

**The psychological burden and life quality in patients with skin disease: A European study in dermatological patients.**



**Flora Balieva**

**Department of Dermatology  
Stavanger University Hospital  
Stavanger, Norway**

**Institute of Clinical Medicine  
Faculty of Medicine  
University of Oslo  
Oslo, Norway**

**September 2019**

© **Flora Balieva, 2019**

*Series of dissertations submitted to the  
Faculty of Medicine, University of Oslo*

ISBN 978-82-8377-505-1

All rights reserved. No part of this publication may be reproduced or transmitted, in any form or by any means, without permission.

Cover: Hanne Baadsgaard Utigard.  
Photo cover: Marius Vervik.  
Print production: Reprosentralen, University of Oslo.

**Summary:**

Knowledge of the psychological burden of skin disease in the general dermatological population is scarce.

We collected data on the distribution of skin disease in Norwegian and European outpatients, explored the prevalence of psychiatric comorbidity and the reduction in life quality in order to draw attention to skin conditions that have the highest risk of negatively impacting health related quality of life (HRQoL).

The thesis shows in its first part the high association between skin disease and psychiatric comorbidity, especially in Norwegian patients, where depression and anxiety are higher than seen in the other participating European countries.

In its second part, the thesis confirms the large impact skin conditions have on patients' wellbeing, differentiating between different aspects of HRQoL. Patients with chronic inflammatory skin diseases reported reduced HRQoL comparable to the reduction experienced by patients with chronic obstructive lung disease, diabetes mellitus, cardio-vascular disease and cancers. These findings are important in the prioritization of resource allocation between medical fields and within dermatological sub-specialities.

Finally, we show that treatment for skin disease contributes considerably to reducing HRQoL: the burden of dermatological treatment should be considered when planning therapy, designing instruments for evaluating HRQoL and when considering new dermatological therapeutic options.



## **Acknowledgements:**

This project was the first big research study I had ever participated in. As I started my research work, my lack of experience and scarce knowledge of academic routines left a lot of educating and mentoring needing to be done on the part of my supervisors.

My first baby steps were meticulously guided, supported, corrected and constructively criticized by a brilliant researcher, clinician, mentor and person, Florence Dalgard. With her vast experience and knowledge, she led me through all practical issues, whether small or big, important or trivial. She helped me with advice in academic, emotional and private matters. I am extremely thankful that she considered having me as her student.

Florence introduced me to Lars Lien. Although not a dermatologist his solid research experience and knowledge in the area of psychiatry gave me necessary further insights when I had to think like a researcher and not like a dermatologist. He taught me to see the big picture, think wider, to abandon my tight inner circle of knowledge, where only dermatology had a place, and open up to looking at the world through the eyes of non-dermatologists (especially when writing my thesis).

In the early months of my research new knowledge had to be acquired. Attending courses was a large part of my first year. A subject I had hardly been exposed to (and knew little about) was statistics. The basics are straightforward to understand. Courses give you some idea of what is going on, you even pass the exam. But then the real work had to start. The baby steps I mentioned in the beginning, yes, it was Florence who had me over at her house, patiently going through the first analyses together with me. A whole day (from morning to late afternoon). This day we spent together (Florence, me and SPSS) gave me a good head start with my Norwegian data. Then she put me in contact with Jörg Kupfer.

In a way, Jörg non-formally also became my supervisor. He had me over to Gießen, Germany, where I spent a whole week with him looking at data, analyzing, brainstorming ideas and was taught the complexities of statistical analyses. During this week I learned so much from him, that I then acquired the confidence I needed to start doing analyses all on my own. No matter what I analysed, Jörg would always check my results, help me find the best analytical methods, do some complicated regression analyses for me, and if necessary even more complex statistics, where I would have been lost without him.

When writing my paper on therapy I got the unique opportunity to work closely with Professor Andrew Finlay. We spent hours discussing our paper. His insights, suggestions

and guidance made the paper truly excellent, quickly accepted by the journal and being published as “Editor’s Choice”. He helped me perfect my writing skills, my spoken and written English and taught me to be meticulous, correct and acquire a sense for detail that has stayed with me ever since. At the end he even agreed to read through my thesis and give me precious feedback. The positive feedback from Andrew gave me something invaluable – a confidence in having written a thesis worthy for submission.

I started my research on an eight-month 50% clinical and 50% research position. I needed to figure out a way to continue my research after this period. Luckily, the head of the Dermatology Department at Stavanger University Hospital, Professor Thomas Ternowitz was very understanding of my situation and was willing to adjust my clinical workload so that I also had time for my project. I depended on his kindness to let me continue my work, while constantly encouraging me to apply for grants. Applying for grants is a time-consuming matter, especially for the inexperienced in the field of research. Days were spent in constructing the perfect application, chasing deadlines while juggling work and Skype meetings, e-mail correspondence and long discussions with Florence and Lars. During that period Thomas afforded me the time to do this and promised to grant me leave if I was lucky to get a research stipend. A fellowship never came, yet I still was given some time off clinics to complete my work.

Saying this, I don’t want to give the impression that I never received any grants. The Norwegian Society of Dermatology and Venereology awarded me several grants. These grants made it possible for me to visit Jörg, cover the costs of my paper on the Norwegian data, work closely with Andrew Finlay and publish my paper on therapy issues. Furthermore, I was granted a considerable amount by The Norwegian Society of Dermatology and Venereology for my paper on life quality, when winning the award: ‘Best research paper of the year’. The grants and awards were of great help on my path to finishing my work.

The Research Department at Stavanger University Hospital (SUS) also granted me something most precious – time. I was granted a stipend to cover some days off clinical work so that I could focus on my project. Furthermore, the Research Department at SUS offered statistical help, a service I made use of several times. Later on, I needed help with literature searching and was promptly helped by Geir Strandenæs Larsen, who helped me, showed me, and taught me to perform good searches. Without a good search of the literature, the work that is done may be useless.

Finally, I wish to thank all my colleagues at the Department of Dermatology in Stavanger, that had to work with me during my research years. Thank you for putting up with my sometimes hectic and too busy attitude, especially in periods when recruiting patients. Thank you for the times I wasn't there and you had to take care of issues with my patients while I was writing my papers. I am very grateful to the secretaries at the Dermatology Department, it was they who addressed my patients and asked them if they wished to participate. The high number of patients agreeing to participate (93%) is extraordinary, and no doubt due to their patience, kind manner and the good atmosphere they created, where patients agreed to use their precious time filling out questionnaires. And yes, this also means that I really thank all my patients for willing to offer their time and participate, also the ones who did not participate, but still had to put up with my somewhat busier schedule that day. The same is true for the healthy controls.

I truly wish to thank the whole ESDAP group for coming up with the idea for the project, the core group, Florence Dalgard, Uwe Gieler, Jörg Kupfer, Lucia Tomas-Aragones and Lars Lien. They implemented this project, did all the pre-work and invited centres across Europe to participate. I had the unique opportunity to attend a class where Uwe was teaching his allergy patients, who had experienced anaphylaxis. They needed education, guidance and the feeling of being prepared for the possibility of new attacks. I got to experience how a group of patients, anxious about their condition, became calm and confident of their ability to tackle anything, under Uwe's expert treatment and education.

I immensely thank my mother Margarita, stepfather Paul and daughter Irina, who on several occasions read through my papers and thesis to give me feedback and suggestions. To my mom and Paul, I thank because they managed to read through all of it, in spite of not being medical practitioners, therefore, probably not the most exciting reading material for them. Irina, who was a medical student, took time from her busy student life to read her mother's papers as if she didn't have her ever-growing curriculum and own research project to attend to. Their help was significant, my mom's writing skills, being a philologist, Paul's experience as a psychology professor and Irina's young mind created unique feedback that I was lucky to receive.

I thank my husband Svetlozar, and my daughter Andrea, who ever so patiently and with understanding accepted my busy schedule, my ever clicking on the computer (especially for Andrea this was very bothersome, but she put up with it), and my sometimes bad mood, when too busy. They also had to put up with hearing about my problems, frustrations,

achievements, stories about research, etc. on a daily basis. Thanks for not getting weary of me.

My dad, Nicolai, a brilliant mathematician and program analyst, supported me emotionally by listening to me and giving me sober advice on how to tackle academic difficulties. Also, his humour and personal experience on a wide range of matters would lighten up my day and make me laugh.

My sister, Ellina, otherwise a talented concert pianist, more artistic than academic, inspired me immensely by completing her own PhD while juggling work, kids, concert performances and teaching.

Lastly, I need to mention the comfort that two purring kittens (Kitty and Lilly) can give during long hours of working in front of a computer.



## Table of Contents:

1. List of papers.....	11
2. Foreword.....	13
3. Abbreviations.....	15
4. Background .....	17
4.1 General health, quality of life and mental health: .....	17
4.2 Characteristics of skin diseases and historical aspects regarding their significance:.....	18
4.3 Skin disease, prevalence and global burden: .....	20
4.4 Mental health, mental disease and global burden: .....	22
4.5 Skin diseases and their psychosocial burden: .....	23
4.6 Factors that can influence the burden of skin disease and mental health: .....	25
4.7 Dermatological treatment and its effect on quality of life: .....	27
4.8 Conclusive remarks: The past, the present and the future:.....	28
5. Objectives .....	31
6. Study population and Methods .....	33
6.1 Design:.....	34
6.2 Preliminary calculations: .....	34
6.3 Ethics: .....	35
6.4 Measurements: .....	35
6.5 Statistical analyses:.....	39
7. Results: Synopsis of papers.....	41
Paper I: Are Common Skin Diseases among Norwegian Dermatological Outpatients Associated with Psychological Problems Compared with Controls? An Observational Study.....	41
Paper II: The burden of common skin diseases assessed with the EQ5D™: a European multicentre study in 13 countries. ....	42
Paper III: The Role of Therapy in Impairing Quality of Life in Dermatological Patients: A Multinational Study.....	43
8. Discussion .....	45
8.1 Main findings:.....	45
8.2 Methodological considerations:.....	53
8.3 Implications for future research:.....	57
9. Conclusion.....	61
9. References .....	63
10. Published papers I-III .....	73
Paper I .....	73
Paper II .....	79
Paper III .....	93
11. Questionnaires.....	103



## 1. List of papers

- 1. Are Common Skin Diseases among Norwegian Dermatological Outpatients Associated with Psychological Problems Compared with Controls? An Observational Study.** Balieva F, Lien L, Kupfer J, Halvorsen JA, Dalgard F. *Acta Derm Venereol.* 2016 Feb;96(2):227-31. doi: 10.2340/00015555-2200.
- 2. The burden of common skin diseases assessed with the EQ5D™: a European multicentre study in 13 countries.** Balieva F, Kupfer J, Lien L, Gieler U, Finlay AY, Tomás-Aragónés L, Poot F, Misery L, Sampogna F, van Middendorp H, Halvorsen JA, Szepietowski JC, Lvov A, Marrón SE, Salek MS, Dalgard FJ. *Br J Dermatol.* 2017 May;176(5):1170-1178. doi: 10.1111/bjd.15280.
- 3. The Role of Therapy in Impairing Quality of Life in Dermatological Patients: A Multinational Study.** Balieva F, Finlay AY, Kupfer J, Tomas Aragonés L, Lien L, Gieler U, Poot F, Jemec G, Misery L, Kemeny L, Sampogna F, van Middendorp H, Halvorsen JA, Ternowitz T, Szepietowski J, Potekaev N, Marron SE, Altunay IK, Salek S, Dalgard FJ. *Acta Derm Venereol* 2018 Jun;98(6):563-569. doi: 10.2340/00015555-2918



## 2. Foreword

In my everyday clinical practice as a dermatologist, I noticed that the standard physician consultation focuses on making a correct diagnosis, giving information about the disease, finding a suitable therapy and instructing the patient in performing or receiving the treatment. Unlike my previous employment, where I worked with psychiatric patients there was barely time, or any routine, to talk to the patient other than about the purely physical symptoms. The difference in how these two groups of patients were approached was huge, as if they were two completely different types of patients.

When studying medicine, we are taught how chronic somatic diseases negatively influence the psyche. Yet, when the patients were in front of me, there was no time, room or advice on how to approach the patient's psychological issues.

There was certainly a lack of awareness and knowledge about the need for addressing psychological issues in patients with chronic diseases by health authorities or institutions when allocating resources, when planning the structure of consultations, or in decisions on how a dermatological consultation should proceed.

Radically changing the structure of dermatological consultations and dermatologists' approach to patients in order to address all issues, including psychosocial suffering, would ideally be the optimal solution, but unrealistically done overnight. Heightening the awareness of the needs of dermatological patients would be the first step in a process that eventually could lead to optimal patient consultations and care. This thought led to performing a study investigating the possible burdens experienced by dermatological patients. Would we find that the results identified problems previously underappreciated by physicians, health authorities and the public?

This thesis presents the studies performed, the scientific background, the objectives, the population, the methods used, the results we obtained and the strengths, weaknesses and implications of the studies.



### 3. Abbreviations

AD: Atopic dermatitis

AK: Actinic keratosis

CI: Confidence interval

DALY: Disability-Adjusted Life Years

DLQI: Dermatology Life Quality Index

HADS: Hospital Anxiety and Depression Scale

HRQoL: Health related quality of life

HS: Hidradenitis suppurativa

IBD: Inflammatory bowel disease

ICD-10: The International Classification of Diseases, 10<sup>th</sup> edition

ICD-11: The International Classification of Diseases, 11<sup>th</sup> edition

LED: Light emitting diode

MM: Malignant melanoma

NMSC: Non-melanoma skin cancer

OR: Odds Ratio

SD: Standard deviation

SPSS: Statistical Package for the Social Sciences

TNF: Tumour necrosis factor

UV: Ultraviolet

VAS: Visual Analogue Scale

WHO: World Health Organisation

YLD: Years Lived with Disability

YLL: Years of Life Lost





## 4. Background

Skin conditions are common in the general population(1) and most inflammatory skin diseases are chronic and without a cure(2), meaning that treatments will reduce symptoms, but flares and recurrences can be expected when treatments are discontinued and even while ongoing. At the same time, mortality for skin disease is very low(3). As the population in the Western world grows older we can expect that more people will be living with a chronic disease, and specifically more dermatological patients will live many years of their life with their existing skin condition(4).

Chronic diseases need lifelong treatments. Specific for skin diseases is the use of topical treatments, often on large areas of the skin. Treatment modalities, such as surgical therapy or other invasive procedures (photodynamic therapy, laser treatments, cryotherapy or intralesional injections) may be painful, time consuming and/or scar the skin. Several treatments for skin diseases may also necessitate frequent, even daily visits to a dermatological unit (examples are phototherapy, ulcer treatments, infusion therapies), which interfere with the patient's leisure activities and consume resources.

Although reduction of symptoms is possible by adequate treatment in many dermatological diseases, the treatments themselves need to be performed regularly over long periods and the disease cannot be fully eliminated. It is therefore not surprising that living with a skin disease will influence a patient's wellbeing, reduce life quality or even lead to developing symptoms of depression and/or anxiety(4, 5).

### 4.1 General health, quality of life and mental health:

Health extends far beyond physical health alone. The World Health Organization (WHO) defines quality of life as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"(6). Quality of life covers several domains: physical health, psychological health, personal beliefs, social relationships and the environment.

Each domain includes a variety of components. The physical domain would include symptoms, disability and level of function. The psychological domain refers to mental health, and the social domain would incorporate areas of work, personal relations and role in the community. These three domains interact with each other and are influenced by an individual's experiences, beliefs, perceptions and expectations, thus the variety of health states is large(7, 8).

#### 4.2 Characteristics of skin diseases and historical aspects regarding their significance:

Skin diseases represent an impressive amount of diagnoses. No other organ can be diseased in so many different ways, and there are well over 1000 dermatological diseases and diagnoses and over 2000 skin disease reaction patterns described(9). Skin diseases are also very prevalent in all ages, across different social groups, educational levels, ethnicity and other socio-demographic varieties. The International Classification of Diseases, 10<sup>th</sup> edition (ICD-10) classifies skin diseases in 100 different categories, each with several subcategories, many of which include more than one separate condition. The 11<sup>th</sup> edition (ICD-11) that is currently being launched includes even more diagnostic categories for skin diseases.

Skin diseases can be mild enough not to require medical care at all. Others may be moderate, but still not need referral to specialized professionals (dermatologists) and are seen and followed by a general practitioner. At the other end of the scale, skin diseases may be extremely severe or have severe enough relapses that patients would need to be hospitalized at some point. Studies performed on dermatological patients, might therefore vary significantly depending on the patient population studied. On the one hand, this leads to difficulties in comparing studies and on the other hand, necessitates thorough description of the specific population studied when reporting data.

As an example, individuals with a skin disease needing in-patient care would represent a small percentage of the dermatological population at a given time. These patients would therefore not be representative for dermatological patients as a whole, yet would still contribute for a severe reduction in life quality or reduced mental health when psychosocial burden is the outcome. Hospitalized patients with a chronic disease are at the extreme end of the normal distribution curve of variations in skin health. This would skew results and findings, making the data only representative for hospitalized patients.

A wide spectrum of disease variation is true for the most prevalent skin conditions. Examples are psoriasis, eczemas (with atopic dermatitis being the commonest in children and young patients), acne, non-melanoma skin cancer and the itchy dermatoses such as urticaria, pruritus, prurigo and allergies(10, 11), all of which may vary widely in severity. Psoriasis and eczemas can be mild, almost unnoticeable to very severe, affecting large areas or the whole skin surface with redness, scaling or oozing. Many skin diseases are accompanied by severe itch and disturb sleep and everyday activities. Acne is a disease most common in adolescents, usually on visible areas of the skin, with a high psychological impact, although not lethal. On the other hand, some

skin cancers are potentially malignant, are more common in older patients and have the capacity to spread.

Why is it important to appreciate that skin diseases are so common and so variable in their severity and at the same time affect wellbeing?

Only recently did patients' wellbeing, i.e. quality of life and mental health in somatic disease come into focus. Around the beginning of the 1990s the first instruments for measuring life quality in dermatological patients emerged(12). The Dermatology Life Quality Index (DLQI) was the first instrument designed to evaluate life quality across patients with skin diseases. The DLQI was followed by the Skindex(13) and several other disease specific instruments(14-16). Studies evaluating skin patient's mental health were becoming of interest.

Skin diseases, such as psoriasis(17-20) and atopic dermatitis(21-23) were among the first to be studied and were shown to impact patients' wellbeing significantly. This led to further investigations and more interest in the field, resulting in more studies being performed, showing that other skin conditions (such as vitiligo(24, 25), acne(26-28), alopecia(29-31) and vascular malformations of the face(32-34)) could burden the patients' life and/or lead to higher risk for psychiatric morbidity.

Although the accumulating knowledge supported the suspicion that skin diseases may have a more significant impact on a patient's wellbeing than was previously assumed, comparisons between studies were not readily performed because of different study designs and different patient populations, e.g. outpatients versus inpatients, different disease severities or different endpoints. Thus, there was still a lack of knowledge on a global and comprehensive level.

Some 20 years after the first life quality instruments for skin diseases appeared, WHO pointed out the extent to which skin diseases exercise their effect on mental health and life quality, and reported the burden of skin diseases as being the fourth leading cause of nonfatal disease burden(35) in The Global Burden of Disease and Skin Health Challenge Studies(35, 36).

During the following years, the burden of skin diseases became, without doubt, an emerging important issue. Yet, methodological studies performed on a large number of patients, investigating all skin diseases and different aspects of the burden, not limited to only a specific diagnosis, were still scarce. There seemed to be an unmet need for finally coming up with robust data on this issue. Solid results would give a realistic perspective of skin diseases' place among other diseases and how patients' needs can be best met.

#### 4.3 Skin disease, prevalence and global burden:

Prevalence refers to the proportion of the population affected by a disorder. Because many skin diseases are nonlethal yet chronic, prevalence is a particularly important measure of frequency in dermatology(2). In spite of being very common(1), the exact distribution of the different skin diseases is still not fully known. Studies evaluating prevalence by using registry data would depend on the patient's need to seek medical care (or ability to do so), while those not seen by a physician would remain undetected. Another factor, essential for evaluating degree of morbidity, is the severity of the condition. Degree of severity may not be readily available from registries or reported in studies.

The first large population-based data on the prevalence of skin disease for the United States were obtained in the first Health and Nutrition Examination Survey, which was conducted in the early 1970s for ages 1-74 years(37). The most prevalent conditions were acne, fungal infections, tumours and eczemas. The study also showed that nearly one third of the U.S. population age 1-74 years had one or more skin conditions about which they complained or expressed concern and nearly 18% of those were conditions not considered serious or significant by the dermatologists. Approximately 56% indicated that the condition was recurrent and 30% had had active disease for more than a year, 50% within the preceding 7-12 months and 21% within the last six months. Handicap from skin disease, limitations of mobility, disfigurement and discomfort were also analysed in this first study(37).

Later in the 1970s Rea et al. conducted a survey in the United Kingdom (in Lambeth, London) and reported the prevalence of skin disease for ages 15-74(38). The study was performed by sending a postal questionnaire and subsequently interviewing patients. The most prevalent skin disease was eczema and the overall prevalence of skin disease thought to justify medical care was 22.5%, but only 21% of those had attended their general practitioner. Rea concluded that skin disease forms a substantial part of the total spectrum of ill health and since studies are usually based on those who present themselves for treatment, the actual prevalence of skin disease may not easily be determined(38).

In the following decades, more studies on the prevalence of separate dermatological diseases in separate countries were investigated, but there have been few on the distribution of common skin diseases among dermatological outpatients as a whole(1, 10, 39-44).

The prevalence of skin conditions changes with the ageing of the population, advances in technologies (for instance better diagnostic tools), innovations in medicine (e.g. novel treatments) and changes in health care policies (e.g. by lowering restriction policies on the use of expensive drugs)(2).

When the first surveillance studies were performed, in the 1970s, diseases such as Acquired Immune Deficiency Syndrome (AIDS) or borreliosis were unknown or would be classified under different diagnostic categories, perhaps misdiagnosed. On the other hand, serious infections such as anthrax, diphtheria or measles had a higher prevalence before the 1940s to become almost non-existent in the western world today(45).

Before the era of the corticosteroids (the first half of the 20<sup>th</sup> century) diseases such as autoimmune conditions (connective tissue disease, pemphigus or other blistering diseases)(46, 47), had high mortality due to lack of adequate treatment options(48, 49). In later decades, patients with these same diseases would die of complications due to the therapies' side effects, not of the skin disease per se(48, 50). And then, during more recent decades, with the advance of immunomodulatory treatments, these diseases have a more chronic course, with patients living significantly longer with the burden of their condition(51, 52).

For many skin conditions, the disease course changed from long-term hospital admissions into management as outpatients, although at the expense of using potentially toxic systemic drugs(2). The era of biological therapies changed the profile of the severe psoriasis patient needing numerous hospital admissions every year to having treatments consisting of as few as four annual subcutaneous injections, taken in the comfort of the patient's own home. Such a patient may now experience close to no psoriasis symptoms(53). The same is becoming true for urticaria(54) and most recently for atopic dermatitis(55), where biological treatments may reduce symptoms significantly with fewer patients needing hospital admission or referral to specialized dermatological clinics(53-55).

Because of the gradual changes in prevalence and classification of disease, studies on the prevalence of skin diseases need to be performed regularly. Studies describing mental disorders in skin patients need to present the current prevalence and distribution of skin diseases in the studied population. It is also of importance that studies evaluating patient burden give a clear updated overview of prevalence and distribution of skin diseases, enabling the comparisons of data over time.

Knowledge of the prevalence of disease and distribution in the community of those seeking medical help, needing dermatological care or hospitalization is important for health economic evaluation to optimize resource allocation. Large population studies, regardless of their primary research aims, may be another source of valuable updated data on the prevalence and distribution of disease. This thesis thus gives current prevalence and distribution of skin diseases across Europe and for the separate countries studied(56, 57), side by side with the research questions. We are not aware of similar recent studies.

The Global Burden of Disease and Skin Health Challenge Studies(35, 36) not only demonstrated that skin diseases were the fourth most frequent cause of human disease(35), but also that they are the fourth leading cause of nonfatal burden as years lived with disability (YLD) and health loss due to premature death, years of life lost (YLL). The sum of these is expressed as disability-adjusted life years (DALYs). There has been a rise in skin disease YLD in both report cycles since 1990: 21.9% for the period 1990-2005 and 11.7% for the period 2005-2015.

In the past decade, dermatology has been characterized by an increase in incidence (newly diagnosed cases) and prevalence of several diseases, leading to a rising need for health care and an increase in resource consumption. For skin cancer and allergies, this increase exceeded the expected rise due to the general ageing of the population(2, 58, 59). In Australia and in European countries skin cancer has steadily increased in incidence, proportion of all skin disease cases and in its burden on society(2). The incidence of atopic dermatitis in the Western World is also rising(60).

The pooled prevalence of psoriasis, eczemas and acne has reached nearly 25% in developed countries. Studies from different geographical areas(61-65) have demonstrated that individuals with itchy skin, eczema and psoriasis are twice as likely as the general population to be depressed. Assessing and treating impaired health quality and depressive comorbidities of chronic skin diseases, and adapting the health care system to target the needs of patients becomes an important issue.

#### 4.4 Mental health, mental disease and global burden:

Mental health is defined by WHO as “a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and

fruitfully, and is able to make a contribution to her or his community”(66). This state, however, is disrupted in one (or more) of every four individuals during their lifetime(67).

Global lifetime prevalence of depression is 14% and of anxiety is 12.9%(67). The key results of the former analysis(67) are that “common mental disorders are highly prevalent, affecting substantial sections of all the populations surveyed”. However, reported lifetime prevalence of depression ranges widely between countries with estimates between 9.9% (Germany and Italy) and 21% (France), and for anxiety between 5.2% (Israel) and 22.3% (France) in the same study(68). Suicidal ideation and suicidal attempts were also seen to vary widely(69).

The World Health Organization (WHO) in 2015 ranked depression as the 3<sup>rd</sup> and anxiety as the 9<sup>th</sup> leading causes of years lived with disability (YLD) worldwide(70). Depression therefore now ranks one place higher compared to previous WHO reports (1990-2015). In 20-24 years old individuals it was the 1<sup>st</sup>, and in 25-50 years old the 2<sup>nd</sup> highest ranking cause for YLD. Across different age groups, anxiety ranks as the 6<sup>th</sup> – 10<sup>th</sup> cause for YLD: its ranking has risen substantially compared to 2005, especially for older adults(70).

With the ageing of the population, the prevalence of physical(71), as well as mental health issues(72) are expected to rise. Some of these issues will be directly related to old age, and others indirectly from side effects of the long term use of drugs, including psychotropic medications(72).

#### 4.5 Skin diseases and their psychosocial burden:

Over the last few years, the clear association between skin disease and depression, anxiety, suicidal ideation(73) and impaired life quality(5) has led to a heightened interest in further investigating this issue. For several skin conditions such as psoriasis(64, 74-78), atopic dermatitis(65, 79-83), acne(84-87), itchy skin conditions(62, 88, 89), vitiligo(90-92), hidradenitis suppurativa(93-95) and others(63, 96-99) data has gradually accumulated, showing the increased burden these diseases pose for the patient. Yet, there is still a lack of knowledge about the precise prevalence of psychiatric morbidity in common skin conditions and the extent of the quality of life impairment among dermatological patients as a whole.

In one Norwegian study Dalgard et al.(61) report sweating, face rash, pimples, and itch to have significant associations with mental distress. Later, Halvorsen and Dalgard confirmed the association between itch and mental distress(62). A German study performed by Niemeier et al. points out the psychological factors associated with the different hand dermatoses(63). A

study on depression and atopic disorders from Australia followed, again providing evidence that skin diseases (allergic disorders) contribute to depression on a worldwide basis(65).

Specifically, depressive morbidity and suicidal ideation have been reported among dermatological patients in single European countries: Italy, Croatia, Denmark and Germany, mostly on small patient samples and using different assessment instruments, making comparisons difficult(100-104). However, these studies point out that dermatological patients who show poor improvement or have a disease affecting visible skin are at a higher risk(103, 104), and that many dermatological patients would be well served by a liaison clinic(105) or early referral to a psychiatrist(100, 104).

More recent studies, including the studies performed by our group, have shown that comorbid depression, anxiety and suicidal ideation are common in patients with skin conditions(57, 69, 85, 101, 105). Depression, anxiety, stress and negative life events have been demonstrated to trigger chronic skin disease and can further worsen the skin condition by low compliance and lack of adherence to the treatment regime(106, 107). Suicidal ideation is more common in patients with depression(108). Depression in dermatological patients may be pre-existing, appear as a complication to the skin disease or be triggered by the dermatological medication(85, 109, 110). As previously mentioned, mortality is low for skin diseases, but suicide related to dermatological disease still needs to be explored. The association between common skin diseases and suicidal ideation has previously been reported among Norwegian adolescents with eczema(86, 111). This draws attention to an important issue in dermatology, deaths caused by suicide triggered by a skin disease. The need for further investigation of this issue is obvious.

WHO's global reports rank the burden of depression and skin diseases (measured by years lived with disability, YLD) higher than other chronic conditions, such as diabetes, chronic respiratory and kidney disease, cardio-vascular diseases and dementia. Anxiety results in less disability than diabetes but still ranks higher than respiratory, kidney and heart diseases(70).

