Contact Dermatitis in the Construction Industry

Contacteczeem in de Bouw

Johan Timmerman

By Johan Timmerman, 2017.
ISBN: 978-94-91602-89-4
Cover design: Anjolieke Dertien, Multimedia DGK
Lay out by Sinds1961
Printed by Print Service Ede

Contact Dermatitis in the Construction Industry

Contacteczeem in de Bouw

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 21 maart 2017 des middags te 12.45 uur

door

Johannes Geertrudes Timmerman

geboren op 21 maart 1988 te Geldermalsen

Promotor: Prof.dr.ir. D.J.J. Heederik

Copromotoren: Dr.ir. L.A.M. Smit
Dr. T. Spee

TABLE OF CONTENTS

CHAPTER 1

Introduction

The construction industry is a major contributing sector of economies worldwide and offers employment to millions of people. In The Netherlands, the construction industry provided 412,000 full-time jobs in 2013.[1] About 120 different job titles can be identified, ranging from common job titles like carpenter and painter to less frequent job titles like oven builder and steel bender.[2]

During their work, construction workers are exposed to many hazards. The combination of physically hard work and hazardous exposures has led to a high prevalence of occupational diseases. Well known examples include physical trauma resulting from falling or falling objects,[3] musculoskeletal disorders due to physically hard work,[4,5] silicosis due to silica dust exposure,[6] chronic solvent-induced encephalopathy (CSE) due to solvent exposure[7,8] and allergic disorders like allergic occupational asthma and allergic skin diseases, due to allergen exposures (e.g. epoxy resins, chromate, nickel, isocyanates).[9-13] In The Netherlands, construction workers have a more than four times higher risk of being involved in an accident during work compared to workers in all other occupational sectors in The Netherlands.[14]

Occupational health care in The Netherlands

According to Dutch legislation, employers are required to ensure their employees' safety and health.[15] To achieve this, employers are required to create working conditions which are as good as reasonably possible and at least are obliged to collaborate with an occupational physician, either internally or externally. Furthermore, employers can hire other occupational experts when needed. In addition, in every company, a so-called prevention employee has to be present. In smaller companies, this may be the company manager, but in companies with more than 25 employees, a special employee has to be assigned to this task. Individuals with prevention tasks must be sufficiently trained and involved in the development of the mandatory Risk Assessment and Evaluation (RA&E). An RA&E is an investigation meant to document working conditions that are potentially hazardous to employees and any health effects associated to these hazards. The RA&E forms a basis for subsequent in depth studies or immediate preventive action. The RA&E is intended to ensure prevention of any adverse health effect or hazardous working condition before it occurs (primary prevention). Primary prevention has to be complemented by secondary prevention. The occupational physician is responsible for this aspect, that involves detection of health effects as early as possible, in order to prevent aggravation. Finally, tertiary prevention is taken care of by the employer and occupational health service experts, who should take care of implementing preventive measures, such as improvement of working conditions, to prevent the occurrence of adverse health effects in the

near future. In addition to providing targeted treatment, occupational physicians also support employers and employees in case of sick leave and returning to work after sick leave. However, the employer has the primary responsibility for these tasks.

To detect work-related health effects at an early stage, Dutch construction workers are entitled to a medical check-up every two years (40 years and older) or four years (below 40 years of age). During this voluntary check-up, a biometric survey is performed, including hearing and vision tests, blood pressure measurement, lung function measurement, blood analysis (blood glucose and cholesterol levels) and an electrocardiogram (above 40 years only) as well as length and weight measurements. In addition, the check-up includes a consult with an occupational physician, which should be guided by the specific health and safety hazards related to the job title and by the results of a symptom-based questionnaire which is filled in by the worker preceding the check-up. Based on the findings of the occupational physician, a follow-up appointment or activity can be planned. In addition, the occupational physician has the legal obligation to notify any suspicion of, or diagnosed occupational disease to a national occupational disease register. In 2014, 48,305 construction workers were invited for a check-up, 23,984 actually showed up (49.7%) and 8,513 occupational disease notifications were registered. CD (contact dermatitis) accounted for 2% of all registered cases.

Three questions on skin symptoms are currently included in the questionnaire: one on skin tumors, one on occupational skin hypersensitivity and one on dermatitis symptoms. The dermatitis symptom questions are based on questions validated in a population of nurses[16] and might not be well suited to signal beginning skin symptoms in construction workers.[17] Recently, it was stated by the Dutch Social and Economic Council that the majority of occupational physicians do not sufficiently recognize or notify occupational diseases, thereby hampering adequate prevention.[18] Therefore, occupational disease records probably underestimate the actual number of CD cases in the construction industry.

Contact dermatitis

The skin is the human body's largest organ and crucial for regulating body temperature, excreting waste materials, and protecting against harmful influences from the external environment. The outer layer of the skin, the epidermis, mainly forms a physical barrier between the human body and the outside environment, the inner layer or dermis contains vessels, nerves and sweat glands, supplying blood, oxygen, strength and elasticity.[19]

CD can be defined as an inflammatory skin condition caused or worsened by skin contact with one or more exogenous agents, with or without a simultaneous exposure to a contributory physical agent (e.g., ultraviolet light).[20] Acute CD is characterized by itch, redness and vesicles of the skin, whereas chronic CD usually is recognized by itch and a dry, thickened and fissured skin.[21] Two major types of CD can be distinguished: irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD is a skin inflammation caused by a chemical or physical agent, whereas ACD is a type IV delayed immune response induced by a specific allergen.[20]

Epidemiology and impact of hand dermatitis

The point prevalence of hand dermatitis in the general population in Western countries was reviewed by Thyssen *et al*. and was shown to be 4.2% on average. The one-year prevalence was much higher: almost 10%, with a considerable difference between studies reporting estimates in men (5%) and women (11%). In males, incidence was reported to be 4.0 cases in 1,000 person years.[22] More than two-thirds of subjects suffering from hand eczema reported visiting a doctor, and almost half of them visiting a dermatologist. In a Swedish study with a fifteen year follow-up time, 66% of subjects suffering from hand eczema reported symptoms during the follow-up and half of all subjects with hand eczema reported symptoms in the 12 months preceding the interview at the conclusion of the follow-up period,[23] revealing the poor prognosis of hand eczema. In another study, sick leave (at least seven days on one occasion during life) and job change due to hand eczema were reported (21% and 8%, respectively) in a population of subjects with diagnosed hand eczema.[24] Taken together, hand eczema seriously decreases quality of life, its physical and psychological burden is estimated to be comparable to diseases such as multiple sclerosis and migraine, and higher than diabetes mellitus.[25] Also economic impact of dermatitis is high: in the Netherlands, the costs of medical care and disability pensions due to occupational skin diseases were estimated to be 42 million euro in 1995.[26] The annual cost for medical care, disability pensions and absenteeism due to occupational skin diseases were estimated at 98 million euro in 2001.[27,28] In the UK, the yearly number of lost working days was estimated to be 4 million days, leading to yearly costs of 200 million pounds.[29] Thus, given the social and economic impact of dermatitis good preventive measures are warranted.

Mechanism of ICD

Although very strong irritants can induce an acute reaction within minutes after first exposure, the clinical signs of ICD usually only appear after repeated

exposures to milder irritants, which include water, soap, low-humidity air but also repetitive rubbing or abrasion.[30] When an irritant penetrates the skin and causes damage, for example a solvent extracting lipids from the skin or anionic surfactants causing structural protein damage, the barrier function of the skin gets disturbed.[31] The impaired barrier function leads to increased transepidermal water loss and subsequent dryness of the skin, leading to even more structural skin damage. Damaged cells lead to activation of the innate immune system by secretion of cytokines like interleukins, interferons and TNF-alpha.[31-33] These pro-inflammatory signaling substances lead to a relatively mild skin inflammation in the case of ICD, while symptoms may be visible only after accumulation of repetitive exposures.[34]

Mechanism of ACD

In addition to the generally relatively mild inflammation in ICD, allergens induce an additional adaptive immune response including antigen specific T-cell activation, intensifying skin inflammation.[35] This type of hypersensitivity is called a delayed-type hypersensitivity and is fully mediated by T-lymphocytes, in contrast to other hypersensitivity reactions which are usually antibody-mediated.[36] Before a T-cell mediated allergic response can take place, sensitization to an allergen has to occur. This can happen when an individual comes into contact with this specific allergen. Chemical allergens usually are so-called haptens: because of their small size, they cannot induce an allergic reaction themselves unless being bound to autologous peptides, a process called haptenization which is being promoted by cytokines. Professional antigen-presenting cells like Langerhans cells take up a hapten-protein complex and then then migrate to the draining lymph node where hapten-protein complexes are presented to antigen-specific T-lymphocytes. A subsequent contact with the allergen, either at the same skin site or elsewhere on the body, will activate these T-cells thus initiating the adaptive immune response leading to the clinical signs of ACD.[37,38]

Atopic dermatitis

Eczema can be caused by skin contact with external agents, in the case of CD, but can also occur without contact to external agents. Atopic dermatitis (AD) is a common form of eczema mainly affecting young children, which remains a risk factor for development of CD later in life.[39] AD is seen as the first step of a natural history of a number of atopic disorders: the so-called “atopic march”.[40] The atopic march typically starts with a child developing AD in the first years of life with concomitant sensitization to food or inhalant allergens, while later in life atopic asthma or allergic rhinitis may develop.[41]

Risk factors for contact dermatitis

Risk factors for contact dermatitis can be divided into two types: endogenous risk factors are risk factors that originate from inside the body, whereas exogenous risk factors are risk factors from the environment. A number of population studies has shown that atopic predisposition is the most important endogenous risk factor for hand dermatitis.[42-44] Female gender is also mentioned to increase susceptibility to hand dermatitis, which might be explained by both occupational and domestic exposure differences between men and women.[22,45] In addition, over 30 genetic variants were reported to increase the risk of AD,[46] including several genes encoding interleukins and other immune system regulating proteins.[47] The most well-known genetic risk factor for AD is formed by loss-of-function mutations in the filaggrin gene (*FLG*),[48,49] which are present in 8-10% of the European population.[48,50,51] Degradation products of the protein filaggrin, so-called natural moisturizing factors (NMFs), play a central role in sustaining skin hydration.[52,53] Filaggrin deficiency, especially in homozygous carriers, was shown to cause ichthyosis vulgaris, a disease characterized by a dry and scaly skin.[54,55] Decreased *FLG* expression leads to a drier and more permeable skin,[56-59] and is a strong risk factor for skin fissures[53] and AD.[48] Heterozygous mutations were reported to increase the risk of CD, atopic rhinitis, and asthma, but only in co-occurrence with AD.[44,60-62]

The relation between *FLG* loss-of-function mutations and dermatitis is complex. A number of studies reported no direct association between *FLG* loss-of-function mutations and dermatitis, but found associations with earlier onset and longer duration of dermatitis.[54,63] However, in other studies, also direct associations with CD were reported.[44,62] Most studies, however, report an association of *FLG* loss-of-function mutations with CD only in the presence of AD.[64,65] Many studies on the interplay between *FLG* mutations and dermatitis have been performed in children.[66,67] Recently, *FLG* mutations were shown to be related to both occupational ICD and ACD in a number of occupational populations,[62,65,68,69] but to date, construction workers were not studied.

Contact dermatitis in the construction industry

When exposure to an agent that leads to the onset or aggravation of CD occurs in the workplace, the CD is considered to be occupational CD (OCD). OCD is one of the most predominant occupational diseases in numerous countries and accounts for more than 95% of all occupational skin diseases.[20,26,70,71] Prevalence and incidence of hand dermatitis are often used as proxy variables for the prevalence and incidence of OCD, as OCD data are rare.[26] The last time the prevalence in construction workers in the Netherlands was reported, was

in 1984, when about 1,700 Dutch construction workers were dermatologically evaluated for the presence of hand dermatitis, which was diagnosed in 7.8% (ICD: 4%, ACD 1.4%),[72] compared to 4.6% in the general population.[73] Recently, the incidence of CD in Dutch construction workers was reported to be 214 in 100.000 workers in 2014 and significantly increasing from 2010 to 2014, based on occupational disease registers.[74] In a Swedish study in construction workers, the incidence of granted disability pensions due to eczema was between 20.4 and 33.3 per 100,000 person years, which was two to three times higher than in control groups.[75] In a German study using occupational disease registers, ACD was more often reported than ICD in the construction industry, especially in bricklayers and cement workers. In other professions within the construction industry, such as wood processors and painters, ICD was more often reported.[10] Some registry based studies showed an increased risk of OCD among various construction professions,[76,77] but there are very few recent observational studies that assessed the prevalence of hand dermatitis in the construction industry as a whole. A systematic literature search on Pubmed using the query "(dermatitis OR eczema OR skin allergy) AND construction AND (work* or industr*)" retrieved 86 results on CD which were published between January 2000 and May 2016, written in English, and relevant for the construction industry. The papers included in this thesis and a related tutorial were excluded from the results. Of the 81 remaining papers, 53 (65%) articles focused on one specific and/or a small group of agents or individual cases. Of the remaining 28 articles, 18 (64%) were based on surveys among subjects who were selected based on CD symptoms (e.g. after showing up in the clinic with symptoms). The remaining 10 articles included a review paper on recognition and management of occupational contact dermatitis,[76] a review article on allergic disorders in the construction industry,[12] an article on tertiary prevention of occupational dermatitis[78] and a study on the effectiveness of skin cream in the prevention of occupational dermatitis.[79] The remaining six articles were the only cross-sectional papers that reported the prevalence of CD in the construction industry as a whole, and are summarized in Table 1. All six articles studied a random sample of construction workers, except for one article that focused on cement workers. Health outcomes were not uniformly assessed and ranged from self-reported skin symptoms to dermatologist-diagnosed CD. This literature search does not only show how few cross-sectional studies on construction industry-wide CD prevalence have been performed but also shows the heterogeneity in methods of diagnosis which complicates the estimation of the CD prevalence based on literature.

Table 1 - Overview of cross-sectional studies on contact dermatitis in the construction industry.

Reference	Year	Location	Study population	N	Diagnosis	CD Prevalence
Shah & Tiwari[80]	2010	India	Construction workers	92	Dermatologists	Occupational Skin Disease: 47.8%, CD: 4.3%
Wang *et al.*[81]	2011	Taiwan	Cement workers	97	Dermatologists	Cement CD: 67% ICD: 44%, ACD: 23%
Banerjee *et al.*[82]	2015	India	Migrant construction workers	340	Dermatologists	CD: 9.7%, itchy rash: 30.9%
Kuruvila *et al.*[83]	2006	India	Construction workers	1000	Dermatologists	Eczema: 17.3%, CD in masons: 12.5%
Quandt *et al.*[84]	2014	US	Latino construction workers	100	Self-administered questionnaire	Skin symptoms: 23%
Zorba *et al.*[85]	2013	Greece	Working population, including construction workers	600	Occupational Physician	Dermatitis: 12-20%

Occupational risk factors of contact dermatitis

An important exogenous risk factor for OCD is “wet work”, i.e. work including exposure to weak irritants like water and detergents for at least two hours a day.[86-88] Also environmental conditions in or around the work place (e.g. low humidity) are risk factors for OCD.[89,90]

In addition to allergenic substances like epoxy resins and chromate, construction workers are exposed to numerous irritant substances like solvents and abrasive materials and they may perform wet work.[10,26,91,92] A striking example of primary prevention of CD was the legislation that decreased the maximum allowed amount of hexavalent chromium in cement within EU countries. This decrease led to a great decline in chromate sensitization among construction workers (from 43.1 to 29.0%).[93]

The use of gloves may protect the skin of the hands against exposure to chemicals and abrasive materials. A large diversity of gloves is available on the market, but only the use of adequate gloves reduces exposure. Using the wrong gloves or wrong usage of the correct gloves is a risk factor for dermatitis.[94,95] Chemicals that get trapped inside a glove or infiltrate through an inappropriate, non-protective glove may not only cause high exposures but also a false feeling of safety.[26,96,97] In addition, wearing occlusive gloves for more than two hours a day is considered wet work, which is a risk factor for dermatitis in itself.[86-88]

Dermal exposure assessment

To estimate skin exposure to substances that form a risk for CD, dermal sampling was used in several occupational populations, like pesticide applicators[98] and hand harvesters.[99] Different methods were developed, including adding a fluorescence tracer to the handled materials, using patches on the workers' hands to sample substances on the skin, and wet wiping and hand washing to resolve substances that deposited on the skin during work. However, all these methods require the substances of interest to be known, either to add a fluorescent tracer or to choose a solvent to dissolve the deposited substances, which might not be the case in the construction industry. In addition, analysis by gas chromatography is expensive, complicated by the various chemical contaminants that might have been resolved and not always possible for the substance of interest (e.g. chromate). Another specific disadvantage of using patches on the hands is that they may hinder construction workers in performing their work.

In addition to dermal sampling, a number of models was constructed to assess dermal exposure to chemical substances,[100-102] mainly based on the conceptual model for assessment of dermal exposure from Schneider *et al*.[103] These models, however, do not take the abrasive, skin damaging effect of wood, stone and other abrasive materials into account. Another main disadvantage for using these models in the construction industry as a whole is the extremely large number of different substances construction workers can be exposed to. In addition, many properties of these substances are unknown which makes application of these models problematic.

Objectives of this thesis

To decrease the burden of skin disease in the Dutch construction industry, Stichting Arbouw, a foundation established by employers' and employees' organizations in the construction industry to improve workers' health and reduce sick leave, initiated a survey to assess the prevalence of CD amongst Dutch construction workers and to make an inventory of the occupational determinants of CD in the Dutch construction industry.

The main objectives of this thesis are to assess the current prevalence of CD in the Dutch construction industry and to discover risk factors of CD in Dutch construction workers. Ultimate goal is to develop a prognostic tool for occupational physicians to detect CD in an early, preferably preclinical, stage.

Thesis outline

Chapter 2 describes the prevalence of self-reported skin symptoms and associations with questionnaire-based occupational determinants, as reported by construction workers during the routine medical check-up. *Chapter 3* provides a validation of a more detailed questionnaire on hand hygiene in a sample of Dutch construction workers. Associations between CD and *FLG* mutations are presented in *Chapter 4*. In this analysis, CD is based on a questionnaire and on dermatological evaluations. *Chapter 5* analyzes the capability of occupational physicians to detect beginning CD, and explores associations between CD and reported use of particular materials and products. *Chapter 6* describes a case-control study on determinants of epoxy allergy in a sample of German construction workers. Finally, *Chapter 7* discusses the overall findings of this thesis.

References

1 Jansen FJ. Bouw in beeld 2013-2014. Available at: http://www.eib.nl/pdf/bouw_in_beeld_2013-2014.pdf (last accessed 7 April 2015).

2 Collectieve Arbeidsovereenkomst Bouw & Infra (Collective Labouragreement Construction Industry). Available at: https://www.fnvbouw.nl/SiteCollectionDocuments/Cao's/Bouw%20en%20Infra/Cao%20Bouw%20Infra%202015-2017.pdf (last accessed 05/09 2016).

3 Dong XS, Choi SD, Borchardt JG, et al. Fatal falls from roofs among U.S. construction workers. *J Safety Res* 2013; **44**:17-24.

4 Boschman JS, van der Molen HF, Sluiter JK, Frings-Dresen MH. Occupational demands and health effects for bricklayers and construction supervisors: A systematic review. *Am J Ind Med* 2011; **54**:55-77.

5 Stocks SJ, Turner S, McNamee R, et al. Occupation and work-related ill-health in UK construction workers. *Occup Med (Lond)* 2011; **61**:407-415.

6 Meijer E, Tjoe Nij E, Kraus T, et al. Pneumoconiosis and emphysema in construction workers: results of HRCT and lung function findings. *Occup Environ Med* 2011; **68**:542-546.

7 Keski-Santti P, Kaukiainen A, Hyvarinen HK, Sainio M. Occupational chronic solvent encephalopathy in Finland 1995-2007: incidence and exposure. *Int Arch Occup Environ Health* 2010; **83**:703-712.

8 Spee T, van Valen E, van Duivenbooden C, van der Laan G. A screening programme on chronic solvent-induced encephalopathy among Dutch painters. *Neurotoxicology* 2012; **33**:727-733.

9 Winder C, Carmody M. The dermal toxicity of cement. *Toxicol Ind Health* 2002; **18**:321-331.

10 Bock M, Schmidt A, Bruckner T, Diepgen TL. Occupational skin disease in the construction industry. *Br J Dermatol* 2003; **149**:1165-1171.

11 Spee T, Van Duivenbooden C, Terwoert J. Epoxy resins in the construction industry. *Ann N Y Acad Sci* 2006; **1076**:429-438.

12 Carino M, Romita P, Foti C. Allergy-related disorders in the construction industry. *ISRN Prev Med* 2013; **2013**:864679.

13 Engfeldt M, Isaksson M, Zimerson E, Bruze M. Several cases of work-related allergic contact dermatitis caused by isocyanates at a company manufacturing heat exchangers. *Contact Dermatitis* 2013; **68**:175-180.

14 Inspectie SZW. Sectoraanpak Bouw 2012-2016. Available at: http://www.inspectieszw.nl/Images/Sectoraanpak-Bouw-2012-2016_tcm335-365372.pdf (last accessed March/03 2016).

15 Dutch Government. Arbeidsomstandighedenwet. Available at: http://wetten.overheid.nl/BWBR0010346/2016-01-01#Opschrift (last accessed 3 March 2016).

16 Smit HA, Coenraads PJ, Lavrijsen AP, Nater JP. Evaluation of a self-administered questionnaire on hand dermatitis. *Contact Dermatitis* 1992; **26**:11-16.

17 Vermeulen R, Kromhout H, Bruynzeel DP, de Boer EM. Ascertainment of hand dermatitis using a symptom-based questionnaire; applicability in an industrial population. *Contact Dermatitis* 2000; **42**:202-206.

