Hand eczema - severity and medical attendance in relation to prognosis

Marianne Hald

This PhD thesis is based on the following manuscripts:

Study Part 1

I Hald M, Veien NK, Laurberg G, Johansen JD. Severity of hand eczema assessed by patients and dermatologist using a photographic guide. *British Journal of Dermatology* 2007; 156: 77-80.

Study Part 2

II Hald M, Berg ND, Elberling J, Johansen JD. Medical consultations in relation to severity of hand eczema in the general population. *British Journal of Dermatology* 2008; 158: 773-7.

Study Part 3

III Hald M, Agner T, Blands J, Veien NK, Laurberg G, Avnstorp C, Menné T, Kaaber K, Kristensen B, Kristensen O, Andersen KE, Paulsen E, Thormann J, Sommerlund M, Nielsen NH, Johansen JD. Clinical severity and prognosis of hand eczema. *British Journal of Dermatology* 2009; 160: 1229-36.

IV Hald M, Agner T, Blands J, Johansen JD. Delay in medical attention to hand eczema- a follow-up study. *British Journal of Dermatology 2009; July 7. [Epub ahead of print]*

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Acknowledgements

This study was prepared at the National Allergy Research Centre, Department of Dermato-Allergology, Gentofte Hospital. The project was supported by grants from the National Board of Health and Aage Bangs Foundation and was carried out in cooperation with the Danish Contact Dermatitis Group.

First of all, I would like to thank my three supervisors: Jeanne Duus Johansen for her excellent guidance, interest in my work and for being such a dedicated researcher; Tove Agner for her invaluable help and expertise in the field of hand eczema; and Jette Blands for inspiring discussions and support. I also wish to thank Torkil Menné, head of the Department of Dermato-Allergology, for sharing his passion on contact eczema and for providing an inspiring working environment.
I am grateful to the members of the Danish Contact Dermatitis Group, without their interest, contribution and help the study would not have been possible. Many thanks to Anne Marie Topp and Vivi Just for their personal commitment and invaluable help in the follow-up study. Thank you also to the healthcare personnel in the Allergy Laboratory for their skilful assistance.
Thank you to Henrik Ravn and Aage Vølund for their statistical help and rewarding scientific discussions. A special thanks to both Jesper Elberling, head of the Danish Research Centre for Chemical Sensitivities, and to Nikolaj Drimer Berg for fruitful cooperation and for the use of their data in the population-based study.
My colleagues at the National Allergy Research Centre, the Danish Research Centre for Chemical Sensitivities and Research Centre for Hairdressers and Beauticians are thanked for company and helpfulness.
Finally, thank you Jon for endless support.

Gentofte, June 2009
Marianne Hald

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1 INTRODUCTION

A chronic course of hand eczema is characteristic with continual or intermittent symptoms over many years[1]. Well known consequence of hand eczema are prolonged sick leave and potential unemployment, leading to both significant personal impairment[2;3] and considerable societal expense. Numerous studies have shed light on the aetiology of hand eczema and have contributed to the primary prophylaxis, focusing on high risk occupations and exposures found to implicate a risk of hand eczema. The dermatological examination is a cornerstone in the secondary prophylaxis, providing medical treatment and information on the individual causes of hand eczema. Studies on the role of the health-care system in relation to the prognosis of hand eczema are sparse but may, in a societal context, reveal potentially unfavourable logistic procedures and contribute with suggestions of a more reasonable way to organize the medical treatment of hand eczema, hopefully leading to an improved prognosis.

2 BACKGROUND

2.1 Epidemiology of hand eczema

The lifetime prevalence of hand eczema in the background population has been estimated to be 17%–26.6% in Scandinavia[4-7]while a point prevalence of 3.3%–6.2% has been reported in different European countries[5;8-12]. The point prevalence includes only subjects with present hand eczema; however, as the natural course of the disease often is characterized by chronic relapsing symptoms, a period prevalence estimate seems more informative. The one-year prevalence is a frequently used unit of measurement, and in population-based studies in adults it has been reported as 8.0%–11.8%[5;12-14]. Hand eczema is a frequent disease among youngsters too; a cross-sectional study among Danish school children (12–16 years) showed a one-year prevalence of 7.3%[15], while a one-year prevalence of 10.5% was found in a Swedish study of 16–18-year-old school pupils[16].

The prevalence of hand eczema has also been investigated in special occupational groups exposed to irritants or allergens, for example, hospital workers, where a one-year prevalence of 23%–32%[17;18] has been reported. A study among hairdressers, another high risk group, showed a one-year prevalence of 18%[19].

2.2 Risk factors for hand eczema

Predisposing endogenous factors and external factors both play important roles in hand eczema. A personal history of atopic dermatitis or present atopic dermatitis has repeatedly been identified as a main risk factor for hand eczema[6;15;16;20-22]. These persons have a defect of the skin barrier, which is not fully understood. Further, heritability of hand eczema, independent of atopic dermatitis, has been demonstrated in a twin study where genetic risk factors were found to have a moderate influence on the liability of developing hand eczema[5;20].

Contact eczema on the hands occurs as a result of exposure to external factors such as allergens or irritants. The most important risk factor for occupational contact eczema is repeated exposures

to irritants[23]. Well known irritants are wet work, detergent, hand cleaners, cutting fluids and abrasives[24]. A recent study of cases of occupational irritant contact eczema where the Danish National Board of Industrial Injuries Registry had been notified revealed that wet work was the most important individual factor recognized in 43% of all cases and in 60% of cases among women[23].

Exposure to various allergens may elicit hand eczema in sensitized individuals. In Denmark, the most frequently recognized exposures causing occupational allergic contact eczema among men are chromium and rubber additives, while rubber additives and biocides are the most common among women[23]. Hence, high-risk occupations are characterised by frequent contact with irritants or a high load of allergen(s)[14;23] Exposures to allergens and irritants often coexist, potentially causing an additive effect[25;26] and both may contribute to maintenance of the disease.

Epidemiological studies of hand eczema show that the one-year prevalence is about twice as high in women than in men [9;12;14-16;23] . Further, younger age is associated with a higher prevalence of hand eczema[1;14]. The highest incidence rate of hand eczema is found among young women aged 20–29 years with an estimate of 11.4 cases /1000 person years[6]. The difference between men and women seems not to be caused by a different function of skin barrier but has been ascribed to different external exposure. Wet work is more frequent in occupations dominated by women, and different domestic duties are probably also a factor that increases the preponderance of women with hand eczema[1;13;23;27].

2.3 Diagnosing hand eczema

Hand eczema is an inflammatory disease confined to the hands. The clinical picture is a polymorphic pattern characterized by features such as erythema, vesicles, oedema, scaling, papules and fissuring; symptoms that may change over a given period. The hand eczema diagnosis relies on the recognition of the clinical signs and symptoms and exclusions of alternative diagnosis (e.g. dermathophytosis and psoriasis). A classification of the different subtypes of hand eczema is based on aetiological factors, morphological signs and localization. Sub-classification of the different types of hand eczema cannot be determined solely from the clinical manifestations[28-31]. To derive a specific diagnosis, a thorough examination of atopic disposition and environmental exposures to various agents is needed, including patch testing. The most common subtypes of hand eczema are irritant contact eczema followed by atopic hand eczema and allergic contact eczema. Minor groups of endogenous forms other than atopic hand eczema are vesicular hand eczema, nummular hand eczema and hyperkeratotic eczema of the palms[1;8;9]

2.4 Prognosis of hand eczema

Hand eczema often runs a chronic course[1;32]. In a large population-based questionnaire study, 44 % reported ongoing hand eczema after 15 years of follow-up; however, 74% claimed to have experienced an improvement[33]. Clearance rates of 26%– 41% have been found in other prospective population-based studies with follow-up periods varying from 6 months to 8 years[8;11;34] In a recent Danish study of hand eczema patients from a private dermatological clinic, 43% of the participants reported that their hand eczema had improved or cleared after one year of follow-up[35].

Hand eczema is one of the most common work-related diseases, and in many studies patients are recruited from departments of occupational dermatology. The length of follow-up varies from a few months up to several years and the prognosis is generally reported as poor [36-39]. Many of these studies include not only hand eczema patients but cases with occupational contact eczema in general, and the different criteria for inclusion hamper a comparison of the results. In most observational studies of hand eczema, follow-up results are obtained via self-administered questionnaires, few of which include a clinical examination[11;34;40-42].

2.5 Risk factors for a poor prognosis of hand eczema

The course of hand eczema is a complex interplay between endogenous and exogenous factors, and many questions remain unanswered. In a long-term population-based study (15 years of follow-up) the main determinants for a poor prognosis were low age of onset of hand eczema (< 20 years), a personal history of atopic dermatitis, allergy to standard allergens, or widespread hand eczema at baseline[33]. A negative influence of atopic dermatitis has also been found in several studies[36-38] and the association of persistent symptoms with initial, widespread symptoms has been supported by one other study[35].

Several studies have reported the prognosis for allergic contact eczema to be worse than for irritant contact eczema [37;43-45]. However, in one study no difference was found [46], and a worse outcome for irritant contact eczema has also been reported [38]

A different course between men and women has also been investigated. The clearance rate was found not to differ between sexes in one population survey[47]. Other studies on patients with hand eczema or occupational skin diseases in general have found a different course between men and women but with inconsistent conclusions[32;37;38;48]

Few studies have focused on a relation between the duration of hand eczema before the diagnosis and the following course of the disease[34;43;46]. In a population-based study a comparison was made of the proportion of complete recoveries among groups with different duration of hand eczema before the examination. Among those with formerly short-lasting symptoms (1–6 months), a clearance rate of 46% was observed at the re- examination, whereas only 20%–22 % of persons with symptoms for more than 25 months had healed[8].

2.6 Medical attention for hand eczema

Many persons with hand eczema never seek medical advice on their disease. In two separate population-based Swedish studies from the 1960s and 1980s, the proportion of persons who had sought medical attention was 77% and 69% respectively[2;8]. These findings were in line with a recent Danish study where 63.4% of persons with a history of hand eczema reported having seen a medical doctor for that reason[34]. The lack of medical attention has been interpreted as a reflection of mild symptoms[18;24]. However, one study found that many persons with hand eczema, despite social impairment, never seek medical advice[33].

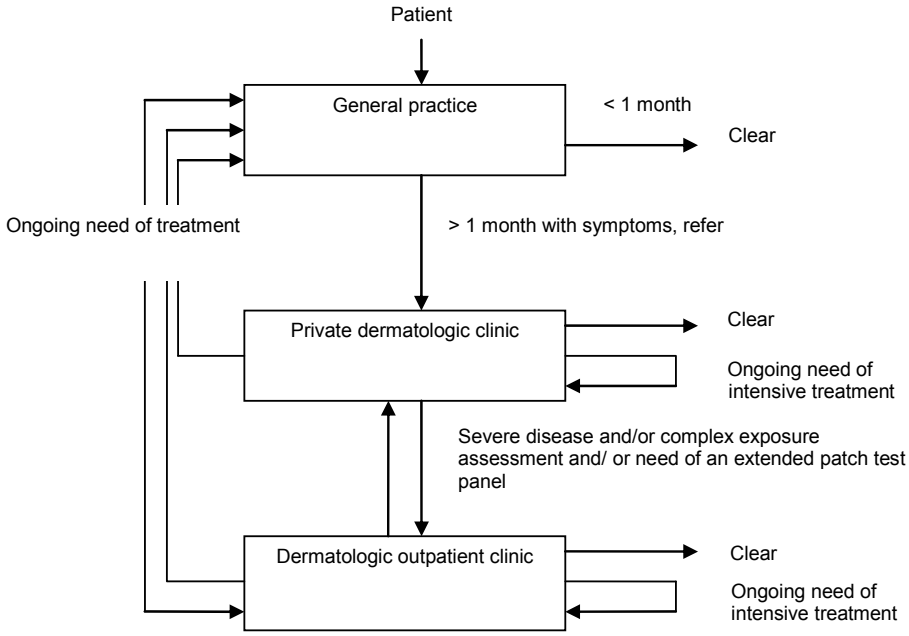
With estimates between 15% and 50% [17;18], the proportion of persons who have sought medical

attention seemed no higher among persons with hand eczema in an occupational setting. These persons miss out on having their cases registered; consequently, they also miss out on any potential occupational injury compensation.

In Denmark the tax-supported health-care system allows free access to medical services, with the general practitioner as gatekeeper. Guidelines from the Danish Contact Dermatitis Group recommend that patients with contact eczema lasting for more than one month despite treatment should be refered to a dermatologist. Furthermore, the dermatological examination leading to an ethiological diagnosis should be concluded within 3 months of the first contact with the health-care system[49]. Figure 1 illustrates the logistic guidelines for patients with hand eczema/ contact eczema in the Danish health-care system inspired by an illustration published by the Danish Contact Dermatitis Group[49].

On average a Danish general practitoner sees about two patients daily because of skin problems[50]. A recent study conducted among Danish general practitioners showed that, to a high extent, the treatment of hand eczema was according to the recommended medical guidelines, although more focus on an early referral to a dermatologist seemed relevant[51].

Figure 1: Flow-diagram illustrating the recommended dynamic of patients with hand eczema/ contact eczema in the Danish health-care system.



2.7 Clinical severity of hand eczema

Clinical severity assessment of hand eczema plays a significant role in daily clinical practice as well as in research. For various dermatological diseases, e.g. atopic dermatitis and acne, different instruments for objective severity assessment exist[52-54], but until recently no attempt had been made to validate a standardized grading system for hand eczema. To overcome the lack of available instruments researchers have used a variety of individually composed grading systems[1;42;55-57].

The lack of a standardized approach has important consequences, as outlined in an editorial comment in the British Journal of Dermatology in 2005[58] with focus on three subjects: (i) one important problem being that the comparison of results becomes difficult when investigators use different rating systems, and generation of systematic reviews is virtually impossible (ii) secondly, a meaningful interpretation of the clinical relevance of score changes is hampered by the fact that data on how much the scores vary between observers are lacking (iii) thirdly, the risk of observer bias is increased when unpublished scales are used in clinical trials, a phenomenon that has formerly been demonstrated in other medical branches[58;59].

In 2005 two new scoring systems for objectively measuring hand eczema severity were published. The hand eczema severity index (HECSI) was published by Held et al, an instrument relying on systematic measurements of a combination of disease extent and clinical signs[60]. Another approach was employed by Coenraads et al, who developed a simple five-point photographic grading system[61].

In 2006 a third scoring system was published: the Osnabruck hand eczema severity index (OHSI), with a construction similar to HECSI but intended to be simpler and, accordingly, aimed also at non-dermatologist[62;63].

3 AIMS OF THE STUDY

The aims of the thesis were to:

Part 1: Validation of a self-administrated photographic guide

- Validate a self-administrated photographic guide for patient-rated severity assessment of hand eczema (Manuscript I)

Part 2: The population-based survey

- Investigate the self-rated severity of hand eczema in a population-based sample and the associated medical consultations (Manuscript II)

Part 3: The follow-up study

- Investigate changes in clinical severity of hand eczema occurring between the first visit to a dermatologist and follow-up six months later and to identify factors associated with severe disease and a poor prognosis (Manuscript III)

- Investigate the delay in receiving medical attention for hand eczema caused by the patients or the health-care system and to identify factors associated with a longer delay (Manuscript IV)

- Investigate if the delay in receiving medical attention influences the hand eczema prognosis (Manuscript IV)

4 MATERIALS AND METHODS

The work in the thesis relies on three different questionnaire-based studies, the main study (Part 3) and two related studies (Part 1 and Part 2). The studies were all approved by the Danish Data Protection Agency. According to Danish legislation, acceptance by the regional ethics committee is not required for questionnaire studies.

