Susceptibility to hand eczema in high risk occupations: Contribution of genetic and environmental factors
Visser, Maaike

Citation for published version (APA):

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GENERAL INTRODUCTION
GENERAL INTRODUCTION

"Your skin. The most important 2m² of your life".

This was the slogan of a recent national campaign for the prevention of skin diseases in Germany. The campaign was launched by a joint effort of the German statutory health and accident insurance institutions, and ran in the whole country during the years 2007 and 2008. Its purpose was to make people more aware of the unique protective function of the skin, its vulnerability to external stress such as contact with moisture, chemicals, mechanical irritation or UV-radiation, and the need for good skin care.

Indeed, the German slogan rightly stressed the importance of paying more attention to the skin, as it is one of the most remarkable organs of our body. The skin forms a barrier between our internal body and the environment – preventing body water loss and blocking entrance of pathogens, toxins, and UV-radiation – and it adds to our experience of that environment through sensation of touch, pressure, heat or cold. Further, it plays an important role in temperature regulation and production of vitamin D. Skin is also an immunological organ; it homes various cells of the immune system that form the first line of defense against pathogens. Thus, our skin comprises several barriers; it not only keeps our inside in, it also actively keeps the outside out.

CONTACT DERMATITIS

The skin is continuously exposed to various stressors which can lead to the damage of one or more of its barriers. Examples are irritants (e.g. chemicals) or allergens which are commonly encountered in the workplace. Although skin has a formidable capability of repairing itself, repetitive damage as e.g. in the occupational setting can lead to changes in the skin barrier. Contact dermatitis, which is one of the most common occupational diseases, occurs as a consequence of a misbalance in inflammatory response aiming at barrier repair after skin damage by external stimuli. If a skin irritating chemical or allergen penetrates the skin, an inflammatory response is usually initiated to get rid of the compound and stimulate repair of skin barrier damage. Normally, the skin recovers and the inflammatory response will be downregulated. In some cases, however, the state of inflammation proceeds into contact dermatitis, an inflammatory skin condition characterized by red, swollen and itchy skin, sometimes with scaling and formation of vesicles. Several subtypes of contact dermatitis can be discerned:

- **Allergic contact dermatitis** occurs when an allergenic compound penetrates the skin and elicits a specific immune response (sensitization and subsequent Type-IV reaction).
- **Acute irritant contact dermatitis** is caused by relatively major damage to the skin, usually the result of a short-time exposure, e.g. an accidental contact with a corrosive chemical.
Chronic irritant contact dermatitis may develop when the skin is repeatedly exposed to one or multiple skin irritating factors that cause only minor damage (usually mild irritants such as soap or water, or mechanical irritation e.g. friction), but there is not enough time between subsequent exposures for the skin to completely recover. The effect of successive inflammatory reactions then accumulates until a threshold is reached and the clinical symptoms of irritant contact dermatitis become visible. If not treated timely, this type of contact dermatitis may develop into a chronic form.

Contact dermatitis often involves the hands. This is not surprising, as this skin area typically comes into contact with a wide range of compounds that are used at work or in the home environment.

**OCCUPATIONAL CONTACT DERMATITIS**

In certain occupational sectors, contact dermatitis is considerably more prevalent than in the general population. This is due to occupational exposure to a variety of chemical substances, allergens, or physical factors, e.g. solvents, metal salts, proteins, plants or animal dander, mechanical friction and “wet work” (exposure to a combination of water, soaps, detergents, disinfectants and occlusive gloves). The most common form of occupational contact dermatitis (OCD) is irritant contact dermatitis (ICD), accounting for 50-80% of OCD, and wet work is a major risk factor for this type of dermatitis. Well-known occupations where workers have an increased risk of developing OCD include hairdressing, nursing, cleaning, kitchen work, floristry, construction work (e.g. bricklaying) and mechanics.

Nevertheless, many workers regard their skin problems as ‘part of the work’ and neglect to seek medical help. As a consequence, OCD is generally underreported in official registries of occupational diseases. Finland, Denmark and Germany have a system of compulsory reporting to national registers, and there OCD is reported with rates of 50-80 cases per 100,000 workers per year. However, a recent questionnaire survey among Danish hospital employees revealed that only 12% of the healthcare workers with hand eczema were actually registered as having occupational hand eczema in the Danish National Board of Industrial Injuries Registry, illustrating substantial underreporting of OCD even among healthcare professionals, who may be expected to be attentive towards disease. In the Netherlands, a voluntary registry is kept by the Netherlands Center for Occupational Diseases. In 2009 the incidence of OCD reported in a related network of dermatologists was 6 cases per 100,000 workers per year, although also here the true incidence was suspected to be higher because of underreporting. A recent review by Nicholson and colleagues estimated that the incidence of OCD in industrialized countries lies between 11 and 86 cases per 100,000 workers per year. Several epidemiological studies have been conducted to assess the prevalence of OCD among workers and apprentices in high risk occupations (Table 1).
The one-year prevalence of OCD found in European surveys in the hairdressing, healthcare and metalworking sectors was about 20-30% and mild skin symptoms were present in up to 50% of the workers or apprentices. In comparison, in the European population, the lifetime prevalence of hand eczema (a generic term which includes irritant and allergic contact dermatitis but also other eczematous lesions on the hands, like atopic dermatitis or hyperkeratosis) is estimated to be 14%, the one-year prevalence is on average 10%, and incidence rates vary from 3.3 cases/1000 person-years to 8.8 cases/1000 person-years.