The data on the burden caused by depression and skin diseases for Western Europe are similar to the global data, while anxiety in Western Europe shows a higher burden than is seen globally, being the 6<sup>th</sup> leading cause for YLD(70).

There are only a few publications that evaluate the risk of psychiatric morbidity and reduced life quality over a wider range of skin conditions(112, 113), and almost no studies have corrected for somatic comorbidities, an important factor, considering that many skin conditions



are associated with other diseases. Knowing the prevalence and distribution of the diseases most likely to cause psychosocial morbidity and that have the potential to impair life quality is important when assessing burden of disease and when informing resource allocation decisions.

Patients with the same disease may be affected differently concerning impairment of health related quality of life (HRQoL) or risk for psychiatric morbidity. This may be partly related to socio-demographic factors such as age, sex, socioeconomic status and the presence of other diseases. Studies typically correct for socio-demographics when data is analysed, but rarely for comorbidities, thus missing the true burden the skin disease itself imposes on the patient.

#### 4.6 Factors that can influence the burden of skin disease and mental health:

##### 4.6.1 Age and gender:

With increasing age, people will be expected to have more comorbidities, poorer health and a lower quality of life due to health issues(49, 114). These factors may influence the responses of older individuals to questionnaires assessing mental health and quality of life, even if they suffer less from their skin condition.

On the other hand, younger, otherwise healthier patients may be burdened more, even by a minor skin condition on account of the visibility of the disease, stigmatization and the higher demands in different spheres of life, such as work, family and social life.

Some skin conditions may be more prevalent in either males or females. One such example is androgenetic alopecia, mainly seen in men. If prevalence calculations are made for patients as a group without adjusting for sex the results will be difficult to interpret. On the other hand, men and women may experience their disease differently(104, 115) because of social values, society's expectations or practical issues, e.g. having fewer treatment options during pregnancy or breastfeeding. Even just a mild skin condition on the breast, posing no discomfort in a male, can result in a painful experience for a mother breastfeeding her baby.

Stratifying for age and gender is necessary in order to understand the more specific burden that age and gender pose for patients with skin disease.(2, 39)

##### 4.6.2 Socioeconomic status:

The association between low grade socioeconomic status and mortality rates, specifically related to cardio-vascular disease prevalence, was demonstrated by Michael Marmot in his famous Whitehall studies(116). He later referred to this observed effect as the 'Status syndrome' (the higher the social position, the better the health).

Conventional explanations, such as unhealthy lifestyles, only partially explain the Status syndrome, whereas multiple other factors may be involved when considering the influence of socioeconomic status on quality of life. Individuals experiencing a lower socioeconomic status may feel more unfortunate or unsuccessful, thus scoring lower on mental health or HRQoL questionnaires(117). Patients with low incomes may feel they can't afford more expensive, perceived to be more effective, therapies(118). These individuals may experience more guilt if their disease is a burden to the family's economic wellbeing. On the other hand, patients with chronic disease may have had fewer opportunities for a successful career, resulting in a lower socioeconomic status(4, 119).

#### 4.6.3 Physical comorbidity:

Today, chronic inflammatory conditions are considered to have effects on multiple organs and can be viewed as systemic diseases associated with multiple comorbidities(120). Chronic inflammatory diseases are the most prevalent skin conditions(1, 35, 42). Many patients have more than one disease: these different conditions may simultaneously affect how these patients feel(121).

The most extensively studied skin disease and its comorbidities is psoriasis, known to be associated with multiple diseases, including psoriatic arthritis, inflammatory bowel disease (IBD), diabetes mellitus, metabolic syndrome, obesity, dyslipidaemia, cancer, osteoporosis, cardiovascular disease and psychological or psychiatric disorders(78, 120, 122, 123). It is estimated that 13-50% of psoriasis patients have hypertension, 7-41% have diabetes, 16-41% metabolic syndrome, with dyslipidaemia and obesity as high as 61% and 41% respectively, 10-40% of psoriatic patients develop psoriatic arthritis(124) and 8-62% are shown to suffer from depression and other psychiatric disorders. A sevenfold increase in incidence for IBD (ulcerative colitis or Morbus Crohn) is observed in patients with psoriasis compared to the general population(122) and this risk is twofold for some forms of cancers(122).

Having in mind the high prevalence of comorbidities in chronic, and especially, inflammatory diseases(96), patients with skin conditions may experience psychiatric comorbidity of depression, anxiety or suicidal ideation because of their skin condition, and/or because of the accompanying comorbidities. It is therefore crucial to adjust for any existing comorbidities when evaluating data and presenting results for impairment in HRQoL or associated psychiatric conditions in dermatological patients.

#### 4.7 Dermatological treatment and its effect on quality of life:

For most chronic diseases, therapies need to be used continuously to avoid relapses or worsening of the condition. Sometimes therapies only ameliorate symptoms without eliminating the disease itself(125). The therapy used to treat the disease may in itself present a burden and impair life quality(126).

Dermatological therapies differ from most other conventional therapies such as taking a pill once or twice a day. The most typical treatments in dermatology are topical therapies (ointments, creams, lotions or mixtures) that might need to be used on the whole body, sometimes more than once a day(82). Topical medications may stain or discolour clothing, may be sticky or sting at application. Therefore, the necessity for topical treatments may pose an extra challenge for the patients as the treatments often are messy, time-consuming, might restrict choice of clothing or have unacceptable side effects(127).

Other topicals are used to create an inflammatory reaction, such as creams or gels for field cancerization. Treating actinic keratosis or non-melanoma skin cancer that appear on sun damaged skin, necessitate applications on large areas, to include visible, as well as not yet visible premalignant changes(128, 129). During the treatment, an inflammatory reaction is stimulated, which is part of the necessary response to eliminate cancer cells. Patients may respond with redness, scaling, irritations, burning, pain and swelling, as well as crusting and ulcerations(130). The reaction may persist for several weeks before the skin is healed, and treatments are usually performed on the visible parts of the body, i.e. the most sun exposed areas such as the face, back of the hands, neck, chest and forearms.

The more invasive treatments in dermatology include surgical intervention(131), laser treatment(33), cryotherapy (freezing a lesion)(132) and irradiation with a light emitting diode (LED) during photodynamic therapy. These treatments are painful, necessitate local anaesthesia, (which in itself is painful)(133) while the resulting wounds, ulcers or erosions need to be cared for during the convalescence period, often one to several weeks. The more aggressively treated lesions may heal with scarring(134).

Phototherapy is another important type of dermatological treatment(135). The therapy needs to be performed regularly, several times a week over the course of many weeks. Patients need to undress, perhaps use oils on the skin and then stand upright for the whole duration of the irradiation. Some patients may get dizzy, feel claustrophobic, too hot, or bored in the ultraviolet (UV) cabinet. When phototherapy is combined with psoralens (light sensitizing agents), these must be applied or ingested at least half an hour before the irradiation. After each treatment

patients must avoid exposing their skin and eyes to light (daylight or other light sources) for the rest of the day. Patients may need to wear sunglasses, even when inside(136), which may interfere with work, leisure activities or social life.

When generalized inflamed dermatoses are treated, daily oil and/or antiseptic baths may be necessary(137). The baths are time consuming, may be messy or discolour skin, hair, nails and clothes and may sting on the skin(138).

The non-topical treatments for skin diseases (infusions, injections and oral medications) may be burdensome because of their side effects. Most systemic medications(139, 140) used in dermatology are immunosuppressive. Others may cause allergic or infusion reactions (139, 141), organ toxicity, including eye toxicity(139, 140, 142, 143) diabetes(140, 144), high blood pressure(140, 143, 144) or even depression and suicidal ideation(145). Some medications cause less serious, but very unpleasant adverse effects such as permanent nausea(139, 140), extreme hair loss(139, 146), stomach cramps(147) or excruciating headaches(143, 146), forcing the patient to have to choose between the skin disease or the side effects of the treatment.

The evaluation of how dermatological therapy affects life quality is almost completely lacking in the literature. The Dermatology Life Quality Index (DLQI) however, includes a question on how much the therapy impairs wellbeing.

#### 4.8 Conclusive remarks: The past, the present and the future:

Accumulating knowledge on the burden of skin disease over the last few decades has changed our views on dermatological conditions, from being viewed solely as skin symptoms, to being considered as diseases influencing multiple aspects of patients' lives due to their chronic, inflammatory character, and their influence on mental health and different aspects of life. Although we have already begun to perceive skin diseases as important in causing psychosocial impairment, we still have a long way to go. We still lack the magnitude and quality of studies needed to convince health authorities of the true burden these patients experience. Our study addresses this topic.

Differences in health policies between countries, differences in global access to health care, population differences and differences in prevalence and distribution of skin disease make comparisons and generalizations between studies difficult. To convince politicians of the true needs of dermatological patients will probably take time, and multiple new studies will need to confirm and regularly update the globally experienced burden to achieve this.

Surely, this broadening of existing knowledge will gradually become apparent to clinicians, making them aware of issues not previously acknowledged. Patient consultations should start to focus on more than just skin symptom reduction. Clinicians are the ones who already have the potential to change the way they communicate with their patients, thus helping patients and addressing patients' needs in a more customized way.

At some future stage, the accumulated knowledge in this area will hopefully become sufficient for the widespread implementation of study results to clinical practice on a global perspective. An idealistic view of the future is one where patients receive consultations according to their needs and customized help to cover all aspects of psychosocial health.



## 5. Objectives

The aim of this thesis is to describe the burden of disease among patients with skin diseases in Norway and across Europe:

5.1 By describing the distribution of skin diseases and psychiatric comorbidity among Norwegian outpatients.

5.1.1 By describing the prevalence of the different skin conditions in a large sample of Norwegian patients.

5.1.2 By describing depression, anxiety, stress and suicidal ideation for different skin conditions in a large European sample compared to the Norwegian patients.

5.1.3 By describing psychiatric morbidity caused by solitary lesions (tumours, cancer and precancerous lesions) versus chronic recurrent extensive skin diseases.

5.2 By measuring health related quality of life (HRQoL) in patients with skin diseases in Europe.

5.2.1 By comparing self-reported health using EQ-VAS in dermatological outpatients and healthy controls and performing the necessary adjustments for confounding factors.

5.2.2 By comparing self-reported health (EQ-VAS) between dermatological outpatients and patients with other chronic diseases.

5.2.3 By evaluating impairment of HRQoL for each diagnosis and assessing how the different skin diseases affect the separate health domains.

5.3 By measuring how much the treatment of skin disease affects the quality of life of patients across Europe.

5.3.1 By reporting the overall impairment as assessed with the DLQI for a large number of dermatological diseases in outpatients, which is previously not reported.

5.3.2 By investigating new aspects of how skin diseases may impair HRQoL (by investigating treatment burden), which is previously not investigated.

5.3.3 By comparing diagnoses according to how much the treatment of the skin disease affects HRQoL.





## 6. Study population and Methods

We included a large number of patients with a large variety of skin conditions from unselected consecutive patients attending for their appointments at dermatology clinics in Norway and across Europe. We collected a sufficient amount of patient parameters and information on their diseases to adjust for all relevant confounding factors and to sort patients into meaningful diagnostic categories.

The study investigated patients from 13 European countries from multiple outpatient dermatological clinics, all from general and public dermatological departments to assure optimal standardisation.

Patients were recruited from November 2011 to February 2013. Dermatology departments from the following centres (in alphabetical order) participated: Erasmus Hospital, Brussels (Belgium), University of Copenhagen, Roskilde Hospital (Denmark), Brest University Hospital (France), Justus-Liebig University (Germany), University of Szeged (Hungary), University of Padua Medical School and Istituto Dermopatico dell'Immacolata, Rome (Italy), Radboud University Medical Centre, Nijmegen (The Netherlands), Oslo University Hospital and Stavanger University Hospital (Norway), Wroclaw Medical University, Wroclaw (Poland), Moscow Medical Academy IM Sechenov (Russia), Aragon Health Sciences Institute, Alcaniz Hospital (Spain), Sisli Etfal Teaching and Research Hospital, Istanbul (Turkey), and Cardiff University (UK). Two countries (Italy and Norway) had two participating centres collecting data from different parts of the country.

Consecutive patients visiting the general dermatological outpatient clinics on random days were invited to participate. Any eligible patients attending for their consultation were asked if they wished to participate and were given brief information on the study, and thereafter handed detailed written information. Those who did not wish to participate could voluntarily give a reason. Non-participants' characteristics were recorded (age, sex and diagnosis). Consent to participate or not did not influence the quality of the dermatological consultation. Recruiting was continued at each centre until a total of at least 250 participating patients was achieved or the inclusion period of the study ended.

In each centre, a control group of 125 subjects was recruited by advertisement from among hospital employees at the same institution, but not from the same department. Only those willing to participate were included. The employees were informed about the study and invited to answer the questionnaire after giving written consent. Controls were recruited with the aim

to achieve a participation rate of at least a third of the patient number. Individuals with a skin condition were excluded.

Some centres had not recorded the number of non-participants. Therefore, a second round was performed to include 25 more patients from each centre and calculate non-participant extrapolated numbers. At the same time, this increased the total number of cases. A total of 5169 participants (4010 patients and 1359 controls) were included.

Inclusion criteria for participation were: age above 18, able to read and write the local language and not suffer from a severe psychiatric disease. The patients thus represented the true adult, consenting patient population at the participating centres, reducing bias to a minimum. Each participant answered questions on socio-demographics (age, sex, education, marital status), self-evaluated socioeconomic status and experienced stress during the last 6 months. They also completed the standardized questionnaires, 'Hospital Anxiety and Depression Scale' (HADS)(148) and the EQ5D(149). Patients, but not the controls answered the 'Dermatology Life Quality Index' (DLQI)(12, 150) since this questionnaire only has dermatology specific questions.

Patients completed a background questionnaire reporting details of their disease such as flare frequency, localization and duration of flares, experienced psychological trauma/stress, worries because of the skin disease, itch and itch intensity, suicidal thoughts/ideation and whether the skin disease had ever been the reason for these thoughts, and finally the patient's satisfaction with the dermatologist. The dermatologists collected information on the patient's other diseases (comorbidities), and whether the patient had more than one skin disease. The dermatologist then assessed disease severity and whether the patient showed signs of depression or anxiety.

#### 6.1 Design:

This was a cross-sectional multicentre European study on depression, anxiety, suicidal ideation and life quality among adult outpatients with skin diseases.

#### 6.2 Preliminary calculations:

Preliminary analyses were performed to ensure there was no violation of the assumption of collinearity. The statistical power of calculation for the project as a whole was calculated on the basis of the prevalence of depression in the general population being 8.5%(67) and the expected prevalence in the dermatological population being higher. In order to have a power of 0.80 and  $\alpha \leq 0.05$ , to identify a difference between the prevalence of depression in controls

and patients, using a one-sided test at least 3500 patients and 1300 controls were to be recruited (about 233 patients and 87 controls in each centre).

### 6.3 Ethics:

The study protocol was approved by the Regional Committee for Medical Research Ethics in Norway, REK 2011/1087. At each site, ethical approval was sought when necessary. The study was conducted in accordance with the Declaration of Helsinki.

Possible inconveniences for the patients being asked to participate in the study posed some ethical considerations. Patients meeting for their appointment may find it difficult to say “No” in the setting of hospital staff asking them to fill out forms. Filling out forms is usually a necessary part of being treated and although the patients were informed that the study was voluntary they may have felt uneasy to show unwillingness to participate. Participating unwillingly in order to please the health workers can potentially lead to giving incorrect or insincere answers.

Another consideration would be that many of the questions were of a sensitive nature and would make patients think actively about unpleasant or emotionally difficult parts of their life. Some questions were also very personal and might have made patients uneasy when answering and then handing the completed questionnaires directly to the dermatologist.

Lastly, the patients who opted to participate had to set aside time for completing the questionnaires. Some patients were indecisive and would think thoroughly before answering each question. The time necessary to fill out the questionnaires could be as long as 30 minutes for some patients (as observed in the Norwegian centre, Stavanger).

### 6.4 Measurements:

#### 6.4.1 Sociodemographic factors:

Patients and controls recorded their age (in years) and sex (male or female) directly on the questionnaire. Participants who either did not wish to record age and/or sex or did not identify with either sex could leave this area blank. Although the study coordinator on receiving the completed questionnaires had access to these data, the patient’s wish not to share this information was respected, therefore there was a small number of missing values on age and sex.

Marital status was given by participants as either “Single”, “Living with a partner”, “Separated/divorced” or “Widow/widower”. The aim was to acquire most precise results, but when analysing the data, in order to avoid multiple variables (e.g. in regression analyses), the results were dichotomized as “Single” and “Not single”.

Participants had four options for educational level: “Primary school”, “Secondary school”, “High school” and “University”. This grading of education led to some difficulties transcribing the data since educational systems are different between countries and the boundary between primary, secondary and high school education are not clear-cut and alike between participating countries.

The socioeconomic status was registered as the participants’ own perceived status level. Participants could choose between “Low”, “Middle” or “High” socioeconomic level without reference to income, status in the community or sphere of employment. Further on, the participants were asked whether they had experienced serious economic difficulties in the last 5 years. Again, we wished to obtain the participant’s own perception of serious economic difficulties, rather than a specified financial loss.

#### 6.4.2 Stress:

Stress was assessed by asking the patient: “Have you experienced a stressful life event (serious illness, accident, divorce..) during the last 6 months?”. Although some examples were given to illustrate what was meant by “stressful life event” the list was not exhaustive, and participants could evaluate any event as stressful if they perceived it as such.

#### 6.4.3 Depression and anxiety:

Symptoms of depression and anxiety were assessed with the *Hospital Anxiety and Depression Scale (HADS)*(148). This scale is widely used among patients in hospital settings. It includes seven items assessing anxiety and seven assessing depression with four possible answers. For each dimension (depression or anxiety), a score from 0-7 is considered normal, from 8-10 marginal and from 11-21 clinical depression or clinical anxiety. Scores higher than 7 will therefore indicate any form of depression or anxiety and is denoted as ‘any’ depression or ‘any’ anxiety in our papers and this thesis. HADS was our choice of instrument since this instrument is easy and quick to use and no special qualifications or programs are needed to evaluate the results. The instrument was well suited for the intended purposes of our study.

#### 6.4.4 Health related Quality of Life:

*The EQ-5D-3L (5 dimensions, 3 levels)*(149) is a generic questionnaire created by the European Euroqol group ([www.euroqol.org](http://www.euroqol.org)) for assessment of HRQoL, independent of disease. Generic instruments are suitable for comparing HRQoL across multiple disciplines, dermatological and non-dermatological conditions, and healthy controls. The EQ5D has previously been little used in dermatology(112, 113).

***The EQ5D consists of 2 parts.***

1. *EQ-VAS* records the respondent's self-rated health on a visual analogue scale, from "0" – "100" (worst to best imaginable health state). This information can be used as a quantitative measure of health outcome as judged by the individual respondent.

2. *The second part of the EQ5D* assesses health status across 5 different dimensions of life: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each health dimension has three response levels: "No problems", "Some problems" and "Extreme problems". The EQ5D reflects the current general health status.

The questionnaire is available in 170 languages, and population norms for 24 countries and regions exist(151). Valid translations for all participating countries' local language were provided for the study.

Results between studies on dermatological patients and studies on non-dermatological conditions are not always readily comparable. This is mainly because results are presented differently between studies. As there are three response options per dimension, the system yields 243 health states. Different authors choose to present results by any of these health states or variations of pooled results. In our study, a simplistic approach was chosen by dichotomising the 3 answers into 2 ("Not impaired" and "Impaired"). This allowed us to obtain separate results for each diagnosis for each of the 5 dimensions. Results obtained in this way are easy to present and understand.

*The DLQI (Dermatology Life Quality Index)*(12), a dermatology specific instrument, has been widely used among dermatological patients from all over the world(152). It evaluates the impact of chronic skin disease in daily life (symptoms/feelings, activity, leisure, work/school, personal relationships and treatment). The scoring is from 0 to 30. A score of 11 or more indicates that the skin disease has a very large effect on the patient's daily life. The DLQI, being specific for dermatological disease, is more suited for evaluating the specific issues dermatological patients experience and can be used to compare HRQoL between different dermatological

conditions(150). However, the DLQI consists of purely skin-specific questions and therefore is not designed to be used by a non-dermatological control group (healthy controls or patients with other diseases).

Some skin conditions might affect personal relationships or leisure significantly more than other diseases. Different skin diseases might have a different profile of effects on the various ways that life quality can be impacted. It is not uncommon that treatments for skin diseases are substantially burdensome and time consuming, thus being the main reason for impairment in daily life. Data comparing degree of impairment between diagnoses for the therapy item in DLQI gives important new knowledge as to how individuals with a certain disease can be given better care by addressing their specific issues.

The advantage of using a generic instrument (e.g. EQ5D) is the ability to compare dermatological conditions to other diseases, as well as to healthy controls. In order to acquire skin specific information on HRQoL, a dermatology specific instrument (DLQI) was used as well.

#### 6.4.5 Suicidal ideation:

To assess suicidal ideation, we included the item: “Have you ever thought of committing suicide?” with possible answers “Yes” or “No”. An additional question was given to the patient group: “Have you ever thought of committing suicide because of your skin?” with an item on frequency (“Every day”, “Every week”, “Every month”, “Sometimes during the year”) if the answer was “Yes”.

#### 6.4.6 Clinical examination:

Each patient was examined by a dermatologist. The diagnosis, a secondary diagnosis and other diseases were recorded. Comorbidities were categorized into the following groups: cardiovascular, rheumatological, respiratory disease, diabetes mellitus or other. The dermatologist also evaluated the severity of the skin disease as mild, moderate or severe and recorded if the patient seemed depressed or anxious. If there were doubts as to whether a skin disease was present (e.g. no diagnosis, no flares, and no itch), the patients were not included in the study.

The diagnoses were organized into 26 disease groups in line with the Lambeth study describing skin disease distribution in the community(38). The skin conditions not fitting in any of the Lambeth-study categories, but represented by at least 25 patients, were assigned into separate diagnostic groups, creating a total of 35 diagnostic groups for the purpose of this study. Controls were not examined by the dermatologist and their comorbidities were self-reported.

### 6.5 Statistical analyses:

Data from all centres were merged in a single file, checked and cleaned. SPSS (Statistical Package for the Social Sciences) 22, and later SPSS 24 were used. Comparisons between patients and controls were performed with t-test for continuous variables and  $\chi^2$ -test for dichotomous or categorical variables.

Data from the Norwegian centres were pooled and analysed for depression, anxiety, stress and suicidal ideation, correcting for confounding factors. Linear regression was performed for continuous variables, adjusting for age, sex, socioeconomic status and comorbidities.

EQ5D levels were dichotomized into “Not impaired” and “Impaired”. Multivariate logistic regression was performed to analyse the dichotomized EQ5D domains, calculated for each disease separately, adjusting for age, sex, socioeconomic status and comorbidity, reporting Odds Ratio (OR) with a 95% Confidence Interval (CI). To prevent an  $\alpha$ -error accumulation because of the great number of regression analyses we corrected for multiple testing (Holm correction for  $n = 216$  regression analyses). We report unadjusted p-values, and unadjusted 95% CI, but only corrected p-values  $< 0.05$  after Holm correction were considered significant (linear regression) and 95% CI not enclosing the 1 (logistic regression) were interpreted as significant(153).

Our next step was to evaluate the separate diagnoses by using the dermatology specific instrument, DLQI. Calculations on frequencies and mean scores for patient and control characteristics (patients with nevi served as a control group) were performed. The data were used to identify which patients, according to diagnosis, country, age, sex, economic status and comorbidity suffer most from the negative impact of dermatological treatments.

The answers to DLQI question 10 (on therapy issues) were dichotomized into “Not impaired” (0) or “Impaired” (1, 2 or 3) when calculating frequencies of positive answers. For each diagnosis, mean scores to question 10 were calculated. Then the percentages of the mean scores of question 10 relative to the mean total DLQI for the diagnosis were achieved:  $(\frac{\text{mean score to Question 10}}{\text{mean total DLQI score}} \times 100)$ , denoted as Q10%. The Q10% was calculated separately for the different countries, age groups (18-35, 36-65 and above 65 years), sex, socioeconomic states (low, medium or high) and comorbidity.

Because the DLQI is dermatology specific, healthy controls did not answer this questionnaire. We wished to find a diagnostic group suitable to use as a control group for regression analysis.

Comparisons between patients with nevi and healthy controls were performed with the t-test for continuous variables and the  $\chi^2$ -test for dichotomous or categorical variables and linear and logistic regressions were used for comparing HRQoL outcomes(56). No significant differences between these two groups were found. Therefore patients with nevi could serve as a ‘healthy’ control group when analysing the DLQI (Table 1). Linear regression analysis was then performed for Q10% for each diagnosis adjusting for age, sex, socioeconomic status and comorbidity.

	Sex N (%)		Age Mean (SD)	Low socio- economy N%	Marital state Single N (%)	Economic difficulty Yes N (%)	Comorbidity None N (%)	
	Male N (%)	Female N (%)						
Healthy	453 (33.4%)	903 (66.6%)	41.1 (13.6)	215 (15.9%)	362 (26.7%)	357 (26.8%)	895 (84.8%)	
Nevi	69 (35.9%)	123 (64.1%)	39.8 (15.2)	31 (16.7%)	58 (31.7%)	42 (22.2%)	160 (86.5%)	
	<b>NS</b>	<b>NS</b>	<b>NS</b>	<b>NS</b>	<b>NS</b>	<b>NS</b>	<b>NS</b>	
<b>NS</b> - Not significant for p<0.01 significance level								
	EQ – Mobility No probl N (%)	EQ- self-care No probl N (%)	EQ-activity No probl N(%)	EQ – pain No pain N(%)	EQ–depr/anx No depr/anx N(%)	EQ-VAS Mean (SD)		
Healthy	1206 (89.3%)	1310 (97,0%)	1194 (88,4%)	925 (68.5%)	926 (68.6%)	82 (15.4)		
Nevi	176 (93.1%)	183 (96,8%)	174 (92,6%)	142 (75.1%)	142 (75.1%)	81 (14.1)		
	<b>NS</b>	<b>NS</b>	<b>NS</b>	<b>NS</b>	<b>NS (p = 0.04*)</b>	<b>NS (p = 0.04)</b>		
<b>NS</b> - Not significant for p<0.01 significance level								
*Nevi actually more with “No depression/anxiety” than controls								
No probl – No problems, No depr/anx – No depression/anxiety								
	Clinical depression (HADS >11) N (%)*		Clinical anxiety (HADS >11) N (%)*		Suicidal ideation = Yes N (%)*		Stress last 6 months = Yes N (%)	
Healthy controls	58 (4.3%)		150 (11.1%)		88 (8.3%)		412 (30.6%)	
Nevi	11 (6%)		19 (11.2%)		22 (12.9%)		57 (30.2%)	
	<b>NS</b>		<b>NS</b>		<b>NS (p = 0.05**)</b>		<b>NS</b>	
<b>NS</b> - Not significant for p<0.01 significance level								
*Dalgard et al. (57). **Border significance for p<0.05 significance level								

Table 1. Comparative analysis between patients with nevi and healthy controls. No significant differences between the two groups, making patients with nevi a suitable ‘healthy’ control group when analysing DLQI data.

### 6.6 The candidate’s contribution:

The candidate was responsible for the Norwegian centre, Stavanger, recruited all patients and controls and registered all data that was then entered in an excel sheet to be transferred to SPSS. Objectives and research questions were formulated by the candidate. Statistical analyses and calculations were performed independently, then controlled by a statistician. Literature search and writing the papers and the thesis was also done independently by the candidate, then checked by the supervisors. Revisions were done independently according to suggestions.



## 7. Results: Synopsis of papers

Paper I: Are Common Skin Diseases among Norwegian Dermatological Outpatients Associated with Psychological Problems Compared with Controls? An Observational Study.

### **Background:**

Dermatological disease has been shown to be associated with psychological comorbidity, but little is known on this issue among Norwegian dermatological patients.

### **Objectives:**

The aim of this observational study is to describe the distribution of skin disease and the prevalence of depression, anxiety and stress among Norwegian dermatological outpatients.

### **Methods:**

The study was conducted in two Norwegian outpatient clinics where patients were asked to complete standardized questionnaires. A healthy control group was recruited from the hospitals' service divisions. Inclusion criteria were adult patients understanding Norwegian and able to give their consent for participation.

### **Results:**

Thirteen per cent of outpatients had clinical anxiety compared with 3.7% of healthy controls, and 5.8% had clinical depression compared with 0.9% in controls. Adjusted odds ratio for clinical anxiety was 4.53 in patients compared with controls, and for clinical depression 6.25, which is much higher than previously described in a larger European study(57). Patients with tumours had less depression. Chronic inflammatory skin conditions had an especially high impact on patients' psychological wellbeing and should not be undervalued relative to, for instance, skin cancer in health resource strategies.

### **Conclusions:**

These results argue strongly for including skin disease prevention and treatment in future health strategies.

Paper II: The burden of common skin diseases assessed with the EQ5D™: a European multicentre study in 13 countries.