18 Sociaal-Economische Raad. Betere zorg voor werkenden - een visie op de toekomst

van de arbeidsgerelateerde zorg. Available at: https://www.ser.nl/~/media/db_adviezen/2010_2019/2014/toekomst-arbeidsgerelateerde-zorg.ashx (last accessed 3 March 2016).
19 Piérard GE, Piérard S, Piérard-Franchimont CF, Delvenne POR. Hand Dermometrology. In: *Textbook of Hand Eczema*(Alikhan A, Lachapelle J, Maibach HI, eds), 1st edn. Berlin Heidelberg: Springer-Verlag, 2014; 11-24.
20 Lushniak BD. Occupational contact dermatitis. *Dermatol Ther* 2004; **17**:272-277.
21 Bourke J, Coulson I, English J, British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for the management of contact dermatitis: an update. *Br J Dermatol* 2009; **160**:946-954.
22 Thyssen JP, Johansen JD, Linneberg A, Menne T. The epidemiology of hand eczema in the general population--prevalence and main findings. *Contact Dermatitis* 2010; **62**:75-87.
23 Meding B, Wrangsjo K, Jarvholm B. Fifteen-year follow-up of hand eczema: persistence and consequences. *Br J Dermatol* 2005; **152**:975-980.
24 Meding B, Swanbeck G. Consequences of having hand eczema. *Contact Dermatitis* 1990; **23**:6-14.
25 Verhoeven EW, Kraaimaat FW, van de Kerkhof PC, et al. Psychosocial well-being of patients with skin diseases in general practice. *J Eur Acad Dermatol Venereol* 2007; **21**:662-668.
26 Diepgen TL, Coenraads PJ. The epidemiology of occupational contact dermatitis. *Int Arch Occup Environ Health* 1999; **72**:496-506.
27 van Gils RF, Bosmans JE, Boot CR, et al. Economic evaluation of an integrated care programme for patients with hand dermatitis. *Contact Dermatitis* 2013; **69**:144-152.
28 Koningsveld EAP, Zwinkels WS, Mossink JCM, et al. (2003) Maatschappelijke kosten van arbeidsomstandigheden van werknemers in 2001.URL http://publications.tno.nl/publication/34613462/JB4vo9/koningsveld-2003-maatschappelijke.pdf [accessed on 22-03-2016].
29 English JS. Current concepts of irritant contact dermatitis. *Occup Environ Med* 2004; **61**:722-6, 674.
30 Cashman MW, Reutemann PA, Ehrlich A. Contact dermatitis in the United States: epidemiology, economic impact, and workplace prevention. *Dermatol Clin* 2012; **30**:87-98, viii.
31 Lee HY, Stieger M, Yawalkar N, Kakeda M. Cytokines and chemokines in irritant contact dermatitis. *Mediators Inflamm* 2013; **2013**:916497.
32 Enk AH, Katz SI. Early molecular events in the induction phase of contact sensitivity. *Proc Natl Acad Sci U S A* 1992; **89**:1398-1402.
33 Fyhrquist-Vanni N, Alenius H, Lauerma A. Contact dermatitis. *Dermatol Clin* 2007; **25**:613-623.
34 Malten KE. Thoughts on irritant contact dermatitis. *Contact Dermatitis* 1981; **7**:238-247.
35 Kimber I, Basketter DA, Gerberick GF, Dearman RJ. Allergic contact dermatitis. *Int Immunopharmacol* 2002; **2**:201-211.
36 Janeway CA, Travers P, Walport M, Shlomchik MJ. Chapter 12: Allergy and hypersensitivity - hypersensitivity diseases. In: *Immunobiology - the Immune System in Health and Disease*(Anonymous), 6th Edition edn. New York & London: Garland Science Publishing, 2005; 544-545-547.
37 Reis e Sousa C. Dendritic cells as sensors of infection. *Immunity* 2001; **14**:495-498.

38 Vocanson M, Hennino A, Rozieres A, et al. Effector and regulatory mechanisms in allergic contact dermatitis. *Allergy* 2009; **64**:1699-1714.

39 Ring J. *Atopic Dermatitis.* Cham: Springer International Publishing, 2016.

40 Thomsen SF. Epidemiology and natural history of atopic diseases. *Eur Clin Respir J* 2015; **2**:10.3402/ecrj.v2.24642. eCollection 2015.

41 Spergel JM. From atopic dermatitis to asthma: the atopic march. *Ann Allergy Asthma Immunol* 2010; **105**:99-106; quiz 107-9, 117.

42 Yngveson M, Svensson A, Johannisson A, Isacsson A. Hand dermatosis in upper secondary school pupils: 2-year comparison and follow-up. *Br J Dermatol* 2000; **142**:485-489.

43 Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. *Br J Dermatol* 2001; **144**:523-532.

44 Visser MJ, Landeck L, Campbell LE, et al. Impact of atopic dermatitis and loss-of-function mutations in the filaggrin gene on the development of occupational irritant contact dermatitis. *Br J Dermatol* 2013; **168**:326-332.

45 Bjornberg A. Skin reactions to primary irritants in men and women. *Acta Derm Venereol* 1975; **55**:191-194.

46 Paternoster L, Standl M, Waage J, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet* 2015; **47**:1449-1456.

47 de Jongh CM, John SM, Bruynzeel DP, et al. Cytokine gene polymorphisms and susceptibility to chronic irritant contact dermatitis. *Contact Dermatitis* 2008; **58**:269-277.

48 Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**:441-446.

49 Weidinger S, Illig T, Baurecht H, et al. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J Allergy Clin Immunol* 2006; **118**:214-219.

50 Thyssen JP, Carlsen BC, Menne T. Nickel sensitization, hand eczema, and loss-of-function mutations in the filaggrin gene. *Dermatitis* 2008; **19**:303-307.

51 Irvine AD, McLean WH. Breaking the (un)sound barrier: filaggrin is a major gene for atopic dermatitis. *J Invest Dermatol* 2006; **126**:1200-1202.

52 Kezic S, Kemperman PM, Koster ES, et al. Loss-of-function mutations in the filaggrin gene lead to reduced level of natural moisturizing factor in the stratum corneum. *J Invest Dermatol* 2008; **128**:2117-2119.

53 Thyssen JP, Ross-Hansen K, Johansen JD, et al. Filaggrin loss-of-function mutation R501X and 2282del4 carrier status is associated with fissured skin on the hands: results from a cross-sectional population study. *Br J Dermatol* 2012; **166**:46-53.

54 Sandilands A, Terron-Kwiatkowski A, Hull PR, et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat Genet* 2007; **39**:650-654.

55 Smith FJ, Irvine AD, Terron-Kwiatkowski A, et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat Genet* 2006; **38**:337-342.

56 Sergeant A, Campbell LE, Hull PR, et al. Heterozygous null alleles in filaggrin contribute

to clinical dry skin in young adults and the elderly. *J Invest Dermatol* 2009; **129**:1042-1045.
57 Novak N, Baurecht H, Schafer T, et al. Loss-of-function mutations in the filaggrin gene and allergic contact sensitization to nickel. *J Invest Dermatol* 2008; **128**:1430-1435.
58 Flohr C, England K, Radulovic S, et al. Filaggrin loss-of-function mutations are associated with early-onset eczema, eczema severity and transepidermal water loss at 3 months of age. *Br J Dermatol* 2010; **163**:1333-1336.
59 Brown SJ, McLean WH. One remarkable molecule: filaggrin. *J Invest Dermatol* 2012; **132**:751-762.
60 Rodriguez E, Baurecht H, Herberich E, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. *J Allergy Clin Immunol* 2009; **123**:1361-70.e7.
61 van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ* 2009; **339**:b2433.
62 Landeck L, Visser M, Skudlik C, et al. Clinical course of occupational irritant contact dermatitis of the hands in relation to filaggrin genotype status and atopy. *Br J Dermatol* 2012; **167**:1302-1309.
63 Carlsen BC, Johansen JD, Menne T, et al. Filaggrin null mutations and association with contact allergy and allergic contact dermatitis: results from a tertiary dermatology clinic. *Contact Dermatitis* 2010; **63**:89-95.
64 Molin S, Vollmer S, Weiss EH, et al. Filaggrin mutations may confer susceptibility to chronic hand eczema characterized by combined allergic and irritant contact dermatitis. *Br J Dermatol* 2009; **161**:801-807.
65 Thyssen JP, Carlsen BC, Menne T, et al. Filaggrin null mutations increase the risk and persistence of hand eczema in subjects with atopic dermatitis: results from a general population study. *Br J Dermatol* 2010; **163**:115-120.
66 Weidinger S, O'Sullivan M, Illig T, et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. *J Allergy Clin Immunol* 2008; **121**:1203-1209.e1.
67 Marenholz I, Nickel R, Ruschendorf F, et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J Allergy Clin Immunol* 2006; **118**:866-871.
68 Henderson J, Northstone K, Lee SP, et al. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. *J Allergy Clin Immunol* 2008; **121**:872-7.e9.
69 Carlsen BC, Meldgaard M, Hamann D, et al. Latex allergy and filaggrin null mutations. *J Dent* 2011; **39**:128-132.
70 Anveden I, Wrangsjo K, Jarvholm B, Meding B. Self-reported skin exposure -- a population-based study. *Contact Dermatitis* 2006; **54**:272-277.
71 English JS. Occupational dermatoses: overview. *Occup Med (Lond)* 2004; **54**:439-440.
72 Coenraads PJ, Nater JP, Jansen HA, Lantinga H. Prevalence of eczema and other dermatoses of the hands and forearms in construction workers in the Netherlands. *Clin Exp Dermatol* 1984; **9**:149-158.
73 Lantinga H, Nater JP, Coenraads PJ. Prevalence, incidence and course of eczema on the hands and forearms in a sample of the general population. *Contact Dermatitis* 1984; **10**:135-139.
74 van der Molen HF, de Vries SC, Stocks SJ, et al. Incidence rates of occupational

diseases in the Dutch construction sector, 2010-2014. *Occup Environ Med* 2016; **73**:350-352.
75 Meding B, Wrangsjo K, Burdorf A, Jarvholm B. Disability Pensions due to Skin Diseases: A Cohort Study in Swedish Construction Workers. *Acta Derm Venereol* 2016; **96**:232-236.
76 Koch P. Occupational contact dermatitis. Recognition and management. *Am J Clin Dermatol* 2001; **2**:353-365.
77 Halioua B, Bensefa-Colas L, Bouquiaux B, et al. Occupational contact dermatitis in 10,582 French patients reported between 2004 and 2007: a descriptive study. *Dermatology* 2012; **225**:354-363.
78 Skudlik C, Wulfhorst B, Gediga G, et al. Tertiary individual prevention of occupational skin diseases: a decade's experience with recalcitrant occupational dermatitis. *Int Arch Occup Environ Health* 2008; **81**:1059-1064.
79 Winker R, Salameh B, Stolkovich S, et al. Effectiveness of skin protection creams in the prevention of occupational dermatitis: results of a randomized, controlled trial. *Int Arch Occup Environ Health* 2009; **82**:653-662.
80 Shah KR, Tiwari RR. Occupational skin problems in construction workers. *Indian J Dermatol* 2010; **55**:348-351.
81 Wang BJ, Wu JD, Sheu SC, et al. Occupational hand dermatitis among cement workers in Taiwan. *J Formos Med Assoc* 2011; **110**:775-779.
82 Banerjee M, Kamath R, Tiwari RR, Nair NP. Dermatological and respiratory problems in migrant construction workers of Udupi, Karnataka. *Indian J Occup Environ Med* 2015; **19**:125-128.
83 Kuruvila M, Dubey S, Gahalaut P. Pattern of skin diseases among migrant construction workers in Mangalore. *Indian J Dermatol Venereol Leprol* 2006; **72**:129-132.
84 Quandt SA, Newman JC, Pichardo-Geisinger R, et al. Self-reported skin symptoms and skin-related quality of life among Latino immigrant poultry processing and other manual workers. *Am J Ind Med* 2014; **57**:605-614.
85 Zorba E, Karpouzis A, Zorbas A, et al. Occupational dermatoses by type of work in Greece. *Saf Health Work* 2013; **4**:142-148.
86 Ramsing DW, Agner T. Effect of glove occlusion on human skin. (I). short-term experimental exposure. *Contact Dermatitis* 1996; **34**:1-5.
87 Held E, Jorgensen LL. The combined use of moisturizers and occlusive gloves: an experimental study. *Am J Contact Dermat* 1999; **10**:146-152.
88 Stingeni L, Lapomarda V, Lisi P. Occupational hand dermatitis in hospital environments. *Contact Dermatitis* 1995; **33**:172-176.
89 Douglas E, Rushton L, Williams HC. Is occupational dermatitis being taken seriously by UK industries? *Occup Med (Lond)* 1999; **49**:85-91.
90 Nixon RL. Contact dermatitis and occupational skin disease. *Med J Aust* 1996; **165**:47-52.
91 Uter W, Ruhl R, Pfahlberg A, et al. Contact allergy in construction workers: results of a multifactorial analysis. *Ann Occup Hyg* 2004; **48**:21-27.
92 Ronmark EP, Ekerljung L, Lotvall J, et al. Eczema among adults: prevalence, risk factors and relation to airway diseases. Results from a large-scale population survey in Sweden. *Br J Dermatol* 2012; **166**:1301-1308.
93 Geier J, Krautheim A, Uter W, et al. Occupational contact allergy in the building trade in Germany: influence of preventive measures and changing exposure. *Int Arch Occup*

Environ Health 2011; **84**:403-411.
94 Clark SC, Zirwas MJ. Management of occupational dermatitis. *Dermatol Clin* 2009; **27**:365-83, vii-viii.
95 Chew AL, Maibach HI. Occupational issues of irritant contact dermatitis. *Int Arch Occup Environ Health* 2003; **76**:339-346.
96 Brown T. Strategies for prevention: occupational contact dermatitis. *Occup Med (Lond)* 2004; **54**:450-457.
97 Diepgen TL, Kanerva L. Occupational skin diseases. *Eur J Dermatol* 2006; **16**:324-330.
98 Aprea MC, Bosi A, Manara M, et al. Assessment of exposure to pesticides during mixing/loading and spraying of tomatoes in the open field. *J Occup Environ Hyg* 2016; **13**:476-489.
99 Sankaran G, Chen L, Chen Z, et al. The Importance of Hand Exposures to Absorbed Dosage of Hand Harvesters. *J Toxicol Environ Health A* 2015; **78**:1369-1383.
100 Van-Wendel-de-Joode B, Brouwer DH, Vermeulen R, et al. DREAM: a method for semi-quantitative dermal exposure assessment. *Ann Occup Hyg* 2003; **47**:71-87.
101 van Hemmen JJ, Auffarth J, Evans PG, et al. RISKOFDERM: risk assessment of occupational dermal exposure to chemicals. An introduction to a series of papers on the development of a toolkit. *Ann Occup Hyg* 2003; **47**:595-598.
102 Delmaar JE, Bokkers BG, ter Burg W, van Engelen JG. First tier modeling of consumer dermal exposure to substances in consumer articles under REACH: a quantitative evaluation of the ECETOC TRA for consumers tool. *Regul Toxicol Pharmacol* 2013; **65**:79-86.
103 Schneider T, Vermeulen R, Brouwer DH, et al. Conceptual model for assessment of dermal exposure. *Occup Environ Med* 1999; **56**:765-773.

CHAPTER 2

2

Skin symptoms in the construction industry: occurrence and determinants

Johan G. Timmerman[1], Dick J.J. Heederik[1], Ton Spee[1,2], Lidwien A.M. Smit[1]

[1] Institute for Risk Assessment Sciences (IRAS), Utrecht University, The Netherlands
[2] Arbouw Research and Development, Harderwijk, The Netherlands

Annals of Occupational Hygiene 2014, Vol 57, pp 660-668

Abstract

Background
In the construction industry, a relatively high hand eczema prevalence can be expected due to exposure to irritating and allergenic agents.

Methods
As part of a regular program of voluntary medical examinations, a questionnaire including items on health symptoms and working circumstances is administered to construction industry personnel. We studied 152,200 male workers (response rate 52%). Associations between possible risk factors and self-reported hand eczema symptoms and skin hypersensitivity were assessed using log-binomial regression analysis.

Results
Hand eczema symptoms prevalence was 25.4% among construction workers and 14.6% among office personnel. Nuisance due to dust exposure was the most important work-related determinant for hand eczema symptoms (Prevalence Ratio (PR) 1.59, 95% confidence interval (95% CI): 1.55-1.63). Cross-sectional findings were supported by longitudinal analyses in a subset of the study population.

Conclusions
Hand eczema symptoms are common among construction workers. Dust exposure was associated with higher prevalences of hand eczema symptoms.

Introduction

Occupational contact dermatitis (OCD) is one of the most prevalent occupational diseases in many countries and accounts for more than 95% of all occupational skin diseases.[1-3] It can be described as an inflammatory skin condition caused by skin contact with one or more exogenous agents in the workplace setting, with or without a concurrent exposure to a contributory physical agent (e.g., ultraviolet light).[2] Two main types of contact dermatitis can be distinguished: irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD is an inflammation of the skin resulting from a direct cytotoxic effect of a chemical or physical agent, whereas ACD is a type IV delayed immune response induced by an allergen.[2]

Data on incidence and prevalence of OCD are rare, often hand eczema is used as a proxy variable for OCD.[1] A literature review of studies on hand eczema in the general population in Western countries showed an average point prevalence of 4.2%. One year prevalence is higher (almost 10%) with considerable difference between men (5%) and women (11%). Incidence in males was found to be 4.0 cases in 1,000 person years.[4] Of subjects suffering from hand eczema, more than two-thirds report visiting a doctor and 44% reports visiting a dermatologist because of their hand eczema. Sick leave (21%) and job change (8%) are also frequently reported.[5,6] Prognosis of hand eczema is generally poor. In a Swedish study with fifteen year follow-up, 66% of almost 1,000 subjects with hand eczema reported to have had symptoms during follow-up and 44% percent of subjects with eczema reported to have had symptoms in the 12 months preceding the interview at the end of the follow-up period.[7] Not much is known about the social impact of OCD[1] but hand eczema seriously hampers social life of people suffering from it.[8] Some studies also estimated the economic impact of occupational skin disease. In the Netherlands, the direct costs of occupational skin diseases in 1995 were estimated to be 45 million euro.[1] In the UK, yearly costs were estimated to be 200 million pound per year due to 4 million lost working days.[3]

Construction workers have a considerable risk of developing OCD as they are often exposed to substances with allergenic and/or irritant properties such as (wet) cement, epoxy resins, solvents and abrasive materials.[1,9-13] In 1984, in a sample of about 1,700 Dutch construction workers, 7.8% showed a form of hand eczema,[14] whereas in the general population, prevalence among men was 4.6%.[15] In the construction industry, ACD is generally more often reported than ICD, in particular in certain occupations such as bricklayers and cement

workers. In other occupations such as wood processors and painters, ICD is more prevalent.[9] Although a few studies indicated an increased risk of OCD among various occupations within the construction industry,[16,17] there is an almost complete lack of studies reporting the prevalence and risk factors of hand eczema in the construction industry as a whole.
In the present study, we analysed questionnaire data on skin symptoms and occupational risk factors from a large sample of Dutch construction workers. We aim to gain more insight into the occurrence of hand eczema among construction workers and possible risk factors and determinants.

Study population and methods

Study population and design

Dutch construction workers (including office workers) are invited for a voluntary periodical medical checkup at an occupational health service every two to four years, depending on their age. Data from the examinations are registered by Arbouw, the Dutch foundation that was established by employers' and employees' organizations in the construction industry to improve workers' health and reduce sick leave. An anonymized dataset was obtained from Arbouw. According to Dutch legislation, medical ethical approval was not required for this study. A cross-sectional study was performed among all construction workers who had a medical checkup between January 2005 and December 2011. Since 2005, questions on skin symptoms were included in the questionnaire. In this period, from a total of 530,412 invitations, 277,710 checkups were performed, giving a response rate of 52.4% (personal communication Arbouw, 2013). Data from 115,379 male construction workers were used. An additional population of 36,821 male office personnel employed in the construction industry (including office workers, supervisors and canteen personnel) was treated as a separate group and only used in analyses that explored differences in risk between job titles. Data from 8,744 subjects were not used in data analyses because we excluded subjects with an inconsistent date of birth at their second visit, subjects aged <16 or >65 years, and female workers. The female population working on the construction yard is relatively small and not usable for meaningful analyses. For 58,772 construction workers and 15,890 office workers, data on at least two checkups were available. Workers were invited all year round. We explored whether seasonal variation existed in reported dermal symptoms and whether the month in which the checkup took place could be a confounder of relations between occupational exposures and reported dermal symptoms.

Data collection

As part of the checkup, construction workers are asked to fill in a questionnaire with questions on personal characteristics, health aspects, and work-related aspects. Six questions on skin symptoms were included. Workers were asked whether they experienced much nuisance from dust, smoke, vapors/gases or chemicals during their work. In addition, questions on personal protective equipment and sanitary facilities at the work place, skin type, smoking habits, and respiratory symptoms were asked. All analyzed questionnaire items are available in Table 1. In the present study, two skin outcomes were studied: "eczema symptoms" and "skin hypersensitivity". Eczema symptoms was defined as one or more positive answers on the questions 'Did you in the last 12 months suffer from: red and swollen hands or fingers? (question1); red hands or fingers with fissures? (q2); vesicles on the hands or between the fingers? (q3); raw or scaling hands with fissures? (q4); itching hands or fingers with fissures? (q5)'. Occupational skin hypersensitivity was defined as a positive answer to the question 'Is your skin hypersensitive for one or more substances you are exposed to at your work? (question 6)'

Table 1 - Questionnaire items on skin symptoms and potential determinants that were used in data analysis.

Question	Answering options
Did you in the last 12 months suffer from: *(multiple answers possible)*	1. Red and swollen hands or fingers? 2. Red hands or fingers with fissures? 3. Vesicles on the hands or between the fingers? 4. Raw or scaling hands with fissures? 5. Itching hands or fingers with fissures?
Is your skin hypersensitive for one or more substances you are exposed to at your work?	Yes/No
During your work, do you experience much nuisance from: *(multiple answers possible)*	Dust? Smoke? Vapor or gas? Chemicals?
Do you wear gloves during work?	Yes/No
Are there proper washing and dressing facilities available on the construction site?	Yes/No
How would you describe your skin type?	Normal/Dry/Oily
Do you have an allergic airway disease?	Yes/No
Do you regularly have respiratory symptoms (coughing, wheezing, shortness of breath)?	Yes/No
What is applicable to you?	I never smoked I smoked in the past I currently smoke

Table 2- Characteristics of the study population. The total construction worker population is divided into 6 job titles (right half of table).

	Office workers	Construction workers	Construction workers (per job title)					
			Carpenters	Painters	Bricklayers	Drivers	Plasterers	Other
N	36,821	115,379	49,001	14,276	10,567	4,880	2,843	33,812
1 checkup	56.85%	49.06%	22797	7600	4713	2145	1742	17610
2 or more checkups	43.15%	50.94%	26204	6676	5854	2735	1101	16202
Age (mean, Q1-Q3)	42.96 (35-52)	40.74 (31-52)	39.55 (28-51)	42.85 (35-52)	42.07 (32-52)	43.45 (36-53)	37.46 (24-48)	41.05 (32-50)
Smoking status:								
never smoked	47.3%	33.9%	39.2%	30.9%	33.3%	31.0%	27.9%	28.6%
quited smoking	29.8%	27.4%	26.9%	29.2%	30.7%	31.1%	25.3%	25.9%
current smoking	22.9%	38.7%	33.9%	39.9%	35.9%	38.0%	40.9%	45.5%
Nuisance due to occupational exposure to:								
dust	11.7%	57.4%	59.4%	69.9%	57.8%	31.3%	76.5%	51.2%
smoke	1.6%	5.0%	2.8%	4.0%	2.2%	9.4%	2.3%	9.0%
vapors/gas	2.1%	6.8%	2.5%	15.4%	1.9%	10.3%	3.1%	10.8%
chemicals	1.9%	8.9%	4.1%	34.3%	3.2%	3.0%	7.0%	7.9%
Glove use	85.1%	37.3%	41.5%	34.9%	42.5%	30.9%	72.5%	28.4%
No suitable washing and dressing facilities available	18.0%	38.4%	36.1%	36.9%	40.3%	45.4%	40.5%	40.5%
Skin type:								
normal	75.4%	76.8%	76.9%	75.5%	76.1%	79.3%	74.5%	77.1%
dry	15.7%	16.2%	15.9%	17.5%	16.7%	13.3%	20.7%	16.2%
oily	4.7%	3.7%	3.3%	4.3%	3.0%	4.2%	3.4%	4.0%

Respiratory symptoms	8.7%	12.4%	10.7%	16.0%	11.3%	9.5%	15.5%	13.9%
Respiratory allergy	8.2%	7.0%	7.0%	7.9%	6.5%	5.4%	9.0%	7.0%
Red hands or fingers with fissures	3.6%	6.2%	6.2%	6.1%	7.9%	3.8%	8.9%	6.0%
Vesicles on the hands or between the fingers	4.1%	4.2%	3.6%	6.1%	4.0%	3.7%	3.8%	4.3%
Raw or scaling hands with fissures	7.8%	15.9%	16.5%	12.7%	20.2%	9.2%	24.3%	15.2%
Itching hands or fingers with fissures	4.7%	6.7%	6.0%	8.3%	7.4%	4.9%	8.6%	7.0%
Hand eczema symptoms	14.6%	25.4%	25.2%	24.7%	30.5%	16.2%	36.1%	24.8%
Work-related skin hypersensitivity	2.9%	9.5%	11.1%	10.9%	9.0%	3.6%	9.1%	7.6%

Data analysis

All statistical analyses were performed using SAS Software version 9.2 (SAS System for Windows, SAS Institute, Cary, NC). Crude and adjusted prevalence ratios (PRs) and 95% confidence intervals (95% CI) were calculated using log-binomial regression analysis according to Deddens and Petersen.[18]

In the longitudinal analyses, only the first two checkups were used in analyses on subjects with two or more checkups. For job title risk analyses, only subjects who had the same job title during the two checkups were included (total N=60,694). Longitudinal analyses were conducted using log-binomial regression analysis. Subjects reporting symptoms at both checkups were considered to have persistent symptoms, subjects with symptoms at the second but not the first checkup were considered to have incident symptoms and subjects with symptoms at the first but not the second checkup were considered to have remittent symptoms. Subjects with no symptoms at both checkups were used as the reference category. Variation of independent variables like exposures and glove use over the two checkups was also taken into account by creating dummy variables for exposure status at both time points. PRs were calculated similarly as in the cross-sectional analysis described above.