OCD can have considerable impact on a person’s workability. In a cross-sectional survey of over 400 hand eczema patients from 10 different European dermatology patch test clinics, 28% of the patients reported sick leave because of their OCD and in 12.3% of the patients this sick leave had lasted for more than 5 weeks. A retrospective interview survey among more than 600 Finnish workers who had been referred to the Finnish Institute of Occupational Health with OCD, conducted 7-14 years after diagnosis, revealed that 25% had become unemployed and another 35% had changed their occupation because of their disease. Only 40% of the patients had completely recovered from their OCD. Among healthcare workers, OCD may lead to decreased compliance with hand hygiene, because applying soap or disinfectants (such as alcohol gel) on damaged skin can be painful, and to increased colonization with bacteria such as Staphylococcus aureus. Furthermore, OCD has been shown to impair quality of life also in the private and social environment.

The adverse effects that OCD has in both the personal and the work situation, together with the fairly high prevalence rates in high risk occupations, indicate that the often observed ignorance of skin symptoms – reflected by workers failing to take preventive measures and delaying to seek treatment as well as by health professionals underreporting OCD – is unjustified. Prevention of OCD as well as early diagnosis and appropriate treatment are important. Especially for work-related ICD, where there is a stepwise progression from mild irritation to chronic eczema threatening workability, early prevention is vital.

For the prevention of contact dermatitis, insight in the mechanisms and factors which contribute to its development is essential. In addition to the effects of environmental exposures, endogenous factors also play a role in this. For example, some individuals have an intrinsically reduced skin barrier, which will be discussed in more depth later in this chapter. An impaired skin barrier may lead to increased penetration of harmful substances into the skin and may even enable entrance of substances which would not have been able to penetrate across a healthy skin, for example, allergens with a large molecular size. Thus, persons with a reduced skin barrier are more susceptible to damaging effects due to environmental exposures, for example, when working in jobs with high exposure to skin irritants or allergens. Understanding of the key elements that are responsible for the composition and structure of the skin will contribute to a better maintenance of the skin barrier and prevention of contact dermatitis in the workplace.
Table 1. Literature overview of the prevalence of OCD among workers and apprentices in high risk occupations