**Background:**

Generic instruments measuring health related quality of life (HRQoL), like EQ5D, are little used in dermatology, but enable comparison of skin diseases with healthy populations and non-dermatological medical conditions, as well as calculation of utility data.

**Objectives:**

The aims were to measure HRQoL in patients with common skin diseases and in healthy controls across Europe using the EQ5D.

**Methods:**

This multi-centre observational cross-sectional study was conducted in 13 European countries. Each dermatology clinic recruited at least 250 consecutive adult outpatients to complete questionnaires, including the EQ5D. A healthy control group was recruited from the hospitals' service divisions. Inclusion criteria were adult patients understanding the local language and able to give their consent for participation.

**Results:**

There were 5369 participants, 4010 patients and 1359 controls. Mean self-rated health state reported by patients was 69.9 (SD 19.7), controls 82.2 (SD 15.5). When adjusted for confounding factors, including comorbidity, mean patient EQ-VAS scores were 10.5 points lower than for controls (standardized  $\beta = -0.23$ ). Odds ratio with 95% confidence interval for impairment in all 5 dimensions of EQ5D adjusted for confounders was doubled for patients compared with controls. Patients with hidradenitis suppurativa (HS), blistering conditions, leg ulcers, psoriasis and eczemas had the highest risk for reduction in HRQoL in most dimensions (two-tenfold). Data on differences of impairment by dimensions offer new insights.

**Conclusions:**

This study confirms the large impact skin conditions have on patients' wellbeing, differentiating between aspects of HRQoL. Patients with HS, blistering diseases, leg ulcers, infections and most chronic skin diseases reported reduced HRQoL comparable to patients with chronic obstructive lung disease, diabetes mellitus, cardio-vascular disease and cancers. These findings are important in the prioritization of resource allocation between medical fields and within dermatological sub-specialities.

Paper III: The Role of Therapy in Impairing Quality of Life in Dermatological Patients: A Multinational Study.

**Background:**

Skin disease and its therapy affect health related quality of life (HRQoL), but therapy issues in dermatology are little explored.

**Objectives:**

We aimed to measure the burden caused by the dermatological therapy in 3846 patients from 13 European countries.

**Methods:**

Adult outpatients completed several questionnaires, including the Dermatology Life Quality Index (DLQI) which has a therapy impact question. A healthy control group answered the same questionnaires, except for the DLQI. Inclusion criteria were adult patients understanding the local language and able to give their consent for participation.

**Results:**

There were 4010 participants with 3846 (96%) valid answers to the DLQI. Therapy issues were reported by a majority of patients with atopic dermatitis (63.4%), psoriasis (60.7%), prurigo (54.4%), hidradenitis suppurativa (54.3%) and blistering conditions (53%). The largest reduction in HRQoL attributable to therapy, as percentage of the total DLQI, adjusted for confounders was seen in blistering conditions (10.7%), allergic/drug reactions (10.2%), psoriasis (9.9%), vasculitis/immunological ulcers (8.8%), atopic dermatitis (8.7%), and venous leg ulcers (8.5%). Although patients with skin cancer reported overall less impact on HRQoL, the reduction due to therapy was relatively high (6.8%).

**Conclusion:**

Treatment for many skin diseases adds considerably to the impairment of quality of life: the burden of dermatological treatment should be considered when planning therapy and designing new dermatological treatments.



## 8. Discussion

### 8.1 Main findings:

In our study, patients with skin diseases suffered significantly more from psychiatric comorbidities (depression, anxiety and suicidal ideation) compared to healthy controls. Those patients also had a significant reduction in HRQoL when using both generic and dermatology specific instruments. Therapy used for treating the skin disease contributes to reducing patients' life quality.

Norwegian dermatological patients have a higher risk for depression and anxiety compared with the patients from the other European countries participating in the study(57). The reason for this higher risk is not clear. One possibility may be that Norwegian patients feel comfortable in answering questions on psychiatric symptoms, thus giving more honest answers in questionnaires. On the other hand, a true higher risk of psychiatric comorbidity in Norwegian dermatological patients could serve as an alert for Norwegian health authorities to further investigate this issue. Comparative studies on health policies across countries would need to be performed in order to shed more light on this issue.

According to multiple studies, patients with chronic inflammatory and itchy, extensive dermatoses score highest for depression, anxiety and suicidal ideation(5, 62, 65, 73, 80, 84-86, 89, 100, 103, 104, 110, 111). Chronic, recurrent and more extensive skin conditions would affect patients differently compared to solitary lesions(114, 154, 155).

In accordance with our findings, several studies show that dermatological patients with skin cancer, tumours and precancerous lesions experience less impairment from their skin disease(154, 155) compared with patients suffering from chronic inflammatory skin conditions. Shah and Coates(114) found that older patients with rashes suffered significantly more than older patients with solitary lesions, even when the lesion was malignant (using HADS for measuring depression and anxiety and DLQI for HRQoL)(114). When grouping our patients in the same two categories (chronic, inflammatory, generalized skin diseases versus solitary lesions) we also found a significant difference in psychiatric morbidity between each of the two groups when compared with healthy controls. This finding is of significance, since some secondary dermatological units have an increased focus on prioritizing cancer, thus generating longer waiting time for patients with all other skin conditions(156).

Considering that psychiatric comorbidities commonly occur in patients with skin diseases, the next concern is that skin diseases have a high prevalence in Norway, and have the second highest number of outpatient appointments. In 2017 the number of outpatients with skin diseases in Norway was 476 199(157) and the population in Norway 5 260 101(158).

Despite this high number of patients with skin conditions attending dermatology clinics, there are no recent updated data on dermatological disease distribution and prevalence according to diagnosis(159). Dermatological patients represent almost 8 per cent of all outpatients across all disciplines in Norway. The current study supplies data on how the different dermatological diagnoses are distributed in the skin patient population. This is of relevance when allocating resources or planning future health strategies. For instance, we showed that chronic inflammatory conditions, those that pose the highest risk for psychiatric comorbidity, represented 69.3% of all dermatological conditions in outpatients in Norway.

The distribution of skin diseases in other European countries for this same period over recent decades(1) shows prevalence rates (for most skin diseases) to be similar to the prevalence described in Norway. In both the European and Norwegian sample, psoriasis and non-melanoma skin cancer (NMSC), were the most prevalent(57).

In Scandinavia, as well as in other northern European countries, several skin diseases are more prevalent than in the rest of the world. One such disease is psoriasis, where the highest prevalence is seen in Norway (8.5%)(160). There are different prevalence numbers across the world: psoriasis is even almost non-existent among Latin American Indians(161). This implies that data from Norway on psychiatric comorbidity in skin disease may differ when compared to other parts of the world.

On the other hand, some skin diseases are less prevalent in Northern European countries (as well as in Norway). A classic example is pemphigus vulgaris, where incidence varies from 0.05 to 2.7 cases per 100 000 population per year between different countries and is endemic in Brazil. Likewise, the autoimmune disease, Morbus Behçet, is endemic in eastern and central Asia and eastern Mediterranean countries and rare in northern European countries, including Norway(2). None of the patients from the Norwegian sample suffered from pemphigus vulgaris or Morbus Behçet, while the European sample as a whole showed pemphigus to be among the most prevalent bullous dermatosis (18 of the 66 patients with bullous diseases). Psychiatric comorbidity will therefore differ between countries on account of the different prevalence of skin conditions, not solely because of differences in health provision and policies.

When the Norwegian data was analyzed for suicidal ideation (all diagnoses pooled), there was no difference between patients and controls (13.8% for patients and 13.5% for controls). This was surprising since odds for depression and anxiety were at least fourfold higher in patients compared with controls, and depression and anxiety are known risk factors for suicidal ideation. Unexpectedly we found a higher prevalence of suicidal ideation in the age group 56-65 years among Norwegian healthy controls versus patients. We also found suicidal ideation as high as 18.6% for the age group 31-45 years in the healthy control group, which is much higher than reported for healthy controls in other European countries(69, 162). Suicidal ideation in USA (all age groups) was 5.6-14.3%(108). Worldwide suicidal ideation numbers vary from 2.1% (Beirut)(162) to 15.9% (New Zealand)(69). The worldwide lifetime prevalence of suicidal ideation is estimated to be 9.2%(108). There are few studies on suicidal thoughts and ideation in healthy individuals from European countries, but common prevalence rates are in the range between 3% (Italy) to 12.4% (France)(162).

One may speculate whether suicidal ideation is extraordinarily high for healthy individuals in Norway or whether there are other factors skewing the results. A recent study on patients with psoriasis from Manchester likewise shows that mental illness was raised in people with psoriasis, but healthy controls showed a slightly higher risk for suicide(163). Such findings confirm the complexity of this issue.

Suicidal ideation is more prevalent among women and younger age groups(69, 108). Our control group was overrepresented by younger women. Thus, the high prevalence of suicidal ideation among the controls might not reflect the true overall prevalence of suicidal ideation in Norway. One could thus question whether prevalence of suicidal ideation in Norway is truly higher than for other European countries, or whether higher suicidal ideation among our healthy controls rather reflects the gender and age of these controls.

One may further speculate whether lower suicidal ideation in patients with actinic keratosis (AK), NMSC, malignant melanoma (MM) and other tumours compared to our other patients reflects the more radical, surgical treatment options for these diagnoses and that not all patients knew their diagnosis at the study inclusion point (if newly referred), and thus were not aware of having a serious condition. Their answers to the questionnaires may have reflected only the extent of discomfort solitary lesions presented, usually not being itchy, painful or generalized. There was no difference in depression, anxiety, stress and suicidal ideation among patients with different solitary lesions, even when analysing separately for malignant and benign tumours(164).

High suicidal ideation in patients with dermatological diseases in Europe has only recently been reported(57). The few other existing studies also show that risk of suicidal ideation in several skin conditions is high(64, 80, 86, 109). Some such conditions are acne conglobata (especially in men)(57, 80), metastatic malignant melanoma(109) and progressive systemic sclerosis(109). Significantly high percentages of patients with psoriasis, itch and atopic dermatitis report suicidal ideation(57, 64, 80, 86).

The patient and control groups in the Norwegian data were not age matched, in fact, there were extremely few controls, only three (all women), in the older age groups (>65 years), limiting calculations of regression analyses and not giving robust data. Patients with NMSC and AK are generally older, and since this diagnostic group comprised one fifth of our patient population it made more sense to see whether odds for suicidal ideation would be different if analyzed stratified by age groups, excluding those above 65 years. Patients and controls between the ages 18-55 showed a prevalence of suicidal ideation of 17.7% for patients and 13.8% for controls.

In parallel to their higher psychiatric comorbidity, patients with skin diseases also had a substantially reduced HRQoL as measured by the EQ5D and the DLQI and across different parameters (self-assessed health, several quality of life domains and therapy issues).

There are existing studies evaluating self-reported health (using EQ-VAS) for different chronic diseases, other than dermatological conditions(165). This allowed us to compare the degree of impaired life quality between skin diseases and some other diseases, that are well known to cause substantial impairment in health, and generally perceived to be severe(166). Such diseases are cardio-vascular diseases, diabetes mellitus, rheumatological and chronic pulmonary diseases, as well as several forms of cancer.

The lowest self-assessed health in our study was for patients with leg ulcers, hidradenitis suppurativa (HS), blistering diseases and prurigo (with an EQ-VAS < 60). This high degree of impairment was similar to the health states assessed for diseases known to cause substantial quality of life impairment, such as pain in rheumatoid arthritis (EQ-VAS: 56.4), cardio-vascular diseases (EQ-VAS: 37-89), cancers (EQ-VAS: 48.0-84.0), liver disease (EQ-VAS: 57-70) and chronic obstructive pulmonary disease (EQ-VAS: 54.7-58.8)(77, 167-170).

The impairment for many of the other chronic skin diseases (psoriasis, atopic eczema, pruritus, hand eczema, connective tissue disease and genital conditions) showed mean values of EQ-VAS between 60 and 70, which is a health state comparable to diabetes mellitus (EQ-VAS: 68.8), cardio-vascular disease (EQ-VAS: 37-89), anxiety (EQ-VAS: 63.8), cancers (EQ-VAS:



48.0-84.0), liver disease (EQ-VAS: 57-70), chronic lymphocytic leukaemia (EQ-VAS: 70.3-77.6), and visual impairment (EQ-VAS: 64.0-82.0)(77, 168, 169, 171-173).

Since comorbidity was adjusted for in our study, even for patients already suffering from any of the other chronic diseases mentioned above, the data presented is valid for how the skin disease impairs self-reported health, instead of reflecting the impairment caused by a comorbidity that the patient may have. Before and after adjustment for confounding factors (age, sex, socio-economic state and comorbidities), patients with HS, prurigo, blistering disorders and leg ulcers rated their health lowest among all dermatological patients.

Treatments for skin diseases contribute to the burden on HRQoL. For some diagnoses we saw that therapy may have a larger impact than was previously known, but we also identify diseases that are affected by therapy to a lesser degree. Older, male patients with lower socioeconomic status and comorbidities suffer more from therapy issues, and differences between countries were higher than expected. In some countries, younger patients suffered more.

Measuring HRQoL is particularly relevant in patients with chronic skin disease, where dermatological treatment might only offer a temporary suppression or remission of symptoms. Alternatively, the treatment regime may even add to the burden of the disease(174-176). When treatment is not expected to cure the disease, and at the same time patients' well-being is adversely affected, dermatological treatment will be mainly directed towards decreasing disease severity and trying to increase HRQoL.

#### *The burden of skin diseases summarized for some diagnoses:*

For a clinician consulting a patient with a specific skin condition, the impact that the specific skin disease has on health status, HRQL and psychological comorbidity are of higher relevance than pooled numbers for skin patients as a whole.

The following is a comprehensive summary of this impact for the most common skin diseases, including psychiatric comorbidity, self-reported health status and therapy issues. The comparison of the impact on HRQoL is compared to other, non-dermatological chronic diseases, other studies on dermatological diseases, and between the dermatological diseases in our study (for the separate dimensions and therapy impact).

#### *Psoriasis and atopic dermatitis (AD):*

Psoriasis and AD are chronic inflammatory skin diseases, and both show similar impairment. Unsurprisingly the burden and impairment of psoriasis and AD also were comparable to the

burden experienced by patients with other chronic diseases. Møller et al.(77) showed life quality impairment in psoriasis to be similar to other chronic diseases (cardio-vascular, end-stage renal and liver disease, diabetes, cancer, and visual disorders). We found the same to be true for psoriasis and AD patients, with an impairment comparable to these same diseases as well as breast cancer(169), anxiety disorder(172) and chronic lymphocytic leukaemia(173).

When assessing how life quality is impaired in its different dimensions, patients with psoriasis and AD showed a more than doubled risk for experiencing depression/anxiety compared to healthy controls. The risk of impairment in leisure activities, self-care and pain/discomfort, was increased more than three- to fourfold, which was substantially higher than for most other skin diseases. In psoriasis, but not in AD, the risk of mobility issues was doubled.

Since we also adjusted for confounding factors, a more precise estimate of this impairment in psoriasis and adult AD patients attending dermatology clinics across Europe was obtained. Adjusting for comorbidities is important since psoriasis(122) and AD(177, 178) may be associated with several other diseases.

Patients with AD did not show significant differences in anxiety compared with the healthy controls, but more than a third (34.5%) had experienced stressful life events. Patients with psoriasis experienced some of the highest suffering from depression, anxiety and stress compared with the other dermatological patients, while for AD this was true only for depression and stress, but not for anxiety.

Suicidal ideation in patients from Europe with psoriasis was 17.3%, and for AD was 15% (8.3% for healthy controls). Psoriasis had one of the highest suicidal scores among all diagnoses, and similar to the scores given by the Norwegian psoriasis patients (18.4%.), but AD patients from Norway showed no significant differences from the Norwegian healthy controls (13.8% for AD patients, 13.5% for controls).

One possible explanation for the lack of significant differences in anxiety and suicidality between Norwegian AD patients and Norwegian healthy controls may be the high prevalence of AD in the Norwegian pediatric population (15-20%), the disease being active mostly in children (80% of children with AD will not have AD symptoms as adults). The prevalence in adults is 2-4%(179). A large number of the healthy controls may have had AD as children, being symptom free from their disease, now as adults, yet still having experienced the burden of AD from the time of their youth, leaving its mark on their anxiety and suicidality profile, as well as on major life changing decisions. It is not easy to explain why a patient with a certain

disease is at higher risk for a specific psychiatric comorbidity, be it anxiety or depression. Further studies on prevalence of anxiety among healthy individuals who suffered from AD as children/adolescents may give interesting results.

Both psoriasis and AD patients recorded substantially reduced life quality regardless of whether self-reported health, EQ5D dimensions or dermatological life quality instruments were used, before and after adjusting for confounders. Therapy for these diseases also played a substantial role in impairing life quality(176). Patients with psoriasis and AD suffer equally from all aspects affecting HRQoL, including the therapy used to treat the diseases.

*Leg ulcers, blistering diseases and hidradenitis suppurativa (HS):*

Patients with leg ulcers evaluated their health lowest among all skin patients, closely followed by patients with HS and blistering diseases. Patients with leg ulcers and blistering disease may be older and have more comorbidities, but their self-reported health remained considerably poorer even after adjusting for age, comorbidity and the other confounding factors.

When compared to patients with other chronic conditions, patients with leg ulcers, blistering disease and HS showed self-reported health similar to that reported by patients with cardiovascular, end stage renal and liver disease, arthritis pain, chronic obstructive pulmonary disease and some cancers(77). The same three skin conditions showed lower health than did patients with diabetes mellitus type 2(77, 171), breast cancer(169), chronic lymphocytic leukaemia(173), anxiety disorder(172) and visual impairment(77).

Adjusted values for the dimensions of the EQ5D, showed substantial impairment of health in four of the five dimensions (not significant only for anxiety/depression). Patients with leg ulcers and HS had an increased risk for impaired HRQoL five- to tenfold compared to healthy individuals. Iglesias et al. also reported impaired HRQoL in all EQ5D dimensions for patients with leg ulcers(99). Severely reduced HRQoL scores in HS when using EQ5D(180) is in accord with other studies, showing mean EQ-VAS scores close to ours(93).

Further investigation of HRQoL in this group of patients is necessary(93, 98, 180). There is little information on HRQoL in bullous diseases: one study reported severe impairment of life quality, consistent with our findings(181).

Leg ulcer patients from the European sample, compared with healthy controls, suffered significantly more from clinical anxiety (17.5%, controls 11.1%) and clinical depression (24.3%, controls 4.3%), as well as suicidal ideation (17.8%, controls 8.3%). These data on prevalence of psychiatric symptoms were some of the highest among all patients, only topped

by psoriasis for anxiety. These data have not been analysed for blistering conditions and HS because of the low number of participants with these diagnoses.

Patients with blistering conditions showed the highest impairment due to therapy issues, followed by patients with leg ulcers, while HS patients experienced therapy to cause less impairment. Our study ranks HS patients to have one of the highest risks for impaired life quality(57, 164) and highest impairment in sexual life(182). Presumably, the symptoms pain and other discomfort cause the high suffering in HS, not the therapy, while for blistering conditions and leg ulcers, the disease, and the therapy used for treating the disease, both have a substantial role in this impairment.

*Acne and facial dermatoses (seborrheic dermatitis, rosacea and others):*

Patients with visible dermatoses reported self-reported health (EQ-VAS scores) similar to healthy controls. The mobility, self-care, activity and pain/discomfort dimensions were not severely impaired, except for pain/discomfort in seborrheic dermatitis. However, the dimension depression/anxiety showed at least a doubled risk for patients with acne and seborrhoea. High self-reported health for acne patients, probably reflects the young age and low associated comorbidity risk, which is true for the other facial dermatoses. The patients with visible dermatoses did however suffer more from depression and anxiety, as also shown by other studies(57, 87, 183-185).

When using HADS to evaluate depression and anxiety in the European patients with acne, rosacea and facial dermatoses (pooled), 25.8% showed any anxiety, 8.1% any depression and 11.5% suicidal ideation(57).

In Norwegian acne patients, clinical anxiety was seen in 14.8% and any anxiety in more than one third (36.7%), while any depression was seen in 18.5%. Clinical anxiety in the whole European sample for acne was similar (15.1%), but clinical depression was not significantly higher for neither the European or the Norwegian group compared with the healthy controls. Likewise, no significant difference was seen for suicidal ideation, neither in the European or Norwegian acne population.

Diseases affecting small areas of the body, such as the facial dermatoses (seborrhoeic dermatitis, rosacea and to some degree acne) as well as psychodermatological conditions rank lower on therapy issues than might be expected relative to their total mean DLQI values. This again demonstrates that it is the disease itself, and to a lesser degree the therapy of the disease, that is causing the patient's impaired HRQoL. Treating these conditions adequately will

alleviate the patient's experienced burden without additional impairment of HRQoL and should be attempted.

*Tumours: Nevi, actinic keratosis (AK), non-melanoma skin cancer (NMSC) and malignant melanoma (MM):*

Patients with nevi and benign tumours reported self-evaluated health and scores in all five dimensions of EQ5D similar to healthy controls. Although MM and NMSC are serious conditions, patients assessed their health higher than did patients with other skin diseases. Other studies have likewise shown relatively low impairment of HRQoL, and low psychological comorbidity caused by solitary lesions, even when malignant(186, 187). This is probably explained by the non-chronic nature and radical treatment options available for tumours. A good correlation between different instruments, and results similar to ours showing low impairment were found when patients with actinic keratosis were evaluated with disease-specific, dermatology specific and generic HRQoL instruments(187).

In contrast, patients with AK and NMSC rank high in impairment when assessing therapy as a percentage of the total DLQI score. AK and NMSC apparently did not have a high impact on HRQoL, nor psychiatric comorbidity in our study population(56, 57, 164), but scored relatively worse when therapy was assessed, ranking them higher on therapy issues than even HS and several other skin conditions.

Previous studies evaluating the burden caused by AK and/or NMSC have shown low impact on HRQoL(154, 186, 187), raising the possibility that currently available measures may be missing therapy issues and that there may be a need for a skin cancer specific HRQoL measure. Existing disease specific instruments do not include questions addressing therapy(187, 188). When developing new instruments, authors should consider including therapy related items in order to adequately assess these patients. Alternatively, therapy specific questions could be used directly in patients with NMSC and AK.

## 8.2 Methodological considerations:

### 8.2.1 Strengths:

The solid data collected on a large European scale including patients from two large Norwegian dermatological clinics at Oslo University Hospital and Stavanger University Hospital allows us to investigate multiple aspects of psychiatric comorbidity and impaired life quality in patients with skin diseases from Norway and Europe.

The large number of patients in this study, recruited without prior selection, but recruited consecutively when attending for their dermatological appointments at a general dermatological outpatient clinic, reduced selection bias to a minimum, reflecting the true reality of dermatological practice. Furthermore, we adjusted for relevant confounding factors achieving robust data on the European dermatological population. The wide range of diagnostic categories that were included, each presenting with differing psychosocial backgrounds, optimally reflect the reality of the studied populations.

We further studied therapy as a factor contributing to impairment in HRQoL. Studies on therapeutic issues are lacking, and studies using DLQI typically have no healthy control group. We circumvented this problem by using patients with nevi as a 'healthy' control group and therefore present regression analyses, which give more accurate results.

The high participation rate, 91.3% for the Norwegian patients and 79.9% for the European patients, indicates that our sample is truly representative for dermatological outpatients in Norway as well as in Europe, and adds to the robustness of the study.

Using validated, internationally established measures for examining depression and anxiety gives valid results that can be used to compare with non-dermatological diseases and healthy controls.

The generic instrument (EQ5D) used for evaluating HRQoL generated data suitable for comparisons between patients with a wide range of conditions, patients with non-dermatological diseases, and healthy controls, while using the dermatology specific measurement (DLQI) generated data suitable for comparison between skin conditions.

Existing studies have used EQ5D or DLQI for calculating data, differences before and after an intervention or after a specific treatment but without comparing with other dermatoses or adjusting for other important variables. Our study has corrected for the common confounders, but also for comorbidity, giving a truer picture of the impact skin diseases per se have on dermatological patients' HRQoL, thus corrected for impairment that may be caused by any other coexisting disease.

It should be mentioned that there were no significant differences in socio-economic status and economic difficulties between patients and healthy controls from Norway. Employed individuals would be expected to be healthier than patients, but we intentionally aimed to have a control group which would best match the World Health Organization's definition of health(189).

Having in mind the above mentioned strengths, generalisability was strong, but some limitations should also be mentioned.

### *8.2.2 Limitations:*

The patient and control groups were not case-control matched even though efforts had been made during the recruitment process of controls. This was not a serious limitation since there were not large differences regarding sex (both groups had more female than male participants), socio-economic status, economic difficulties and marital status. Age differences were significant between patients and controls, the latter being younger. When analysing variables, we adjusted for these confounding factors, yet diagnoses affecting older patients may not have had good matches among the controls in the Norwegian sample, suggesting the need for careful interpretation of data. This was particularly true when analysing data on actinic keratosis (AK) and non-melanoma skin cancer (NMSC) in the Norwegian patients concerning suicidality.

Higher suicidal ideation among dermatological patients from Norway (which was true for the European patients as a whole) was part of our hypothesis, but this could neither be confirmed nor rejected due to the low number of controls in the older age groups. Results for suicidality were therefore not published, although initially planned. The results are discussed in this thesis, with limitations mentioned in the text, allowing the reader to get an idea of the possible issues, but we acknowledge the lack of robustness. There were many missing answers to suicidality in the control group. This may have inadequately reflected the true prevalence of suicidality in the Norwegian control group.

When publishing results on the European data, these were not presented separately for each country because of the different distribution of skin diseases across the separate centres. The number of patients within the separate diagnostic categories per centre was too small for optimal analysis and for comparing data between centres. Much larger studies would be required in individual countries to make such comparisons.

Although the patient population was large, there were not enough patients from each country to use regression analysis for each diagnosis and show true differences between countries on therapy issues. The pooled results may therefore be less applicable to the separate countries, but do pose interesting questions that warrant further studies. When crudely analyzed, there were large differences in therapy impairment between countries which could not be readily explained. An understanding of national health policies and guidelines for dermatological treatments across Europe might clarify some of these issues. However, the burden of the treatment per se, an important aspect of life quality impairment, is brought to light by our study.

Some diagnostic groups were represented by a lower number of patients, even when pooled for all countries. We presented all results, even when the participant numbers were low. We chose to do so because there are no previously published data on HRQoL issues, neither on impairment caused by therapy for many of the diagnoses. Although interesting, these results should be interpreted with caution. Furthermore, we cannot dismiss some degree of variation in recruitment, reflecting specific interests of the centre, differing referral patterns, variations in disease frequency and economic differences.

A universal limitation when performing multinational studies with standardized instruments is the validity of translations and bias that may arise from cultural differences. We chose widely validated instruments with existing valid translations in multiple languages. Cultural differences, although impossible to eliminate completely, were not extreme in our study since participants constituted a relatively homogeneous sample of European citizens. Immigrants were not excluded as we considered them to be sufficiently adapted to their place of residency to know the local language well enough to be able to participate. One could speculate if this (at least theoretically) may have lead to some imprecise answers.

Collecting an immense amount of data has its strengths, but also limitations as random errors will accumulate when working with multiple variables and multiple regression analyses. We partly compensated for this by performing a Holm's correction where needed.

Although comparisons between skin diseases in our study and other (non-dermatological) diseases was not possible for the second part of the EQ5D, mainly because previous studies had not presented their results the same way as us, the approach was well suited to compare differences between the separate dermatological diseases in the current study. We analysed HRQoL according to degree of impairment and according to which dimensions were most affected. Not comparing between dermatological and non-dermatological diseases using the second part of the EQ5D can be considered only a minor limitation, since we already had performed multidisciplinary comparisons by using the data from the first part of the EQ5D (EQ-VAS) and had already obtained robust results for comparisons.

The very wide range of mean total DLQI scores between countries is very striking. This cannot be solely explained by the different distribution of skin diseases, nor solely by the different availability of drugs or health policies. At this point, we can not give a reasonable answer to this question. Cultural differences in seeking help may be one reason.



Many of the questions were of a sensitive nature or very personal where patients (and/or controls) may not have felt comfortable answering completely honestly. Specifically, the patients who might already have had a long-standing doctor-patient relationship with the recruiting dermatologist might have felt uncomfortable in giving honest answers to embarrassing questions. Although all participants were informed that their anonymity was guaranteed, the act of handing over their answers directly to another person might have promoted some degree of dishonesty.

### 8.3 Implications for future research:

Few studies have evaluated psychiatric comorbidity in such a wide range of patients with skin diseases. Almost no other studies have evaluated the burden of benign tumours, non-melanoma skin cancer (NMSC) and actinic keratosis (AK), or compared the burden with the extensive, chronic, generalised skin conditions. Our and other studies(114, 154) show results, warranting further investigation of this issue and argue strongly for more focus on including skin disease prevention and treatment in future national health strategies. Currently, strategies for skin cancer are being implemented in Norway. One concern is that prioritizing cancer patients inevitably will lead to under-prioritizing other skin diseases, if appropriate measures are not taken. Studies showing the high burden of skin diseases, including skin cancer, is therefore a prerequisite for motivating health authorities to allocate resources equitably.