4.1 Part 1: Validation of a self-administrated photographic guide

4.1.1 Study population

The self-administrated photographic guide was validated in a group of hand eczema patients. The study population consisted of 53 consecutive patients, recruited among patients attending the Dermatology Clinic in Aalborg, Denmark. Enrolment was over 9 weeks, November 2005–January 2006. Patients had to fulfill the following criteria: men or women aged 18 years or older who attended the clinic with hand eczema, without distinction between subtypes or duration of hand eczema.

4.1.2 Construction of the self-administered photographic guide

The development of the self-administrated photographic guide was based on a photographic guide constructed as a five-point photographic grading system designed and validated for consistent assessment by dermatologists[61]. The original photographic guide was modified by omitting the group representing “clear”, which left the self-administrated photographic guide with 16 photographs distributed over four groups of severity of hand eczema: almost clear, moderate, severe and very severe. Each group was represented by pictures of male and female hands, dorsal and palmar views and different morphological features of hand eczema. The groups were designated 1–4, with one being the mildest form. Further, a 5-item questionnaire was included. By comparing their hand eczema with that in the pictures the patients were asked to rate the severity of their hand eczema:

1. The time their hands had been the most severely affected
2. On average, over the past 12 months
3. At present. The patients were requested to select the more severely affected hand. They were also offered the option: “I don’t have hand eczema right now”.

Participants were also requested to evaluate the average severity of their hand eczema over the past 12 months and at present on a global scale. The instrument was designed as a visual analogue scale (VAS) of 10 centimetres, with the anchors of 0 corresponding to no eczema and 10 meaning the most severe symptoms. The VAS construction was inspired by a template in the NOSQ-2002[64].

The development process of the self-administrated photographic guide was based on preliminary tests on volunteer outpatients from Gentofte University Hospital and was conducted in two steps:

1. After vocal information, 8 consecutive patients wrote down the self-assessed severity of their present hand eczema by using the original photographic guide. Secondly, the hand eczema was assessed by the author. The ratings were performed independently followed by a comparison of the results. The procedure was followed by an interview with the patient to explore any problems concerning the applicability of the photographs.
2. After written instruction outlined in a questionnaire, a corresponding procedure was done with 3 consecutive patients. The preliminary questionnaires were evaluated and revised based on comments from each patient until a satisfactory result was obtained.

4.1.3 Collection of data

Participants were examined by one of two experienced dermatologists with special interest in hand eczema. After the clinical examination patients were informed about the study and asked to complete the self-administrated photographic guide. Likewise, the dermatologist graded the hand eczema in one of four groups as it appeared at the examination on the more severely affected hand. The dermatologist could also choose the option “There is no hand eczema right now”. The patients and the dermatologist were not informed of each other’s assessment.

4.1.4 Data entering

The marks on the VAS scales were evaluated by the author with an accuracy of 5 millimetres. Data were entered by the author using Microsoft Office Excel 2003. A control for typing errors was made by a systematic check against the original records.

4.1.5 Statistical analyses

The concordance of assessment was measured by viewing the ability of the patients to classify severity of their present hand eczema in the same group as that determined by the dermatologist. The agreement was expressed in two different ways: Cohen’s kappa coefficient and Spearman’s rank correlation rho. Cohen’s kappa coefficient measures the proportion of agreement between ratings adjusted for agreement expected by chance. It has a maximum of 1.00 when agreement is perfect whereas a value of zero indicates no agreement better than chance. To interpret values between 0 and 1 the following guideline should be applied:< 0.20 may be taken to represent poor reliability, values between 0.21–0.40 represent fair reliability, values between 0.41–0.60 is moderate, 0.61–0.80 is good and 0.81–1.00 represents very good reliability[65]. Kappa statistic takes no account of the degree of disagreement as all deviations are treated equally without considering the magnitude of discrepancy. Spearman’s rho is based on a ranked analysis, relevant for ordinal data of two variables. The correlation coefficient can have any value from -1 to +1, measuring the degree of association between the two variables. A correlation around 0 indicates no association between the variables. A coefficient below 0.5 represents a weak correlation, whereas values above 0.9 represent strong correlation.

All p-values were 2-sided and a 5% significance level was used. All analyses were done using APL*PLUS®, STSC, Inc. Rockville MD, USA.
The necessary number of participants was calculated before the study, expecting Cohen’s kappa

to correspond to a fair agreement between the assessors and choosing a 5% significance level. On the assumption that most assessments would be in groups 1, 2 and 3, the necessary sample size would be 50 subjects to obtain a power of 76%. A more even or skewed distribution with few subjects in the two highest (or lowest) groups would have given power estimates of 94% or 86% respectively.

4.2 Part 2: The population-based survey

4.2.1 Study population and design

A cross-sectional study in two steps was conducted February 2006–February 2007. In February 2006 a random sample of 6000 individuals was drawn from the Danish Civil Registration System. The participants were all Danish citizens living in the suburban area of Copenhagen and were 18–69 years old. A primary questionnaire focusing on self-reported symptoms of allergy and hypersensitivity from various organs related to airborne chemicals was posted to the population in March and April 2006[66]. The questionnaire also included two questions on hand eczema. Persons with hand eczema were identified by the questions: “Have you ever had hand eczema?” and “Have you had hand eczema on some occasion within the past 12 months?” The response rate of the primary questionnaire was 71% (n= 4242).

In all, 759 respondents reported ongoing hand eczema, defined as presence of hand eczema within the past 12 months. Of these persons, 752 received a second postal questionnaire in November 2006; of the remaining 7 persons, 3 had died, 2 had moved abroad and 2 could not be reached due to an unknown address. As was the primary questionnaire, the second questionnaire was posted with a stamped self-addressed return envelope and non-respondents received one reminder.

4.2.2 The second questionnaire

In the second 17-item questionnaire respondents verified the self-reported hand eczema diagnosis by the question “Have you ever had hand eczema?” Participants who answered “no” to this question were requested to skip all further questions and merely return the questionnaire.

The subsequent questions concerned the calendar year of the first episode of hand eczema as an adult (from 15 years of age onwards) and questions on atopic dermatitis based on the UK Working Party’s Diagnostic criteria, question-only version[67-69]. Medico-social consequences of hand eczema were evaluated by questions on sick leave over the past 12 months and use of prescription drugs in the same period. Previous examinations for hand eczema by a general practitioner or a dermatologist were asked about separately and participants were further requested to state the calendar year of their first visit(s). Given five options, patients were asked about the periods of symptoms the past 12 months choosing between: constant symptoms, symptoms more than half the time, symptoms about half the time, symptoms less than half the time, and no symptoms. The chosen categories were inspired by the applied method in a Swedish study[33]. The self-administered photographic guide accompanied the questionnaire. Information

concerning date of birth and sex of the participants was tracked by the Danish Civil Registration System.

4.2.3 Definitions

The age of onset was estimated by subtracting the year of birth from the calendar year of onset. Duration of hand eczema was calculated by subtracting the year of onset from the current year, ignoring disease-free periods. The time until seeking medical advice was calculated by subtracting the year of onset from the year of the first medical examination. Atopic dermatitis was defined according to the UK working Party's Diagnostic criteria, question-only version as persons fulfilling the major criteria plus a minimum of two out of four minor criteria[67-69].

4.2.4 Data entering

The primary questionnaire was scanned by the Danish company UNI·C using Read Soft Eyes & Hands.

The second questionnaire was entered by the author using SPSS Data Entry Builder 4.0 for Windows. The resulting data material was checked for errors by re-entering 120 (21%) randomly chosen questionnaires. The frequency of missing data in the second questionnaire was in general below 2%. In the self-administrated photographic guide, 4.7% and 5.9% had not completed the questions concerning the present severity of hand eczema and their most severe hand eczema ever.

4.2.5 Statistical analyses

Analyses comprised prevalence proportions, and the chi-square test was used for comparison of categorical variables. All p-values were two-sided with statistical significance defined as $p<0.05$. The outcomes of medical attention by a general practitioner (yes/no) or dermatologist (yes/no), respectively were analysed using logistic regression models. The explanatory factors studied were the most severe hand eczema ever, sex and atopic dermatitis. Multivariable statistical results were expressed as odds ratios (OR) with 95% confidence intervals. All analyses were done using Statistical Products and Service Solutions package (SPSS Inc, Chicago; IL, USA) for Windows (release 13.0).

4.3 Part 3: The follow-up study

4.3.1 Study population and design

Nine clinics participated in the study: 6 private dermatological clinics and 3 outpatient clinics at university hospitals. Together, these clinics cover the three main areas of Denmark with four clinics in Jutland (one outpatient clinic and three private clinics), one in Funen (one outpatient clinic) and four on Zealand (one outpatient clinic and three private clinics). All the participating clinics were characterised by employment of at least one dermatologist with membership of the Danish Contact Dermatitis Group.

Before the study, members of the Danish Contact Dermatitis group were thoroughly informed about the study design and the implementation with all practical details. The information was provided by the author at two separate meetings and further at a meeting joined by staff representatives from the participating clinics. All clinics were visited by the author to assure that the collaborating dermatologists and health-care personal were well informed about how to accomplish the study and ensuring that the participating dermatologists were able to assess the severity of hand eczema with the hand eczema severity index (HECSI). Further, comprehensive written information, including a DVD showing how to use the HECSI, was provided in all clinics.

The study population consisted of consecutive hand eczema patients, aged 18 years or older, enrolled January 2006–February 2007. Patients referred to the clinics with present hand eczema were invited to participate in the study. At the first consultation the patients received information about the study, vocally as well as written. Hand eczema severity was assessed by the dermatologist using the HECSI and by the patients using the self-administered photographic guide. In relation to patch test applications a self-administrated questionnaire was handed out and recollected at the patch test reading. Patients who had not completed the questionnaire received a reminder by post. Patients who of some reason were not patch tested were subsequently eliminated from the cohort.

Approximately 6 months after enrolment the patients were sent a follow-up questionnaire and a photographic guide. Two stamped self-addressed return envelopes and a reply card were included. Recipients were asked to tick one of two boxes on the card, marking whether they would like to attempt a follow-up clinical severity assessment of their hand eczema. Individuals willing to participate were requested to write down their telephone number on the card. Non-respondents received a reminder after three weeks. Geographically, follow-up examinations took place at the same clinics as the patients had visited at baseline. Severity assessment at the 6-months follow-up was performed by the author in collaboration with a nurse and an auxiliary nurse, both experienced in dermatologic diseases. Both nurses had been carefully instructed by the author in how to use the HECSI with a practical training session included.

4.3.2 Severity assessment of hand eczema

The assessment by the dermatologists was performed with the HECSI. The measurement of the HECSI is based on a combination of the extent of the disease on defined sub-areas (wrists, palms and back of hands, fingertips and fingers) and the severity of morphological signs (erythema, fissures, vesicles, scaling, oedema and papules). The range of HECSI is 0–360, where 0 corresponds to no eczema and 360 indicates the most severe eczema[60]. In the present study, severity of hand eczema was defined as mild (score of 0–11), moderate (score 12–27) and severe (score ≥28), which divided the cohort into three equally sized groups at baseline. Clinical changes in severity from baseline to follow-up were categorized as unchanged/ aggravated or improved: “unchanged/ aggravated” comprised patients whose symptoms were more severe at follow-up than at baseline and those whose symptoms did not change from the initial classification of moderate or severe.

The patient-rated severity assessment of present hand eczema was done using the self-administrated photographic guide. The self-administered photographic guide was also used to measure changes between baseline and follow-up. Clinical changes in severity from baseline to follow-up were categorized as improved or unchanged/ aggravated. “Unchanged/ aggravated” cases included all patients classified in a group of more severe symptoms at follow-up compared to baseline and unchanged cases initially reported as almost clear until very severe hand eczema.

Measurements by the HECSI and the self-administrated photographic guide were used in manuscript III. Measurements with the self-administrated photographic guide were used in manuscript IV.

4.3.3 Patch testing

Participants were tested with the European Baseline patch test series[70], and patients underwent additional patch tests when indicated. Trolab® (Hermal Reinbek, Germany) and Chemotechnique Diagnostics® (Malmö, Sweden) were used in 7 clinics and 2 clinics used the TRUE test® (panel 1 and 2) (Hilleroed, Denmark). Patch tests readings were according to the International Contact Dermatitis Research Groups (ICDRG) criteria and were performed as a minimum on D3[71]. Examinations were performed by nurses trained in patch testing or the doctor responsible. All patch test results were entered in to the Clinical Database as a well implemented part of the general operating procedure in clinics with membership of the Danish Contact Dermatitis Group.

4.3.4 The baseline questionnaire

A main focus of the baseline questionnaire was previous medical consultations for hand eczema with a general practitioner or with a dermatologist. Two almost identical questionnaires were generated, one for patients enrolled in the private clinics (56 items) and another for outpatients at the university hospitals (59 items).

Derived from preliminary interviews with volunteer hand eczema patients, questions on medical attention were constructed in an attempt to comply with the often complex medical histories that arise from a chronic relapsing disease. One section of the questionnaire concerned former medical visits for hand eczema through adult life. Patients were asked to report the calendar year of their first dermatological consultation for hand eczema.

The subsequent section concerned the present eruption of hand eczema that had led to medical attention. Present hand eczema was explained by the following sentence: “Present eruption of hand eczema means the new symptoms or the flare up that led to medical attention”. Patients were asked about the date (month and year) of the first examination by a general practitioner. Secondly, they were asked about the interval from onset of present hand eczema until seeking medical advice. Five categories were applied: Less than a month, 1–2 months, 2–4 months, 4–12 months and more than 12 months.

Wet work was estimated by questions on daily number of hand washing, hours with direct skin contact with water or detergents and hours with use of occlusive gloves. These questions were

adapted from the NOSQ-2002[64]. Questions on the year of onset of hand eczema, sick leave and atopic dermatitis were posed as described in the manuscript II. The patients were asked about the periods of symptoms the past 12 months given the 4 options: constant symptoms, symptoms more than half the time, symptoms about half the time, symptoms less than half the time[33].

The development of the questionnaire was based on studies on volunteer hand eczema patients from one of the participating hospitals and a private clinic. Preliminary questionnaires were evaluated and revised on the basis on interviews with 33 hand eczema patients. Special concern was given to questions concerning previous medical visits. The development process passed over six steps until it was ensured that the questions were considered relevant and easy to understand.

4.3.5 The follow-up questionnaire

The follow-up questionnaire was composed of 36 items one of them concerning sick leave the past 3 months. Cases of occupational hand eczema comprised all cases that had been reported to the Danish National Board of Industrial Injuries, information also obtained by the follow-up questionnaire.