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Study population</th>
<th>Design</th>
<th>Definition of outcome(s)</th>
<th>Susceptibility factors assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smit and Coenraads 1993</td>
<td>The Netherlands</td>
<td>Nurses (N = 371)</td>
<td>Retrospective questionnaire survey covering 33 months of follow-up, among newly hired nurses.</td>
<td>Hand eczema based on reported symptoms*.</td>
<td>Not reported in detail.</td>
</tr>
<tr>
<td>Schmid et al. 2005</td>
<td>Germany</td>
<td>Apprentice Nurses (N = 104)</td>
<td>Prospective cohort study with follow-up measurements at 1 year and at 3 years after the start of the study.</td>
<td>Hand eczema based on reported symptoms*. Self-reported hand eczema*. Hand eczema diagnosed by dermatological examination. Skin barrier function assessed by TEWL.</td>
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<tr>
<td>Smit et al. 1994</td>
<td>The Netherlands</td>
<td>Apprentice Nurses (N = 111)</td>
<td>Prospective cohort study; two ‘waves’ of inclusion with follow-up measurements after 1 year and after 2 years (only for the first wave).</td>
<td>Hand eczema based on a combination of self-reported symptoms* and dermatological examination. Skin barrier function assessed by TEWL.</td>
<td>Self-report of childhood eczema, dry skin, asthma and hay fever; patch testing; skin prick testing.</td>
</tr>
<tr>
<td>Jungbauer et al. 2004</td>
<td>The Netherlands</td>
<td>Nurses (N = 822)</td>
<td>Cross-sectional questionnaire survey.</td>
<td>Hand eczema based on reported symptoms*.</td>
<td>Self-report of atopic dermatitis (based on localization and onset of reported eczema), dry skin, asthma, hay fever or chronic bronchitis</td>
</tr>
<tr>
<td>Exposure factors assessed</td>
<td>Results</td>
<td>Remarks</td>
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<tr>
<td>Not reported in detail.</td>
<td>Period prevalence (33 months): 28.8%. Overall incidence rate (0-33 months): 7.8/100 person-years. Incidence rate 0-3 months: 11.3/100 person-years.</td>
<td>83% of the newly hired nurses had already worked as a nurse before they were hired by the studied hospital.</td>
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<tr>
<td>Self-administered questionnaire including items on frequency of hand washing, hand disinfection products, glove use and use of skin care products.</td>
<td>Point prevalence of hand eczema assessed by dermatological examination increased from 21.2% at inclusion to 36.5% in the third year. The 1-year prevalence of hand eczema based on reported symptoms was 25.0% in the first year and 26.9% in the third year; the corresponding 1-year prevalence values of self-reported hand eczema were 36.5% and 43.3%, respectively. Incidence of symptom-based hand eczema was 13.5% in the first year and 17.3% in the third year; for self-reported hand eczema it was 6.7% and 4.8%, respectively.</td>
<td>Baseline TEWL was not a predictor for hand eczema, but presence of symptoms was significantly associated with higher TEWL values during follow-up.</td>
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<tr>
<td>Self-administered questionnaire (taken at inclusion) including items on frequency of hand washing, hand disinfection products, glove use, contact with medicaments and use of skin care products.</td>
<td>Incidence rate: 19.8/100 person-years in the first year; 5.2/100 person-years in the second year.</td>
<td>Baseline TEWL was not a predictor for hand eczema. Hand eczema was associated with mucosal atopy (asthma/hay fever) and dry skin, but not with childhood eczema or positive patch or prick tests.</td>
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<tr>
<td>Not reported in detail.</td>
<td>Point prevalence: 14%. 1-year prevalence: 25%.</td>
<td>Dermatological consultation was offered to those who reported hand eczema. 46% of those invited accepted the invitation, of which 58% had present HE and another 30% had indications for HE in the past 12 months.</td>
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<tr>
<td>Questionnaire items on job description, use of protective gloves, hand washing, use of hand disinfectants, and use of skin care products.</td>
<td>Point prevalence: 8.7%. 1-year prevalence: 22.8%. The 1-year prevalence among different job groups varied between 7.9% - 32.1%, with the highest prevalences in nursing aids, nurses, and assistant nurses.</td>
<td>1-year prevalence of hand eczema was associated with female sex, younger age (&lt; 40 vs &gt; 40 years old), atopic dermatitis, rhinitis, asthma, use of protective gloves, and hand washing, but not with use of hand disinfectants.</td>
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</table>
Table 1. Literature overview of the prevalence of OCD among workers and apprentices in high risk occupations (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Study population</th>
<th>Design</th>
<th>Definition of outcome(s)</th>
<th>Susceptibility factors assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. 2006</td>
<td>Korea</td>
<td>Apprentice nurses (N = 202)</td>
<td>Cross-sectional questionnaire survey.</td>
<td>Hand eczema based on a combination of self-reported symptoms*</td>
<td>Systemic allergic disease: asthma, allergic rhinitis, hay fever and latex allergy</td>
</tr>
<tr>
<td>Smith and Leggat 2004</td>
<td>Australia</td>
<td>Apprentice nurses (N = 232)</td>
<td>Cross-sectional questionnaire survey.</td>
<td>Hand eczema based on a combination of self-reported symptoms*</td>
<td>Self-reported atopic dermatitis and allergy</td>
</tr>
<tr>
<td>Smit et al. 1994</td>
<td>The Netherlands</td>
<td>Apprentice hairdressers (N = 74)</td>
<td>Prospective cohort study with a follow-up time of 10 months (until the end of practical training)</td>
<td>Hand eczema based on a combination of self-reported symptoms* and dermatological examination. Skin barrier function assessed by TEWL.</td>
<td>Self-report of childhood eczema, dry skin, asthma and hay fever; patch testing; skin prick testing</td>
</tr>
<tr>
<td>Uter et al. 1998, 1999</td>
<td>Germany</td>
<td>Apprentice hairdressers (N = 2352)</td>
<td>Prospective cohort study with follow-up measurements after 1 year and after 3 years (&quot;POSH&quot; study)</td>
<td>Dermatological examination of skin changes on the hands, following a definition based on morphology, localization and severity*</td>
<td>Self-report of family and personal history of atopy</td>
</tr>
<tr>
<td>John et al. 2000</td>
<td>Germany</td>
<td>Apprentice hairdressers (N = 66)</td>
<td>Prospective cohort study with follow-up time of 3 years</td>
<td>Clinical examination</td>
<td>Anamnesis with emphasis on atopy, history of flexural eczema, hand eczema, allergic rhinitis and asthma</td>
</tr>
<tr>
<td>Roberts et al. 2006</td>
<td>Australia</td>
<td>Apprentice hairdressers (N = 195) and hairdressers (N = 184)</td>
<td>Crosssectional survey</td>
<td>Dermatological examination, classifying the hands as 'normal', 'mild skin changes', or 'moderate or severe skin changes&quot;</td>
<td>Interview on past or present atopic dermatitis, skin problems on the hands, hay fever and asthma</td>
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</tbody>
</table>

