimated to be 8.5. The authors estimated that the sample consisted of patients with more severe psoriasis who were seeking specialist help and thus, were more likely to participate in their study (14). In this study (14), mean DLQI was 8.7, with 35% of patients reporting DLQI values over 10, indicating a large negative effect on their QOL.

PASI and DLQI measure different aspects of psoriasis (22). There is increasing interest in the impact of psoriasis on the QOL of patients (31), possibly because lower QOL may predict societal costs more accurately than high clinical severity (32-34). However, clinical decision makers have been found to rely on clinical severity more than on QOL (22). PASI values do not distinguish between lesions on visible and non-visible areas, or whether the lesions have an effect on wellbeing. In contrast, DLQI requires patients to be able to estimate the effects that psoriasis has on their wellbeing and QOL (22).

Although PASI values and DLQI values have earlier been shown to correlate only poorly ($r=0.23$) (34), a stronger correlation ($r=0.81$) was recently reported (23). A Dutch study (35) found no significant association between the clinical severity of psoriasis and QOL

measured by the sub-dimensions of SF-36. However, when the authors assessed specific components of PASI, they found a significant correlation between psoriasis lesions located on visible parts of the body and impaired QOL (35).

3.1.2. The costs of psoriasis treatment

Recent reviews highlight the importance of economic aspects of psoriasis treatment (26,36,37). With a growing concern about rising treatment costs, there is a need for information on the cost-effectiveness of novel treatments as well as studies on the total economic burden of chronic diseases, such as psoriasis (36-38). Being a chronic disease, psoriasis requires treatment over a long period and thus costs accumulate, which is important for health service providers, health insurers, and to patients (36,39).

Although there are many studies that include some cost analysis of psoriasis, there is limited number of good quality cost-of-illness studies. A review (26), published in 2012, acknowledged only seven cost of illness studies performed that reached the entry criteria. Even in these studies, the methodologies and results showed wide variations (26). There is a recognized need for harmonization in the methodologies used in these studies (26). Despite the variability between different studies, there are no indications that psoriasis has a small or insignificant economic burden. In large observational case-control studies, patients with psoriasis have been shown to have significantly higher health care costs and higher health care use than matched (at least by sex and age) control patients (40-42).

Even though psoriasis is not a life-threatening disease, it has been stated that the impact of psoriasis on a patient's QOL is so great that high monetary costs may be acceptable (36). However it has been stated that, these costs should only arise from treatments that benefit the patients by relieving symptoms in order to contain the costs for the community (37). Consequently, there is a need for cost-benefit, cost-effectiveness, and cost-utility analyses. In principle, cost-effectiveness analysis is used to estimate the cost to produce a common clinical response (e.g., PASI response) (43). Cost-benefit analysis is used to compare the costs and possible benefits or outcomes in monetary terms of different treatment strategies (43). Cost-utility analysis is used to estimate gained health over time in, e.g., quality adjusted life years (QALYs) and the respective costs of each QALY (43). This enables comparisons between therapies and helps decision makers. While cost-effectiveness analyses may be suitable for testing novel drugs or comparing treatments, cost-utility analysis may be more suitable for decision makers providing treatment policies (37). Cost-benefit analysis may assess treatments with a broader perspective, take future benefits into account, e.g., using an expensive treatment in the early stages of a disease, and may prove to have obvious cost-benefits compared to a more conservative approach (37).

3.2. Health service providers costs

In the USA, Yu et al. (40) and Fowler et al. (42) estimated that the increased need for health care services in patients with psoriasis resulted in an increased cost of around USD 1000 higher than for age- and sex-matched controls in their studies (40,42). Fowler et al. also presented results from a univariate analysis in which comorbidities were not controlled (42). In these analyses the incremental direct costs for patients with psoriasis were around USD 4000 (42). Both studies included patients who had at least one psoriasis diagnosis in their medical records during the study period. In another U.S. study by Crown et al. (41), patients had to have been using systemic medications or to have received UV-phototherapy that resulted in a cohort with moderate to severe psoriasis. The study (41) estimated an annual health service cost of USD 7778, which was over twice the cost of the matched (by age, sex, geographical regions, follow-up time) control group and higher than the costs estimated by Yu et al. (40) and by Fowler et al.(42), who studyied a wider range of patients with psoriasis. After controlling for comorbidities and socioeconomic background factors, the differences between psoriasis patients and the controls remained at a significant level in Crown et al. study (41).

In another U.S. study from 2002, Javiz et al. (44) estimated the annual costs of psoriasis to be around USD 718 per person, of which 22% were the costs of medical service providers (44). There were no control subjects in this study. The lower cost of treatment than found in the studies by Fowler et al., Yu et al. and Crown et al. may be explained by the different methods used. Javiz et al. (44) estimated the costs of psoriasis treatment and not the total healthcare resource consumption of patients with psoriasis. Another U.S study (45), examining the cost of psoriasis treatment from a large insurance database, estimated all visits to health care services before and after initiation of a biologic medication. This resulted in a significantly higher estimated annual cost per patient than estimated by Javiz et al. (44), possibly due to the selection of patients with more severe disease and the inclusion of all possible visits to healthcare service providers, which was similar to the studies by Fowler et al. (42) and Yu et al (40).

3.2.1. Inpatient or outpatient treatment

Inpatient treatment has been reported to generate a substantial proportion of the costs to health service providers. The terminology used to describe patients treated in a hospital ward varies from study to study and includes hospitalization and inpatient treatment. Here, both terms are used according to use in the source paper.

With an 80% drop in hospitalization rate for psoriasis from 1975 to 1995 noted in a U.S. study, Stern et al. (46) stated that hospitalization is a vanishing practice. The decline in the proportion of patients being hospitalized for psoriasis treatment was also evident in a German study (47) using data from 2005 to 2007. However, in 2007, the proportion of patients with psoriasis who were hospitalized for treatment was still considerable at

20% (47). Hospitalization for psoriasis treatment may have decreased due to improved medications, higher usage of systemic medications, increased use of outpatient clinics, and cost containing practices (44,47).

The treatment process, goals, and costs may be different for inpatient and outpatient treatment of psoriasis. Today, a patient with psoriasis is hospitalized only rarely and mainly due to acute flares and exacerbations (48). These hospitalizations enable and require more rapid control and stabilization of symptoms than treatment in an outpatient setting, where the patient seldom is treated due to an acute flare and the time course for symptom relief can be measured in years (48). When deciding the treatments during hospitalization, long-term safety concerns may be of less concern, whereas they are a great concern for a patient treated in an outpatient clinic (48). Such issues can also lead to different cost patterns.

There are only few studies (49,50) about the efficacy of inpatient versus outpatient treatment and these have several acknowledged limitations. In a study (49) from 2000, hospitalized patients were estimated to sustain a better QOL than patients treated in an outpatient setting. However, this study lacked randomization, and the patient sample was small with differences in severity of psoriasis between the patients hospitalized and those treated in outpatient clinics. Thus, the study (49) only implies that inpatient treatment might have been a good choice for patients with severe symptoms and lower QOL compared to treating them in an outpatient setting. In a more recent (2013) study (51) from Germany, patients being hospitalized required extensive treatments, including biologics, though many relapses occurred soon after discharge. In a randomized study (50), inpatient treatment was more effective than the selected outpatient treatment with clearance rates of 85% and 55%, respectively. However, inpatient treatment did not significantly improve the number of days in remission compared with outpatient treatment (50). These findings indicate that hospitalization may be an effective treatment but does not necessarily result in long lasting remission.

3.2.2. The cost of hospitalizations

Hospitalizations are needed for some patients with psoriasis because of acute exacerbations or severe symptoms. These flares may not be adequately treated in an outpatient setting and thus, some hospitalizations cannot be avoided. A comprehensive review (26) stated that the costs of hospitalization have been significant in many studies. In a recent (2013) German study (51), hospitalizing a patient was predicted to increase the direct costs 128% versus treating a patient in an outpatient setting. Overall, there was a 5-fold increase in total costs for the hospitalized patients compared with patients who were not hospitalized (51). In recent studies using data from 2000 to 2012, the proportion of total costs attributed to hospitalization has varied significantly ranging from a few percent up to approximately 80% of the total

costs (26,52-58). There are many issues that affect the differences in costs that are described below.

In recent studies claiming to approximate societal costs, there has been 10-fold variation in the cost of a day hospitalized. In European cost-of-illness studies, the cost used is approximately 250 € per day per patient, whereas a U.S. study used a cost estimate of USD 2196 per day (53,55,56,59). Although this variability in unit costs used in analyses makes it difficult to compare studies, both ends of the cost scale can be justified. In the high cost estimate used in the U.S study (59) more hospital expenses were probably included than in studies with lower estimates that may omit some not so obvious costs, such as the cost of real estate. In all previously mentioned studies, the cost of an inpatient day was from insurance providers cost estimations or a nationally used cost estimate. Diagnosis-related groups (DRG) are one way of determining the costs of hospitalizations (60). They condense large patient populations into meaningful groupings (60). The mean costs to treat these patients can be determined and such figures can be used to charge the final payers (60). According to the Accounting office of the Hospital District of Southwest Finland, the DRG cost per day used for psoriasis patients hospitalization in the Hospital District of Southwest Finland was 2666 €, in 2009 (Appendix 1). There were only two different DRG costs used for dermatological patients, one for severe dermatological diseases and one for not severe patients. Psoriasis and PsA patients were in the "severe patients" category. A German study (61) estimated that psoriasis inpatient treatment was one of the most costly, compared to ten other common dermatological conditions treated in a university dermatology ward. The costs of each dermatological disease were compared to diagnostic related groups costs, and a correlation (r=0.48) was found, which the authors considered was only modest (61).

3.2.3. Proportion and length of hospitalizations

In studies of psoriasis, the proportion of hospitalized patients varies widely from 1 to 40%, even when studies were conducted during the past decade and used similar inclusion criteria (51,53,55-57). The length of inpatient treatment has also been inconsistent in the studies conducted during the past decade with the annual average length of hospitalizations varying from 3 to 40 days (44,51,53,56,58).

As previously described, the rate of hospitalizations decreased significantly. For example, studies that used data collected during 2003 to 2004 reported that 30 to 45% of patients with psoriasis were hospitalized compared with a study from 2012, using data from 2009, which found less than 1% of patients hospitalized (54-56). This significant decrease may have been partly due to increased use of biologics. In the study from 2012 by Ghatnekar et al. (55) one-fifth of patients received biologic medications, whereas in the studies from 2003 to 2004, none of the patients were receiving biologic medications (54-56). A recently published (2013) German study using data from 2005 to 2006 found

a high proportion (40%) of patients hospitalized, although few patients were using biologics (51). In contrast, a large French study that estimated health resource costs after the initiation of biologics, found that patients treated with biologics had higher costs for hospitalizations than those treated with traditional systemic medications or UV-phototherapy (62). In that study (62), the patients treated with biologics may have more severe psoriasis than the patients treated with other treatments, thus producing higher costs. However, the authors conclude that the costs of initiation of biologics were not offset by reduced costs of other health resources (62).

The time frame for data collection may also have an impact on the number or proportion of hospitalizations. A Swedish study (55) from 2012 employed a month long observation of resource use and found only one out of the 164 patients hospitalized in this period, whereas most recent studies assess resource use over a period of a year. Using a short time frame to estimate infrequent events like hospitalizations in patients with psoriasis may lead to under- or over-estimation.

3.2.4. Background factors affecting hospitalization costs

In studies with inclusion criteria resulting in cohorts with severe disease, hospitalization costs were more likely to be higher than in studies where all patients attending a clinic were included (53-56). In a German study by Sohn et al. (56) and in an Italian study by Colombo et al. (54), the mean PASI values were over 15 and hospitalizations constituted the majority of the total costs, whereas in a Swedish study by Ghatnekar et al. (55), the mean PASI value was only 5.6 and hospitalization costs were only a few percent of total costs. The association between hospitalization costs and severity of psoriasis has been noted in many studies (53,54,63). For example, in the study by Colombo et al. (54), patients with PASI over 20 were more likely to be hospitalized and accumulated higher costs of hospitalization than patients with lower PASI values. The same trend was seen in a Spanish study (53). However, the Spanish study (53) reported a low proportion (1%) of patients being hospitalized despite relatively high PASI levels.

QOL has been suggested to be a good predictor of the cost of psoriasis with studies showing higher costs in patients with higher DLQI values (32,34). Sato et al. (34) found a statistically significant 4-fold increase in hospitalizations in patients with higher DLQI values compared to patients with lower DLQI values. This finding remained significant in a regression analysis that controlled for clinical severity (using BSA), age, and gender. In a Swedish study by Ekelund et al. (32) patients with a DLQI below 5 had less than a third of the costs from inpatient care than patients with DLQI values over 10. However, this finding was not statistically significant, which may be partly due to the low overall costs of inpatient treatment in the study (32). However, the total costs of resource use were estimated to be statistically significantly higher for the patients with higher DLQI values (32).

Patients receiving systemic medications or UV-phototherapy have higher rates of hospitalizations than patients treated with topical treatments only (41,51,56). In a study by Steinke et al. (51), 22% of patients treated topically were hospitalized, whereas 55% and 42% were hospitalized when treated with traditional systemic medications or UV-phototherapy, respectively. In a study by Sohn et al (56), the costs of hospitalization were 60% lower for patients with no systemic treatment than for patients treated systemic medications.

In a Dutch study (64) from 2010, the estimated hospitalization rate of patients with psoriasis decreased 94% after biologics were initiated. This result may be biased, as only patients who received biologics for a whole year were included. Although this limitation was discussed in their paper, the authors considered this to be a minor factor as only few patients discontinued the therapy (64). Furthermore, the study may be generalizable, because patients who received biologics were selected when they were unable to tolerate or failed to respond to traditional systemic agents or UV-phototherapy, which is consistent with routine findings found in clinical practice (64). In other studies studying the effect of biologics, a significant decrease in hospitalization costs was reported in a cohort study (65) from 2010, which was conducted in England. Also, an Italian study from 2014 (66) reported similar findings, but the decrease in the hospitalization costs was not statistically significant. On the contrary, in a recent large French study from 2013 (62), initiation of biologics did not lower the cost of hospitalizations, which were significantly higher for patients using biologics than for the patients treated with traditional systemic treatment.

3.2.5. Outpatient treatment

The costs of outpatient treatment vary widely. The reasons behind the differences are very similar to those behind the variation in hospitalization costs. One major influencing factor is the reported cost of an outpatient visit, which varied almost 10-fold from 22 € (53) to 187 € (55).

In a Swedish study from 2012 (55), outpatient costs were half of the total direct costs, which were more than in any other cost-of-illness study. These high costs may be partly due to the high per visit cost used in this study (55). Furthermore, estimating the number of visits from medical records from one month may have overestimated the number of visits. To assess the reliability of these estimations, the authors used an alternative method based on a patient questionnaire about the number of visits during a 1-year time frame and self-reported outpatient visits were four times lower than extrapolated from medical records (55). This finding may be due to the short time frame and bias introduced by selecting patients visiting a dermatological clinic to follow for a month. Extrapolating the visits to an annual level led to each patient having at least one visit per month due to the patient selection and time frame used. This may not be a legitimate finding considering also the fluctuating nature of psoriasis. The results from the patient

questionnaire, with a 1-year perspective, are likely to be the more reliable of the two estimates (55).

In a German study (56), most patients (73%) were treated by one physician during the study period. In this study (56), the annual outpatient costs were low at 204 €. Only one physician may lead to lower costs as the patient is known to the physician and special needs may be taken into account before prescribing therapies. Being able to ensure access to the same physician has been a challenge in the Finnish healthcare system and further improvement of the patient-doctor relationship may reduce costs.

3.2.6. Location of care

Psoriasis is mainly treated by doctors specialized in dermatology (34,44,67-69), although there are considerable differences between countries in the organization of psoriasis treatment (69). In a U.S. study (44), 94% of patients were treated by dermatologists and the remainder by internists and General Practitioners (GPs). The low proportion of internists and GPs may have been partly due to miscoding of visits (44,45). In another U.S study (68) using data from 14.1 million outpatient visits, 70% of the patients with psoriasis were seen by dermatologists and the remainder by internists, GPs, or family practitioners. The results of U.S. studies should be treated with caution, because the health care system differs from many European countries. In a European study (34), psoriasis patients visited dermatologists around five times more often than a GP and few patients visited other specialists. In another European study by Fouéré et al. (69), psoriasis patients from five European countries were studied. The UK was the only country where patients with psoriasis were mainly prescribed medications from GPs, whereas in the other four countries, patients were treated mainly by dermatologists (69).

In Finnish health care setting, the reference system of treatment is guided by the Current Care Guidelines (29). According to them, moderate to severe psoriasis is treated in secondary or tertiary level clinics. Also if psoriasis causes productivity loss, does not react to treatments, or causes substantial subjective hindrance the patients should be treated in secondary or tertiary level clinics. Some of these patients may be treated in primary care after consultation. Most psoriasis patients have mild psoriasis and do not need specialist care and possibly no care at all (70).

Overall, there are few studies on the typical organization of psoriasis treatment, and most studies of psoriasis have been of patients visiting a dermatology clinic. Studying patients from dermatology clinics may underestimate the role of GPs and family doctors, as patients with less severe psoriasis may be excluded. However, patients that do not require specialist care may not cause high costs to society. Thus, when studying costs, selecting patients from a dermatology clinic may be justified. When estimating the total burden for all patients with psoriasis, such issues should be considered.

To overcome these issues, studies of prescriptions for patients with psoriasis have been undertaken, including the qualifications of the prescribing physician (67,69). These studies indicate that dermatologists typically initiate treatment for patients with psoriasis, particularly when UV-phototherapy or systemic medications were initiated. GPs initiated some topical treatments to some psoriasis patients (67,69). However, once symptoms were reduced, patients previously treated by dermatologists, were managed by GPs (67,69). In Germany, Augustin et al. (67) estimated that after a diagnosis of psoriasis, 62% of patients received a prescription from a dermatologist, whereas only 28% received one from a GP. After the first prescription, the proportions reversed, and GPs prescribed most of the medications (67).

3.3. Psoriasis treatment patterns and typical costs of therapies

As noted previously, a variety of treatments are available for psoriasis. It is usually treated with topical corticosteroids, vitamin D analogues, UV-phototherapy, traditional systemic medications (methotrexate, acitretin and ciclopsorin) or biologic medications (adalimumab, etanercept, infliximab and ustekinumab) (18,68,71-76). The following sections detail the treatment options and their typical costs.