4.3.6 Definitions

Wet work was defined as: exposure to water or detergents > 2 h per day, use of occlusive gloves > 2 h per day or very frequent hand washing > 20 times per day[24]. For persons gainfully employed, socioeconomic status was adapted from the socioeconomic classification system DISCO-88[72], a Danish version of the international nomenclature ISCO-88. This is a system based on education and managerial responsibilities. In the present study three categories were used: medium to high level, basic level and unskilled. Socioeconomic data were concluded by the registered hand written job title in the baseline questionnaire. If missing data occurred, information was obtained from the Clinical Database run by the Danish Contact Dermatitis Group where the DISCO-88 codes are registered along with the patch test results. For persons outside the labour market the three subgroups were: unemployed (including housewives/husbands), students and pensioners. The 9 participating clinics were divided into two groups: a capital group and a provincial group. The capital group included the 3 clinics (one outpatient clinic and 2 private clinics) placed in the Capital Region of Denmark, and the provincial group consisted of the 6 remaining clinics located in the other 4 regions of Denmark.

Patients who had sought a dermatologist for the first time for hand eczema were preselected for analyses in manuscript IV. Indirectly, participants were categorized as “first time patients” if they had reported their first dermatological visit to be in the year 2006–2007, corresponding to the year of their enrolment. Hospital outpatients further had to tick a box indicating that they had not consulted a dermatologist outside the hospital because of hand eczema. The results in Manuscript III are based on the total cohort. In Manuscript IV only first-time patients were eligible for analyses.

A main topic of Manuscript IV was medical delay. Medical delay was divided into two groups:

1. Patient delay: the interval from onset of symptoms of present hand eczema until seeing a general practitioner. A period of < 1 month was defined as no patient delay.

2. Health-care delay: the interval from the first consultation at the general practitioner for present hand eczema until seeing a dermatologist. A period of < 1 month was defined as no health-care delay.

Health-care delay was obtained by subtracting the date (month and year) of first seeing a general practitioner from the date of enrolment (month and year). Further, the total delay was calculated as the sum of patient delay and health-care delay.

4.3.7 Data entering

The baseline questionnaires were scanned by the Danish company UNI·C using Eyes & Hands. The resulting data material was checked for errors by a systematic manual comparison including all questionnaire items. In the data analysing process range checks were made for any outlying values, and controls were made for inconsistencies. The calendar month of seeing a general practitioner for present hand eczema seemed difficult to remember, as many as 13.8% of first-time patients did not answer the question.

The follow-up questionnaire, the two photographic guides and the two HECSI sheets were entered by an assistant experienced in questionnaire typing using SPSS Data Entry Builder 4.0 for Windows. Re-entering of the baseline photographic guide was done by the author. The average mismatch detected per entered value was 1.6%. A re-entering of a random sample of 32 (5%) follow-up questionnaires revealed a mismatch of 0.2%. Typing errors of the HECSI sheets were checked afterwards by comparing the total score with the manual calculated values.

4.3.8 Statistical analyses

4.3.8.1 Manuscript III

Non-parametric analysis was used in the descriptive analyses of the cohort. The chi-square test was used for comparison of categorical variables. The data from the self-administered photographic guide were analysed by non-parametric statistics. Wilcoxon signed rank test was used to compare paired data, and Mann-Whitney test was used for analysis of two independent groups. After a logarithmic transformation, the HECSI scores became normally distributed assessed by Kolmogorov-Smirnov test ($p= 0.06$) allowing t-tests. The association between background factors and the likelihood of having an HECSI score ≥28 (severe symptoms) was analysed using a logistic regression model. The association between the severity of hand eczema at baseline and severe hand eczema at follow-up (HECSI score≥28) was also analysed by logistic regression as was the analysis of the clinical course. Statistical results were expressed as odds ratios (OR) with 95% confidence intervals. All p-values were two-sided with statistical significance defined as $p<0.05$.

With data adapted from the HECSI sheets, the clinical course was further analysed in relation to the area affected by hand eczema and the different morphological signs at baseline. The area is theoretically given from 0 to 20 points. In the present analysis, cut-off points were made to divide the area score in three groups. Each group had the same number of patients and comprised one of the following: those with a small area of hand eczema (0–2 points), those with a moderate area of hand eczema (3–5 points), or those with a large area of hand eczema (> 5 points). The presence of the different morphological signs at baseline was registered with no intensity ratings. All analyses were done using Statistical Products and Service Solutions package (SPSS Inc, Chicago; IL, USA) for Windows (release 15.0).

4.3.8.2 Manuscript IV

Non-parametric analysis was used in the descriptive analyses of the cohort. The chi-square test was used for comparison of categorical variables. The associations between background factors with the delay periods were analyzed by using non-parametric statistics; the Mann-Whitney test was used for comparing data from two independent groups and Kruskal-Wallis test was used if more than two groups were compared. The median and inter-quartile range (IQR) was calculated.

Data on patient delay were transformed for analyses by the following nomenclature: less than a month= 0.5, 1–2 months= 1.5, 2–4 months = 3.0, 4–12 months= 8.0, more than 12 months= 12.0. The accuracy of the stated date of seeing a general practitioner will depend on how far back in time the examination was performed. The issue was dealt with by categorising the health-care delay variable. For health-care delay up to 5 months the original calculated numbers were used except for no delay that was assigned 0.5 month. Considering the decreasing reliability of the stated date, a health-care delay of 6–12 months was assigned the median count of 9 months and the same value was chosen if the patient was unable to remember the month of the medical contact but could recall that it had been within a year. For patients with a health-care delay of ≥ 12 months or if they could recall only that it had been more than a year ago, the count was set to 24 months. The number represented the median value of the other original data of health-care delay ≥ 12 months. The risk of having a poor prognosis (yes/no) was analysed in a multivariable logistic regression model including the explanatory factors of patient delay, health-care delay and total delay adjusted for the baseline characteristics sex and age; and socioeconomic group and geography as these factors were found to be significant risk factors for patient delay or health-care delay. Patient delay and health-care delay were included in the regression analyses as continuous variables after accepting linearity using likelihood ratio tests. Statistical results were expressed as odds ratios (OR) with 95% confidence intervals. All p-values were two-sided with statistical significance defined as $p<0.05$. All analyses were done using Statistical Products and Service Solutions package (SPSS Inc, Chicago; IL, USA) for Windows (release 15.0).

The necessary number of participants was calculated before the study. A priori we wanted to test the hypothesis saying that a patient delay or health-care delay exceeding 3 months would implicate an increased risk of unchanged/ deteriorated clinical symptoms by the 6 months follow-up. It was assumed that 40% of patients without patient delay would improve clinically and that there would be a difference of 18% in clinical outcome between participants with patient delay compared with

those without. Based on that model, and choosing a two-sided 5% significance level, the necessary sample size was estimated to be 200. Expecting about 40% to be first-time patients and a follow up rate of 60%, we intended to include at least 800 patients. A similar calculation was performed for health-care delay. In the final data analysis, however, we chose a different statistical model.

5 RESULTS

5.1 Part 1: Validation of a self-administrated photographic guide

5.1.1 Descriptive statistics

A total of 53 patients participated: 47 women and 6 men (mean age 38 years, range 18–70 years). On average, the patients reported an improvement in hand eczema, when comparing the present severity of hand eczema with that of the past 12 months, as assessed by the VAS and by using the self-administered photographic guide (Table 1).

Table 1: Results of severity assessments of hand eczema by the patients and the dermatologists

Patient-rated severity [a]	**Mean ± SD**	**Range**	**MD** [c]
VAS	4.5 ± 2.6	0-10	1
VAS-12	5.5 ± 2.3	0.5-9.5	2
Photographic guide	1.84 ±0.92	0-4	2
Photographic guide- 12	2.24 ± 0.80	1-4	3
Dermatologist-rated severity [b]	1.81 ± 0.98	0-4	0

[a] VAS, global score on a visual analogue scale for present hand eczema; VAS-12, global score on the visual analogue scale for hand eczema over the past 12 months; photographic guide, patient-rated severity of present hand eczema using the photographic guide; photographic guide-12; patient-rated severity of hand eczema over the past 12 months using the photographic guide.
[b] Photographic guide, dermatologist-rated severity of present hand eczema using the photographic guide.
[c] MD: missing data

5.1.2 Reliability and correlations

Two patients did not correctly complete the question on present severity of hand eczema. Of the 51 patients grading their present hand eczema, identical grades were obtained for 37 (72.5%). The other 14 patients assigned a grade next to the group assessed by the dermatologist (Table 2). The inter-rater reliability analyzed by Spearman's rho provided a coefficient of 0.82. The inter-rater agreement estimated by Cohen's kappa, only giving credits for identical grades, was 0.61 and represents good reliability (Table 3). In the group of more severely affected cases, defined as groups 3 and 4, identical grades were obtained for 91.0%, whereas the absolute level of agreement was 67.5% among the milder cases defined as group 0, 1 and 2. The difference was not statistically significant (Fisher's exact test, p= 0.47).
The correlation, estimated by Spearman's rho, was calculated between the patient-rated clinical severity using the photographic guide and the score on the VAS. A correlation coefficient of 0.68

was found for present hand eczema and may be taken as good, whereas the correlation decreased to 0.45 for the past 12 months.

The score on the VAS for present hand eczema showed a moderate correlation (Spearman's rho=0.52) with the physician-rated clinical severity (Table 3).

Table 2: Severity ratings of present hand eczema by the patients and dermatologist using the same photographic guide [a]

	Dermatologist-rated severity					
Patient-rated severity	**0**	**1**	**2**	**3**	**4**	**Total**
0	3					3
1	2	9	4			15
2		5	15	2		22
3			1	8		9
4					2	2
Total	5	14	20	10	2	51

[a] The patient and dermatologist used the same photographic guide rating the present hand eczema in one of four groups(1-4) as it appeared on the more severily affected hand. They were also offered the option " There is no hand eczema right now"(group 0). The table only illustrates assessments performed by both the dermatologist and the patients.

Table 3: Relationship between clinical severity assessment by the patients and the dermatologists

Identical rating by patients and dermatologists using the self-administrated photographic guide described as:	
Absolute level of agreement (95 % CI)	72.5 % (58.3- 84.1 %)
Inter-rater agreement (Cohen's kappa)	0.612 (p< 0.0001)
SEM (Cohen's kappa)	0.09
Correlation of agreement (Spearman's rho)	0.82 (p<0.0001)
Correlation between visual analogue scale and:	
Patient-rated present severity [a]	0.68 (p<0.0001)
Patient-rated severity – for the last 12 months [a]	0.45 (p<0.001)
Dermatologist-rated present severity [b]	0.52 (p<0.0001)

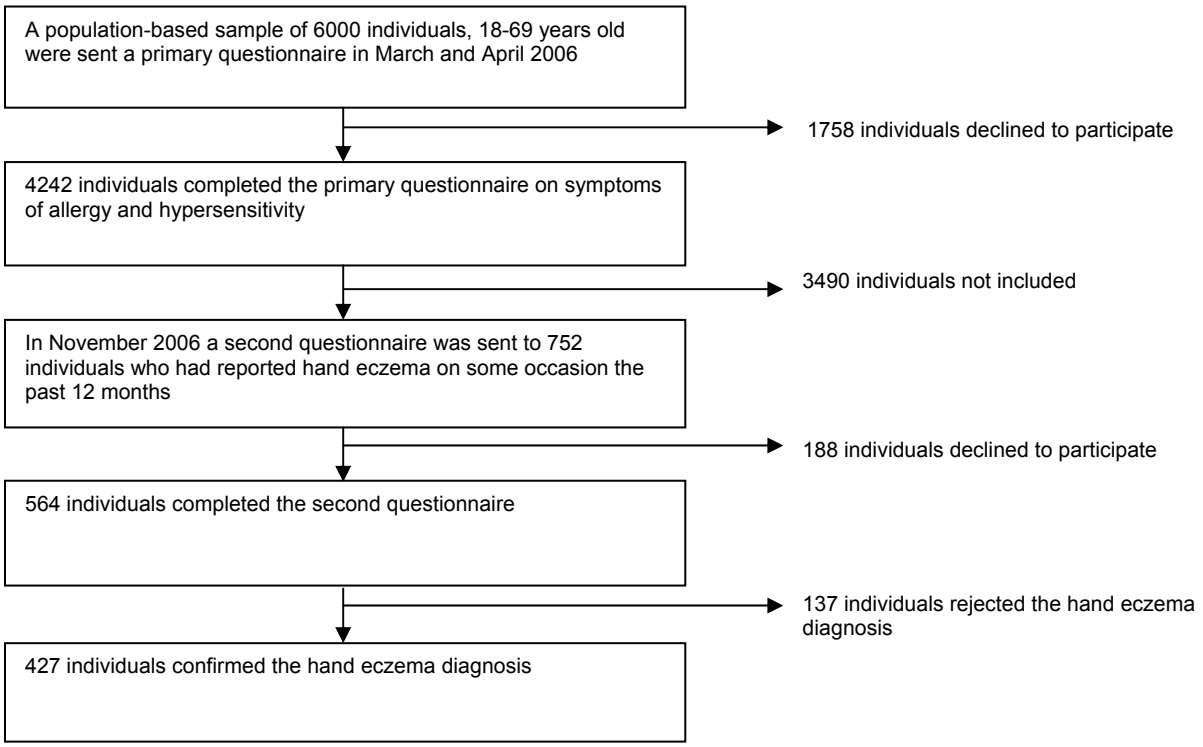
[a] Rank correlation between patient-rated severity using the self-administered photographic guide and the corresponding global score on the visual analogue scale of present hand eczema and hand eczema during the last 12 months, respectively.
[b] Rank correlation between dermatologist-rated severity of present hand eczema using the self-administrated photographic guide and the corresponding global score on the visual analogue scale.

5.2 Part 2: The population-based survey

5.2.1 Response rate:

Among the 752 potential respondents, 564 returned the second questionnaire (response rate 75%): 375 women and 189 men. The first question of the second questionnaire: "Have you ever had hand eczema?" was answered negatively by 23.4% (n= 132) of the respondents, leaving 427 individuals with a confirmed hand eczema diagnosis. Five questionnaires were returned unanswered. Figure 2 gives an overview of the recruitment of participants.

Figure 2: Flow chart showing the recruitment of participants in the two cross-sectional population-based studies.



5.2.2 Drop-out analysis

In relation to the primary questionnaire a higher response-rate was found among women (75.8%) than among men (65.5%), ($p<0.001$). Further, young age was associated with being a non-respondent ($p<0.001$)[66].

In relation to sex ($p= 0.140$) or age ($p= 0.631$) persons who confirmed the hand eczema diagnosis in the second questionnaire were no different from persons who rejected it.

5.2.3 Descriptive statistics and prevalence measures

Based on an extrapolation of the data from the second questionnaire the one-year prevalence of hand eczema was estimated as 14%.The following results are based on this group.
Baseline characteristics of the group regarding sex and age as well as prevalence measures of atopic dermatitis and age at onset of hand eczema are provided in Table 4. The median duration of hand eczema was estimated as 16 years (SD 11.7)

Table 4: Descriptive data on cases with self-reported hand eczema in the background population (n=427).

Sex % (n)	
Men	32.1 (137)
Women	67.9 (290)
Mean age years	45.7 (SD 12.5)
Mean age at onset of hand eczema years	27.0 (SD 11.9)
Men	28.0 (SD 12.6)
Women	26.0 (SD 11.5)
Atopic dermatitis[1] % (n)	34.8 (149)
Men	25.5 (35)
Women	39.3 (114)

[1] The UK Working Party's diagnostic criteria
SD: Standard deviation

5.2.4 Severity of hand eczema and medical examinations

In all, 56.2% of the patients assessed the most severe hand eczema ever experienced as "almost clear", 28.1% had suffered from moderate hand eczema, while severe or very severe hand eczema was reported by 10.2% and 5.5%, respectively. No clear association between the most severe hand eczema ever experienced and a history of atopic dermatitis was found.