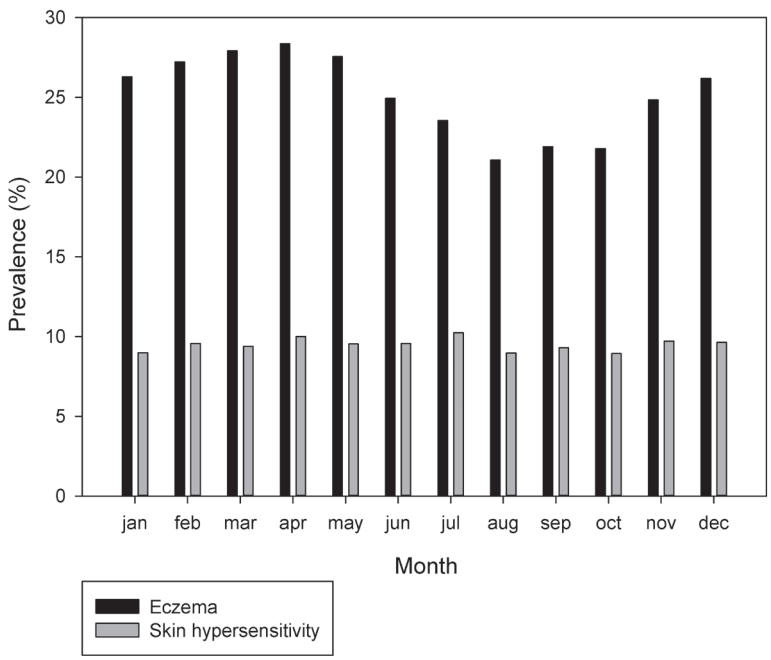
Results

Table 2 shows personal characteristics, occupational exposures, and prevalence of skin symptoms according to the main job titles. Among the 115,379 construction workers, nuisance resulting from dust exposure was reported by more than half of the workers (57.4%), whereas nuisance due to chemicals (8.9%), vapors or gases (6.8%), or smoke (5.0%) were reported less often.
One out of four workers (25.4%) reported at least one skin symptom that defined hand eczema symptoms. The most frequently reported skin symptom was 'raw or scaling hands with fissures' (15.9%). Office workers reported lower prevalences (14.6% eczema symptoms, 2.9% skin hypersensitivity).

Seasonal variation in skin symptom prevalence

We observed a clear seasonal pattern in reported eczema symptoms (Figure 1). During winter (December-February; 26.6%) and spring (March-May; 27.9%) reported prevalence was higher than during summer (June-August; 23.6%) and autumn (September-November; 23.0%). There was no such effect in reporting skin hypersensitivity (Figure 1). In subsequent regression analyses we adjusted results for season.

Figure 1: Seasonal variation in reported crude prevalences of eczema and skin hypersensitivity among construction workers.



Determinants

In Table 3, univariate and adjusted PRs are given for associations between personal characteristics, occupational exposures and skin outcomes. Nuisance due to occupational dust and chemicals exposure was significantly associated with both hand eczema symptoms and skin hypersensitivity. After adjusting, exposure to vapors or gases or exposure to smoke were not significantly related to either hand eczema symptoms or skin hypersensitivity. Construction workers reported slightly more often hand eczema symptoms and skin hypersensitivity when suitable washing and dressing facilities at the workplace were absent. Use of gloves was negatively associated with skin hypersensitivity (adjusted PR 0.61, 95% CI: 0.58-0.63). A dry skin type was associated with a two-fold increase of both hand eczema symptoms and skin hypersensitivity compared with a normal skin type. To a lesser extent, also an oily skin type was associated with both eczema symptoms and skin hypersensitivity. Respiratory symptoms were positively related to both hand eczema symptoms and skin hypersensitivity. These effects were strongest for skin hypersensitivity (adjusted PR 1.36, 95% CI: 1.29-1.42). The observed change in PRs after adjusting was mainly caused by adjusting for the occupational exposures. PRs that were mutually adjusted for occupational exposures, did not change meaningfully after adding all other variables in Table 3.

Relations between job titles and skin symptoms are shown in Table 4. In this analysis, office workers were also included. Drivers (both on the road and off-road) were used as a reference as they work on the construction site but usually have much lower dermal exposures compared to other job titles. The job group with highest adjusted PR for hand eczema symptoms were plasterers (PR 1.98, 95% CI: 1.83-2.14) and bricklayers (PR 1.80, 95% CI: 1.68-1.93) whereas office workers had a significantly lower prevalence than drivers (PR 0.90, 95% CI: 0.84-0.96). For skin hypersensitivity, highest adjusted PR were found in carpenters (PR 2.98, 95% CI: 2.57-3.46) and painters (PR 2.70, 95% CI: 2.32-3.15), whereas office workers again had a significantly lower prevalence than drivers (PR 0.78, 95% CI: 0.66-0.91).

Table 3 - Associations of eczema symptoms and skin hypersensitivity with potential determinants in 115,379 male construction workers.

	Eczema symptoms		Skin hypersensitivity	
	crude PR (95% CI)	adjusted PR (95% CI)	crude PR (95% CI)	adjusted PR (95% CI)
Age (per 10 years increase)	1.04 (1.03-1.05)	1.03 (1.02-1.04)	1.06 (1.05-1.08)	1.06 (1.05-1.08)
Smoking status:				
never smoked	(reference)	(reference)	(reference)	(reference)
quited smoking	1.28 (1.25-1.31)	1.15 (1.12-1.19)	1.23 (1.18-1.29)	1.06 (1.01-1.11)
current smoking	1.27 (1.24-1.30)	1.11 (1.08-1.14)	1.19 (1.14-1.24)	0.98 (0.94-1.03)
Nuisance due to occupational exposure to:				
dust	1.90 (1.87-1.94)	1.59 (1.55-1.63)	2.76 (2.65-2.86)	1.78 (1.71-1.86)
smoke	1.40 (1.35-1.45)	1.03 (0.98-1.08)	1.66 (1.55-1.78)	0.99 (0.92-1.07)
Vapors/gases	1.44 (1.39-1.48)	1.04 (0.99-1.08)	1.87 (1.77-1.98)	0.98 (0.92-1.04)
chemicals	1.50 (1.45-1.54)	1.09 (1.06-1.14)	2.49 (2.38-2.61)	1.55 (1.48-1.63)
Glove use	0.76 (0.74-0.77)	0.98 (0.95-1.00)	0.39 (0.38-0.41)	0.61 (0.58-0.63)
No suitable washing and dressing facilities	1.21 (1.19-1.23)	1.06 (1.04-1.09)	1.30 (1.25-1.34)	1.06 (1.02-1.10)
Skin type:				
normal	(reference)	(reference)	(reference)	(reference)
dry	2.16 (2.12-2.20)	2.01 (1.96-2.06)	2.74 (2.64-2.84)	2.28 (2.19-2.36)
oily	1.20 (1.15-1.26)	1.16 (1.09-1.23)	1.41 (1.30-1.54)	1.35 (1.23-1.47)
Respiratory allergy	1.29 (1.25-1.33)	1.09 (1.05-1.14)	2.08 (1.98-2.18)	1.49 (1.41-1.57)
Respiratory symptoms	1.47 (1.44-1.51)	1.20 (1.16-1.24)	2.08 (2.00-2.17)	1.36 (1.29-1.42)
Season:				
Autumn	(reference)	(reference)	(reference)	(reference)
Winter	1.16 (1.13-1.19)	1.13 (1.10-1.17)	1.01 (0.96-1.06)	0.97 (0.92-1.02)
Spring	1.22 (1.18-1.25)	1.16 (1.12-1.19)	1.03 (0.98-1.08)	0.96 (0.92-1.01)
Summer	1.03 (1.00-1.06)	1.00 (0.97-1.04)	1.03 (0.97-1.08)	1.00 (0.95-1.06)

PR were adjusted for all other determinants shown in the table.

Table 4 - Associations between job titles and eczema symptoms and skin hypersensitivity.

	Eczema symptoms at first checkup	Crude PR (95% CI)	Adjusted PR (95% CI)	Skin allergy at first checkup	Crude PR (95% CI)	Adjusted PR (95% CI)
Drivers	16.2%	(reference)	(reference)	3.6%	(reference)	(reference)
Carpenters	25.2%	1.56 (1.46-1.66)	1.54 (1.44-1.65)	11.1%	3.10 (2.67-3.60)	2.98 (2.57-3.46)
Bricklayers	30.5%	1.88 (1.76-2.02)	1.80 (1.68-1.93)	9.0%	2.50 (2.13-2.93)	2.37 (2.02-2.77)
Painters	24.7%	1.53 (1.42-1.64)	1.43 (1.33-1.53)	10.9%	3.02 (2.59-3.53)	2.70 (2.32-3.15)
Plasterers	36.1%	2.23 (2.05-2.41)	1.98 (1.83-2.14)	9.1%	2.53 (2.09-3.05)	2.25 (1.86-2.71)
Other construction workers	24.8%	1.53 (1.43-1.63)	1.47 (1.37-1.57)	7.6%	2.11 (1.81-2.46)	1.99 (1.71-2.31)
Office workers	14.6%	0.90 (0.84-0.96)	0.90 (0.84-0.96)	2.9%	0.81 (0.69-0.96)	0.78 (0.66-0.91)

PR were adjusted for age, smoking, skin type, respiratory symptoms, respiratory allergy, available sanitary facilities and season.

Longitudinal analysis

Among subjects with at least two checkups, 23.7% reported eczema symptoms at their first visit and 23.4% reported eczema symptoms at their second visit. Eczema symptoms at both visits were reported by 11.8%, incident eczema symptoms by 11.6% and remittent eczema symptoms by 11.8% of subjects. Results of the regression analysis are shown in Table 5. Reporting nuisance due to occupational dust exposure at both checkups was strongly related to both eczema symptoms and skin hypersensitivity (PR > 1.50), regardless if the symptoms were reported at only the first, only the second or both checkups. In addition, a pattern was observed that suggested a temporal relation between exposure and symptoms: associations of exposure reported at the second but not the first checkup were strongest with incident eczema symptoms and skin hypersensitivity, whereas associations of exposure reported at the first but not the second checkup were strongest with remittent eczema symptoms and skin hypersensitivity. A similar temporal pattern was seen for associations between chemical exposures and reporting skin hypersensitivity, whereas associations of chemical exposures with hand eczema symptoms were much weaker.

As in the cross-sectional analysis, longitudinal analyses showed only weak associations with PR close to unity for occupational exposure to smoke, or exposure to vapors or gases (data not shown).

Reporting glove use at both check-ups was strongly negatively associated with skin hypersensitivity, regardless if symptoms were reported at only the first, only the second or both checkups (PR ranging from 0.43 to 0.56). Interestingly, glove use at the second but not the first checkup was positively associated with remittent skin hypersensitivity, and glove use at the first but not the second checkup was positively associated with incident skin hypersensitivity, again suggesting a temporal relation. All construction yard job titles shown in Table 5 except painters had a statistically significantly increased prevalence of incident, remittent and persistent eczema symptoms compared with drivers. Carpenters and bricklayers had significantly higher prevalences of incident, remittent and persistent skin hypersensitivity than drivers. Painters had higher prevalences of remittent skin hypersensitivity, plasterers had higher prevalences of persistent skin hypersensitivity and other construction workers had higher prevalences for both remittent as well as persistent skin hypersensitivity. Office job titles had a statistically significantly lower risk of incident skin hypersensitivity.

Table 5 - Associations of incident, remittent and persistent eczema symptoms and skin hypersensitivity in the subpopulation of construction workers with at least two checkups.

	Eczema symptoms			Skin hypersensitiviy		
	Incident	*Remittent*	*Persistent*	*Incident*	*Remittent*	*Persistent*
Nuisance due to occupational dust exposure						
no/no	(reference)	(reference)	(reference)	(reference)	(reference)	(reference)
no/yes	1.70 (1.59-1.82)	1.15 (1.06-1.25)	1.49 (1.37-1.62)	2.07 (1.82-2.36)	1.51 (1.31-1.75)	1.87 (1.61-2.17)
yes/no	1.13 (1.04-1.22)	1.67 (1.56-1.78)	1.56 (1.44-1.69)	1.35 (1.17-1.57)	2.06 (1.82-2.34)	1.88 (1.62-2.19)
yes/yes	1.51 (1.43-1.60)	1.57 (1.48-1.66)	2.30 (2.16-2.45)	2.12 (1.90-2.37)	2.22 (1.99-2.47)	2.72 (2.41-3.06)
Nuisance due to occupational chemicals exposure						
no/no	(reference)	(reference)	(reference)	(reference)	(reference)	(reference)
no/yes	1.18 (1.07-1.30)	0.92 (0.82-1.03)	1.08 (0.98-1.18)	1.81 (1.58-2.08)	1.13 (0.95-1.35)	1.59 (1.37-1.84)
yes/no	0.94 (0.84-1.05)	1.17 (1.07-1.28)	1.04 (0.96-1.14)	1.18 (1.00-1.41)	1.69 (1.48-1.93)	1.59 (1.38-1.84)
yes/yes	0.99 (0.88-1.12)	1.10 (0.99-1.23)	1.16 (1.07-1.26)	1.50 (1.27-1.77)	1.34 (1.13-1.59)	1.95 (1.73-2.20)
Glove use						
no/no	(reference)	(reference)	(reference)	(reference)	(reference)	(reference)
no/yes	1.04 (0.97-1.12)	1.10 (1.03-1.17)	0.92 (0.86-0.99)	0.68 (0.59-0.79)	1.40 (1.27-1.55)	0.61 (0.53-0.70)
yes/no	1.12 (1.05-1.19)	1.11 (1.05-1.18)	0.99 (0.93-1.05)	1.41 (1.28-1.54)	0.70 (0.62-0.79)	0.65 (0.57-0.73)
yes/yes	0.97 (0.91-1.02)	0.94 (0.88-0.99)	0.89 (0.85-0.94)	0.54 (0.48-0.61)	0.56 (0.50-0.62)	0.43 (0.38-0.49)
Job title						
Drivers	(reference)	(reference)	(reference)	(reference)	(reference)	(reference)
Carpenters	1.48 (1.30-1.68)	1.39 (1.22-1.58)	1.55 (1.31-1.85)	1.83 (1.43-2.35)	2.56 (1.91-3.43)	2.82 (2.05-3.89)
Bricklayers	1.70 (1.48-1.96)	1.63 (1.42-1.88)	1.94 (1.61-2.33)	1.45 (1.10-1.91)	2.01 (1.47-2.74)	2.44 (1.74-3.41)
Painters	1.15 (0.99-1.32)	1.20 (1.04-1.38)	1.12 (0.93-1.35)	1.20 (0.92-1.58)	1.73 (1.27-2.36)	1.38 (0.98-1.93)
Plasterers	1.56 (1.29-1.90)	1.60 (1.33-1.93)	1.84 (1.48-2.29)	1.01 (0.68-1.51)	1.50 (0.99-2.27)	2.29 (1.54-3.40)
Other construction workers	1.30 (1.14-1.48)	1.32 (1.16-1.51)	1.36 (1.14-1.62)	1.20 (0.93-1.55)	1.67 (1.24-2.25)	1.50 (1.08-2.08)
Office workers	0.94 (0.82-1.08)	1.07 (0.94-1.23)	0.97 (0.81-1.17)	0.62 (0.47-0.82)	1.06 (0.77-1.44)	0.98 (0.69-1.38)

PR were adjusted for age, smoking status, skin type, respiratory symptoms, season and all other determinants in the table except for job title. Job title associations were adjusted for age, smoking, skin type, respiratory symptoms, allergic airway diseases, available sanitary facilities and season.

Discussion

In this large-scale questionnaire survey, self-reported prevalence and determinants of eczema symptoms and skin hypersensitivity among 152,200 Dutch construction workers were analysed. Among male construction workers, one year eczema symptoms and occupational skin hypersensitivity prevalences were 25.4% and 9.5%, respectively. Nuisance due to exposure to dust was the main work-related determinant.

To our knowledge, this is the first time since 1984 that eczema prevalence was studied across the construction industry as a whole, thus giving a unique insight in this large occupational group. We had a wealth of data available, with self-reported routine data from no less than 152,200 subjects which provided ample statistical power. The response rate was 52.4%, which is lower than in a study among Swedish construction workers in an equivalent setting, where a response rate of at least 80% was achieved.[19] A non-response survey was performed to evaluate the reasons why invited workers did not visit the checkup. Already undergoing medical treatment (19.6%) was the most frequently mentioned reason for non-response, followed by lack of interest (14.3%) and not being able to visit the checkup (11.1%) (personal communication Arbouw, 2013). Prevalence estimates in our study might be somewhat influenced by selection bias. Underreporting might happen because some workers with skin symptoms may not have visited the checkup as they were already receiving medical treatment for these symptoms. On the other hand, overreporting might happen because subjects who feel healthy are also likely to be underrepresented. In general however, we assume that the presence of skin symptoms during the past year may not have had a large influence on the decision to attend the checkup.

Self-reported exposure assessment can lead to reporting bias as subjects with symptoms tend to report more exposure. The questions on nuisance due to occupational exposures were not skin specific, exposure to dust can, for example, also lead to respiratory symptoms. We do not expect subjects with hand eczema symptoms to overreport nuisance due to dust compared with workers with similar exposures but no hand symptoms. Moreover job title analysis also showed more symptoms in workers with dusty jobs.In our study sample, a one-year eczema symptoms prevalence of 25.4% was found. This is considerably higher than the 5% eczema prevalence that was found in the general male population[4] and the prevalence of 7.8% found by Coenraads *et al*. in Dutch construction workers. In these studies, different methods of diagnosis

were used (different methods of self-reporting eczema, doctor diagnoses). The lack of a standard definition for hand eczema makes it difficult to compare the observed prevalence with other studies. Within our study, every subject completed the same questionnaire. For internal comparisions, e.g. between job titles, the lack of a standard definition is less important. The questions we used in the present study to determine eczema prevalence, were developed to be used together with two additional questions that were not included in our routine survey questionnaire data. A positive answer to one of these additional questions, “Did one or more of these symptoms last for more than 2 weeks?” and “Did one or more of these symptoms occur more than once?”, is needed for a reliable indication of hand eczema, as was validated in a population of nurses.[20] Due to the high sensitivity (100%) and moderate specificity (64%) of this symptom-based diagnosis, Smit *et al.* recommended to subsequently perform a dermatological examination in the positively scoring subjects. Vermeulen *et al*. found that the specificity and sensitivity of this method was different in an industrial population and they recommended the symptom-based questionnaire to be validated in other populations.[21] Therefore we plan to validate the questionnaire in a population of construction workers during ongoing research. In this study, also a more detailed exposure assessment will be performed.

As we did not have data on the additional questions as used by Smit *et al*., we used a less strict definition of hand eczema. This method was also evaluated by Vermeulen *et al*. and they found considerably higher prevalences with the less strict method we used (38.1% vs. 27.2% with the additional two questions). As the original method by Smit *et al.* had high sensitivity but moderate specificity and we were not able to include the two additional questions, we expect the prevalence found in the present study to overestimate the actual prevalence. On the other hand, underreporting may have happened in our present study, as in a study amongst Danish hairdressers, it became apparent that many workers and physicians underreport hand eczema to the National Board of Industrial Injuries.[22] Especially milder forms of eczema may not be considered a serious health disorder and many people are not fully aware of the risks of developing chronic hand eczema from a mild form of eczema.[23]

In literature it has been reported that weather conditions can influence the prevalence of hand eczema.[24-26] Although the questionnaire asked for the occurrence of symptoms in the last 12 months, we investigated whether there was a seasonal effect of symptom reporting, as subjects people might tend to report symptoms more frequently when they experienced the symptoms shortly

before. It appeared there was a seasonal variation, with almost 5% more hand eczema symptoms reported in spring than in autumn, indicating that subjects tend to report symptoms that occurred shortly before filling in the questionnaire as was earlier suggested by Diepgen and Coenraads[1] This finding indicates that year-prevalence obtained by questionnaire on symptoms in the last 12 months should be interpreted carefully, as the data could have a tendency towards a point prevalence rather than a one-year prevalence and thus underestimate the one year prevalence.

Office personnel reported a hand eczema symptoms prevalence of 14.6% which is still considerably higher than 5% hand eczema in the male general population. In addition to the broad eczema definition we used, this may be due to the fact that in many small companies in the construction industry, office personnel works at least part of the time at the construction site.

In our study, survivor bias may have influenced prevalences and risk estimates as subjects with severe hand eczema may leave jobs.[1] Moreover, we could only make use of self-reported nuisance due to occupational exposures. Although we subdivided the construction workers population into six job title groups, a lot of variation between the job titles in the 'other job titles' group remains. For example, floor layers very commonly report exposures to dust (86.2%) and chemicals (62.1%) whereas steel fixers (dust: 35.6%) and road pavers (chemicals: 1.8%) much less often report these exposures. In addition, there is a lot of variation within the job titles. Carpenters, for instance, all have the same job title but may perform different tasks and consequently have different exposure patterns.

It is well-known that dust may contain eczema causing components, for instance allergenic wood species dust and gypsum drywall dust that dehydrates the skin. This might explain the high prevalence of skin hypersensitivity in carpenters (11.1%) and the high percentage of plasterers reporting a dry skin (20.7%) or eczema symptoms (36.1%). The effect on skin conditions of both exposure to wood dust and gypsum may be exacerbated by the use of abrasive materials. Although not asked for in the questionnaire, many construction workers handle abrasive materials that damage the skin, creating a port of entry for small particles to enter the skin and underlying tissues, provoking a skin inflammation. We only had access to a crude proxy for occupational exposure and a limited number of determinants. In our questionnaire, no questions on wet work were included. Wet work is a major risk factor for OCD[27] and construction workers may also be exposed to wet work either by direct contact with water or wet

materials such as cement, wearing occlusive gloves or high hand washing frequencies. In our job title analysis, bricklayers showed a high prevalence of eczema symptoms. This might be due to wet characteristics of cement but also due to allergenic components of cement or due to abrasive characteristics of bricks. Another important risk factor for hand eczema is a history of atopy or childhood eczema.[1,4] As a proxy for atopy, we corrected for respiratory allergy in our analysis but this hardly influenced the risk estimates.