3.3.1. Topical medications

In practice, all patients with psoriasis use or have used at some point topical medications to treat their skin lesions (14,72). Topical therapies include corticosteroids, vitamin D analogues, emollients, and combinations of these (68,77-79). These are used as a primary therapy for patients with mild psoriasis (PASI<10) (78). If remission is not achieved, UV-phototherapy or systemic medications may be initiated (78). Topical medications can also be combined with other treatment options and can be used as a controller medication during remission (78-80).

A large systematic review (81) published in 2012 found high variability in the efficacy of different topical agents. Consequently the authors were unable to make recommendations about the optimal use and stated only that topical treatment should rely on expert opinion (81). In other reports, vitamin D analogues have been shown to be more effective when combined with topical steroids (77). It has been estimated that patients using topical medications have better health than those who do not (80). This finding may not be entirely due to the effects of topical medications but may reflect the better health of patients treating themselves than those who do not. However, topical medications use as controller medications was encouraged (80).

Topical medications have few adverse effects. However, topical corticosteroids are known to cause skin atrophy with prolonged use of high potency agents, and corticosteroids may also adversely affect the hypothalamo-pituitary-adrenal axis. A recently published

review (79) assessing articles from 1980 to 2011 found 22 randomized clinical trials that examined skin atrophy. Skin atrophy was not common and was apparent in only 0 to 5% of patients using topical steroids of different potencies for durations ranging from 4 weeks to 1 year (79). In the same review, no evidence of clinically significant hypothalamo-pituitary-adrenal axis suppression was evident (79). Although, caution is required as most clinical trials are of limited duration, when used correctly, topical treatments have few adverse effects (78).

In cost of illness studies, the share of total medication costs attributed to topical medications depends on many issues. The severity of psoriasis has a significant effect on the share and costs of topical medications, with more severe disease resulting in greater use of systemic medications and/or UV-phototherapy, although topical medications may be combined in treatment protocols. However, patients with severe psoriasis may have a large area of affected skin and thus, may need to use more topical medications, resulting in higher costs. The share of the costs is also influenced by the relative cost of other medications used, e.g., if the use of costly biological treatments is common, the relative contribution of topical medications may be small.

In most analyses of psoriasis treatment costs, studies focus on patients with moderate to severe disease and rarely consider the costs of topical medications (38,71,73,76,82). The overall costs may be high with considerable variation arising from differing proportions of patients being hospitalized and using biologics as well as different per visit costs used in analyses. Consequently, it is difficult to compare the proportion of topical medications costs in the overall costs of psoriasis treatment found in different studies. Thus it can be valid to report typical annual costs of topical treatments and not their proportion of the total medication costs. In recent studies, the annual costs of topical medications range from 211 to 684 € (52-55).

When assessing the costs of topical medications, the time required for application should be taken into consideration. This is reviewed later when considering the burden for patients.

3.3.2. UV-Phototherapy

UV-phototherapy is a common treatment for psoriasis that uses ultraviolet (UV) light. More than a century ago, UV light was shown to improve skin conditions (83). UV-phototherapy is usually given in series, typically 2 to 3 times per week for around 12 weeks (78,84). UV-light that is used in phototherapy can be divided into UVA and UVB by their wavelengths (320-400 nm and 280-320 nm, correspondingly). Both broadband (280-320nm) and narrowband (309-313 nm) UVB treatments are used. The latter is most commonly used. Many studies reported that around half the patients with psoriasis (24–65%) received UV-phototherapy (14,54,55,57,67,85), though other studies estimated this proportion to be around a fifth (18,74,75). These differences

may be explained by variation in study inclusion criteria and treatment patterns in different countries (69).

Some studies and reviews found that UVB alone or UVA-phototherapy combined with psoralen (PUVA) were the most cost-efficient methods of treating psoriasis (71,73,76). However UV-phototherapy is a treatment that has a high consumption of many different resources, as it is usually given in series and in a hospital outpatient setting. These studies often fail to account for all the costs (e.g., direct and indirect costs of travelling and lost productivity), which have often been omitted from total cost estimates of therapies (26,71,73,76). For example, in the study by Staidle et al. (76), the cost of office visits and providing UV-phototherapy were included, but travel expenses and lost productivity were not considered. However, this approach by Staidle et al. (76) can be considered reasonable as they studied the costs from a provider's perspective. UV-phototherapy is a fine example of the multidimensional ways that a disease and its treatment may impose a burden on patients and society.

Studies to assess the costs of UV-phototherapy have used varying methods with highly variable results (26,38,53-55,73,76). Some studies only take into account the direct costs to the service provider or a third party payer (38,53,54,71,73,86), whereas other studies also consider the indirect costs of lost time and/or travel costs (36,55,74). This may explain the wide range of estimates (from 3 to 26%) for the proportion of total costs of psoriasis treatment attributed to phototherapy (32,34,54,55). Recent cost-of-illness studies have estimated that UV-phototherapy accounts for around a fifth of the total costs of psoriasis treatment (32,55).

3.3.2.1. Costs of UV-phototherapy to health service providers

De Rie et al. (87) and Langan et al. (86) estimated the costs from the UV-phototherapy provider's perspective – assessing the work hours of the different staff and use of different equipment. In contrast, Beyer et al. (38) and Miller & Feldman (73) used the cost of a single visit from previous literature or hospital fees.

Beyer et al. estimated the annual cost of UV-phototherapy for the healthcare provider to be around USD 3083 for UVB and USD 7288 for PUVA (38). Beyer et al. included costs of outpatient visits required during UV-phototherapy initiation and maintenance as well as the costs of UV-phototherapy itself to the estimated total costs (38). Miller & Feldman presented similar estimates in a review (73) with the annual costs for UVB of USD 4600 to 4800. Driessen et al. (64) estimated the annual cost of treatment with UVB to be 1105 €. The considerably lower cost estimate by Driessen et al. (64) was mainly due the lower unit cost of a single visit. Also, the costs of office visits were not included, whereas these costs were included in the studies by Miller & Feldman (73) and Beyer et al. (38).

Langan et al. (86) estimated the actual costs for the hospital of providing UVB. They observed the number of UV-phototherapy visits during a 2-year study period and estimated staff time, equipment use, and operational costs of the hospital. They estimated that patients made an average of 10 to 30 visits during the 2 years. This resulted in a cost estimate of around a tenth (325 €) of the cost estimates per patient per year made by Beyer et al. (86). Beyer et al. used a higher estimate for treatment times per year and outpatient visits and a higher cost per treatment session and this resulted in a relatively high cost estimate (38,86).

In different cost-of-illness studies (32,53-55) annual UV-phototherapy costs have ranged from 39 € to 3060 € (32,53-55). In a Spanish study by Carrascosa et al. (53), the total annual cost of UV-phototherapy per patient was around a half of the cost of a treatment session used by Ghatnekar et al. (55) in a study made in Sweden. Furthermore, in some studies the costs of visits are not mentioned, which make direct comparisons impossible (32,85).

3.3.2.2. Costs of UV-phototherapy to patients

The proportion of the cost to patients of UV-phototherapy may be somewhat debatable, as the time lost during treatments is not necessarily lost leisure time, and in many cases the lost work time results in costs for the employer rather than the patient. Travel costs and co-payments, however, are usually solely a cost for patients, although some costs may be reimbursed. Whether comprising costs to the patient or to the health insurer and employer, UV-phototherapy may result in a considerable burden for patients having to organize their schedules so that treatment can be administered in a hospital up to three times per week for months.

The indirect costs of UV-phototherapy have been estimated to be significant. Time and travel costs comprised 75% (around 36 € per treatment session) of the total costs of UV-phototherapy in a Dutch study by de Rie et al. (87). In their study (87), one UV-phototherapy session and the travel back and forth were estimated to take 110 minutes of which 60 minutes were for travelling. In a study by Meyer et al. (74), UV-phototherapy was estimated to have taken an average of 33 hours per year per patient. Although some cost-of-illness studies considered indirect costs when assessing the costs of psoriasis treatments, the proportion of costs related to UV-phototherapy was not mentioned (55,56).

Yenzer et al. (88) estimated that travelling for a 3-month treatment course with UVB, administered three times a week, would cost a patient from USD 461 to 2306 depending on the travel distance (10 miles and 50 miles, respectively).

The cost of UV-phototherapy to patients after reimbursement varies according to the different social and private insurance systems used in different countries. In some

studies, the patient's costs have been estimated to be significant, e.g., in a recent U.S. study co-payments were estimated to be around USD 720 during a typical 3-month course of UV-phototherapy (88). In review by Miller & Feldman (73), the high cost of UV-phototherapy for patients resulted in dermatologists and patients favoring other less cost-effective treatments (such as biologics). Longer travel time and treatment time may affect the choice of treatment a patient makes. Patients who live further away from UV-treatment facilities tend not to want UV-treatment (89), preferring traditional systemic treatments (90,91).

3.3.2.3. Home UV-phototherapy

Home UV-phototherapy has been estimated to be as safe, efficient, and cost-efficient as clinic-based UV-phototherapy, while also being more satisfactory to the patient (88,90,92,93). These studies and reviews did not find any evidence of possible misuse or danger in home UV-phototherapy, and it was suggested as the primary choice for UV-phototherapy in a recent cost-effectiveness trial (93). In the Hospital District of Southwest Finland, however, home UV-phototherapy is not used due to uncertainties about patient behavior, lack of equipment and that, patients receiving UV-phototherapy in an outpatient clinic may also receive psychosocial support from the healthcare professionals. Finnish Psoriasis Association (FPA) has UVB-lamps that they rent for patients and some may have been used in the Hospital District of Southwest Finland.

3.3.2.4. Risks of UV-phototherapy

UVB-phototherapy may cause erythema and conjunctivitis and keratitis of the eyes. These effects on eyes are reduced with wearing protective goggles during UVB-phototherapy. Long-term UVB-phototherapy may induce carcinogenic risks for the skin, although the risks are not well-established (94-96). Oral psoralen plus UVA-phototherapy has been associated with increased risk of squamous cell skin carcinoma (96,97). In the same study (96), bath-PUVA was not associated with increased risk of squamous cell skin carcinoma.

3.3.3. Traditional systemic medications

Psoriasis can be effectively treated with systemic agents. Methotrexate, acitretin, and ciclosporin are typically used as systemic medications. Each of these medications has specific adverse side effects and thus, they are not prescribed lightly. It has been stated that patients with severe psoriasis should be treated either with a systemic medication or with UV-phototherapy (37). It has been estimated that around a fifth of all patients with psoriasis require systemic treatment (98,99) with studies reporting a range of 10 to 50% of patients that were pre-treated with oral traditional systemic medications (18,32,47,55,56,67,69). The proportion of patients receiving systemic medications varies between different study settings and between countries, as described below.

As systemic medications are primarily used with patients with severe psoriasis, studies (56,72) including these patients report a higher proportion of patients using systemic medications than studies (67,74) analysing patients with the full range of psoriasis severity. Country-to-country variation was also present in a European study (69), in which there were 2-fold differences in the proportions of patients receiving systemic medications (21% in Germany and 43% in France). A recent study also found considerable country-to-country variation in the prescribing of systemic drugs (100). These differences may also be a source of variances in the cost estimations of systemic medications.

When assessing the costs of systemic treatments, there are other costs to consider in addition to the actual cost of the drug. As the systemic treatments have adverse effects, systematic safety measures are required, thereby increasing the overall costs. Furthermore, when side effects occur they may result in additional costs. These safety measures and possible side-effects should be considered when estimating the cost-effectiveness of a medication or a therapy. However, considering these costs can be demanding as determining the cause-effect order and the underlying cause of each symptom may be difficult and may be incorrectly coded or recorded into medical records.

A U.S. study (71) from 2005 estimated the annual monitoring costs of typical systemic medications, which ranged from USD 618 for acitretin to USD 1794 for ciclosporin. In comparison the monitoring costs of UVB treatment were USD 106 in that study. The monitoring requirements and possible adverse-effects for each systemic medication are discussed below.

3.3.3.1. Methotrexate

Methotrexate inhibits synthesis of folate, which is needed for DNA and RNA synthesis and thus affects mainly rapidly dividing cells (76). It has been on the market from the 1950's and was the first systemic agent approved for psoriasis treatment. Recent studies have found methotrexate to be the most cost-efficient systemic medication for psoriasis (73,76). The annual costs per patient when treated with methotrexate have been estimated to be around USD 1200 to 1600 (38,71,76,82). These estimates include the costs of the monitoring required, which comprise the majority of the costs. Methotrexate may cause haematological and hepatic toxicities, and it is severely teratogenic also for sperm (76). The highest monitoring costs are due to the need for liver biopsy when the cumulative dosage reaches 1.5 g. In Finland, liver biopsies are not made routinely on this basis, due to high risks of this procedure (101). Possible costly adverse effects are due to hepatic and haematological toxicity, as even liver transplantation may be needed.

3.3.3.2. Ciclosporin

Ciclosporin is an immunosuppressant that decreases the activity of T-cells and inflammatory cytokines, bringing benefits in psoriasis (76). Ciclosporin should not be

used for prolonged periods of time due to its cumulative nephrotoxicity (73). It has been stated that ciclosporin is best suited for treating acute flares and after remission it should be changed to other treatment modalities (73). Ciclosporin may increase risks of skin cancers in patients that have received large quantities of UV-phototherapy (102). Annual cost estimates for ciclosporin should be treated with caution, as it is rarely used for an entire year. These estimates have ranged from USD 6500 to 10 000 (71,73,76,82). Ciclosporin has been estimated to have higher acquisition costs than methotrexate (38).

3.3.3.3. Acitretin

Acitretin is an oral retinoid, which acts by affecting nuclear transcription factors via retinoid receptors and decreases keratinocyte proliferation (76,83). Acitretin is also highly teratogenic and 2 years of discontinuation of the drug is recommended before childbearing, however, it is not teratogenic for sperm (73). Acitretin may be used in combination with UV-phototherapy, and when used in combination treatment, lower doses have been estimated to be effective, thus reducing the probability of long-term side effects (73,76). The side effects include dry and itchy skin, dry mucous membranes, and joint pains (83). Safety measures for acitretin include laboratory tests. The annual cost estimations for acitretin range from USD 4500 to 9163 (38,73).

3.3.4. Biologics

Biologic medications have changed the field of psoriasis treatment (62,83). Before biologics, treatments may have been time consuming (e.g., UV-phototherapy, topical treatments) or may have included safety issues for the patients using them (traditional systemic medications) (45). Biologics have been estimated to be efficient and to have fewer side effects than traditional systemic medications (65,103,104), though these may be serious (such as increased risk of infections and cancers) (83). Although biologics are no longer considered novel, they have been used for only a limited time. Thus, some adverse effects associated with long-term use may still appear when more patient years are recorded. As with traditional systemic medications, biological drugs may have adverse effects, necessitating regular laboratory tests, tuberculosis screening, and X-rays (83).

The improvements that biological medications offer have not come without a cost. The use of biologics has increased the overall cost of psoriasis medications (37,38,45,59,62,65). The high acquisition costs of biologics may decrease the frequency that they are prescribed (37,62). The high acquisition costs and estimations of lower cost-efficiency have led to biological therapies being recommended only for patients who have failed to respond to traditional systemic treatments or traditional systemic medications are contraindicated (66,71,76,105,106). However, biologics have been recommended to be used alongside traditional systemic medications (45,73,107).

There are four biological agents available for the treatment of psoriasis: adalimumab, etanercept, infliximab, and ustekinumab (62,104,108). There have been only minor differences in the efficacy of these drugs and recent studies have shown that they may be considered as clinical equivalents (66,105,109). These drugs differ in dosage regime but all have to be injected or infused. Infliximab is the only one of these agents that must be infused intravenously, which usually requires an outpatient visit to a clinic in a hospital or other health facility. In a recent (2012) study (110), adalimumab was estimated to be the most cost-efficient of biologic treatments for psoriasis having 50% lower costs for significant clinical improvement (PASI 75% improvement) than ustekinumab or infliximab (110). In that study (110), the cost-efficiency of etanercept varied according to the doses and length of treatment used and resulted in a cost-efficiency between the previously mentioned biologics.

Quality-adjusted life-years (QALY) are a way of estimating the cost-utility of a medication. QALYs are used by regulatory authorities, e.g., in the U.K. to guide them in decision-making (37). They represent quality-weighted life years gained by using a treatment (111). QALYs may be used to compare treatments and the costs of treating different diseases and conditions (111). The high costs of biologic therapies have created a need for estimating cost-efficiencies in psoriasis treatment (82). In a recent Spanish study (66), the QALYs of three biologic medications (etanercept, infliximab, and adalimumab) were estimated. The mean cost per QALY was 28656 €. Inliximab had the highest costs at 53525 € and etanercept had the lowest at 25839 €, although the differences were not statistically significant (66). This study (66) included all direct costs to health service providers and the medication costs. The UK National Institute of Health and Care Excellence (NICE) evaluate the cost efficiencies of treatments and makes judgments on whether the costs are acceptable from a social perspective. It often uses QALYs as a measurement and a threshold around 30000 £ has been used for recommending treatments(112). For biological drugs used for psoriasis treatment, they have concluded that the costs per QALY gained are acceptable (66,105,106).

3.3.4.1. Trends in therapy

When estimating the current proportion of patients using biological drugs, it is necessary to consider the total use of systemic therapies and to account for differences between studies in disease severity and inclusion criteria. In many studies published in the past decade, in which some biologics were used, biologics accounted for 8 to 50% of the total use of systemic drugs (14,51,55,67,75,85). The proportion was found to be as low as 3.6% in a recent French study (62), although in that study UV-phototherapy was a treatment option along with traditional systemic medications and biologics. The large variation in use of biologics may be due to different insurance policies and treatment methods. In a recent (2013) European study (100) using psoriasis registers, there were significant differences in the proportions of patients that had used systemic medications

or UV-phototherapy before the initiation of biological medications. For example, in that study (100), almost all (98%) of Dutch patients with psoriasis had received UV-phototherapy before initiation of a biological drug, whereas the corresponding figure of Danish patients with psoriasis was only 11%. Considerable variation between countries was also noted for use of traditional systemic medications before initiation of biologics (100).

A recent study from Italy (99) describes the factors underlying decisions made by clinicians to prescribe biologic or traditional systemic medications. Younger patients and patients with previous use of traditional systemic medications were more likely to receive biologic medications. In this study (99), patients were almost equally divided between those receiving biologic therapies and those receiving traditional systemic medications. However, the proportion using biologics was decreasing, which was thought to be due to the economic crisis and "wearing out" of initial enthusiasm for the treatment (99).