*Definition of outcome(s): Mild, moderate, severe, or no eczema.
<table>
<thead>
<tr>
<th>Exposure factors assessed</th>
<th>Results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reported in detail.</td>
<td>Prevalence of symptoms: scaling 19.3%, dryness 11.9%, irritation 6.9%, and redness 6.4%. Overall prevalence of HE: 10.4%. HE prevalence increased from 6.9% in the 1st year to 22.9% in 4th year.</td>
<td>Prevalence of HE was associated with presence of systemic allergic diseases, with increasing year of study and with living with a flatmate compared to living alone.</td>
</tr>
<tr>
<td>Self-reported previous nursing work and alcohol or tobacco intake</td>
<td>1-year prevalence: 18.5%. The 1-year prevalence increased from 10.8% in the first year to 17.0% in the second year and 27.4% in the third year.</td>
<td>The 1-year prevalence was associated with self-reported atopics dermatitis.</td>
</tr>
<tr>
<td>Self-administered questionnaire (taken at inclusion) including items on frequency of hand washing, hand disinfection products, glove use, contact with medicaments and use of skin care products.</td>
<td>Incidence rate: 32.8/100 person-years. Cumulative incidence over one year: 27.9% The incidence rate was highest in the first 6 months of practical training.</td>
<td>Dry skin was a significant susceptibility factor for developing hand eczema.</td>
</tr>
<tr>
<td>Self-administered questionnaire including questions on occupational tasks, skin protection, cleansing and skin care.</td>
<td>Point prevalence of skin changes: 35.4% at baseline, 47.5% after 1 year and 55.1% after 3 years. Period prevalence of mild skin changes: 46.5%. Period prevalence of hand eczema: 28.5%. Incidence rate of hand eczema: 36.7/100 person-years. The incidence rate declined after the first year of follow-up.</td>
<td>Wet work for more than 2 hours a day was a significant risk factor.</td>
</tr>
<tr>
<td>Questions about leisure activities, occupational tasks and skin protection habits, asked during clinical examination.</td>
<td>Incidence rate in the first year: 31.7/100 person-years. Incidence rate over 3 years: 21.1/100 person-years. Cumulative incidence: 29%.</td>
<td>The higher incidence in the first year was related to high wet work exposure.</td>
</tr>
<tr>
<td>Interview on use of gloves, job tasks, prevocational exposure and knowledge of skin hazards</td>
<td>In apprentice hairdressers, 28.0% had mild dermatitis and 4.7% had moderate to severe dermatitis upon clinical examination. In hairdressers, 17.4% had mild and 8.1 had moderate to severe dermatitis.</td>
<td>A self-reported history of atopy, especially atopic dermatitis, and female sex were associated with skin problems on the hands. Of the participants with clinically examined skin changes present, 34.9% considered themselves to have normal skin.</td>
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<tr>
<td>Reference</td>
<td>Country</td>
<td>Study population</td>
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<tr>
<td>Berndt et al. 1999, 2000</td>
<td>Switzerland</td>
<td>Metalworker apprentices (N = 201)</td>
</tr>
<tr>
<td>Funke et al. 2001</td>
<td>Germany</td>
<td>Apprentices in the car industry (N = 2078)</td>
</tr>
<tr>
<td>Apfelbacher et al. 2008</td>
<td>Germany</td>
<td>Workers in the car industry (N = 1494)</td>
</tr>
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</table>

\(^a\) Hand eczema was defined as having had two or more of the following (combinations of) symptoms: 1) Red and swollen hands or fingers 2) Red hands or fingers and fissures 3) Vesicles on hand or between fingers 4) Scaling hands or fingers with fissures 5) Itching hands or fingers with fissures, plus a duration of more than 3 weeks or recurrence of the symptoms.

\(^b\) Hand eczema was defined as having had one or more of the following (combinations of) symptoms: 1) Red and swollen hands or fingers 2) Red hands or fingers and fissures 3) Vesicles on hand or between fingers 4) Scaling hands or fingers with fissures 5) Itching hands or fingers with fissures.
<table>
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<th>Exposure factors assessed</th>
<th>Results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure assessment based on diaries of job tasks in combination with job-specific exposure checklists formulated beforehand. Self-report of domestic exposures and frequency of hand washing and skin care.</td>
<td>Cumulative incidence: 23%. Incidence during the first 6 months of follow-up: 9%. Incidence during the last 6 months of follow-up: 3%.</td>
<td>A history of flexural eczema (but not atopic skin diathesis in general) was associated with higher risk of hand eczema. Apart from irritant exposure, mechanical friction was a risk factor for hand eczema. A lack of recovery time was also related to increased risk of hand eczema.</td>
</tr>
<tr>
<td>Questionnaire used during dermatological examination; including items on domestic exposure, exposure to irritants (task-based), skin cleansing and use of barrier creams</td>
<td>1-year cumulative incidence: 8.6% 3-year cumulative incidence: 14.1% Incidence was highest during the first 6 months of follow-up and declined thereafter.</td>
<td>Diagnosed hand eczema was predominantly of the irritant type (93.8%). Exposure was a relevant risk factor.</td>
</tr>
<tr>
<td>Not reported</td>
<td>Point prevalence: 9.4% Period prevalence: 21.0% Cumulative incidence since start of apprenticeship: 29.3% Cumulative incidence since start of employment (end of apprenticeship): 18.0%. In 40.0% of apprentices with hand eczema, hand eczema was persisting or recurrent during employment.</td>
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</table>