In our study we had the strength of longitudinal data which made it possible to analyze the change in symptom prevalence in association with a change in exposure. The longitudinal data support the hypothetic temporal relation between dust exposure and eczema symptoms, as incident eczema symptoms are most strongly associated with reported exposure at the second but not the first checkup, and remitting eczema symptoms are most strongly associated with exposure at the first but not the second checkup. In the longitudinal analysis, also a temporal relationship between glove use and eczema symptoms was suggested as incident eczema symptoms were most strongly associated with glove use at the first but not the second checkup and remittent eczema symptoms were strongest associated with glove use at the second but not the first checkup. Glove use at both checkups was also negatively associated with eczema symptoms at both checkups. To prevent OCD in construction workers, preventing the skin from contact with the inducing agent is essential.[1] The first approach in prevention is to eliminate the harmful substance.[1,28] Wearing appropriate gloves to protect the skin from OCD causing agents and contributory factors is recommended as an alternative measure. [16,29] It is remarkable that in our data painters report high nuisance due to chemicals exposure (34.3%) but glove use is low amongst painters (34.9%). This might stress the need of gloves that are both protective and suitable for the working tasks of the construction workers. At the moment, many workers might not use gloves as they bother them in doing their work.

Conclusions

In Dutch male construction workers, high eczema symptom and skin hypersensitivity prevalence was observed compared to the general population. Main occupational determinants were dust and chemical exposures. These findings need to be confirmed by using a complete set of validated eczema questions supplemented by a dermatologist's diagnosis. Moreover, in-depth analysis of high-risk job titles will give more insight into the determinants of OCD, and will help to develop a prevention policy.

References

1 Diepgen TL, Coenraads PJ. The epidemiology of occupational contact dermatitis. *Int Arch Occup Environ Health* 1999; **72**:496-506.
2 Lushniak BD. Occupational contact dermatitis. *Dermatol Ther* 2004; **17**:272-277.
3 English JS. Occupational dermatoses: overview. *Occup Med (Lond)* 2004; **54**:439-440.
4 Thyssen JP, Johansen JD, Linneberg A, Menne T. The epidemiology of hand eczema in the general population--prevalence and main findings. *Contact Dermatitis* 2010; **62**:75-87.
5 Hald M, Berg ND, Elberling J, Johansen JD. Medical consultations in relation to severity of hand eczema in the general population. *Br J Dermatol* 2008; **158**:773-777.
6 Meding B, Swanbeck G. Consequences of having hand eczema. *Contact Dermatitis* 1990; **23**:6-14.
7 Meding B, Wrangsjo K, Jarvholm B. Fifteen-year follow-up of hand eczema: persistence and consequences. *Br J Dermatol* 2005; **152**:975-980.
8 Moberg C, Alderling M, Meding B. Hand eczema and quality of life: a population-based study. *Br J Dermatol* 2009; **161**:397-403.
9 Bock M, Schmidt A, Bruckner T, Diepgen TL. Occupational skin disease in the construction industry. *Br J Dermatol* 2003; **149**:1165-1171.
10 Winder C, Carmody M. The dermal toxicity of cement. *Toxicol Ind Health* 2002; **18**:321-331.
11 Geraut C, Tripodi D, Brunet-Courtois B, et al. Occupational dermatitis to epoxydic and phenolic resins. *Eur J Dermatol* 2009; **19**:205-213.
12 Uter W, Ruhl R, Pfahlberg A, et al. Contact allergy in construction workers: results of a multifactorial analysis. *Ann Occup Hyg* 2004; **48**:21-27.
13 Ronmark EP, Ekerljung L, Lotvall J, et al. Eczema among adults: prevalence, risk factors and relation to airway diseases. Results from a large-scale population survey in Sweden. *Br J Dermatol* 2012; **166**:1301-1308.
14 Coenraads PJ, Nater JP, Jansen HA, Lantinga H. Prevalence of eczema and other dermatoses of the hands and forearms in construction workers in the Netherlands. *Clin Exp Dermatol* 1984; **9**:149-158.
15 Lantinga H, Nater JP, Coenraads PJ. Prevalence, incidence and course of eczema on the hands and forearms in a sample of the general population. *Contact Dermatitis* 1984; **10**:135-139.
16 Koch P. Occupational contact dermatitis. Recognition and management. *Am J Clin Dermatol* 2001; **2**:353-365.
17 Halioua B, Bensefa-Colas L, Bouquiaux B, et al. Occupational contact dermatitis in 10,582 French patients reported between 2004 and 2007: a descriptive study. *Dermatology* 2012; **225**:354-363.
18 Deddens JA, Petersen MR. Approaches for estimating prevalence ratios. *Occup Environ Med* 2008; **65**:481, 501-6.
19 Toren K, Qvarfordt I, Bergdahl IA, Jarvholm B. Increased mortality from infectious pneumonia after occupational exposure to inorganic dust, metal fumes and chemicals. *Thorax* 2011; **66**:992-996.
20 Smit HA, Coenraads PJ, Lavrijsen AP, Nater JP. Evaluation of a self-administered questionnaire on hand dermatitis. *Contact Dermatitis* 1992; **26**:11-16.

21 Vermeulen R, Kromhout H, Bruynzeel DP, de Boer EM. Ascertainment of hand dermatitis using a symptom-based questionnaire; applicability in an industrial population. *Contact Dermatitis* 2000; **42**:202-206.
22 Lysdal SH, Sosted H, Johansen JD. Do hairdressers in Denmark have their hand eczema reported as an occupational disease? Results from a register-based questionnaire study. *Contact Dermatitis* 2012; **66**:72-78.
23 Coenraads PJ. Hand eczema. *N Engl J Med* 2012; **367**:1829-1837.
24 Silverberg JI, Hanifin J, Simpson EL. Climatic factors are associated with childhood eczema prevalence in the United States. *J Invest Dermatol* 2013; **133**:1752-1759.
25 Suarez-Varela MM, Garcia-Marcos Alvarez L, Kogan MD, et al. Climate and prevalence of atopic eczema in 6- to 7-year-old school children in Spain. ISAAC phase III. *Int J Biometeorol* 2008; **52**:833-840.
26 Weiland SK, Husing A, Strachan DP, et al. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup Environ Med* 2004; **61**:609-615.
27 Visser MJ, Verberk MM, van Dijk FJ, et al. Wet work and hand eczema in apprentice nurses; part I of a prospective cohort study. *Contact Dermatitis* 2014; **70**:44-55.
28 English JS. Current concepts of irritant contact dermatitis. *Occup Environ Med* 2004; **61**:722-6, 674.
29 Agner T, Held E. Skin protection programmes. *Contact Dermatitis* 2002; **47**:253-256.

CHAPTER 3

3

Validation of a questionnaire on hand hygiene in the construction industry

Johan G. Timmerman[1], Hicham Zilaout[1], Dick J.J. Heederik[1], Ton Spee[1,2], Lidwien A.M. Smit[1]

[1] Institute for Risk Assessment Sciences (IRAS), Utrecht University, The Netherlands
[2] Arbouw Research and Development, Harderwijk, The Netherlands

Annals of Occupational Hygiene 2014, Vol. 58, pp 1046-1056

Abstract

Background

Construction workers are at risk of developing occupational contact dermatitis. Gloves, when used properly, may protect against chemicals and coarse materials. We investigated the prevalence and determinants of contact dermatitis in a population of Dutch construction workers and aimed at validating questionnaire items on hand hygiene.

Methods

A cross-sectional study was conducted at 13 construction sites, yielding data of 177 subjects (95% response rate). A questionnaire covering questions on hand hygiene and contact dermatitis symptoms was used. Agreement between workplace observations and a number of questionnaire items was assessed by calculating Cohen's kappa. Log binomial regression analysis was used to assess the association between contact dermatitis and various hand hygiene-related determinants.

Results

The one-year prevalence of self-reported contact dermatitis in our study sample was 46.9%. Multiple regression analysis showed a positive association with difficulties with hand cleaning (Prevalence Ratio (PR): 1.26, 95% Confidence Interval (95% CI) : 1.05-1.52), hand contamination at the end of the working day (PR 2.30, 95% CI: 1.14-4.65) and intensive hand cream use (PR 2.07, 95% CI: 1.42-3.01). Observations of hand contamination, glove use and glove types were found to agree well with the self-reported data from the questionnaire (Cohen's kappa's 0.75, 0.97 and 0.88).

Conclusions

Self-reported contact dermatitis prevalence in construction workers was high and related to hand hygiene. A strong agreement was found between workplace observations and self-reported questionnaire data.

Introduction

Contact dermatitis is a common inflammatory skin disease that occurs after contact with an external agent.[1] Symptoms of contact dermatitis differ in severity, frequency, duration and recurrence among individuals and mostly include itching and scaling. Symptoms mainly affect the hands, although other body parts like arms, face or eyelids may also be involved.[2] Contact dermatitis-inducing substances can be chemicals, but also physical, mechanical and environmental factors, such as transpiration and excessive temperature differences.[3]
Occupational contact dermatitis is the most common occupational skin disease in many countries, accounting for more than 95% of all cases of work-related skin disorders.[4-6] Usually the prevalence of hand eczema is used as a proxy for OCD prevalence, resulting in a one-year prevalence of 6-10%.[7] Studies focusing on the social and economic impact of occupational contact dermatitis, reported that it seriously impedes social life of patients.[8]
Several population studies have shown that atopic predisposition is the most important endogenous risk factor for hand dermatitis[9-11] and also a risk factor for occupational contact dermatitis.[12] A well-known exogenous factor in occupational contact dermatitis is “wet work”, work involving exposure to weak irritants, e.g. water and detergents for more than 2 hours a day.[13-15] Also environmental factors (such as low humidity) are risk factors for occupational contact dermatitis and may enhance the effect of irritants and/or allergens.[16,17]

Construction workers have a substantial risk for developing occupational contact dermatitis.[18,19] The risk of developing occupational contact dermatitis among construction workers is probably related to occupational exposure to chemicals (e.g. epoxides[20] and isocyanates[21]) and coarse materials, like bricks. Small skin injuries may arise while handling coarse materials and thereby enable irritants and allergens to penetrate the skin, thus facilitating the development of contact dermatitis.
Glove use may protect against dermal exposure to chemicals and coarse materials. A large variety of gloves is available, but only use of adequate gloves greatly reduces harmful exposures and wrong usage can even be a risk factor for dermatitis.[22,23] However, using gloves may be a risk factor itself as wearing occlusive gloves for more than two hours a day is considered wet work.[13-15] Chemicals that are trapped inside the glove or permeate through an inappropriate glove may cause a high exposure and a false feeling of safety.[24-26] Existing questionnaires, as being used for construction workers’ periodical medical checkup contain only one question: ‘do you use gloves during work: yes or no?’[27] This is not detailed enough to collect information on

the type of gloves construction workers use. Therefore, we have developed a questionnaire which includes more detailed questions on glove use and self-reported hand contamination as a proxy for dermal exposure. The purpose of this questionnaire is to develop a prognostic tool for occupational physicians to use during medical checkups. We recently reported a high prevalence of skin symptoms using the routinely collected data of medical checkups in Dutch construction workers.[27] The present study aims to further investigate contact dermatitis in the construction industry, by means of workplace observations and an interview-based questionnaire. Specific aims are to (1) determine the one-year prevalence of contact dermatitis in construction workers; (2) to validate a number of questionnaire items on hand hygiene; and (3) to assess the association between contact dermatitis and various possible risk factors in the construction industry.

Study population and methods

Study population and design

This cross-sectional study was conducted in May and June 2012 and was carried out in a population of Dutch male construction workers. The study involved field work comprising observations, an interview-based questionnaire and photography of the workers' both hands. In total, 177 out of 186 workers agreed to participate (response 95%). Participants were working in housing and utility construction or civil construction. In total, fifteen construction sites were visited. Site visits were facilitated by the Arbouw Foundation, the Dutch foundation established by employers' and employees' organizations in the construction industry to improve working conditions and reduce sick leave in the construction industry. At construction sites where less than 15 male workers were employed, all male workers were asked to participate. At larger construction sites, a maximum of 15 workers was randomly asked to participate. Subjects were informed about the purpose of the study, and all data were treated anonymously.

Observations

Construction workers were observed at a random moment during a regular working day for 3 to 5 minutes. During this observation, glove use, the type of glove they used and the contamination of their hands was assessed by the observer. After the observation, these questionnaire items were filled in by the observer (H.Z.) to enable their validation (see Table 1).

Table 1 - Demographic characteristics of the study population: age, type of construction site, job title, hand dermatitis prevalence and questions that were validated in this study.

	mean	SD	N	%
Age	39.2	11.7		
Type of construction site				
Civil construction site			35	19.8
Housing and utility construction site			142	80.2
Job title				
Carpenter			52	29.4
Bricklayer			26	14.7
Electrician			10	5.7
Metal stud wall/modular ceiling assembler			9	5.1
Central heating assembler			7	4.0
Concrete form carpenter			7	4.0
Painter			6	3.4
Scaffolder			6	3.4
Floor layer (screed floor)			6	3.4
Plumber			5	2.8
Roofer (bituminous)			5	2.8
Other (all n< 5)			33	18.6
Skin symptoms				
Did you have one of the following symptoms on your hands or fingers in the past 12 months?				
(1pt) Red and swollen hands or fingers			12	6.8
(1pt) Scaly hands or fingers			16	9.0
(1pt) Itchy hands or fingers			28	15.8
(2pts) Hands or fingers with fissures			98	55.4
(2pts) Vesicles on the hands or between the fingers			13	7.3
(2pts) Red bumps on hands or fingers			8	4.5
(1pt) Did one or more of these symptoms last for more than three weeks?			53	29.9
(1pt) Did one or more of these symptoms occur more than once the past 12 months?			69	39.0
Hand dermatitis (score of 3 or more points of the above questions)			83	46.9

Table 1 - continued

Validated questions:		
How dirty are your hands at the end of a working day?		
Not dirty (for example because you carry good protection)	25	14.1
A bit dirty	93	52.5
Very dirty (more than half of your skin surface is dirty)	59	33.3
How often do you wear gloves while working?		
(Almost) always	48	27.1
Mostly	30	17.0
Sometimes	79	44.6
(Almost) never	20	11.3
If you use hand gloves during the work, what type of gloves do you usually use? [a]		
Disposable gloves	0	0.0
Latex housekeeping gloves	7	4.0
Cotton gloves	30	16.9
Semi dipped tricot gloves	115	65
To the cuff dipped tricot gloves	1	0.6
Neoprene gloves	5	2.8
Leather gloves	7	4.0

SD: standard deviation
[a] Total percentage exceeds 100% as some subjects reported to use more than one type of glove

Questionnaire

The used questionnaire was filled in during an interview between the observer and the participant following the observation. The questionnaire consists of a selection of questions from the new questionnaire we developed. Three questions were validated in this study, the skin symptom questions were validated before[28] and other questions were simple questions with a minor chance of misinterpretation. The questionnaire covered general aspects such as age and job title; in addition, questions regarding symptoms of contact dermatitis during the last 12 months, use of personal protective equipment (PPE) and hand hygiene were included in the questionnaire. Three items from the questionnaire were validated in this study using workplace observations: “How dirty are your hands at the end of a working day?”, “How often do you wear gloves while working?” and “If you use gloves during work, what type of gloves do you usually use?” The validated items from the questionnaire are shown in Table 1, the complete questionnaire is given in *Supplement 1*.

Presence of contact dermatitis was defined according to the ‘Netherlands Society of

Occupational Medicine-guideline: prevention of contact eczema',[29] which is based on a questionnaire developed by Smit and colleagues.[28] Three questions were used to indicate the presence of contact dermatitis in construction workers: "Did you have one of the following symptoms on your hands or fingers in the past 12 months: red and swollen hands or fingers, scaly hands or fingers, itchy hands or fingers, hands or fingers with fissures, vesicles on the hands or between the fingers or red bumps on hands or fingers?" (question 4 of our questionnaire), "Did one or more of these symptoms last for more than three weeks?" (q5) and "Did one or more of these symptoms occur more than once the past 12 months?" (q6). The dermatitis definition is based on a scoring system: one point is being scored by a positive answer to one of the first three symptoms of question 4 as well as for a positive answer to question 5 or question 6. A positive answer to every of the last 3 symptoms of question 4 yields 2 points. A total of 11 points can be scored when all questions are answered positively. According to the guidelines, a score of at least 3 points is being classified as 'possible dermatitis', a score of at least 5 points is being classified as 'definite dermatitis.' In this study, the health outcome hand dermatitis was defined as a score of at least 3 points.

Inter-observer reliability

Inter-observer reliability of the classification of hand contamination during the observations was assessed during three working days, on which two observers (H.Z. and J.G.T.) observed the same subjects simultaneously (n=40). The contamination of the hands was rated as not dirty, a bit dirty ($\leq$50% of the hand surface is contaminated) or very dirty (>50% of the hand surface is contaminated), equivalent to the corresponding question in the questionnaire (see Table 1).

Data analysis and statistics

Statistical analyses were performed using SAS Software version 9.2 (SAS System for Windows, SAS Institute, Cary, NC). In order to validate the three questionnaire items and to assess the agreement between the interview-based questionnaire and the observations, Cohen's kappa was calculated. The question on glove use was validated in a subset of the population: only subjects reporting to use gloves (almost) always or (almost) never were taken into account (N=83) as the observer could only rate "yes" (corresponding to (almost) always) or "no" (corresponding to (almost) never) during the five minutes observation. To calculate agreement between the two observers, Cohen's kappa was also used. To assess the agreement between the nine observers in rating the photographs, Fleiss's kappa was calculated using the mkappa macro.[30]

Crude and adjusted prevalence ratios (PR) and 95% confidence intervals (95% CI) were calculated using log-binomial regression analysis.[31]

Results

Demographic characteristics and visited locations

The study population consisted of 177 male construction workers with a mean age of 39.2 years (range 18- 63 years). During field work activities in thirteen cities in the Netherlands, fifteen construction sites were visited, including twelve housing and utility construction locations (142 subjects, one construction sites was visited twice) and three civil construction locations (35 subjects). The majority of subjects worked as a carpenter (29%), followed by bricklayers (15%) and electricians (6%) (Table 1).

Prevalence of hand dermatitis

Table 1 shows the skin symptoms that characterize hand dermatitis. According to the diagnosis based on the questionnaire, “hands or fingers with fissures” was the most common symptom in construction workers (n = 98 (55.4%)) whereas only 8 persons reported “red or swollen hands or fingers” (4.5%). A total of 114 subjects (64.4%) reported at least one symptom of question 4. A positive response to all the questions q4 (at least one symptom), q5 and q6 was given by 41 (23.2%) out of the 177 subjects . Overall, 81 of the construction workers met the definitions for contact dermatitis, giving a one-year prevalence of 46.9% among this population.

Answers to questionnaire items that were to be validated are shown in Table 1. Frequency tables for the other questionnaire items can be found in *Supplement 2*. Most of the subjects reported that cleaning their hands was easy (73.5%). Hand washing frequencies were low (71.8% reported hand washing less than 5 times a day), the majority of subjects used irritative substances to clean their hands: 71% used abrasive soap. A small minority reported to never use gloves (11.3%), most subjects reported to use gloves sometimes (44.6%) or (almost) always (27.1%). The majority of the subjects used semi-dipped cotton gloves (65.0%), waterproof gloves were used by 14.1% of all subjects. Only 12.1% of glove wearing subjects changed gloves at regular moments, 87.9% changed gloves when dirty or torn. Half of the population never used hand cream (49.7), whereas 10.2% used hand cream several times a day.

Table 2 - Validity statistics of the validated questions on hand hygiene.

	Hand contamination	
	Cohen's Kappa	95% CI
Questionnaire vs. direct observation	0.75	0.68-0.83
Inter-observer variability (2 observers, n = 40)	0.86	0.73-0.99
	Glove use	
	Cohen's Kappa	95% CI
Questionnaire vs. direct observation (subset n=83)	0.97	0.90-1.00
Inter-observer variability (2 observers, n = 40)	0.96	0.91-1.00
	Glove type	
	Cohen's Kappa	95% CI
Questionnaire vs. direct observation	0.88	0.73-1.00
Inter-observer variability (2 observers, n = 40)	1	1.00-1.00

95% CI: 95% confidence interval

Validity and inter-observer reliability

Table 2 shows the degree of agreement between direct observations and questionnaire items for hand contamination, glove use and the type of used glove. Agreement between observations and questionnaire was good for hand contamination (Cohen's kappa 0.75, (95% CI: 0.68 – 0.83)) and very good for the type of glove used (0.88, 95% CI: 0.73 – 1.00). Agreement was also very good for glove use (0.97, 95% CI: 0.90 – 1.00) in the subset of subjects reporting to use gloves (almost) always or (almost) never. No subjects reporting to use gloves sometimes or most of the times, however, actually wore gloves during the observation.

To study reliability of the semi-quantitative exposure assessment during the observations, the inter-observer reliability was assessed. The inter-observer agreement among the two observers using Cohen's kappa for hand contamination (0.86 (0.73-0.99)) and glove use (0.96 (0.91- 1.00)) were very good. There was a 100% agreement between the observers regarding glove types used by the constructions workers

Determinants of hand dermatitis

Univariate and adjusted associations between questionnaire items and hand dermatitis are shown in Table 3. Adjusted prevalence ratio's (PR) were adjusted for age and hand cream use. The use of hand cream (either several times a day or more than once a week) was significantly and positively associated with contact dermatitis (PR 2.07 and 2.71, respetively). Construction workers whose hands were very dirty at the end of the working day reported contact dermatitis significantly more often than construction workers whose hands were not dirty (PR 2.30, 95% CI: 1.14-4.65). Furthermore, subjects reporting that usually cleaning their hands was 'not easy but not difficult' or 'difficult' had significantly higher dermatitis prevalence (PR 1.26, 95% CI: 1.05-1.52). Also using gloves 'sometimes' was significantly related with higher hand dermatitis prevalence (PR 1.93, 95% CI: 1.00-3.73). Hand washing frequencies higher than five times a day were associated with higher dermatitis prevalence but not after adjustment for age and hand cream use.

Table 3 - Results of the log-binomial regression analyses of questionnaire items and CD.