There is limited information of the share of individual biological medications. In a Finnish study (113) from 2011, adalimumab and etanercept were slightly less used compared to infliximab, with adalimumab and etanercept having similar shares. However, this study estimated the total use of these medications, not solely the treatment of psoriasis. There were also large differences between different areas of Finland in the quantity of use and the shares of these biologicals(113). In the Hospital District of Southwest Finland, the total consumption of these biologicals was close to the national average, but the use of infliximab was relatively high(113). However, it has been stated that etanercept was the most commonly prescribed biologic medication, accounting for almost two-thirds of the biologics used for psoriasis (64,99,114). Adalimumab and ustekinumab were used in relatively similar shares and infliximab was the least used biological drug (99).

3.3.5. Non-treatment

In this paragraph, the term "non-treatment" was used to define either inadequate treatment or not receiving any treatment. When considering treatment, the fluctuating nature of psoriasis should be taken into account. Patients in remission may not need any systemic medications and may be adequately controlled with topical treatments. Patients may not receive any treatment or may receive inadequate treatment, both defined here as "non-treatment." It has been stated that despite the lack of treatment, patients in remission should not feel unsatisfied (115).

Many patients have been estimated to be unhappy or not to comply with their current therapy or to be undertreated (14,69,75,114-117). Augustin et al. stated that systemic medications should be used more extensively (37). Inadequate control of psoriasis was associated with high costs in Sohn et al. study (56). It has also been stated that the initiation of systemic agents may improve QOL in patients with psoriasis (118).

However, a significant delay in the initiation of systemic treatment was found in a recent French study (119), with half of patients having uncontrolled psoriasis for 3 years before initiation of systemic treatment. The level of control was determined by both patients and physicians with physicians assessing the period of uncontrolled psoriasis shorter than the one assessed by the patients. In this study (119), the PASI values were high at the initiation of systemic treatment (mean 18) with DLQI values also high (mean 12).

In a recent large scale study (114) conducted in the U.S., the proportion of patients not receiving any treatments decreased from 36% in 2003 to 24% in 2011 in patients with moderate psoriasis and from 30% to 9% over the same time period in patients with severe psoriasis. Conversely, non-treatment increased from 42% to 49% in patients with mild psoriasis. In this study (114), half of the respondents in 2011 were dissatisfied with their current treatment. During this time period, the proportion of patients with moderate or severe psoriasis treated with only topical therapies increased, which may have resulted in dissatisfaction with treatment (114). It has been also noted that patients treated with systemic therapies are more satisfied with their therapy than patients treated with topical medications only (115).

Patients have a role in non-treatment. Storm et al. (120) estimated that almost half of patients with psoriasis did not redeem their prescribed medication within the first month. Thus, it can be questioned if "non-treatment" is at least partially non-adherence. In the recent study by Storm et al. (120), topical medications was the least redeemed therapy. Furthermore, it has been estimated that one fifth of patients with psoriasis had no psoriasis-related contact with any health care professional in the past year (115), which could lead to non-treatment.

The most important factors affecting non-adherence with systemic medications were found to be patient dissatisfaction with efficacy, inconvenience of treatments, and fears for side-effects (115,121). Patients may not be alone with their fears of adverse-effects, as they may be a significant factor for physicians who may be reluctant to start systemic medications (118). A recent (2012) review (122) found that non-adherence with topical medications was caused by low efficacy and the time required for administration. Non-adherence was considered to be a significant problem, and the authors suggested that education and clear instructions are needed to improve adherence (122). Patients with psoriasis who adhere to treatment have been estimated to have better clinical results and lower overall treatment costs than non-adherent patients (123,124).

3.3.6. Treatment failure

Treatment failure has been associated with high overall treatment costs in patients with psoriasis (56,98,125). There are estimates of cost per successful treatment by Miller et al. (73). This study (73) found that a successful treatment (e.g., with methotrexate) was

approximately twice the typical annual cost of treatment per patient and this suggests that treatment failure should be accounted for in studies of treatment costs.

Defining treatment failure has been challenging and has not been consistent in previous studies. In a U.S study by Pearce et al. (125), treatment failure was defined as lack of significant clinical improvement (measured as 75% improvement in PASI during 12 weeks). In a German study by Sohn et al. (56), treatment failure was not directly defined and instead the patients who were intolerant to treatment or could not use two different systemic medications were defined as "high-need patients." In a U.S. study by Feldman et al. (98), switching therapies, discontinuing therapy, need of adjunctive therapies (other than topical), or hospitalization of a patient due to psoriasis were considered treatment failures. Of these different approaches, those used by Feldman et al. (98) and Sohn et al. (56) may estimate actual treatment failure, whereas that used by Pearce et al. (125) may also include slow and gradual improvement of symptoms as treatment failure.

In the study by Feldman et al. (98) failure rates for systemic therapies were 4.5% to 17.4% over 12 weeks and 17.5% to 28.4% over 52 weeks. In the study from 2006 by Pearce et al. (125), the costs of treatment failures per successful treatments ranged from USD 187 to 50383. The highest costs were for the biological medications and the lowest for methotrexate. In their analyses, ciclosporin and PUVA were the most cost-efficient when accounting for treatment failure (125). In a German study (56), the high need patients had higher costs for inpatient treatment, patient-borne expenses, and productivity losses but lower medication costs than for patients using systemic treatments.

Psoriasis treatment is usually initiated with the least toxic and harmful medications or UV-phototherapy with switching to more potent medications and then biological drugs if needed. These treatment protocols may result in multiple treatment failure for a patient. It can be argued that this kind of treatment protocol minimizes adverse events, but studies have estimated that there is significant patient dissatisfaction and lowered QOL in patients who are not adequately controlled, as discussed earlier. In other autoimmune diseases, such as rheumatoid arthritis, good results have been obtained by initiating potent medications immediately on diagnosis or a flare of the disease (126). However, psoriasis does not permanently damage skin, whereas rheumatoid arthritis is a more progressive disease that may cause permanent damage, and thus different approaches may be justified.

3.4. The economic burden of psoriasis to patients

When studying the economic burden or costs of psoriasis treatments, it is important to consider the perspective of the patients (26,36). It is well established that psoriasis negatively affects the QOL of patients in many ways (14,26,35,57,69,72,107,115,116,127-131). The adverse impact of psoriasis on QOL has been shown to be comparable to the impact of other health conditions such as heart disease and cancer (132). Furthermore,

psoriasis negatively affects patients' leisure time activities (133). The family of patients with psoriasis have also been shown to be adversely affected (134).

In an Italian study, Colombo et al. (54) claimed to have included QOL life issues as "intangible costs," but no costs were reported. Other than impaired QOL, psoriasis has been shown to impose an economic burden on patients (26,52-55,58,74,130). The main cost drivers have been estimated to be co-payments for medications and emollients and lost time due to treatments has also been estimated to cause a substantial burden to patients (52,53,56-58,74).

In Europe, the cost of psoriasis to patients has been estimated to be in the range of 543 to 1562 € (52,56,58,74). The methods of assessing these costs have been inconsistent and the cost items included have varied between studies. In a French study from 2010, Meyer et al. (74) estimated the economic burden in 590 psoriasis patients and found costs of 543 €, most of which arose from specific products such as hygiene or moisturizing products with minor costs attributed to paid assistance and water cures. The authors estimated lost time from cleaning, laundry and skin care and assistance received due to psoriasis, but they did not estimate the financial cost of this burden. In a German study from 2006, Sohn et al. (56) included more possible costs sources to the patient and resulted in an annual estimate of 791 € to the patient. In that study, co-payments for medical services and medications, transportation, and ointments were the major cost drivers (56). This study also omitted cost estimations for lost time due to psoriasis.

Navarini et al. (58) estimated the financial burden of psoriasis in Swiss patients in 2010. The annual cost for patients with mild psoriasis was estimated at 400 €, whereas patients with severe psoriasis had higher annual costs of 1560 €. No indirect costs were included (58). In a recent Swedish study by Ghatnekar et al. (55), the indirect costs of lost time to travelling and skin care were estimated together with other patient expenses. However, the different cost sources or proportion of costs cannot be identified from the results reported.

3.4.1. Time required for skin care

The time required for skin care has been estimated to be a considerable burden for some patients with psoriasis (55,57,74,116,130). However, the estimates of this time vary widely from study to study. In a German study (130), patients were estimated to use on average 58 minutes per day for skin care. In contrast, a French study (74) estimated that patients used on average 5 to 15 minutes per day for skin care. No cost estimates were made in either of these studies.

In the French study mentioned above (74), half of the patients administered topical medications and skin care products once a day and a third of patients applied treatment two or three times per day. In this study (74), the methods section does not reveal whether the skin care time needed to treat their psoriasis was asked about specifically

or if it was just a general estimate of time needed for skin care. This may have caused biased estimates of the time needed due to psoriasis. Significantly higher estimates of time needed for skin care have been reported (130). In a German study, Schoffski et al. (130) estimated the daily time needed for skin care at 50 to 61.5 minutes depending on the treatment type the patient was using. However, it is impossible to determine how accurate self-determined time estimates are. In that study (130), the patients who had experienced multiple treatment failures needed most time for daily skin care, whereas patients using systemic therapies continuously had the lowest reported time for skin care, and the time for daily skin care for patients using topical treatment was between these groups. The authors of the study (130) stated that all questions were asked so that only the effects and symptoms of psoriasis would be captured.

Although the time required for skin care has been considered to be an important part of the overall burden of psoriasis on patients, estimates of the costs of this time have not been directly reported. When using the higher estimates of time needed each day (50–60 minutes, Schoffski et al. (130)), the economic burden may be significant, regardless of the methodology used to estimate costs. In the Swedish study by Ghatnekar et al. (55), the application time of topical treatments constituted 40% of the costs of these medications, which were 369 € per month for the patients using such treatments. This estimate results in an annual cost of the application time of topical treatments was 1771 €, however the time needed for skin care was not reported (55). In this study (55), the cost of applying topical treatments were estimated at 648 € per year for women and 420 € for men for all patients regardless of the therapy they received.

3.4.2. Household chores and assistance

There is limited information of the effects of psoriasis on household chores and no studies have estimated the economic impact of this burden. In a French study, Meyer et al. (74) estimated that half of the patients cleaned their house more often because of psoriasis with a consequent impact on time needed. In this study (74), a third of the patients received assistance, mostly from friends and relatives and partly from employed persons with help being mainly moral support followed by physical assistance with daily tasks. Patients with severe psoriasis were more likely to report a need for assistance and cleaning than patients with mild psoriasis. In another study (135), initiation of etanercept was estimated to decrease the number of days when assistance was needed and the proportion of patients needing assistance.

3.4.3. Travel Costs

In a Dutch study (64) from 2010, patients were estimated to travel on average 881 kilometres annually because of their psoriasis. Few studies have estimated the actual travel costs attributed to psoriasis (55-57). Average travel costs per year were estimated

at 177 € in a German study (56) and 204 € in a recent Swedish study (55), which also found that indirect costs due to travel time were almost as high as the travel costs. In a recent Malaysian study (57), travel costs comprised 10% of total costs of psoriasis.

UV-phototherapy has been associated with significant travel expenses. Time and travel costs comprised 75% (around 36 € per treatment session) of the total costs of UV-phototherapy in a Dutch study by de Rie et al. (87). In their study, one UV-phototherapy session and the travel back and forth was estimated to take 110 minutes of which 60 minutes were for travelling (87). Yenzer et al. estimated that the cost of travelling for a 3-month treatment course with UVB, administered three times a week, would cost a patient from USD 461 to 2306 depending on the travel distance 10 miles and 50 miles, respectively) (88).

3.5. Productivity costs

The negative effect of psoriasis on productivity has been well-established using many different methods of calculation. Indirect costs due to productivity loss should be included in health economic evaluations of the impact of psoriasis (107,136). Not including productivity, losses may lead to sub-optimal health decision making (136). It has been stated that indirect costs should be included in studies of the costs of chronic autoimmune diseases, and novel treatments should be looked at in new light as they may enable long-term remission, thus possibly decreasing productivity losses (137,138).

Psoriasis may have a negative effect on the income of patients (139). In Canada, patients with psoriasis missed on average twice the number of working days as the general population (85). In case-control studies, the indirect costs and work impairment of patients with psoriasis have been found to be substantially higher than those of the control patients (42,140). Indirect costs due to lost productivity have been estimated to exceed those of direct costs among patients with psoriasis and other chronic inflammatory diseases (33,52,137,141,142). However, some studies suggest that although indirect costs are substantial, they only contribute around 20% to 43% of the total costs (32,42,54-56,85). These large variations in cost estimates exist as there is no consensus on the methods to use for estimating productivity costs, as described below (136).

3.5.1. Types of productivity losses

Of the possible productivity losses, absenteeism has been most commonly included (32,33,52,55-57,85,143). Measuring presenteeism is also gaining in popularity and has been included in recent studies (129,143-146). However, little is known about the costs of presenteeism (33). In health economic reviews, absenteeism and presenteeism are mentioned as the most important aspects of productivity loss, which should be included

when making a health-economic study (136,147). Absenteeism and presenteeism are described in detail below.

There are also studies showing that psoriasis may cause unemployment or even early retirement (52,55,56,127-130,148,149). In the few studies that have assessed the costs of early retirement due to psoriasis, it has been estimated to cause 32 to 92% of the costs of lost productivity (52,55). In Schoffski et al.'s study (130), cost estimates of lost productivity included retraining, unemployment, and absenteeism, but the proportions of each were not mentioned. Unfortunately, this limitation in the description of methods is not an exception in studies of psoriasis-related productivity loss. As these proportions of the productivity loss used in the Schoffski et al. study (130) remain uncertain, it is not possible to compare the results to other studies.

At least one study (85) of psoriasis also includes lost leisure time as a component of lost productivity. In this Canadian study (85), leisure time constituted a majority of the productivity costs. Most cost-evaluations do not include unpaid labour such as household chores, which could also be assessed as productivity losses (136). Including lost leisure time as a productivity cost could be a method of accounting for the unpaid labor.

The selection of the productivity costs to include in a study should be based on the perspective chosen for the study. As the selection has a great impact on the total costs, they should be carefully described and discussed in any given study (136). The perspective of the study can validate many different approaches. For example, if the aim of the study was to analyse the costs of productivity loss to the employer, then leisure time, household chores, and even retirement can be omitted, depending on the country's social security system and which costs fall to the employer. In contrast, studies with a social perspective should assess all feasible costs.

3.5.2. Impact of patient characteristics

There are no reported or observed differences between genders in costs of lost productivity due to psoriasis (55,74). However, differences between genders were found for the impact of psoriasis on work (128). In Ayala et al.'s study (128), women had more observed limitations in work than men, reporting different treatment in the work place- and work/education-related problems. However, the methods used in this study (128) limit the strength to the claims that the differences found could result in higher costs as the productivity loss was not defined specifically and open questions of possible interactions between psoriasis and the experiences or feelings of patients were studied. For example, the following question was used to determine the impact of psoriasis on work: "To date, has psoriasis affected/limited your expectations or your work career plans in general?" (128). However, the study showed that men and women experience their psoriasis differently (128). Similar findings have been presented by Armstrong et al. (127) who found a greater likelihood of unemployment among women with psoriasis than men. Studies of other diseases have

estimated that presenteeism is more common for women (150,151), and there are mixed results for absenteeism (150,152). In a study (74) of psoriasis, increasing age has been shown to be associated with increased cost of lost productivity.

Psoriasis with joint involvement or in patients diagnosed with PsA is associated with lost productivity (32,52,74). In a German study (52), PsA was an important factor in early retirement, with four of six patients who retired early having arthritis, although the share of PsA in the total sample was 7%.

The clinical severity of psoriasis has been shown in several studies to have an effect on the cost of lost productivity and the extent of productivity impairment (53,57,72,85,145,153). In one study (145), there was a difference in productivity loss between patients with mild and moderate (determined by PASI <10>) psoriasis, but not between those with moderate and severe disease. Some studies (32,34,74) suggest that clinical severity does not significantly affect the magnitude or cost of lost productivity. These studies suggest that the subjective assessment of patients about their QOL should be used when trying to predict the costs of lost productivity. Worse QOL measured using the DLQI predicted higher production losses in these recent studies (32-34,74). In one study (34), this was apparent even when the clinical severity of psoriasis was controlled. A recent Japanese study (153), reported similar findings using different measures; PDI values showed better correlation with productivity losses than PASI values did.

Concomitant diseases have a significant effect on the overall wellbeing of patients and significantly increase the costs of lost productivity for patients with psoriasis (42) and other chronic diseases (137). Low education level was found to increase the likelihood of a patient with psoriasis reporting limitations or problems at work (128).

3.5.3. Structured questionnaires – measuring productivity losses

There are many ways to estimate productivity losses. Of the many structured questionnaires measuring productivity loss that are available, the work productivity and activity impairment questionnaire WPAI (74,143,154) and work limitations questionnaire (WLQ) (33) have been used most extensively when studying the cost of health-related lost productivity in patients with psoriasis. A recent review (155) of productivity loss questionnaires recommends the use of WPAI and WLQ although the review was of general health problems and not specifically about psoriasis.

The WPAI is a generic (not disease- or occupation-specific) questionnaire, which uses a 1-week recall period to estimate overall reduction in productivity (155). The WLQ is used to evaluate the impact of chronic conditions on work performance, which uses a 2- to 4-week timeframe. However, these questionnaires do not capture the proportion of each disease on the productivity losses and do not separate the studied disease from other health problems (136,156,157). Zhang et al. (158) stated that although there are many

different structured measurements used to estimate productivity loss, none of them are ideal and they give highly variable results.

3.5.4. Converting productivity losses to monetary values

The overall costs of sick leave have been estimated to be significant to the society (159). The cost to third party payers (e.g., private and social insurance providers), patients themselves, and employers is influenced by social security or health insurance policies in each country. When assessing the cost of lost productivity, a specific approach must be chosen (136,147,156). In a health economic article (136), Krol et al. stated that productivity costs are not important in studies aimed at decision makers who are responsible for health care budgets and maximization of health care achieved with given resources. In contrast, political decision makers should also be interested in indirect costs such as productivity losses, although they need to consider equality of patients, regardless of employment status (136).

A new standard that includes two perspectives, a strict health care perspective, and a societal perspective has been proposed (160). This could help decision makers weigh the costs as they consider appropriate. This two-pronged approach is recommended by national health economic guidelines in Norway and Italy (136). If productivity losses are measured for paid workers rather than all patients, cost-of-illness studies will favor treatments aimed at working people, which raises important ethical questions (136).

Whichever perspective is chosen to study productivity costs, the estimates have to be converted to monetary values to be able to make comparisons with other types of costs. Many studies of productivity loss associated with psoriasis (74,128,145,154) do not take this step and settle for reporting the amount of impairment rather than the monetary cost. Brooks et al. (156) warrant caution in their study, when productivity losses are extrapolated into estimates of productivity loss costs. Recent studies of psoriasis have most commonly used the human capital approach (HCA) and friction cost approach (FCA) to make this conversion to monetary value.