1. Self-reported hand eczema was defined as a positive answer to the question “Did you suffer from hand eczema in the past year?”
2. TEWL: Transepidermal water loss.
3. For detailed definition of skin changes, see Uter et al. (1998).
4. Mild skin changes included dry skin; moderate to severe skin changes included redness, scaling, flaking, peeling, weeping and cracking.
5. According to the score system proposed by Diepgen et al. in 1991, as reported by Coenraads and Diepgen (1998).
THE SKIN AND ITS BARRIER FUNCTION

Structure of the skin

From the inside to the outer surface, the skin consists of two primary layers: the inner layer or dermis, and the outer layer or epidermis. The dermis mainly consists of collagen fibers, elastic fibers and connective tissue and contains nerves, blood vessels, hair follicles and sweat glands. The epidermis forms the outer layer of the skin. It can be divided into several sublayers (Fig. 1). The main cell type in the epidermis is the keratinocyte. Other cells that are found in the epidermis include melanocytes (cells that produce pigment upon UV-radiation) and Langerhans cells (antigen-presenting cells). Keratinocytes divide in the basal layer or Stratum Basale, and then move up across the prickle layer (Stratum Spinosum) and granular layer (Stratum Granulosum) until they reach the horny layer (Stratum Corneum). Along the way they undergo multiple changes; their nucleus is digested and their shape changes from round to flat. The dead, flattened keratinocytes that finally form the Stratum Corneum (SC) are called corneocytes or squame cells. The SC has an average thickness of 20 cell layers, but the thickness depends on body site, i.e. it is thinner at the eyelids and thicker at the soles of the feet. Corneocytes are shed from the top layer of the SC in a process called desquamation. On average, one cell layer per day is shed. As new
keratinocytes are continuously formed and migrate upwards while corneocytes are shed, the epidermis completely renews itself within a month. 

**Skin barrier function**

The uppermost layer of the epidermis, the Stratum Corneum, is the key layer with regard to skin barrier function. The cells in the SC can be compared to a brick wall; the so-called ‘brick and mortar’ model. In this model, the corneocytes are the bricks, and they are surrounded by a mortar consisting of intercellular lipid bilayers. The corneocytes are further connected to each other by proteins called desmosomes, which can be seen as the equivalent of iron rods that are passed through the bricks to increase the stability of a brick wall. The resulting structure prevents water loss through the skin and blocks substances from diffusing into the skin (Fig. 2).

However, despite the physical barrier provided by the SC, some substances may still be able to cross the SC via the lipid bilayers (intercellular pathway) or, in the case of small hydrophilic compounds, through the corneocytes (transcellular pathway). In general, small molecular size (< 500 kDa) and lipophilicity favor diffusion across the

**Fig. 2.** ‘Brick and mortar’ model of the skin barrier in the stratum corneum
SC. Naturally occurring interruptions of the brick and mortar configuration, like hair shafts and sweat pores, may allow the entering of also larger molecules. The skin barrier may be mechanically damaged, e.g. by scratching in individuals who suffer from an itchy skin condition such as atopic dermatitis (AD), a chronic inflammatory skin disease characterized by dry skin, pruritus, and erythematous lesions. In addition, various chemical and physical stressors are known to break down the skin barrier by causing disruption of the brick and mortar system, for example, detergents, oils and lubricants, and water. Water can cause excess hydration of the SC, causing the corneocytes to swell and increasing the permeability for foreign substances. Exposure to detergents (soaps and surfactants) causes a rise in pH, which will enhance the activity of some pH-sensitive enzymes that are involved in the breakdown of corneodesmosomes during desquamation. Furthermore, detergents are able to solubilize the lipids in the lipid bilayers. Oils and lubricants may also cause spatial disorganization of the lipids in the SC. Both composition and organization of the lipids are important for skin barrier function. Another potential damaging factor to skin barrier function is occlusion of the skin, for example by prolonged wearing of impermeable gloves. Skin occlusion affects hydration, temperature and pH of the skin, which all can influence the organization of the lipid bilayers essential for the barrier function. As a result, the permeability of the skin barrier increases. In addition, in case occlusive gloves are put on shortly after skin contact with irritants or allergens, occlusion prevents removal of substances from the skin surface (which would otherwise occur by evaporation or wiping), thus creating a ‘reservoir’ for prolonged exposure. This may for example occur when a nurse puts on gloves shortly after washing her hands, while the skin is still moist. The presence of a reservoir effect is supported by several experimental studies showing that application of occlusive patches or chambers on irritant-exposed skin caused more severe damage of the skin barrier than occlusion of unexposed skin.

