Summary
SUMMARY

Hand eczema is a prevalent skin disease, which can significantly impact several aspects of life in terms of daily activities, social activities, psychological well-being, work-related aspects, and quality of life. The pathogenesis of hand eczema is far from fully elucidated yet, and is most likely dependent on the etiology with a complex interaction between intrinsic and extrinsic factors such as atopic dermatitis, genetic factors, and exposure to irritants, friction, or contact allergens. Treatment is based on the identification and avoidance of causative exogenous factors on one hand, and symptom treatment by applying emollients, topical corticosteroids or the (off-label) use of systemic treatment on the other hand. This thesis was divided into three parts, focusing on pathogenesis in the first part, followed by epidemiology in the second part. The last part included different aspects of patient care.

Part I - Pathogenesis

Hyperkeratotic hand eczema

Chapter 2 provides insight into the pathogenesis of hyperkeratotic hand eczema by investigating differences in expression of important keratins (K), epidermal barrier proteins, and adhesion molecules by immunofluorescence staining of biopsies of lesional, nonlesional, and healthy control skin. Immunofluorescence staining showed a significant reduction of K9 and K14 in lesional skin. Upregulation was found for K5, K6, K16, and K17 in lesional skin compared with perilesional and healthy palmar skin. Further, upregulation of involucrin and alternating loricrin staining was found. Filaggrin expression was similar in lesional, perilesional, and control skin. No monogenetic mutations were found. Currently, the phenotype of hyperkeratotic hand eczema is included in the hand eczema classification system; however, it can be argued whether this is justified. The evident expression of filaggrin and involucrin in lesional skin did not support a pathogenesis of atopic eczema. The upregulation of K6, K16, and K17 and reduction of K9 and K14 might contribute to the underlying pathogenesis. Unfortunately, comparison with hand eczema studies is not possible because similar protein expression studies are lacking.

Part II – Epidemiology

Prevalence and severity

Until now, most epidemiologic studies regarding the prevalence of hand eczema in the general population have been conducted in Scandinavian countries. In addition, data on chronic hand eczema and severity of hand eczema in the general population is scarce, while it can provide perspective on the patient burden of hand eczema and identify the proportion of patients in need for counseling and treatment. Therefore, in chapter 3, a cross-sectional, questionnaire-based study was conducted among the adult participants...
of the Lifelines Cohort Study to investigate the prevalence and severity of hand eczema in the Dutch general population. In total, 57,798 subjects were included. It was found that the lifetime prevalence of hand eczema was 15.0% and the 1-year prevalence 7.3%. The majority (56.9%) of the subjects with hand eczema in the general population had almost clear hand eczema at worst ever. The prevalence of severe to very severe hand eczema at worst ever in the general population was 1.9%. It was found that the majority of subjects with hand eczema in the past year had chronic hand eczema (1-year prevalence of chronic hand eczema: 4.7%), and severity among subjects with chronic hand eczema was higher compared to subjects with hand eczema that was not chronic.

Irritant contact dermatitis
An important etiological subtype of hand eczema is irritant contact dermatitis (ICD). Chapter 4 describes the characteristics, including demographics, anatomical sites, occupation, and sensitization profile of patients who were patch tested and diagnosed with irritant contact dermatitis in the European Surveillance System on Contact Allergies (ESSCA) database. In total, 8,702/68,072 (12.8%) patients were diagnosed with ICD (without concomitant allergic contact dermatitis [ACD]). The hand and face were the most reported anatomical sites for ICD, and the hands were mainly involved in occupational ICD (OICD). Almost half of the patients with ICD had OICD. The highest proportions of OICD were found in metal turners, bakers, pastry-cooks, and confectionery makers. Furthermore, almost half of the patients diagnosed with ICD had at least one contact sensitization, with a similar sensitization pattern compared to the group containing all other diagnoses, albeit on a (much) lower level of relative frequency, if prevalence ratios are considered. The focus on prevention of ICD should include the identified high-risk occupations with special attention given to exposure to the hands. In addition, in difficult-to-treat contact dermatitis, unrecognized contact allergy, or unrecognized clinical relevance of identified allergies owing to incomplete or wrong product ingredient information must always be considered.

Lifestyle factors
The association between dermatological diseases and lifestyle is increasingly subject of research. Diverse lifestyle factors can influence the immune system and alter inflammatory processes. Therefore, it is hypothesized that when improving overall health, hand eczema might benefit in conjunction. Lifestyle and behavioral changes might be of great importance in future complementary medicine, with a possible role for prevention and personalized treatment programs for hand eczema. However, evidence regarding the association between lifestyle factors and hand eczema is limited. To extensively investigate the association between lifestyle factors and hand eczema, a systematic review and meta-analysis were conducted in chapter 5. Fifty-five
studies were included. The meta-analysis (17 studies) found very low quality evidence that smoking is associated with a higher prevalence of hand eczema (odds ratio 1.18, 95% confidence interval 1.09-1.26). No convincing evidence of associations for the other lifestyle factors with hand eczema was found, mostly due to heterogeneity, conflicting results, and/or the limited number of studies per outcome. In addition to the systematic review and meta-analysis, the possible association between hand eczema several lifestyle factors was also investigated among the participants of the Lifelines Cohort Study (chapter 6). It was found that hand eczema in the past year was more common in individuals who reported smoking, chronic stress, obesity, or a higher waist circumference. When focusing on the association between lifestyle factors and chronic hand eczema and severity of hand eczema, similar results were found regarding the associations for smoking, stress, and obesity (chapter 7). Reporting less physical activity was associated particularly with severe-to-very severe hand eczema. Stress and being overweight were positively associated with chronic hand eczema. In conclusion, these studies showed positive associations between hand eczema and smoking and obesity. Because personalized medicine is a subject of increased interest, attention to lifestyle interventions as reducing stress, losing weight, and quitting smoking to promote better overall health may be important to include when counseling patients with hand eczema. However, further longitudinal studies are necessary to get a better understanding of the direction of these associations. In addition, further research will be needed to evaluate if secondary prevention strategies in clinical practice are of added value when counseling patients with hand eczema.