Recent reviews on lost productivity recommend using the HCA (136,158). It uses the hours not worked and hourly wage of the employee for economic cost estimations of the hours lost (158,161). In this method, the hours of lost productivity may continue until a patient is retired. In contrast, the FCA takes the perspective of the employer and only estimates the costs of hours missed until a substitute employee is found to replace the missing worker, a time called “the friction period” (158,161). In recent studies of psoriasis and productivity losses, the friction period of 6 months has been used (161).

In short periods of absenteeism (under 6 months), HCA and FCA may produce similar results, but in longer absenteeism periods (e.g., retirement), the FCA method produces

lower cost estimations (161). In studies comparing the two methods, the HCA has produced cost estimates 25 times higher than FCA in breast cancer or 6 times higher in rheumatoid arthritis (161,162). This major difference is evident solely in very long sick leaves and retirement. HCA is criticized for its possible overestimation of productivity costs and for the way it estimates potential costs, not actual lost costs, especially in long periods of absenteeism (161). On the other hand, there may be an economic burden associated with a patient who has had to retire early due to health-related reasons long after a substitute has been found to replace him/her (e.g., a patient receiving pension and not working at working age may be costly for the social insurer and the society as a whole). HCA and FCA methods have also been criticized for their focus on earning capacity that may lead to ignoring the retired and the young (158). One possible method to reduce this bias is to use the national average wage and apply it as the value of an hour for the retired and unemployed (147).

It should be noted that the estimated costs of absenteeism may be significantly higher than the hourly wage of an absent worker, which is used for cost estimations in the HCA (158). In Finland it has been estimated that the cost of absenteeism is as high as three times as much as the patient's hourly wage (159).

3.5.5. Improving productivity – biologic medications

In studies assessing biologic medications (e.g., etanercept, infliximab, ustekinumab) productivity losses have often been considered (144,146,154,163). In all of these studies, the initiation of biologics has improved productivity although none of the studies has estimated the actual costs of productivity losses and there has been considerable variation in methods and study settings (144,146,154,163). There are also several limitations in these studies. For example, in the study by Vender et al. (154), the patients could not have received any therapies prior to the study while they had to have high disease activity. This kind of a study setting resulted in a 70% decrease in productivity loss after initiation of etanercept estimated with WPAI (154). Also the proportion of patients with PsA (43%) was high in the study and these patients scored higher scores of the WPAI questionnaire than patients without PsA (154).

The results of these studies only imply that biologics could make improvement in productivity in patients with psoriasis with many concluding that the costs of biologics may be partly subsided by improved productivity. These results should be treated with caution as there are no studies on productivity losses where biologic medications were compared against traditional systemic medications or UV-phototherapy. However, in a cost of illness study by Ghatnekar et al. (55), patients who used biologics had lower indirect costs of absenteeism and early retirement than patients using traditional systemic medications.

3.5.6. Productivity losses – UV-phototherapy

As UV-phototherapy is given in series and in a hospital outpatient setting often during working hours, it may cause productivity losses. De Rie et al. considered that UV-phototherapy is always given during work time and the time lost is directly applicable as a productivity loss (87). In another study (88), the cost of productivity loss for a typical 3-month treatment with UVB was from USD 690 to 1840 depending on the travelling distance. There are studies that indicate that the work of patients with psoriasis is affected only slightly by UV-phototherapy as patients are often able to schedule the treatment sessions so that work is not hampered or is often compensated during other hours (74,90). However, in such approach leisure time is not been assigned any value.

3.5.7. Absenteeism

Absenteeism occurs when a patient is out of work for health-related reasons. Absenteeism due to psoriasis may lead to significant costs, although reported findings have not been consistent. In the majority of recent cost-of-illness studies, the annual costs of absenteeism are estimated to be around 1000-2500 € (32,52,55,56,85,143).

The prevalence of absenteeism varies in previous studies, ranging from 3.6% (55) to 31% (56) of patients included. The mean length of absenteeism for these patients also varied widely from 2 to 3 (53,74) to 49 days (52) per year.

Although, measuring absenteeism can be relatively straightforward (155), discrepancies between studies may arise from different definitions of absenteeism. Typically, the definition of absenteeism and methods used to measure it have only been vaguely described or are not described at all (52-56,128). There may be only a mention that the number of absenteeism days was collected with a patient questionnaire but without defining the time frames used or specifying the reasons for absenteeism (52,54,128). For example, Sohn et al. (56) described the methods of data collection of the patient questionnaires on productivity loss as: “Patient questionnaires: information about the severity, past therapies, … …and production losses.” When absenteeism is estimated with tailored questions rather than established index measures with well-known questions, the questions used should be clearly described in the article to allow assessment of validity of the results. The few structured questionnaires (e.g., WPAI, WLQ) used to estimate absenteeism in patients with psoriasis give results on a general level not absenteeism that is a result of psoriasis (155).

Patient selection for the study sample may have a considerable effect on the extent and cost of absenteeism. Some studies (52,56) may report high absenteeism partly because of the sample formed by strict inclusion ciriteria (e.g., PASI greater than 10 to 12 in the above mentioned studies) when compared to studies that use the full spectrum of patients (74). This was apparent in the study by Sohn et al. (56) in which a third of the

patients with high PASI values (mean PASI 18) reported absenteeism for an average of 46 days per year. Likewise in the study by Berger et al. (52), 10.3% of patients with relatively high PASI values had been absent from work for an average of 49 days per year. In comparison, the mean length of absenteeism was 3 days in the study by Meyer et al. (74), which included patients with lower PASI values than in the Sohn et al. study.

3.5.7.1. Impact of patient characteristics on absenteeism

The severity of psoriasis has been shown, in many studies, to affect productivity costs and is mainly due to absenteeism (47,53,54,56,57,67). In many recent studies the impact of the severity of psoriasis on absenteeism has been questioned and QOL measures are suggested as better measures to predict the cost of absenteeism (32-34). Ekelund et al. (32) found that in patients with DLQI less than 5 the cost of absenteeism was 560 €, whereas the cost was 4-fold (2060 €) in patients with DLQI values over 10, a statistically significant difference ($p<0.005$). In contrast, PASI values did not significantly correlate with productivity costs (32). Also, receiving systemic medications was shown to be a stronger predictor of high absenteeism costs than clinical severity in the study by Berger et al. (52).

In a study by Schoffski et al. (130), patients were divided into groups stratified by the therapy given. Patients treated with systemic medications had similar costs of lost productivity as those receiving only topical medications, whereas patients who were not able to receive at least two different systemic medications had twice the costs of lost productivity than other patients (130).

Cross-sectional and observational studies cannot answer whether systemic medications or treatment failure has been the cause of high productivity costs. As the patients are not followed after initiation of systemic medications, no certain conclusions can be made about the effect of systemic medications. These types of studies can only raise questions and speculate about the possible reasons behind the high costs measured. Observational studies are, however, needed to estimate the proportion of patients receiving different types of treatments and the magnitude of resources allocated to them. Follow-up studies can then be planned, based on this information, to answer questions about causes and effects.

3.5.7.2. Time frame

When absenteeism is estimated, a decision must be made about the time frame used. In previous studies a time frame of anything from one week (74) to one year (85) has been used. This decision may have a major effect on the results yielded by the study. In a German study Berger et al. (52) evaluated absenteeism in two ways: prospective data during a six-week flaring period and retrospectively with a questionnaire to assess a 3-month time

frame prior to the flare. The proportion of patients absent from work during the flare (3.9%) was lower than during the time before the flare (10.3%) (52). This may have partly resulted from the use of different timeframes of 6 weeks and 3 months. The number of days absent from work was similar (12.3 and 11.5, respectively) in both methods of data collection, but extrapolating the results to an annual estimation of absenteeism leads to 49 and 100 days per year, respectively (52).

There is no consensus on what time frames is most appropriate to estimate absenteeism when studying psoriasis. In recent reviews, a 3-month timeframe has been suggested to capture absenteeism, minimizing recall bias and enhancing generalizability of the results (136,156). Significant recall bias has been shown when a long recall period is used compared with a shorter recall period (155).

3.5.8. Presenteeism

Costs due to presenteeism have been difficult to determine and have been often left out of studies, although they are considered important when assessing the overall economic burden of psoriasis and other chronic diseases (32,107,136,164). In the past decade, the costs of presenteeism have increasingly been included in studies, although the methods of measuring presenteeism are not consistent (107,136,142,156,164). Presenteeism in patients with psoriasis may contribute around half of the indirect costs (33,55). Many studies estimate the extent of presenteeism but do not make estimations of the corresponding cost (127,129,144-146,154,163). However, some of these studies show that psoriasis has a substantial effect on productivity with estimates ranging from 7.6% to 40% of lost productivity due to presenteeism (33,145,154,163).

The few studies that estimated the costs of presenteeism due to psoriasis have provided variable results. Ghatnekar et al. estimated that presenteeism causes 48% of the costs of lost productivity with the other half caused by absenteeism and early retirement (55). The study (55) estimated costs during a month's time frame, which gives a yearly estimate of the costs to be 936 € per patient. Schmitt and Ford (33) estimated that 7.6% of lost work productivity while working was attributed to presenteeism at an annual cost of USD 2642 and thus over half of the total productivity loss costs.

In a study (151) estimating the costs of ten common diseases, presenteeism was estimated to cause up to 61% of the overall costs (including pharmaceuticals, outpatient visits, absenteeism, presenteeism). Overall presenteeism costs were estimated to be higher in conditions where flares happen, such as allergies, migraine, arthritis, and asthma compared to chronic more stable conditions such as cancer and diabetes (151). Psoriasis was not included in this study, but flares are typical in psoriasis, so presenteeism costs could be expected to be high.

3.5.8.1. Background factors associated with presenteeism

There is limited information about factors affecting presenteeism costs in psoriasis. In studies by Ghatnekar et al. and Schmitt and Ford (33,55), the total productivity losses were assessed and several background factors were analysed in their studies. However, neither of these studies attempted to especially analyse how patient characteristics affected the cost of presenteeism. In the study by Schmitt et al. (33), health-related QOL was a strong predictor of total costs. Women psoriasis patients were more likely to report limitations in education and work and being treated differently in their working place than men (128). This suggests that psoriasis may cause women more hindrance than men (128). In general, women report more presenteeism than men (151) and in some chronic diseases, such as ankylosing spondylitis, women were more prone to presenteeism than men (165).

3.5.8.2. Causes of presenteeism

Health-related presenteeism is usually caused by the employee deciding to go to work while feeling or being sick (142). There are many factors that influence this decision, e.g., the social insurance system, labour laws and the financial situation of the patient. If a patient does not receive pay from the first days of absenteeism (as in Sweden) and is in a sub-optimal financial state, the threshold for reporting sick may be higher than in countries where the reimbursements for sick leave are higher (as in Norway), as estimated in a study by Johansen et al. (166). This study (166) also showed that a desire not to burden work colleagues may lead to presenteeism. Patients who enjoyed their work had higher levels of presenteeism than other patients. This finding may have been due to not wanting to stay away from work. The study also concluded that the reasons behind the decisions leading to presenteeism may vary even between two seemingly similar Scandinavian countries (166).

3.5.8.3. Measuring presenteeism

There are several methods to evaluate presenteeism – indeed, a recent review stated that it can be assessed with 16 popularly used questionnaires (156). In addition, there are also non-structured ways for assessment (55). The methods chosen may have a significant effect on the results yielded as shown in a study of rheumatoid arthritis that found a four-fold difference between the lowest and highest estimates of presenteeism for the same patients assessed using four different questionnaires (157). There is a need to standardize the methods used to estimate presenteeism, although this presents several problems (136). Structured questionnaires are rarely applicable to a variety of different diseases, but they may capture the specific impact a disease has on productivity (136,156,157). Until there is a consensus about the most appropriate method to use, it is critical to sustaining high standards of reporting the methods used to measure presenteeism.

3.5.8.4. Time frame for estimating presenteeism

Two reviews concluded that a time frame of 1 to 2 weeks produces the most accurate estimates of presenteeism (147,156). This suggested time-frame is shorter than for estimating absenteeism due to the higher prevalence of presenteeism. On the other hand using two different time frames for soliciting data of absenteeism and presenteeism may be confusing to a patient and the fluctuating nature of psoriasis may cause problems when using a short time frame. Any time frame used in a study always has its advantages and disadvantages. A long time frame is susceptible to recall bias, whereas a short time frame may not observe rare events.

3.5.8.5. Conversion of presenteeism into monetary values

In a study (151) estimating the costs of ten common diseases, the estimated cost for presenteeism ranged from 18% to 61% of the total costs of lost productivity, depending on how conservative were the estimates used. Conversion of presenteeism into monetary values has recently been criticized, although alternative approaches have not been proposed (142). The answers of an employee may represent the perceived reduction of input and not the reduction of productivity. This may result in over- or underestimations as health conditions may or may not affect the productivity while sick (147). It has been suggested that an employer may be in a better position to evaluate the lost productivity as an output (147). However, in a study (167) that estimated the association between patient-reported work limitations and the decrease in work productivity, a significant correlation was found.

3.6. Cost of psoriasis compared to other illnesses

The economic burden of psoriasis has been estimated to be similar to many other chronic conditions. In a large U.S. study (39), healthcare expenditure on psoriasis was greater than on hypertension, COPD or asthma, but lower than diabetes or stroke. Ghatnekar et al. (55) estimated that the cost of psoriasis may be on par with other autoimmune diseases like rheumatoid arthritis and Crohn's disease.

3.7. Finnish healthcare system

The Finnish health care system covers the whole population. It is mainly produced by the public sector. The major part of public health care services is financed through general taxation. The Finnish healthcare system is decentralized and even the smallest municipalities arrange and finance primary services. They are also responsible for financing the Hospital Districts, which produce the special services. The National Health Insurance (NHI) is another public financing system, partly overlapping the prior municipal system, but also reimburses services provided by the private sector. NHI also

finances occupational and student health services as well as reimburses medications (168).

In practice, mild psoriasis patients are treated in primary care. Moderate to severe psoriasis patients receive specialist care from secondary and tertiary level public hospitals. These patients need referrals from primary care doctors, for which there are guidelines in Finland (Current Care Guidelines (29)). After diagnosis or successful treatment, a patient's treatment may be shifted to primary care. A few patients may be treated in the private sector. Patients pay visiting charges to all public hospitals and primary care providers, except occupational health care. These charges are capped at an annual level. For private sector, patients pay per visit and may receive reimbursements from Kela. In case a patient has private health insurances, it may cover all or a part of patients' costs.

3.7.1. Reimbursement system for medications

Kela reimbursements cover necessary medicine expenses, which have to be bought for three months use at a time in the most economical package size. Emollients that have been prescribed by a doctor for treating chronic skin conditions are reimbursed. In 2009, there were three reimbursement rates: basic, lower special, and higher special reimbursements, and they cover 42%, 72% and 100% of the costs correspondingly. In 2009, if the annual reimbursable medication and emollient costs were over 672 € the costs were reimbursed at a rate of 100%. However there was a small 1.5 € cost per purchased medication for the patient after which the remaining costs were reimbursed. Psoriasis medications are reimbursed according to basic and lower special reimbursement rates. To receive reimbursements for some medications, the patient must provide a medical B certificate to Kela. This certificate is done by a doctor and in some cases a doctor specialized in dermatology.

4. AIMS OF THE STUDY

The aim of the thesis was to estimate the economic burden of psoriasis from various perspectives and to estimate the background factors that may have led to high costs. The specific aims were:

I. To estimate the costs of psoriasis treatment in a tertiary level clinic from a health service provider's perspective and to evaluate how the costs differ between patients receiving different types of therapies.

II. To estimate the economic burden from a patient's perspective and to account for various costs that psoriasis imposes on patients. Secondary to this, the aim was to estimate whether the type of treatment that the patient received affected the overall cost to patients.

III. To estimate the costs of medications from a societal perspective. A secondary aim to this was to estimate whether the number of treatment types needed affected the quality of life of patients or the cost of medications.

IV. To estimate the costs of productivity losses due to psoriasis and the proportion of the total health related productivity losses, which were due to psoriasis. These cost estimates were done from the employers' perspective.

5. MATERIAL AND METHODS

In this section, the patient sample and general data gathering are described initially and then the methods, perspective, and data reported in each original paper are described in more detail.

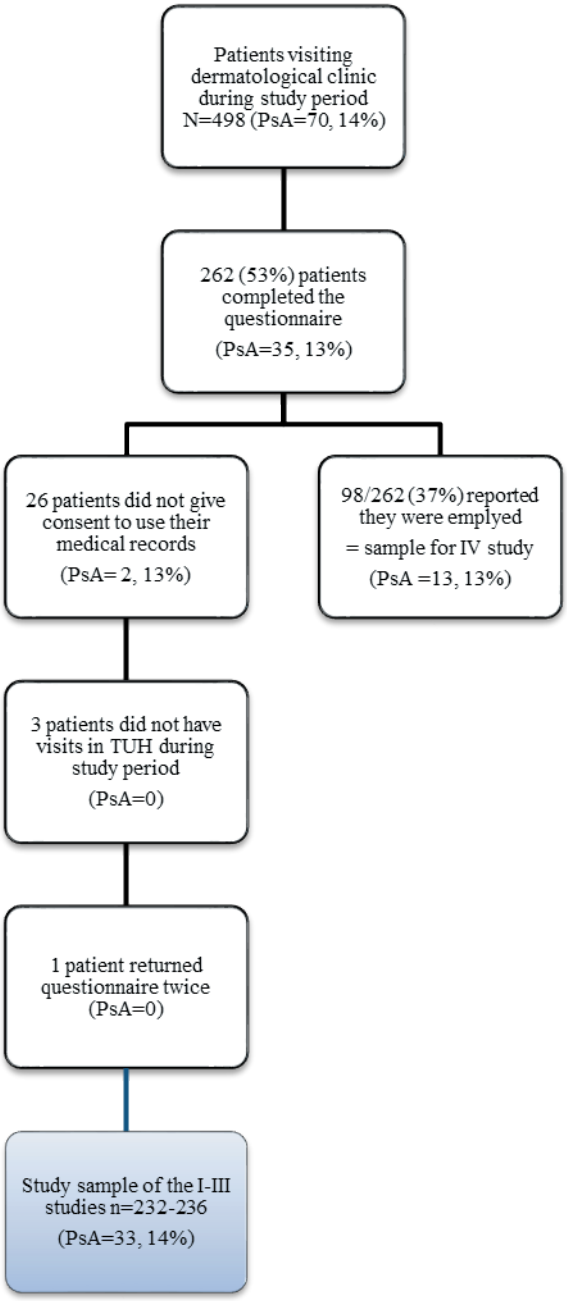

Figure 1. Flow-chart of patient selection.