INDIVIDUAL SUSCEPTIBILITY TO IRRITANT CONTACTDERMATITIS

Atopic dermatitis
As stated before, although exposure to irritants is a prerequisite for developing ICD, some persons are more prone to develop this disease. The best-known and most firmly established susceptibility factor for the development of ICD is presence or previous presence of AD. The prevalence of AD is 10-20% in children and up to 10% in adults in the general European population. The increased risk of developing work-related hand eczema for individuals with a history of AD has been recognized since decades, and recent population studies reported odds ratios of about 4 to 5 for the development of hand eczema in subjects with AD or childhood eczema. The mechanisms through which AD predisposes to contact dermatitis in an environment with skin threatening factors are not completely clear. An immunological
pathogenesis is plausible; the cytokine milieu in the skin of AD patients is dominated by pro-inflammatory cytokines, so that contact with irritants may more easily lead to immune hyperreactivity. Furthermore, Langerhans cells are more active in AD skin.\textsuperscript{38,53} Following the hypothesis that atopy (a genetic predisposition to develop allergic diseases) in general could be one of the causal factors for ICD, several studies have investigated associations between contact dermatitis and atopic features other than AD, like rhinitis, asthma, or allergy. However, results are contradictory and inconclusive although most of the studies conclude that respiratory atopy does not increase the risk for ICD.\textsuperscript{3,12,19,48,54} Lately, the focus in AD etiology has shifted from immunological pathogenesis to defects in the skin barrier function. This was mainly caused by a breakthrough discovery that loss-of function mutations in the gene encoding for the epidermal protein \textit{filaggrin} are a major risk factor for development of AD and for the development of other atopic diseases (e.g. asthma) in combination with AD. Several studies have convincingly shown that even in uninvolved skin of AD patients, the barrier function is less strong than that of healthy controls.\textsuperscript{6,55-57} The mechanisms that underlay a skin barrier defect in AD are not completely understood, but aberrant composition and structure of lipid bilayers and proteins of the cornified skin envelope have been shown to play a role.\textsuperscript{38,40,58-60} Another unresolved issue is whether a diminished skin barrier in AD is intrinsic and thus a primary event in the development of AD, or a consequence or event secondary to inflammation. Probably, as several mechanisms are operative, both factors contribute to a reduced skin barrier (the ‘outside-inside-back to outside’ paradigm).\textsuperscript{45,61,62} which may at least partly explain why AD patients are more prone to develop contact dermatitis.

\textbf{Filaggrin}

One possible factor contributing to an impaired skin barrier function in AD is a decreased level of filaggrin in the skin. The main function of filaggrin is to aggregate keratin filaments in the transition of keratinocytes into corneocytes (hence the name filaggrin, short for ‘filament aggregating protein’). This aggregation is essential for optimal development of the skin barrier, because it strengthens the ‘brick and mortar’ structure. Filaggrin is derived from profilaggrin, a very large insoluble molecule that is present in the granules of the Stratum Granulosum. During epidermal proliferation, profilaggrin is enzymatically dephosphorylated and cleaved into filaggrin monomers. In the SC, filaggrin itself is degraded into several hygroscopic amino acids known as natural moisturizing factors (NMF). As the name suggests, NMF contribute to the hydration of the stratum corneum and inhibit water loss through the skin by attracting moisture. One of the NMF constituents, urocanic acid, also functions as an immunosuppressant, has antibacterial effects and protects against UV-radiation.\textsuperscript{65} Furthermore, the presence of the acidic NMF helps to maintain a slightly acidic pH in the outer layer of the skin. Thus, a decreased amount of filaggrin not only leads to impaired skin barrier function in terms of structure, but also via decreased skin hydration (leading to dry skin) and changes in the skin surface pH. The latter is important because pH influences...
the activity of various skin proteases (enzymes that are important for desquamation) and the release of inflammatory cytokines \cite{64,66}. Furthermore, an elevated skin surface pH leads to increased bacterial colonization of the skin (especially by \textit{Staphylococcus aureus}) which in turn may shift the skin immune system towards a Th2-mediated inflammatory response \cite{45,67}. Superinfections and colonization with \textit{Staphylococcus aureus} are one of the main features of AD \cite{68,69}. Larger numbers of microorganisms have also been found on the skin of healthcare workers who were affected by contact dermatitis compared with non-affected colleagues \cite{70,72}.