Wet exposure and work related factors
Hand eczema is the most frequently occurring occupational skin disease. An important risk factor associated with hand eczema is wet work. However, studies on non-occupational wet exposure, occupations not considered as high-risk, and socioeconomic factors regarding hand eczema are scarce. In chapter 8 the association between hand eczema and occupational and non-occupational wet exposure, and work-related and socioeconomic factors in the general population of the Netherlands within the Lifelines Cohort Study was investigated. Occupational and non-occupational wet exposure were positively associated with hand eczema. Positive associations for high-risk occupations and occupations not considered as high-risk and higher levels of education were found. No association was found for socio-economic status, income, employment status, or number of working hours. In daily practice, preventive strategies should focus on avoidance of all exposure to wet activities, regardless of origin. Special attention to occupations considered as high-risk remains necessary, however, occupations not considered as high-risk occupations should not be overlooked. Furthermore, to determine whether an individual is working in a high-risk occupation, job tasks instead
of job title should be considered. As previous results on the association between hand eczema and socioeconomic factors differ between studies, future research should focus on a validated definition of socio-economic status for investigating the association with hand eczema.

Part III – Patient Care
New treatment options
For patients with chronic hand eczema who are refractory or intolerant to alitretinoin, treatments options are limited, as no other systemic treatments are currently licensed for the treatment of chronic hand eczema. This thesis includes some first promising results of the (off-label) use of dupilumab in three cases with non-atopic hyperkeratotic hand eczema, and the use of baricitinib in two cases of atopic and non-atopic hand eczema (chapter 9 and chapter 10). Dupilumab, a monoclonal antibody inhibiting interleukin (IL)-4 and IL-13 signaling, and baricitinib, an oral Janus Kinase (JAK)1/2 inhibitor, are approved for the treatment of moderate-to-severe atopic dermatitis. Due to similarities in clinical signs and overlap in pathogenesis with atopic dermatitis, it was hypothesized that these new therapies could have potential in the treatment of chronic hand eczema as well. In addition, considering that JAK inhibitors target several cytokine pathways instead of one single pathway, it is hypothesized that this could be an effective therapy for several subtypes of chronic hand eczema.

Patients’ perspective on care
To optimally tailor hand eczema care to patients’ needs, it is essential to include the patients’ perspective. Chapter 11 reports the results of the focus groups conducted among patients with chronic hand eczema to investigate the patients’ perspective of the perceived care. Fifteen patients participated in four focus groups. Time and attention, together with being listened to and understood by the health care professional, were the most important aspects of care for hand eczema mentioned by participants. Other aspects of care that were regarded as important were that diagnoses, causes and follow-up of hand eczema were not always clear to the participant; more psychosocial support was needed, and that participants experienced frequent changes in doctors. Information provided by nurses was valuable, but more individualized advice was needed. To better meet the needs of patients, more explanation should be given about the causes of hand eczema and final diagnosis. Besides focusing on the treatment, it is also important to focus on its impact on the patient and options for psychosocial and peer support should be discussed. Furthermore, the beneficial role of the specialized nurse as part of integrated care was emphasized. Further studies could also investigate the improvement of care after the implementation of the recommendations for daily
practice discussed in the current study, in which psychosocial support should be of particular concern.

Health literacy
Finally, in chapter 12, aspects of functional, communicative, and critical health literacy were addressed in a large sample of subjects with self-reported hand eczema from the Lifelines Cohort Study to create awareness about this unexposed topic. A substantial proportion of subjects with hand eczema reported limited health literacy. It was found that almost a quarter had limited functional health literacy. In addition, almost half of the subjects with hand eczema never or occasionally talk about their condition, and nearly 40% never or occasionally collect information about their condition. Fewer years of completed education appeared to be an important factor for limited functional health literacy in subjects with hand eczema. This study emphasizes the need for more awareness of limited health literacy among clinicians treating this patient population. Clinicians should especially pay attention and adapt their communication and information provision to patients with lower levels of education in daily practice. As this is the first study measuring health literacy in subjects with hand eczema, many recommendations for future research can be made. These recommendations include the use of validated tools, including both functional, communicative, and critical health literacy, combining objective measure instruments and subjective measure instruments and focusing on the impact of limited health literacy on health outcomes in subjects with hand eczema. After identifying the extent of the problem and the impact on health outcomes, the next steps should include interventions to increase organizational health literacy to eventually improve patient care.

Conclusion
The three parts together encompass very diverse aspects of hand eczema, resulting in a thesis with a broad vision on hand eczema, which is hopefully also what you, as reader of my thesis, will keep in mind; a broad vision when counseling patients with hand eczema to cover all related aspects that are necessary to provide optimal personalized care.