	N	%	crude PR	95% CI	adjusted PR [a]	95% CI
Age (per ten years increase)			1.04	0.90-1.19	0.97	0.87-1.09
Use of hand cream						
Never	88	49.7	*reference*		*reference*	
Once a week / every other day / once a day	71	40.2	2.00	1.37-2.92	2.71	1.78-4.13
Several times a day	18	10.2	2.44	1.59-3.76	2.07	1.42-3.01
Difficulties with hand cleaning						
Easy	130	73.5	*reference*		*reference*	
Not easy, but not difficult / difficult	47	26.5	1.46	1.07-2.00	1.26	1.05-1.52
Hand washing frequency						
Less than 5 times a day	127	71.8	*reference*			
At least 5 times a day	50	28.2	1.42	1.03-1.94	1.27	0.94-1.71
Hand washing methods						
never with irrritants [b]	52	29.4	*reference*			
with irritants	125	70.6	0.93	0.66-1.31	0.85	0.62-1.15

Table 3 - continued

Glove changing						
On regular moments	19	12.1	*reference*			
When dirty or torn	138	87.9	1.36	0.74-2.50	1.47	0.82-2.61
Protective glove use						
(Almost) never	20	11.3	*reference*			
Sometimes	79	44.6	2.23	1.02-4.88	1.93	1.00-3.73
Mostly	30	17.0	2.13	0.93-4.89	1.87	0.95-3.67
(Almost) always	48	27.1	1.33	0.57-3.14	1.18	0.58-2.42
Use of waterproof gloves						
No	152	85.9	*reference*			
Yes	25	14.1	0.91	0.59-1.40	0.74	0.45-1.22
Level of hand contamination						
Not dirty	25	14.1	*reference*		*reference*	
A bit dirty	93	52.5	2.11	1.02-4.35	1.87	0.91-3.82
Very dirty	59	33.3	1.98	0.94-4.18	2.30	1.14-4.65
Used glove types						
No glove use	20	11.3	*reference*			
Cotton gloves	27	15.3	2.22	0.97-5.10	1.64	0.73-3.70
Semi dipped cotton gloves	115	65.0	2.05	0.94-4.48	1.81	0.85-3.87
Other glove types	15	8.5	0.53	0.12-2.38	0.48	0.11-2.09

PR: prevalence ratio; 95% CI : 95% confidence interval
[a] adjusted PR were adjusted for age and hand cream use
[b] subjects reporting to never use abrasive soap or solvents to clean their hands

Discussion

The self-reported one-year prevalence of contact dermatitis among Dutch construction workers in this study sample was 46.9%. This is high compared to the prevalence found in a study published by Coenraads *et al.*,[32] who reported a hand dermatitis prevalence of 7.8% based on examination of the hands and forearms of a sample of construction workers. This is to be expected as the questionnaire based prevalence corresponds to 'possible dermatitis' whereas an examination-based prevalence will correspond to 'definite dermatitis'. This is caused by the screening purpose of the questionnaire: a high sensitivity

is needed to screen workers for high risk of dermatitis, whereas a physical examination will be more specific. Using the same questionnaire-based method as used in the present study, Smit *et al.* reported a hand dermatitis prevalence of 47.7% among Dutch nurses.[28] Although in a different occupational population, this prevalence is similar to the prevalence in our study. The prevalence found in the present study is higher than those previously reported in other high-risk populations, such as rubber workers (38.1%),[33] veterinarians (31%),[34] flower industry workers (29.5%)[35] and farmers (9.8%).[36]

In this study, questionnaire items regarding hand contamination, glove use and used glove type were validated using direct workplace observations. The results suggest a substantial (0.75) to almost perfect (0.97) agreement between observations and these three questionnaire items. Also in other occupational groups, observations and questionnaires provide reliable information on exposure to chemicals inside the protective gloves.[37]

A strong positive association was found between contact dermatitis and frequent use of hand cream, having dirty hands and difficulty of hand cleaning. Given the cross-sectional design of our study, the first finding is probably due to reverse causation. Frequent use of hand cream is supposed to protect against skin dryness and roughness[24] but it is likely that subjects start using hand cream when they experience hand dermatitis symptoms. Alternatively, it could be speculated that workers who use hand creams experience softer skin which makes them more prone to skin injuries. The type of glove used was not found to significantly influence the prevalence of contact dermatitis. Although the use of occlusive gloves, when no cotton under gloves are worn, is a risk factor for occupational contact dermatitis,[38] in the present study no effect of wearing occlusive gloves for more than two hours a day was found. Washing hands more than 5 times a day was not related to a higher contact dermatitis prevalence in the present study, whereas in some studies, high frequencies of hand washing were associated with hand dermatitis.[11,39] However, in the latter studies, high hand washing frequencies were defined as >8 or >20 times a working-day. In our study population, hand washing frequencies were much lower: only 2 subjects reported hand washing frequencies of >10 times a working-day. This may explain the absence of a relationship between hand washing frequencies and contact dermatitis in our study.

Subjects reporting to use gloves ‘sometimes’ reported a higher dermatitis prevalence than subjects reporting no glove use, which possibly is also due to reverse causation. In an earlier study, we found a small protective effect of glove use on skin symptom reporting,[27] but in the present study we were able to adjust for a larger number of other variables. The majority of workers (71.8%) reported to wear protective gloves “because the materials I work with are dirty/

coarse". The most common reason why workers do not use gloves is because they are uncomfortable or do not fit well, and thus hamper precise hand work.[23] In the present study, 11.3% of workers did not wear any gloves at all, thus increasing exposure to irritating or allergenic substances and increasing the risk of having injuries. Skin that has been previously injured was shown to be more susceptible to irritant contact dermatitis.[3] In our study population, 66.7% used "semi-dipped tricot gloves" which indeed protect against coarse materials but not against chemicals.[20] Unfortunately, only 1.1% reported to use gloves because of received information or training on the use of protective gloves. This may indicate lack of management commitment towards protective gloves enforcement.

In the present study, 177 construction workers were observed and interviewed. We consider this observation, albeit short and not repeated, to be representative of their working day. As construction workers sometimes work at different parts of the construction yard, it can be complex to get back to them and observe them more than once, particularly on bigger construction yards. To avoid language problems and translation issues with the questionnaire and during the field work which might affect the accuracy of our comparisons, only Dutch speaking subjects were included. In order to reduce the impact of selection bias, the subjects were randomly chosen at construction sites located in various cities in The Netherlands. Since Stichting Arbouw, who facilitated the construction site visits, mainly has contacts with larger construction companies, our study population may be slightly biased to construction workers who work for larger companies. This potential bias will probably be neutralized by the fact that larger companies usually subcontract smaller companies and these workers also participated in the study.

To our knowledge, this is the first validation of a questionnaire on hand contamination and glove use in construction workers by direct workplace observation. Limitations of the present study include the short period of time during which the observation took place. As we were only able to perform one short observation per worker, possibly a non-representative moment in time was observed, although most construction workers performed one activity over the day. In addition, the question on hand contamination asks for contamination of the hands at the end of the working day, whereas the observation might be at any moment of the working day. This may have hampered the validation, leading to a lower agreement, although agreement was still considered good.

No detailed quantitative exposure assessment was performed in the present study. The main disadvantage of a self-reported exposure assessment question ("how dirty are your hands at the end of the working day?") is that

it only considers visible contamination whereas exposure also can lead to invisible contamination of the skin. There are several ways of performing more detailed dermal exposure assessment like UV-fluorescence,[40] patching,[41] hand washing[42] and the wet wiping method.[43] UV-fluorescence is impractical at the construction site as fluorescent tracers would have to be added to the building materials. All other methods have in common that analysis of the substance that was retrieved from the skin or patch has to be analyzed using gas chromatography–mass spectrometry (GC-MS) or a likewise method. Given the large number of potentially hazardous exposures at the construction site, this method is not feasible unless specific exposures are studied. Therefore, we used a self-reported exposure assessment, resulting in significant relations between hand contamination and difficulty in hand cleaning and contact dermatitis. Despite of the validation taking place at one moment of time during a working day (and not at the end of the working day), the agreement between the self-reported hand contamination and observed hand contamination was good. We therefore suggest these questions are suitable for use as a qualitative exposure assessment in future studies in the construction industry.

Conclusions

The one-year prevalence of hand dermatitis was 46.9% which is high compared to previous studies of hand dermatitis in construction workers as well as the general population. Hand cream use, using gloves sometimes, difficulty of hand cleaning and dirty hands at the end of the working day were positively associated with having contact dermatitis. There is a strong agreement between direct observations and questionnaire-reported hand contamination, glove use and used glove type. Therefore, it is reasonable to consider that these questionnaire items are suitable to be used in future epidemiological studies.

References

1 Usatine RP, Riojas M. Diagnosis and management of contact dermatitis. *Am Fam Physician* 2010; **82**:249-255.
2 Rietschel RL, Mathias CG, Fowler JF,Jr, et al. Relationship of occupation to contact dermatitis: evaluation in patients tested from 1998 to 2000. *Am J Contact Dermat* 2002; **13**:170-176.
3 Slodownik D, Lee A, Nixon R. Irritant contact dermatitis: a review. *Australas J Dermatol* 2008; **49**:1-9; quiz 10-1.
4 Keegel T, Moyle M, Dharmage S, et al. The epidemiology of occupational contact dermatitis (1990-2007): a systematic review. *Int J Dermatol* 2009; **48**:571-578.
5 Lushniak BD. Occupational skin diseases. *Prim Care* 2000; **27**:895-916.
6 Anveden I, Wrangsjo K, Jarvholm B, Meding B. Self-reported skin exposure -- a population-based study. *Contact Dermatitis* 2006; **54**:272-277.
7 Belsito DV. Occupational contact dermatitis: etiology, prevalence, and resultant impairment/disability. *J Am Acad Dermatol* 2005; **53**:303-313.
8 Moberg C, Alderling M, Meding B. Hand eczema and quality of life: a population-based study. *Br J Dermatol* 2009; **161**:397-403.
9 Yngveson M, Svensson A, Johannisson A, Isacsson A. Hand dermatosis in upper secondary school pupils: 2-year comparison and follow-up. *Br J Dermatol* 2000; **142**:485-489.
10 Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. *Br J Dermatol* 2001; **144**:523-532.
11 Visser MJ, Verberk MM, Campbell LE, et al. Filaggrin loss-of-function mutations and atopic dermatitis as risk factors for hand eczema in apprentice nurses: part II of a prospective cohort study. *Contact Dermatitis* 2014; **70**:139-150.
12 Coenraads PJ, Diepgen TL. Risk for hand eczema in employees with past or present atopic dermatitis. *Int Arch Occup Environ Health* 1998; **71**:7-13.
13 Ramsing DW, Agner T. Effect of glove occlusion on human skin. (I). short-term experimental exposure. *Contact Dermatitis* 1996; **34**:1-5.
14 Held E, Jorgensen LL. The combined use of moisturizers and occlusive gloves: an experimental study. *Am J Contact Dermat* 1999; **10**:146-152.
15 Stingeni L, Lapomarda V, Lisi P. Occupational hand dermatitis in hospital environments. *Contact Dermatitis* 1995; **33**:172-176.
16 Douglas E, Rushton L, Williams HC. Is occupational dermatitis being taken seriously by UK industries? *Occup Med (Lond)* 1999; **49**:85-91.
17 Nixon RL. Contact dermatitis and occupational skin disease. *Med J Aust* 1996; **165**:47-52.
18 Bock M, Schmidt A, Bruckner T, Diepgen TL. Occupational skin disease in the construction industry. *Br J Dermatol* 2003; **149**:1165-1171.
19 Rycroft R, Frosch P. Occupational Contact Dermatitis. In: *Contact Dermatitis*(Frosch P, Menné T, Lepoittevin J, eds), 4th edn. Berlin Heidelberg New York: Springer, 2006; 717-734.
20 Spee T, Van Duivenbooden C, Terwoert J. Epoxy resins in the construction industry. *Ann*

N Y Acad Sci 2006; **1076**:429-438.
21 Frick M, Isaksson M, Bjorkner B, et al. Occupational allergic contact dermatitis in a company manufacturing boards coated with isocyanate lacquer. *Contact Dermatitis* 2003; **48**:255-260.
22 Chew AL, Maibach HI. Occupational issues of irritant contact dermatitis. *Int Arch Occup Environ Health* 2003; **76**:339-346.
23 Clark SC, Zirwas MJ. Management of occupational dermatitis. *Dermatol Clin* 2009; **27**:365-83, vii-viii.
24 Brown T. Strategies for prevention: occupational contact dermatitis. *Occup Med (Lond)* 2004; **54**:450-457.
25 Diepgen TL, Coenraads PJ. The epidemiology of occupational contact dermatitis. *Int Arch Occup Environ Health* 1999; **72**:496-506.
26 Diepgen TL, Kanerva L. Occupational skin diseases. *Eur J Dermatol* 2006; **16**:324-330.
27 Timmerman JG, Heederik D, Spee T, Smit LA. Skin symptoms in the construction industry: occurrence and determinants. *Am J Ind Med* 2014; **57**:660-668.
28 Smit HA, Coenraads PJ, Lavrijsen AP, Nater JP. Evaluation of a self-administered questionnaire on hand dermatitis. *Contact Dermatitis* 1992; **26**:11-16.
29 Jungbauer FH, Piebenga WP, ten Berge EE, et al. NVAB-richtlijn: Preventie Contacteczeem (NVAB guideline: Prevention of Contact Dermatitis). Available at: https://www.nvab-online.nl/sites/default/files/bestanden-webpaginas/Contacteczeem%20RL.pdf (last accessed 7 April 2015).
30 Chen B, Zaebst D, Seel L. A Macro to Calculate Kappa Statistics for Categorizations by Multiple Raters. *Proceedings of the Thirtieth Annual SAS® Users Group International Conference,* Philadelphia, Pennsylvania, 10-13 April 2005. Available at: http://www2.sas.com/proceedings/sugi30/155-30.pdf (last accessed 6 October 2016).
31 Deddens JA, Petersen MR. Approaches for estimating prevalence ratios. *Occup Environ Med* 2008; **65**:481, 501-6.
32 Coenraads PJ, Nater JP, Jansen HA, Lantinga H. Prevalence of eczema and other dermatoses of the hands and forearms in construction workers in the Netherlands. *Clin Exp Dermatol* 1984; **9**:149-158.
33 Kilpikari I. Occupational contact dermatitis among rubber workers. *Contact Dermatitis* 1982; **8**:359-362.
34 Tauscher AE, Belsito DV. Frequency and etiology of hand and forearm dermatoses among veterinarians. *Am J Contact Dermat* 2002; **13**:116-124.
35 Pereira F. Hand dermatitis in florists. *Contact Dermatitis* 1996; **34**:144-145.
36 Susitaival P, Husman L, Hollmen A, Horsmanheimo M. Dermatoses determined in a population of farmers in a questionnaire-based clinical study including methodology validation. *Scand J Work Environ Health* 1995; **21**:30-35.
37 Anveden I, Meding B. Skin exposure in geriatric care - a comparison between observation and self-assessment of exposure. *Contact Dermatitis* 2007; **57**:253-258.
38 Kezic S, Visser MJ, Verberk MM. Individual susceptibility to occupational contact dermatitis. *Ind Health* 2009; **47**:469-478.
39 Jungbauer FH, Lensen GJ, Groothoff JW, Coenraads PJ. Exposure of the hands to wet work in nurses. *Contact Dermatitis* 2004; **50**:225-229.
40 Cherrie JW, Brouwer DH, Roff M, et al. Use of qualitative and quantitative fluorescence techniques to assess dermal exposure. *Ann Occup Hyg* 2000; **44**:519-522.
41 Soutar A, Semple S, Aitken RJ, Robertson A. Use of patches and whole body sampling

for the assessment of dermal exposure. *Ann Occup Hyg* 2000; **44**:511-518.
42 Brouwer DH, Boeniger MF, van Hemmen J. Hand wash and manual skin wipes. *Ann Occup Hyg* 2000; **44**:501-510.
43 Geno PW, Camann DE, Harding HJ, et al. Handwipe sampling and analysis procedure for the measurement of dermal contact with pesticides. *Arch Environ Contam Toxicol* 1996; **30**:132-138.

CHAPTER 4

Contact dermatitis in the construction industry: the role of filaggrin loss-of-function mutations

Johan G. Timmerman[1], Dick J.J. Heederik[1], Ton Spee[1,2], Frits G. van Rooy[1,3], Esmeralda J.M. Krop[1], Gerard H. Koppelman[4], Thomas Rustemeyer[5], Lidwien A.M. Smit[1]

[1] Institute for Risk Assessment Sciences (IRAS), Utrecht University, The Netherlands
[2] Arbouw Research and Development, Harderwijk, The Netherlands
[3] Arbo Unie Expert Centre for Chemical Risk Management, Haarlem, The Netherlands
[4] Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital and GRIAC Research Institute, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
[5] Department of Dermatology, VU University Medical Centre, Amsterdam, The Netherlands

British Journal of Dermatology 2016, Vol. 174, pp 348-355

Abstract

Background

A high prevalence of contact dermatitis (CD) and respiratory symptoms has been observed in the construction industry, probably due to widespread exposure to irritants and allergens. It is unknown if carriers of loss-of-function mutations in the gene encoding filaggrin (*FLG*), a known risk gene for eczema and asthma, are at increased risk.

Methods

A questionnaire including items on dermal and respiratory symptoms such as wheeze, shortness of breath and asthma was administered to construction workers. Total and specific serum IgE was analysed by enzyme immunoassays. Four *FLG* loss-of-function mutations were genotyped. CD was diagnosed by a team of a dermatologist and a clinical occupational medicine specialist using photographs of the subjects' hands and self-reported questionnaire data.

Results

Of the 506 participating workers, 6.3% carried at least one *FLG* mutation. Mild CD was diagnosed by the specialists in 34.0%, severe CD in an additional 24.3%. CD was considered work-related in 282 subjects (95.6%). Carriers of *FLG* variants had an increased risk of CD compared to subjects carrying wild-type alleles (odds ratio (OR) mild CD: 5.71, 95% confidence interval (95% CI): 1.63-20.06; OR severe CD: 8.26, 95% CI: 2.32-29.39). *FLG* variants and the presence of CD were not associated with respiratory symptoms and atopy.

Conclusions

CD prevalence in construction workers is high. *FLG* loss-of function mutations increase the risk of CD even further. *FLG* mutations were not associated with respiratory symptoms or atopy.

Introduction

Contact dermatitis (CD) is an inflammation of the skin, caused or worsened by contact with an exogenous substance. This substance can be either irritant, causing irritant contact dermatitis (ICD), or allergenic, causing allergic contact dermatitis (ACD). When the contact occurs in the workplace setting, the CD is considered to be occupational contact dermatitis (OCD).[1]

In the general population, the one-year prevalence of CD is estimated to be around 5% for men and 11% for women.[2] In a routine occupational health survey among more than 152,000 Dutch construction workers, we recently found higher prevalences of self-reported skin symptoms (25%).[3] An even higher prevalence of self-reported CD was found using a validated questionnaire during visits to construction sites (47%).[4]

Construction workers have a considerable risk of developing CD as they may come into contact with various allergenic and/or irritant substances like cement, epoxy products, solvents and abrasive materials.[5-10] In addition to these external risk factors, a number of intrinsic risk factors may increase susceptibility to CD, such as female gender and atopic predisposition.[2] Moreover, well-known loss-of-function mutations in the filaggrin gene (*FLG*) were reported to increase the risk of atopic dermatitis,[11,12] but also other atopic diseases like atopic rhinitis and asthma in co-occurrence with atopic dermatitis.[13,14] *FLG* encodes the protein profilaggrin, which is cleaved to filaggrin monomers.[15] Their degradation products, so-called natural moisturizing factors (NMFs), play an important role in maintaining skin hydration.[16,17] Disruption of filaggrin expression leads to a dry and more permeable skin,[18-21] making it a strong risk factor for metal allergy and skin fissures. [17,19,22] Loss-of-function mutations in *FLG* are carried by 8-10% of the European population.[11,23,24] The interplay between *FLG* variants and dermatitis is complex. Some studies report no direct association with dermatitis but an association with earlier onset and longer duration of dermatitis[25,26] but also direct associations with ICD and combined ACD and ICD are reported.[27,28] However, most studies report that *FLG* variants are only associated with CD in the presence of atopic dermatitis.[29,30] Many studies on *FLG* variants have been performed in children.[31-33] Only recently, an increased risk of both occupational ICD and ACD related to *FLG* mutations has been shown in several high risk occupational populations,[27,30,34-36] mainly in nurses and cleaners.

We hypothesized that carriage of *FLG* mutations may predispose to CD in construction workers. Therefore we aimed to investigate the prevalence of four

major *FLG* loss-of-function mutations[11,23] and the associations between these mutations and CD, atopy and (allergic) airway symptoms in a sample of Dutch construction workers. Better understanding of these associations may help to improve strategies for prevention of skin disorders.

Study population and methods

Study population and design

In this cross-sectional study, two approaches were used to recruit subjects. First, we collaborated with a large occupational health service where construction workers are seen for their voluntary periodical medical checkup. For the purpose of this study, an additional 'skin module' was added to the regular checkup, consisting of a questionnaire, the drawing of 10ml extra blood (blood is routinely drawn at the checkup) and photographing of the skin of the hands of all subjects. The second approach was to visit a number of construction companies during an education session on skin protection and glove use in the construction industry. After this session, the participating companies facilitated the participation of their employees. In both approaches, only subjects who worked on the construction site were invited; office personnel was not included. Written informed consent was obtained from all study subjects. The study was approved by the Medical Ethical Committee of the University Medical Centre, Utrecht, The Netherlands.

Dermatological evaluations

Dermatological evaluations were performed by a team consisting of a dermatologist and an occupational physician specialized in dermatological problems ('the expert panel'). Photographs of the subjects' hands and questionnaire data were assessed. Photographs of both sides of the hands of the subjects were taken using a Nikon Coolpix S1100 pj, NIKKOR 5X WIDE OPTICAL ZOOM 5.0-25.0 mm 1:3.9-5.8 VR. A specially constructed lighting chamber was used to ensure standardized, sufficient and homogeneous lighting of the hands, see *Supplement 3*.

Using a standardized protocol and blinded for FLG status, the expert panel assessed the following possible symptoms of CD: erythema, papules, skin scales, crusts, pigment changes and atrophy (all mild symptoms); fissures, vesicles, bullae and ulceration (severe symptoms).[37] When at least two mild symptoms were present, the subjects were diagnosed with mild or beginning CD, when (also) one or more severe symptoms were present, severe CD was

diagnosed. Example photos of these symptoms as seen in the study population are given in *Supplement 4*. Type of CD (e.g. ICD, ACD), atopic predisposition, and occupational relevance were assessed based on aetiological information in the questionnaire data: when skin allergy or allergen exposure were not reported in the questionnaire, subjects were diagnosed with irritant CD. Occupational relevance was mainly based on job title and hobbies. Relevant questions for assessing atopic predisposition are given in *Supplement 5*.

Questionnaire

Construction workers were asked to fill in a questionnaire including items on skin symptoms; respiratory symptoms, like wheezing, shortness-of-breath and asthma; hand hygiene and occupational activities and exposures. The questionnaire consisted of parts of other, validated, questionnaires[4,38,39] and relevant questions can be found translated in *Supplement 5*. Self-reported CD was defined using questionnaire items, based on questions that were taken from the 'Dutch Society of Occupational Medicine guideline: prevention of contact eczema',[40] used by occupational physicians to screen workers for CD as we described before[4] (Table 1).

Table 1 - Scoring table for contact dermatitis (CD) according to Jungbauer *et al.*, 2006.[40]

Question	Points for positive answer
Did you have one of the following symptoms on your hands or fingers in the past 12 months?	
Red and swollen hands or fingers	1
Scaly hands or fingers	1
Itchy hands or fingers	1
Hands or fingers with fissures	2
Vesicles on the hands or between the fingers	2
Red bumps on hands or fingers	2
Did one or more of these symptoms last for more than three weeks?	1
Did one or more of these symptoms occur more than once the past 12 months?	1
Scores	
0-2 points:	no CD
3-5 points:	possible CD
>5 points:	CD

Atopic sensitization

Serum samples were collected and analysed for IgE by enzyme immunoassays as described before.[41] IgE sensitization was defined as specific serum IgE to one or more of the following common allergens: house dust mite, cat, dog, and grass and birch pollen; high IgE was defined as serum total IgE levels >100kU/l. Atopy status was also calculated according to Jungbauer *et al.*,[40] who provided a guideline to signal an increased risk for dermatitis based on self-reported atopy symptoms. This method is based on self-reported itch and eczema (current and past), childhood eczema, asthma, hay fever and a dry skin.