\textbf{Loss-of-function mutations in the filaggrin gene (FLG)}

Filaggrin is derived from profilaggrin, the production of which is encoded in the filaggrin gene (FLG). FLG is located within the epidermal differentiation complex on chromosome 1q21, a dense cluster of genes involved in the terminal epidermal differentiation and formation of the stratum corneum \cite{73}. It consists of a so-called N-terminal domain (important for calcium binding and nuclear localization) followed by 10, 11 or 12 nearly identical filaggrin repeats and a C-terminal domain, which is required for correct processing of the profilaggrin into filaggrin \cite{65,74}. Although the large size of the gene and the highly repetitive DNA-sequence have made sequencing difficult for a long time, recent studies have identified a large number of loss-of-function mutations in the \textit{FLG} gene leading to incomplete processing or even complete absence of filaggrin in the skin \cite{74,75}. These mutations were first discovered in patients with ichtyosis vulgaris (mostly homozygous or compound heterozygous carriers of \textit{FLG} loss-of-function mutations), an inheritable skin disease characterized by dry skin with fine scaling \cite{76}. The two most common \textit{FLG} mutations in European populations are 2282del4 and R501X, both of which are located on the first filaggrin repeat \cite{64}. In total, over 40 different mutations have been described in European and Asian populations and in the general population of Western Europe the total prevalence amounts to 5-9\% \cite{77-83}. The impact of \textit{FLG} loss-of-function mutations on skin barrier function has been demonstrated in experimental studies as well as in clinical studies involving ichtyosis vulgaris and AD patients. Using filaggrin deficient mice (\textit{ft/ft} or “flaky tail” mice), Scharschmidt and colleagues showed that compared to wildtype mice, the \textit{ft/ft} mice had abnormal barrier function, enhanced penetration of water-soluble tracers and haptens, and that they expressed reduced inflammatory thresholds to irritants as well as allergens. Exposure to low-dose hapten applications elicited a Th2 inflammatory response, which in turn worsened the barrier function \cite{62}. Grüber and colleagues demonstrated that ichtyosis vulgaris patients had increased skin surface pH and a delayed barrier recovery after tape stripping as compared to controls with the wildtype genotype for \textit{FLG}. Furthermore, ichtyosis vulgaris patients showed an increased permeability of a tracer substance and decreased corneocyte integrity in cultured skin cells compared to controls, indicating decreased barrier function \cite{84}. Angelova-Fisher and colleagues performed tape stripping in AD patients and healthy, nonatopic controls, and showed that skin barrier integrity (assessed
by measurement of water loss from the skin) was significantly lower in AD patients carrying FLG mutations as compared to AD patients who were wildtype for FLG and controls. Multiple epidemiological studies convincingly showed that FLG loss-of-function mutations were strongly associated with AD. Up to half of the individuals with moderate to severe AD carry one or more FLG mutations and a recent meta-analysis revealed an OR of 3.4 (95% CI 2.7 – 4.2) for R501X and 2282del4 mutations in AD patients compared with controls.

Because it is evident that the amount of filaggrin in the skin influences skin barrier function, FLG loss-of-function mutations may also be a risk factor for ICD. However, studies focusing on FLG mutations and ICD are scarce. In 2009, Molin and colleagues investigated FLG loss-of-function mutations in 122 German non-atopic patients with different subtypes of chronic hand eczema and compared them to 95 healthy controls. They found a positive association in the subgroup of patients diagnosed with a combination of irritant and allergic contact dermatitis, but not in the subgroup with ICD alone. However, the number of patients in this study was small (25 – 28 patients per subgroup). In 2010, Thyssen and colleagues reported a cross-sectional study in which they genotyped R501X and 2282del14 polymorphisms in 3335 adults recruited from a random sample (n = 7931) of the Danish general population. The effect of FLG loss-of-function mutations on the prevalence of hand eczema – including ICD, AD and allergic CD – was significant in subjects with a history of AD (OR 3.0: 95% CI: 1.3 – 7.0), but not in subjects without AD (OR 0.8; 95% CI 0.4-1.7). A combined presence of AD and FLG loss-of-function mutation status yielded an OR of 3.2 (95% CI: 1.5 – 6.9).

Other factors affecting filaggrin levels in the skin and susceptibility to ICD

Apart from loss-of-function mutations, the amount of filaggrin in the skin can be influenced by other factors as well. One of these factors is variation in the amount of filaggrin repeats in the FLG gene, known as copy number variation (CNV). The repetitive part of the FLG gene may consist of 10, 11, or 12 filaggrin repeats. The more repeats are present, the more profilaggrin protein will be produced, which will eventually result in more filaggrin in the skin. Recently, Brown and colleagues showed in Irish AD patients compared with Irish population controls that CNV in the filaggrin gene also affect the risk of AD. The odds ratio for AD between a person with 20 filaggrin repeats (2x 10 repeats) and a person with 24 repeats (2 x 12) was 1.67. The CNV are common in the population: in the genotyped Irish population the allelic variant of 10 repeats was present in 33.9%; 11 repeats in 51.5% and 12 repeats in 14.6%. CNV appeared to influence the amount of urocanic acid, one of the breakdown products of filaggrin, in the stratum corneum of atopic dermatitis patients. The expression of filaggrin in the SC may further be regulated by enzymatic activity, e.g. of enzymes responsible for the processing of profilaggrin into filaggrin or for the breakdown of filaggrin into NMF and by the cytokine milieu in the skin. Studies in cultured keratinocytes have shown that filaggrin expression is reduced by the presence of pro-inflammatory cytokines like...
interleukin (IL)-4, IL-13, IL-22, IL-25 and tumor necrosis factor (TNF)-α. This may be one of the reasons why reduced levels of NMF – the breakdown products of filaggrin – are also found in the skin of AD patients without FLG loss-of-function mutations.

Susceptibility to ICD may also be influenced by genetic variation in genes involved in immunologic response. The G to A-transition on position 308 of the gene encoding TNF-α (TNFA-308A), which is related to increased production of TNF-α, has been associated with increased reactivity to skin irritation and increased risk of ICD. A protective effect of the variant IL1A-889T allele towards hand dermatitis was found in apprentices involved in activities with high risk of skin irritation. Accordingly, the same research group reported that carriers of a variant IL1A-889T allele have a reduced amount of IL-1α in their stratum corneum. It might be speculated that an intrinsic favourable cytokine balance reflected in a high IL-1RA /IL-1α ratio due to the reduced amount of IL-1α might result in a better resistance against skin irritants.