5.1. Patient sample

The sample was based on all patients with a diagnosis of psoriasis or psoriatic arthritis (PsA) who visited the Department of Dermatology in Turku University Hospital (TUH) between 1 October 2009 and 30 September 2010. In the Finnish health care system, patients with mild psoriasis are usually treated in primary health care settings and only moderate to severe cases are referred to tertiary level hospital for further treatment. In practice, all patients with PsA in this study sample also had skin symptoms, hence the visit to a dermatological clinic.

A total of 498 patients attended the clinic during the study period (428 with psoriasis and 70 with PsA) (Figure 1). The patients were sent a questionnaire by mail and the mailing was sent again to those who did not respond initially. A total of 262 patients completed and returned the questionnaire (52.6% of the total study sample). A small proportion of patients (n=26) who returned the questionnaire did not give a written consent to use their medical records. In the productivity loss study (IV), analyses were done with employed

patients who had given consent to use their medical records and the few employed patients who had returned the questionnaire but had not given written consent.

At first there were 236 alleged patients who had given consent. This value was used in the medication cost (III) study. After this study was published, three patients were noticed to have missing information and no visits to TUH during the study period, and thus, these patients were then removed from the study sample of that time, resulting in an n value of 233, which used in one of the studies (I). The n value decreased further by one patient, when it was noticed that one patient had returned the questionnaire twice, resulting in an n value of 232, used in the second study (II). The n value in the medication cost study should have been 232 and the falsely high n value resulted in a higher value of patients not receiving any treatments. Fortunately, this had only a minor insignificant effect on the results presented. In the first (I) study, there was one subject whose information was represented twice, as she had returned the questionnaire twice and clinical information was collected twice. Fortunately, this had little effect on the results and the statistical significances were not altered by this mistake.

5.2. Data gathering

Three main data sources were used: a questionnaire (Appendix 2. in Finnish) to the patients, patient medical records of TUH, and the records of Finnish Social Insurance Institution (Kela). Patients gave a written consent allowing the use of their medical records and to gather data from Kela. The exact wording of consent statement was developed in co-operation with and approved by the ethical committee of The Hospital District of Southwest Finland. Patients personal identification number was used to link the patients to corresponding data collected from the medical records and the Kela. All information was collected for the one year study period (1.10.2009-30.1.2010). Each source is described below.

5.3. Questionnaire

The questionnaire (Appendix 2.) collected socio-demographic information (sex, age, home municipality, number of people living in the same household, income level) and disease duration. Subjects were asked to report whether they were employed, retired, studying or unemployed, with multiple choices allowed.

To evaluate the use of different medical services and associated out-of-pocket expenses and time, the subjects were asked the number of visits they had made because of psoriasis to a private or occupational health care provider, tertiary level hospital, and health centre during the study period of one year. The visits to doctors and nurses in each health care facility were recorded separately. The time spent, in hours per year,

was recorded for each health service provider. The subjects were asked to evaluate the out-of-pocket expenses associated with the different health care providers. The subjects were also asked to estimate the distance from their home to each health care provider in kilometres.

The subjects were asked to report how many minutes per week they currently spend on caring for their skin, cleaning and laundry, and to estimate the time in minutes per week they would have spent in a hypothetical situation if they did not have psoriasis and the difference was taken as that caused by psoriasis. The subjects were asked if they received any assistance with running errands or household chores because of psoriasis and the corresponding cost (in € per month).

The subjects were asked to report the time spent in hours on sick leave and when they had been working while sick. These questions are described in detail below.

5.4. Medical records

Clinical information was collected from the medical records of 232 subjects who gave consent for the same time period covered in the questionnaire data. Outpatient and UV-phototherapy visits and days hospitalized were collected from the treatment provider's (TUH) records. The actual costs per patient of laboratory and pathology tests were collected from the records separately, as they are separately charged from the municipalities. The data consisted of every test ordered by the dermatological clinic during the study period.

The PASI score, DLQI values, and the diagnosis International Classification of Diseases (ICD-10) of psoriasis (L40.0) or PsA (L40.5) were extracted from clinical records to classify the severity and the type of psoriasis. If there were many PASI scores or DLQI values recorded for the same patient during the study period, the arithmetical mean value was calculated and used in the analyses. When analysing the subgroups with recorded PASI values (n=72 patients), the median value was used to divide patients into those with more severe (PASI > 5.5, n=37) and less severe psoriasis (PASI </= 5.5, n=35). Only a few patients (n=10) had PASI values above 10; using such an index value for categorising would have produced a subgroup of severe psoriasis patients, which would have been too small for statistical analysis. DLQI values (n=36) were analysed as a continuous variable.

Different types of outpatient visits and hospitalized days have varying costs. There were 12 types of outpatient visits, 8 of which were present in this study and one diagnosis-related group (DRG) charge used for hospitalized days (Appendix 1). Each cost item was based on the assumption of actual costs used to charge the local communities that cover the costs of their residents. The costs have been estimated to include all

medications given in the hospital, medical equipment, diagnostic tests, time used by doctors, and other medical staff members and other expenses for the tertiary level clinic, during outpatient visits, UV-phototherapy or hospitalization. During outpatient visits, medications are not usually provided, although infusible biologic medications (infliximab) may be administered during an outpatient visit. A UV-phototherapy visit had two different cost categories depending on the type of UV-phototherapy given (bath-PUVA or UVB).

5.5. Medications

Kela reimburses part of the cost of medicines. In practice, patients with psoriasis receive reimbursement for all psoriasis-related medications and emollients, as long as a doctor prescribes them. Kela provided data on all psoriasis-related medication for the study patients who gave consent. Psoriasis-related medication in this study comprised biologic medications (including adalimumab, etanercept, infliximab, and ustekinumab), traditional systemic medications (including methotrexate, acitretin, and ciclosporin), topical drugs (including vitamin-D analogues, corticosteroid creams and combinations of these), and supportive drugs (leflunomide, topical fungal medicine, antihistamines and emollients). A dermatologist defined the medications used for psoriasis treatment and ATC-codes were used to identify the appropriate medications from Kela records. All purchases during the study period between 1 October 2009 and 30 September 2010 were recorded.

Kela records, of each purchase, contained the total cost of the drug as well as specific information about the reimbursements and the costs to the patient. Anatomical Therapeutic Chemical Classification-code (ATC-code) of the purchase as well as the amount of packages purchased. ATC-codes were used to identify each drug. Drugs were clustered based on their active ingredients, regardless of their brand names.

5.6. Patient categorisation in original articles

Table 1. Patient categorisation in the original studies*.

Article	Division criteria	Final Groups	Noticeable
I	By treatment modality (1 - 5)	Topical treatment (n=74, 32%) UV-phototherapy (n=63, 27%) Traditional per oral medications (n=66, 28%) Combination treatment (n=17, 7%) Biological treatment (n=12, 5%)	Patients receiving emollients were categorised in topical treatment group. Patients could only be in one group, the selection was done according to the most intensive treatment.
II	Use of traditional systemic medications (0/1)	Did not use traditional systemic medications (n=147, 63%) Used traditional systemic medications (n=85, 37%)	Patients using biological medications could be in either group
II	Receiving phototherapy (1)	Received phototherapy (n=83, 36%)	
III	Number of treatment options (0 - 4+)	Received no treatments (n=21, 9%) Received 1 treatment option (n=67, 28%) Received 2 treatment options (n=120, 52%) Received 3 treatment options (n=21, 9%) Received 4 or more treatment options (n=3, 1%)	Patients using only emollients were considered to receive no treatments. Each systemic medication was considered as a separate treatment option. Phototherapy was one treatment option; PUVA and UVB were not considered separately. Biological drugs were pooled.
III	Medication received	Topical medication (n=193, 83%) Methotrexate (n= 43, 19%) Acitretin (n= 46, 20%) Ciclosporin (n=3, 1%) Biologicial treatment (n=11, 5%)	Groups were formed using information from Kela. Thus, a patient receiving infliximab was not categorised as receiving biological treatment. Patients could be in multiple groups.

Footnote: The n values of similar groups vary. This was due to different criteria used in the divisions in each original study. Each categorisation is described in detail in the following sections.

*= Patients were also divided by other background factors (e.g., sex, Ps/PsA, severity of psoriasis). These divisions are described in detail in the text.

5.7. I Treatment costs in a tertiary level clinic

Information from all three data sets (questionnaire, medical records, and Kela) was used although medical records were the main source of information in this study. The cost estimates were done from a final payers' perspective. The number and typical cost of each visit to the hospital were used to estimate the cost of psoriasis treatment from a provider's perspective (Appendix 1). Laboratory and pathology costs were also included. Patients were divided into subgroups for further assessment by diagnosis of psoriasis (psoriasis and PsA) and the severity of psoriasis. Demographic data were used from the questionnaire.

Information on medication use was used to divide patients into five groups: 1. only topical treatment (including corticosteroids, vitamin D analogues, emollients, and combinations of these); 2. UV-phototherapy (UVB or PUVA); 3. Traditional systemic medications (acitretin, ciclosporin, methotrexate); 4. Combination treatment (treatments from both groups 2 and 3); 5. biological medications (adalimumab, etanercept, infliximab, ustekinumab). Patients in groups 2–5 may have also received topical treatments and patients in group 5 may have also received UV-phototherapy and/or traditional systemic medications. A patient could only be in one group as described above (Table 1).

5.8. II The Costs to a Patient

Information from all three data sets was used in this study and all cost estimates were from a patient's perspective.

5.8.1. Time cost

All time estimates were computed to hours per year. In this study (II), the economic burden was determined by approaching it from the perspective of purchasing power of the families. The value of an hour was based on the overall net monthly income in the family divided by the number of family members. The monthly values were then computed to an hour. The same formula was applied to retired and unemployed respondents. This was used for cost estimates for the time consumed for household chores, running errands, skin care, and treatment-related time.

5.8.2. Clinical data

Patients were divided into subgroups for further assessment by type of psoriasis (psoriasis with PsA or skin psoriasis alone) and by the severity of psoriasis. For division according to severity, the median value of PASI (5.5) was used as a cut-point. The subgroups were: more severe (PASI more than 5.5 (n = 37) and less severe psoriasis (PASI less or equal than 5.5, (n=35)). Patients were categorised to those who had received UV-phototherapy and those who had not, and as those who received traditional systemic medications (including methotrexate, acitretin, and ciclosporin) and those who had not (patients treated mainly with UV-phototherapy and/or topical therapy). Patients may have been included in more than one group, as combined therapy was possible.

5.8.3. Pharmaceuticals

All medication purchase data (from Kela) included the cost for the patient and the amount reimbursed as well as the type of medication purchased. There was a cap of 672 € as out-of-pocket expenses for medicine and emollients above this level in a calendar year are reimbursed at a rate of 100%.

5.8.4. Travel costs and time

Travel costs were estimated using the distances, which patients gave between their home and different health care providers, together with the number of visits to each destination. If the distance to a service provider was less than 12.5 km, a typical regional bus fee of 2.5 € was applied. For distances beyond 12.5 km, 0.20 €/km (derived from Kela reimbursement rate for travelling cost) was used for cost calculations.

The time patients spent on travelling to different health service providers was estimated using the distance to the service provider from their home municipality and the number of visits to each provider. An approximation of 1.5 minutes per kilometre was used with an additional fixed amount of 5 minutes representing the time needed to park the car or walk from the bus stop to the hospital. In the few cases where the estimated travel time to a service provider and back home exceeded 2.5 hours, it was capped at 2.5 hours.

5.8.5. Visit time

The time spent at different health care providers was solicited in the questionnaire and used to evaluate the cost of the time needed for visits. Due to the considerable time needed for UV-phototherapy, a separate survey was conducted, where the actual time needed by 40 patients with psoriasis attending UV-phototherapy at TUH was observed, recording separately the time for UVB and bath-PUVA therapies. UVB visits took on average 16 minutes and bath-PUVA took 43 minutes and other forms of PUVA treatment were not used. These times were used to calculate the cost of time used for UV-phototherapy.

5.8.6. Visiting charges

The charge for an outpatient visit to a tertiary level hospital in 2009 was 27.40 €. For a course of treatment (e.g., UV-phototherapy) the charge was 7.00 € per visit. For appointments that were missed without prior cancellation, there was a charge of 33.80 € on each occasion. For inpatient treatment, the daily charge to the patient was 32.50 €. The combined inpatient and outpatient fees for a patient to a tertiary level hospital were capped at 633 € during a year, as beyond this level, further visits to hospital are free of charge to the patient. TUH charges were based on register data of number of visits, and the number of other visits was derived from the questionnaire.

A visit to a private specialist was valued at 100 € per visit and a visit to a private nurse was valued at 50 € per visit. These approximate costs were derived from the average charges of the largest private health service providers. Kela reimbursed 20.25 € for a visit to a private specialist and an average of 8 € for a visit to a private nurse. These reimbursements were deducted from the average charges to compute the cost to a patient of visiting the private sector. For visiting the health centre the charge for the patient is 12.80 €, which is only claimed for the first three visits. Patients do not pay

a visiting fee when visiting a public health sector nurse or an occupational health care provider.

5.9. III The costs of medications

The data obtained from Kela was the main source of information in this study, although some clinical information and demographic data were also used. The direct medication costs were estimated from a societal perspective.

5.9.1. Treatment options

To analyse how many different types of treatments each patient used, treatment options were formed as following. All topical medications (not including emollients) were pooled as one treatment option. Traditional systemic medications (methotrexate, acitretin, and ciclosporin) were analysed separately and each of them formed one treatment option. All biological medications formed one treatment option and they were pooled because of the low number of patients using them. UV-phototherapy was considered as one treatment option. Emollients, fungal medicines, antihistamines, and other medications that might have been used as supportive medications were not considered as a separate treatment option. However, these medications were included in the total cost computation of medications, although the costs of UV-phototherapy were not included.

5.9.2. Medication costs

The total medication cost was used as the societal cost in all calculations without any reimbursement deductions. All medication costs were analysed for the annual cost of medications per patient. When analyzing the costs of different treatment options, only the medications in each treatment option were included for the cost calculations and the cost of UV-phototherapy was not included.

5.10. IV The costs of productivity losses

In this study (IV), patients currently in employment were studied (n=98). The study was mainly based on questionnaire data.

Having been on sick leave (absenteeism) was assessed by asking: “How many hours during the past 4 weeks have you been away from work due to psoriasis?” A similar question followed to assess absenteeism due to other medical reasons.

Having worked despite being sick (presenteeism) was assessed by asking: “How many hours during the past 4 weeks have you been working while sick, when you felt that you should have stayed at home because of your psoriasis?” To quantify the extent of

productivity lost during the hours a patient worked while sick, a 100 mm visual analogue scale (VAS) was used, with 0 representing not at all affected and 100 representing affected very much with the following question: "Please mark an X on the line to describe the decrease in effectiveness at work because of your psoriasis during the hours in the last 4 weeks that you worked while sick?" Similar questions were used to determine the amount and impact of presenteeism due to other medical reasons.

All time estimates were computed to hours per year. The VAS score (mm) of lost productivity for presenteeism was divided by 100 to indicate the proportional magnitude of lost productivity during the hours the patient worked while sick. This was used to weight the hours of presenteeism per year to give an estimate of productivity loss due to presenteeism.

To estimate the monetary value of the productivity loss from an employer's perspective a time-cost assessment was used. The value of an hour was estimated using the HCA. The value was based on the average monthly income in Finland of 2807 € for women and 3422 € for men (Statistics Finland 2011). The monthly income levels were computed to an hour based on average working hours (157 hours per month) in Finland for people working full-time. The gross income per family member, asked in the questionnaire, was not used for time-cost computations as it could have resulted in underestimation of costs for patients with many family members. It was only used in the analyses as a background factor indicating purchasing power.

Logistic and linear regression models of the productivity costs were used with the following background factors: sex (dichotomy: 0 = women, 1 = men), disease duration (in years), concomitant diseases (dichotomy: 0 = no other illnesses, 1 = having at least one concomitant disease), and level of income per family member. There were no statistically significant differences between patients with skin symptoms only and patients with skin symptoms and arthritis in any of the analyses made. Thus, these two patient groups were finally analysed as one psoriasis group. The use of different treatments, disease severity and quality of life were similar and without statistical significance between men and women. Thus, these background factors were not included in final statistical models.

5.11. Statistical analyses

The following statistical methods were used in the original articles and in this thesis. The statistical evaluation of the data was based on Student's t-test for means and chi-square test for proportions. Patients with missing data were not included in respective cost estimations and statistical analyses. Linear and logistic regression models were used to study the impact of different factors on the estimated costs. Correlation of naturally distributed factors was evaluated with Pearson's correlation. The distribution of DLQI values was skewed and to account for this, a Spearman's non-parametric correlation

was used. In case of skewed distribution to the higher end of costs, natural logarithmic transformation was used to obtain close to normal distribution of the dependent variable, which was necessary for linear modelling. Subjects with missing data in any category were excluded from respective cost estimations. Thus, the total loss estimates may differ from summing up costs.

5.12. Ethical considerations

The ethical committee of The Hospital District of Southwest Finland approved the study. The patients received a written description of the sampling procedure and study purpose, as well as the planned use and storage of the information they were to provide. This was followed by a description of the subject's rights according to the Helsinki declaration. The patients were asked to give written consent to use their medical records for the study.

6. RESULTS

Overall psoriasis was estimated to cause a substantial economic burden for the patient, health service provider, social insurance system, and the society as a whole (Table 2). The patients' share of these costs as co-payments and charges was relatively low (<20%) (Table 2). However, patients suffered from a substantial economic burden from time lost because of psoriasis (Table 2). Psoriasis also caused a substantial productivity loss for the employers (Table 2). The direct costs to both service provider (tertiary level clinic) and Kela were close to the total costs to patients and productivity loss costs to the employers.

Table 2 Mean annual costs per patient (€) of psoriasis treatment and productivity losses. The costs are estimated from different perspectives according to the original studies. The 95% confidence intervals (95% CI) presented in parenthesis.