Genotyping

DNA was extracted from EDTA anti-coagulated blood using the Qiagen Qiamp® DNA blood mini kit. DNA extracts were analysed for the R501X, S3247X, 2282Del4 and R2447X[11,23,24] loss-of-function mutations in the filaggrin gene using the Kompetitive Allele Specific Polymerase Chain Reaction (KASP) single nucleotide polymorphism genotyping system by LGC Genomics (Hoddesdon, UK) as was performed earlier.[42,43] The call rates for the different *FLG* variants were 96.6% (R501X), 93.0% (2282del4), 95.9% (R2447X) and 97.1% (S3247X).

Data analysis

All statistical analyses were performed using SAS 9.4 (SAS System for Windows, SAS Institute, Cary, NC). Univariate associations of *FLG* variants with the various CD and respiratory outcomes were calculated using logistic regression analysis, and presented as odds ratios (OR) with 95% confidence intervals (95% CI). Carrying one or more *FLG* variants was the main explanatory variable. Method of recruitment, season and job title were also explored as independent variables, but not associated with *FLG* genotype and therefore not corrected for.

Results

A total of 1,157 construction workers were invited in the study, of whom 860 participated (response 74.3%). A flow chart of the population is presented in Figure 1. After exclusion of subjects with incomplete data (only blood received, n=14; no/poor quality photos of the hands, n=19; only part of the questionnaire filled in, n=8), age below 18 years (n=5), or who never worked on a construction site (n=63), 751 subjects had complete data on questionnaire and doctors' diagnosis, of whom 561 subjects had blood samples available (DNA and serum). Analyses for this paper were confined to subjects with successful genotyping of all four *FLG* variants (n=506).

Almost all subjects were male: 2 subjects (0.4%) were female and for 15 subjects gender data were missing. This is representative for the percentage of female construction site workers attending the occupational health services that were included in our study during the study period (0.3%). Mean age was 43.6 years (standard deviation 12.8 years, Table 2). *FLG* variants were found in 32 subjects (6.3%). The most common variant was the 2282del4 variant (n=18, 3.6%), followed by R501X (n=10; 2.0%), R2447X (n=3; 0.6%) and S3247X (n=1; 0.2%). One subject was homozygous for the 2282del4 variant.

Figure 1 - Flowchart of subject inclusion.

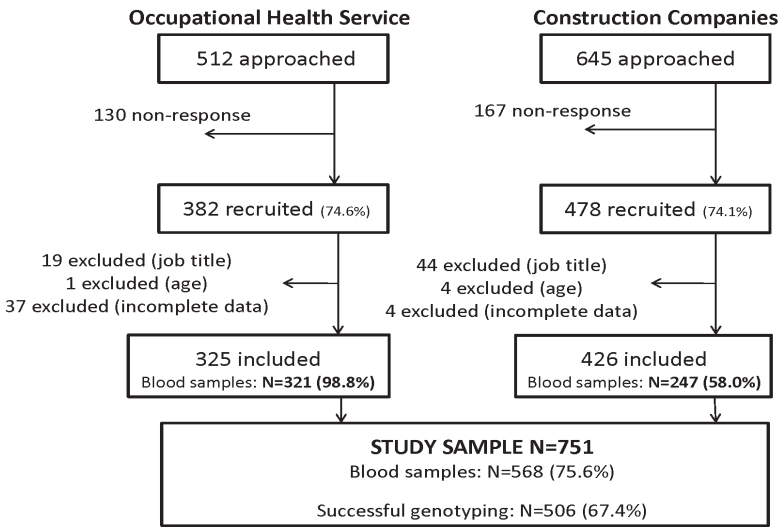


Table 2 - Study sample demographics and prevalence of FLG variants.

	Occupational Health Services		Construction companies		Total	
	mean	**SD**	**mean**	**SD**	**mean**	**SD**
Age	46.2	11.5	40.0	13.6	43.6	12.8
	N	**%**	**N**	**%**	**N**	**%**
Female gender	0	0.0	2	1.0	2	0.4
Job title						
Carpenter	123	42.1	102	52.3	225	46.0
Bricklayer	34	11.6	10	5.1	44	9.0
Painter	34	11.6	28	14.4	62	12.7
Other	101	34.6	55	28.2	156	32.0
FLG variant						
R501X	6	2.0	4	1.9	10	2.0
2282del4	10	3.4	8 [(a)]	3.8	18	3.6
R2447X	0	0.0	3	1.4	3	0.6
S3247X	0	0.0	1	0.5	1	0.2
Total	16	5.4	16	7.6	32	6.3

[(a)] 1 subject was homozygous mutation carrier

Prevalence of CD and respiratory symptoms and their associations with *FLG* variants are shown in Table 3. CD was diagnosed by the expert panel in 295 subjects (55.7%), of whom 123 (24.3%) subjects were considered severe cases. Carrying a *FLG* variant was significantly associated with both mild and severe CD (OR 5.71, 95% CI: 1.63-20.06 and OR 8.26 (95% CI 2.32-29.39), respectively). A strong association was found between *FLG* variants and CD with an atopic predisposition according to the expert panel (OR: 17.15, 95% CI: 4.31-68.29). CD was considered work-related in 282 subjects (95.6%), 89% of CD was diagnosed as ICD, which was diagnosed in 263 subjects.

Self-reported CD was less prevalent than doctor-diagnosed CD, and associations with *FLG* variants were less pronounced for self-reported CD. A total of 25.9% of all subjects reported symptoms leading to a 'possible CD' classification (OR for *FLG* variants: 2.74, 95% CI: 1.27-5.91), an additional 8.1% were classified as 'CD' (OR: 2.47, 95% CI: 0.77-7.90). Prevalence of all symptoms and their association with *FLG* status are provided in *Supplement 6*. Workers who refused blood collection and those who provided a sample did not differ with regard to self-reported symptoms prevalence (p>0.05).

A total of 13.0% of the subjects reported to suffer from symptoms indicating atopy. Serum total IgE levels >100kU/l were found in 31.6% of subjects, specific IgE against at least one of five common allergens was found in 28.3% of all subjects. No significant associations were found between *FLG* variants and self-reported atopy, IgE sensitization, total IgE, allergy or respiratory symptoms as listed in Table 3. The number of *FLG* mutation carriers was too small to conduct separate analyses within subjects with and without CD.

Table 3 - Prevalence of contact dermatitis (CD) and respiratory symptoms and associations with FLG loss-of-function mutations.

	***FLG* variants (n=32)**		***FLG* wildtype (n=474)**		**OR**	
	N	%	N	%	OR	95% CI
CD						
Doctors' diagnosis						
No CD	3	9.4	205	43.3	*Reference*	
Mild CD	15	46.9	157	33.1	5.71	1.63-20.06**
Severe CD	14	43.8	109	23.0	8.26	2.32-29.39**
No CD	3	9.4	205	43.3	*Reference*	
CD with no atopic predisposition	21	65.6	248	52.3	5.61	1.65-19.07**
CD with atopic predisposition	8	25.0	30	6.3	17.15	4.31-68.29***
Self-reported symptoms of CD						
No CD	14	43.8	320	67.5	*Reference*	
Possible CD	14	43.8	117	24.7	2.74	1.27-5.91*
CD	4	12.5	37	7.8	2.47	0.77-7.90
Self-reported respiratory symptoms						
Wheeze in past 12 months	0	0.0	61	12.9	-	-
Woken up due to shortness-of-breath in past 12m	0	0.0	28	5.9	-	-
Asthma (ever)	2	6.3	41	8.6	0.75	0.17-3.25
Doctor diagnosed asthma	2	6.3	41	8.6	0.75	0.17-3.25
Asthma attack in past 12m	0	0.0	5	1.1	-	-
Current asthma drug use	1	3.1	15	3.2	1.04	0.13-8.18
Current treatment (skin/respiratory disease)	2	6.3	22	4.6	1.36	0.31-6.06

Table 3 - continued

Allergy	5	15.6	105	22.2	0.72	0.27-1.92
Airway allergy, including hay fever	5	15.6	80	16.9	1.01	0.37-2.73
Atopy/IgE sensitization						
Based on serology						
Total IgE >100 kU/L	8	25.0	152	32.1	0.70	0.31-1.59
Specific IgE [(a)]	9	28.1	134	28.3	0.99	0.45-2.19
Based on self-reported questionnaire [(b)]	4	12.5	62	13.1	1.02	0.34-3.02

* p<0.05, ** p<0.01, *** p<0.001
[(a)] Against house dust mite, cat, dog, and grass or birch pollen
[(b)] Based on Jungbauer *et al.*, 2006[40]

Discussion

This study amongst Dutch construction workers shows a high prevalence of self-reported CD and still higher prevalence of CD as diagnosed by an expert panel consisting of a dermatologist and an occupational physician specialized in dermatological problems. More than 95% of CD was of occupational origin. A strong positive association was found between loss-of-function *FLG* mutations and doctor-diagnosed presence of CD. Positive but less pronounced associations were observed between *FLG* variants and self-reported CD. No associations were found between *FLG* variants and respiratory symptoms or atopy.

This is the first study focussing on doctor-diagnosed CD amongst construction workers in The Netherlands in more than 25 years.[44] Recently, we reported high prevalences of self-reported skin symptoms[3] and self-reported CD.[4] However, the current study was not confined to self-reported data. Instead, we used doctors' diagnoses, providing a well-characterized disease endpoint. Prevalence of CD was high, both self-reported and doctor-diagnosed, although self-reported prevalence was not as high as in one of our earlier studies that was carried out at construction sites.[4]

The self-reported one-year prevalence is expected to be higher than the doctor-diagnosed point prevalence, although subjects may not recall symptoms that have disappeared some time ago.[3] However, self-reported prevalences were much lower than doctor-diagnosed prevalences. This may be explained by the

fact that the expert panel also reported the mild and beginning symptoms of CD (like redness, scaling), whereas construction workers tend to report only the more severe symptoms like fissures.

Another important strength of the current study was the high response of 74.3%. Moreover, we attempted to recruit a random sample of subjects, which increases generalizability of the study sample to the construction industry as a whole, and reduces the potential of selection bias. Distribution of job titles in our study sample was comparable to the Dutch construction industry as a whole.[45]

In this study, we used two different recruitment approaches: at the occupational health service and at construction companies. Main advantage of subject recruitment at the occupational health service is the representative sample regarding different job titles. However, only ~50% of all construction workers visit the voluntary medical check-up.[3] Construction workers visiting the check-up may be more aware of their health or may have symptoms, including skin symptoms. In the second approach, companies that signed in for the education session on skin health and glove use may be companies that are more aware of health and safety at work than the average construction company, resulting in better working circumstances and less skin problems in this population.. However, among subjects recruited at the occupational health services, CD was less frequently diagnosed than among subjects recruited at construction companies (52.6% vs. 67.1%, p=0.001), which might be due to the fact that the construction company visits were performed during the spring, when dermatitis symptoms are most frequently reported.[3] In both recruitment approaches, subjects might have been more willing to participate if they experienced skin symptoms. Nevertheless, it is unlikely for selection bias to explain the strong associations between *FLG* variants and CD. Subjects are not aware of their genotype, and we found no evidence that subjects with *FLG* mutations were over-represented in our sample. In addition, genetic variants do not change over time, and confounding by variables such as age, recruitment method, job title or season is therefore unlikely to occur. As non-Caucasians form only a small part of the construction workers in The Netherlands, underrepresentation of *FLG* mutations in our study population is unlikely.

In our study sample, 6.3% (95% CI: 4.2%-8.4%) carried a *FLG* variant, a somewhat lower percentage than those reported in literature in the general population (8-10%).[11,23,24] This might indicate a healthy worker effect: construction workers carrying a *FLG* variant might be more likely to develop skin problems and leave their job as a result. Moreover, Bandier *et al.*[46] reported that *FLG*

mutation carriers who report having had hand eczema before 15 years of age avoid occupational exposure to irritants, indicating a so-called healthy worker hire effect. In our cross-sectional study, healthy worker selection bias would lead to underestimation of the risk of carrying a *FLG* variant. A longitudinal study investigating newly hired construction workers would be needed to estimate the impact of a possible healthy worker survival effect on the association between *FLG* mutations and the development of skin and respiratory problems.

The positive association between *FLG* variants and CD corresponds with recent findings in various other high risk job sectors i.e. health care, metal and construction, hairdressing, food and catering, and cleaning.[30,36] The weaker association of *FLG* variants with self-reported CD advocates the use of dermatological evaluations instead of self-reported questionnaires in construction workers.

No associations were found between *FLG* variants and respiratory symptoms, asthma, or IgE sensitization. None of the *FLG* variant carriers reported to have woken up due to shortness-of-breath or suffered from wheeze or an asthma attack in the past 12 months. In earlier studies in children, *FLG* null mutations were positively associated with wheeze, asthma and hay fever in the context of prior eczema[11,14,32,33,42,47] but an extensive meta-analysis showed associations of *FLG* null mutations and asthma, independent of eczema.[13] In a recent study in adults, asthma was not over-represented in subjects carrying *FLG* variants,[48] but in that study and in a number of studies in children, higher total serum IgE levels were found in *FLG* null mutation carriers.[12,48,49] The low number of subjects with respiratory symptoms in our contact dermatitis group did not permit a stratified analysis in the dermatitis group only. Although our study is underpowered to exclude modest associations between *FLG* variants and respiratory symptoms and atopy, the OR were all around 1.0. The lack of a trend towards an association between *FLG* variants and asthma and airway allergies might again point to a healthy worker effect. A healthy worker hire effect has been shown for subjects with pre-existing asthma[50], and it could be hypothesized that *FLG* variant carriers with early respiratory symptoms are more likely to choose a different occupation. Moreover, construction workers with (severe) respiratory symptoms might be forced to search other employment due to their symptoms.

Atopy prevalence based on self-reported data from the questionnaire was much lower than based on IgE serology (13.6% vs. 42.7%), which can be explained by the fact that IgE sensitized subjects are not necessarily symptomatic. The

expert panel in our study used the self-reported atopy data to assess whether subjects with CD had an atopic predisposition. The association of *FLG* variants with CD with an atopic predisposition was stronger than with CD without atopic predisposition (OR: 17.15, 95% CI.: 4.31-68.29 vs. 5.61(1.65-19.07)) although 95% CIs overlap.

The question can be raised how the strong relation between *FLG* loss-of-function mutations and CD can be used to improve occupational health care in the construction industry. Several authors have mentioned the advantages but also the great ethical challenges of genetic screening in occupational health care.[48,51] Workers who are more susceptible to occupational exposures than others could be protected by providing them with personalized education, prevention and (medical) supervision. This targeted, personalized care could help reduce the burden of CD in the construction industry. For this purpose, a genetic test should have a very high positive predictive value (PPV).[52] In our study, the genetic test had a PPV of 91% for CD (i.e., 29 out of 32 subjects with *FLG* variants had mild or severe CD), which we consider to be high enough to be used in practice. However, the attributable fraction[53] for CD of the four *FLG* variants was only 8.5%, indicating that many other factors play a role than these *FLG* variants. Although the relationship between *FLG* loss-of-function mutations and skin problems is well established, and genotyping tests are useful, differences across populations (e.g. race) can occur[54] and should also be taken into account to avoid discrimination in (occupational) health care.

Conclusions

The prevalence of CD in the construction industry is high and underreported. Although the self-reported prevalence is lower than prevalence of symptoms as diagnosed by a dermatological expert panel, it is still high compared to earlier studies among Dutch construction workers but in line with our earlier reports.[3,4] A strong association of *FLG* loss-of-function mutations was found with doctor-diagnosed CD and to a lesser extent also with self-reported CD, but not with respiratory symptoms or atopy. Health care and prevention should be improved, especially in workers who are more susceptible. Testing for *FLG* variants as part of occupational health care in construction workers may help to target workers at increased risk of developing skin problems.

Acknowledgements

The authors like to thank Nena Burger, Jack Spithoven and Siegfried de Wind (IRAS) for laboratory analyses; Henny Bastiaans, Petra Beurskens and Ardi Brouwer (Arbo Unie) for coordinating field work at the occupational health services; Tamara Onos for coordinating and supporting field work at the construction companies; Hans Bouwman, Hans Clemenkowff, Mariska Droog, Tamara Onos and Jan Snijder for giving the presentations during the educational sessions at the construction companies and Saskia Martens for supporting the field work and data processing.

References

1 Lushniak BD. Occupational contact dermatitis. *Dermatol Ther* 2004; **17**:272-277.
2 Thyssen JP, Johansen JD, Linneberg A, Menne T. The epidemiology of hand eczema in the general population--prevalence and main findings. *Contact Dermatitis* 2010; **62**:75-87.
3 Timmerman JG, Heederik D, Spee T, Smit LA. Skin symptoms in the construction industry: occurrence and determinants. *Am J Ind Med* 2014; **57**:660-668.
4 Timmerman JG, Zilaout H, Heederik D, et al. Validation of a questionnaire on hand hygiene in the construction industry. *Ann Occup Hyg* 2014; **58**:1046-1056.
5 Diepgen TL, Coenraads PJ. The epidemiology of occupational contact dermatitis. *Int Arch Occup Environ Health* 1999; **72**:496-506.
6 Winder C, Carmody M. The dermal toxicity of cement. *Toxicol Ind Health* 2002; **18**:321-331.
7 Bock M, Schmidt A, Bruckner T, Diepgen TL. Occupational skin disease in the construction industry. *Br J Dermatol* 2003; **149**:1165-1171.
8 Uter W, Ruhl R, Pfahlberg A, et al. Contact allergy in construction workers: results of a multifactorial analysis. *Ann Occup Hyg* 2004; **48**:21-27.
9 Geraut C, Tripodi D, Brunet-Courtois B, et al. Occupational dermatitis to epoxydic and phenolic resins. *Eur J Dermatol* 2009; **19**:205-213.
10 Ronmark EP, Ekerljung L, Lotvall J, et al. Eczema among adults: prevalence, risk factors and relation to airway diseases. Results from a large-scale population survey in Sweden. *Br J Dermatol* 2012; **166**:1301-1308.
11 Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**:441-446.
12 Weidinger S, Illig T, Baurecht H, et al. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J Allergy Clin Immunol* 2006; **118**:214-219.
13 Rodriguez E, Baurecht H, Herberich E, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. *J Allergy Clin Immunol* 2009; **123**:1361-70.e7.
14 van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ* 2009; **339**:b2433.
15 McGrath JA, Uitto J. The filaggrin story: novel insights into skin-barrier function and disease. *Trends Mol Med* 2008; **14**:20-27.
16 Kezic S, Kemperman PM, Koster ES, et al. Loss-of-function mutations in the filaggrin gene lead to reduced level of natural moisturizing factor in the stratum corneum. *J Invest Dermatol* 2008; **128**:2117-2119.
17 Thyssen JP, Ross-Hansen K, Johansen JD, et al. Filaggrin loss-of-function mutation R501X and 2282del4 carrier status is associated with fissured skin on the hands: results from a cross-sectional population study. *Br J Dermatol* 2012; **166**:46-53.
18 Sergeant A, Campbell LE, Hull PR, et al. Heterozygous null alleles in filaggrin contribute to clinical dry skin in young adults and the elderly. *J Invest Dermatol* 2009; **129**:1042-1045.

19 Novak N, Baurecht H, Schafer T, et al. Loss-of-function mutations in the filaggrin gene and allergic contact sensitization to nickel. *J Invest Dermatol* 2008; **128**:1430-1435.
20 Flohr C, England K, Radulovic S, et al. Filaggrin loss-of-function mutations are associated with early-onset eczema, eczema severity and transepidermal water loss at 3 months of age. *Br J Dermatol* 2010; **163**:1333-1336.
21 Brown SJ, McLean WH. One remarkable molecule: filaggrin. *J Invest Dermatol* 2012; **132**:751-762.
22 Thyssen JP, Carlsen BC, Menne T. Nickel sensitization, hand eczema, and loss-of-function mutations in the filaggrin gene. *Dermatitis* 2008; **19**:303-307.
23 Irvine AD, McLean WH. Breaking the (un)sound barrier: filaggrin is a major gene for atopic dermatitis. *J Invest Dermatol* 2006; **126**:1200-1202.
24 Sandilands A, Terron-Kwiatkowski A, Hull PR, et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat Genet* 2007; **39**:650-654.
25 Carlsen BC, Johansen JD, Menne T, et al. Filaggrin null mutations and association with contact allergy and allergic contact dermatitis: results from a tertiary dermatology clinic. *Contact Dermatitis* 2010; **63**:89-95.
26 Landeck L, Visser M, Skudlik C, et al. Clinical course of occupational irritant contact dermatitis of the hands in relation to filaggrin genotype status and atopy. *Br J Dermatol* 2012; **167**:1302-1309.
27 Visser MJ, Landeck L, Campbell LE, et al. Impact of atopic dermatitis and loss-of-function mutations in the filaggrin gene on the development of occupational irritant contact dermatitis. *Br J Dermatol* 2013; **168**:326-332.
28 Molin S, Vollmer S, Weiss EH, et al. Filaggrin mutations may confer susceptibility to chronic hand eczema characterized by combined allergic and irritant contact dermatitis. *Br J Dermatol* 2009; **161**:801-807.
29 Thyssen JP, Carlsen BC, Menne T, et al. Filaggrin null mutations increase the risk and persistence of hand eczema in subjects with atopic dermatitis: results from a general population study. *Br J Dermatol* 2010; **163**:115-120.
30 Visser MJ, Verberk MM, Campbell LE, et al. Filaggrin loss-of-function mutations and atopic dermatitis as risk factors for hand eczema in apprentice nurses: part II of a prospective cohort study. *Contact Dermatitis* 2014; **70**:139-150.
31 Weiland SK, Bjorksten B, Brunekreef B, et al. Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. *Eur Respir J* 2004; **24**:406-412.
32 Marenholz I, Nickel R, Ruschendorf F, et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J Allergy Clin Immunol* 2006; **118**:866-871.
33 Henderson J, Northstone K, Lee SP, et al. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. *J Allergy Clin Immunol* 2008; **121**:872-7.e9.
34 Carlsen BC, Meldgaard M, Hamann D, et al. Latex allergy and filaggrin null mutations. *J Dent* 2011; **39**:128-132.
35 Kezic S, Visser MJ, Verberk MM. Individual susceptibility to occupational contact dermatitis. *Ind Health* 2009; **47**:469-478.
36 de Jongh CM, Khrenova L, Verberk MM, et al. Loss-of-function polymorphisms in the filaggrin gene are associated with an increased susceptibility to chronic irritant contact

dermatitis: a case-control study. *Br J Dermatol* 2008; **159**:621-627.
37 Jansen LH. *Huid- En Geslachtsziekten. Een Handboek Voor De Praktijk Van Huis- En Huidarts [Skin Diseases and Venereology: A Practical Handbook for General Practitioners and Dermatologists].* Utrecht: Scheltema & Holkema, 1975.
38 Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994; **7**:954-960.
39 Smit HA, Coenraads PJ, Lavrijsen AP, Nater JP. Evaluation of a self-administered questionnaire on hand dermatitis. *Contact Dermatitis* 1992; **26**:11-16.
40 Jungbauer FH, Piebenga WP, ten Berge EE, et al. (2006) NVAB-richtlijn: Preventie Contacteczeem (NVAB guideline: Prevention of Contact Dermatitis) [WWW document]. URL https://www.nvab-online.nl/sites/default/files/bestanden-webpaginas/Contacteczeem%20RL.pdf [accessed on 7 april2015].
41 Doekes G, Douwes J, Wouters I, et al. Enzyme immunoassays for total and allergen specific IgE in population studies. *Occup Environ Med* 1996; **53**:63-70.
42 Schuttelaar ML, Kerkhof M, Jonkman MF, et al. Filaggrin mutations in the onset of eczema, sensitization, asthma, hay fever and the interaction with cat exposure. *Allergy* 2009; **64**:1758-1765.
43 van Ginkel CD, Flokstra-de Blok BM, Kollen BJ, et al. Loss-of-function variants of the filaggrin gene are associated with clinical reactivity to foods. *Allergy* 2015; .
44 Coenraads PJ, Nater JP, Jansen HA, Lantinga H. Prevalence of eczema and other dermatoses of the hands and forearms in construction workers in the Netherlands. *Clin Exp Dermatol* 1984; **9**:149-158.
45 Jansen FJ. (2014) Bouw in beeld 2013-2014 [WWW document]. URL http://www.eib.nl/pdf/bouw_in_beeld_2013-2014.pdf [accessed on 7 April2015].
46 Bandier J, Ross-Hansen K, Carlsen BC, et al. Carriers of filaggrin gene (FLG) mutations avoid professional exposure to irritants in adulthood. *Contact Dermatitis* 2013; **69**:355-362.
47 Weidinger S, O'Sullivan M, Illig T, et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. *J Allergy Clin Immunol* 2008; **121**:1203-1209.e1.
48 Landeck L, Visser M, Kezic S, John SM. Genotype-phenotype associations in filaggrin loss-of-function mutation carriers. *Contact Dermatitis* 2013; **68**:149-155.
49 Weidinger S, Rodriguez E, Stahl C, et al. Filaggrin mutations strongly predispose to early-onset and extrinsic atopic dermatitis. *J Invest Dermatol* 2007; **127**:724-726.
50 Dumas O, Smit LA, Pin I, et al. Do young adults with childhood asthma avoid occupational exposures at first hire? *Eur Respir J* 2011; **37**:1043-1049.
51 Schulte P, Howard J. Genetic susceptibility and the setting of occupational health standards. *Annu Rev Public Health* 2011; **32**:149-159.
52 Nelson HH, Kelsey KT. Genetic susceptibility in the workplace: a scientific and ethical challenge. *Occup Environ Med* 2014; **71**:229-230.
53 Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999; **54**:268-272.
54 Polcari I, Becker L, Stein SL, et al. Filaggrin gene mutations in African Americans with both ichthyosis vulgaris and atopic dermatitis. *Pediatr Dermatol* 2014; **31**:489-492.