Recently, a genome-wide association study identified the gene ORMDL3 on chromosome 17q21 to be associated with asthma. The presumed function of this gene is regulation of sphingolipid synthesis and unfolded protein response in endoplasmatic reticulum. Because sphingosine is, together with ceramide, needed for skin barrier integrity, this ORMDL3 gene may also influence skin barrier function.

However, the investigation of these other genetic susceptibility factors falls beyond the scope of this thesis.

**THE ROLE OF GENETIC SUSCEPTIBILITY IN THE PREVENTION OF OCCUPATIONAL CONTACT DERMATITIS**

Knowledge of a worker’s personal susceptibility to develop occupational disease may contribute to more effective, targeted prevention. The first, historic reference to genetic susceptibility screening was made as early as 1938 by a scientist named Haldane, who recognized that some potters developed bronchitis while others did not, and suggested that “we could eliminate potter’s bronchitis by rejecting entrants into the pottery industry who are congenitally disposed to it”. Another historic example is the discovery made during the 1950s Korean war that a genetically determined deficiency of a certain enzyme (G6PD) caused some soldiers to develop acute hemolytic anaemia after taking antimalaria drugs. Recent examples of research on genetic susceptibility to occupational disease include increased susceptibility to beryllium, polycyclic aromatic hydrocarbons (PAHs), di-isocyanates, dust and pesticides. Personal susceptibility could be taken into account in job counseling to advice against high-risk professions for susceptible youngsters while they still have the opportunity to choose another vocational training program. Workers with increased susceptibility could be granted access to extra protective measures, e.g. personal protection equipment (like special gloves in case of OCD), or adjustment of their work tasks. This type of personal prevention is already being applied in some occupational sectors, for example, in Germany and in the Netherlands a prevention program exists in which nurses – being...
at risk for developing OCD due to frequent wet work – undergo pre-employment examination including questions about AD and (history of) hand eczema symptoms as indicators of increased susceptibility to develop OCD. Susceptible individuals receive extra preventive measures and should be regularly followed-up by their occupational physician. Possibly, genotyping for genes involved in skin barrier function, such as FLG, could improve the evaluation of susceptibility to OCD during various kind of screenings. FLG genotyping could also be deployed in diagnostics and targeted interventions or therapy for workers suffering from OCD.

However, before actually offering and applying such a genetic susceptibility test for OCD, several ethical issues need to be considered. The advantages of predictive, and especially genetic tests, have to be weighed against the disadvantages. Well-known disadvantages include the potential for discrimination, the shift of focus from a safe environment for all workers to selection of non-susceptible workers (which is against the priorities set by occupational health and safety professionals), the compromise of autonomy or social pressure to perform the test, the difficulty of informed consent in the face of complex risk knowledge and problems in risk communication. Besides, the clinical validity or predictive value of susceptibility tests is often difficult to assess, both on population and individual level, as it is dependent on many factors. Those factors are not only directly related to the test characteristics itself, but may also be related to the prevalence of the disease and the susceptibility factor in the population, the presence of other, un-tested, susceptibility factors in the population or in the individual and the extent of (future) exposure. Furthermore, the practical consequences of false-positive and false-negative results should be considered. These issues cannot be ignored when investigating the role of FLG genotyping in the prevention of OCD.

AIMS AND OUTLINE OF THIS THESIS

The primary aim of this thesis was to gain more insight into the contributions of FLG loss-of-function mutations, AD, and occupational exposure as risk factors for OCD. A secondary goal was to investigate whether it would be recommendable to include FLG genotyping in susceptibility screening programs for OCD in addition to the usual examination of present or past AD.

The thesis is outlined as follows:

Chapter 2 focuses on exposure to wet work as a risk factor for the development of OCD. In Chapter 2.1, the use of a newly developed sampler designed to quantify wet work exposure is evaluated among nurses. Chapter 2.2 describes exposure to wet work and the occurrence of hand eczema during practical training periods among Dutch apprentice nurses in a prospective cohort study.

In Chapter 3, the influence of AD and FLG mutations as risk factors for OCD is studied. Two different study designs were used for this purpose: in Chapter 3.1, patients with chronic OCD are compared with apprentices in training for high risk occupations in
a case-control study; and in Chapter 3.2, the effects of FLG loss-of-function mutations, AD and exposure to wet work on the risk of hand eczema are described in the prospective cohort of Dutch apprentice nurses mentioned in Chapter 2.2.

Chapter 4 pays attention to the ethical implications of using FLG genotyping in susceptibility testing for OCD. A qualitative study design is applied to investigate the opinions of apprentice nurses – as a stakeholder group – on the use of a genetic test for susceptibility to hand eczema. The advantages and disadvantages of using such a test mentioned by the students are subsequently compared with international guidelines on genetic screening for susceptibility to occupational diseases.

Finally, Chapter 5 gives a general discussion of the results, including recommendations for further research and for practice.

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