	Mean cost € (95% CI €)
UV-phototherapy costs *	266 (209-323)
Other outpatient visit costs *	469 (334-604)
Laboratory and pathology costs *	66 (54-78)
Hospitalization costs *	618 (120-1116)
Total tertiary level clinic costs (n=232) *	**1419** (884-1953)
Total medication costs (n=232) **	**1102** (601-1603)
Patients' share on medication costs ***	194 (168-221)
Patients' visit costs [a] ***	390 (324-456)
Patients' time spent on skin care ***	950 (779-1122)
Patients' time spent on cleaning and laundry ***	313 (202-426)
Assistance ***	296 (197-396)
Costs for patients (n=232) *	**2145** (1868-2421)
Total costs (n=232) ^	**4471** (3637-5343)
Absenteeism ^^	1105 (48-2258)
Presenteeism ^^	1037 (398-1675)
Productivity loss due to psoriasis (n=80) ^^	**2250** (771-3728)

Footnote: Subjects with missing data in any category were excluded from respective cost estimations. Thus, the total loss estimates may differ from summing up costs.
* Costs estimated from the final payers perspective, in this case the municipalities
** Costs estimated from a societal perspective, includes costs for patients and Kela
*** Costs estimated from a patients perspective.
[a]includes all cost items of visits to all service providers: charges, travel, travel time, and visit time
^Total costs estimated from a societal perspective, thus, including costs to the patients, final payers and Kela
^^Costs estimated from employers perspective

6.1. Patient characteristics

Patients (n=232) in the total study sample (I, II, and III) were on average 57 years (95% CI 55.7-59.2 years) old and 55% (n=127) were male. Half of the patients (n=118) were retired, 38% were currently working (n=90), and 13% (n=31) were unemployed. On average, the duration of psoriasis was 21 years (95% CI 18.5-22.7 years) and 14% (n=33) of patients had PsA. The mean PASI score (n=72) was 6.5 (95% CI 5.5-7.5) and the mean DLQI score (n=36) was 11.0 (95% CI 8.2-13.8). When only the highest PASI values were estimated instead of the arithmetic mean, the mean value of those highest PASI values was 7.2 and a median of 5.7.

The employed (n=98) patients, who comprised the sample for study IV, were significantly ($p<0.05$) younger (mean 49 years (95% CI 47.1-51.0 years)) than the total sample but had the same proportion of male patients and those with PsA. PASI (n=30) and DLQI (n=16) values were very similar to values in the whole sample (6.9 and 10.4, respectively (95% CI 5.0-8.7 and 5.7-15.0)).

Patients own estimate of visits to doctors' office in TUH correlated ($r=0.240$) statistically significantly ($p<0.001$) to observed number of visits the doctors' office in TUH from the medical records with patients reporting slightly higher number of visits 2.0 (95% CI 1.8-2.2) than the figure from the medical records 1.5 (95% CI 1.4-1.7).

6.2. Treatment options (III)

The treatment options and treatment types were studied with various aspects in the different sections of the thesis, as described in the methods section (Table 1). Thus, the proportions of patients in different sub-categories may vary. Topical medications were used by 83% of the patients (Table 1). Different traditional systemic medications (acitretin, methotrexate, and ciclosporin) were used by 20%, 19%, and 1% of patients, respectively (Table 1). UV-phototherapy was received by 36% of patients (Table 1). Self-administered biologics (etanercept or adalimumab) were used by 5% of patients and one patient received an infusible biologic medication (infliximab) (Table 1).

Many patients received different types of combination therapy and topical treatment was most often combined with other treatment options (III). Patients were categorized into groups by the number of treatment options they received (Table 1) (III). A considerable proportion (9% of patients) did not receive any treatment options during the study period. During the 1-year follow-up period 29% of patients received one treatment option, 51% received two, 9% received three, and 1% received four (Table 1) (III). Patients who received no treatments during the study period were more likely ($p<0.05$) unemployed (6 unemployed out of 21) than patients receiving any treatments (25 unemployed out of 211) (III).

6.3. Medication costs (II & III)

Patients receiving multiple treatment options (III) (Table 1) had considerably higher medication costs than patients receiving fewer treatment options the differences between all groups were significant ($p<0.05$).

From a societal perspective, the total costs for medications were 1102 € (95% CI 653-1736 €) per patient per year (III). Topical treatments were most often purchased medications and they comprised 18% of the total medication cost. Biologics and ciclosporin were the most expensive medications but were rarely used. Biologics were used by only 5% of the patients, but they accounted for 67% of total medication cost. Methotrexate was used by 19% of patients but accounted for only 0.6% of all medication costs (III). Co-payments by patients for medications and emollients were on average 20% of the total medication cost (Table 2) (II).

6.4. Costs of UV-phototherapy (I & II)

Approximately a third of the patients received UV-phototherapy (Table 1) and on average they received 14.9 (95% CI 13.3-16.4) UV-phototherapy sessions per year (I). 78 (34%) patients received UVB, 25 (11%) patients received bath-PUVA, and 21 (9%) patients received both PUVA and UVB treatment. The societal cost of phototherapy was estimated to be 1230 € (95% CI 1059-1375) per patient per year. On average, tertiary level clinic UV-phototherapy costs comprised 20% of all costs to tertiary level hospital (Table 2) (I). For those receiving UV-phototherapy, the costs were on average 760 € (95% CI 650-842 €) (I). The patients who received UV-phototherapy paid on average 104 € (95% CI 93-115 €) as charges or co-payments for UV-phototherapy (II).

The majority (64%) of the total costs of UV-phototherapy (471 €, 95% CI 336-553€) for patients arose from travel costs (119 €, 95% CI 87-152 €) and travel time costs (181 €, 95% CI 135-227 €) (II). Patients receiving UV-phototherapy lived on average 10 km closer to TUH than those who did not receive UV-phototherapy ($p<0.05$) (II). Treatment time comprised only 14% (66 €, 95% CI 55-76 €) of the total costs of UV-phototherapy for the patients (II).

6.5. Other visit costs (I & II)

Patients were categorized according to the treatment type they had received during the year, when costs to tertiary level clinic were analysed (I). There were only minor differences between the patient characteristics of different treatment modality groups (I). The annual cost of tertiary level treatment per patient with psoriasis varied widely, from 32 € to 43842 €, with a mean of 1419 € (95% CI 822-1883 €). Half of the patients accounted for costs less than 600 €, and 95% of patients accounted for costs less than

2500 € (I). Patient charges for visiting tertiary level clinic were relatively low with patients paying on average 85 € (95% CI 74-97 €) per year for their visits (II).

A majority of the total visit costs incurred by patients were from visiting tertiary level clinic and only a small proportion from visiting primary health care providers (II). A great majority of patients (n=224) had only outpatient visits to the clinic (I), as only eight patients (3.4%) were hospitalized because of psoriasis during the study period (for an average of 7 days 95% CI 3.1-10.4 days) (I). However, the costs of these hospitalizations formed 45% (617 € 95% CI 120-1120 €) of all the treatment costs for tertiary level clinic in the entire study population (I). On average the hospitalized patients had costs that were 31-fold higher than for non-hospitalized patients ($p<0.0001$) (I). Patients from all different treatment modality groups were hospitalized although patients receiving combination therapy or biological medications had higher costs of hospitalization than in other treatment groups (I).

Patients receiving combination therapy or biological therapy accounted for the highest cost to the tertiary level clinic (I) (Table 3) with patients who received UV-phototherapy more costly than those who were treated with topical treatments only, but lower costs than patients in the other treatment modality groups (I) (Table 3).

Table 3. Average annual costs (€) of psoriasis treatment per patient in a tertiary level clinic for each treatment modality. The costs assessed from a final payer's perspective (in this case the municipality). 95% CI (€) are in parenthesis.

	Topical therapy (n=74)	**Phototherapy (n=63)**	**Traditional systemic therapy (n=66)**	**Combination therapy (n=17)**	**Biological therapy (n=12)**
Total costs	559 (193-925)	1381 (934-1829)	1422 (390-2454)	3808 (1505-9120)	6915 (804-7982)

When the effects of other studied factors were simultaneously controlled in a linear regression model, being hospitalized and receiving UV-phototherapy were the strongest predictors of high treatment costs. Increasing age and income level were also significantly related to increased costs; sex and type of psoriasis (psoriasis or PsA) had a minor and non-significant effect on overall treatment costs (I).

6.6. Costs to patients (II)

Time required for skin care was estimated to account for almost half of the total economic burden of psoriasis to the patient, while medications and UV-phototherapy co-payments contributed only 18% (Table 1). Patients spent on average 85 hours (95% CI 70-100 hours) on skin care due to psoriasis. UV-phototherapy and biologic medications were the costliest therapies for a patient to receive. Patients were analysed in sub-categories

of those receiving or not receiving traditional systemic medications. Patients receiving traditional systemic medications had higher costs for skin care than those who did not. Only visit costs were higher for patients not receiving traditional systemic medications, mainly because their costs of UV-phototherapy (217 € 95% CI 159-275 €) were higher ($p<0.001$) than for those who received systemic medications (82 €, 95% CI 33-131 €).

Sex, age, type of psoriasis, the severity of psoriasis, or receiving UV-phototherapy did not have a statistically significant effect on skin care costs. A quarter of the study group received assistance for household chores because of psoriasis. For those patients who received assistance, the annual cost was estimated to be 1014 € (95% CI 835-1427 €) (II).

6.7. Productivity losses (IV)

During the last 4-week time period assessed in the questionnaire, approximately one fifth of employed patients (n=16/86,19%) had been on sick leave (absenteeism) due to psoriasis and around a third (n= 22/80), 28%, of patients reported that they had worked despite being sick with psoriasis (presenteeism). Absenteeism and presenteeism due to psoriasis comprised similar shares of the total annual cost of lost productivity due to psoriasis (Table 2). Psoriasis accounted for 38% of the total cost (2250 € / 5409 €) of lost productivity due to any health reasons.

Absenteeism due to other health reasons was 2.5 times more common than absenteeism due to psoriasis. For the patients who reported absenteeism due to psoriasis, the estimated mean annual work time lost due to psoriasis was 306 hours (95% CI 12-658 hours), which corresponded to a mean cost of absenteeism of 6296 € (95% CI 533-12060 €) per year and a median cost of 2092 € per year.

Presenteeism due to psoriasis was more common than absenteeism. The estimated presenteeism costs due to psoriasis were around 50% lower than for presenteeism due to other medical reasons. For the patients who reported presenteeism due to psoriasis, the estimated mean annual duration was 391 hours (95% CI 227-557 hours). During these hours, the decrease in productivity was on average 45% (range 8–85%, 95% CI 34-54%), which led to a mean cost estimate of 3605 € (95% CI 1751-5460 €) per year and a median cost of 1647 € for presenteeism due to psoriasis.

Men worked while sick due to psoriasis for a longer period of time and had a greater decrease in productivity than women and thus, higher costs of presenteeism. However, the costs of absenteeism due to psoriasis were lower for men than for women. Costs of absenteeism and presenteeism due to other medical reasons were both higher for men than women.

In a linear regression model for absenteeism costs due to psoriasis, the costs were significantly higher for men than women. For presenteeism, the only statistically

significant background factor affecting costs due to psoriasis was having concomitant diseases. All other studied background factors did not have a statistically significant effect on absenteeism or presenteeism costs due to psoriasis.

6.8. Severity of psoriasis and effect on quality of life (I – IV)

The clinical severity of psoriasis was a good predictor of many types of costs. Patients with more severe psoriasis (PASI >5.5 n=37) had more visits to tertiary level hospital and were more often hospitalized than those with less severe psoriasis (n=35). Thus, costs to tertiary level clinic were significantly ($p<0.05$) higher for patients with more severe psoriasis (PASI > 5.5) (2683 €, 95% CI 181-5184 €) than patients with less severe psoriasis (PASI </= 5.5) (562 €, 95% CI 426-716 €) (I). For patients, the visiting costs (including travelling costs and time, charges, and treatment time) were significantly ($p<0.05$) higher for patients with more severe psoriasis (673 €, 95% CI 390-956 €) than for patients with less severe psoriasis (359 €, 95% CI 230-487) (II).

Patients with more severe psoriasis also had significantly ($p<0.05$) higher total medication costs (2559 €, 95% CI -26-5018 €) than patients with less severe psoriasis (1375 €, 95% CI -140-2454 €) (III). When each treatment option was analysed separately, only the costs of topical medications were significantly ($p<0.05$) higher for those with more severe (394 €, 95% CI 242-481 €) than with less severe psoriasis (163 €, 95% CI 76-173 €). There was no significant difference in the probability of receiving topical treatments between the two severity groups. However, according to Kela records, the total number of purchased packages of topical medications was significantly ($p<0.001$) higher for patients with more severe (8.7 packages/year, 95% CI 6.0-11.3 packages/year) than for patients with less severe psoriasis (mean 2.4 packages/year, 95% CI 1.5-3.4 packages/year). Methotrexate, ciclosporin, and biologic medications formed higher (NS) medication costs for patients with more severe than less severe psoriasis. There was no significant difference in the amount of acitretin prescriptions for participants with less or more severe psoriasis.

Higher DLQI values were significantly ($p<0.05$) correlated with increasing number of treatment options a patient received during the study period (III). DLQI was assessed or recorded more likely ($p<0.05$) of patients using biologics (5 of 12 patients) than those who were not using biologics (31 out of 220). Use of biologics was not significantly related to occurrence of PASI recordings in the medical records.

7. DISCUSSION

The findings of this thesis suggest that psoriasis causes a substantial economic burden. The estimated annual costs for patients and employers were almost twice the costs to health service providers or the Kela. On the other hand, co-payments for medications and charges from treatment providers were relatively low. The costs that were laid upon patients and their employers were mainly indirect costs, which may be difficult to reimburse or measure accurately. These indirect costs have often been omitted in previous cost-of-illness studies, or the methodology and measurements used were so ambiguous that comparison of the findings with published studies is problematic or impossible. A recent review (26) of the burden of psoriasis urged more harmonization of methods used for cost assessments.

Although, the aim of the thesis was not to provide results for this harmonization of methodologies, our study shows that different parties bear a substantial burden from psoriasis and that the perspective chosen has a significant effect on the conclusions drawn. When the aim is to create a comprehensive picture, none of the parties involved should be ignored and none of them should be considered as more important than the others.

The aim of this thesis was to understand the economic burden of psoriasis from various perspectives. To do this, data was gathered from multiple sources. Combining information from a questionnaire and different registries allowed estimations of the economic burden of psoriasis to patients, their employers, and health service provider. If the focus of the study had been on one of these perspectives, instead of a wider scope like in this work, a different study setting could have been chosen. Focusing on one perspective alone would have enabled more thorough estimates of that particular approach, but a view to more comprehensive comparison would probably have been more superficial.

In a solely register-based study, we could have used all of the 498 patients' medical records with medication data from the Kela. The larger sample size would have brought more statistical power. More importantly, this would have allowed us to generalize the yielded results with more confidence, as there would have been none or only limited dropout of patients during the data collection phase. This type of register-based study could have also been designed and been implemented in addition to our current study. This would have enabled comparisons between the patients who returned the questionnaire and those who did not.

On the other hand, only a questionnaire-based study could also be conducted. In this study setting, no clinical information of the patients would have been available. Thus, the assessment of the health service providers' burden and the medication cost to the society

would have been difficult and unreliable. However, the questionnaire-based study could have been conducted to a larger sample with no restrictions of being treated in TUH during a year. The patients registered in for example the Finnish Psoriasis Association (FPA) could have been studied or the sample could have also included patients from other hospital districts. However, as in this thesis, a relatively high rate of non-returned questionnaires could have been expected. Also the patients from FPA members would probably include subjects who have not been diagnosed with psoriasis at all or who have minor symptoms. Subjects with more severe symptoms and those with higher overall social activity could be expected to be more active to participate and be over-represented in such sample.

The study sample could have been partially collected from private dermatologists, primary health care centres, and occupational health service centres. This may have led to higher proportion of false positive cases and other uncertainties in the patient sample, as diagnosis may be falsely coded or totally missing in patient records of such institutes. Also, organizing a comprehensive sampling from such institutes, collecting relevant information consistently, and getting patients consent correctly, would have been very challenging when considering the amount and the diversity of patients these institutes handle daily.

The patients returning the questionnaire could be expected to be, e.g., more motivated towards treating their psoriasis or more educated than other psoriasis patients. This problem is present in all questionnaire-based studies. It would have been interesting to compare the patients who did and did not return the questionnaire. However, there were no possibilities to do this, as the ethical permissions did not allow using medical records without written consent from the patient participating in this study.

Our patient sample and the return rate of questionnaires were estimated to be sufficient to allow generalizations of the results. Also the sample size allowed enough statistical power to find statistical significances. The sample size in the first three studies (I-III) is higher than in many earlier studies of the costs of psoriasis (52,54-56,65,85,130). In the productivity loss study (IV), the sample size of 98 was achieved using all patients returning the questionnaire and reporting to be employed. Although the sample size was smaller in this study (IV), it was also comparable to recent studies on productivity losses (143). However, more caution is warranted when generalizing the results of the productivity loss cost study (IV) than the first three studies (I-III).

In the hospital district of Southwest Finland, there are no separate secondary level hospitals treating psoriasis. Thus TUH can be considered to be both secondary and tertiary level hospital. In the Finnish Current Care Guidelines (29), psoriasis patients are treated by specialists or specialists are consulted, when psoriasis is not adequately controlled with topical treatments, diagnosis is unclear, psoriasis progresses quickly or is widely spread, or when psoriasis causes productivity losses. These criteria are

applicable to the patients in this study sample. Although, the proportion of patients that were only consulted for diagnosis and or treatment and were not treated mainly in TUH remains unclear. In some areas in Finland there are also secondary level hospitals with dermatological clinics. In such areas, the patients visiting a tertiary level hospital may on average have more severe disease and may accumulate higher costs per patient than in this sample. However, secondary level hospitals seldom consult tertiary level hospitals.

Compared to recent Continental European studies, the patients studied had relatively mild psoriasis, when assessed with available PASI values (52-54,56). In a recent Scandinavian study (55), the severity of psoriasis was similar to the one found in this study's patient sample. Their study sample was gathered from a secondary and tertiary level hospital, which suggests that this patient sample may represent typical psoriasis patients, which need specialist care in Nordic countries. The proportion of patients receiving phototherapy or systemic treatment is similar or lower compared to some European countries (52,54,56). This implies that psoriasis patients in Nordic countries may have been treated more intensively, while having lower severity psoriasis. However, as these studies are not directly comparable, no certain conclusions can be drawn from these differences.

The Finnish Social Security System with its multiple financing sources is unique internationally and thus, comparisons between countries should take this into consideration. One example of how the Finnish social insurance system may encourage or discourage the use of some medications is infusible and injectable medications. When a patient receives infusible biologic medications during outpatient visits or during hospitalization, the costs are bared by the hospital. If the patient receives injectable biologic medications during hospital visits, the health service provider would cover the costs. However, if injectable biologics are prescribed to the patient and are injected at home, Kela and/or the patient cover the costs, without any costs to the hospital. Thus, most commonly, patients receive the prescriptions and biologics, which are used at home, and the cost burden to the hospital is avoided and directed to other parties, mainly Kela. This may discourage the use of infusible medications, as the specialists who prescribe therapies may prioritize the costs of the clinic over the costs for the society, although, the final economic burden will in any case be on the tax payer.