Data on the Norwegian sample gives new and interesting results on prevalence of skin diseases in Norway, the psychiatric comorbidities in Norwegian dermatological outpatients, including suicidal ideation, suggest that prevalence of suicidal ideation in Norway may be higher than expected. New studies on prevalence of suicidal ideation in healthy individuals from Norway across different age groups and gender would clarify this issue. We see a need for studies on suicidal ideation among the Norwegian healthy population and thereafter exploring suicidal ideation among dermatological patients, performed with matched case-controls, specifically stratifying by age groups. Furthermore, knowing which diseases occur most commonly, and which are most likely to cause psychiatric morbidity, including suicidal ideation will help future health resource planning(57, 164).

With this study, we are able to show health authorities the scope of expected resource needs for dermatology patients. We show that the issue is significant and important. The study gives a perspective on which skin diseases need more psychiatric attention and how they are distributed

among outpatients. Research on treatment and wider aspects of care will hopefully elicit better options for those suffering from both the dermatological and psychiatric problems.

Comparison between disease incidence, prevalence, and severity, impairment and therapy issues between different countries could serve as ground for a balanced debate on health policies internationally. Gaining experience and adopting optimal health policies from countries showing the best patient satisfaction and least suffering would be a first step in optimizing health policies internationally. Using these existing differences for explaining how different diseases lead to multi-morbidity, psychiatric comorbidity and reduction in functional health are important for future health system planning and resource allocation.

Our study points out aspects of HRQoL that previously may have been overlooked. Clinicians are made aware of the different domains that may be affected by the different diagnoses.

Further studies investigating the issue of impaired HRQoL will expand the existing knowledge on the burden of skin diseases and have great potential importance for giving the quality of care skin patients need. When conducting further studies it is important to address associated conditions in order to ensure effective response to dermatological therapy(106), since for some disease categories skin disease and psychiatric comorbidity need common targeted intervention.

For diseases such as acne, pruritus, urticaria, prurigo, connective tissue disease, hand eczema, seborrheic dermatitis and alopecias there was less impairment in mobility and/or self-care, but high risk for pain/discomfort and depression/anxiety. The dermatologist should be aware of the need for psychiatric support and adequate pain/discomfort management to enhance HRQoL in these patients. Recent research has shown that physicians who are not trained as psychiatrists may miss depression in their patients(190). Therefore, making clinicians aware of the risk for psychiatric comorbidity for their dermatological patients seems to be especially important for the diseases mentioned above where depression is significantly high. Research on dermatological patients' satisfaction with their health care and health care providers may help in this regard.

In contrast to the conditions mentioned above, leg ulcers, hidradenitis suppurativa, vasculitis/immunological ulcers and blistering conditions showed a high risk of impairment in mobility, self-care, usual activities and pain/discomfort but less for anxiety/depression. These patients suffer more from the somatic aspect of their disease. Therefore, this group of patients will need targeted strategies for managing discomfort, pain, mobility and self-care issues. The clinician should be advised how to give optimal care for this different group of patients. Further research to see why these patients – despite their pain, reduced mobility and impaired self-care

– do not tend to be more depressed or anxious, could be interesting.

Our study points out previously not investigated issues, such as the importance in addressing therapy impact on HRQoL and promoting adherence to therapy.

Burdensome treatments have a negative effect on adherence to therapy(191) and can be the reason for undertreatment and relapse of disease. Measuring impairment of HRQoL without taking into account the therapy issues may not give the true extent of suffering that dermatological patients experience. On the other hand, knowing which diseases have the highest potential to cause problems with treatments can alert clinicians to patients who need a different approach, by giving them, for instance, better information, providing a variety of options, offering training in therapy application or at least acknowledging the issue.

When developing clinical guidelines in dermatology, optimization of therapy and minimising burden of treatment should be considered. Developers of HRQoL instruments should pay attention to therapy issues when measuring HRQoL in some specific diagnoses such as skin cancer and precancerous skin lesions, as this burden may go undetected using current available measures(164, 176).

Studies specifically created for analyzing therapy issues and differences between countries are warranted because of the large differences between countries. Analysis of the source for country differences may elucidate important issues and potentially serve as a guide to optimal health policies and creating optimal treatment guidelines.

Instruments for use in dermatology for evaluating different aspects of HRQoL that include questions on therapy issues should be created. This is particularly true when assessing skin cancer and precancerous lesions. Focusing on therapy issues reveals an existing impairment, overseen when using standard methods. Instruments for specifically evaluating therapy issues in patients with AK and NMSC are as of today lacking. Developers of HRQoL instruments should therefore consider including therapy related questions in their measurements.

Pharmaceutical companies should address ease of use of their products. The ultimate goal would be to reduce the burden of skin disease and promote adherence.



## 9. Conclusion

We have demonstrated the specific and nuanced impact that skin diseases have on dermatological patients' wellbeing, changing our view of the needs of these patients. Such findings are important for clinicians, and in the prioritization of resource allocation in the care of these patients and when optimizing policies on treatment strategies.

Norwegian dermatological patients have a higher risk of suffering from depression and anxiety than their European counterparts. For the younger age groups, there is also a higher risk of suicidal ideation. This higher risk of psychiatric comorbidity in dermatological patients from Norway should alert clinicians in offering psychiatric help for the patients, by either discussing the issue or referring to a psychiatrist or psychologist. Implementation of these findings should include access to multidisciplinary team work for patients in need, as is the case in some units in the UK(192).

Health related quality of life (HRQoL) is severely impaired for many of the dermatological patients from the 13 European countries participating in our study. We also point out differences between diagnoses across different HRQoL dimensions. Our data imply that there should be different approaches to alleviating a patient's daily suffering according to the dermatological diagnosis. For some dermatological diseases treating pain and discomfort may be more urgent than addressing depression and anxiety issues. For others, this may be reversed.

Concerning self-reported health, dermatological diseases have been shown to be as burdensome as other chronic diseases, including those usually regarded as more serious (cardio-vascular, pulmonary, liver disease, rheumatological pain, diabetes and some cancers).

Dermatological therapies may be more burdensome than treatments for other diseases. Skin diseases burdened little by the type of therapy are more straightforward to adequately treat since the treatment will not further impair life quality. However, for diseases where therapy is more burdensome, treatment options should be more thoroughly discussed with the patient and the extra burden taken into account by the dermatologist in their therapy decisions and in planning the education of the patient about treatment techniques. Dermatologists may find that using a quality of life instrument that includes the burden of therapy is helpful in informing their decision taking. Not all instruments assessing life quality address therapy issues; for skin cancer this extra burden may go undetected unless appropriate measures are used.

Caring for dermatological patients should not solely focus on symptom reduction and psychological support, but also include strategies for improving HRQoL and meeting patients' specific needs, appreciating the risk of psychiatric comorbidity and of therapy issues.

## 9. References

1. Williams H, Svensson A, Diepgen T, Naldi L, Coenraads PJ, Elsner P, et al. Epidemiology of skin diseases in Europe. *Eur J Dermatol.* 2006;16(2):212-8.
2. Augustin M, Krensler M. Health Economics and Skin Disease. In: Christopher Griffiths JB, Tanya Bleiker, Robert Chalmers & Daniel Creamer, editor. *Rook's Textbook of Dermatology 9<sup>th</sup> Edition Chapter 6: Wiley-Blackwell; 2016.*
3. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2095-128.
4. Augustin M. Cumulative life course impairment: identifying patients at risk. *Curr Probl Dermatol.* 2013;44:74-81.
5. Zachariae R, Zachariae C, Ibsen HH, Mortensen JT, Wulf HC. Psychological symptoms and quality of life of dermatology outpatients and hospitalized dermatology patients. *Acta Derm Venereol.* 2004;84(3):205-12.
6. The-Whoqol-Group. Development of the WHOQOL: Rationale and Current Status. *International Journal of Mental Health.* 2015;23(3):24-56.
7. Muldoon MF, Barger SD, Flory JD, Manuck SB. What are quality of life measurements measuring? *BMJ.* 1998;316(7130):542-5.
8. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. *N Engl J Med.* 1996;334(13):835-40.
9. Burton JL. The logic of dermatological diagnosis. Dowling oration 1980. *Clin Exp Dermatol.* 1981;6(1):1-21.
10. Schaefer I, Rustenbach SJ, Zimmer L, Augustin M. Prevalence of skin diseases in a cohort of 48,665 employees in Germany. *Dermatology.* 2008;217(2):169-72.
11. Basra MK, Shahrukh M. Burden of skin diseases. *Expert Rev Pharmacoecon Outcomes Res.* 2009;9(3):271-83.
12. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol.* 1994;19(3):210-6.
13. Chren MM, Lasek RJ, Quinn LM, Mostow EN, Zyzanski SJ. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. *J Invest Dermatol.* 1996;107(5):707-13.
14. Dreno B, Finlay AY, Nocera T, Verriere F, Taieb C, Myon E. The Cardiff Acne Disability Index: cultural and linguistic validation in French. *Dermatology.* 2004;208(2):104-8.
15. Finlay AY, Kelly SE. Psoriasis--an index of disability. *Clin Exp Dermatol.* 1987;12(1):8-11.
16. Anderson RT, Rajagopalan R. Development and validation of a quality of life instrument for cutaneous diseases. *J Am Acad Dermatol.* 1997;37(1):41-50.
17. Polenghi MM, Molinari E, Gala C, Guzzi R, Garutti C, Finzi AF. Experience with psoriasis in a psychosomatic dermatology clinic. *Acta Derm Venereol Suppl (Stockh).* 1994;186:65-6.
18. Gupta MA, Gupta AK, Ellis CN, Voorhees JJ. Some psychosomatic aspects of psoriasis. *Adv Dermatol.* 1990;5:21-30; discussion 1.
19. Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. *Br J Dermatol.* 1995;132(2):236-44.
20. Wahl A. The impact of psoriasis on psychosocial life domains. A review. *Scand J Caring Sci.* 1997;11(4):243-9.
21. Hunecke P, Bosse K, Finckh H. [The disease course and psychosocial events in inpatient treatment of atopic eczema patients--a pilot study]. *Z Hautkr.* 1990;65(5):428-34.
22. Daud LR, Garralda ME, David TJ. Psychosocial adjustment in preschool children with atopic eczema. *Arch Dis Child.* 1993;69(6):670-6.
23. Fennessy M, Coupland S, Popay J, Naysmith K. The epidemiology and experience of atopic eczema during childhood: a discussion paper on the implications of current knowledge for health care, public health policy and research. *J Epidemiol Community Health.* 2000;54(8):581-9.

24. Mason PJ. Vitiligo: the psychosocial effects. *Medsurg Nurs*. 1997;6(4):216-8, 32.
25. Porter JR, Beuf AH, Lerner A, Nordlund J. Psychosocial effect of vitiligo: a comparison of vitiligo patients with "normal" control subjects, with psoriasis patients, and with patients with other pigmentary disorders. *J Am Acad Dermatol*. 1986;15(2 Pt 1):220-4.
26. Lasek RJ, Chren MM. Acne vulgaris and the quality of life of adult dermatology patients. *Arch Dermatol*. 1998;134(4):454-8.
27. Krowchuk DP, Stancin T, Keskinen R, Walker R, Bass J, Anglin TM. The psychosocial effects of acne on adolescents. *Pediatr Dermatol*. 1991;8(4):332-8.
28. Koo J. The psychosocial impact of acne: patients' perceptions. *J Am Acad Dermatol*. 1995;32(5 Pt 3):S26-30.
29. Cash TF. The psychosocial consequences of androgenetic alopecia: a review of the research literature. *Br J Dermatol*. 1999;141(3):398-405.
30. Gupta MA, Gupta AK, Watteel GN. Stress and alopecia areata: a psychodermatologic study. *Acta Derm Venereol*. 1997;77(4):296-8.
31. Van Der Donk J, Hunfeld JA, Passchier J, Knegt-Junk KJ, Nieboer C. Quality of life and maladjustment associated with hair loss in women with alopecia androgenetica. *Soc Sci Med*. 1994;38(1):159-63.
32. Augustin M, Zschocke I, Wiek K, Peschen M, Vanscheidt W. Psychosocial stress of patients with port wine stains and expectations of dye laser treatment. *Dermatology*. 1998;197(4):353-60.
33. Augustin M, Zschocke I, Wiek K, Bergmann A, Peschen M, Schopf E, et al. [Coping with illness and quality of life of patients with port-wine stains treated with laser therapy]. *Hautarzt*. 1998;49(9):714-8.
34. Miller AC, Pit-Ten Cate IM, Watson HS, Geronemus RG. Stress and family satisfaction in parents of children with facial port-wine stains. *Pediatr Dermatol*. 1999;16(3):190-7.
35. Hay RJ, Augustin M, Griffiths CE, Sterry W. Board of the International League of Dermatological Societies. The Grand Challenges Consultation Groups. The global challenge for skin health. *Br J Dermatol*. 2015;172(6):1469-72.
36. Hay RJ, Johns NE, Williams HC, Bolliger IW, Dellavalle RP, Margolis DJ, et al. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol*. 2014;134(6):1527-34.
37. Johnson MT, Roberts J. Skin conditions and related need for medical care among persons 1-74 years. United States, 1971-1974. *Vital Health Stat* 11. 1978(212):i-v, 1-72.
38. Rea JN, Newhouse ML, Halil T. Skin disease in Lambeth. A community study of prevalence and use of medical care. *Br J Prev Soc Med*. 1976;30(2):107-14.
39. Nijsten T, Stern RS. How epidemiology has contributed to a better understanding of skin disease. *J Invest Dermatol*. 2012;132(3 Pt 2):994-1002.
40. Lomholt G. Prevalence of Skin Diseases in a Population; a Census Study from the Faroe Islands. *Dan Med Bull*. 1964;11:1-7.
41. Schofield JK, Fleming D, Grindlay D, Williams H. Skin conditions are the commonest new reason people present to general practitioners in England and Wales. *Br J Dermatol*. 2011;165(5):1044-50.
42. Lowell BA, Froelich CW, Federman DG, Kirsner RS. Dermatology in primary care: Prevalence and patient disposition. *J Am Acad Dermatol*. 2001;45(2):250-5.
43. Ferguson JA, Goldacre MJ, Newton JN, Dawber RP. An epidemiological profile of in-patient workload in dermatology. *Clin Exp Dermatol*. 1992;17(6):407-12.
44. Williams HC. Beyond the year 2000: How may epidemiology influence future clinical practice in dermatology? *Clin Dermatol*. 2001;19(1):55-8.
45. Weinstock MA, Chren M-M. The Epidemiology and Burden of Skin Disease. *Fitzpatrick's Dermatology in General Medicine* 8Ed. Volume 1, Chapter 1. In: Goldsmith LA, Katz SI, Gilchrist BA, Paller AS, Leffell DJ, Klaus W, editors.: McGraw-Hill; 2012. p. 1-9.
46. Lamb JH, Lain ES, et al. Steroid hormones; metabolic studies in dermatomyositis, lupus erythematosus and polymorphic light-sensitive eruptions. *Arch Derm Syphilol*. 1948;57(5):785-801.



47. Savin JA. International mortality from bullous diseases since 1950. *Br J Dermatol*. 1976;94(2):179-89.
48. Razzaque Ahmed A, Moy R. Death in pemphigus. *J Am Acad Dermatol*. 1982;7(2):221-8.
49. Rzany B, Partscht K, Jung M, Kippes W, Mecking D, Baima B, et al. Risk factors for lethal outcome in patients with bullous pemphigoid: low serum albumin level, high dosage of glucocorticosteroids, and old age. *Arch Dermatol*. 2002;138(7):903-8.
50. Carson PJ, Hameed A, Ahmed AR. Influence of treatment on the clinical course of pemphigus vulgaris. *J Am Acad Dermatol*. 1996;34(4):645-52.
51. Duvert-Lehembre S, Joly P. [Autoimmune blistering diseases]. *Rev Med Interne*. 2014;35(3):166-73.
52. Anandan V, Jameela WA, Sowmiya R, Kumar MMS, Lavanya P. Rituximab: A Magic Bullet for Pemphigus. *J Clin Diagn Res*. 2017;11(4):WC01-WC6.
53. Loos AM, Liu S, Segel C, Ollendorf DA, Pearson SD, Linder JA. Comparative effectiveness of targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: A systematic review and network meta-analysis. *J Am Acad Dermatol*. 2018;79(1):135-44 e7.
54. Bernstein JA, Kavati A, Tharp MD, Ortiz B, MacDonald K, Denhaerynck K, et al. Effectiveness of omalizumab in adolescent and adult patients with chronic idiopathic/spontaneous urticaria: a systematic review of 'real-world' evidence. *Expert Opin Biol Ther*. 2018;18(4):425-48.
55. Gooderham MJ, Hong HC, Eshtiaghi P, Papp KA. Dupilumab: A review of its use in the treatment of atopic dermatitis. *J Am Acad Dermatol*. 2018;78(3S1):S28-S36.
56. Balieva F, Kupfer J, Lien L, Gieler U, Finlay AY, Tomas-Aragones L, et al. The burden of common skin diseases assessed with the EQ5D: a European multicentre study in 13 countries. *Br J Dermatol*. 2017;176(5):1170-8.
57. Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GBE, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *J Invest Dermatol*. 2015;135(4):984-91.
58. Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjaer SK. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978-2007: Rapid incidence increase among young Danish women. *Int J Cancer*. 2010;127(9):2190-8.
59. Simpson CR, Newton J, Hippisley-Cox J, Sheikh A. Trends in the epidemiology and prescribing of medication for eczema in England. *J R Soc Med*. 2009;102(3):108-17.
60. Apalla Z, Lallas A, Sotiriou E, Lazaridou E, Ioannides D. Epidemiological trends in skin cancer. *Dermatol Pract Concept*. 2017;7(2):1-6.
61. Dalgard F, Svensson A, Sundby J, Dalgard OS. Self-reported skin morbidity and mental health. A population survey among adults in a Norwegian city. *Br J Dermatol*. 2005;153(1):145-9.
62. Halvorsen JA, Dalgard F, Thoresen M, Bjertness E, Lien L. Itch and mental distress: a cross-sectional study among late adolescents. *Acta Derm Venereol*. 2009;89(1):39-44.
63. Niemeier V, Nippesen M, Kupfer J, Schill WB, Gieler U. Psychological factors associated with hand dermatoses: which subgroup needs additional psychological care? *Br J Dermatol*. 2002;146(6):1031-7.
64. Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. *Arch Dermatol*. 2010;146(8):891-5.
65. Sanna L, Stuart AL, Pasco JA, Jacka FN, Berk M, Maes M, et al. Atopic disorders and depression: findings from a large, population-based study. *J Affect Disord*. 2014;155(0):261-5.
66. WHO. Mental health: a state of well-being. 2015 [updated Dec 27, 2015. Available from: [http://www.who.int/features/factfiles/mental\\_health/en/](http://www.who.int/features/factfiles/mental_health/en/)].
67. Steel Z, Marnane C, Iranpour C, Chey T, Jackson JW, Patel V, et al. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *Int J Epidemiol*. 2014;43(2):476-93.

68. Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, et al. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. *Epidemiol Psychiatr Soc.* 2009;18(1):23-33.
69. Weissman MM, Bland RC, Canino GJ, Greenwald S, Hwu HG, Joyce PR, et al. Prevalence of suicide ideation and suicide attempts in nine countries. *Psychol Med.* 1999;29(1):9-17.
70. Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet.* 2016;388(10053):1545-602.
71. Bone AE, Gomes B, Etkind SN, Verne J, Murtagh FEM, Evans CJ, et al. What is the impact of population ageing on the future provision of end-of-life care? Population-based projections of place of death. *Palliat Med.* 2018;32(2):329-36.
72. Green JS, Magee JC, Steiner ARW, Teachman BA. When the "Golden Years" Turn Blue: Using the Healthy Aging Literature to Elucidate Anxious and Depressive Disorders in Older Adulthood. *Int J Behav Dev.* 2017;41(2):295-307.
73. Ginsburg IH. The psychosocial impact of skin disease. An overview. *Dermatol Clin.* 1996;14(3):473-84.
74. Linder D. Better data on psoriasis and psyche: but do they really reach the clinician? *J Eur Acad Dermatol Venereol.* 2017;31(5):760.
75. Michalek IM, Loring B, John SM. World Health Organization. Global report on psoriasis. In: Patient needs and goals related to treatment. p. 27-2016.
76. Fleming P, Bai JW, Pratt M, Sibbald C, Lynde C, Gulliver WP. The prevalence of anxiety in patients with psoriasis: a systematic review of observational studies and clinical trials. *J Eur Acad Dermatol Venereol.* 2017;31(5):798-807.
77. Moller AH, Erntoft S, Vinding GR, Jemec GB. A systematic literature review to compare quality of life in psoriasis with other chronic diseases using EQ-5D-derived utility values. *Patient Relat Outcome Meas.* 2015;6:167-77.
78. Puig L, Kirby B, Mallbris L, Strohal R. Psoriasis beyond the skin: a review of the literature on cardiometabolic and psychological co-morbidities of psoriasis. *Eur J Dermatol.* 2014;24(3):305-11.
79. Maksimovic N, Jankovic S, Marinkovic J, Sekulovic LK, Zivkovic Z, Spiric VT. Health-related quality of life in patients with atopic dermatitis. *J Dermatol.* 2012;39(1):42-7.
80. Dieris-Hirche J, Gieler U, Kupfer JP, Milch WE. [Suicidal ideation, anxiety and depression in adult patients with atopic dermatitis]. *Hautarzt.* 2009;60(8):641-6.
81. Wittkowski A, Richards HL, Griffiths CE, Main CJ. The impact of psychological and clinical factors on quality of life in individuals with atopic dermatitis. *J Psychosom Res.* 2004;57(2):195-200.
82. Torreló A, Ortiz J, Alomar A, Ros S, Pedrosa E, Cuervo J. Health-related quality of life, patient satisfaction, and adherence to treatment in patients with moderate or severe atopic dermatitis on maintenance therapy: the CONDA-SAT study. *Actas Dermosifiliogr.* 2013;104(5):409-17.
83. Chernyshov PV, Tomas-Aragones L, Manolache L, Marron SE, Salek MS, Poot F, et al. Quality of life measurement in atopic dermatitis. Position paper of the European Academy of Dermatology and Venereology (EADV) Task Force on quality of life. *J Eur Acad Dermatol Venereol.* 2017;31(4):576-93.
84. Saitta P, Keehan P, Yousif J, Way BV, Grekin S, Brancaccio R. An update on the presence of psychiatric comorbidities in acne patients, part 1: overview of prevalence. *Cutis.* 2011;88(1):33-40.
85. Saitta P, Keehan P, Yousif J, Way BV, Grekin S, Brancaccio R. An update on the presence of psychiatric comorbidities in acne patients, Part 2: Depression, anxiety, and suicide. *Cutis.* 2011;88(2):92-7.
86. Halvorsen JA, Stern RS, Dalgard F, Thoresen M, Bjertness E, Lien L. Suicidal ideation, mental health problems, and social impairment are increased in adolescents with acne: a population-based study. *J Invest Dermatol.* 2011;131(2):363-70.
87. Ghaderi R, Saadatjoo A, Ghaderi F. Evaluating of life quality in patients with acne vulgaris using generic and specific questionnaires. *Dermatol Res Pract.* 2013;2013:108624.

88. Warlich B, Fritz F, Osada N, Bruland P, Stumpf A, Schneider G, et al. Health-Related Quality of Life in Chronic Pruritus: An Analysis Related to Disease Etiology, Clinical Skin Conditions and Itch Intensity. *Dermatology*. 2015;231(3):253-9.
89. Halvorsen JA, Dalgard F, Thoresen M, Bjertness E, Lien L. Itch and pain in adolescents are associated with suicidal ideation: a population-based cross-sectional study. *Acta Derm Venereol*. 2012;92(5):543-6.
90. Ghajarzadeh M, Ghiasi M, Kheirkhah S. Associations between skin diseases and quality of life: a comparison of psoriasis, vitiligo, and alopecia areata. *Acta Med Iran*. 2012;50(7):511-5.
91. Ongenaes K, Dierckxsens L, Brochez L, van Geel N, Naeyaert JM. Quality of life and stigmatization profile in a cohort of vitiligo patients and effect of the use of camouflage. *Dermatology*. 2005;210(4):279-85.
92. Kruger C, Schallreuter KU. Cumulative life course impairment in vitiligo. *Curr Probl Dermatol*. 2013;44:102-17.
93. Riis PT, Vinding GR, Ring HC, Jemec GB. Disutility in Patients with Hidradenitis Suppurativa: A Cross-sectional Study Using EuroQoL-5D. *Acta Derm Venereol*. 2016;96(2):222-6.
94. Onderdijk AJ, van der Zee HH, Esmann S, Lophaven S, Dufour DN, Jemec GB, et al. Depression in patients with hidradenitis suppurativa. *J Eur Acad Dermatol Venereol*. 2013;27(4):473-8.
95. Matusiak L, Bieniek A, Szepietowski JC. Psychophysical aspects of hidradenitis suppurativa. *Acta Derm Venereol*. 2010;90(3):264-8.
96. Ibler KS, Jemec GB. Cumulative life course impairment in other chronic or recurrent dermatologic diseases. *Curr Probl Dermatol*. 2013;44:130-6.
97. Arbabi M, Ghodsi Z, Mahdanian A, Noormohammadi N, Shalileh K, Darvish F, et al. Mental health in patients with pemphigus: an issue worth consideration. *Indian J Dermatol*. 2011;56(5):541-5.
98. Ghodsi SZ, Chams-Davatchi C, Daneshpazhooh M, Valikhani M, Esmaili N. Quality of life and psychological status of patients with pemphigus vulgaris using Dermatology Life Quality Index and General Health Questionnaires. *J Dermatol*. 2012;39(2):141-4.
99. Iglesias CP, Birks Y, Nelson EA, Scanlon E, Cullum NA. Quality of life of people with venous leg ulcers: a comparison of the discriminative and responsive characteristics of two generic and a disease specific instruments. *Qual Life Res*. 2005;14(7):1705-18.
100. Bashir K, Dar NR, Rao SU. Depression in adult dermatology outpatients. *J Coll Physicians Surg Pak*. 2010;20(12):811-3.
101. Cotterill JA, Cunliffe WJ. Suicide in dermatological patients. *Br J Dermatol*. 1997;137(2):246-50.
102. Picardi A, Abeni D, Renzi C, Braga M, Melchi CF, Pasquini P. Treatment outcome and incidence of psychiatric disorders in dermatological out-patients. *J Eur Acad Dermatol Venereol*. 2003;17(2):155-9.
103. Picardi A, Abeni D, Melchi CF, Puddu P, Pasquini P. Psychiatric morbidity in dermatological outpatients: an issue to be recognized. *Br J Dermatol*. 2000;143(5):983-91.
104. Picardi A, Abeni D, Renzi C, Braga M, Puddu P, Pasquini P. Increased psychiatric morbidity in female outpatients with skin lesions on visible parts of the body. *Acta Derm Venereol*. 2001;81(6):410-4.
105. Picardi A, Lega I, Tarolla E. Suicide risk in skin disorders. *Clin Dermatol*. 2013;31(1):47-56.
106. Renzi C, Picardi A, Abeni D, Agostini E, Baliva G, Pasquini P, et al. Association of dissatisfaction with care and psychiatric morbidity with poor treatment compliance. *Arch Dermatol*. 2002;138(3):337-42.
107. DiMatteo MR, Lepper HS, Croghan TW. Depression Is a Risk Factor for Noncompliance With Medical Treatment. *Arch Intern Med*. 2000;160(14):2101-7.
108. Nock MK, Borges G, Bromet EJ, Cha CB, Kessler RC, Lee S. Suicide and suicidal behavior. *Epidemiol Rev*. 2008;30:133-54.
109. Harth W, Hillert A, Hermes B, Seikowski K, Niemeier V, Freudenmann RW. [Suicidal behavior in dermatology]. *Hautarzt*. 2008;59(4):289-96.
110. Gupta MA, Gupta AK. Psychiatric and psychological co-morbidity in patients with dermatologic disorders: epidemiology and management. *Am J Clin Dermatol*. 2003;4(12):833-42.