A total of 348 (81.5%) individuals reported hand eczema within the past 12 months. In all, 136 (32.0%) had symptoms about half the time or more, while continuous symptoms the preceding year were reported by 46 (10.8%) individuals (Table 5). Present hand eczema was reported by 185 (43.3%). Of these, 42 (22.8%) classified their hand eczema as "moderate" to "very severe" (Table 6). Sick leave because of hand eczema within the past 12 months was found in 5 (1.2%) cases with 6 days as the total average duration. Prescribed medication had been used by 108 (25.3%) within the past 12 months.

Of the respondents, 288 (67.4 %) had sought their general practitioner because of hand eczema, relative more women than men (70.9% versus 59.9%, p=0.023). Atopic dermatitis was also positively associated with seeking medical advice (p=0.008). A dermatologist had been consulted by 186 (43.6%) of the participants. The mean interval from first episode of hand eczema until seeing a general practitioner was 1.4 years (SD 4.11) and 2.1 years (SD 4.14) before seeing a dermatologist.

The tendency to seek medical advice reflected the severity of hand eczema estimated as "the most severe hand eczema ever" rated by the self-administered photographic guide (Figure 3). Among persons who had experienced only "almost clear" hand eczema, 54.4% had been seen by their general practitioner. The proportion increased with severity to include all persons who had experienced "very severe hand eczema". Correspondingly, more severe hand eczema was related to seeing a dermatologist (Figure 3). In a multivariable logistic regression analysis "the most severe hand eczema ever" was significantly associated with having consulted a general practitioner as well as a dermatologist when adjusted for sex and atopic dermatitis (Table 7). The association between atopic dermatitis and consulting a general practitioner disappeared when including

severity of hand eczema in the logistic regression model. The increased association between female sex and consulting a general practitioner remained (Table 7).

The group that had never sought medical advice (n=139) consisted mainly of individuals with infrequent episodes of hand eczema; however, 17.4% reported symptoms half the time or more (Table 5). The median period of time since the first eruption of hand eczema was 12 years (SD 10.2) and present symptoms was reported by 30.2% (n= 42). Sick leave due to hand eczema was not observed in this group.

Among individuals who had sought advice from their general practitioner, 35.4% (n=102) had never seen a dermatologist. The median duration of hand eczema was 12 years (SD 12.3) in this group, 15% had experienced severe or very severe hand eczema and 32.3% reported symptoms half the time or more the past 12 months. Among persons reporting present hand eczema, 19.0% had moderate to very severe symptoms (Table 6).

Table 5: Self-reported duration of hand eczema symptoms within the past 12 months in relation to: all respondents, respondents that have never consulted a medical doctor, respondents that have only consulted a general practitioner and respondent that have consulted a general practitioner and a dermatologist.

	Total (n=424; MD=3) % (n)	**Not seen by a medical doctor (n=138; MD=1) % (n)**	**Seen by a GP but not a dermatologist (n= 102) % (n)**	**Seen by a GP and a dermatologist (n= 184; MD =2) % (n)**
All the time	10.8 (46)	3.6 (5)	9.8 (10)	16.8 (31)
> ½ time	10.6 (45)	8.0 (11)	12.7 (13)	11.4 (21)
= ½ time	10.6 (45)	5.8 (8)	9.8 (10)	14.7 (27)
< ½ time	50.0 (212)	63.0 (87)	45.1 (46)	42.9 (79)
No symptoms	17.9 (76)	19.6 (27)	22.5 (23)	14.1 (26)

GP: general practitioner
MD: missing data

Table 6: Self-rated severity of hand eczema at present related to medical consultations using a self-administrated photographic guide.

	Severity of present hand eczema			
	Total population % (n); n= 427	**Not seen by a medical doctor % (n); n=139**	**Seen by a general practitioner but not a dermatologist % (n); n=102**	**Seen by a general practitioner and a dermatologist % (n); n=186**
Reported eczema	185	42	42	101
Almost clear	77.3 (143)	92.9 (39)	81.0 (34)	69.3 (70)
Moderate	14.1 (26)	7.1(3)	9.5 (4)	18.8 (19)
Severe	6.5 (12)	0.0 (0)	7.1 (3)	8.9 (9)
Very severe	2.2 (4)	0.0 (0)	2.4 (1)	3.0 (3)

Figure 3: The proportion of persons who had visited a general practitioner or a dermatologist related to most severe hand eczema ever experienced

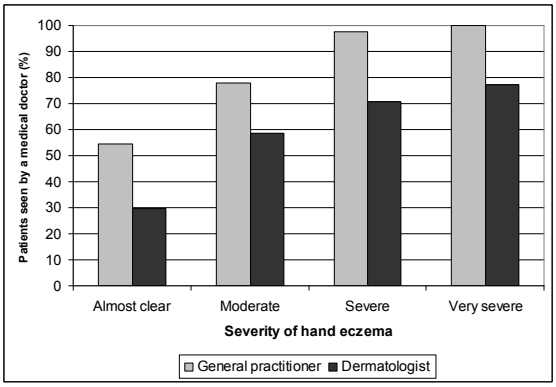


Table 7: Multivariable logistic regression analysis of self-rated "most severe hand eczema ever" based on the self-administrated photographic guide in relation to medical consultations adjusted for sex and atopic dermatitis.

Most severe hand eczema ever	General practitioner[3] OR (95% CI)	Dermatologist[4] OR (95% CI)
Almost clear (reference)	1	1
Moderate	2.9 (1.7-5)	3.4 (2.1-5.4)
Severe	30.7 (4.1-228.1)	5.4 (2.6-11.4)
Very severe	∞	8.1 (2.9-23)
Atopic dermatitis [1]	1.5 (0.9-2.4)	1.18 (0.7-1.9)
Sex [2]	1.7 (1.1-2.7)	0.9 (0.6-1.4)

[1] Atopic dermatitis versus no atopic dermatitis.
[2] Women versus men.
[3] Multivariable logistic regression of persons seen by a general practitioner (yes/no)
[4] Multivariable logistic regression of persons seen by a general practitioner and a dermatologist (yes/no)
CI: confidence interval

5.3 Part 3: The follow-up study

5.3.1 Manuscript III

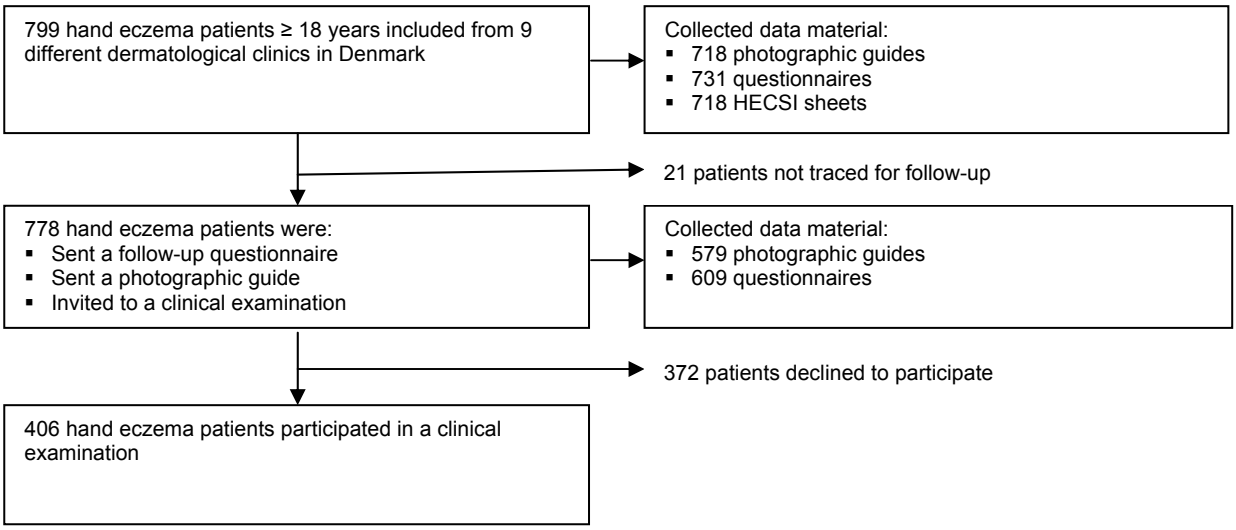
5.3.1.1 Participation and response rate

The study population comprised 799 patients, each centre provided from 18 to 184 subjects. The data collection resulted in 727 HECSI sheets, of which 718 were fully completed (completion rate 89.9%); 718 self-administered photographic guides (response rate 89.9%); and 731 questionnaires (response rate 91.5%).

In all, 21 (2.6%) patients from the initial cohort were lost to follow-up: 4 could not be traced and baseline data on 17 patients were not received by the author until long after the inclusion period had ended. Of the remaining 778 patients, 609 (78.2%) completed the follow-up questionnaire. The self-administered photographic guide was returned by 579 (74.4%) patients, of whom 534

answered the question about present severity of hand eczema. Of those invited, 406 (52.2%) underwent the follow-up clinical examination. Figure 4 gives an overview of the recruitment of patients.

Figure 4: Flow diagram of the 799 patients enrolled in the cohort and the number of collected data.



5.3.1.2 Drop-out analysis

At baseline no differences were found between questionnaire respondents and non-respondents regarding sex (p= 0.79), age (p= 0.19) or HECSI score at baseline (t-test, p=0.15). A drop-out analysis of the attendees/ non-attendees at the 6-month follow-up was performed on the group of patients with a completed HECSI at baseline. No differences regarding age or socioeconomic group were demonstrated. There was a trend (p=0.05) of more women (53.8%) than men (45.8%) attending the follow-up examination. No statistically significant differences were found between the two groups in relation to HECSI at baseline (t-test, p= 0.06) or the present severity at follow-up registered from the self-administered photographic guide (Mann-Whitney test p= 0.09).

5.3.1.3 Descriptive statistics and prevalence measures

The median age of the cohort was 41 years (range 18–84). Baseline characteristics of the cohort as well as prevalence measures for atopic dermatitis, wet work and the proportion of patients with a positive patch test are displayed in Table 8. More men (84.8%) were gainfully employed than were women (78.1%), (p=0.02), while no socioeconomic differences were found between men and women (p= 0.23) in employment. Being a nurse was the most common position in the medium to high level group, and being an auxiliary nurse was the commonest in the basic level group. Being a cleaner was the most common job among unskilled patients. More women (52.1%) than men (33.8%) were employed in wet occupations (p<0.001). A higher prevalence of positive patch test results was found in patients from the hospital sector (56.9%) compared with patients from private clinics (40.9%) (p< 0.001), but no difference was found between the different private clinics (p=0.21).

Table 8: Baseline characteristics of 799 hand eczema patients.

Number of included patients	% (n)
Total	799
Men (%)	34.8 (278)
Women (%)	65.2 (521)
Age groups (years)	
18–29	24.9 (199)
30–39	22.2 (177)
40–49	21.2 (169)
+ 50	31.8 (254)
Atopic dermatitis n= 714	28.7 (205)
Symptoms the past 12 months n= 719	
< ½ the time	18.1 (130)
≥ ½ the time	81.9 (589)
Socioeconomic status n= 798	
Unskilled	9.1 (73)
Basic level	47.2 (377)
Medium/ high level	24.0 (192)
Unemployed	6.1 (49)
Student	3.0 (24)
Retired	10.4 (83)
Wet work[1] n=5 51	45.6 (251)
≥ 1 positive patch test	45.6 (364)

[1] Reports obtained among the 642 employed patients.

5.3.1.4 Baseline clinical severity of hand eczema

The mean HECSI score at baseline was19.9 points (range 0–209 points). Moderate to very severe hand eczema was reported by 60.3% of the patients using the self-administered photographic guide (Figure 5).

5.3.1.5 Risk factors for severe hand eczema at baseline

In a logistic regression model severe hand eczema (HECSI≥28) was found to be associated with increasing age, atopic dermatitis, frequent eruptions during the past 12 months and one or more positive patch test (Table 9).

5.3.1.6 Clinical prognosis at the 6-month follow-up

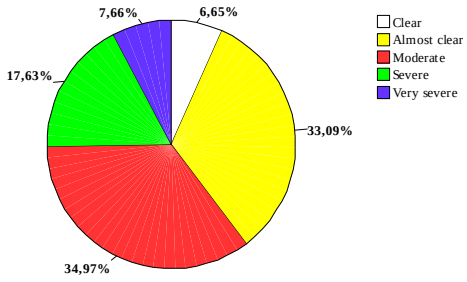
Measured by the photographic guide, moderate to very severe hand eczema was reported by 193 of 534 (36.1%) patients at follow-up (Figure 5). Among patients with a self-rated severity assessment at baseline as well as at follow-up (n=467) a general improvement was demonstrated (Wilcoxon signed rank test, $p<0.001$).

The mean HECSI score was 11.2 points at follow-up, a score improvement of 44% compared with that at baseline. In total, 366 patients had a severity assessment by the HECSI performed both at baseline and follow-up. A paired sample t-test of this group showed a statistically significant improvement ($p<0.001$).

Analysed by the HECSI as an ordinal scale, 60.4% patients had improved. Clinical severity at baseline was found to be a predominant risk factor for the severity at follow-up. For patients with severe hand eczema at baseline, the odds ratio of severe hand eczema at follow-up was 7.62 (95% CI: 3.53- 16.45) adjusted for sex and age group; an odds ratio of 1.98 (95% CI: 0.84–4.62) was estimated for patients with initial moderate hand eczema. Being an unskilled worker was found to be a risk factor of a poor prognosis as was frequent eruptions the past 12 months (Table 10). There was a trend towards a poor prognosis among persons employed in a wet occupation; however, this did not reach statistical significance. With respect to morphology, the presence of fissures or scaling at baseline was associated with a poor prognosis (Table 11).

Figure 5: Patient rated severity of hand eczema using a photographic guide

a. Patient rated severity of present hand eczema at baseline using the self-administrated photographic guide (n=692).



b. Patient rated severity of present hand eczema at follow-up using the self-administrated photographic guide (n=534).

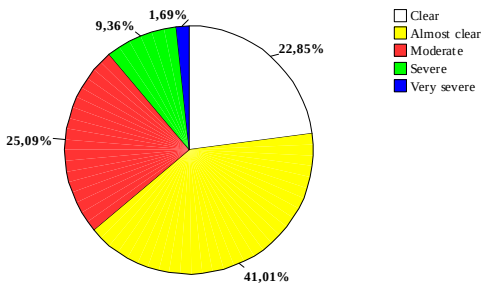


Table 9: Severity of hand eczema at baseline (n=718) and multivariable logistic regression analysis with the outcome of severe hand eczema at baseline.