There has been speculation that third parties' reimbursement policies may discourage the use of UV-phototherapy with low and partial reimbursements to the patient and high out-of-pocket costs. It has been estimated that physicians do not prioritize cost-efficiency when making decisions about treatments, especially if the costs are paid by a third party such as insurance companies (82,169). In contrast, costs to patients may have an effect on prescribing decision. This may lead to higher overall costs to society, if more expensive treatments are fully reimbursed and less expensive treatments have high costs for the patients (73,170). There were no implications of biologics being prioritized over phototherapy in the results of this thesis.

Also, indirect costs do not result in costs for the health service providers and may seem as only a small hindrance to the specialist prescribing treatments and sick leave. However, clinical specialists, who base their decisions on clinical efficiency, should also consider cost-containing practices. Efforts to control the indirect costs should be the task of all sectors in health care. Health policy makers may guide specialists and patients to use more cost-effective treatments, bearing in mind that the majority of costs of a chronic disease may arise from indirect costs (33).

The co-payments of drugs and visits vary between countries and individuals with different types of health insurances. Thus, these factors may have a significant effect on the economic burden for the patient. In countries with an extensive social insurance system or for patients with inclusive private insurance, the direct costs to patients may be lower due to high reimbursement rates or small co-payments than in other health care systems. In Finland, psoriasis patients paid on average a fifth of the costs of drugs. Unfortunately, there are only few studies reporting the costs of medications to the patients. In two German studies (52,56) the co-payments for medications were 5 – 10% of the total medication costs. However, when accounting for over the counter-medications, the proportion of patients' expenses rose to 30% in Germany (52). Many studies do not give information of the proportion of patient co-payments and this reduces the possibility to make comparisons between countries.

On the other hand, when considering patients as taxpayers, they also contribute to the financing of these systems via taxes or insurance payments. These costs are not usually directly linkable to specific patients or treatments and thus, cannot be included in the assessment of the economic burden to patients. However, a recent (2012) U.S study (39) estimated that patients with psoriasis have significantly higher insurance expenses than the general population and also that their out-of-pocket expenses for medical services are significantly higher than for the general population. Finnish social insurance system is funded from several sources, which could be characterized mainly as tax money and psoriasis patients pay the same amount of taxes as other people. The majority of psoriasis patients are treated in public hospitals, thus Finnish patients do not pay extra for their psoriasis treatments. There were only a few visits to private specialists according to our study (III), thus, not many patients can be expected to have separate private health insurance and treat their psoriasis in the private sector. However, this study may underestimate the role of private dermatologists as the patient sample was collected from a public hospital.

One of the shortcomings of the data collection phase in this study was the limited number of available PASI and DLQI values. TUH dermatological clinic had instructions for doctors to always determine and register the PASI and DLQI values when meeting a psoriasis patient. Thus, a higher number of values were expected to be found from the medical records. However, the values were only found from a small proportion of the

patents' medical records. This problem could have been bypassed with adding a DLQI and possibly self-administrable-PASI (SAPASI) forms to the questionnaire. On the other hand, it could be expected that the longer the questionnaire, the lower is the return rate of the questionnaire. In retrospect, DLQI would have been a valuable addition to the questionnaire. However, the economics of psoriasis were only a part of the questionnaire, which was an extensive survey of the burden of psoriasis.

As there were relatively few PASI and DLQI values, they might be biased and should be considered with caution. One possible explanation for when these values were registered is when patients apply for reimbursements for their therapies from Kela. That requires documentation of DLQI and PASI values when applying reimbursements for biological drugs. Of the patients receiving biological medications, there were more DLQI values recorded than in those patients not using biologicals. However, a similar relationship with occurrence of PASI values was not observed. In previous literature, it has been estimated that physicians make decisions more based on the clinical severity than QOL (22). In this study sample, such conclusion could not be drawn, at least when estimating the values coded into medical records.

When DLQI and PASI values were collected from the medical records, a few patients had more than one value during the study period. We decided to use the arithmetic mean values for describing the patients' severity. In a study by Steinke et al. (51), the highest PASI value during the study period was used to describe the psoriasis severity. Both approaches are feasible. Our approach was chosen to better describe the severity of the whole study period, because a value during a flare or a single value during remission may lead to either over- or underestimate the severity. Subsequently, a study estimated that patients own estimation of their psoriasis at its worse during the past two years was a better indicator for high costs than PASI values at a certain time (32). However, the arithmetic mean and the highest PASI were close to one another in our study sample, and it would have not affected the results significantly if highest PASI values had been used. The arithmetic mean value was used as it was estimated to be representative for the total economic burden that psoriasis affects during the study period of one year. However, the highest PASI could have been more clinically descriptive about the severity of patients' psoriasis, whereas a flare may not generate high annual economic burden.

Alternative background factors were used in this thesis to evade problems from small n values of patients with PASI and DLQI values. The therapies patients receive have been commonly used as background factors to describe the severity of psoriasis. Some studies consider all patients receiving systemic medications or UV-phototherapy to have moderate to severe psoriasis (55,62,74,80). The treatment method may indicate the severity of psoriasis, as there is a stepwise approach to therapy for patients also in the care guidelines. There are also studies (32,52) in which the treatment type received affects the costs (absenteeism, retirement) more significantly than the severity of psoriasis. In two

(I-II) of the studies in this thesis, therapy options were used to describe the severity of psoriasis. A different approach was selected in each study to describe the sample to best meet the requirements of the perspective chosen in each study.

The QOL of patients should play a significant role in the process of selecting from the treatment options. As psoriasis is not a life threatening disease, treatments should aim mainly at improving QOL for patients. This may be challenging, as specialists treating the patients may mainly rely on the clinical aspects of the disease, which may also be more easily definable, whereas symptoms and lowered QOL can only be described by the patient. If the treatment provided improves the clinical symptoms but does not improve QOL, one might question the adequacy of the chosen treatment.

Our results from practically all perspectives show considerable variation and a wide range in costs. Most cost distributions were skewed to the higher end of the costs. These findings corroborate those of earlier studies (51,171), which have also found a small proportion of psoriasis patients producing high costs estimates and skewedness to distribution.

Our results indicated that few patients generate a significant proportion of the total costs. The patients being hospitalized were a minority, whereas they generated a large proportion of the total costs to the tertiary level clinic. High costs of hospitalizations may be due to relatively high unit cost of hospitalizations used in this study. This even at its best is only an approximation of the actual costs formed to health service providers from treating individual patients and may be an over- or underestimate. Further studies could be designed to provide information of the dispersion of specific costs of hospitalization of each patient or procedure, which could be compared to the DRG costs used in this study. The costs for the majority of patients were relatively low and most patients were treated with costs that could be considered reasonable. Biological medications had similar effect on medication costs. Thus, using as few biological medications and reducing hospitalizations would decrease costs significantly. However, our results indicate that neither treatment was given frequently. The small number of patients being hospitalized and receiving biological medications hindered further estimations of the background factors affecting these rare occurrences.

There was relatively high number of patients not receiving any treatments. As all of these patients had diagnosed psoriasis or PsA, it may be safe to assume that they have probably been offered a treatment. These patients did not redeem their treatment for some reason. A considerable proportion of these patients were unemployed, which may have had an effect on the economical possibility of using the prescribed treatments. These patients may benefit from more complete economic assistance from the social security system. However, many psoriasis patients do not need any treatment or choose to not treat their skin. Patients receiving no treatments should not be highly presented in our studies due to the patient selection towards moderate and severe psoriasis. Thus, the results of these

studies should not be generalized to cover all psoriasis patients and especially the ones with mild psoriasis may be treated with low costs.

Our data enabled comparisons between the patient reported TUH visits and the ones retrieved from the registries. Although, there were some issues regarding the comparisons, for example, a doctor's telephone call to the patients was coded with the same code as a patients visit to the nurse's office at TUH. If these values would have been directly compared, then a misleadingly weak correlation between patient-reported visit number and visit numbers collected from the registries would have been found. Thus, only visits to doctor's office were compared to patient reported visits. The numbers correlated significantly and gave positive signs of equivalence in the patients' answers and medical record data.

One of the aims of this study was to estimate the economic burden that a psoriasis patient experiences. For example, lost time for skin care was an indicator that was used to estimate that burden. These indicators may have been influenced or biased by patients' answers, as she or he might have over or underestimated the actual time. On the other hand, this possible bias may describe the actual burden experienced by the patients. If a patient experiences something to be unpleasant, for example, skin care, he or she may likely overestimate the time needed to do it. This aspect is present in all patient questionnaires and it may be considered as a possible source of bias and all estimations of skin care time should be considered with caution.

Also a question in the questionnaire may be interpreted in many ways. The questionnaire used in this thesis was designed to be as unambiguous as possible. However, it is uncertain how patients understood, for example, the questions about absenteeism that was due to psoriasis. Some may have included side effects or co-morbidities to the answer, but most likely most have not, as side effects or co-morbidities were not mentioned in the questions used in the questionnaire.

There are also other methods to estimate the burden of a disease. Generic QOL-measures can be used, and then the results may be comparable to other diseases, which have also been assessed with same generic measure. However, these questionnaires can rarely take into account for typical hindrances of diseases. Whereas, cost estimations can easily account for various aspects of a disease and the final costs can then be compared to other diseases' costs. Also, using money as a measure of a burden, the burden may be more tangible and may appeal to the public, clinicians, and certainly to decision makers more easily than an index figure produced from a questionnaire.

The monetary value of the time used for patients' home care or productivity loss depends very much on the value given for a unit of time. To estimate the monetary value of lost time, HCA was used in these studies. However, two different values for an hour were used according to which perspective the costs were estimated from. When assessing the

patient's burden (II), the families' net income divided by the number of family members was used. This was estimated to describe the financial resources family had available for each of its members had financially available. This resulted in a significantly lower value than the one used in the productivity loss (IV) study, in which average gross wages comprised the value of an hour to represent the cost of productivity loss to the society. The average wages were estimated to best represent the costs from the chosen perspective, although there have been estimates that societal costs are even up to three times higher than the average wage (159). There is no consensus of which methods should be used to make these estimations, adding variability and difficulties in interpretation and comparisons of different studies.

The aim of this work was to estimate the proportion of productivity loss that psoriasis causes and not to study the overall generalization of different questionnaires or study methods. This aim was achieved with relatively few questions and could not have been achievable with general or psoriasis-specific questionnaires. On the other hand, using a general questionnaire (for example, WPAI) to estimate productivity loss would have added more reliability and generalizability of the results. Adding more pages to the questionnaire could have reduced the number of patients returning the questionnaire and thus, a compromise not to use a general questionnaire was established.

One possibility of evaluating absenteeism of psoriasis patients would have been to link our patients to Kela records of sick leave of these patients. This was not done because these records were thought to be an underestimate of the actual absenteeism time. Kela only receives information from sick leaves lasting over nine days (not including Sundays). These long sick leaves were estimated to represent a minority of the total sick leaves to psoriasis patients, in retrospect they may have provided valuable information and in future studies should be considered as an alternative source of information. Also, having information of patients' sick leaves during a year are only indicative when comparing them with the patients' answers from a four-week time period and may not add reliability for the results. In those cases when patients have been prescribed longer sick leaves (more than 9 days) due to psoriasis, the employers would have received reimbursements from Kela for the days exceeding the 10^{th} day. This information could have been a useful addition and would have enabled estimations of the reimbursements that employers receive from Kela, in case these longer sick leaves would have commonly occurred.

In previous studies, productivity losses have been measured either as specifically due to psoriasis or generally due to health problems. In some studies, the methods do not make this distinction clear. There is no previously published information on the proportion of health-related productivity losses that are due to psoriasis and those due to other health-related reasons in patients with psoriasis. In our sample, the proportion of productivity loss that was due to psoriasis was less than half of the total health-related productivity loss. In several studies (33,42,143), the productivity losses have been estimated in a

general level due to any health problems, which may have led to overestimating the role of psoriasis in the indirect costs. On the other hand, in several other studies (47,52,55,56,85,149), the costs of productivity losses have been only those due to or related to psoriasis.

In a registry-based study (42), estimations of the indirect costs for patients with psoriasis were similar to the ones in this thesis. In their study, Fowler et al. (42) estimated that the total indirect costs for psoriasis patients were USD 2748 per patient per year, and the control patients with no psoriasis were found to have indirect costs of USD 1200 per patient per year (42). In the present study, the total productivity loss costs were higher than the ones presented above, but the productivity loss costs due to psoriasis were lower. Thus, using the overall health-related productivity loss would probably have resulted in overestimations of the burden of psoriasis.

Fowler et al's study (42) described the difference in total production losses for the patients and those likely to be due to psoriasis. Although they (42) did not claim that the incremental indirect costs were solely due to sick leave or disability arising from psoriasis, the study gives a rough estimation of the burden on patients with psoriasis compared to a control group. Similarly, another study (128) estimated the amount of work impairment due to health reasons and found that patients with psoriasis have higher levels of absenteeism and presenteeism than a control group.

A review (147) recommended a more general approach to assess productivity costs, to account for co-morbidities, possible toxicities of medications, and adverse effects of treatments. However, other illnesses that are not related to psoriasis may affect the results of a more general approach, which can easily lead to overestimation (147). According to Zhang et al. (147), this effect can be minimized by randomization and large sample sizes, although this is not always possible in cost-of-illness studies and thus, outliers (e.g., high costs from other illnesses) may form a significant problem when using a general approach to estimate productivity losses.

When estimating productivity losses of psoriasis in the past decade, accounting for presenteeism has been gaining popularity. Our results indicate that this has been well-justified, as presenteeism comprised a significant proportion of the total productivity losses due to psoriasis. In this study presenteeism due to psoriasis caused a higher share of productivity losses than absenteeism due to psoriasis, when compared to presenteeism or absenteeism due other health-related reasons. Indicating that it should be further studied especially in studies of psoriasis. However, aiming to decrease presenteeism may increase absenteeism and vice versa.

In our patient sample, all patients with PsA also had skin psoriasis and they were mainly treated for their skin manifestations rather than joint pains, as the sample was selected from a dermatological clinic. In many previous studies, PsA and psoriasis patients

have been estimated as one sample with PsA being a background factor rather than a discriminating factor in the analysis (40,51,55). On the other hand, there are also several studies evaluating the costs of treating PsA (135,172-175). In many of these studies skin manifestations or their treatment costs have not been considered. In the future, comparisons between patients with PsA and psoriasis patients, who were attending rheumatological and dermatological clinics, would be interesting to compare, because these diseases differ in the ways that they affect patients' QOL, and because also that they overlap each other significantly. At least in the Finnish health care setting, the data collection to achieve representative and comparable samples for such study would be very challenging.

Biological medications have changed the treatment of psoriasis and their introduction has had a significant impact on the shares of treatment costs. When the samples used in this thesis were collected, biologics were just gaining popularity, and if it was done again, the proportion of patients using biologics could be expected to be much higher. This change could be an interesting subject to study in the future. The evident increase in medication costs (38) requires cost analysis and cost studies to help clinicians and health policy makers target the expensive treatments to those who most benefit from them. It has been estimated that social insurance policies may have an effect on which treatment option is chosen (170). UV-phototherapy may seem less attractive when large proportions of the cost and many inconveniences are covered by patients. This, however, may result in suboptimal treatment decisions from a socio-economic point of view. The relatively low proportion of patients using biologicals in our study population implies that biologicals have not been favored over UV-phototherapy. On the other hand, many studies estimating the cost-effectiveness of UV-phototherapy have excluded at least part of the indirect cost for the patients and employers. Home UV-phototherapy may be a more feasible treatment option for some patients and may be especially attractive to patients living a longer distance from treatment providers. An open-minded approach to various treatment options might produce cost-effective choices and improve patient compliance.

8. CONCLUSIONS

The economic burden of psoriasis during the study period of one year may not be high, but as a chronic disease that economic burden psoriasis generates during the life time of a patient may become substantial. In addition to the societal perspective, the cost shares of patients and employers should be considered when assessing the overall burden of different treatments and outcomes. Methods to assess these costs should be well-justified and described clearly. Future research should provide results from the viewpoint of different parties to allow interpretations and conclusions from multiple aspects. Similar studies of other diseases would allow comparing the cost distributions to different parties of different diseases, which would be interesting and could have an effect on reimbursement policies or treatment practices.

Although, no previous study has reported estimates of a minor burden or low cost due to psoriasis, overestimations of the effect that it has on costs should be avoided. These risks may be reduced using explicit data collection procedures that capture only the burden caused by psoriasis – not the total burden that a patient with psoriasis experiences. This problem has been most noticeable in studies of lost productivity, although it has not yet been adequately tackled in previous literature. However, future studies should bear in mind that productivity losses in patients with psoriasis may not all be due to psoriasis as they may also be due to other non-psoriasis-related health reasons. Failing to take this into account may result in overestimation of the cost of productivity losses due to psoriasis.

Generalization of the results of this work to other societies with different type of social insurance, treatment protocols, or pricing structure may be difficult. However, this thesis adds knowledge of the burden that psoriasis causes to patients and other parties and how the burden is spread in a typical Nordic welfare state. The large proportion of costs that patients and employers carry may be of use to decision makers and clinicians, and these results may be used when estimating how future resources should be used.

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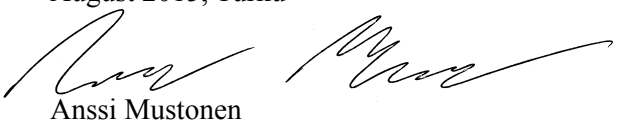

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11. APPENDICES

11.1. Appendix 1.

Price list: Hospital District of Southwest Finland 2010 (translated from Finnish original)

Dermatological unit

This list is used to charge the local communities, which cover the costs of patients' treatments.

Visit type	Description	Cost (euro)
P1	Serial treatment (under 30 min), e.g. UVB treatment	32
P2	Short consultation (doctor), calling the patient, skin care by a nurse (30 – 60 minutes)	51
P3	Outpatient visit (doctors office, no procedures), bath-PUVA, skin care by nurse (over 60 minutes)	100
P4	Demanding outpatient visit (doctors office, includes possible procedures, e.g. skin biopsy)	167
P5	Demanding outpatient visit to a specialist	266
P6	Outpatient visit demanding an extensive operation, or extensive planning for rehabilitation	534
P7	Outpatient visit demanding multiple operations, day-care in a dermatological ward	1 129
P8	Outpatient visit demanding an expensive medication (e.g. infusion of a biological drug) (includes the cost of the drug)	2 222
DRG 272	Inpatient treatment of a difficult skin disorder	2 666

11.2. Appendix 2.

TYKS
TURUN YLIOPISTOLLINEN
KESKUSSAIRAALA
ÅUCS/ÅBO UNIVERSITETS-
CENTRALSJUKHUS

Psoriasiksen aiheuttama taakka potilaalle

Tutkimus

Arvoisa tutkimuskyselyn vastaanottaja!