111. Halvorsen JA, Lien L, Dalgard F, Bjertness E, Stern RS. Suicidal ideation, mental health problems, and social function in adolescents with eczema: a population-based study. *J Invest Dermatol.* 2014;134(7):1847-54.
112. Yang Y, Brazier J, Longworth L. EQ-5D in skin conditions: an assessment of validity and responsiveness. *Eur J Health Econ.* 2015;16(9):927-39.
113. Pereira FR, Basra MK, Finlay AY, Salek MS. The role of the EQ-5D in the economic evaluation of dermatological conditions and therapies. *Dermatology.* 2012;225(1):45-53.
114. Shah M, Coates M. An assessment of the quality of life in older patients with skin disease. *Br J Dermatol.* 2006;154(1):150-3.
115. Mabuchi T, Yamaoka H, Kojima T, Ikoma N, Akasaka E, Ozawa A. Psoriasis affects patient's quality of life more seriously in female than in male in Japan. *Tokai J Exp Clin Med.* 2012;37(3):84-8.
116. Marmot MG. Status syndrome: a challenge to medicine. *JAMA.* 2006;295(11):1304-7.
117. Sampogna F. Life course impairment and quality of life over time. *Curr Probl Dermatol.* 2013;44:47-51.
118. Warren RB, Kleyn CE, Gulliver WP. Cumulative life course impairment in psoriasis: patient perception of disease-related impairment throughout the life course. *Br J Dermatol.* 2011;164 Suppl 1:1-14.
119. Bhatti ZU, Salek S, Finlay AY. Concept of major life-changing decisions in life course research. *Curr Probl Dermatol.* 2013;44:52-66.
120. Lotti T, Hercogova J, Prignano F. The concept of psoriatic disease: can cutaneous psoriasis any longer be separated by the systemic comorbidities? *Dermatol Ther.* 2010;23(2):119-22.
121. Shah K, Mellars L, Changolkar A, Feldman SR. Real-world burden of comorbidities in US patients with psoriasis. *J Am Acad Dermatol.* 2017;77(2):287-92 e4.
122. Naldi L, Mercuri SR. Epidemiology of comorbidities in psoriasis. *Dermatol Ther.* 2010;23(2):114-8.
123. Phan C, Sigal ML, Lhafa M, Barthelemy H, Maccari F, Esteve E, et al. Metabolic comorbidities and hypertension in psoriasis patients in France. Comparisons with French national databases. *Ann Dermatol Venereol.* 2016;143(4):264-74.
124. Abuabara K, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. *Br J Dermatol.* 2010;163(3):586-92.
125. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet.* 2007;370(9590):851-8.
126. Delestras S, Roustit M, Bedouch P, Minoves M, Dobremez V, Mazet R, et al. Comparison between two generic questionnaires to assess satisfaction with medication in chronic diseases. *PLoS One.* 2013;8(2):e56247.
127. Revicki DA, Willian MK, Menter A, Saurat JH, Harnam N, Kaul M. Relationship between clinical response to therapy and health-related quality of life outcomes in patients with moderate to severe plaque psoriasis. *Dermatology.* 2008;216(3):260-70.
128. Micali G, Lacarrubba F, Nasca MR, Schwartz RA. Topical pharmacotherapy for skin cancer: part I. Pharmacology. *J Am Acad Dermatol.* 2014;70(6):965 e1-12; quiz 77-8.
129. Micali G, Lacarrubba F, Nasca MR, Ferraro S, Schwartz RA. Topical pharmacotherapy for skin cancer: part II. Clinical applications. *J Am Acad Dermatol.* 2014;70(6):979 e1-12; quiz 9912.
130. Attili SK, Dawe R, Ibbotson S. A review of pain experienced during topical photodynamic therapy--our experience in Dundee. *Photodiagnosis Photodyn Ther.* 2011;8(1):53-7.
131. Piaserico S. Cumulative life course impairment in melanoma and nonmelanoma skin cancer. *Curr Probl Dermatol.* 2013;44:118-24.
132. Kohl E, Koller M, Zeman F, Szeimies RM, Philipp-Dormston WG, Prager W, et al. Daylight photodynamic therapy versus cryosurgery for the treatment and prophylaxis of actinic keratoses of the face - protocol of a multicenter, prospective, randomized, controlled, two-armed study. *BMC Dermatol.* 2017;17(1):12.

133. Halldin CB, Gonzalez H, Wennberg AM, Lepp M. Patients' experiences of pain and pain relief during photodynamic therapy on actinic keratoses: an interview study. *Acta Derm Venereol.* 2013;93(4):433-7.
134. Lee EH, Klassen AF, Nehal KS, Cano SJ, Waters J, Pusic AL. A systematic review of patient-reported outcome instruments of nonmelanoma skin cancer in the dermatologic population. *J Am Acad Dermatol.* 2013;69(2):e59-67.
135. Mehta D, Lim HW. Ultraviolet B Phototherapy for Psoriasis: Review of Practical Guidelines. *Am J Clin Dermatol.* 2016;17(2):125-33.
136. Alshiyab D, Chin MF, Edwards C, Anstey AV. An evaluation of the preferences of patients with psoriasis between systemic psoralen plus ultraviolet A and bath psoralen plus ultraviolet A. *Br J Dermatol.* 2015;172(5):1457-8.
137. Assarian Z, O'Brien TJ, Nixon R. Soak and smear: an effective treatment for eczematous dermatoses. *Australas J Dermatol.* 2015;56(3):215-7.
138. Shi VY, Foolad N, Ornelas JN, Hassoun LA, Monico G, Takeda N, et al. Comparing the effect of bleach and water baths on skin barrier function in atopic dermatitis: a split-body randomized controlled trial. *Br J Dermatol.* 2016;175(1):212-4.
139. Sbidian E, Chaimani A, Garcia-Doval I, Do G, Hua C, Mazaud C, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev.* 2017;12:CD011535.
140. Wolverton SE, Remlinger K. Suggested guidelines for patient monitoring: hepatic and hematologic toxicity attributable to systemic dermatologic drugs. *Dermatol Clin.* 2007;25(2):195-205, vi-ii.
141. Napolitano M, Abeni D, Didona B. Biologics for pityriasis rubra pilaris treatment: A review of the literature. *J Am Acad Dermatol.* 2018;79(2):353-9 e11.
142. Rodriguez-Caruncho C, Bielsa Marsol I. Antimalarials in dermatology: mechanism of action, indications, and side effects. *Actas Dermosifiliogr.* 2014;105(3):243-52.
143. Maza A, Montaudie H, Sbidian E, Gallini A, Aractingi S, Aubin F, et al. Oral cyclosporin in psoriasis: a systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. *J Eur Acad Dermatol Venereol.* 2011;25 Suppl 2:19-27.
144. Caplan A, Fett N, Rosenbach M, Werth VP, Micheletti RG. Prevention and management of glucocorticoid-induced side effects: A comprehensive review: Ocular, cardiovascular, muscular, and psychiatric side effects and issues unique to pediatric patients. *J Am Acad Dermatol.* 2017;76(2):201-7.
145. Ludot M, Mouchabac S, Ferreri F. Inter-relationships between isotretinoin treatment and psychiatric disorders: Depression, bipolar disorder, anxiety, psychosis and suicide risks. *World J Psychiatry.* 2015;5(2):222-7.
146. Amann PM, Merk HF, Baron JM. [Retinoids in dermatopharmacology]. *Hautarzt.* 2014;65(2):98-105.
147. Fallah Arani S, Neumann H, Hop WC, Thio HB. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled clinical trial. *Br J Dermatol.* 2011;164(4):855-61.
148. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res.* 1997;42(1):17-41.
149. EuroQolGroup. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16(3):199-208.
150. Finlay AY, Basra MKA, Piguet V, Salek MS. Dermatology life quality index (DLQI): a paradigm shift to patient-centered outcomes. *J Invest Dermatol.* 2012;132(10):2464-5.
151. Janssen B, Szende A. Population Norms for the EQ-5D. In: Szende A, Janssen B, Cabases J, editors. *Self-Reported Population Health: An International Perspective based on EQ-5D.* Dordrecht: Springer Netherlands; 2014. p. 19-30.

152. Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol*. 2008;159(5):997-1035.
153. Aickin M, Gensler H. Adjusting for multiple testing when reporting research results: the Bonferroni vs Holm methods. *Am J Public Health*. 1996;86(5):726-8.
154. Blackford S, Roberts D, Salek MS, Finlay A. Basal cell carcinomas cause little handicap. *Qual Life Res*. 1996;5(2):191-4.
155. Rhee J, Matthews BA, Neuburg M, Smith T, Burzynski M, Nattinger A. Skin cancer and quality of life: assessment with the Dermatology Life Quality Index. *Dermatol Surg*. 2004;30(4):525-9.
156. Helsedirektoratet. Prioriteringsveileder Hud - og veneriske sykdommer. 2015 [Available from: <https://helsedirektoratet.no/retningslinjer/hud-og-veneriske-sykdommer/seksjon?Tittel=tilstander-for-hud-og-9470> ].
157. Helsedirektoratet. Somatikk Årsrapport 2017 Tabell V3. Antall polikliniske kontakter ved somatiske sykehus fordelt på hoveddiagnosegruppe. 2017 [Available from: [https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/1435/Somatikk\\_%C3%85rsrapport\\_2017.pdf](https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/1435/Somatikk_%C3%85rsrapport_2017.pdf) ].
158. Eurostat. European Commission. Population (demography, migration and projections): Statistical office of the European Union; 2018 [updated 30.12.2018. Available from: <https://ec.europa.eu/eurostat/en/web/population-demography-migration-projections/statistics-illustrated> ].
159. Helsedirektoratet. Utviklingstrekkrapport Folkehelsearbeidet – veien til god helse for alle [Health Promotion – achieving good health for all]: RK Grafisk AS; 2010 [Available from: <https://helsedirektoratet.no/publikasjoner/utviklingstrekkrapport-2010-folkehelsearbeidet-veien-til-god-helse-for-alle> ].
160. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol*. 2013;133(2):377-85.
161. Jacinto C. Proceedings of the XIIth Congress on Dermatology. Amsterdam. Exerpta Medica Foundation. 1962;196.
162. Nock MK, Borges G, Bromet EJ, Alonso J, Angermeyer M, Beautrais A, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *Br J Psychiatry*. 2008;192(2):98-105.
163. Parisi R, Webb RT, Kleyn CE, Carr MJ, Kapur N, Griffiths CEM, et al. Psychiatric morbidity and suicidal behaviour in psoriasis: a primary care cohort study. *Br J Dermatol*. 2019;180(1):108-15.
164. Balieva F, Lien L, Kupfer J, Halvorsen JA, Dalgard F. Are Common Skin Diseases among Norwegian Dermatological Outpatients Associated with Psychological Problems Compared with Controls? An Observational Study. *Acta Derm Venereol*. 2016;96(2):227-31.
165. Schlenk EA, Erlen JA, Dunbar-Jacob J, McDowell J, Engberg S, Sereika SM, et al. Health-related quality of life in chronic disorders: a comparison across studies using the MOS SF-36. *Qual Life Res*. 1998;7(1):57-65.
166. Apfelbacher CJ, Ofenloch RF. The impact of skin conditions on generic health-related quality of life. *Br J Dermatol*. 2017;176(5):1109-10.
167. Hunter DJ, Riordan EA. The impact of arthritis on pain and quality of life: an Australian survey. *Int J Rheum Dis*. 2014;17(2):149-55.
168. De Smedt D, Clays E, Annemans L, Pardaens S, Kotseva K, De Bacquer D. Self-reported health status in coronary heart disease patients: a comparison with the general population. *Eur J Cardiovasc Nurs*. 2015;14(2):117-25.
169. Kimman ML, Dirksen CD, Lambin P, Boersma LJ. Responsiveness of the EQ-5D in breast cancer patients in their first year after treatment. *Health Qual Life Outcomes*. 2009;7:11.
170. Sundh J, Johansson G, Larsson K, Linden A, Lofdahl CG, Janson C, et al. Comorbidity and health-related quality of life in patients with severe chronic obstructive pulmonary disease attending Swedish secondary care units. *Int J Chron Obstruct Pulmon Dis*. 2015;10:173-83.

171. Matza LS, Boye KS, Yurgin N. Validation of two generic patient-reported outcome measures in patients with type 2 diabetes. *Health Qual Life Outcomes*. 2007;5:47.
172. Konig HH, Born A, Gunther O, Matschinger H, Heinrich S, Riedel-Heller SG, et al. Validity and responsiveness of the EQ-5D in assessing and valuing health status in patients with anxiety disorders. *Health Qual Life Outcomes*. 2010;8(1):47.
173. Holtzer-Goor KM, Schaafsma MR, Joosten P, Posthuma EF, Wittebol S, Huijgens PC, et al. Quality of life of patients with chronic lymphocytic leukaemia in the Netherlands: results of a longitudinal multicentre study. *Qual Life Res*. 2015;24(12):2895-906.
174. National Quality Measures C. "Global Satisfaction" scale of the Treatment Satisfaction Questionnaire for Medication (TSQM): the mean scale score for the "Global Satisfaction" items on the TSQM (version II). 2006.
175. Ruiz MA, Pardo A, Rejas J, Soto J, Villasante F, Aranguren JL. Development and validation of the "Treatment Satisfaction with Medicines Questionnaire" (SATMED-Q). *Value Health*. 2008;11(5):913-26.
176. Balieva FN, Finlay AY, Kupfer J, Aragones LT, Lien L, Gieler U, et al. The Role of Therapy in Impairing Quality of Life in Dermatological Patients: A Multinational Study. *Acta Derm Venereol*. 2018;98(6):563-9.
177. Ronnstad ATM, Halling-Overgaard AS, Hamann CR, Skov L, Egeberg A, Thyssen JP. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: A systematic review and meta-analysis. *J Am Acad Dermatol*. 2018;79(3):448-56 e30.
178. Cipriani F, Marzatico A, Ricci G. Autoimmune diseases involving skin and intestinal mucosa are more frequent in adolescents and young adults suffering from atopic dermatitis. *J Dermatol*. 2017;44(12):1341-8.
179. NAAF-legerådet. Nyttig å vite om eksem - NAAFs faktaark Norges Astma og Allergiforbundets faktablad om eksem [The Norwegian Asthma and Allergy Association: Useful facts on eczema]: NAAF; 2017 [updated 23.06.2017. Available from: <http://www.naaf.no/fokusomrader/eksem/fakta-om-eksem/>].
180. Matusiak L, Bieniek A, Szepietowski J. Psychophysical aspects of hidradenitis suppurativa. *Acta Derm Venereol*. 2010;90(3):264-8.
181. Penha MA, Farat JG, Miot HA, Barraviera SR. Quality of life index in autoimmune bullous dermatosis patients. *An Bras Dermatol*. 2015;90(2):190-4.
182. Sampogna F, Abeni D, Gieler U, Tomas-Aragones L, Lien L, Titeca G, et al. Impairment of Sexual Life in 3,485 Dermatological Outpatients From a Multicentre Study in 13 European Countries. *Acta Derm Venereol*. 2017;97(4):478-82.
183. Dalgard F, Gieler U, Holm JO, Bjertness E, Hauser S. Self-esteem and body satisfaction among late adolescents with acne: results from a population survey. *J Am Acad Dermatol*. 2008;59(5):746-51.
184. Orion E, Wolf R. Psychologic factors in the development of facial dermatoses. *Clin Dermatol*. 2014;32(6):763-6.
185. Moustafa F, Lewallen RS, Feldman SR. The psychological impact of rosacea and the influence of current management options. *J Am Acad Dermatol*. 2014;71(5):973-80.
186. Rhee JS, Matthews BA, Neuburg M, Smith TL, Burzynski M, Nattinger AB. Skin cancer and quality of life: assessment with the Dermatology Life Quality Index. *Dermatol Surg*. 2004;30(4 Pt 1):525-9.
187. Tennvall GR, Norlin JM, Malmberg I, Erlendsson AM, Haedersdal M. Health related quality of life in patients with actinic keratosis--an observational study of patients treated in dermatology specialist care in Denmark. *Health Qual Life Outcomes*. 2015;13:111.
188. Esmann S, Vinding GR, Christensen KB, Jemec GB. Assessing the influence of actinic keratosis on patients' quality of life: the AKQoL questionnaire. *Br J Dermatol*. 2013;168(2):277-83.
189. Lewis DM. WHO definition of health remains fit for purpose. *BMJ*. 2011;343:d5357.
190. Dalgard FJ, Svensson A, Gieler U, Tomas-Aragones L, Lien L, Poot F, et al. Dermatologists across Europe underestimate depression and anxiety: results from 3635 dermatological consultations. *Br J Dermatol*. 2017;179(2):464-70.

191. Feldman SR, Vrijens B, Gieler U, Piaserico S, Puig L, van de Kerkhof P. Treatment Adherence Intervention Studies in Dermatology and Guidance on How to Support Adherence. *Am J Clin Dermatol.* 2017;18(2):253-71.
192. Bewley A, Affleck A, Bundy C, Higgins E, McBride S. Psychodermatology services guidance: the report of the British Association of Dermatologists' Psychodermatology Working Party. *Br J Dermatol.* 2013;168(6):1149-50.



## 10. Published papers I-III

### Paper I

Acta Derm Venereol 2016; 96: 227–231

#### CLINICAL REPORT

## Are Common Skin Diseases among Norwegian Dermatological Outpatients Associated with Psychological Problems Compared with Controls? An Observational Study

Flora BALIEVA<sup>1</sup>, Lars LIEN<sup>2,3</sup>, Jörg KUPFER<sup>4</sup>, Jon Anders HALVORSEN<sup>5</sup> and Florence DALGARD<sup>2,5</sup>

<sup>1</sup>Department of Dermatology, Stavanger University Hospital, Stavanger; <sup>2</sup>Innlandet Hospital Trust, Brumundal; <sup>3</sup>Hedmark University College, Elverum, Norway; <sup>4</sup>Institute of Medical Psychology, Justus Liebig University, Giessen, Germany; and <sup>5</sup>Department of Dermatology, Oslo University Hospital and Institute of Clinical Medicine University of Oslo, Oslo, Norway

**Dermatological disease has been shown to be associated with psychological comorbidity. The aim of this observational study is to describe the distribution of skin disease and the prevalence of depression, anxiety and stress among Norwegian dermatological outpatients. Thirteen percent of outpatients had clinical anxiety compared with 3.7% of healthy controls, and 5.8% had clinical depression compared with 0.9% of controls. Adjusted odds ratio for clinical anxiety was 4.53 in patients compared with controls, and for clinical depression 6.25, which is much higher than previously described in a larger European study. Patients with tumours had less depression. Chronic inflammatory skin conditions had an especially high impact on patient's psychological wellbeing and should not be undervalued relative to, for instance, skin cancer in health strategies. These results argue strongly for including skin disease prevention and treatment in future health strategies. Key words: depression; anxiety; psychiatric comorbidity; distribution of dermatological disease; skin cancer; chronic skin diseases.**

Accepted Aug 4, 2015, Epub ahead of print Aug 10, 2015

Acta Derm Venereol 2016; 96: 227–231.

Flora Balieva, Department of Dermatology, Stavanger University Hospital, PB 8100, NO-4068 Stavanger, Norway. E-mail: florabalieva@gmail.com

Skin conditions are common in the community (1), but their distribution and association with psychological problems are not fully known. There are studies on the prevalence of the separate dermatological diseases, but few on the distribution of common skin diseases among dermatological outpatients (1, 2).

The most prevalent conditions in dermatology are the chronic inflammatory diseases. Psoriasis, eczemas, acne and hand eczema have a combined prevalence of approximately 25% in developed countries, followed by non-melanoma skin cancer and precancerous conditions (3).

From community studies in Norway (4, 5) and other countries (6–8), we know that individuals with itchy skin, eczema and psoriasis are twice as likely to be depressed as the general population (9). Our group has recently shown

that comorbid depression, anxiety and suicidal ideation are common in patients with skin conditions (10).

Depression, anxiety, stress and negative life events have been demonstrated to trigger chronic skin disease and can further worsen the skin condition through low compliance and lack of adherence to the treatment regimen (11, 12). Suicidal ideation is more common in patients with depression, which may be pre-existing, appear as a complication to the skin condition or be triggered by the dermatological medication (13–15). Overall mortality is relatively low for skin diseases, but further research is needed into suicide related to dermatological disease.

The aim of this study is to describe the distribution of skin diseases, specifically among Norwegian outpatients, and to study the association between depression, anxiety and stress for different skin conditions, especially benign tumours, cancer, precancerous lesions and chronic recurrent skin diseases compared with healthy controls.

#### METHODS

This is an observational case-controlled study. Patients were recruited from 2 Norwegian dermatological outpatient clinics: Stavanger University Hospital and Oslo University Hospital, Department of Dermatology during the period November 2011 to February 2013. This present study is part of a larger European multi-centre study (10).

The study protocol was approved by the Regional Committee for Medical Research Ethics in Norway in August 2011 and the study was performed in full accordance with the World Medical Association's Declaration of Helsinki.

Consecutive patients were invited to participate on random days at each centre. The patients were informed about the study by a research assistant just before their consultation and provided written consent. Inclusion criteria were: age over 18 years; able to read and write Norwegian; and not having a diagnosed severe mental disease. Each participant in the patient group was handed 5 questionnaires, which they returned to the consultant on entering the consultation room. The first part of the questionnaire included socio-demographic variables, such as sex, age, ethnicity, education, self-reported socio-economic status, economic difficulties during the last 5 years and stressful life events during the last 6 months.

Symptoms of depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS). This scale is widely used among patients in hospital settings (16); it includes



7 items for assessing anxiety and 7 items for depression with 4 possible answers each. For each dimension of anxiety and depression, a score of 0–7 is considered normal, 8–10 marginal, and 11–21 clinical depression or clinical anxiety.

A clinical examination was performed by the dermatologist for each patient and an objective assessment sheet was completed after the examination including the dermatological diagnosis. Physical co-morbidities were registered by the clinician if the patient had treatment for any of the following conditions: cardiovascular disease, chronic respiratory disease, diabetes mellitus, rheumatological disease, or other. In the control group, information on treated comorbidities was self-reported.

The control group was recruited on a voluntary basis at each centre from among employees of the service division of the hospital. They returned the completed questionnaires to the researcher. The controls were not examined clinically.

Patients in the current study presented a high variety of diagnoses, arranged into 27 groups. Skin diseases can be generalized, chronic and extensive, need long-term treatments and are perhaps incurable (eczemas, psoriasis, pruritic conditions, connective tissue disease, chronic ulcers, chronic infections and alopecias). Other conditions, however, are solitary, non-extensive, without periods of exacerbation in their course and mostly have radical short-term treatments (benign tumours, naevi, non-melanoma skin cancer (NMSC) and malignant melanoma), or need no treatment at all. For the purpose of regression analysis, we merged the skin conditions into 2 categories: the chronic, recurrent, inflammatory conditions and solitary lesions (tumours, cancers, melanoma and precancerous lesions) (17). In our outpatient population, only a few conditions could not be classified as belonging to either of the 2 groups.

It is important to note that patients with malignant melanoma and skin cancer in our clinics may be quite different from patients seen by dermatologists in other countries. Our patients would be consulted in outpatient clinics mainly for primary diagnostics, primary excisions, and, to a lesser degree, for extensive re-excisions or complex oncological treatments. Metastatic melanoma or metastatic skin cancer were not represented in our study. The data thus truly reflects how patients with solitary, uncomplicated lesions are affected compared with extensive chronic disease, specifically outpatients in Norway.

#### Statistical analysis

SPSS version 22 software was used. Continuous variables were analysed in terms of difference between the means, using *t*-test and analysis of variance (ANOVA). Dichotomous variables were analysed in terms of difference between proportions, using the  $\chi^2$  test. Bivariate and multivariate logistic regression models were tested to study the associations between variables, simultaneously controlling for potential confounding factors. For regression analyses, diagnoses were grouped into 2 large groups, as described above.

## RESULTS

The total number of participants was 795, with 577 patients and 218 controls (Table I). The participation rate of the patients was 91.3%. There were more females in both groups. The mean age of the patients was 50.1 years. The distribution according to socio-economic level was comparable in the 2 groups. Compared with controls, patients

had a slightly lower education and had more comorbidities regarding cardiological, rheumatological and other diseases, but not respiratory diseases or diabetes mellitus. More than one-third (35.3%) of the patients had at least one comorbidity vs. 15.6% of the controls.

The overall distribution of skin diseases is presented in Table II. The most common diagnosis overall, and for both sex, was psoriasis (21%), followed by NMSC (10.6%) and actinic keratosis (AK) (8.7%). The chronic inflammatory dermatoses accounted for nearly half of our patients' pathology (44.9%). Together with other itchy dermatoses and hand dermatoses the chronic inflammatory skin conditions accounted for more than half (55.6%) of the pathology in our dermatological population. When adding the rest of the chronic conditions to this group (e.g. autoimmune disorders, chronic infections, chronic ulcers, alopecias, hyperhidrosis and monogenetic diseases), we see that 69.3% of the conditions in our Norwegian outpatients are chronic, recurrent and mainly inflammatory diseases. The benign tumours, naevi and actinic keratosis accounted for 14.1% of the skin conditions, while skin cancer and malignant melanoma accounted for 14.2%.

Table SI<sup>1</sup> shows the percentages of depression, anxiety and stress. Significantly more patients were depressed (HADS  $\geq 8$ ) compared with controls (13.3% vs. 5.6%). Among those, significantly more had a clinical depression (5.8% of the patients vs. 0.9% of the controls) defined as HADS  $\geq 11$ . Anxiety as HADS  $\geq 8$  was registered

<sup>1</sup><http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2200>

Table I. Population characteristics of the Norwegian sample (n=795)

	Patients n=577	Controls n=218	p-value
Sex, n (%)			<0.05
Female	336 (58.3)	149 (68.7)	
Male	240 (41.7)	68 (31.3)	
Age years, mean (SD) [range]	50.1 (17.7) [18–92]	42.2 (12.5) [19–67]	<0.05
Females	49.2 (17.7)	43.6 (12.8)	<0.05
Males	51.2 (17.8)	39.2 (11.4)	<0.05
Socio-economic status, n (%)			
Low	69 (12.8)	29 (13.5)	
Middle	407 (75.5)	168 (78.1)	NS
High	63 (11.7)	18 (8.4)	
Educational level, n (%)			
Lower	82 (15.2)	16 (7.5)	<0.05
Higher or university	457 (84.7)	197 (92.5)	
Economic difficulties, n (%)			NS
Yes	64 (11.9)	19 (8.8)	
No	472 (88.1)	196 (91.2)	
Physical comorbidities, n (%)			
Yes	200 (35.3)	33 (15.6)	<0.05
Cardiovascular, n (%)	128 (23.3)	10 (4.7)	<0.05
Respiratory, n (%)	39 (7.2)	16 (7.6)	NS
Diabetes, n (%)	28 (5)	5 (2.4)	NS
Rheumatological, n (%)	68 (12.3)	9 (4.3)	<0.05
Other comorbidities, n (%)	141 (25.2)	18 (8.9)	<0.05

Missing values: patients 1–41; controls 1–6.



Table II. Distribution of skin diseases in a Norwegian sample of dermatological outpatients (n = 577). Distribution of skin disease by sex (n = 576)

Diagnosis <sup>a</sup>	All n = 577 n (%)	Male n = 240 n (%)	Female n = 336 n (%)
1 Psoriasis	121 (21)	65 (27.1)	56 (16.7)
2 Non-melanoma skin cancer	61 (10.6)	24 (10)	37 (11)
3 Actinic keratosis	50 (8.7)	16 (16.7)	34 (10.1)
4 Eczemas and contact allergy	39 (6.8)	13 (5.4)	25 (7.4)
5 Acne	31 (5.4)	13 (5.4)	18 (5.4)
6 Atopic dermatitis	31 (5.4)	13 (5.4)	18 (5.4)
7 Naevi and benign tumours	31 (5.4)	9 (3.8)	21 (6.3)
8 Rosacea, perioral dermatitis, facial erythema	27 (4.7)	5 (2.1)	22 (6.5)
9 Autoimmune diseases <sup>b</sup>	23 (4)	8 (3.3)	15 (4.5)
10 Malignant melanoma	21 (3.6)	8 (3.3)	13 (3.9)
11 Hand eczema	19 (3.3)	11 (4.6)	8 (2.4)
12 Pustulosis palmoplantaris	17 (2.9)	6 (2.5)	11 (3.3)
13 Infections (not venereal)	17 (2.9)	9 (3.8)	8 (2.4)
14 Urticaria	13 (2.3)	6 (2.5)	7 (2.1)
15 Pruritus and prurigo	13 (2.3)	7 (2.9)	6 (1.8)
16 Ulcus cruris, stasis dermatitis and chronic venous insufficiency	10 (1.3)	5 (2.1)	5 (1.5)
17 Genital, not venereal	9 (1.6)	6 (2.5)	3 (0.9)
18 Monogenetic conditions <sup>c</sup>	8 (1.4)	1 (0.4)	7 (2.1)
19 Other <sup>d</sup>	8 (1.4)	2 (0.8)	6 (1.8)
20 Vitiligo	6 (1)	3 (1.3)	3 (0.9)
21 Seborrhoeic dermatitis	5 (0.9)	5 (2.1)	0
22 Hidradenitis suppurativa	4 (0.7)	2 (0.8)	2 (0.6)
23 Sarcoidosis and granuloma	3 (0.5)	1 (0.4)	2 (0.6)
24 Lichen planus	3 (0.5)	1 (0.4)	2 (0.6)
25 Alopecias	3 (0.5)	0	3 (0.9)
26 Pyoderma gangrenosum	2 (0.3)	0	2 (0.6)
27 Hyperhidrosis	2 (0.3)	1 (0.4)	1 (0.3)

<sup>a</sup>Some of the monogenetic and some of the genital conditions were classified as "inflammatory", while other monogenetic and genital were classified as "solitary" for the purpose of regression analysis in order to give more correct values. Numbers in Table II will thus slightly vary from those given for the regression analysis. <sup>b</sup>Autoimmune disease: connective tissue disease, vasculitis, autoimmune blistering. <sup>c</sup>Monogenetic conditions: 2 Hailey-Hailey; 1 tuberous sclerosis; 1 microtia; 1 ichthyosis linearis circumflexa; 1 congenital malformation of face and neck; 1 vascular malformations (male); 1 Morbus Darier. <sup>d</sup>Other: 6 unspecified skin conditions, 1 cheilitis (female), 1 dermatitis artefacta (female).

in 27.1% of the patients and 14.8% of the controls, while 13% of the patients had clinical anxiety (HADS  $\geq 11$ ) vs. 3.7% of the controls. Experienced stress was 30.1% for patients vs. 20.1% for controls. Patients with tumours, cancer and precancerous lesions, however, did not show any significant difference in depression, anxiety and stress compared with the healthy controls. On the other hand, nearly a third of the patients with chronic recurrent dermatoses were anxious or experienced stress.