		Clinical severity			OR[2] (95 % CI)	P- value
	Total	**No/mild n (%)**	**Moderate n (%)**	**Severe n (%)**		
Sex						0.88
Men	252	70 (27.8)	92 (36.5)	90 (35.7)	1.00	
Women	466	161 (34.5)	149 (32.0)	156 (33.5)	0.98 (0.70-1.36)	
Age groups (years)						<0.001
18–29	177	68 (38.4)	67 (37.9)	42 (23.7)	1.00	
30–39	158	47 (29.7)	67 (42.4)	44 (27.8)	1.24 (0.76-2.03)	
40–49	154	49 (31.8)	52 (33.8)	53 (34.4)	1.69 (1.04-2.72)	
>50	229	67 (29.3)	55 (24.0)	107 (46.7)	2.81 (1.82-4.34)	
Atopic dermatitis[3] n= 638						0.01
No	454	152 (33.5)	148 (32.6)	154 (33.9)	1.00	
Yes	184	50 (27.2)	66 (35.9)	68 (37.0)	1.65 (1.11-2.46)	
Symptoms the past 12 months n= 644						0.02
< ½ the time	120	50 (41.7)	38 (31.7)	32 (26.7)	1.00	
≥ ½ the time	524	155 (29.6)	176 (33.6)	193 (36.8)	1.73 (1.10-2.72)	
Socioeconomic groups n= 717						0.94
Unskilled	65	17 (26.2)	25 (38.5)	23 (35.4)	1.00	
Basic level	340	117 (34.4)	114 (33.5)	109 (32.1)	0.92 (0.52-1.62)	
Medium/high level	167	53 (31.7)	58 (34.7)	56 (33.5)	0.99 (0.54-1.82)	
Outside the labour market	145	44 (30.3)	43 (29.7)	58 (40.0)	1.04 (0.55-1.94)	
Wet work n= 489[1]						0.82
No	268	84 (31.3)	96 (35.8)	88 (32.8)	1.00	
Yes	221	78 (35.3)	74 (33.5)	69 (31.2)	1.05 (0.71-1.56)	
≥ 1 positive patch test						<0.001
No	395	143 (36.2)	152 (38.5)	100 (25.3)	1.00	
Yes	323	88 (27.2)	89 (27.6)	146 (45.2)	2.37 (1.71-3.30)	
Total	718	231 (32.2)	241 (33.6)	246 (34.3)		

[1]Reports obtained among the 642 employed patients.
[2] Multivariable logistic regression analysis with the outcome odds ratio (OR) of severe hand eczema at baseline, adjusted by the variables sex and age group.
[3] The UK Working Party's diagnostic criteria
CI: confidence interval.

Table 10: Changes of severity of hand eczema at follow-up (n=366) and multivariable logistic regression analysis with the outcome of unchanged/ aggravated hand eczema at follow-up.

		Prognosis			
	Total	**Improved n (%)**	**unchanged/ aggravated n (%)**	**OR [2] (95 % CI)**	**P-value**
Sex					0.62
Men	116	72 (62.1)	44 (37.9)	1.00	
Women	250	153 (61.2)	97 (38.8)	1.12 (0.71-1.78)	
Age groups (years)					0.68
18–29	79	52 (65.8)	27 (34.2)	1.00	
30–39	80	46 (57.5)	34 (42.5)	1.43 (0.75-2.73)	
40–49	83	48 (57.8)	35 (42.2)	1.41 (0.75-2.67)	
>50	124	75 (60.5)	49(39.5)	1.28 (0.71-2.32)	
Atopic dermatitis[3] n= 345					0.13
No	233	146 (62.7)	87 (37.3)	1.00	
Yes	112	65 (58.0)	47 (42.0)	1.47 (0.89-2.44)	
Symptoms the past 12 months n=348					0.04
< ½ the time	59	43 (72.9)	16 (27.1)	1.00	
≥ ½ the time	289	171 (59.2)	118 (40.8)	1.96 (1.05-3.66)	
Socioeconomic groups n= 365					0.04
Unskilled	29	11 (37.9)	18 (62.1)	1.00	
Basic level	161	94 (58.4)	67 (41.6)	0.44 (0.20-1.00)	
Medium/high level	95	64 (67.4)	31 (32.6)	0.30 (0.12-0.71)	
Outside the labour market	80	51 (63.8)	29 (36.3)	0.36 (0.15-0.88)	
Wet work n= 263[1]					0.07
No	147	96 (65.3)	51 (34.7)	1.00	
Yes	116	63 (54.3)	53 (45.7)	1.61 (0.97-2.68)	
≥ 1 positive patch test					0.17
No	187	120 (64.2)	67 (35.8)	1.00	
Yes	179	101(56.4)	78 (43.6)	1.35 (0.88-2.09)	
Total	366	221 (60.4)	145 (39.6)		

[1]Reports obtained among the 642 employed patients.

[2]Multivariable logistic regression analysis with the outcome odds ratio (OR) of unchanged/ aggravated hand eczema at follow-up adjusted by the variables sex and age group.

[3] The UK Working Party's diagnostic criteria

CI: confidence interval

Table 11: Morphological signs at baseline, changes of severity of hand eczema at follow-up and multivariable logistic regression analysis with the outcome unchanged/ aggravated hand eczema (n=366).

	% of patients at baseline (n)	**Improved** % (n)	**Unchanged/ aggravated** % (n)	**OR[2] (95 % CI)**	**P-value**
Erythema	92.6 (339)	60.5 (205)	39.5 (134)	0.97 (0.44-2.16)	0.94
Papules	83.3 (305)	59.3 (181)	40.7 (124)	1.31 (0.73-2.35)	0.36
Vesicles	50.5 (185)	58.9 (109)	41.1 (76)	1.13 (0.74-1.73)	0.56
Fissures	65.0 (238)	54.6 (130)	45.4 (108)	2.00 (1.26-3.19)	**<0.01**
Scaling	89.3 (327)	58.1 (190)	41.9 (137)	2.92 (1.29-6.27)	**0.01**
Oedema	57.4 (210)	60.0 (126)	40.0 (84)	1.03 (0.67-1.58)	0.89
Large area [1]	30.6 (112)	53.6 (60)	46.4 (52)	1.48 (0.93-2.33)	0.10
Total	366	60.4 (221)	39.6 (145)		

[1] Reference: The pooled group of small and moderate area of hand eczema.
[2] Multivariable logistic regression analyses with the outcome: odds ratio (OR) of unchanged/ aggravated hand eczema, adjusted by the variables sex and age group.
CI: confidence interval.

5.3.2 Manuscript IV

5.3.2.1 Participation and response rate

A total of 333 first-time patients were eligible for analyses, each centre provided 3–93 individuals. From the private dermatological clinics 305 (53.8%) out of 567 were first-time patients compared with 28 (12.1%) out of 232 patients from the hospital sector.

At baseline, the photographic guide was returned by 304, of whom the question on present severity of hand eczema was completed by 302 (response rate 90.7%).

Among the 333 enrolled patients, 12 (3.6%) were not traced for follow-up. Of the remaining 321 patients, the follow-up photographic guide was returned by 238 patients (74.1%) and the present hand eczema was assessed by 219 (68.2%). The follow-up questionnaire was completed by 257 patients (80.1%).

5.3.2.2 Drop-out analysis

A drop-out analysis among the group of patients with a self-reported severity assessment at baseline showed no statistically significant difference between respondents/ non-respondents of the follow-up severity assessments regarding age (p=0.610), geography (p=0.354), patient delay (p=0.164), health-care delay (p=0.178) or severity at baseline (p=0.274). Relatively more women than men reported the severity at follow-up (70.7% versus 57.7%, p=0.029). A statistically significant difference was also observed among the socioeconomic groups (p= 0.005), with the highest response rate among medium/high level patients (83.3%) and the lowest among the unskilled (51.5%).

5.3.2.3 Descriptive statistics and prevalence measures

The median age of the cohort was 36 years (IQR 28–50 years) and the median duration of hand eczema, ignoring disease-free periods, at study baseline was 1 year (IQR: 0–6 years). Baseline characteristics of the cohort as well as prevalence measures for atopic dermatitis, wet work, sick leave, occupational hand eczema, type of dermatologic clinic and the proportion of patients with a positive patch test are shown in Table 12.

Table 12: Baseline characteristics of first-time patients referred with hand eczema to see a dermatologist (n= 333).

	% of patients (n)
Sex	
Men	34.2 (114)
Women	65.8 (219)
Age groups (years)	
18-29	29.1 (97)
30-39	25.8 (86)
40-49	19.5 (65)
+ 50	25.5 (85)
Socio-economic groups	
Unskilled	11.1 (37)
Basic level	52.3 (174)
Medium/high level	20.7 (69)
Outside the labour market	15.9 (53)
≥1 positive patch test	
Yes	36.9 (123)
No	63.1 (210)
Atopic dermatitis[1] n= 326	
Yes	24.2 (79)
No	75.8 (247)
Sick leave n= 320	
Yes	9.4 (30)
No	90.6 (290)
Wet work n= 302	
Yes	39.4 (119)
No	60.6 (183)
Occupational n= 237	
Yes	26.2 (62)
No	73.8 (175)
Geography	
Capital	34.5 (115)
Provincial	65.5 (218)
Dermatological clinics	
Private	91.6 (305)
Hospital clinics	8.4 (28)
Total	333

[1] UK Working Party's diagnostic criteria

5.3.2.4 Medical delay

The median patient delay was 3 months (IQR 1.5–8.0 months) and the median health-care delay was 3 months (IQR 1.0–8.0 months) (Figure 6). A total delay of more than 6 months was experienced by 52.2% of the patients and 23.6% were not seen by a dermatologist until after 12 months. No association was found between patient delay and health-care delay (Kruskal Wallis test, p= 0.354). In relation to socioeconomic classification, a substantially longer patient delay was found among the medium/high level class. Patients living in provincial districts had a longer health-care delay compared with patients from the Capital Region. Longer health-care delay was also experienced among the youngest patients (Table 13).

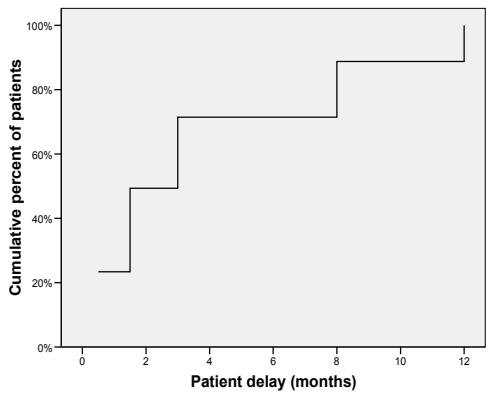
5.3.2.5 Self-reported severity of hand eczema and risk factors of a poor prognosis

Moderate to very severe hand eczema was reported by 54.7% of the patients at baseline (Table 14). Analysed by Kruskal Wallis test, the clinical severity at baseline was not associated with patient delay (p= 0.206) or health-care delay (p= 0.075).

By the 6-month follow-up 25.6% reported moderate to very severe hand eczema and 28.3% had healed (Table 14). A total of 52.5% had improved, whereas 47.5% had unchanged/ aggravated hand eczema. Patient delay was found to be associated with the clinical course, finding a poor prognosis in 32.4% of patients without delay increasing to 72.0% of patients with a delay exceeding 12 months (Figure 7a). Among patients without health-care delay, 26.7% had a poor prognosis compared with 72.2% of those with more than 12 months of delay (Figure 7b). In a multivariable logistic regression model, the odds ratio of a poor prognosis increased by a factor of 1.11 (95%CI 1.02–1.21) per month of patient delay and 1.05 (95% CI 1.00–1.10) per month of health-care delay, although the latter did not reach statistical significance (Table 15). For every month of total delay, the odds ratio of a poor prognosis increased by a factor of 1.06 (1.02–1.11) (Figure 7c and Table 15). By the 6-month follow-up, 13 patients had reported sick leave within the past 3 months.

Figure 6: The count of months of patient-delay and health-care delay, respectively.

a. Patient-delay (n =312, missing data =21)



b. Health-care delay (n= 304, missing data=29)

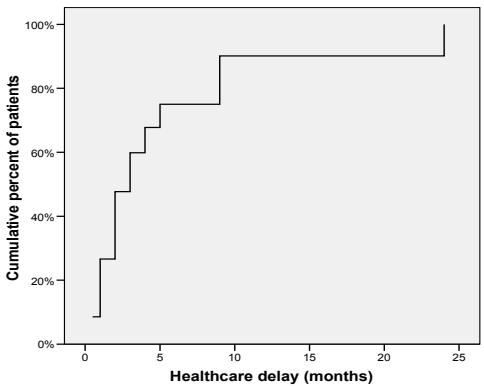


Table 13: Months of patient delay and months of health-care delay in the cohort of hand eczema patients.

	Patient delay			Health-care delay		
	% of patients (n) n= 312	**Months of delay Median (IQR)**	**Mann-Whitney test P-value**	**% of patients (n) n= 304**	**Months of delay Median (IQR)**	**Mann-Whitney test P-value**
Sex			p= 0.107			p= 0.412
Men	34.9 (109)	1.5 (0.5-5.5)		36.2 (110)	3.0 (1.0-9.0)	
Women	65.1 (203)	3.0 (1.5-8.0)		63.8 (194)	2.0 (1.75-5.0)	
Age groups (years)			p= 0.090[1]			p= 0.012[1]
18-29	29.8 (93)	1.5 (1.5-3.0)		29.6 (90)	3.0 (2.0-9.0)	
30-39	25.6 (80)	2.25 (1.5-8.0)		24.7 (75)	3.0 (1.0-5.0)	
40-49	19.6 (61)	3.0 (1.5-8.0)		20.1 (61)	2.0 (1.0-4.0)	
+ 50	25.0 (78)	1.5 (0.5-8.0)		25.7 (78)	2.0 (1.0-5.0)	
Socio-economic groups			p= 0.045[1]			P= 0.763[1]
Unskilled	11.5 (36)	1.5 (1.5-6.75)		10.5 (32)	3.0 (1.0-9.0)	
Basic level	52.5 (164)	1.5 (0.75-6.75)		52.3 (159)	3.0 (1.0-5.0)	
Medium/high level	20.2 (63)	3.0 (1.5-8.0)		20.7 (63)	3.0 (1.0-5.0)	
Outside the labour market	15.7 (49)	1.5 (0.5-8.0)		16.4 (50)	3.0 (2.0-9.0)	
Sick leave n=294 /n=302			p= 0.179			p= 0.292
Yes	9.5 (28)	1.5 (0.5-3.0)		9.6 (29)	2.0 (1.0-9.0)	
No	90.5(266)	3.0 (1.5-8.0)		90.4 (273)	3.0 (2.0-6.0)	
Wet work n=282/ n=276			p= 0.767			p= 0.144
Yes	39.0 (110)	1.5 (1.5-8.0)		38.8 (107)	2.0 (1.0-5.0)	
No	61.0 (172)	3.0 (1.5-8.0)		61.2 (169)	3.0 (2.0-9.0)	
Occupational n=220/ n= 216			p= 0.520			p =0.276
Yes	25.5 (56)	2.25 (0.75-3.0)		25.5 (55)	2.0 (1.0-5.0)	
No	74.5 (164)	1.5 (1.5-8.0)		74.5 (161)	3.0 (2.0-7.0)	
Geography			p= 0.081			p= 0.040
Capital	34.6 (108)	1.5 (0.5-8.0)		33.9 (103)	2.0 (1.0-5.0)	
Provincial	65.4 (204)	3.0 (1.5-8.0)		66.1 (201)	3.0 (2.0-9.0)	
Dermatological clinics			p=0.312			p=0.555
Private	92.9 (290)	3.0 (1.5-8.0)		93.1 (283)	3.0 (1.0-9.0)	
Hospital	7.1 (22)	1.5 (0.5-4.25)		6.9 (21)	3.0 (1.0-4.0)	

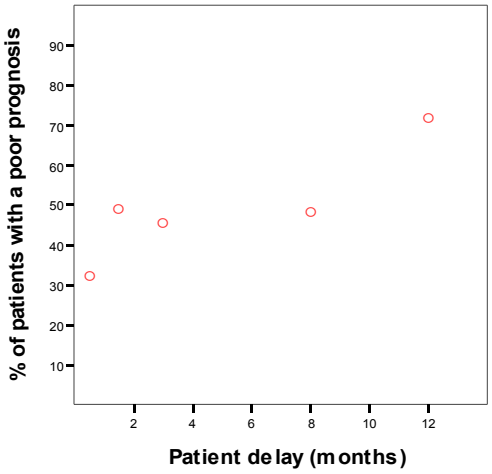
[1] Kruskal Wallis test,
IQR: Interquartile range

Table 14: Severity of hand eczema assessed by patients at baseline and 6-months follow-up using a self- administered photographic guide.