CHAPTER 5

Contact dermatitis in the construction industry: an unrecognized problem

Johan G. Timmerman[1], Dick J.J. Heederik[1], Ton Spee[1,2], Frits G. van Rooy[1,3], Esmeralda J.M. Krop[1], Thomas Rustemeyer[4], Lidwien A.M. Smit[1]

[1] Institute for Risk Assessment Sciences (IRAS), Utrecht University, The Netherlands
[2] Arbouw Research and Development, Harderwijk, The Netherlands
[3] Arbo Unie Expert Centre for Chemical Risk Management, Haarlem, The Netherlands
[4] Department of Dermatology, VU University Medical Centre, Amsterdam, The Netherlands

Submitted

Abstract

Background
A high prevalence of contact dermatitis (CD) symptoms has been observed in the Dutch construction industry. This has not yet resulted in a coordinated response from occupational health care services. The objectives of this study were investigate the prevalence and determinants of CD in Dutch construction workers and the occupational physicians (OPs)' ability to recognize CD symptoms.

Methods
A questionnaire was administered to construction workers. CD was diagnosed by an expert panel using questionnaire data and photographs of 751 subjects' hands. A photograph subset was evaluated by two OPs. Their diagnoses were compared to those of the expert panel. Associations between CD and determinants were assessed using log-binomial regression analysis.

Results
CD prevalence was high: 61.4% (N=461, expert panel's diagnosis) and 32.9% (N=247, self-reported). Agreement between OPs' and the expert panel's diagnoses was low but increased after training. Washing hands with solvents and performing job-related tasks at home were related to CD.

Conclusions
CD prevalence among Dutch construction workers is high. Recognition of CD by OPs is poor but can be improved by training. Awareness of skin disorders should be raised among both workers and OPs to reduce the burden of CD.

Introduction

The construction industry is an important component of worldwide economies, providing employment for millions of people. In The Netherlands, the construction industry provided 412,000 full time jobs in 2013.[1] Construction workers are exposed to a wide array of hazards during their work, including potentially hazardous substances.[2-7] The combination of physically demanding work and exposure to these various hazards has led to a high prevalence of occupational diseases.[2,5,8-18]

Due to the wide range of workplace hazards, safety measures and good preventive health care are of paramount importance to ensure construction workers' health. However, the large array of possible health impairments complicates health screening. In recent years, in The Netherlands, occupational health care in construction workers has focussed on several occupational diseases,[3,19,20] but hardly on skin diseases. As skin diseases can have a gradual and intermittent course, it can be difficult to detect these diseases at an early stage by means of periodical check-ups.[21] For Dutch construction workers, these periodical check-ups are not obligatory and rely for a large part on self-reported symptoms. Self-administered hand dermatitis symptom questionnaires have been proven to be valid in nurses,[22] but validity is questionable in industrial populations.[23] Doctor-diagnosed CD was strongly associated with filaggrin loss-of-function mutations in construction workers, whereas self-reported symptoms resulted in relatively weak associations.[24]

An important role of hygiene measures in prevention of contact allergy to epoxy resins was recently observed in German construction workers.[25] Besides allergenic substances, construction workers also come into contact with various irritant substances like solvents and abrasive materials, and they may perform wet work, which may all cause contact dermatitis (CD).[8,11,21,26] Although a number of models was constructed to assess dermal exposure to chemical substances,[27,28] these models, mostly based on the conceptual model of Schneider *et al.*,[29] never took the abrasive, skin destructing effect of stones and other abrasive materials into account.

CD prevalence was found to be high in a subset of the current study population.[24] In the present study, as part of a study to develop a predictive tool for occupational physicians (OPs) to screen Dutch construction workers for CD, we aim to evaluate the effectiveness of questionnaires on dermal symptoms and OPs' diagnoses at check-ups, compared to an expert panel's diagnosis. In

addition, we aim to explore associations between materials or working methods and CD in construction workers. Results of this study may contribute to improved occupational health care and prevention of CD in construction workers.

Study population and methods

Study population

Details of the subject recruitment, the questionnaire and methods of dermatological evaluation were in *Chapter 3* of this thesis.[24] Briefly, two approaches were used to recruit subjects. First, a 'skin module', consisting of a questionnaire, and photographing of the skin of the hands of the subjects, was added to the regular check-up at a number of occupational health services. Second, a number of construction companies was visited during an education session on skin protection and glove use. In the current study, all subjects with complete questionnaire data and photos were included (n=751). A flowchart of subject inclusion is shown in *Chapter 4*. The study was approved by the Medical Ethical Committee of the University Medical Centre, Utrecht, The Netherlands.

Dermatological evaluations

Dermatological evaluations were carried out by an expert panel consisting of a dermatologist and an OP specialized in dermatological problems using questionnaire data and assessing photographs of the subjects' hands that were made using a standardized photo lighting chamber.[24] The following symptoms of CD were assessed: erythema, papules, skin scales, crusts, pigment changes and atrophy (all mild symptoms), fissures, vesicles, bullae and ulceration (severe symptoms).[30] Presence of two or more mild symptoms was diagnosed as mild (or beginning) CD; when at least one severe symptom was present, severe CD was diagnosed. In addition, based on the questionnaire data, atopic predisposition, and relation with occupation were assessed. Also based on the questionnaire data, an assessment was made of the type of CD (e.g. irritant CD, allergic CD) but this was not confirmed by patch testings, and therefore qualified as "potentially irritant" CD etc.

Additionally, to assess the ability of OPs to recognize CD symptoms, a subset of 150 randomly chosen photos were also evaluated and scored by two OPs working at an occupational health service. The first half of this subset was scored before they received a one-day course in occupational dermatology by the expert panel, the second half was scored after this training. Diagnosis of the expert panel served as a reference standard.

Questionnaire

The questionnaire included items on skin symptoms, respiratory symptoms, hand hygiene and occupational activities and exposures. Relevant questions can be found in *Supplement 5*. Questionnaire-items used for assessing self-reported CD according to Jungbauer *et al*.[31] can be found in Table 1. An additional questionnaire was used, showing pictures of dermatitis of increasing severity ("pictionnaire").[32]

Data analysis

All statistical analyses were performed using SAS 9.4 (SAS System for Windows, SAS Institute, Cary, NC). Agreement between the expert panel's diagnosis (reference) and OPs' diagnoses, self-reported CD based on the questionnaire and self-reported CD based on the pictionnaire were calculated and presented as Cohen's kappa. For the OPs' diagnoses, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

Using log-binomial regression analysis,[33] associations between CD (mild CD and severe CD according to the expert panels' diagnosis were analyzed together as "CD") and the various risk factors were presented as crude and adjusted prevalence ratios (PR) and 95% confidence intervals (95% CI). Job titles were categorized into 4 main categories: carpenters, bricklayer, painters and other job titles. In regression analyses, painters were used as reference group as CD prevalence was lowest in this group. PR were adjusted for age, method of recruitment and season, where "eczema season" was defined as the 6 months in which skin symptom prevalence was found highest (December until May).[9] A multiple regression model was built, based on backwards selection of variables with *p*-values <0.2 in univariate regression analysis. Subsequently, the variable with highest *p*-value was eliminated. This step was repeated until only variables with p-values <0.05 remained in the model. We did not find associations of CD with atopy, both IgE serology-based and questionnaire based.[24] Therefore, atopy-related variables were not included in current analyses.

Table 1 - Scoring table for contact dermatitis according to Jungbauer *et al.*[31] and prevalence of contact dermatitis symptoms.

		Occupational Health Services N=325		Construction companies N=426		Total N=751	
Question	**Points for positive answer**	**Self-reported**	**Dermatologist-diagnosed**	**Self-reported**	**Dermatologist-diagnosed**	**Self-reported**	**Dermatologist-diagnosed**
Dermal symptoms on hands or fingers in the past 12 months:		**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Red and swollen hands or fingers	1	13 (4.0)	198 (60.9)	20 (4.7)	320 (75.1)	33 (4.4)	518 (69.0)
Scaly hands or fingers	1	35 (10.8)	186 (57.2)	44 (10.3)	292 (68.5)	59 (10.5)	478 (63.7)
Itchy hands or fingers	1	43 (13.2)	-	67 (15.7)	-	110 (14.7)	-
Hands or fingers with fissures	2	100 (30.8)	97 (29.9)	134 (31.5)	77 (18.1)	234 (31.2)	174 (23.2)
Vesicles on the hands or between the fingers	2	13 (4.0)	1 (0.3)	23 (5.4)	0 (0)	36 (4.8)	1 (0.1)
Red bumps on hands or fingers	2	9 (2.8)	6 (1.9)	22 (5.2)	1 (0.2)	31 (4.1)	7 (0.9)
One or more of these symptoms lasting for more than three weeks	1	61 (18.8)	-	71 (16.7)	-	132 (17.6)	-
One or more of these symptoms occurring more than once in the past 12 months	1	95 (29.2)	-	135 (31.7)	-	230 (30.6)	-

Scores: 0-2 points: no contact dermatitis; 3-5 points: possible contact dermatitis; >5 points: contact dematitis

Results

A total of 1,157 construction workers were invited in the study, of whom 860 participated (response 74.3%) and 751 subjects had complete data on questionnaire and doctor's diagnosis.

Three subjects (0.4%) were female, mean age was 42.5 (standard deviation (SD): 12.9) years (Table 2). Carpenter was the most frequently mentioned job title (45.3%), followed by painters (13.3%) and bricklayers (9.1%). Other job titles were reported by 28.1% of the subjects, 4.3% did not report their job title.

Table 2 - Study sample demographics and prevalence of dermatitis.

	Occupational Health Services N=325		Construction companies N=426		Total N=751	
	mean	**SD**	**mean**	**SD**	**mean**	**SD**
Age	46.1	11.6	39.7	13.2	42.5	12.9
	N	**%**	**N**	**%**	**N**	**%**
Female gender	0	0.0	3	0.7	3	0.4
Job title						
Carpenter	135	41.5	205	48.1	340	45.3
Bricklayer	38	11.7	30	7.0	68	9.1
Painter	37	11.4	63	14.8	100	13.3
Other	112	34.5	99	23.2	211	28.1
Contact dermatitis						
Doctor's diagnosis						
Contact dermatitis						
Mild contact dermatitis	74	22.8	213	50.0	287	38.2
Severe contact dermatitis	97	29.8	77	18.1	174	23.2
Type of contact dermatitis						
Potentially irritant contact dermatitis	153	47.1	269	63.1	422	56.2
Potentially allergic contact dermatitis	1	0.3	-	-	1	0.1
Potentially irritant + allergic contact dermatitis	13	4.0	7	1.6	20	2.7
Potentially other type of contact dermatitis	1	0.3	8	1.9	9	1.2
Contact dermatitis with atopic predisposition	22	6.8	24	5.6	46	6.1

Table 2 - continued

Occupational contact dermatitis	164	50.5	275	64.6	439	58.5
Self-reported symptom-based contact dermatitis (written questionnaire)						
Possible contact dermatitis	82	25.2	105	24.7	187	24.9
Contact dermatitis	26	8.0	34	8.0	60	8.0
Self-reported symptom-based contact dermatitis (pictionnaire)						
Mild self-reported symptoms of dermatitis	18	5.5	13	3.1	31	4.1
Moderate to severe self-reported symptoms of dermatitis	47	14.5	64	15.0	111	14.8

Prevalence of CD

The expert panel diagnosed a total of 38.2% of all subjects with mild CD, and another 23.2% with severe CD, leading to a total CD prevalence, either mild or severe, of 61.4% (Table 2). The vast majority of CD cases were classified as potentially irritant CD (91.5%) and/or occupational CD (95.2%). In 10.0% of all subjects with CD, an atopic predisposition was proposed by the expert panel.

Self-reported CD prevalence was lower; 24.9% reported symptoms leading to a score between 2 and 5, indicating possible CD, another 8% scored more than 5 points, indicating CD (see Table 1). This leads to a combined (either possible or definitive) self-reported symptom-based CD prevalence of 32.9%. Based on the pictionnaire, 4.1% reported mild CD symptoms and another 14.8% reported moderate to severe CD, yielding a total CD prevalence of 18.9%.

Most frequently doctor-diagnosed symptoms were redness, scaly skin and fissures, whereas fissures were the most frequently self-reported symptom, followed by itchy hands or fingers and scaly hands or fingers, see Table 1.

Agreement and predictive values

Agreement between the expert panel's diagnosis and the various questionnaire-derived outcomes and the predictive values of these outcomes are shown in Table 3. Cohen's kappa values were low, indicating poor agreement. Almost all subjects with self-reported CD were diagnosed with CD by the expert panel, resulting in a high PPV. However, a large proportion of subjects who did not report CD were actually diagnosed with CD by the expert panel, yielding a NPV of 47%. For severe CD, questionnaire-derived outcomes had lower PPVs but higher NPVs.

Table 3 - Comparison of self-reported outcomes with the expert panel's diagnoses.

	Sensitivity	Specificity	PPV	NPV	Cohen's kappa (95% CI)
Compared to contact dermatitis (mild and/or severe; doctor-diagnosed)					
Possible contact dermatitis (questionnaire-derived)	42%	82%	79%	47%	0.21 (0.15-0.27)
Contact dermatitis (questionnaire-derived)	12%	99%	95%	41%	0.09 (0.06-0.11)
Fissures (questionnaire-derived)	42%	86%	83%	48%	0.25 (0.19-0.30)
Mild hand eczema (pictionnaire-derived)	23%	85%	72%	41%	0.07 (0.02-0.12)
Severe hand eczema (pictionnaire-derived)	20%	90%	76%	41%	0.08 (0.03-0.12)
Compared to severe contact dermatitis (doctor-diagnosed)					
Contact dermatitis (questionnaire-derived)	15%	94%	43%	78%	0.12 (0.04-0.19)
Fissures (questionnaire-derived)	52%	75%	38%	84%	0.24 (0.16-0.31)
Severe hand eczema (pictionnaire-derived)	25%	87%	36%	79%	0.13 (0.05-0.21)

Performance of occupational physicians

Mild CD was diagnosed by the two OPs in 8.0% and 16.0% of the subjects before the training and in 21.3% and 25.3% after the refresher course by the expert panel. Severe CD was diagnosed in 32.0% and 36.0% before the training and in 18.7% and 34.7% of the subjects after the training, see Table 4.

Mutual agreement between the two OPs was fair for CD (Cohens kappa: 0.46, 95% CI: 0.27-0.66) and increased slightly after the training (0.51 (0.34-0.69)). For severe CD, mutual agreement was moderate before the training (0.58 (0.38-0.77)) but decreased after the training (0.47 (0.26-0.68)). Agreement of the OPs with the expert panel was lower but increased after the training, both for CD and severe CD. NPVs of the OPs diagnoses of mild CD increased after the training: from 41.9% to 53.3% and from 37.1% to 60.0%. For severe CD, the NPV was high and did not change by training (from 80.9% to 81.6% and from 87.8% to 85.2%). PPVs of the OPs' diagnoses of both CD (either mild or severe) and severe CD increased after the training.

Table 4 - Comparison of occupational physicians' outcomes with the expert panel's diagnoses.

	Before training	After training
Prevalence		
Occupational physician #1		
Mild contact dermatitis	8.0%	21.3%
Severe contact dermatitis	32.0%	18.7%
Occupational physician #2		
Mild contact dermatitis	16.0%	25.3%
Severe contact dermatitis	36.0%	34.7%
	Before training	**After training**
	Cohen's kappa (95% CI)	Cohen's kappa (95% CI)
Mutual agreement		
Contact dermatitis (either mild or severe)	0.46 (0.27-0.66)	0.51 (0.34-0.69)
Severe contact dermatitis	0.58 (0.38-0.77)	0.47 (0.26-0.68)
Agreement with expert panel		
Occupational physician #1		
Contact dermatitis (either mild or severe)	0.23 (0.04-0.42)	0.45 (0.28-0.62)
Severe contact dermatitis	0.40 (0.18-0.63)	0.55 (0.33-0.77)
Occupational physician #2		
Contact dermatitis (either mild or severe)	0.12 (--0.10-0.33)	0.46 (0.25-0.66)
Severe contact dermatitis	0.15 (--0.07-0.38)	0.25 (0.03-0.48)
	Before training	**After training**
	%	**%**
Negative Predictive Value		
Occupational physician #1		
Contact dermatitis (either mild or severe)	41.9%	53.3%
Severe contact dermatitis	87.8%	85.2%
Occupational physician #2		
Contact dermatitis (either mild or severe)	37.1%	60.0%
Severe contact dermatitis	80.9%	81.6%
Positive Predictive Value		
Occupational physician #1		
Contact dermatitis (either mild or severe)	83.3%	96.7%
Severe contact dermatitis	50.0%	78.6%
Occupational physician #2		
Contact dermatitis (either mild or severe)	74.4%	84.4%
Severe contact dermatitis	33.3%	42.3%

Determinants

Crude and adjusted PR for possible determinants of CD (either mild or severe, expert panel's diagnosis) are shown in Table 5. A number of determinants were significantly associated with CD in the multiple regression model: recruitment at a construction company; use of hand cream; performing job-related activities at home for more than four hours a week; age; job title; and regularly washing the hands with solvents. Generally, the magnitude of associations decreased after adjustment for covariates, except for regularly washing the hands with solvents, which was not associated with CD in univariate analysis.

Reporting "cleaning the hands after work is not easy" was also significant after adjustment for all variables in the full model. However, this variable and "reporting very dirty hands after work", were not included in the stepwise variable selection as subjects with self-reported skin symptoms may be more aware of hand contamination, or may have more problems to clean their hands. Subjects reporting dermal symptoms indeed stated their hands to be dirty and/or difficult to clean more often than subjects without self-reported dermal symptoms, independent from the expert panel's diagnosis (data not shown).

Sensitivity analyses with mild CD and severe CD as health endpoint showed a stronger effect of job title for severe CD (PR >3 for all job titles compared to painters), see *Supplement 7* for all results. Analyses within job titles did not identify additional occupational determinants of CD (shown in *Supplement 8*).

Table 5 Determinants of contact dermatitis in the Dutch construction industry.

			Crude		Adjusted[a]	
	N	%	PR	95% CI	PR	95% CI
General variables						
Age per 10y increase	-	-	**1.06**	**1.02-1.11**	**1.04**	**1.01-1.09**
Recruited at company	426	56.7	**1.29**	**1.14-1.46**	**1.25**	**1.09-1.43**
Recruited during “eczema season”	510	67.9	**1.21**	**1.06-1.38**	1.01	0.87-1.16
Family history of eczema	171	23.3	1.07	0.94-1.21	1.01	0.91-1.12
Uses hand cream	315	42.1	**1.38**	**1.24-1.54**	**1.21**	**1.10-1.34**
General occupational variables						
Job title:						
Painter	100	13.3	(reference)		(reference)	
Carpenter	340	45.3	**2.31**	**1.70-3.14**	**1.92**	**1.45-2.54**
Bricklayer	68	9.1	**2.30**	**1.64-3.23**	**2.05**	**1.50-2.81**
Other	211	28.1	**1.99**	**1.45-2.74**	**1.93**	**1.45-2.58**
Had information on contact dermatitis in the past	78	10.4	0.93	0.76-1.14	0.96	0.83-1.11
Changed working methods after receiving information on contact dermatitis	56	7.5	0.92	0.73-1.17	1.00	0.83-1.19
Uses gloves	349	46.5	**0.80**	**0.71-0.90**	0.92	0.83-1.01
Does not change gloves at regular moments	570	79.5	1.06	0.91-1.23	1.10	0.97-1.25
Uses waterproof gloves	74	9.9	0.96	0.79-1.17	1.03	0.87-1.22
Reports very dirty hands after work	113	15.1	1.16	1.01-1.33	1.07	0.96-1.20
Reports cleaning hands after work not easy	305	40.8	1.26	1.12-1.40	**1.13**	**1.04-1.24**
Washes hands more than five times/day	197	26.3	0.98	0.86-1.12	0.96	0.87-1.08
Washes hands with solvents	46	6.2	1.10	0.89-1.36	**1.17**	**1.03-1.34**
Washes hands using abrasive soap	221	29.6	0.94	0.83-1.07	0.98	0.88-1.09
Works more than 4h/week at home performing job-related tasks	351	47.0	**1.26**	**1.12-1.41**	**1.14**	**1.04-1.26**

PR: Prevalence Ratio, 95% CI: 95% Confidence Interval

[a] adjusted for age, method of recruitment, eczema season, hand cream use, job title and performing job-related task at home for more than four hours a week. Regularly washing hands with solvents after work was not included in the model as the p-value for this determinant was >0.2 in univariate regression analysis, but after adjustment for all variables in the full model, a positive association with CD was found.

Discussion

In this study, a high prevalence of both mild and severe CD was found in Dutch construction workers. Agreement of the expert panel's diagnosis (the reference standard in our study) with self-reported questionnaire items on CD and with OPs' diagnoses was low. Regularly washing the hands with solvents and performing work-related tasks at home for more than four hours a week were associated with a modestly increased risk of CD.

Recently, we reported a high prevalence of self-reported skin symptoms[9] and self-reported CD.[10] In earlier analyses in a subset of the current study population, also a high prevalence of doctor-diagnosed CD was reported.[24] This was confirmed by the results in the full study population presented in the current report (mild CD: 38.3%, severe CD: 23.2%). In 1984, the last time the doctor-diagnosed prevalence of CD in Dutch construction workers was reported, a prevalence of 7.8% was found.[34] It is uncertain whether the much higher prevalence in the present study is due to a more rigorous diagnosis, or due to changes in occupational exposures that may have caused a strong increase in hand dermatitis over time.