In Table III we present odds ratio (OR) with 95% confidence interval (95% CI) for Norwegian outpatients to have depression, anxiety and stress, all adjusted for age, sex, socio-economic status, education and physical comorbidity. Compared to the figures from a European study (10) patients had more than 3 times higher odds to be depressed than healthy controls (OR 3.12), nearly 3 times higher odds for anxiety (OR 2.87) and experienced twice as much stress (OR 2.1). The odds for clinical depression and clinical anxiety were even higher, showing that the odds for patients to be clinically depressed was 6.25, and to have clinical anxiety 4.53. Norwegian dermatological outpatients have odds 2 and 3 times higher for anxiety and depression compared with controls than do patients from other European countries.

Especially high odds for depression were seen among patients with chronic, inflammatory, recurrent skin conditions with OR as high as 7.3, confirming significant psychological suffering in this group. Patients with benign or malignant solitary lesions showed 2-fold higher odds to experience stress (OR 1.95) and anxiety (OR 2.18). The odds for depression were not higher than for controls (OR 1), and only just slightly higher for clinical depression (OR 1.38) (Table III).

## DISCUSSION

In this Norwegian study we found that the most common conditions among dermatological outpatients were psoriasis and NMSC, followed by AK. More than two-thirds of the patients had a chronic inflammatory skin condition. The distribution of skin diseases in our study shows prevalence rates similar to these described in other European countries (1). A European multicentre study found the same 2 diseases, psoriasis and NMSC, to be most common among dermatological outpatients in Europe (10). In accordance with the European study, our study showed clinical depression and clinical anxiety to be significantly higher for patients compared



Table III. Logistic regression analysis with odds ratio (OR) and 95% confidence interval (95% CI) for being an outpatient compared with healthy controls for depression, anxiety and stressful life events. Adjusted for age, sex, education, social status and comorbidities

Patients and diagnostic group	Any anxiety (HADS $\geq 8$ ) OR (95% CI)	Clinical anxiety (HADS $\geq 11$ ) OR (95% CI)	Any depression (HADS $\geq 8$ ) OR (95% CI)	Clinical depression (HADS $\geq 11$ ) OR (95% CI)	Stressful life events last 6 months OR (95% CI)
European study (9) ( $n=4,994$ )	1.76 (1.48; 2.09) Missing: 107	2.18 (1.68; 2.82) Missing: 107	2.40 (1.67; 3.47) Missing: 102	2.40 (1.67; 3.47) Missing: 102	
All patients Norway ( $n=577$ )	2.87 (1.79; 4.62) Missing: 92	4.53 (2.09; 9.81) Missing: 92	3.12 (1.57; 6.2) Missing: 91	6.25 (1.45; 26.96) Missing: 91	2.1 (1.39; 3.18) Missing: 87
Chronic, recurrent skin diseases Norway ( $n=400$ )	2.98 (1.83; 4.83) Missing: 61	4.59 (2.09; 10.04) Missing: 61	3.47 (1.74; 6.92) Missing: 60	7.31 (1.69; 31.57) Missing: 60	2.04 (1.34; 3.12) Missing: 55
All tumours, benign and malignant and precancerous Norway ( $n=168$ )	1.61 (0.81; 3.21) Missing: 30	2.18 (0.75; 6.31) Missing: 30	1 (0.34; 2.91) Missing: 30	1.38 (0.18; 10.63) Missing: 30	1.95 (1.08; 3.5) Missing: 31

Missing controls Norway: anxiety and depression: 8, stress: 11. Missing controls Europe: anxiety: 9, depression: 7.

with the healthy controls, with more than 4-fold higher odds for clinical anxiety and 6-fold higher odds for clinical depression, i.e. higher than for the European study (2.2. and 2.4, respectively). The extent of psychiatric comorbidity may vary between countries, or may reflect differences in patient populations. Further studies addressing this difference may be warranted.

Chronic, recurrent and more extensive skin conditions would be expected to affect a patient's wellbeing differently from solitary lesions (17–20). According to multiple studies (5, 7, 8, 14, 15, 21–27), patients with chronic inflammatory and pruritic generalized dermatoses score highest for depression and anxiety. Other studies show that patients with cancer, tumours and pre-cancerous lesions experience less psychiatric comorbidity from their skin disease (18, 19), surprisingly, even for serious conditions such as malignant melanoma, especially in the early stages (28, 29). In an older study by Cassileth et al. (20) patients with malignant melanoma were strikingly superior to other dermatology patients in terms of emotional well-being, perhaps because of the better support they receive. Shah & Coates (17) found that older patients with rashes suffered significantly more than did older patients with solitary lesions, even when the lesion was malignant. When grouping our patients in the same 2 categories we found a significant difference in psychiatric comorbidity compared to healthy control with each of these 2 categories.

Odds for depression in patients with chronic recurrent skin diseases were more than 3-fold higher compared with healthy controls, nearly as much for anxiety and 2-fold for stress. Odds for clinical depression and clinical anxiety in the same patient group showed even higher values. Especially high were odds for clinical depression, 7 times higher (OR 7.31) than for the healthy controls, confirming a significant impact on dermatological patients' mental health. This finding may be of significance as dermatological units increase their focus on prioritizing cancer, thus generating longer waiting times for patients with other skin conditions.

The group of patients with tumours, NMSC, malignant melanoma and pre-cancerous lesions in our study showed no difference in odds for depression. Few studies have evaluated psychiatric comorbidity in patients with benign tumours, NMSC and AK, but our study shows results in accordance with other existing studies (17). Less psychiatric comorbidity in patients with solitary lesions compared with our other patients might reflect the more radical, surgical treatment options for skin cancer, AK, malignant melanoma and other tumours. Patients who were newly referred might not have been aware of the seriousness of their diagnosis. Their answers to the questionnaires reflect the true extent of discomfort solitary lesions present, usually not being itchy, painful or generalized.

There was no difference in depression, anxiety and stress even when analysing separately for malignant and benign tumours (data not shown). Malignant melanoma may be regarded as a more distinct condition because of its serious prognosis, but besides higher experienced stress, patients with malignant melanoma did not show more depression. We therefore included them in the group of solitary lesions, precisely to show that solitary lesions with more radical treatment and shorter course, even when serious, have a lower impact on a patient's mental state, at least in the initial stages.

#### Study limitations and strengths<sup>2</sup>

In conclusion, the most common skin conditions among dermatological outpatients in Norway are psoriasis and NMSC. Overall, dermatological patients have significantly more psychiatric comorbidities, but this is not the case for patients with benign tumours, skin cancer and precancerous lesions. Chronic skin conditions have a high impact on patients' psychological wellbeing and should not be undervalued relative to skin cancer in health strategies and waiting lists. These findings have implications for care management and prioritizing dermatological patients.



## ACKNOWLEDGEMENTS

Uwe Gieler, Clinic of Dermatology, Justus Liebig University, Giessen, Germany and Thomas Tervowitz, Department of Dermatology, Stavanger University Hospital, Norway.

The authors declare no conflicts of interest.

## REFERENCES

- Williams H, Svensson A, Diepgen T, Naldi L, Coenraads PJ, Elsner P, et al. Epidemiology of skin diseases in Europe. *Eur J Dermatol* 2006; 16: 212–218.
- Nijsten T, Stern RS. How epidemiology has contributed to a better understanding of skin disease. *J Invest Dermatol* 2012; 132: 994–1002.
- Karimkhani C, Boyers LN, Prescott L, Welch V, Delamere FM, Nasser M, et al. Global burden of skin disease as reflected in cochrane database of systematic reviews. *JAMA Dermatol* 2014; 150: 945–951.
- Dalgard F, Svensson A, Sundby J, Dalgard OS. Self-reported skin morbidity and mental health. A population survey among adults in a Norwegian city. *Br J Dermatol* 2005; 153: 145–149.
- Halvorsen JA, Dalgard F, Thoresen M, Bjertness E, Lien L. Itch and mental distress: a cross-sectional study among late adolescents. *Acta Derm Venereol* 2009; 89: 39–44.
- Niemeier V, Nippesen M, Kupfer J, Schill WB, Gieler U. Psychological factors associated with hand dermatoses: which subgroup needs additional psychological care? *Br J Dermatol* 2002; 146: 1031–1037.
- Kurd S, Troxel A, Crits Christoph P, Gelfand J. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. *Arch Dermatol* 2010; 146: 891–895.
- Sanna L, Stuart AL, Pasco JA, Jacka FN, Berk M, Maes M, et al. Atopic disorders and depression: Findings from a large, population-based study. *J Affect Disord* 2014; 155: 261–265.
- Halvorsen JA, Stern RS, Dalgard F, Thoresen M, Bjertness E, Lien L. Suicidal ideation, mental health problems, and social impairment are increased in adolescents with acne: a population-based study. *J Invest Dermatol* 2011; 131: 363–370.
- Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GB, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *J Inv Dermatol* 2015; 135: 984–991.
- Renzi C, Picardi A, Abeni D, Agostini E, Baliva G, Pasquini P, et al. Association of dissatisfaction with care and psychiatric morbidity with poor treatment compliance. *Arch Dermatol* 2002; 138: 337–342.
- DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med* 2000; 160: 2101–2107.
- Harth W, Hillert A, Hermes B, Seikowski K, Niemeier V, Freudenmann RW. Suizidalität in der Dermatologie. *Hautarzt* 2008; 59: 289–296.
- Gupta M, Gupta A. Psychiatric and psychological co-morbidity in patients with dermatologic disorders: epidemiology and management. *Am J Clin Dermatol* 2003; 4: 833–842.
- Saitta P, Keehan P, Yousif J, Way B, Grekin S, Brancaccio R. An update on the presence of psychiatric comorbidities in acne patients, Part 2: Depression, anxiety, and suicide. *Cutis* 2011; 88: 92–97.
- Herrmann C. International experiences with the Hospital Anxiety and Depression Scale – a review of validation data and clinical results. *J Psychosom Res* 1997; 42: 17–41.
- Shah M, Coates M. An assessment of the quality of life in older patients with skin disease. *Br J Dermatol* 2006; 154: 150–153.
- Blackford S, Roberts D, Salek MS, Finlay A. Basal cell carcinomas cause little handicap. *Qual Life Res* 1996; 5: 191–194.
- Rhee J, Matthews BA, Neuburg M, Smith T, Burzynski M, Nattinger A. Skin cancer and quality of life: assessment with the Dermatology Life Quality Index. *Dermatol Surg* 2004; 30: 525–529.
- Cassileth BR, Lusk EJ, Tenaglia AN. A psychological comparison of patients with malignant melanoma and other dermatologic disorders. *J Am Acad Dermatol* 1982; 7: 742–746.
- Picardi A, Abeni D, Melchi CF, Puddu P, Pasquini P. Psychiatric morbidity in dermatological outpatients: an issue to be recognized. *Br J Dermatol* 2000; 143: 983–991.
- Picardi A, Lega I, Tarolla E. Suicide risk in skin disorders. *Clin Dermatol* 2013; 31: 47–56.
- Zachariae R, Zachariae C, Ibsen HHW, Mortensen J, Wulf H. Psychological symptoms and quality of life of dermatology outpatients and hospitalized dermatology patients. *Acta Derm Venereol* 2004; 84: 205–212.
- Bashir K, Dar NR, Rao SU. Depression in adult dermatology outpatients. *J Coll Physicians Surg Pak* 2010; 20: 811–813.
- Dieris-Hirche J, Gieler U, Kupfer JP, Milch WE. Suizidge-danken, Angst und Depression bei erwachsenen Neuroder-mitikern. *Hautarzt* 2009; 60: 641–646.
- Halvorsen JA, Lien L, Dalgard F, Bjertness E, Stern RS. Suicidal ideation, mental health problems, and social function in adolescents with eczema: a population-based study. *J Invest Dermatol* 2014; 134: 1847–1854.
- Halvorsen JA, Dalgard F, Thoresen M, Bjertness E, Lien L. Itch and pain in adolescents are associated with suicidal ideation: a population-based cross-sectional study. *Acta Derm Venereol* 2012; 92: 543–546.
- Beesley VL, Smithers BM, Khosrotehrani K, Khatun M, O'Rourke P, Hughes MC, et al. Supportive care needs, anxiety, depression and quality of life amongst newly diagnosed patients with localised invasive cutaneous melanoma in Queensland, Australia. *Psychooncol* 2015; 24: 763–770.
- Vurnek Zivkovic M, Buljan M, Blajic I, Situm M. Psychological status and illness perceptions in patients with melanoma. *Coll Antropol* 2008; 32 Suppl 2: 75–78.

<sup>2</sup>Limitations: The patient and control groups were not case-matched. Still, there was no significant difference in socio-economic status and economic difficulties between the 2 groups. The staff at the hospital was over-represented by females and younger individuals. Employed personnel would be expected to be healthier than patients, but we intentionally aimed to have a control group, which would best match the World Health Organization (WHO)'s definition of health (30). The results for psychiatric comorbidity in the group with solitary lesions are precisely valid for Norwegian dermatological outpatients, since we would consult patients with malignant melanoma or skin cancer only in the initial phase of their disease. We cannot conclude that those patients will not develop more significant psychiatric symptoms during the course of their disease; a depression may need time to evolve. The results may be less applicable to other countries, but do pose interesting questions that may warrant further studies. Strengths: There are few recent studies on the distribution of skin diseases in dermatological outpatients. We present here data on a patient population from 2 large dermatological clinics in Norway. This is the first study on depression, anxiety and stress among outpatients with common skin conditions compared with controls.

We further evaluated psychiatric comorbidity according to the 2 main diagnostic categories; chronic, recurrent skin conditions and solitary lesions, showing the large psychological impact chronic skin conditions have. There are few other studies comparing these 2 very different categories. The significant higher psychiatric comorbidity in the former group may open for better prioritizing, support and resource allocation for all dermatological patients, not only those with a malignant disease.

We have the opportunity to compare our results with the European study as a whole. Depression and anxiety are higher for dermatological outpatients in Norway, warranting further studies on depression and anxiety in Norwegian dermatological outpatients. We encourage other European countries to evaluate these issues, as numbers may vary widely from country to country.

Table SI. Distribution of depression, anxiety and stressful life events among dermatological patients

Diagnosis (if valid $n > 15$ )	Any anxiety (HADS $\geq 8$ ) $n$ (%)	Clinical anxiety (HADS $\geq 11$ ) $n$ (%)	Any depression (HADS $\geq 8$ ) $n$ (%)	Clinical depression (HADS $\geq 11$ ) $n$ (%)	Stressful events last 6 months $n$ (%)
Healthy controls ( $n=218$ )	32/216 (14.8)	8/216 (3.7)	12/216 (5.6)	2/216 (0.9)	44/215 (20.5)
All patients ( $n=577$ )	144/532 (27.1)*	69/532 (13)*	71/532 (13.3)*	31/532 (5.8)*	162/538 (30.1)*
Chronic recurrent skin diseases ( $n=400$ )	111/372 (29.8)*	54/372 (14.5)*	61/372 (16.4)*	28/372 (7.5)*	121/379 (31.9)*
Tumours, benign, malignant and precancerous ( $n=168$ )	26/151 (17.2)	10/151 (6.6)	8/151 (5.3)	2/151 (1.3)	36/151 (23.8)
Psoriasis ( $n=121$ )	44/113 (38.9)*	25/113 (22.1)*	25/112 (22.3)*	12/112 (10.7)*	40/116 (34.5)*
Urticaria, pruritus, prurigo ( $n=26$ )	8/24 (33.3)**	6/24 (25)*	7/24 (29.2)*	2/24 (8.3)	10/25 (40)**
Autoimmune disease <sup>a</sup> ( $n=26$ )	8/25 (32)**	3/25 (12)	6/25 (24)**	2/25 (8)	9/25 (36)
Atopic dermatitis ( $n=29$ )	8/28 (28.6)	2/28 (7.1)	3/28 (10.7)	3/28 (10.7)*	11/29 (37.9)**
Acne, rosacea, other facial ( $n=64$ )	16/62 (25.8)**	5/62 (8.1)	5/62 (8.1)	2/62 (3.2)	14/61 (23)
Pustulosis palmoplantaris ( $n=17$ )	4/16 (25)	2/16 (12.5)	2/15 (13.3)	1/15 (6.7)	3/15 (20)
Malignant melanoma ( $n=21$ )	5/21 (23.8)	4/21 (19)**	2/21 (9.5)	0/21 (0)	10/20 (50)*
Eczemas and contact allergy ( $n=39$ )	8/35 (22.9)	4/35 (11.4)	6/37 (16.2)**	3/37 (8.1)	10/38 (26.3)
Actinic keratosis ( $n=50$ )	10/45 (22.2)	4/45 (8.9)	3/45 (6.7)	0/45 (0)	7/45 (15.6)
Hand eczema ( $n=19$ )	4/18 (22.2)	1/18 (5.6)	2/18 (11.1)	1/18 (5.6)	6/18 (33.3)
Non-melanoma skin cancer ( $n=61$ )	9/55 (16.4)	1/55 (1.8)	2/55 (3.6)	1/55 (1.8)	12/55 (21.8)
Naevi and benign tumours ( $n=29$ )	1/24 (4.2)	1/24 (4.2)	1/24 (4.2)	1/24 (4.2)	5/25 (20)

\* $p < 0.01$ , significant at 1% significance level compared with healthy controls using  $\chi^2$  test. \*\* $p < 0.05$ , significant at 5% significance level compared with healthy controls using  $\chi^2$  test.

<sup>a</sup>Autoimmune disease: connective tissue disease, vasculitis, autoimmune blistering.





## The Role of Therapy in Impairing Quality of Life in Dermatological Patients: A Multinational Study

Flora N. BALIEVA<sup>1</sup>, Andrew Y. FINLAY<sup>2</sup>, Jörg KUPFER<sup>3</sup>, Lucia TOMAS ARAGONES<sup>4</sup>, Lars LIEN<sup>5,6</sup>, Uwe GIELER<sup>7</sup>, Françoise POOT<sup>8</sup>, Gregor B. E. JEMEC<sup>9</sup>, Laurent MISERY<sup>10</sup>, Lajos KEMENY<sup>11</sup>, Francesca SAMPOGNA<sup>12</sup>, Henriët VAN MIDDENDORP<sup>13</sup>, Jon Anders HALVORSEN<sup>14,15</sup>, Thomas TERNOWITZ<sup>1</sup>, Jacek C. SZEPIETOWSKI<sup>16</sup>, Nikolay POTEKAEV<sup>17,18</sup>, Servando E. MARRON<sup>19</sup>, Ilknur K. ALTUNAY<sup>20</sup>, Sam S. SALEK<sup>21,22</sup> and Florence J. DALGARD<sup>5,23</sup>

*Departments of Dermatology:* <sup>1</sup>Stavanger University Hospital, Stavanger, Norway, <sup>2</sup>Justus Liebig University, Giessen, Germany, <sup>3</sup>ULB-Erasme Hospital, Brussels, Belgium, <sup>4</sup>Zealand University Hospital, Roskilde, Denmark, <sup>5</sup>University Hospital of Brest, Brest, France, <sup>6</sup>Oslo University Hospital, Rikshospitalet, <sup>7</sup>University of Oslo, Oslo, Norway, <sup>8</sup>Russian National Research Medical University Pirogov, Moscow, Russia, <sup>9</sup>Royo Villanova Hospital, Aragon Health Sciences Institute, Zaragoza, Spain and <sup>10</sup>Sisli Etfal Teaching and Research Hospital, Istanbul, Turkey, <sup>11</sup>Department of Dermatology and Wound Healing, Cardiff University School of Medicine, Cardiff, UK, <sup>12</sup>Institute of Medical Psychology, Justus Liebig University, Giessen, Germany, <sup>13</sup>Department of Psychology, University of Zaragoza, Aragon Health Sciences Institute, Zaragoza, Spain, <sup>14</sup>National Norwegian advisory board for concurrent addiction and mental health problems, Innlandet Hospital Trust, Brumunddal, <sup>15</sup>Department of Public Health, Innlandet University College, Elverum, Norway, <sup>16</sup>Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary, <sup>17</sup>Clinical Epidemiology Unit, Istituto Dermopatico dell'Immacolata, Rome, Italy, <sup>18</sup>Health, Medical and Neuropsychology Unit, Faculty of Social and Behavioural Sciences, Leiden University, Leiden, The Netherlands, <sup>19</sup>Department of Dermatology, Venereology and Allergology, Wrocław Medical University, Wrocław, Poland, <sup>20</sup>Moscow Scientific and Practical Centre of Dermatovenereology and Cosmetology, <sup>21</sup>School of Life & Medical Sciences, University of Hertfordshire, Hatfield, <sup>22</sup>Institute for Medicines Development Cardiff, UK, and <sup>23</sup>Department of Dermatology and Venereology, Skåne University Hospital, Lund University, Malmö, Sweden

**Skin disease and its therapy affect health-related quality of life (HRQoL). The aim of this study was to measure the burden caused by dermatological therapy in 3,846 patients from 13 European countries. Adult outpatients completed questionnaires, including the Dermatology Life Quality Index (DLQI), which has a therapy impact question. Therapy issues were reported by a majority of patients with atopic dermatitis (63.4%), psoriasis (60.7%), prurigo (54.4%), hidradenitis suppurativa (54.3%) and blistering conditions (53%). The largest reduction in HRQoL attributable to therapy, as a percentage of total DLQI, adjusted for confounders, was seen in blistering conditions (10.7%), allergic/drug reactions (10.2%), psoriasis (9.9%), vasculitis/immunological ulcers (8.8%), atopic dermatitis (8.7%), and venous leg ulcers (8.5%). In skin cancer, although it had less impact on HRQoL, the reduction due to therapy was 6.8%. Treatment for skin disease contributes considerably to reducing HRQoL: the burden of dermatological treatment should be considered when planning therapy and designing new dermatological therapies.**

**Key words:** quality of life; HRQoL; DLQI; dermatological therapy; burden of skin disease; therapy burden.

Accepted Mar 1, 2018; Epub ahead of print Mar 2, 2018

Acta Derm Venereol 2018; 98; 563–569.

**Corr:** Flora Balieva, Department of Dermatology, Stavanger University Hospital, Pb. 8100, NO-4068 Stavanger, Norway. E-mail: florabalieva@gmail.com

Topical and other dermatological therapies can add to the burden of skin disease, as they may be time-consuming, messy, intervene with clothing choice, and impact on health-related quality of life (HRQoL) in ways that are unique to the skin (1, 2). This contrasts with the relatively low burden of oral therapy in other diseases (3) where, for most, oral medication becomes routine.

### SIGNIFICANCE

Treatments for skin diseases differ from those used for other diseases. They may be messy, time-consuming, affect clothing or be painful. Some diseases are burdensome (psoriasis, eczemas, itching) and their therapy causes extra impairment, which should be appreciated. Others showed little impact from therapy, although the diseases themselves were serious (hidradenitis suppurativa, psychodermatological conditions, acne). Adequate therapy should be sought to alleviate symptoms without adding further impairment. Lastly, some skin diseases stood out as more burdened by therapy than by the disease itself (cancer, allergies, scars). For these patients, choice of therapy is most important for providing optimal help.

However, even systemic dermatological medications, such as cytotoxic drugs, corticosteroids, retinoids, intravenous or injected biologics, may have an associated burden. Topical and injection routes of drug administration have the lowest levels of convenience and global satisfaction (4).

Impairment of HRQoL due to dermatological therapy is little explored, even though the burden caused by skin disease treatment is very important, both to patients and because it contributes to poor adherence (5).

Most generic measures of HRQoL were developed without including skin diseases. It is therefore unsurprising that they miss the burden experienced by dermatological patients. In measures designed for use across skin diseases, only the Dermatology Life Quality Index (DLQI) includes a question concerning the impact of treatment on everyday life (6).

The aim of this study was to measure how therapy for skin disease contributes to reducing HRQoL in outpatients across Europe.



## METHODS

Data were obtained from a cross-sectional multicentre study on patients recruited from 15 dermatological outpatient clinics in 13 European countries; details have been previously reported (7). The study was approved by the Regional Committee for Medical Research Ethics in Norway. Separate ethical approvals were obtained where necessary. The study was conducted in accordance with the Declaration of Helsinki.

Consecutive patients, age over 18 years, understanding the local language and not having severe mental disease were invited to participate on random days, giving written consent. Participants completed questionnaires on sociodemographics (sex, age, ethnicity, education, marital and socioeconomic status), the DLQI and other questionnaires (7–11).

Patients were examined by the dermatologist, who recorded comorbidities: diabetes mellitus, cardiovascular, chronic respiratory, rheumatological or other disease. Workers from each hospital's service division were invited to participate as controls.

The DLQI, a 10-item questionnaire, was used to assess impairment in HRQoL. Question 10, which concerns the impact of therapy, was used to assess how treatment impaired HRQoL: "How much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?" with possible answers "very much" (scored 3), "a lot" (2), "a little" (1) or "not at all/not relevant" (0).

The DLQI was not designed for use by healthy individuals. Patients with naevi ( $n=192$ ) served as "healthy" controls, since there were no significant differences between the patients with naevi and healthy controls (7, 8).

### Statistical analysis

Data from all centres were merged. Diagnoses were organized into 35 disease groups (8, 12).

SPSS 24 software was used for statistical analysis. Frequencies and means for patient and control characteristics were calculated.

The answers to DLQI question 10 were dichotomized into "no impairment" (0) or "impaired" (1, 2 or 3) when calculating frequencies of positive answers.

For each diagnosis the mean scores for question 10 and total DLQI were calculated. Their relationship was calculated as  $(\text{mean score Question 10} \times 100) / \text{mean total DLQI score}$ , denoted as Q10%.

Comparisons between patients with naevi and healthy controls were performed with the *t*-test for continuous variables (age) and the  $\chi^2$  test for categorical variables (sex, marital status, socioeconomic status, comorbidities, economic difficulties, stress, depression and anxiety (7)) and linear (EQ-VAS) and logistic regressions (EQ5D) for comparing HRQoL outcomes (8).

Linear regression was performed to analyse Q10% for each diagnosis, adjusting for age, sex, socioeconomic status and comorbidity with "naevi" as controls.

A search for publications on therapy issues in dermatology using DLQI or other instruments was performed using MEDLINE, EMBASE and Cochrane Library following standard search strategies. Search terms and medical descriptors (MeSH) included skin disease, dermatosis, dermatoses, quality of life, DLQI, skin therapy, topical therapy, photodynamic therapy, cryotherapy, cryosurgery, cryoablation, laser, phototherapy, photochemotherapy, ultraviolet B (UVB), UVA, UVA1, psoralen plus UVA (PUVA), retinoid plus PUVA (RePUVA), topical drug administration, parenteral administration, biological therapy, tumour necrosis factor (TNF)- $\alpha$  inhibitors, infusion therapy, skin cancer therapy, and surgical dermatological therapy.

## RESULTS

### Participants

There were 4,010 participants and 1,359 healthy controls. Comparative details have been published previously (7–11) and are given briefly in Table S1<sup>†</sup>.