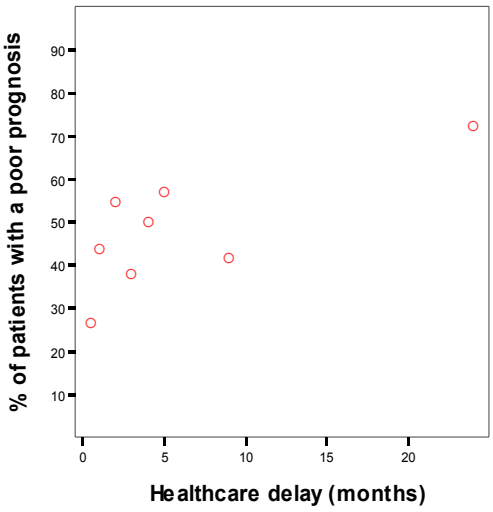
Severity of hand eczema	% of patients at baseline (n)	% of patients at follow-up (n)
Clear	9.9 (30)	28.3 (62)
Almost clear	35.4 (107)	46.1 (101)
Moderate	35.8 (108)	19.2 (42)
Severe	15.6 (47)	5.5 (12)
Very severe	3.3 (10)	0.9 (2)
Total	302	219

Figure 7: The proportion of patients with a poor prognosis defined as unchanged/aggravated clinical severity by the 6-months follow-up related to patient delay, health care delay and total delay.

a:



b:



c:

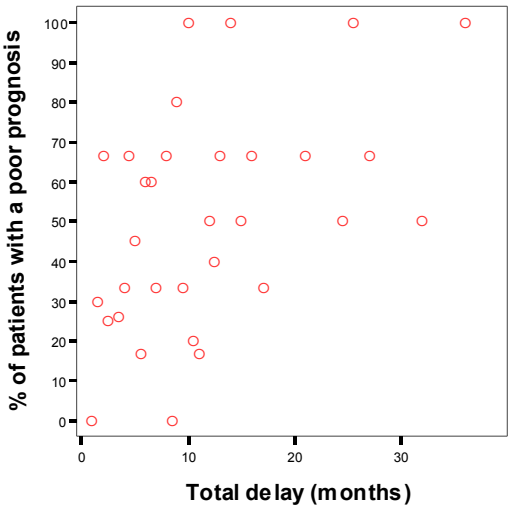


Table 15: Changes of severity of hand eczema at follow-up and logistic regression analyses with the outcome of unchanged/ aggravated hand eczema at follow-up.

	Total N=200	% Unchanged/ aggravated (n/N)	Odds ratio[1] (95 % CI) N=200	P-value	Odds ratio [2] (95 % CI) N=200	P-value
Sex				0.440		0.336
Men	60	51.7 (31/ 60)	1.00		1.00	
Women	140	45.7 (64/140)	0.79 (0.43-1.44)		0.73 (0.39-1.38)	
Age groups (years)				0.207		0.175
18-29	55	52.7 (29/55)	1.00		1.00	
30-39	59	54.2 (32/59)	1.06 (0.51-2.22)		0.97 (0.46-2.07)	
40-49	38	34.2(13/38)	0.47 (0.20-1.10)		0.42 (0.17-1.01)	
+ 50	48	43.8 (21/48)	0.70 (0.32-1.52)		0.66 (0.28-1.53)	
Socioeconomic groups				0.754		0.710
Unskilled	17	52.9 (9/17)	1.00		1.00	
Basic level	100	48.0 (48/100)	0.82 (0.29-2.30)		0.81 (0.28-2.31)	
Medium/high level	50	50.0 (25/50)	0.89 (0.30-2.68)		1.04 (0.33-3.26)	
Outside the labour market	33	39.4 (13/33)	0.58 (0.18-1.88)		0.60 (0.18-2.05)	
≥ 1 positive patch test				0.076		0.239
No	124	52.4 (65/124)	1.00		1.00	
Yes	76	39.5 (30/76)	0.59 (0.33-1.06)		0.68 (0.36-1.29)	
Atopic dermatitis[3] N= 194				0.781		0.488
No	141	47.5 (67/141)	1.00		1.00	
Yes	53	45.3 (24/53)	0.91 (0.49-1.72)		0.77 (0.37-1.60)	
Geography				0.079		0.062
Capital	56	37.5 (21/56)	1.00		1.00	
Provincial	144	51.4 (74/144)	1.76 (0.94-3.32)		1.88 (0.97-3.63)	
Dermatological clinics				0.332		0.489
Private clinics	181	48.6 (88/181)	1.00		1.00	
Hospital clinics	19	36.8 (7/19)	0.62 (0.23-1.64)		0.70 (0.25-1.93)	
Wet work N=183				0.097		0.125
No	118	44.1 (52/118)	1.00		1.00	
Yes	65	56.9 (37/65)	1.68 (0.91-3.09)		1.73 (0.86-3.50)	
Sick leave N=191				0.337		0.361
No	174	46.6 (81/174)	1.00		1.00	
Yes	17	58.8 (10/17)	1.64 (0.60-4.51)		1.65 (0.56-4.87)	
Patient-delay (months)	186	*	1.10 (1.02-1.19)	0.012	1.11(1.02-1.21)	0.012
Health-care delay (months)	183	**	1.05 (1.00-1.10)	0.038	1.05 (1.00-1.10)	0.079
Total delay	178	***	1.06 (1.02-1.11)	0.005	1.06(1.02-1.11)	0.008

[1] Univariable logistic regression analyses.

[2] Multivariable logistic regression analyses adjusted for sex, age group, socioeconomic group and geography.

[3] UK Working Party's criteria

[*] Illustrated in Figure 7a

[**] Illustrated in Figure 7b

[****] Illustrated in Figure 7c

6 DISCUSSION

6.1 General discussion

6.1.1 Part 1: Validation of a self-administrated photographic guide

The spectrum of hand eczema comprises very mild cases to severe illness, and clinical severity is a fundamental aspect when debating the burden of the disease in an epidemiological context. In epidemiological studies, it has been necessary to base self-reported severity assessments on indirect parameters such as application of topical steroids, medical attention and the frequency of eruptions[48;73]. Additionally, measurements of impairment of life quality have been applied[3;36;74]. Clinical examinations allow for severity assessments but put a limit on the number of participants. If a reliable instrument for self-reported severity assessment of hand eczema were employed in questionnaire-based studies, it would be an interesting alternative as it would allow for larger study populations. This study indicates that the photographic guide for self-assessment of hand eczema is an instrument that contributes to a consistent grading and makes it possible to obtain direct information of the clinical severity in a group of patients.

The VAS is a subjective instrument in which various unknown factors contribute to a global score. The severity assessment will not only depend on the clinical severity but conceptually also on the individual perception of the burden of the disease. In the present study a mean global score of 4.5 (SD ± 2.6) was found. VAS estimates have been used in only a limited number of epidemiological studies on hand eczema and not in a uniform way[75;76]. Consequently, a standard of reference is difficult to obtain.

6.1.2 Part 2: The population-based survey

A one-year prevalence of 14% was found among Danish citizens, which must be considered as in agreement with previously published data [5;12-14] although slightly higher.
The study revealed a considerable interpersonal variation of the severity of hand eczema in the background population. Most individuals had mild disease; however, 32.1% reported symptoms half the time or more over the past 12 months and 43.8% had clinically moderate to very severe hand eczema on some occasion.

In all, 67.4% had sought advice from their general practitioner and 43.6% had also consulted a dermatologist. Prescribed medicine had been used by 25.3% in the past 12 months. The results highlight the considerable impact of hand eczema on the health-care system due to examinations and treatment. The findings of the present study are similar to previous population-based studies reporting that around 63%–77 % of persons with hand eczema have consulted a medical doctor on some occasion[2;8;34]. Many individuals had never sought medical advice, mostly those with mild or infrequent eruptions. It is reasonable to believe that the cause of this absence is that many individuals with mild symptoms do not consider these as signs of disease or accept them as a normal hazard of life. Despite lack of medical advice, the natural course of hand eczema in these persons seemed to be mild. However, relying on the reported years of duration, symptoms were long lasting in this group too.

An excess of women had sought medical advice. A reason for this difference was not sought, but a sex difference in the health-care utilization pattern is a general finding in socio-medical studies[77-79]. Atopic dermatitis was also associated with seeking medical advice, a finding that may indicate more severe symptoms, although not clearly demonstrated in this study. Hand eczema often emerges at an early age in persons with atopic dermatitis and presumably with a low clearance rate[1;36;37;46;47]. In a cross-sectional study design like the present one, the higher proportion of medical attention may be explained by long-lasting symptoms. Other aspects that may encourage medical attention can only be hypothetical, but different social background and working tasks would be interesting options to explore.

Sick leave due to hand eczema within the past 12 months was reported by only 1%. In previous population- based studies with a follow-up of 8–15 years, sick leave was reported by 12% and 6%, respectively. The frequencies of sick leave have been reported as much higher in studies based on occupational hand eczema[37;80].

Of those seen by a general practitioner, 35.4% had not consulted a dermatologist. A considerable part had experienced more significant symptoms, hence 15% had had severe to very severe hand eczema, and 32.3% reported symptoms half the time or more over the past 12 months. Further, 19.0% of those with present hand eczema reported moderate to very severe disease. These patients miss out on the potential benefit of a dermatologic examination, patch testing and a thorough exploration of environmental factors, and this may impair their prognosis.

6.1.3 Part 3: The follow-up study

6.1.3.1 Manuscript III

According to the dermatologist-rated severity assessments, 60.4% of patients had improved when examined 6 months after the initial dermatological consultation, and 36.1% of patients reported moderate to very severe hand eczema. Atopic dermatitis, a positive patch test, older age and frequent symptoms the past 12 months were risk factors of severe hand eczema at baseline, whereas frequent symptoms and being an unskilled worker were associated with a poor prognosis. With respect to morphology, fissures and scaling were identified as risk factors for a poor prognosis.

The preponderance of female patients and the age distribution of the cohort were in line with previous studies [32;74;80] obviously reflecting the profile of persons with hand eczema in the general population with a predominance of women and younger persons[9;12-14;16]. More women than men were employed in wet occupations, which seems primarily to be a result of a high frequency of women in the health-care sector and among cleaners and hairdressers[23;81].

The mean score of the HECSI at baseline was 19.9 points with a range of 0–209 points illustrating that the potential maximum score of 360 points was far from reached. In line with our result, a median score of 17.0 was found in a study including patients from different European patch test clinics[74]. A Danish study reported a mean HECSI score of 12.0, but as the study population was recruited from the background population, a lower mean score was to be expected[34].

The clinical assessment demonstrates the severity at a certain moment only and does not take into account hand eczema as a fluctuating disease with changing symptoms over a given period. The present results showed, however, a statistically significant association between severity assessment by the HECSI and the duration of symptoms the past 12 months. This finding further establishes the role of the HECSI as a valuable tool for severity scoring of hand eczema.

Atopic dermatitis was a risk factor for severe hand eczema at baseline, a finding in accordance with other cross-sectional studies[1;36]. A positive patch test was also found to be a risk factor for severe hand eczema. Results from a large cross-sectional study found that persons with allergic contact eczema often had severe hand eczema compared with persons with irritant contact eczema (although not as frequent as persons with atopic hand eczema)[1]. A divergent result was found in a recent Danish study where irritant hand eczema was associated with more severe symptoms determined by a medico-legal assessment[80]; however, this difference disappeared after the 6-month follow-up. In the present study, no assumption was made about the present relevance of the individual allergens as no validated methods to assess exposure have been established. Including such estimation could therefore lead to classification bias. Older patients had more severe hand eczema. This relationship has been described previously[80] but is generally not reported in the literature. Hypothetical, other subtypes of hand eczema among older persons could be present and explain this finding.

The improvement rate six months after the dermatological consultation was 60.4%. Using the self-administrated photographic guide, 22.9% of patients rated their hand eczema as clear at follow-up, and 36.1% assessed the symptoms as moderate to very severe. The results demonstrate that hand eczema is a disease of a low clearance rate and, in many cases, a disease with persistent, significant symptoms. Clearance rates of 26%– 41% have been found in other prospective population-based studies with follow-up periods varying from 6 months to 8 years[8;11;34]. In a Danish study of hand eczema patients from a private dermatological clinic, 43% reported their hand eczema to be improved or cleared after one year of follow-up[35]. In a large population-base study with 15 years of follow-up, 74% of the participants had experienced an improvement[33]. Studies on cases of occupational contact dermatitis/hand eczema registered as industrial injuries have reported improvement rates ranging from 41% to 76% after 1–5 years of follow-up [36-38;46]. The result of the present study is interesting because the improvement rate is based on clinical assessments by dermatologists.

Being an unskilled worker was a risk factor of a poor prognosis as was wet work, although the latter did not reach statistical significance. Wet work and potentially low influence on own tasks with limited possibilities of changing unfavourable work procedures may well explain these findings. Various social backgrounds may also be related to difficulties in reading ingredient labels[82] which may be major problem for patients with contact allergy.
A positive patch test result did not impair the prognosis. The influence of contact allergy on the course may depend on the type of intervention and the information given to patients about avoidance of allergens. The prognosis may also vary according to the individual allergens. Hence, subsequent analyses revealed chromium allergy as an independent risk factor of a poor prognosis, a finding published in a separate paper[83]. A poor prognosis was found in patients with scaling and fissure. In the interpretation of the clinical process of hand eczema, fissures and scaling may

reflect a more chronic stage of the disease more difficult to treat. In contrast to other studies[32;84] more extended hand eczema was not a risk factor for a poor prognosis.

In contrast to findings in many previous studies[36;37;46;47], the present study could not confirm an association of atopic dermatitis with a poor prognosis. This may potentially be ascribed to the method of severity assessment or the relative short follow-up.

6.1.3.2 Manuscript IV

Measured by the self-administrated photographic guide, 54.7% of patients had moderate to very severe hand eczema at baseline and 52.5% had improved by the 6-month follow-up. The median patient delay to seek a general practitioner was 3 months with a wide range, 23.4% went without delay while 11.2% waited more than a year. The median health-care delay was likewise 3 months, 9.9% of the patients waited 12 months or more to see a dermatologist.