Teidät on valittu tähän tutkimukseen Turun yliopistollisen keskussairaalan (TYKS) ihotautiklinikan potilasrekisteristä. Edustatte suurta psoriasispotilaiden ryhmää, ja siksi vastauksenne ovat meille hyvin tärkeitä. Tähän tutkimukseen osallistuminen on teille täysin vapaaehtoista.

Seuraavalla sivulla on suostumuslomake, jossa pyydämme suostumustanne siihen, että voimme luvallanne kerätä TYKS:n, Kelan sekä mahdollisten muiden terveydenhoitopaikkojen potilastiedoista tämän tutkimuksen kannalta tärkeitä tietoja psoriasikseenne liittyen.

TUTKIMUKSEN TARKOITUS

Monia psoriasiksesta aiheutuvia oireita ja vaivoja on tavattoman vaikea arvioida rahallisesti. Psoriasiksesta aiheutuu kuitenkin monia toiminta- ja työkykyyn vaikuttavia tekijöitä, joilla voi olla suuria taloudellisia vaikutuksia sekä potilaille että heidän läheisilleen.

Tämän tutkimuksen tavoitteena on selvittää psoriasin aiheuttamaa kokonaistaakkaa sekä potilaalle, terveydenhuollolle että yhteiskunnalle. Antamienne vastausten avulla toivomme saavamme luotettavaa tietoa psoriasin potilaalle aiheuttamista taloudellisista ja muista rasitteista. Tämä tieto on arvokasta sekä psoriasista sairastavien potilaiden hoidon kehittämistyössä että suunniteltaessa psoriasispotilaiden sosiaali- ja terveydenhuoltoa kokonaisuutena.

Tietoja käsitellään ja julkaistaan vain ryhmäkeskiarvoina ja prosenttiosuuksina, eikä yksittäistä vastaajaa kyetä tunnistamaan tuloksista. Kaikki antamanne vastaukset sekä kerätyt tiedot tulevat säilymään ehdottoman luottamuksellisina.

Tähän tutkimukseen osallistuminen on teille täysin vapaaehtoista. Tutkimukseen osallistuminen ja antamanne vastaukset eivät tule vaikuttamaan saamaanne hoitoon tai sen toteutukseen, vaan antamianne tietoja käytetään luottamuksellisesti psoriasiksen hoidon kokonaisvaltaisessa kehittämistyössä.

Suostumus lääketieteelliseen tutkimukseen

Minua on pyydetty osallistumaan tutkimukseen Psoriasiksen aiheuttama taakka potilaalle, joka toteutetaan Turun yliopistollisen keskussairaalan ja Turun yliopiston yhteistyönä. Tutkimuksen vastuullisina johtajina toimivat ylilääkäri Leena Koulu TYKS:stä ja professori Risto Tuominen Turun yliopiston lääketieteellisestä tiedekunnasta.

Olen lukenut tutkimuksesta kertovan edellisellä sivulla olevan tiedotteen ja tutustunut siihen. Tiedotteesta olen saanut riittävän selvityksen tutkimuksesta ja sen yhteydessä suoritettavasta tietojen keräämisestä, käsittelystä ja luovuttamisesta. Minulla on ollut riittävästi aikaa harkita osallistumistani tutkimukseen.

Annan luvan itseäni koskevien potilastietojen keräämiseen tutkimusrekisteriin. Tietoja voidaan tutkimuksen sitä edellyttäessä pyytää niistä hoitopaikoista tai rekistereistä, joissa on psoriasikseen liittyviä potilastietojani. Tätä tarkoitusta varten lääkäri saa kirjata henkilötunnukseni sekä käyttää sitä tietojen saamiseksi.

Vain tutkimusryhmän jäsenet voivat käsitellä minua koskevia tietoja. Tutkimuksessa kerätyt tiedot koodataan siten, ettei henkilöllisyyden selvittäminen ole myöhemmin mahdollista ilman purkukoodia. Purkukoodi säilytetään suljettuna professori Risto Tuomisen arkistossa.

Ymmärrän, että osallistumiseni tähän tutkimukseen on täysin vapaaehtoista. Minulla on oikeus milloin tahansa tutkimuksen aikana ja syytä ilmoittamatta keskeyttää tutkimukseen osallistuminen. Tutkimukseen osallistuminen, siitä kieltäytyminen tai sen keskeyttäminen ei vaikuta jatkohoitooni. Olen tietoinen siitä, että minusta keskeyttämiseen mennessä kerättyjä tietoja käytetään osana tutkimusaineistoa.

Allekirjoituksellani vahvistan osallistumiseni tähän tutkimukseen ja suostun vapaaehtoisesti tutkimushenkilöksi**.**

_____ _____

potilaan allekirjoitus päiväys

_____ _____

nimen selvennys henkilötunnus

Suostumus vastaanotettu

_____ _____

tutkijalääkärin allekirjoitus päiväys

_____

nimen selvennys

Pyrkikää vastaamaan kaikkiin teitä koskeviin kysymyksiin. Kirjoittakaa vastauksenne kysymyksen perässä olevalle viivalle, ympyröikää itseänne koskeva tieto tai merkitkää janalta se kohta joka parhaiten kuvaa omaa tilannettanne.

Taustatiedot

1. Ikä _____ vuotta

2. Sukupuoli a) nainen b) mies

3. Minkä kaupungin tai kunnan alueella nykyisin asutte? _____

4. Kuinka monta henkilöä asuu teidän lisäksenne samassa taloudessa kanssanne tällä hetkellä? _____ henkilöä , joista lapsia_____ ja aikuisia ____

5. Merkitkää ympyröimällä alla olevista vaihtoehdoista se joka parhaiten kuvaa teidän ja kanssanne asuvien perheenjäsenten yhteenlaskettuja nettotuloja kuukaudessa (siis käteen jääviä osuuksia verojen vähentämisen jälkeen)?

a) alle 900 euroa	f) 1700-1899 euroa	k) 2700-2899 euroa
b) 900-1099 euroa	g) 1900-2099 euroa	l) 2900-3099 euroa
c) 1100-1299 euroa	h) 2100-2299 euroa	m) 3100-3299 euroa
d) 1300-1499 euroa	i) 2300-2499 euroa	n) 3300-3499 euroa
e) 1500-1699 euroa	j) 2500-2699 euroa	o) 3500 euroa tai enemmän

Työ ja eläke

6. Oletteko tällä hetkellä pääasiassa a) työssä b) eläkkeellä c) työtön d) opiskelija (voitte valita useamman teitä koskevan vaihtoehdon)

7. Jos olette työelämässä, mikä on tämänhetkinen pääasiallinen työtehtävänne?
   _____

8. Kuinka monta tuntia arvionne mukaan teette tällä hetkellä ansiotyötänne viikossa? ___ tuntia

9. Jos olette eläkkeellä tai muuten ette ole tällä hetkellä työelämässä mikä on ollut aiempi pääasiallinen työtehtävänne?
   _____

10. Jos olette eläkkeellä, oletteko a) sairauseläkkeellä b) vanhuuseläkkeellä

11. Jos olette eläkkeellä, oletteko oman arvionne mukaan eläkkeellä pääasiassa psoriasiksen takia a) kyllä b) ei

Terveyspalveluiden käyttö

12. Kuinka monta vuotta teillä on oman arvionne mukaan ollut psoriasis? _____ vuotta

13. Mikäli teillä on muita pitkäaikaissairauksia, luetelkaa ne alla olevalle viivalle
    _____

14. Merkitkää alla oleviin kohtiin mitä terveyspalveluita olette käyttänyt **psoriasiksen vuoksi** ja kuinka monta vastaanottokäyntiä näissä paikoissa teillä on yhteensä ollut viimeksi kuluneen vuoden aikana?
    TYKS
    _____ vastaanottokäyntiä, joista lääkärillä ____ ja hoitajalla____
    oma terveyskeskus

    _____ vastaanottokäyntiä, joista lääkärillä ____ ja hoitajalla____

työterveyshuolto

_____ vastaanottokäyntiä, joista lääkärillä ____ ja hoitajalla____
yksityinen palveluntarjoaja

_____ vastaanottokäyntiä, joista lääkärillä ____ ja hoitajalla____
joku muu, mikä _____

_____ vastaanottokäyntiä, joista lääkärillä ____ ja hoitajalla____

15. Kuinka monta **tuntia** arvioisitte viettäneenne kussakin alla mainitussa terveydenhuollon yksikössä **psoriasiksen vuoksi** viimeksi kuluneen vuoden aikana?
    a) TYKS _____ tuntia
    b) oma terveyskeskus _____ tuntia
    c) työterveyshuolto _____ tuntia
    d) yksityinen palveluntarjoaja _____ tuntia
    e) joku muu, mikä _____,_____ tuntia

16. Kuinka paljon arvioisitte, että teille on koitunut itsellenne maksettavia kustannuksia kussakin alla mainitussa terveydenhuollon yksikössä **psoriasiksen vuoksi** asioimisesta viimeksi kuluneen vuoden aikana?
    a) TYKS _____ euroa
    b) oma terveyskeskus _____ euroa
    c) työterveyshuolto _____ euroa
    d) yksityinen palveluntarjoaja _____ euroa
    e) joku muu, mikä _____,_____ euroa

17. Kuinka pitkä yhdensuuntainen matka teillä on oman arvionne mukaan kodistanne kuhunkin alla mainittuun terveydenhuollon yksikköön, jota olette käyttänyt viimeksi kuluneen vuoden aikana **psoriasiksen vuoksi**?
    a) TYKS _____ kilometriä
    b) oma terveyskeskus _____ kilometriä
    c) työterveyshuolto _____ kilometriä
    d) yksityinen palveluntarjoaja _____ kilometriä
    e) joku muu, mikä _____,_____ kilometriä

Työn muutokset

18. Onko teillä työuranne aikana psoriasikseen sairastumisenne jälkeen ollut psoriasiksesta johtuvia työpaikan vaihdoksia? a) ei b) kyllä
    jos on, niin kuinka monta _____
    jos on, niin miksi _____
    _____

19. Oletteko joutunut työuranne aikana muuttamaan tai muokkaamaan työtänne psoriasiksen takia?
    a) ei b) kyllä
    jos olette, niin
    miten_____
    _____

Sairauspoissaolot ja sairaana työskentely

20. Kuinka monta **tuntia** arvionne mukaan olette ollut poissa töistä viimeksi kuluneen 4 viikon aikana **psoriasiksesta** johtuen? _____ tuntia

21. Kuinka monta **tuntia** olette ollut työssä viimeksi kuluneen 4 viikon aikana vaikka olisittekin ajatellut että **psoriasiksesta** johtuen teidän olisi pitänyt jäädä kotiin, eli olette ollut ”sairaana töissä”? _____ tuntia

22. Merkitkää alla olevalle janalle X siihen kohtaan, joka parhaiten kuvaa käsitystänne siitä, kuinka paljon koette työskentelytehonne alentuneen **psoriasiksesta** johtuen viimeksi kuluneen 4 viikon aikana, niinä tunteina kun olitte ”sairaana töissä**”**
Ei lainkaan 0 _____ 100 Äärimmäisen paljon

23. Kuinka monta **tuntia** olette ollut poissa töistä viimeksi kuluneen 4 viikon aikana **muista terveydellisistä syistä** kuin psoriasiksesta johtuen? _____ tuntia

24. Kuinka monta **tuntia** olette ollut työssä viimeksi kuluneen 4 viikon aikana vaikka olisittekin ajatellut että **muista terveydellisistä syistä** kuin psoriasiksesta johtuen teidän olisi pitänyt jäädä kotiin, eli olette ollut ”sairaana töissä”? _____ tuntia

25. Merkitkää alla olevalle janalle X siihen kohtaan, joka parhaiten kuvaa käsitystänne siitä, kuinka paljon koette työskentelytehonne alentuneen **muista terveydellisistä syistä** kuin psoriasiksesta johtuen viimeksi kuluneen 4 viikon aikana, niinä tunteina kun olitte ”sairaana töissä”?
Ei lainkaan 0 _____ 100 Äärimmäisen paljon

Työssä suoriutuminen

26. Merkitkää alla olevalle janalle X siihen kohtaan, joka parhaiten kuvaa käsitystänne siitä, kuinka hyvin suoriudutte tavanomaisista työtehtävistänne nyt kun teillä on psoriasis?
Ei lainkaan 0 _____ 100 Äärimmäisen hyvin

27. Merkitkää alla olevalle janalle X siihen kohtaan, joka parhaiten kuvaa käsitystänne siitä, kuinka hyvin suoriutuisitte tavanomaisista työtehtävistänne, mikäli teillä **ei** olisi psoriasista?
Ei lainkaan 0 _____ 100 Äärimmäisen hyvin

28. Minkä työtehtävien suorittamista koette psoriasiksen erityisesti haittaavan?
_____
_____

Kotitoimista suoriutuminen

29. Merkitkää alla olevalle janalle X siihen kohtaan, joka parhaiten kuvaa käsitystänne siitä, kuinka hyvin suoriudutte kotitoimista tai päivittäisistä askareistanne nyt kun teillä on psoriasis?
Ei lainkaan 0 _____ 100 Äärimmäisen hyvin

30. Merkitkää alla olevalle janalle X siihen kohtaan, joka parhaiten kuvaa käsitystänne siitä, kuinka hyvin suoriutuisitte kotitoimista tai päivittäisistä askareistanne, mikäli teillä **ei** olisi psoriasista?
Ei lainkaan 0 _____ 100 Äärimmäisen hyvin

31. Minkä kotitoimien tai päivittäisten askareiden suorittamista koette psoriasiksen erityisesti haittaavan?
_____
_____

Siivous

32. Kuinka monta **minuuttia** arvionne mukaan olette itse käyttänyt siivoukseen viimeksi kuluneen viikon aikana? _____minuuttia

33. Kuinka monta **minuuttia** arvionne mukaan olisitte itse käyttänyt siivoukseen mikäli teillä **ei** olisi psoriasista? _____minuuttia

Pyykinpesu

34. Kuinka monta **minuuttia** arvionne mukaan olette itse käyttänyt pyykinpesuun viimeksi kuluneen viikon aikana? _____minuuttia

35. Kuinka monta minuuttia arvionne mukaan olisitte itse käyttänyt pyykinpesuun viimeksi kuluneen viikon aikana mikäli teillä **ei** olisi psoriasista? _____minuuttia

Ihon hoito

36. Kuinka monta **minuuttia** arvionne mukaan olette käyttänyt ihon hoitoon psoriasiksen vuoksi viimeksi kuluneen viikon aikana? _____minuuttia

37. Kuinka monta **minuuttia** arvionne mukaan olisitte käyttänyt ihon hoitoon viimeksi kuluneen viikon aikana, mikäli teillä **ei** olisi psoriasista? _____minuuttia

Avuntarve

38. Saatteko kotitoimiinne tai päivittäisten askareittenne hoitamiseen omaisten tai ulkopuolisten apua psoriasiksen vuoksi? a) ei b) kyllä
Jos saatte, niin mihin_____

39. Kuinka monta **minuuttia viikossa** saatte apua? _____ minuuttia viikossa

40. Kuinka paljon tästä avusta aiheutuu teille arvionne mukaan teidän itse maksettavia kustannuksia **kuukaudessa**? _____euroa kuukaudessa

41. Saatteko omasta mielestänne tarpeeksi apua kotitoimiinne tai päivittäisten askareittenne hoitamiseen? a) kyllä b) ei

42. Jos ette, montako **minuuttia** lisää apua omasta mielestänne tarvitsisitte **viikossa**? _____ minuuttia viikossa

Harrastukset ja vapaa-ajan vietto

43. Kirjoittakaa alla olevalle viivalle pääasialliset harrastuksenne tai vapaa-ajanviettotapanne

_____

44. Kuinka monta tuntia viikossa käytätte arvionne mukaan aikaa yllä mainitsemiinne harrastuksiin tai vapaa-ajanviettotapoihin? _____ **tuntia viikossa**

45. Kuinka monta tuntia arvionne mukaan käyttäisitte yllä mainitsemiinne harrastuksiin tai vapaa-ajanviettotapoihin, mikäli teillä ei olisi psoriaasia? _____ **tuntia viikossa**

46. Merkitkää alla olevalla janalle X siihen kohtaan, joka parhaiten kuvaa käsitystänne siitä kuinka hyvin olette oman arvionne mukaan kyennyt suoriutumaan nykyisistä harrastuksistanne tai vapaa-ajan vietostanne nyt kun teillä on **psoriaasi**?
Ei lainkaan 0 _____ 100 Äärimmäisen hyvin

47. Merkitkää alla olevalle janalle X siihen kohtaan, joka parhaiten kuvaa käsitystänne siitä kuinka hyvin oman arvionne mukaan suoriutuisitte nykyisistä harrastuksistanne tai vapaa-ajan vietostanne jos teillä **ei** olisi psoriasista?
    Ei lainkaan 0 _____ 100 Äärimmäisen hyvin

48. Oletteko joutunut vähentämään jotain harrastusta tai vapaa-ajan viettoa psoriaasin vuoksi?
    a) ei b) kyllä
    jos olette ,mitä _____

49. Oletteko joutunut kokonaan luopumaan jostain harrastuksesta tai vapaa-ajan vietosta psoriaasin takia?
    a) ei b) kyllä
    jos olette, mistä_____

Kiitos vaivannäöstänne!

Tarkastakaa vielä, että olette vastannut kaikkiin teitä koskeviin kysymyksiin.

Alla oleville viivoille voitte vielä halutessanne vapaasti kirjoittaa kommenttejanne tai mielipiteitänne psoriaasin hoidosta, hoidon kustannuksista ja psoriaasista potilaalle aiheutuvista taloudellisista ja muista rasitteista. Kaikki viestit tullaan yliopistolla kirjaamaan sellaisenaan ja toimittamaan nimettöminä TYKS:n vastuuhenkilön tiedoksi.

Vapaat kommentit

Lopuksi postittakaa tämä lomake mukana tulleessa vastauskuoressa suoraan meille Turun yliopiston Terveydenhuollon tutkimusyksikköön. Postimaksu on jo valmiiksi maksettu, postimerkkiä ei tarvita.