### Dermatology Life Quality Index data

There were 3,846 (96%) valid answers to DLQI, 5.2% of which had a DLQI >20 (extremely large effect on HRQoL). One-fifth (20.3%) experienced at least a very large effect (DLQI >11) and 44.9% had a DLQI >6, mea-

<sup>†</sup><https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-2918>

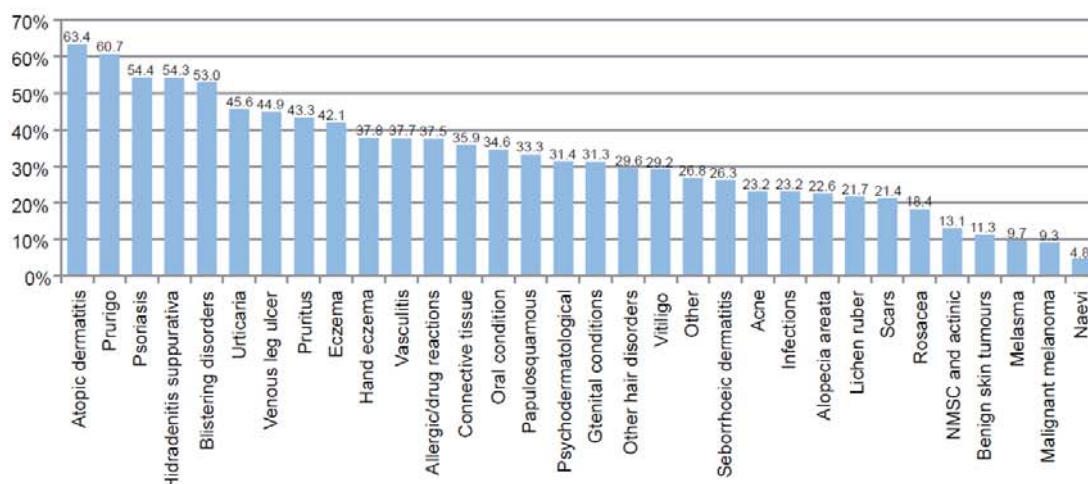
**Table I. Frequencies of Dermatology Life Quality Index (DLQI) scores ( $n=3,846$ )**

DLQI score band descriptors (ref. 6, 13)	Valid %	Number	Cumulative % DLQI score									
Extremely large (21–30)	5.2	200	5.2% >20									
Very large (11–20)	20.3	782	25.5% >11									
Moderate (6–10)	19.4	745	44.9% >6									
Small (2–5)	26.6	1,023	71.5% >2									
No (0–1)	28.5	1,096										
Total		3,846										
Mean DLQI (SD). <i>n</i> =Valid number of patients												
Sex	Male: 6.4 (6.7) <i>n</i> =1,686	Female: 7 (6.8) <i>n</i> =2,168										
Age groups	18–35 years: 7.34 (6.8) <i>n</i> =1,247	36–65 years: 6.94 (7) <i>n</i> =1,880	>66 years: 5.06 (5.9) <i>n</i> =652									
Socioeconomic status	Low: 8.22 (7.2) <i>n</i> =720	Middle: 6.44 (6.6) <i>n</i> =2,844	High: 5.88 (5.9) <i>n</i> =327									
Comorbidity	None: 6.74 (6.7) <i>N</i> =2,573	Any: 6.89 (6.9) <i>N</i> =1,033										
BE	DK	FR	GER	HU	IT <sup>a</sup>	NL	NO <sup>b</sup>	PL	RUS	ES	TR	UK
3.38 (3.9) <i>n</i> =250	5.79 (6.7) <i>n</i> =265	4.58 (5.3) <i>n</i> =126	7.14 (7.4) <i>n</i> =290	7.26 (7.3) <i>n</i> =261	8.01 (6.7) <i>n</i> =527	5.09 (5.7) <i>n</i> =235	6.99 (6.7) <i>n</i> =534	10.89 (7.8) <i>n</i> =275	10.38 (7.0) <i>n</i> =273	2.26 (3.6) <i>n</i> =274	7.35 (5.6) <i>n</i> =270	5.23 (6.8) <i>n</i> =213

<sup>a</sup>Padua and Rome. <sup>b</sup>Oslo and Stavanger.

BE: Belgium; DK: Denmark; FR: France; GER: Germany; HU: Hungary; IT: Italy; NL: The Netherlands; NO: Norway; PL: Poland; RUS: Russia; ES: Spain; TR: Turkey; UK: United Kingdom.





**Fig. 1.** The percentage of positive answers to having therapy issues (Question 10 of the DLQI) for each diagnosis. Diagnoses represented by fewer than 20 valid answers (hyperhidrosis (12), nail diseases (17) and granuloma annulare (13) excluded). NMSC: non-melanoma skin cancer.

ning at least a moderate effect on HRQoL (13) caused by their skin disease (Table I).

The total patient population ( $n=3,846$ ) had a mean  $\pm$  standard deviation (SD) DLQI score of  $6.7 \pm 6.8$ , meaning moderately impaired HRQoL. Except for naevi, no skin disease had a mean score  $<2$ , so all had at least a small effect on patients' HRQoL. Twenty-seven of the 35 (77%) skin conditions had mean DLQI scores  $>5$ , indicating at least a moderate effect on a patient's life (Table SII<sup>†</sup>).

Higher DLQI values, indicating higher impairment, were seen in females, younger age groups, patients with comorbidities and those with lower socioeconomic status.

#### Therapy impact data (DLQI question 10)

Question 10 in the DLQI addresses therapy-related issues. The numbers of patients answering with "a little", "a lot" or "very much", i.e. other than "no impact/not relevant", are given in Fig. 1. More than half of the patients with atopic dermatitis (AD) (63.4%), prurigo (60.7%), psoriasis (54.4%), hidradenitis suppurativa (HS) (54.3%) or blistering disorders (53%) answered positively. Fifteen of 32 skin conditions had  $>33.3\%$  patients scoring positively.

The mean scores with SD for question 10 and Q10% for each diagnosis are presented in Table II. There are no existing cut-off values for interpreting results from single questions of the DLQI, and isolated values may not give a clear perspective as to how large the impact is. Q10% is not a standardized method for interpreting DLQI data, but does provide perspective on how therapy issues relate to the total HRQoL impairment. Table II lists the diseases in descending values according to Q10%, adjusted for age, sex, socioeconomic status and comorbidity. The positive standardized  $\beta$  coefficients for all diseases denote

influence of therapy on HRQoL even when adjusted. For many diseases the  $\beta$  coefficient was relatively high, indicating robustness of the presented results.

When assessing Q10%, males and older patients showed more impairment, the reverse of what was seen for total mean DLQI. The impairment was highest in patients with comorbidities or those of low socioeconomic status.

When considering the impact of therapy on HRQoL, highest mean scores and most positive answers to question 10 were seen in diseases that commonly affect large areas of the skin (e.g. AD, psoriasis, allergic/drug/phototoxic conditions, prurigo, papulosquamous diseases, eczemas, connective tissue disease and vitiligo), as well as diseases accompanied by blisters/erosions, ulceration or crusting (blistering diseases, venous leg ulcer, vasculitis, immunological ulcers and oral diseases) and pruritic dermatoses (prurigo, urticaria and pruritus) (Table II, Fig. 1).

Q10% reveals which diagnostic groups are most affected by therapy relative to their total HRQoL impairment. Blistering conditions showed the highest value (10.7), followed by allergic, drug, phototoxic/-allergic reactions (10.2) and psoriasis (9.9), a ranking that differs from total mean DLQI values (Table SII<sup>†</sup>). This gives insight into the true extra burden of therapy for different diseases.

HS, prurigo, pruritus and urticaria show the highest impairment when mean DLQI scores are evaluated, but drop in ranking when therapy is assessed. Likewise, acne, rosacea and psychodermatological conditions, scoring among the average impaired as measured by mean DLQI scores, were some of the least affected by therapy. Conversely, blistering conditions, non-melanoma skin cancer (NMSC), actinic keratoses (AK), allergic/drug reactions, vasculitis and venous leg ulcers rank higher when evaluated according to therapy-related impairment.



**Table II. Effect of treatment on Dermatology Life Quality Index (DLQI).** Ranking according to the percentage of Question 10 of the DLQI (therapy issues) to the mean total DLQI (Q10%) for diagnoses with at least 20 valid answers (hyperhidrosis (12), nail diseases (17) and granuloma annulare (13) excluded). Linear regression (standardized  $\beta$ ) with "naevi" as a "healthy" control group, adjusting for age, sex, socioeconomic status and comorbidity (diabetes mellitus, cardiological, respiratory, rheumatological or other disease)

Diagnosis	Q10% <sup>a</sup>	Standardized $\beta$	Question 10 Mean $\pm$ SD	DLQI Mean $\pm$ SD	Valid n/Valid n $\beta^b$								
All patients <sup>c</sup>	7.73	0.06	0.52 $\pm$ 0.8	6.73 $\pm$ 6.8	3,846/3,553								
1 Blistering conditions	10.71	0.47	0.92 $\pm$ 1.0	8.59 $\pm$ 7.4	66/49								
2 Allergic, drug, phototoxic/-allergic reactions	10.21	0.39	0.54 $\pm$ 0.8	5.29 $\pm$ 4.3	24/21								
3 Psoriasis	9.85	0.19	0.90 $\pm$ 1.0	9.14 $\pm$ 7.6	660/615								
4 Vasculitis and immunological ulcers <sup>d</sup>	8.78	0.28	0.62 $\pm$ 0.9	7.06 $\pm$ 6.1	67/60								
5 Atopic dermatitis	8.67	0.33	1.0 $\pm$ 0.9	11.53 $\pm$ 7.2	172/150								
6 Vitiligo	8.62	0.36	0.33 $\pm$ 0.6	3.83 $\pm$ 3.7	24								
7 Venous leg ulcers	8.47	0.27	0.80 $\pm$ 1.0	9.45 $\pm$ 7.3	113/87								
8 Other hair disorders <sup>e</sup>	8.38	0.27	0.42 $\pm$ 0.8	5.01 $\pm$ 5.4	82/76								
9 Prurigo	8.13	0.33	0.93 $\pm$ 0.9	11.44 $\pm$ 8.2	27/24								
10 Scars, fibrosis of the skin, morphea	8.11	0.24	0.43 $\pm$ 0.9	5.3 $\pm$ 4.8	27								
11 Papulosquamous skin diseases <sup>f</sup>	7.69	0.21	0.49 $\pm$ 0.8	6.37 $\pm$ 6.4	113/103								
12 Connective tissue disease	7.43	0.20	0.58 $\pm$ 0.9	7.81 $\pm$ 7.0	91/74								
13 Oral conditions <sup>g</sup>	7.39	0.24	0.50 $\pm$ 0.8	6.77 $\pm$ 6.6	26								
14 Eczema	7.36	0.21	0.62 $\pm$ 0.9	8.42 $\pm$ 7.2	234								
15 Urticaria	7.09	0.35	0.68 $\pm$ 0.9	9.59 $\pm$ 6.7	69/60								
16 Hand eczema	7.05	0.18	0.60 $\pm$ 0.9	8.51 $\pm$ 7.2	156/146								
17 Alopecia areata	6.99	0.18	0.39 $\pm$ 0.8	5.58 $\pm$ 6.8	31/30								
18 Pruritus	6.84	0.24	0.75 $\pm$ 1.0	10.97 $\pm$ 7.1	60/58								
19 Non-melanoma skin cancer and actinic keratosis	6.75	0.11	0.16 $\pm$ 0.5	2.37 $\pm$ 5.0	401/372								
20 Genital (non-venereal) <sup>h</sup>	6.36	0.22	0.56 $\pm$ 0.8	8.81 $\pm$ 6.4	32/30								
21 Other <sup>i</sup>	6.15	0.20	0.39 $\pm$ 0.7	6.34 $\pm$ 6.6	96/67								
22 Hidradenitis suppurativa	6.14	0.24	0.78 $\pm$ 0.8	12.7 $\pm$ 7.6	46/44								
23 Infections of the skin	6.09	0.21	0.38 $\pm$ 0.8	6.24 $\pm$ 5.8	253/244								
24 Benign skin tumours	5.51	0.09	0.15 $\pm$ 0.5	2.72 $\pm$ 3.7	159/154								
25 Lichen planus	5.42	0.07	0.33 $\pm$ 0.7	6.09 $\pm$ 5.4	46/41								
26 Seborrhoeic dermatitis	5.41	0.23	0.34 $\pm$ 0.6	6.28 $\pm$ 4.4	75/74								
27 Psychodermatological conditions	5.41	0.14	0.46 $\pm$ 0.8	8.5 $\pm$ 7.1	34								
28 Acne	4.99	0.16	0.31 $\pm$ 0.6	6.21 $\pm$ 5.2	234/228								
29 Rosacea	4.66	0.09	0.25 $\pm$ 0.6	5.37 $\pm$ 5.3	75/68								
30 Naevi	4.61	-	0.07 $\pm$ 0.3	1.52 $\pm$ 2.9	186								
31 Malignant melanoma	4.41	0.03	0.12 $\pm$ 0.4	2.72 $\pm$ 4.4	86/75								
32 Melasma, pigment disorders	2.01	0.16	0.10 $\pm$ 0.3	4.97 $\pm$ 4.7	32/30								
Sex	Age groups	Socioeconomic status		Comorbidity									
Q10% <sup>a</sup> (N) Male: 8.03 (1,686) Female: 7.41 (2,168)	18-35 years: 6.62 (1,247) 36-65 years: 8.10 (1,880) > 66 years: 8.7 (652)	Low: 8.23 (720) Middle: 7.4 (2,844) High: 8.17 (327)		None: 7.33 (2,573) Any: 8.77 (1,033)									
Country	BE	DK	FR	GER	HU	IT	NL	NO	PL	RUS	ES	TR	UK
Q10% <sup>a</sup> (n)	4.2 (250)	6.8 (265)	2.1 (126)	7.2 (290)	6.7 (261)	9.6 (527)	5.6 (235)	9.8 (534)	8.4 (275)	9 (273)	7.4 (274)	4 (270)	6.5 (213)

<sup>a</sup>The percentage of the mean score of Question 10 (therapy issues) relative to the mean total DLQI score. <sup>b</sup>Different values due to more missing numbers when regression analysis is performed. <sup>c</sup>Including nail diseases, hyperhidrosis and granuloma annulare. <sup>d</sup>Including pyoderma gangrenosum, Behçet's syndrome, panniculitis, necrobiosis lipoidica. <sup>e</sup>Effluvium, androgenic alopecia, cicatricial alopecia, other hair/scalp conditions. <sup>f</sup>Other than psoriasis: parapsoriasis; pityriasis rubra pilaris, pityriasis lichenoides, pityriasis rosea, Darier's disease. <sup>g</sup>Stomatitis, glossitis, cheilitis, aphthae. <sup>h</sup>Lichen sclerosus, pruritus/eczema vulvae, scroti et ani, balanitis/balanoposthitis. <sup>i</sup>Skin check of organ transplant recipients, other follow-up or uncertain diagnosis. SD: standard deviation; BE: Belgium; DK: Denmark; FR: France; GER: Germany; HU: Hungary; IT: Italy; NL: The Netherlands; NO: Norway; PL: Poland; RUS: Russia; ES: Spain; TR: Turkey; UK: United Kingdom.

## DISCUSSION

Using a dermatology-specific measure this study identified the extent of the reduced HRQoL associated with therapy. For several diseases, patients experience a high burden associated with therapy (blistering conditions, allergic/drug reactions, psoriasis, vasculitis, vitiligo and venous leg ulcers). Ranking the diseases according to what percentage of the burden is caused by therapy gives new insight into this specific impairment for the separate diagnoses.

Most skin diseases are treated with topical therapy. However, dermatological treatments include oral therapy, phototherapy, photodynamic therapy, lasers, cryotherapy, intralesional and surgical procedures and parenteral administrations, which may be painful, time-consuming

or cause infusion reactions. The use of these specific dermatological medications and therapeutic approaches presents issues and challenges unique to skin disease.

Generic HRQoL measures have been developed without specific reference to the impact of therapy for skin disease (Table III). Assessment may therefore be inaccurate if this burden experienced by dermatological patients is missed. There are no questions related to the impact of therapy in the most commonly used generic measures. However, the generic measures Treatment Satisfaction with Medicines Questionnaire (SATMED-Q) (3) and Treatment Satisfaction Questionnaire for Medication (TSQM) (4) are designed to address issues with medication, but are little used in dermatology. The DLQI is the only non-disease-specific dermatological measure



**Table III. Overview of dermatology-specific, disease-specific and generic instruments assessing quality of life with comments on whether the impact of therapy is addressed in the questionnaire**

Type and name of instrument	Therapy impact	Authors, year
<i>Dermatology-specific instruments</i>		
<b>DLQI</b>	Yes	Finlay & Khan 1994 (6)
Skindex, Skindex-29, Skindex-16, Skindex-17	No	Chren et al. 1996 (28), Nijsten et al. 2006 (29)
DSQL	No	Anderson & Rajagopalan 1997 (30)
DQOLS	No	Morgan et al. 1997 (31)
<i>Disease-specific instruments</i>		
<b>PDI</b>	Yes	Finlay & Kelly 1987 (32)
<b>PSORIQoL</b>	Yes	McKenna et al. 2003 (33)
<b>RosaQuol</b>	Yes	Nicholson et al. 2007 (34)
<b>QOLHEQ</b>	Yes	Ofenloch et al. 2014 (35)
<b>VEINES-QoL</b>	Yes	Bland et al. 2015 (36)
CADI	No	Motley & Finlay 1992 (37)
DSQL – Contact dermatitis	No	Anderson & Rajagopalan 1997 (30)
DSQL – Acne version	No	Anderson & Rajagopalan 1997 (30)
WAA Questionnaire	No	Dolte et al. 2000 (38)
Acne-QoL Questionnaire	No	Martin et al. 2001 (39)
PSS-AD in adults	No	Ando et al. 2006 (40)
SCI	No	Rhee et al. 2006 (41)
AAQ	No	Endo et al. 2012 (42)
MELASQoL Scale	No	Lieu & Pandaya 2012 (43)
AKQoL questionnaire	No	Esman et al. 2013 (25)
AA-QLI	No	Fabbrocini et al. 2013 (44)
FQL index	No	Heisterberg et al. 2013 (45)
VitiQoL	No	Lilly et al. 2013 (46)
ABQoL	No	Sebaratnam et al. 2013 (47)
<i>Generic instruments*</i>		
<b>TSQM</b>	Yes	Atkinson et al. 2004 (4)
<b>SATMED-Q</b>	Yes	Ruiz et al. 2008 (3)
EuroQoL (EQ5D)	No	EuroQoLGroup 1990 (48)
Medical Outcome Study (MOS)	No	Ware & Sherbourne 1992 (49)
MOS Short-Form 36 (SF-36)	No	
WHOQoL-100	No	WHO 1996 (50)
WHOQoL-BREF	No	WHO 1998 (51)

\*Only the most commonly used generic instruments that do not address therapeutic issues are shown here.

DLQI: Dermatology Life Quality Index; DSQL: Dermatology-Specific Quality of Life; DQOLS: Dermatology Quality of Life Scales; PDI: Psoriasis Disability Index; PSORIQoL: Psoriasis Index of Quality of Life; RosaQuol: Rosacea Quality of Life; QOLHEQ: Quality of Life Hand Eczema Questionnaire; VEINES-QoL: Venous Insufficiency Epidemiological and Economic Study; CADI: Cardiff Acne Disability Index; WAA: Women with Androgenetic Alopecia; Acne-QoL: Acne-specific Quality of Life; PSS-AD: Psychosomatic Scale for Atopic Dermatitis; SCI: Skin Cancer Index; AAQ: Alopecia Areata Quality of Life; MELASQoL: Melasma Quality of Life; AKQoL: Actinic Keratosis Quality of Life; AA-QLI: Alopecia Areata Quality of Life Index; FQL index: Fragrance Allergy QoL instrument; VitiQoL: Vitiligo Quality of Life Index; ABQoL: Autoimmune Bullous Disease QoL Questionnaire; TSQM: Treatment Satisfaction Questionnaire for Medication; SATMED-Q: Satisfaction with Medicines Questionnaire.

that addresses therapy burden (Table III), although the DLQI is the most widely used measure in dermatology (14) the issue of therapy is little explored.

There are very few studies evaluating the contribution of therapy to impairment of HRQoL. In 3 studies (15–17) the generic instrument Short Form Health Survey (SF-36) was used in random samples of the population. A large proportion of patients reported dermatological problems and those using topical therapies on prescription showed greater impairment of HRQoL than those not using topical prescription medicines (15). An overview of the most relevant results for several diagnoses is given below.

Blistering diseases showed the highest impairment due to therapy and positive standardized  $\beta$  values as high as 0.5, in support of the high impairment caused by the

disease and its therapy and not because of the age, sex, comorbidity or socioeconomic status of the patients.

HS results in severely impaired HRQoL (18, 19), has the highest mean DLQI, but scores for Q10% are low. Studies of the same data-set rank HS patients with some of the lowest HRQoL (8), highest risk for psychiatric comorbidity (7, 20) and impairment in sexual life (9). Despite very high impairment of HRQoL, therapy contributes little to this burden.

AD and psoriasis rank highly when mean DLQI, positive answers to therapy issues or Q10% are evaluated, suggesting that these patients are equally adversely affected by all aspects of HRQoL, including therapy.

Diseases affecting small areas of the body, such as facial dermatoses (seborrhoeic dermatitis, rosacea and acne), as well as psychodermatological conditions rank lower on therapy relative to the total DLQI than might be expected, demonstrating that it is the disease itself and not the therapy that is the driving cause of HRQoL impairment. Treating these conditions adequately should alleviate the patient's experienced burden without additional impairment.

In contrast, patients with AK, NMSC, allergic/drug reactions, scars/fibrosis and morphea, who do not report severe impairment of HRQoL as measured by the mean DLQI, rank highly in impairment when assessing therapy as a percentage of this total score. AK and NMSC do not apparently have a high impact on HRQoL, nor psychiatric comorbidity (7, 8, 20), but score relatively worse when therapy is assessed, ranking them higher than HS and several other diseases.

Studies evaluating the burden caused by AK and/or NMSC have shown low impact on HRQoL of these diseases (21–24), raising the possibility that currently available measures may be missing therapy issues and that there may be a need for a skin-cancer-specific HRQoL measure. Existing disease-specific instruments do not include therapy questions (22, 25) (Table III).

Burdensome treatments have a negative effect on adherence to therapy (5) and can be the reason for undertreatment and relapse of disease. Measuring HRQoL without taking into account therapy issues may not represent the true extent of suffering that dermatological patients experience. On the other hand, knowing which diseases have the highest potential to cause therapy issues can alert clinicians to which patients need a different approach, by giving them better information, providing a variety of options, offering training in therapy application, or at least acknowledging the issue.

When developing clinical guidelines in dermatology, optimization of therapy and minimizing the burden of treatment should be considered. Developers of HRQoL instruments should pay attention to therapy issues when measuring HRQoL in some specific diagnoses, such as



skin cancer, as this burden may go undetected using currently available measures (7, 8, 20–23).

#### *Strengths and limitations*

The high number of patients in this study, the unbiased selection of participants and adjusting for confounding factors resulted in robust data on therapy as a factor contributing to impairment in HRQoL. Similar studies on therapeutic issues are lacking and studies using DLQI typically have no healthy control group.

One potential limitation is in the detail of the wording of DLQI question 10: “...by making your home messy, or by taking up time”, which may bias the respondents into only considering topical therapy. However, the main question itself is neutral on this point “...how much of a problem has the treatment for your skin been...”.

Detailed information on all treatments used by our patients was not obtained systematically. The presented data evaluate therapy issues on a general basis. Further studies evaluating specific dermatological treatments are warranted.

Although we refer to data from each country, the data was based on 1 centre from each country (apart from Italy and Norway). The recruitment centres may not have been representative of clinical practice across each country. There were large differences between countries in scores assessing impairment, which cannot be readily explained. The cross-cultural issue is one that is of relevance to all HRQoL measures (26). The same limitation may apply when comparing diseases (27). The cultural and language factors leading to these differences are not fully understood, though they should be taken into account when making any cross-cultural comparisons and when using HRQoL data as a guide to optimal health policies and creating optimal treatment guidelines. Analysis of the source for country differences may be able to serve as a guide to optimal health policies and creating optimal treatment guidelines.

#### *Conclusion*

Treatments for skin diseases contribute to the burden on HRQoL. For some diagnoses, therapy may have a larger impact than was previously known, but we also identify diseases that are affected by therapy to a lesser degree. Older, male patients with lower socioeconomic status and comorbidities experience more adverse issues with therapy. This study highlights new aspects to HRQoL that may have previously been overlooked. Clinicians are made aware of the importance in addressing therapy issues and promoting adherence to therapy, and pharmaceutical companies of the ease of use of their products. Developers of HRQoL instruments should consider including therapy-related questions. The ultimate goal would be to reduce the burden of skin disease and promote adherence to therapy.

## ACKNOWLEDGEMENTS

The European Society for Dermatology and Psychiatry (ESDaP) initiated the study. The authors thank the ESDaP Group who collected and validated the data and Geir Strandenæs Larsen who helped with data search.

AYF is joint copyright owner of the DLQI. Cardiff University and AYF receive royalties (though not from this study). The other authors have no conflicts of interest to declare.

## REFERENCES

1. Ruiz MA, Heras F, Alomar A, Conde-Salazar L, de la Cuadra J, Serra E, et al. Development and validation of a questionnaire on 'Satisfaction with dermatological treatment of hand eczema' (DermaSat). *Health Qual Life Outcomes* 2010; 8: 127.
2. Jubert-Esteve E, Del Pozo-Hernando LJ, Izquierdo-Herce N, Bauza-Alonso A, Martin-Santiago A, Jones-Caballero M. Quality of life and side effects in patients with actinic keratosis treated with ingenol mebutate: a pilot study. *Actas Dermosifiliogr* 2015; 106: 644–650.
3. Ruiz MA, Pardo A, Rejas J, Soto J, Villasante F, Aranguren JL. Development and validation of the "Treatment Satisfaction with Medicines Questionnaire" (SATMED-Q). *Value Health* 2008; 11: 913–926.
4. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes* 2004; 2: 12.
5. Feldman SR, Vrijens B, Gieler U, Piaserico S, Puig L, van de Kerkhof P. Treatment adherence intervention studies in dermatology and guidance on how to support adherence. *Am J Clin Dermatol* 2017; 18: 253–271.
6. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; 19: 210–216.
7. Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GBE, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *J Invest Dermatol* 2015; 135: 984–991.
8. Balieva F, Kupfer J, Lien L, Gieler U, Finlay AY, Tomas-Aragones L, et al. The burden of common skin diseases assessed with the EQ5D: a European multicentre study in 13 countries. *Br J Dermatol* 2017; 176: 1170–1178.
9. Sampogna F, Abeni D, Gieler U, Tomas-Aragones L, Lien L, Titeca G, et al. Impairment of sexual life in 3,485 dermatological outpatients from a multicentre study in 13 European countries. *Acta Derm Venereol* 2017; 97: 478–482.
10. Szabo C, Altmayer A, Lien L, Poot F, Gieler U, Tomas-Aragones L, et al. Attachment styles of dermatological patients in Europe: a multi-centre study in 13 countries. *Acta Derm Venereol* 2017; 97: 813–818.
11. Lesner K, Reich A, Szepietowski JC, Dalgard FJ, Gieler U, Tomas-Aragones L, et al. Determinants of psychosocial health in psoriatic patients: a multi-national study. *Acta Derm Venereol* 2017; 97: 1182–1188.
12. Rea JN, Newhouse ML, Halil T. Skin disease in Lambeth. A community study of prevalence and use of medical care. *Br J Prev Soc Med* 1976; 30: 107–114.
13. Hongbo Y, Thomas C, Harrison M, Salek MS, Finlay AY. Translating the science of quality of life into practice: what do dermatology life quality index scores mean? *J Invest Dermatol* 2005; 125: 659–664.
14. Ali FM, Cueva AC, Vyas J, Atwan AA, Salek MS, Finlay AY, et al. A systematic review of the use of quality-of-life instruments in randomized controlled trials for psoriasis. *Br J Dermatol* 2017; 176: 577–593.
15. Bingefors K, Lindberg M, Isacson D. Self-reported dermatological problems and use of prescribed topical drugs correlate with decreased quality of life: an epidemiological survey. *Br J Dermatol* 2002; 147: 285–290.