According to the prevalence proportions illustrated in Figure 7a and Figure 7b, a more favourable prognosis was associated with a minimum of patient delay or health-care delay. In contrast, persons with a patient delay or health-care delay exceeding 12 months seemed more resistant in terms of improvement. In the multivariable logistic regression analysis, longer patient delay was found to be associated with a poor prognosis. Longer health-care delay seemed also associated with a poor prognosis; however, it did not reach statistical significance in the multivariable regression model. Total delay, including the effect of patient delay as well as health-care delay, was found to be associated with a poor prognosis. The prevalence proportions of unchanged / aggravated hand eczema varied substantially in relation to total delay as illustrated in Figure 7c. This variability may partly be explained by less accurate estimates of the total delay compared with the single estimates of patient delay and health-care delay. However, the variability may also illustrate the fact that fast medical service is far from the only determinant in the course of hand eczema.

The tendency of a poor prognosis of hand eczema is well established, and several epidemiological studies have evaluated the prognosis of hand eczema with focus on etiological factors such as atopic eczema, irritant contact eczema and allergic contact eczema[36;44;47;48;85]. Only a limited number of studies have investigated the association between the duration of symptoms before the diagnosis with course of hand eczema. In a population-based study, it was found that persons with hand eczema who were diagnosed and treated within 6 months after onset had a more favourable prognosis[8]. Two other studies about occupational contact eczema found a more favourable prognosis[86]associated with shorter-lasting symptoms or exposure to the causative agent(s) before the diagnosis[43].

With the finding of a median health-care delay of three months, it must be stated that the fast track recommendations of 3 months, given by the Danish Contact Dermatitis Group, are poorly met. Alternative specific guidelines cannot be suggested from the present study, but a minimum of patient delay and health-care delay seems associated with a more favourable prognosis.

Stratified by socioeconomic groups, patients from the socioeconomic medium/ high level had a

substantially longer patient delay. Working routines among unskilled and basic level individuals may implicate more manual tasks compared with those of persons from socioeconomic medium/ high level groups. Due to occupational impairment, the incentive of these groups to seek medical advice soon may therefore be more pronounced. Young age was associated with longer health-care delay. The finding is worrying as hand eczema is a disease known to potentially affect labour participation with sick leave and unemployment[33;34;80], serious consequences especially to young patients having most of their working life in front of them. Patients living in the provincial districts had a longer health-care delay compared with that of patients living in the capital/ suburban areas. An explanation of the finding may be a relative lower count of dermatologists in the provincial districts, leading to less access to dermatological examinations. This circumstance might implicate a higher threshold of clinical severity or a longer period of symptoms before the patients are referred by their general practitioner.

In Manuscript III, a poor prognosis was found associated with being an unskilled worker. However, this could not be retrieved in Manuscript IV. A reason may be the high number of non-respondents at follow-up among unskilled persons, inducing selection bias in Manuscript IV.

6.2 Methological considerations

6.2.1 Part 1: Validation of a self-administrated photographic guide

6.2.1.1 Validity of the self-administrated photographic guide

The self-administrated photographic guide is fundamentally based on the construction of the original guide in which the reliability has been comprehensively addressed. The original guide was developed as a standardized approach for dermatologist to assess the severity of hand eczema[61]. Pictures were chosen in attempt to represent a wide spectrum of hand eczema in terms of various morphological features, affected sub-areas as well as different levels of severity. A verbal description of individual signs and extension corresponding to each severity level has also been published[87]. The content validity was supported by the selection process of images. Twenty out of 50 eligible photographs were selected by a panel of five experienced dermatologists, identifying the most representative pictures and achieving a consensus rating of the images. The reliability of the photographic guide was evaluated in a test-retest session involving 11 dermatologists grading the hand eczema of 28 patients on two subsequent days. Inter-rater reliability derived from the intraclass correlations coefficient and Kendall's coefficient of concordance showed an excellent reproducibility with values above 0.75 and 0.78, respectively. The test-retest reproducibility for each of the 11 raters, evaluated by weighted kappa coefficients, was 0.60–0.92.

The original photographic guide has subsequently been employed in a large randomized, double-blind, placebo-controlled, multicentre trial published in 2008, where the primary effect parameter was measured by the guide[87].

Application of the self-administrated photographic guide requires the ability to assess the actual hand eczema by comparison with photographs and identifying those representing the same grade. Not only the appearance of morphological signs but also the location and skin type can only be an approximation, and clinical experience will be a factor increasing consistency[61]. The dermatologists

in the present study were experienced with a presumed high level of inter-rater reliability. An equal reliability cannot be expected from lay individuals. Nevertheless, the relative high kappa value indicates that non-physicians with no former experience are able to assess the severity of their hand eczema on an acceptable level. There was a tendency that the agreement was inferior in the groups representing mild symptoms, but it did not reach statistical significance. The applicability of the photographic guide is highly dependent on the quality of pictures, and minor clinical symptoms may be difficult to visualize on a photograph. To avoid the pictures representing “clear of hand eczema” being misinterpreted as illustrating minor symptoms difficult to see, we decided to leave out those pictures. Instead, we applied the verbal concept: “no hand eczema”.

The construct validity of the self-administrated photographic guide was supported by the significant, positive correlation with the patient-rated global score, both for the patient-rated assessments and the assessments performed by the dermatologists. Previous studies have reported a poor correlation between the physician-rated clinical severity and the corresponding patient-rated severity on a global scale[75;88] In the present study a moderate correlation was found, which supports the usefulness of a simply constructed instrument as the photographic guide.

A main objective of the self-administrated photographic guide was to develop an instrument to assess only the objective clinical symptoms. However, a higher correlation was found between the patient-rated global score and the patient-rated clinical severity compared with the dermatological assessment. This may indicate an interaction between how the patients perceive the impairment of hand eczema and their visual perception of the severity. The close connection might be a consequence of the combination of photographs and the VAS in the same questionnaire.

As with the original photographic guide, the self-administrated photographic guide was solely tested on Caucasians. For ethnic groups with darkly pigmented skin further studies are necessary. Patients were introduced to the study by the dermatologists in relation to the clinical examination. The patients and the dermatologists were not allowed to discuss each other’s assessment. However, it cannot be ruled out that the patients might have had a preconceived opinion of the severity from the preceding consultation, leading to a higher level of agreement.

6.2.2 Part 2: The population-based survey

6.2.2.1 Validity of questions on hand eczema and severity assessments

Traditionally, two different approaches have been used to identify persons with hand eczema in epidemiological studies: self-reported symptoms of hand eczema and a self-reported diagnosis. Self-reported diagnosis was used in the present study. The applicability of the question with respect to self-reported hand eczema has been validated. In a study conducted among 3 different occupational groups, the self-reported hand eczema within the past 12 months was concluded to have a high specificity (96%–99%) and a more moderate sensitivity (53%–59%)[89] when tested against the diagnosis performed by a dermatologist. The predictive values of the question as having a high specificity and a moderate sensitivity have been supported by other studies[90;91]. The results implicate that reports based on self-reported hand eczema tend to underestimate the true prevalence of hand eczema. The concept of self-reported symptoms relies on the recognition of different clinical signs. The sensitivity of the symptom-based hand eczema diagnosis can be high

but has proved to be inconsistent and with a moderate specificity (64%–76%)[90;92]. Moreover, a study investigating the agreement between patients and a dermatologist on different morphological signs found that it was difficult for lay individuals to identify skin signs correctly[93]. The self-reported hand eczema question has previously been used in Danish population-based studies[4;7;34]but a validation of the translated version of the question has never been done.

In a test-retest session 5 months apart, the self-reported hand eczema question was estimated to have a kappa value of 0.79[94], so it was to be expected that some individuals would reject the hand eczema diagnosis in the second questionnaire[94]. It was, nevertheless, surprisingly that as many as 23.4% could not confirm the diagnosis. The primary questionnaire concerned various aspects of symptoms from different organs and included only two questions on hand eczema. In contrast, the second questionnaire included primarily questions on hand eczema. The different context may have induced more reflection from the participants and the photos in the photographic guide might have enhanced the ability to recognise the symptoms of hand eczema.

The validation session of the self-administered photographic guide included only dermatological patients and to date no validation has been performed in the background population. Mild symptoms were proportionally more frequent in the population-based sample compared with the dermatological patients. Although it did not reach statistical significance in the validation study, lower agreements between the patients and the dermatologists were found for mild cases of hand eczema, indicating that the self-administrated photographic guide might be a less reliable instrument for severity assessment in the background population.

The reliability of onset of hand eczema has been tested in a previous study where the question was retested among 36 persons. Among the 35 respondents, 11 persons gave identical answers, 12 persons differed by one year, 6 persons differed by two years, 3 persons differed by 3 years , in 1 person the difference was 6 years and finally the difference was 7 years in 2 persons[94].

The UK Working Party's diagnostic criteria were used for diagnosing atopic dermatitis. The criteria are based on clinical features suggested by Hanifin and Rajka [95]and have been thoroughly validated, mostly, but not only, on children[67-69]In an outpatient validation study on adults, the proposed question-only version (presence of the major criteria plus minimum of two out of four minor criteria) performed well with a sensitivity of 92% and a specificity of 85%[67-69]. The criteria have been validated in a community setting but only among children[96].

Access to medical services due to e.g. the logistic structures of the health-care system or health-care payments, varies between countries. The design of the present study is extensively based on the Danish health-care model.

6.2.2.2 Bias

The higher response rate among women may have caused selection bias and higher estimates of the one-year prevalence of hand eczema; however, lower participation rates among younger individuals may have had a counteracting effect. A lower prevalence proportion of hand eczema among non-respondents has been published in a previous questionnaire study, and that would

contribute to an increased estimate[37]. The primary questionnaire, however, included only two questions concerning hand eczema, diminishing the risk of selection-bias. If more persons with atopic dermatitis had completed the primary questionnaire this may have led to an increased estimate of the hand eczema prevalence.

A high proportion of persons rejected the hand eczema diagnosis in the second questionnaire. More focus on hand eczema in the second questionnaire may have turned false positive individuals into true negatives as suggested. However, it cannot be excluded that some of those persons actually had hand eczema. According to findings of a previous study, false negative answers are mostly obtained among persons with mild symptoms[89].

6.2.3 Part 3: The follow-up study

6.2.3.1 Manuscript III

6.2.3.1.1 Validity of the HECSI and questions on risk factors

The hand eczema severity index is a grading system, recently developed for objective assessment of the clinical severity of hand eczema. The HECSI is based on a combination of the severity of clinical signs and includes erythema, fissures, vesicles, scaling, oedema, papules and a measurement of the area affected by the disease[60].

The reliability of the HECSI was assessed in a test-retest session on two successive days with 12 dermatologists rating the hand eczema of 15 patients. The intraclass correlation coefficient for absolute agreement was 0.79 and must be viewed as excellent. In terms of the measurement of extent, the intraclass correlations coefficient was also high (ICC: 0.82), whereas agreement on the some of the different clinical signs seemed to be more troublesome with the lowest range of vesicles (ICC: 0.38) and fissuring (ICC: 0.42). To estimate how well assessments for an individual were likely to agree between the different observers, the interlimit of agreement was evaluated; the 50% limit was estimated as 18.2 points and the 95% limit was found to be 52.9 points. Further, the intraobserver 50% limit of agreement was13.3 points[60], indicating that if the same observer rated the same patient twice, there would be a 50% chance that the assessments would differ more than 13.3 points.

Validity of a scale refers to its ability to measure what it is intended to measure and is a fundamental assumption of its utility. The evidence of validity of the HECSI is still sparse; however, construct validity was tested in a cross-sectional study of 416 hand eczema patients. An analysis of the association of the clinical severity measured by the HECSI with the impairment on quality of life measured by the dermatology life quality index (DLQI)[97] showed a significant, positive correlation[74]. The DLQI is a widely used dermatology-specific instrument that has been thoroughly validated[98] and the correlation between the two instruments provided evidence in support of the HECSI.

In attempt to overcome the relatively wide ranges of interlimits of agreement, a different statistical approach was used in the present study. The numerical scale of the HECSI was converted into an ordinal scale composed of 3 different groups of mild, moderate and severe hand eczema,

respectively. The cut-off points were made arbitrarily dividing the cohort into three equally sized groups at baseline. A transformation of a continuous scale into ordinal groups will conceptually decrease the discrimination ability of the instrument. However, regarding the accuracy of the HECSI estimated by the interlimits of agreement, a categorical measurement was considered to be more reliable.

A significant issue with the HECSI is how to interpret the clinical meaning of the score and the lack of availability of benchmarks for the minimal important difference. In theory, these issues are dealt with when categorising the HECSI; conclusions should, however, be drawn with caution as the choice of cut-off points may affect the outcomes of statistical analyses. For future studies, a potentially more clinically relevant division of the HECSI could be done by a dermatologist as a comparative study of the HECSI and the photographic guide.

Wet work was included in the study as a potential risk factor for severe hand eczema at baseline or a poor prognosis. The validity of information concerning wet work has been evaluated by a comparison of self-reported duration and frequency of wet working procedures and the exposures registered by an observer. One study estimated the frequency of self-reported hand washing to be underestimated by a factor two, whereas the period of water exposure was overestimates by an equal factor[99]. Another study reported a strong correlation between observations and self-reported exposures, yet the correlation was only moderate regarding hand washing and in general the participants tended to overestimate the time of exposure[100].

Another evaluated risk factor was atopic dermatitis. The definition of atopic dermatitis relied on the UK-Working Party's diagnostic criteria question-only version. The validity of the criteria has been addressed in the section relating to Manuscript II.

6.2.3.1.2 Bias

Participation rate in the follow-up examination was low, which inevitable will increase the risk of selection bias. Drop-out analyses showed no differences between attendees/ non-attendees according to sex, age, socioeconomic group or severity at baseline. Non-attendance has been reported as associated with mild symptoms in epidemiological studies of hand eczema [8;12] However, analyses made on the photographic guide showed no statistically significant differences between attendees and non-attendees in terms of the main outcomes of the investigation. Nevertheless, it cannot be excluded that non-attendees who also declined to complete the photographic guide at follow-up had less severe symptoms.

The severity assessments at follow-up were performed by three different observers, of whom the two assistants were non-physicians. Consistency between observers should, however, be provided by the fact that the two assistants were trained by the third observer (the author). Results derived from the HECSI scoring at baseline were unknown at follow-up, diminishing a potential risk of observer bias.

Clinically more severe hand eczema is shown to be a risk factor for sick leave[80]. Persons with more severe symptoms may to a higher extent remember periods with symptoms the past 12

months due to occupational or other social consequences of the disease. Recall bias may therefore induce an increased association of periods with symptoms the past 12 months with the clinical severity at baseline.

6.2.3.1 Manuscript IV

6.2.3.1.1 The severity assessment and intervention in the follow-up period

The main strengths of the study are the prospective data collection and the uniformly organized health-care system with free medical care, allowing a population-based design. The weakness of the study is the inability to obtain data at the onset of symptoms and to assess the severity of hand eczema at the time the patients were seen by the general practitioner.

Medical delay was found to be associated with a poor prognosis. The clinical outcome will, however, depend on many different factors. The present study did not provide information on individual medical treatment or on other interventions during the follow-up. Adequate medical treatment is essential to achieve good clinical results and should be individualised according to the severity of symptoms, also in terms of need and adherence of the patient. Different outcomes might be a result of different kinds of treatment not adjusted for in the present analyses. It was not investigated, even thought it would have been interesting to explore, if medical treatment prescribed by the general practitioners differed from the treatment provided by the dermatologists.

The self-administrated photographic guide was used to measure the clinical prognosis. The validity of the guide is essential for this study and has been addressed in the section relating to Manuscript I.

Measurements with the HECSI were not used in Manuscript IV due to the low participation rate at the 6-month follow-up. This implied that only few first-time patients had a severity assessment performed both at baseline and at the 6-month follow-up.

6.2.3.1.2 Bias and confounding

The duration of hand eczema symptoms may be difficult for patients to remember, which implicates a risk of inaccurate reports of patient delay. The symptoms can be vague or neglected and disease consciousness might be influenced by external factors, e.g. interference with working projects, which increases the risk of information bias. Similar to patient delay, dates of medical consultations might be difficult to remember. That was emphasised by the relatively high number of missing data on the question concerning the month (and year) of seeing a general practitioner. The estimated health-care delay will be hampered by inaccurate reports of this date.

The prognosis was most convincingly associated with patient delay, emphasising the importance of early baseline treatment performed by the general practitioner, e.g. topical steroids and information on general skin preventive measures. Due to non-adherence, inadequate medical treatment is reported to be frequent among dermatological patients[101;102], a potential source of lack of clinical improvement. A better prognosis among persons with a short patient delay may to a high extent

reflect compliance and other uncovered behavioural patterns that could not be adjusted for in the regression analysis.

7 CONCLUSION

Manuscript I

Self-rated severity assessment is feasible in hand eczema. For research purposes the self-administrated photographic guide is a reliable tool for hand eczema patients to grade the severity of their hand eczema.

Manuscript II

Hand eczema is a frequent disease in the Danish population. A large proportion of individuals have mild symptoms; however, 43.8% had experienced more significant symptoms. In total 67.4% had sought medical advice and 43.6% had consulted a dermatologist. In this study, seeking medical attention depended on the clinical severity. A considerable number of individuals, who sought medical attention, including those with more severe disease, were never referred to a dermatologist; this may have consequences for their prognosis.

Manuscript III

The overall severity of hand eczema had improved six months after the first dermatological examination; nevertheless, many patients continued to have considerable symptoms. Severe hand eczema at the initial consultation was an indicator of severe symptoms 6 months later. Frequent eruptions during the past 12 months and being an unskilled worker were risk factors of a poor prognosis. In relation to the individual morphological signs, fissures and scaling were predictors of a poor prognosis. A positive patch test was associated with severe hand eczema at the initial consultation but not at follow-up, which may be due to the instructions given by the dermatologist as part of the standard operating procedure. Special attention should therefore be paid to this group of patients too.

Manuscript IV

Hand eczema patients often had symptoms for several months before seeing a dermatologist. Hence, among first-time patients 52.2% had experienced a total delay of more than 6 months and 23.6% were not seen by a dermatologist until after 12 months. The median health-care delay was 3 months, indicating that the Danish fast track recommendations are being poorly met. Longer patient delay was associated with a poor prognosis. In a multivariable logistic regression analysis health-care delay was not a statistically significant risk factor of a poor prognosis. However, patients with a health-care delay of more than 12 months seemed to have a poorer prognosis compared with those diagnosed earlier, and the best prognosis was found for individuals with a minimum health-care delay.

8 PERSPECTIVES AND FUTURE STUDIES

The thesis verifies that hand eczema is a frequent disease in the Danish population. The number of persons who had sought medical attention and the use of prescribed medicine illustrate the substantial individual impairment of hand eczema as well as the burden on the health-care system.

Despite the lack of medical advice, many persons with a long history of hand eczema had experienced only mild sporadic outbreaks. These persons might be able to control symptoms by avoidance of irritants and use of moisturizers, indicating that medical treatment is not crucial to all individuals. Nonetheless, minor symptoms of hand eczema must be considered as potential precursors of a more severe disease, and persons who develop hand eczema should in general be encouraged to seek medical advice. It should further be noted that prolonged symptoms of hand eczema was found to be associated with a poor prognosis, indicating that medical advice should be sought without an expectative attitude.

According to the Danish guidelines illustrated in Figure1, patients with hand eczema should be treated on different levels of medical expertise. From a socioeconomic perspective it seems reasonably that persons with uncomplicated brief symptoms of hand eczema are treated by their general practitioner. However, as demonstrated in this thesis, a significant proportion of persons not seen by a dermatologist had more severe symptoms or persistent hand eczema. These persons miss out on the potential benefit of a dermatological examination, and that may have a negative influence on their prognosis. It should further be emphasised that the severity of clinical symptoms and the impairment of daily life do not necessarily correlate. Mild symptoms of hand eczema may be unacceptable to some persons (e.g. interfere with their working capacity) and the threshold for referring patients with hand eczema should, in general, be low.

The delay of the patients and the delay of the health-care system contributed to the total delay in a comparable manner. For many patients the symptoms had often persisted for several months before seeing a dermatologist. Considering the association of total delay with a poor prognosis, the long waiting time seems problematic. In conclusion, the secondary intervention of hand eczema should not only be aimed towards a short patient delay but also towards a health-care system without bottlenecks.

After a concluded dermatologic diagnosis and treatment some patients will be healed. For many patients, however, hand eczema will be a chronic disease. These patients have a need of regular medical advice, a task often managed by their general practitioner (Figure1). A principal aim for patients with a chronic disease is coherent medical treatment and care[103]. To achieve an optimal follow-up treatment, a well implemented corporation between the dermatological specialist and the general practitioner is crucial. Intensive treatment in a dermatological clinic should be followed by intermittent medical contacts. Further sharing of know-how between the dermatological specialist, the general practitioner and other health-care professionals involved in the rehabilitation seems essential to achieve a favourable prognosis of hand eczema.

Published data from epidemiological studies have showed that a low socioeconomic status is a

significant risk factor for sick leave in relation to hand eczema[34;36]. We could further demonstrate that unskilled workers have a higher risk of a poor clinical prognosis. This specific finding indicates a need for special attention to susceptible groups of patients.

Studies on primary and secondary prevention in high-risk occupations have shown that an intense intervention programme can lead to a higher information level, a different behaviour and fewer skin symptoms[104;105]. The role of the individual patient is increasingly acknowledged, but only sparse information exists on the adherence of hand eczema patients, e.g. how they comply with instructions about precautions and with medical treatment. It may be possible that a long-term intervention programme in relation to the dermatological examination would benefit some patients, a subject of interest for future studies.

The recent years have brought more emphasis on evidence-based practice. Despite the abundance of topical and systemic treatments of hand eczema, only few randomized controlled trials exists to provide evidence-based recommendations for the therapy of patients[106]. Consequently, studies have been called for that comply with the criteria outlined by the Cochrane Collaboration[107]. These criteria include a description of pre-treatment variables, such as disease severity estimates. Further, the efficacy parameters employed should be outlined and it should be stated whether they were validated. For clinical trials on hand eczema an important shortcoming has been the lack of a validated scale for severity assessments.

Well defined methods of measuring the outcome should not only be integrated in clinical trials but also in observational studies. In this thesis we applied two new tools for severity rating of hand eczema that have both been evaluated in reliability tests. Former studies gainfully applying the HECSI and the photographic guide would have strengthen the validity of the instruments, but only few studies existed[34;74;87;108]. To gain general acceptance, these new instruments for severity assessment of hand eczema should be further validated and implemented in other studies, a long-term process but an important challenge, nevertheless.

It seems reasonable to believe that the hand eczema diagnosis covers a spectrum of different underlying diseases. Today, no single universal classification system for hand eczema exists, and most published classification systems include combinations of aetiological factors, morphological signs and localization. Achieving consensus on classification of subtypes of hand eczema is seemingly important in order to obtain a better understanding of the disease.

The recent finding of the null allele genes of filaggrin has created new insight into the dysfunctional skin barrier of persons with atopic dermatitis[109]. The independent role of the mutation of the fillagrin genes for hand eczema and contact allergy is, however, still debated[110-114]. More insight into the role of genetics may be crucial for a better classification of hand eczema. Identifications of genetic alleles associated with hand eczema or subtypes of hand eczema could, ultimately, lead to improved secondary intervention in terms of individualized medical treatment and stratified counselling.

9 SUMMARY

Hand eczema is a frequent disease, often with a chronic course. In the Danish health-care system, a general practitioner is the first medical contact for persons with hand eczema, initiating a first line treatment. To obtain a specific diagnosis and thereby to offer individual information on protective precautions, a dermatological examination is needed. The aims of this thesis were to investigate: (i) the proportion of persons in the background population who have visited a general practitioner because of hand eczema and the proportion who has also been seen by a dermatologist; (ii) changes in clinical severity of hand eczema occurring between the first visit to a dermatologist and follow-up six months later and to identify factors associated with severe disease and a poor prognosis (iii) to analyse the time span from onset of hand eczema until the patient seeks medical advice (patient-delay) and the period from the first consultation with the general practitioner until seeing a dermatologist (health-care delay); and (iiii) to investigate if the delay had any influence on the prognosis. The results of the thesis are based on two separate epidemiological studies. In addition, a study was performed to validate a patient-administrated photographic guide. The photographic guide was used for assessment of severity of hand eczema in the two epidemiological studies.

The first study was designed as a population survey based on a random sample, initially including 6000 individuals. The one-year prevalence of hand eczema was estimated to 14%. In all, 67.4% had visited a general practitioner and 43.6% had seen a dermatologist. Among persons who had never seen a medical doctor, the majority claimed to have experienced mild symptoms only. A considerable number of individuals (35%), who sought medical attention, including those with more significant symptoms, were never referred to a dermatologist. In conclusion, seeking medical attention depended on the clinical severity. A considerable number of individuals who sought medical attention, including those with more severe disease, were never referred to a dermatologist, and this may have consequences for their prognosis.

The main study was a multicentre study and comprised nine dermatology clinics, covering the three main areas of Denmark. In all, 799 patients referred with hand eczema were enrolled, January 2006– February 2007. The study was designed as a follow-up study, where the severity of hand eczema was assessed by a clinical examination at baseline which was repeated after six months. Furthermore the patients assessed the clinical severity using a self-administered photographic guide and supplementary information was collected by questionnaires. At baseline, 60.3% of the patients reported having moderate to very severe hand eczema, 33.1% had only mild symptoms while 6.6% did not have present symptoms. Assessed by the clinical examination, severe hand eczema at baseline was associated with higher age, atopic dermatitis and contact allergy. At the clinical examination performed at the 6-month follow-up, 60.4% had improved. In all, 22.9% reported being clear of hand eczema. Socioeconomic stratification revealed that being unskilled was a predictor of a poor prognosis.

Among individuals who had sought a dermatologist for the first time ever due to hand eczema, the median patient-delay was three months. The median health-care delay was likewise three months. Longer patient delay was associated with a poor prognosis. Health-care delay was not found to be significantly associated with a poor prognosis. However, patients with a health-care delay of more

than 12 months seemed to have a poorer prognosis compared with those diagnosed earlier, and the best prognosis was found for individuals with a minimum health-care delay. In conclusion, many patients had symptoms for a relative long period before the dermatology examination, and more prolonged symptoms seemed associated with a poorer prognosis.

10 SUMMARY IN DANISH

Håndeksem er almindeligt forekommende og har ofte et kronisk forløb. Patientens praktiserende læge vil normalt instituere den primære behandling og give generel rådgivning. Diagnostisk udredning hos en dermatologisk speciallæge gør det muligt, at rådgive patienten om, hvilke specifikke miljømæssige eksponeringer de skal undgå. Formålet med denne afhandling var: a) at undersøge i hvilken udstrækning personer med håndeksem har konsulteret deres praktiserende læge og en dermatologisk speciallæge b) at beskrive de kliniske ændringer fra første besøg hos en hudlæge og igen efter 6 måneder og definere faktorer med betydning for sværhedsgraden og en dårlig prognose c) at kortlægge processen, i et tidsmæssigt perspektiv, fra debut af håndeksemet til patienten opsøger sin egen læge (patient-forsinkelse) og til vedkommende undersøges af dermatologisk speciallæge (system-forsinkelse) d) at undersøge om tidsforløbet har en prognostisk betydning.

Afhandlingen er baseret på resultaterne fra to separate epidemiologiske undersøgelser. Desuden indgår et valideringsstudie af en fotografisk guide, der anvendes til selvvurderet sværhedsgrad af håndeksem og som blev anvendt i de to øvrige studier.

Det første studie var en populationsbaseret spørgeskemaundersøgelse initialt baseret på 6000 voksne personer. Etårs prævalensen af håndeksem blev estimeret til 14 % i befolkningen. Heriblandt havde 67,4 % på et tidspunkt været hos egen læge, mens 43,6 % havde været hos en dermatolog. Blandt de personer, som aldrig havde søgt læge vurderede flertallet, ud fra den fotografiske guide, at de kun havde haft milde symptomer. Blandt dem, som søgte lægehjælp blev 35 % aldrig henvist videre til dermatolog, hvilket også inkluderede personer med betydelige kliniske forandringer. Vi fandt således, at det at søge læge afhænger af hånd eksemets sværhedsgrad. En del henvises ikke til en dermatolog, trods mere udtalte symptomer. Dette kan have konsekvenser for prognosen af håndeksemet.

Hovedstudiet var en multicenterundersøgelse med bidrag fra i alt ni dermatologiske klinikker fordelt geografisk i Danmark. I perioden januar 2006 til udgangen af februar 2007 blev i alt 799 patienter, nyhenvist med håndeksem, inkluderet i studiet. Undersøgelsen var designet som et opfølgende studie, hvor sværhedsgraden af håndeksemet blev vurderet klinisk ved indgangen i studiet samt igen seks måneder senere. Tilsvarende angav patienterne en selvvurderet sværhedsgrad af eksemet ved hjælp af en fotografiske guide og supplerende information blev indhentet via spørgeskemaer. Ved indgangen i studiet rapporterede 60,3 % af patienterne moderat til meget svært eksem, mens 33,1 % havde mildt eksem og 6,6 % ikke havde aktuelle symptomer. Ved den kliniske undersøgelse var svært håndeksem relateret til stigende alder, atopisk eksem og kontaktallergi. Ved den opfølgende undersøgelse havde 60,4 % af patienterne en klinisk målbar bedring af deres håndeksem. I alt 22,9 % af patienterne var blevet raske. En socioøkonomisk stratificering viste, at ufaglærte havde den dårligste prognose.

De patienter, som havde konsulteret en dermatolog for første gang nogensinde pga. håndeksem. havde en median patient-forsinkelse på tre måneder. Median system-forsinkelsen var ligeledes tre måneder. Undersøgelsen viste, at en dårlig prognose var associeret til en længere patient-

forsinkelse. Systemforsinkelsen var ikke signifikant associeret til en dårligere prognose. Dog viste resultaterne, at patienter uden system-forsinkelse havde den bedste prognose evalueret efter opfølgningsperiodens afslutning. Modsvarende havde patienter, der måtte vente over et år den dårligste prognose. Det kan således konkluderes, at mange patienter er forholdsvis længe undervejs i sundhedssystemet, hvilket synes associeret med en ringere prognose.

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