16. Lindberg M, Isacson D, Binge-fors K. Self-reported skin diseases, quality of life and medication use: a nationwide pharmaco-epidemiological survey in Sweden. *Acta Derm Venereol* 2014; 94: 188–191.
17. Binge-fors K, Lindberg M, Isacson D. Quality of life, use of topical medications and socio-economic data in hand eczema: a Swedish nationwide survey. *Acta Derm Venereol* 2011; 91: 452–458.
18. Riis PT, Vinding GR, Ring HC, Jemec GB. Disutility in patients with hidradenitis suppurativa: a cross-sectional study using EuroQoL-5D. *Acta Derm Venereol* 2016; 96: 222–226.
19. Matusiak L, Bieniek A, Szepietowski JC. Psychophysical aspects of hidradenitis suppurativa. *Acta Derm Venereol* 2010; 90: 264–268.
20. Balieva F, Lien L, Kupfer J, Halvorsen JA, Dalgard F. Are common skin diseases among Norwegian dermatological outpatients associated with psychological problems compared with controls? An observational study. *Acta Derm Venereol* 2016; 96: 227–231.
21. Rhee JS, Matthews BA, Neuburg M, Smith TL, Burzynski M, Nattinger AB. Skin cancer and quality of life: assessment with the Dermatology Life Quality Index. *Dermatol Surg* 2004; 30: 525–529.
22. Tennvall GR, Norlin JM, Malmberg I, Erendsson AM, Hadersdal M. Health related quality of life in patients with actinic keratosis-an observational study of patients treated in dermatology specialist care in Denmark. *Health Qual Life Outcomes* 2015; 13: 111.
23. Blackford S, Roberts D, Salek MS, Finlay AY. Basal cell carcinomas cause little handicap. *Qual Life Res* 1996; 5: 191–194.
24. Lee EH, Klassen AF, Nehal KS, Cano SJ, Waters J, Pusic AL. A systematic review of patient-reported outcome instruments of nonmelanoma skin cancer in the dermatologic population. *J Am Acad Dermatol* 2013; 69: e59–67.
25. Esmann S, Vinding GR, Christensen KB, Jemec GB. Assessing the influence of actinic keratosis on patients' quality of life: the AKQoL questionnaire. *Br J Dermatol* 2013; 168: 277–283.
26. Nijsten T, Meads DM, de Korte J, Sampogna F, Gelfand JM, Ongenaes K, et al. Cross-cultural inequivalence of dermatology-specific health-related quality of life instruments in psoriasis patients. *J Invest Dermatol* 2007; 127: 2315–2322.
27. Twiss J, Meads DM, Preston EP, Crawford SR, McKenna SP. Can we rely on the Dermatology Life Quality Index as a measure of the impact of psoriasis or atopic dermatitis? *J Invest Dermatol* 2012; 132: 76–84.
28. Chren MM, Lasek RJ, Quinn LM, Mostow EN, Zyzanski SJ. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. *J Invest Dermatol* 1996; 107: 707–713.
29. Nijsten TE, Sampogna F, Chren MM, Abeni DD. Testing and reducing Skindex-29 using Rasch analysis: Skindex-17. *J Invest Dermatol* 2006; 126: 1244–1250.
30. Anderson RT, Rajagopalan R. Development and validation of a quality of life instrument for cutaneous diseases. *J Am Acad Dermatol* 1997; 37: 41–50.
31. Morgan M, McCreedy R, Simpson J, Hay RJ. Dermatology quality of life scales – a measure of the impact of skin diseases. *Br J Dermatol* 1997; 136: 202–206.
32. Finlay AY, Kelly SE. Psoriasis – an index of disability. *Clin Exp Dermatol* 1987; 12: 8–11.
33. McKenna SP, Cook SA, Whalley D, Doward LC, Richards HL, Griffiths CE, et al. Development of the PSORIQoL, a psoriasis-specific measure of quality of life designed for use in clinical practice and trials. *Br J Dermatol* 2003; 149: 323–331.
34. Nicholson K, Abramova L, Chren MM, Yeung J, Chon SY, Chen SC. A pilot quality-of-life instrument for acne rosacea. *J Am Acad Dermatol* 2007; 57: 213–221.
35. Ofenloch RF, Weisshaar E, Dumke AK, Molin S, Diepgen TL, Apfelbacher C. The Quality of Life in Hand Eczema Questionnaire (QOLHEQ): validation of the German version of a new disease-specific measure of quality of life for patients with hand eczema. *Br J Dermatol* 2014; 171: 304–312.
36. Bland JM, Dumville JC, Ashby RL, Gabe R, Stubbs N, Ad-dlerley U, et al. Validation of the VEINES-QOL quality of life instrument in venous leg ulcers: repeatability and validity study embedded in a randomised clinical trial. *BMC Cardio-vasc Disord* 2015; 15: 85.
37. Motley RJ, Finlay AY. Practical use of a disability index in the routine management of acne. *Clin Exp Dermatol* 1992; 17: 1–3.
38. Dolte KS, Girman CJ, Hartmaier S, Roberts J, Bergfeld W, Waldstreicher J. Development of a health-related quality of life questionnaire for women with androgenetic alopecia. *Clin Exp Dermatol* 2000; 25: 637–642.
39. Martin AR, Lookingbill DP, Botek A, Light J, Thiboutot D, Girman CJ. Health-related quality of life among patients with facial acne – assessment of a new acne-specific questionnaire. *Clin Exp Dermatol* 2001; 26: 380–385.
40. Ando T, Hashiro M, Noda K, Adachi J, Hosoya R, Kamide R, et al. Development and validation of the psychosomatic scale for atopic dermatitis in adults. *J Dermatol* 2006; 33: 439–450.
41. Rhee JS, Matthews BA, Neuburg M, Logan BR, Burzynski M, Nattinger AB. Validation of a quality-of-life instrument for patients with nonmelanoma skin cancer. *Arch Facial Plast Surg* 2006; 8: 314–318.
42. Endo Y, Miyachi Y, Arakawa A. Development of a disease-specific instrument to measure quality of life in patients with alopecia areata. *Eur J Dermatol* 2012; 22: 531–536.
43. Lieu TJ, Pandya AG. Melasma quality of life measures. *Dermatol Clin* 2012; 30: 269–280.
44. Fabbrocini G, Panariello L, De Vita V, Vincenzi C, Lauro C, Nappo D, et al. Quality of life in alopecia areata: a disease-specific questionnaire. *J Eur Acad Dermatol Venereol* 2013; 27: e276–281.
45. Heisterberg MV, Menné T, Johansen JD. Fragrance allergy and quality of life – development and validation of a disease-specific quality of life instrument. *Contact Dermatitis* 2014; 70: 69–80.
46. Lilly E, Lu PD, Borovicka JH, Victorson D, Kwasny MJ, West DP, et al. Development and validation of a vitiligo-specific quality-of-life instrument (VitiQoL). *J Am Acad Dermatol* 2013; 69: e11–18.
47. Sebaratnam DF, Hanna AM, Chee SN, Frew JW, Venugopal SS, Daniel BS, et al. Development of a quality-of-life instrument for autoimmune bullous disease: the Autoimmune Bullous Disease Quality of Life questionnaire. *JAMA Dermatol* 2013; 149: 1186–1191.
48. EuroQoLGroup. EuroQoL – a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16: 199–208.
49. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30: 473–483.
50. The-WHOQOL-Group. What quality of life? World Health Organization Quality of Life Assessment. *World Health Forum* 1996; 17: 354–356.
51. The-WHOQOL-Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. *Psychol Med* 1998; 28: 551–558.

Supplementary material to article by F. N. Balieva et al. "The Role of Therapy in Impairing Quality of Life in Dermatological Patients: A Multinational Study"

**Table SI. Participant characteristics. Reproduced with modification from JID (Dalgard, Gieler et al. 2015) (7)**

	Patients <i>n</i> (%)	Controls <i>n</i> (%)	<i>p</i> -value
Total, <i>n</i>	<b>4,010</b>	<b>1,359</b>	
Sex, <i>n</i> (%)			
Male	1,746 (43.7)	453 (33.4)	<0.05
Female	2,250 (56.3)	903 (66.6)	<0.05
Missing	14	3	
Age, years, mean±SD	47.1±18	41.1±13.6	<0.05
Male	48.5±18.2	41.1±14.2	<0.05
Female	46.0±17.8	41.1±13.3	<0.05
Socioeconomic status (self-reported), <i>n</i> (%)			
Low	723 (18.5)	215 (15.9)	NS
Medium	2,848 (73.1)	1,012 (75.1)	NS
High	327 (8.4)	121 (9)	NS
Missing	112	11	
Comorbidities (any), <i>n</i> (%)	<b>1,089 (29.1)</b>	<b>170 (16)</b>	<0.05
Cardiological	667 (17.8)	78 (7.3)	<0.05
Respiratory	206 (5.5)	47 (4.4)	NS
Diabetes mellitus	224 (6.0)	24 (2.2)	<0.05
Rheumatological	310 (8.3)	48 (4.5)	<0.05
Other	609 (16.3)	111 (10.4)	<0.05

NS: not significant.

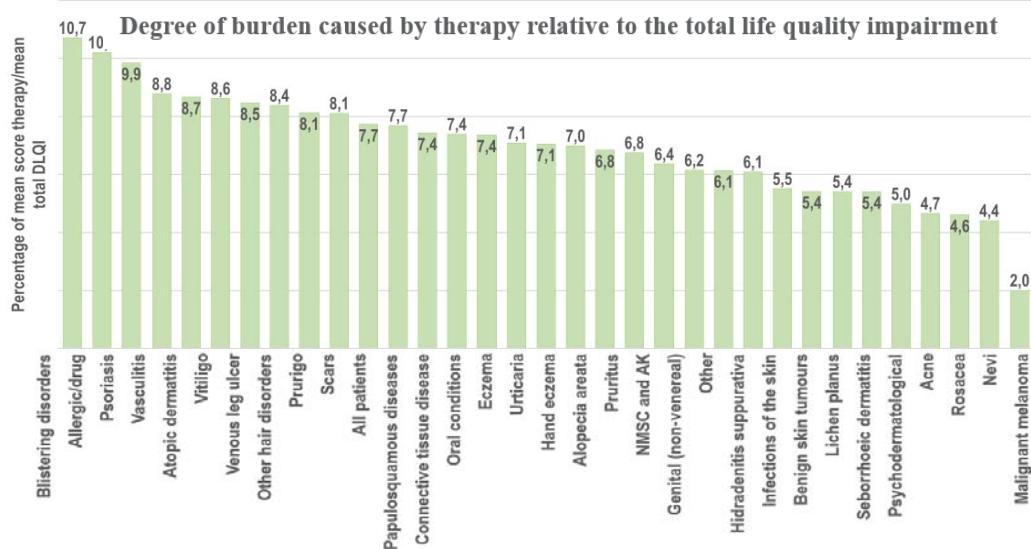


Supplementary material to article by F. N. Balieva et al. "The Role of Therapy in Impairing Quality of Life in Dermatological Patients: A Multinational Study"

**Table SII. Distribution by Dermatology Life Quality Index (DLQI) score band descriptors for each diagnosis and their effect on quality of life (QoL)**

Diagnosis	n	DLQI Mean±SD	DLQI ≥ 6 (at least moderate) % (n)	DLQI ≥ 11 (at least very large) % (n)	Effect on QoL					DLQI score descriptor
					Extremely large (≥ 20) % (n)	Very large (11–20) % (n)	Moderate (6–10) % (n)	Small (2–5) % (n)	No effect (0 or 1) % (n)	
Total	3,846	6.73±6.8	44.9 (1,711)	25.5 (977)	5.2 (200)	20.3 (777)	19.4 (734)	26.6 (988)	28.5 (920)	Moderate
Hidradenitis suppurativa	46	12.70±7.6	80.4 (37)	58.7 (27)	17.4 (8)	41.3 (19)	21.7 (10)	15.2 (7)	4.3 (2)	Very large (11–20)
Atopic dermatitis	172	11.53±7.2	74.4 (128)	50 (86)	13.4 (23)	36.6 (63)	24.4 (42)	22.7 (39)	2.9 (5)	
Prurigo	27	11.44±8.2	52.9 (17)	48.1 (13)	18.5 (5)	29.6 (8)	14.8 (4)	22.2 (6)	14.8 (4)	Moderate (6–10) <sup>9</sup>
Pruritus	60	10.97±7.1	74.9 (45)	46.6 (28)	13.3 (8)	33.3 (20)	28.3 (17)	18.3 (11)	6.7 (4)	
Urticaria	69	9.59±6.7	70.9 (49)	40.5 (28)	4.3 (3)	36.2 (25)	30.4 (21)	17.4 (12)	11.6 (8)	Moderate (6–10) <sup>9</sup>
Venous leg ulcers	113	9.45±7.3	66.4 (74)	44.3 (49)	8 (9)	35.3 (40)	22.1 (25)	16.8 (19)	17.7 (20)	
Psoriasis	660	9.14±7.6	57.6 (380)	38.8 (256)	9.4 (62)	29.4 (194)	18.8 (124)	24.1 (159)	18.3 (121)	Moderate (6–10) <sup>9</sup>
Genital (non-venereal) <sup>a</sup>	32	8.81±6.4	65.6 (21)	37.5 (12)	9.4 (3)	28.1 (9)	28.1 (9)	21.9 (7)	12.5 (4)	
Blistering conditions	66	8.59±7.4	54.6 (36)	34.9 (23)	7.6 (5)	27.3 (18)	19.7 (13)	27.3 (18)	18.2 (12)	Moderate (6–10) <sup>9</sup>
Hand eczema	156	8.51±7.2	55.1 (86)	30.8 (48)	10.3 (16)	20.5 (32)	24.4 (38)	32.7 (51)	12.2 (19)	
Psychodermatological conditions	34	8.5±7.1	57.7 (19)	38.2 (13)	2.9 (1)	35.3 (12)	17.6 (6)	29.4 (10)	14.7 (5)	Moderate (6–10) <sup>9</sup>
Eczema	241	8.42±7.2	54 (130)	36.6 (88)	7.1 (17)	29.5 (71)	17.4 (42)	28.6 (69)	17.4 (42)	
Hyperhidrosis	12	8.08±7.6	50 (6)	33.3 (4)	8.3 (1)	25 (3)	16.7 (2)	25 (3)	25 (3)	Moderate (6–10) <sup>9</sup>
Vasculitis, immunological ulcers <sup>b</sup>	67	7.06±6.1	52.2 (35)	25.3 (17)	4.5 (3)	20.9 (14)	26.9 (18)	26.9 (18)	20.9 (14)	
Connective tissue disease	91	7.81±7.0	51.7 (47)	30.8 (28)	7.7 (7)	23.1 (21)	20.9 (19)	24.2 (22)	24.2 (22)	Moderate (6–10) <sup>9</sup>
Oral conditions <sup>c</sup>	26	6.77±6.6	50 (13)	23.1 (6)	7.7 (2)	15.4 (4)	26.9 (7)	23.1 (6)	26.9 (7)	
Papulosquamous diseases <sup>d</sup>	113	6.37±6.4	44.3 (50)	19.5 (22)	7.1 (8)	12.4 (14)	24.8 (28)	28.3 (32)	27.4 (31)	Moderate (6–10) <sup>9</sup>
Other <sup>e</sup>	96	6.34±6.6	43.8 (42)	24 (23)	4.2 (4)	19.8 (19)	19.8 (19)	24 (23)	32.3 (31)	
Seborrhoeic dermatitis	75	6.28±4.4	52 (39)	16 (12)	0	16 (12)	36 (27)	37.3 (28)	10.7 (8)	Moderate (6–10) <sup>9</sup>
Infections of the skin	253	6.24±5.8	45.4 (115)	22.9 (58)	1.6 (4)	21.3 (54)	22.5 (57)	30.4 (77)	23.1 (61)	
Acne	234	6.21±5.2	40.6 (103)	20.6 (48)	1.4 (3)	19.2 (45)	20 (55)	35.5 (83)	20.5 (48)	Moderate (6–10) <sup>9</sup>
Lichen planus	46	6.09±5.4	48.9 (22)	20 (9)	2.2 (1)	17.8 (8)	28.9 (13)	26.7 (12)	24.4 (11)	
Alopecia areata	31	5.58±6.8	38.7 (12)	16.1 (5)	3.2 (1)	12.9 (4)	22.6 (7)	22.6 (7)	38.7 (12)	Moderate (6–10) <sup>9</sup>
Rosacea	75	5.37±5.3	40 (30)	20 (15)	1.3 (1)	18.7 (14)	20 (15)	25.3 (19)	34.7 (26)	
Scars, skin fibrosis, morphea	27	5.3±4.8	33.2 (9)	18.5 (5)	0	18.5 (5)	14.8 (4)	48.1 (13)	18.5 (5)	Moderate (6–10) <sup>9</sup>
Allergic, drug, phototoxic/-allergic	24	5.29±4.3	41.7 (10)	12.5 (3)	0	12.5 (3)	29.2 (7)	33.3 (8)	25 (6)	
Other hair disorders <sup>f</sup>	82	5.01±5.4	35.3 (29)	15.8 (13)	2.4 (2)	13.4 (11)	19.5 (16)	31.7 (26)	32.9 (27)	Moderate (6–10) <sup>9</sup>
Melasma, pigment disorders	32	4.97±4.7	40.6 (13)	15.6 (5)	0	15.6 (5)	25 (8)	21.9 (7)	37.5 (12)	
Granuloma annulare	13	4.0±2.9	30.8 (4)	0	0	0	30.8 (4)	46.2 (6)	23.1 (3)	Moderate (6–10) <sup>9</sup>
Nail diseases	17	3.88±4.3	35.3 (6)	5.9 (1)	0	5.9 (1)	29.4 (5)	17.6 (3)	47.1 (8)	
Vitiligo	24	3.83±3.7	29.2 (7)	4.2 (1)	0	4.2 (1)	25 (6)	33.3 (8)	37.5 (9)	Moderate (6–10) <sup>9</sup>
Malignant melanoma	86	2.72±4.4	15.2 (13)	8.2 (7)	1.2 (1)	7 (6)	7 (6)	30.2 (26)	54.7 (47)	
Benign skin tumours	159	2.72±3.7	18.8 (30)	5 (8)	0	5 (8)	13.8 (22)	24.5 (39)	56.6 (90)	Moderate (6–10) <sup>9</sup>
NMSC and AK	401	2.37±5.0	13.5 (54)	4 (16)	0.5 (2)	3.5 (14)	9.5 (38)	28.4 (114)	58.1 (233)	
Naevi (91.4% - no or small)	186	1.52±2.9	8.6 (14)	2.7 (5)	0	2.7 (5)	5.9 (11)	18.8 (35)	72.6 (135)	Moderate (6–10) <sup>9</sup>

<sup>a</sup>Lichen sclerosus, pruritus/eczema vulvae, scroti et ani, balanitis/balanoposthitis. <sup>b</sup>Including pyoderma gangrenosum, Behçet's syndrome, panniculitis, necrobiosis lipoidica. <sup>c</sup>Stomatitis, glossitis, cheilitis, aphthae. <sup>d</sup>Other than psoriasis: parapsoriasis, pityriasis rubra pilaris, pityriasis lichenoides, pityriasis rosea, Darier's disease. <sup>e</sup>Skin check of organ transplant recipients, other follow-up, or uncertain diagnosis. <sup>f</sup>Effluvium, androgenic alopecia, cicatricial alopecia, other hair/scalp conditions. <sup>9</sup>Values > -0.5 rounded up. Values < -0.5 rounded down. NMSC: non-melanoma skin cancer; AK: actinic keratosis.



**Effect of treatment on Dermatology Life Quality Index (DLQI).** Ranking according to the percentage of Question 10 of the DLQI (therapy issues) to the mean total DLQI (Q10%) for diagnoses with at least 20 valid answers (hyperhidrosis (12), nail diseases (17) and granuloma annulare (13) excluded). Detailed numbers shown in Table II





## 11. Questionnaires

(all available in the local language of the participants)

### 11.1 Request for participation:

## **Request for participation in a research project**

### **“Skin diseases’ influence on quality of life, relationships and mental health”**

#### **Background and purpose**

This is a request for you to participate in a research study that intends to describe how common skin disease has an influence on quality of life, close relationships and mental health among people. We know too little on this topic and it is important to do more research in order to understand the burden of having a skin disease, to give a better quality of treatment and to improve the health care of common skin diseases. We ask 150 random persons in this clinic to participate in this study. The responsible institution for this research is the University of...and this study is part of a larger European study.

#### **What does the study entail?**

If you participate you should fill in the four joined questionnaires prior to the consultation and bring them in to your treating dermatologist. The filling time takes approximatively 20 min.

#### **Potential advantages and disadvantages**

The advantage of participating in this study is that you might have a higher quality of consultation and have the possibility to raise questions that you maybe didn't think of. The disadvantage is that it might take 20 min more of your time.

#### **What will happen to the information about you?**

All information is anonymous. This means that the answers given by you will be processed without name, ID number or other recognisable type of information. A code number will link you to your data. It will not be possible to identify you in the results of the study when these are published.

#### **Voluntary participation**

Participation in the study is voluntary. You can at any time withdraw your consent to participate in the study, without stating any particular reason. This will not have any consequences for your further treatment. If you wish to participate now, please sign the declaration of consent on the final page. If you agree to participate now, but later wish to withdraw, your treatment will not be affected in any way. If you later have questions regarding the study or later wish to withdraw, you may contact ...(insert name and phone of projectleader at your center)

## Consent for participation in the study

I am willing to participate in the study

.....

(Signed by participant, date)

I confirm that I have given information about the study

.....

(Signed, role in the study, date)

## 11.2 Questionnaire on background variables:

ID number \_\_\_\_\_ Center \_\_\_\_\_ Date \_\_\_/\_\_\_/\_\_\_

### Questionnaire

(On all questions tick next to the right answer, you may skip questions you do not wish to answer)

Age \_\_\_\_\_

Gender: Male  Female

Which is your country of origin? \_\_\_\_\_

Which is your highest education?

- Primary school   
 Secondary school   
 High school   
 University

Which is your marital status?

- Single   
 With a partner   
 Separated/divorced   
 Widow/widower

Which is your socioeconomical level?

- Low   
 Middle   
 High

Did you experience serious economical difficulties in the last 5 years? Yes  No

Have you had any stressful life events during the last 6 months (serious illness, accident, divorce..)?

Yes  No

How concerned are you about your skin disease?

- Very little   
 A bit   
 Very much

Do you know your diagnosis? Yes  No

How long has your skin disease lasted? Since: \_\_\_\_\_ (year)

Duration of symptoms:

- Less than one month   
 One month   
 More than one month

Did you ever have suicidal ideation? Yes  No

Did you ever have suicidal ideation because of your skin disease? Yes  No

If yes: how often does it happen?

Every day	<input type="checkbox"/>
Every week	<input type="checkbox"/>
Every month	<input type="checkbox"/>
Sometimes during the year	<input type="checkbox"/>

How often did your skin disease flare during the last year?

Every day	<input type="checkbox"/>
Every week	<input type="checkbox"/>
Every month	<input type="checkbox"/>
Sometimes during the year	<input type="checkbox"/>

Localisation of flare now (you can tick more than one localisation)

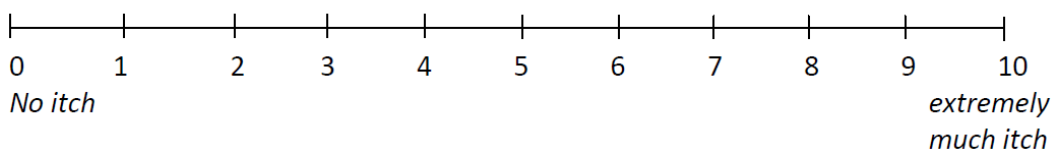
Face	<input type="checkbox"/>
Scalp	<input type="checkbox"/>
Hands	<input type="checkbox"/>
Torso	<input type="checkbox"/>
Other place on the body	<input type="checkbox"/>

Do you itch now? Yes  No

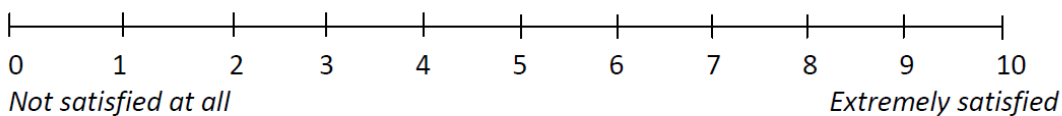
If yes: for how long?

Less than 6 weeks	<input type="checkbox"/>
6 weeks or more	<input type="checkbox"/>

How intense is your itch? (indicate on the line below, 0=no itch, 10=extremely much itch)



How satisfied are you with your current dermatologist? (indicate on the line below, 0=not satisfied at all, 10=extremely satisfied)



ID number

Center

Date

<b>For the consultant</b>
---------------------------

**Dermatological Diagnosis I** \_\_\_\_\_

**Severity:**

Mild	<input type="checkbox"/>
Moderate	<input type="checkbox"/>
Severe	<input type="checkbox"/>

**Dermatological Diagnosis II** \_\_\_\_\_

**Severity:**

Mild	<input type="checkbox"/>
Moderate	<input type="checkbox"/>
Severe	<input type="checkbox"/>

**Do you see depressive signs in the patient?**    Yes     No

**Do you see anxiety signs in the patient?**    Yes     No

**Is the patient treated for any other chronic condition?**

Cardiovascular disease	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Chronic respiratory disease	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Diabetes	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Rheumatological disease	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Other disease	Yes <input type="checkbox"/>	No <input type="checkbox"/>

If yes, specify \_\_\_\_\_

### 11.3 Hospital Anxiety and Depression Scale (HADS):

#### Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.  
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		<b>I feel tense or 'wound up':</b>			<b>I feel as if I am slowed down:</b>
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		<b>I still enjoy the things I used to enjoy:</b>			<b>I get a sort of frightened feeling like 'butterflies' in the stomach:</b>
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		<b>I get a sort of frightened feeling as if something awful is about to happen:</b>			<b>I have lost interest in my appearance:</b>
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		<b>I can laugh and see the funny side of things:</b>			<b>I feel restless as I have to be on the move:</b>
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		<b>Worrying thoughts go through my mind:</b>			<b>I look forward with enjoyment to things:</b>
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		<b>I feel cheerful:</b>			<b>I get sudden feelings of panic:</b>
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		<b>I can sit at ease and feel relaxed:</b>			<b>I can enjoy a good book or radio or TV program:</b>
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

#### Scoring:

Total score: Depression (D) \_\_\_\_\_ Anxiety (A) \_\_\_\_\_

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

## 11.4 The EQ-5D:



### **Health Questionnaire**

***English version for the UK  
(validated for Ireland)***

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities** (*e.g. work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed



To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own  
health state  
today**

Best  
imaginable  
health state

100

90

80

70

60

50

40

30

20

10

0

90

80

70

60

50

40

30

20

10

0

90

80

70

60

50

40

30

20

10

0

90

80

70

60

50

40

30

20

10

0

Worst  
imaginable  
health state

11.5 The Dermatology Life Quality Index (DLQI):**DERMATOLOGY LIFE QUALITY INDEX (DLQI)**

Hospital No: .....

Date: .....

Name: .....

Score: .....

Address: .....

Diagnosis: .....

.....

**The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.**

- |   |            |                          |                                       |
|---|------------|--------------------------|---------------------------------------|
| 1. Over the last week, how <b>itchy</b> , <b>sore</b> , <b>painful</b> or <b>stinging</b> has your skin been?   | Very much  | <input type="checkbox"/> |                                       |
|   | A lot      | <input type="checkbox"/> |                                       |
|   | A little   | <input type="checkbox"/> |                                       |
|   | Not at all | <input type="checkbox"/> |                                       |
| 2. Over the last week, how <b>embarrassed</b> or <b>self conscious</b> have you been because of your skin?  | Very much  | <input type="checkbox"/> |                                       |
|   | A lot      | <input type="checkbox"/> |                                       |
|   | A little   | <input type="checkbox"/> |                                       |
|   | Not at all | <input type="checkbox"/> |                                       |
| 3. Over the last week, how much has your skin interfered with you going <b>shopping</b> or looking after your <b>home</b> or <b>garden</b> ?            | Very much  | <input type="checkbox"/> |                                       |
|   | A lot      | <input type="checkbox"/> |                                       |
|   | A little   | <input type="checkbox"/> |                                       |
|   | Not at all | <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 4. Over the last week, how much has your skin influenced the <b>clothes</b> you wear?   | Very much  | <input type="checkbox"/> |                                       |
|   | A lot      | <input type="checkbox"/> |                                       |
|   | A little   | <input type="checkbox"/> |                                       |
|   | Not at all | <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 5. Over the last week, how much has your skin affected any <b>social</b> or <b>leisure</b> activities?  | Very much  | <input type="checkbox"/> |                                       |
|   | A lot      | <input type="checkbox"/> |                                       |
|   | A little   | <input type="checkbox"/> |                                       |
|   | Not at all | <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 6. Over the last week, how much has your skin made it difficult for you to do any <b>sport</b> ?  | Very much  | <input type="checkbox"/> |                                       |
|   | A lot      | <input type="checkbox"/> |                                       |
|   | A little   | <input type="checkbox"/> |                                       |
|   | Not at all | <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 7. Over the last week, has your skin prevented you from <b>working</b> or <b>studying</b> ?   | Yes        | <input type="checkbox"/> |                                       |
|   | No         | <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| If "No", over the last week how much has your skin been a problem at <b>work</b> or <b>studying</b> ?   | A lot      | <input type="checkbox"/> |                                       |
|   | A little   | <input type="checkbox"/> |                                       |
|   | Not at all | <input type="checkbox"/> |                                       |
| 8. Over the last week, how much has your skin created problems with your <b>partner</b> or any of your <b>close friends</b> or <b>relatives</b> ?       | Very much  | <input type="checkbox"/> |                                       |
|   | A lot      | <input type="checkbox"/> |                                       |
|   | A little   | <input type="checkbox"/> |                                       |
|   | Not at all | <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 9. Over the last week, how much has your skin caused any <b>sexual difficulties</b> ?   | Very much  | <input type="checkbox"/> |                                       |
|   | A lot      | <input type="checkbox"/> |                                       |
|   | A little   | <input type="checkbox"/> |                                       |
|   | Not at all | <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 10. Over the last week, how much of a problem has the <b>treatment</b> for your skin been, for example by making your home messy, or by taking up time? | Very much  | <input type="checkbox"/> |                                       |
|   | A lot      | <input type="checkbox"/> |                                       |
|   | A little   | <input type="checkbox"/> |                                       |
|   | Not at all | <input type="checkbox"/> | Not relevant <input type="checkbox"/> |

**Please check you have answered EVERY question. Thank you.**

## DERMATOLOGY LIFE QUALITY INDEX (DLQI) - INSTRUCTIONS FOR USE

The Dermatology Life Quality Index questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one or two minutes.

### SCORING

The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question 7, 'prevented work or studying'	scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

### HOW TO INTERPRET MEANING OF DLQI SCORES

0 – 1	no effect at all on patient's life
2 – 5	small effect on patient's life
6 – 10	moderate effect on patient's life
11 – 20	very large effect on patient's life
21 – 30	extremely large effect on patient's life

### REFERENCES

Finlay AY and Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**:210-216.

Basra MK, Fenech R, Gatt RM, Salek MS and Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159**:997-1035.

Hongbo Y, Thomas CL, Harrison MA, Salek MS and Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *J Invest Dermatol* 2005; **125**:659-64.

*There is more information about the DLQI, including over 85 translations, at [www.dermatology.org.uk](http://www.dermatology.org.uk). The DLQI is copyright but may be used without seeking permission by clinicians for routine clinical purposes. For other purposes, please contact the copyright owners.*