The expert panel diagnosed CD more often than reported by workers, either based on the questionnaire (possible CD: 24.9%, CD: 8.0%) or the pictionnaire (CD: 4.1%, moderate to severe CD: 14.8%). Mild symptoms (red skin, scaly skin) were often reported by the expert panel (69.0% and 63.7%) but not by the construction workers (4.4% and 10.5%). The fact that construction workers did not report mild symptoms may well explain why the score of self-reported symptoms often stays below 3 points (the threshold score for "possible CD") even if they report to have severe symptoms like fissures. Construction workers may not recognize mild symptoms, and only start reporting symptoms when their CD has become severe: fissures were reported most frequently by construction workers, which was also seen in earlier studies.[9,10] As the questionnaire asked for symptoms over the last 12 months and the expert panel judged a momentary picture of the hands, true one-year prevalence might be even higher than observed.

The symptom-based questionnaire is used by OPs to screen construction workers for CD. However, it was developed for and validated in nurses,[22] and was less useful in industrial populations.[23,24] In our population, the self-reported questionnaire correctly predicted a diagnosis of mild CD in 79% of the symptomatic subjects, but only 47% of the negative self-reports were correct.

Interestingly, the self-reported question on fissures alone performed as good as the complete questionnaire in predicting mild CD, but not severe CD.

Both before and after the dermatological course, OPs reported a lower mild CD prevalence than CD the expert panel did but higher severe CD prevalence. Agreement, PPV and NPV generally increased after the course. This implicates the usefulness of a course on dermatology for OPs, increasing their ability to diagnose (early) signs of CD correctly. The OPs acknowledged that in practice, construction workers were almost never referred to their general practitioner or a dermatologist for their skin problems. Thus, in regular occupational health care practice, CD symptoms remain untreated. As construction workers themselves hardly report mild symptoms, they will not report symptoms before they develop severe CD symptoms. To detect CD in an early stage, recognition of a red and scaly skin by the OP is of importance. As many construction workers do have a red and scaly skin, these visible, early CD symptoms may however be overlooked because this may be regarded normal for a construction worker.

In our study, standardized photographs of the hands were used by the expert panel and the OPs to diagnose CD. Using physical examinations would be much more expensive and time-consuming, and would not fit in the routine check-up infrastructure. Moreover, according to the expert panel, the used method is as reliable as a physical examination. We did not perform patch tests to confirm allergic CD. Generally, when skin allergy or allergen exposure were not reported in the questionnaire, subjects were diagnosed with potentially irritant CD.

Despite the high prevalence, a limited number of determinants appeared statistically significantly associated with CD. The present study aimed to evaluate the occurrence of CD in the construction industry as a whole. However, construction workers, use a great diversity of materials and products, in different ways and amounts. A questionnaire is a rather crude approach to assess relevant occupational exposures, leading to misclassification and underestimation of associations. Moreover, the majority of cases potentially had irritant CD, which can be caused by multiple non-specific exposures. We adjusted for job title because CD prevalence was lower amongst painters compared to other job titles and because several determinants were expected to be associated with particular job titles. Stratification for job title, however, did not show job title specific risk factors. The positive associations with age, hand washing with a solvent and performing job-related tasks at home for more than four hours a week suggest that cumulative exposure to mildly irritant substances is the main risk factor for CD in the construction industry but interpretation is limited by the

cross-sectional study design. The present analysis and our previous longitudinal analysis of check-up records support a protective effect of glove use on skin symptoms,[9] which was not found in our earlier cross-sectional study.[10]

Hand cream use was positively associated with CD, likely due to reverse causation.[10] Hand cream was reported to be used by only 42.1% of the subjects, and only 18.6% reported daily hand cream use. This may explain the high prevalence of red and scaly skin. The expert panel remarked in 10% of subjects with CD that hands were badly cared for. As a dry skin is more prone to be damaged, permeation of irritants and allergens into the skin is more likely to happen than with an intact skin.

Given the high prevalence of CD amongst construction workers and the few occupational determinants identified, we decided not to develop a predictive tool but to advocate specific attention of the OP to CD in all construction workers visiting a medical check-up, especially when they report fissures.

Conclusions

CD prevalence is high among Dutch construction workers, but not sufficiently recognized by themselves and by OPs. Protection against relatively mild irritants and good skin care to ensure a vital skin are recommended for construction workers to reduce the high prevalence of mild CD and prevent it from worsening to severe CD. Better awareness of the problem of CD among workers, employers, and OPs is needed to ensure lower prevalence and earlier and better diagnosis of CD in the construction industry.

Acknowledgements

We thank Henny Bastiaans, Petra Beurskens and Ardi Brouwer (Arbo Unie) and Tamara Onos for coordinating and supporting field work; Hans Bouman, Hans Clemenkowff, Mariska Droog, Tamara Onos and Jan Snijder for giving the presentations during the educational sessions at construction companies; Saskia Martens for supporting field work and data processing and Daan Heynsdijk and Paul Vredebregt for assessing the photographs.

References

1 Jansen FJ. Bouw in beeld 2013-2014. Available at: http://www.eib.nl/pdf/bouw_in_beeld_2013-2014.pdf (last accessed 7 April 2015).
2 Carino M, Romita P, Foti C. Allergy-related disorders in the construction industry. *ISRN Prev Med* 2013; **2013**:864679.
3 Spee T, van Valen E, van Duivenbooden C, van der Laan G. A screening programme on chronic solvent-induced encephalopathy among Dutch painters. *Neurotoxicology* 2012; **33**:727-733.
4 Jarvholm B, Silverman D. Lung cancer in heavy equipment operators and truck drivers with diesel exhaust exposure in the construction industry. *Occup Environ Med* 2003; **60**:516-520.
5 Antonini JM, Lewis AB, Roberts JR, Whaley DA. Pulmonary effects of welding fumes: review of worker and experimental animal studies. *Am J Ind Med* 2003; **43**:350-360.
6 Linch KD. Respirable concrete dust--silicosis hazard in the construction industry. *Appl Occup Environ Hyg* 2002; **17**:209-221.
7 van Deurssen E, Pronk A, Spaan S, et al. Quartz and respirable dust in the Dutch construction industry: a baseline exposure assessment as part of a multidimensional intervention approach. *Ann Occup Hyg* 2014; **58**:724-738.
8 Bock M, Schmidt A, Bruckner T, Diepgen TL. Occupational skin disease in the construction industry. *Br J Dermatol* 2003; **149**:1165-1171.
9 Timmerman JG, Heederik D, Spee T, Smit LA. Skin symptoms in the construction industry: occurrence and determinants. *Am J Ind Med* 2014; **57**:660-668.
10 Timmerman JG, Zilaout H, Heederik D, et al. Validation of a questionnaire on hand hygiene in the construction industry. *Ann Occup Hyg* 2014; **58**:1046-1056.
11 Uter W, Ruhl R, Pfahlberg A, et al. Contact allergy in construction workers: results of a multifactorial analysis. *Ann Occup Hyg* 2004; **48**:21-27.
12 Keski-Santti P, Kaukiainen A, Hyvarinen HK, Sainio M. Occupational chronic solvent encephalopathy in Finland 1995-2007: incidence and exposure. *Int Arch Occup Environ Health* 2010; **83**:703-712.
13 Ulvestad B, Lund MB, Bakke B, et al. Short-term lung function decline in tunnel construction workers. *Occup Environ Med* 2015; **72**:108-113.
14 Tak S, Calvert GM. Hearing difficulty attributable to employment by industry and occupation: an analysis of the National Health Interview Survey--United States, 1997 to 2003. *J Occup Environ Med* 2008; **50**:46-56.
15 Nelson DI, Nelson RY, Concha-Barrientos M, Fingerhut M. The global burden of occupational noise-induced hearing loss. *Am J Ind Med* 2005; **48**:446-458.
16 Stichting Arbouw. Bedrijfstakatlas 2015. Available at: http://www.arbouw.nl/media/2716/bedrijfstakatlas-2015.pdf (last accessed July 2015).
17 Boschman JS, van der Molen HF, Sluiter JK, Frings-Dresen MH. Occupational demands and health effects for bricklayers and construction supervisors: A systematic review. *Am J Ind Med* 2011; **54**:55-77.
18 Stocks SJ, Turner S, McNamee R, et al. Occupation and work-related ill-health in UK construction workers. *Occup Med (Lond)* 2011; **61**:407-415.
19 Leensen MC, Dreschler WA. The applicability of a speech-in-noise screening test in occupational hearing conservation. *Int J Audiol* 2013; **52**:455-465.

20 Suarthana E, Moons KG, Heederik D, Meijer E. A simple diagnostic model for ruling out pneumoconiosis among construction workers. *Occup Environ Med* 2007; **64**:595-601.
21 Diepgen TL, Coenraads PJ. The epidemiology of occupational contact dermatitis. *Int Arch Occup Environ Health* 1999; **72**:496-506.
22 Smit HA, Coenraads PJ, Lavrijsen AP, Nater JP. Evaluation of a self-administered questionnaire on hand dermatitis. *Contact Dermatitis* 1992; **26**:11-16.
23 Vermeulen R, Kromhout H, Bruynzeel DP, de Boer EM. Ascertainment of hand dermatitis using a symptom-based questionnaire; applicability in an industrial population. *Contact Dermatitis* 2000; **42**:202-206.
24 Timmerman JG, Heederik D, Spee T, et al. Contact dermatitis in the construction industry: the role of filaggrin loss-of-function mutations. *Br J Dermatol* 2015; **174**:348-355.
25 Spee T, Timmerman JG, Rühl R, et al. Determinants of epoxy allergy in the construction industry: a case-control study.
. *Contact dermatitis* 2016; **74(5)**:259-266.
26 Ronmark EP, Ekerljung L, Lotvall J, et al. Eczema among adults: prevalence, risk factors and relation to airway diseases. Results from a large-scale population survey in Sweden. *Br J Dermatol* 2012; **166**:1301-1308.
27 Van-Wendel-de-Joode B, Brouwer DH, Vermeulen R, et al. DREAM: a method for semi-quantitative dermal exposure assessment. *Ann Occup Hyg* 2003; **47**:71-87.
28 van Hemmen JJ, Auffarth J, Evans PG, et al. RISKOFDERM: risk assessment of occupational dermal exposure to chemicals. An introduction to a series of papers on the development of a toolkit. *Ann Occup Hyg* 2003; **47**:595-598.
29 Schneider T, Vermeulen R, Brouwer DH, et al. Conceptual model for assessment of dermal exposure. *Occup Environ Med* 1999; **56**:765-773.
30 Jansen LH. *Huid- En Geslachtsziekten. Een Handboek Voor De Praktijk Van Huis- En Huidarts [Skin Diseases and Venereology: A Practical Handbook for General Practitioners and Dermatologists].* Utrecht: Scheltema & Holkema, 1975.
31 Jungbauer FH, Piebenga WP, ten Berge EE, et al. NVAB-richtlijn: Preventie Contacteczeem (NVAB guideline: Prevention of Contact Dermatitis). Available at: https://www.nvab-online.nl/sites/default/files/bestanden-webpaginas/Contacteczeem%20RL.pdf (last accessed 7 april 2015).
32 Van der Walle HB, Piebenga WP. In: *Skin and Occupation*(Anonymous) Arnhem: Centre for Skin and Occupation, 2004; 75-76,77.
33 Deddens JA, Petersen MR. Approaches for estimating prevalence ratios. *Occup Environ Med* 2008; **65**:481, 501-6.
34 Coenraads PJ, Nater JP, Jansen HA, Lantinga H. Prevalence of eczema and other dermatoses of the hands and forearms in construction workers in the Netherlands. *Clin Exp Dermatol* 1984; **9**:149-158.

CHAPTER 6

6

Determinants of epoxy allergy in the construction industry: a case-control study

Ton Spee[1,2], Johan G. Timmerman[1], Reinhold Rühl[3], Klaus Kersting[3],
Dick J.J. Heederik[1], Lidwien A.M. Smit[1]

[1] Institute for Risk Assessment Sciences, Division Environmental Epidemiology,
Utrecht University, Utrecht, the Netherlands
[2] Arbouw Research and Development,
Harderwijk, The Netherlands
[3] Berufsgenossenschaft für die Bauwirtschaft,
Frankfurt, Germany

Contact Dermatitis 2016, Vol. 74, pp 259-266

Abstract

Background

Workers exposed to epoxy products are at risk of developing allergic contact dermatitis. This case-control study aims to compare workers throughout the German construction industry with and without a skin allergy against epoxy resins, hardeners and/or reactive diluents, and to investigate which determinants are related to developing epoxy allergy.

Methods

A questionnaire was completed by 179 epoxy allergy cases, and 151 epoxy workers as controls. Crude and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using backwards stepwise logistic regression analysis. A multiple imputation approach was used to deal with missing data.

Results

Epoxy allergy was associated with an unusually high exposure to epoxy products (OR 2.13, 95% CI: 1.01-4.51), wearing short sleeves or pants (OR 2.38, 95% CI: 1.03-5.52), and not always using the right type of gloves (OR 2.12, 95% CI: 1.12-4.01). A monotonic increasing risk was found with increasing exposure hours per week (OR 1.72, 95% CI: 1.39-2.14). Not using skin cream was inversely associated with epoxy allergy (OR 0.22, 95% CI: (0.08-0.59). Working years with epoxy products were inversely associated with epoxy allergy (OR 0.41, 95% CI: 0.27-0.61 per 10 years increase), suggesting a healthy worker survivor effect.

Conclusions

Occupational epoxy allergy may be prevented by improving hygienic behaviour and personal protection.

Introduction

Because of their unique technical properties, epoxy products are widely used in the construction industry. Effective substitutes are hardly available, and the number of applications is still growing.[1] Unfortunately, epoxies are strong sensitizers. Although chromate is still the most common cause of allergy in the German construction industry, more than ten percent of all occupational allergies among construction workers is due to epoxy resin systems.[2] In the Netherlands, it is estimated that about one out of every five epoxy exposed workers develops symptomatic dermal sensitization, often serious enough to lead to a change of job.[3] Rømyhr *et al*. report an incidence rate of 4.5/1000 person years, which corresponds to nearly one out of five industrial painters who regularly work with epoxy resin systems, over a 40 year career.[4]
The economic impact of epoxy allergies to society are high. Rühl and Wriedt estimated the cost of occupational epoxy allergies for the whole European Union in 2003 at 40 million euro.[5] Financial compensation for work disability alone accounted for over 1.4 million euro in Germany in 2007. Furthermore, there are costs for medical treatment, absenteeism, employee replacement and retraining, etc.
A few previous studies in epoxy workers suggested that unhygienic behaviour may enhance the risk of skin exposure[6] and developing epoxy allergy.[1,7] These studies evaluated working practices in 21 workers,[6] and epoxy sensitization in eight[1] and 22 workers.[7] To the best of our knowledge, there are no adequately powered epidemiologic studies that systematically evaluate determinants of epoxy allergy among a larger group of workers from different companies, representative for the industrial sector.
This case-control study aims to investigate which determinants are related to developing a contact allergy against epoxy resins, hardeners and/or reactive diluents. This will yield policy information which can form the basis for intervention strategies. The study focuses on working practices, hygienic behaviour, and personal protection.

Study population and methods

Study design and population

A case-control study was conducted among epoxy workers with a recognized epoxy skin allergy and epoxy workers without such an allergy. Cases were ascertained from the files of the German statutory accident insurance of the construction sector (Berufsgenossenschaft der Bauwirtschaft; BGBAU). Epoxy

allergy is confirmed in about 100 to150 persons annually by BG BAU, so we decided to collect data over a 4-year period retrospectively to include an adequate number of cases. Workers with an epoxy allergy recognized as an occupational disease between January 1, 2004 and December 31, 2007, were invited in the study. For recognition as an occupational disease, epoxy allergy has to be confirmed by means of a patch test. Controls were recruited at companies that regularly work with epoxy products and in part at instruction sessions for working with epoxies.
Cases received a questionnaire at their home address. Controls received a questionnaire at the end of the instruction session or by mail. They were asked to complete the questionnaire at home. Postage-free return envelopes were supplied for both groups. Questionnaires were distributed between 2011 and 2012 (cases) and between 2011 and 2013 (controls).
Subjects who did not complete the questionnaire, or stated not to have worked with epoxy products, were excluded from analysis. In the case group, subjects who stated not to be allergic to epoxies were excluded from data analysis as well. In the control group, workers who stated to be allergic to epoxy products, seldom or never work with epoxy products, only recently started working for the current employer, or did not complete the questionnaire, were excluded from data analysis.

Questionnaire
Data on epoxy exposure and potential confounders was collected by means of a self-administered questionnaire. The questionnaire included items on personal characteristics, atopic predisposition, respiratory symptoms, skin symptoms (for cases: skin symptoms at the time that the allergy was manifest), products used, tasks performed and working practices, personal protection and hygiene, and education and training. Questions about respiratory[8] and skin[9] symptoms were adopted from existing, validated questionnaires. The questions about epoxy products, tasks, working practices, personal protection and hygiene, and education and training were developed by two persons (TS and KK) who are familiar with working with epoxy products in the construction industry. The questions about glove use were validated in a separate study,[10] which is described in *Chapter 3* of this thesis.

To score subjects for hand dermatitis, we used a questionnaire based on Smit *et al*.[9] and Jungbauer *et al*.[11] with a score for each question, as presented in Table 1. A positive answer to all questions yields 9 points. A score of at least 3 points is classified as ‘possible hand dermatitis’, a score of at least 5 points as ‘hand dermatitis’.

We used an additional questionnaire, which showed pictures of dermatitis of increasing severity on the hands, but also on other parts of the body (example of the pictures can be found via http://huidenarbeid.nl/test). This photo-questionnaire, developed by the Dutch Centre for Occupational Skin Diseases, which is reported to have a negative predictive value of 99%,[12] was used for comparison with the symptom-based questionnaire and to estimate the severity of the symptoms.

Table 1 - Symptom score used to define dermatitis and possible dermatitis.

Question	Points[(a)]
Did you have one of the following symptoms on your hands or fingers in the past 12 months:	
- red and swollen hands or fingers	1
- red hands or fingers with fissures	2
- vesicles on the hands or between the fingers	2
- raw or scaly hands with fissures	1
- itchy hands or fingers with fissures	1
Did one or more of these symptoms last for more than three weeks?	1
Did one or more of these symptoms occur more than once the past 12 months?	1

[(a)] A score of at least 3 points is classified as 'possible dermatitis', a score of at least 5 points as 'dermatitis.' The latter two questions were not asked in the case group as, among people suffering from epoxy allergy, these are true by definition. So cases always score at least two points.

Statistical analyses

Statistical analyses were carried out using SAS version 9.4 (SAS System for Windows, SAS Institute, Cary, NC) and R studio for Windows (version 3.0.2).

To assess the association between epoxy allergy and various possible risk factors, crude and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using backwards stepwise logistic regression analysis. All determinants with univariate p-values smaller than 0.2 were included in the initial model. At each step, the determinant with the highest p-value was removed from the model. The final model consisted of all variables that remained significant (p-value <0.05). Determinants were corrected for all determinants in the final model to calculate adjusted OR. A number of categorical questionnaire items were dichotomized for use in the regression analysis. Associations with continuous variables (years of working experience and hours per week working with epoxy products) were also analyzed using a generalized additive model to evaluate the shape of the relationship.

As a sensitivity analysis, the analyses were repeated in a population in which controls with self- reported skin symptoms (but not necessarily epoxy allergy)

were excluded. Analyses were also performed using only those cases who reported severe symptoms.
To deal with missing data, we used a multiple imputation approach. Assuming missing data is missing at random, this method results in more precise estimates than those obtained in complete case analysis. A fully conditional specification (FCS) method[13] was used to impute missing values. In total, 25 complete data sets were generated, analysed and combined using the MI and MIANALYZE procedures in SAS. Imputations were based on case status and all variables presented in Table 3. Average attributable fractions were calculated according to Eide *et al.*,[14] using the SAS macro provided by Rückinger *et al.*[15]

Medical-ethical issues
The project was carried out in accordance with the code of conduct "Use of data in health research" from the Dutch Federation of Biomedical Scientific Societies, which is in accordance with EU regulations.[16] The purpose of the study was explained in a cover letter. Participation in the study was entirely voluntary, as was filling in the telephone number to retrieve additional information. This was stated on the questionnaire. All participants signed an informed consent form.

Results

Response to the questionnaire
All 527 cases of epoxy allergy registered in the period under study received a questionnaire, of which 159 were returned as undeliverable. Of the remaining 368 cases, 185 (50%) returned the questionnaire.
Among the control group, 828 questionnaires were disseminated, and 242 of them returned the questionnaire (29%). Instruction sessions yielded 85 respondents, the remaining 157 were recruited directly at companies. Due to logistic limitations, data collection from controls ran from 2009 till 2012. A total of 81 respondents were recruited at two large companies. Working practices were clearly different at these companies compared with other companies using epoxy products. To avoid spurious results due to selection of controls from non-representative companies, it was decided to exclude workers from the large companies from data analysis.
Six respondents (3%) from the case group and 10 respondents (7%) from the control group were excluded from data analysis, for reasons mentioned in the Methods section. Consequently, 179 cases and 151 controls were included in the analyses.

Characteristics and activities of the respondents

Characteristics of the study population are summarized in Table 2. Respondents could specify 16 different activities that applied to their tasks, and more than one answer was allowed. 'Corrosion protection' was most frequently mentioned (56.4%, n=186), followed by concrete repair by injection (48.8%, n=161) and industrial floor laying (43.0%, n=142). On average, people in the control group had slightly more different tasks per person than in the case group (control group: 4.2 tasks per person, case group: 3.4 tasks per person).

According to the symptom-based questionnaire, 159 (88.8%) cases possibly had hand dermatitis, with 100 of them having hand dermatitis. A total of 2 controls met the criteria for hand dermatitis, and 12 more for possible hand dermatitis (14 in total, 9.3%).

According to the photo-questionnaire, 150 cases reported eczematous skin conditions (83.8%) and 124 of them reported severe skin conditions (69.3% of all cases). Among the controls, 23 subjects reported to have at least one of the skin conditions as depicted in the photo-questionnaire (15.2%), of whom 14 reported severe skin conditions (9.3% of all controls). Symptoms at the fingers (including fingertips (117, 65.4%) were most often reported in the case group, followed by arms (98, 54.7%), face (87, 48.6%) and hands (75, 41.9%). In the control group, eight persons (5.3%) reported eczematous skin conditions at the fingertips/fingers/hands. Six of them reported severe skin conditions.

Table 2 - Characteristics of the study population of epoxy allergy cases and controls.

	cases		**controls**	
N	179		151	
	median	**q1-q3**	**median**	**q1-q3**
Age	41.5[a]	32.0-49.0	41.0[b]	29.0-49.0
Years of working with epoxy products	6.0[b]	3.0-12.0	12.0[b]	7.0-20.0
Hours per week working with epoxy products	25.0	9.0-40.0	5.0	2.0-15.0
Amount of product used per week (l or kg)	30.0	10.0-50.0	20.0	4.0-150.0
Number of years between starting to work with epoxy products and epoxy allergy diagnosis (N=74)	3.0	2.0-8.0	-	-
Number of years between epoxy allergy diagnosis and filling in the questionnaire (N=137)	5.0	3.0-8.0	-	-
Number of years between stopping to work with epoxy products and filling in the questionnaire (N=87)	4.0	2.0-7.0	-	-

Table 2 - continued

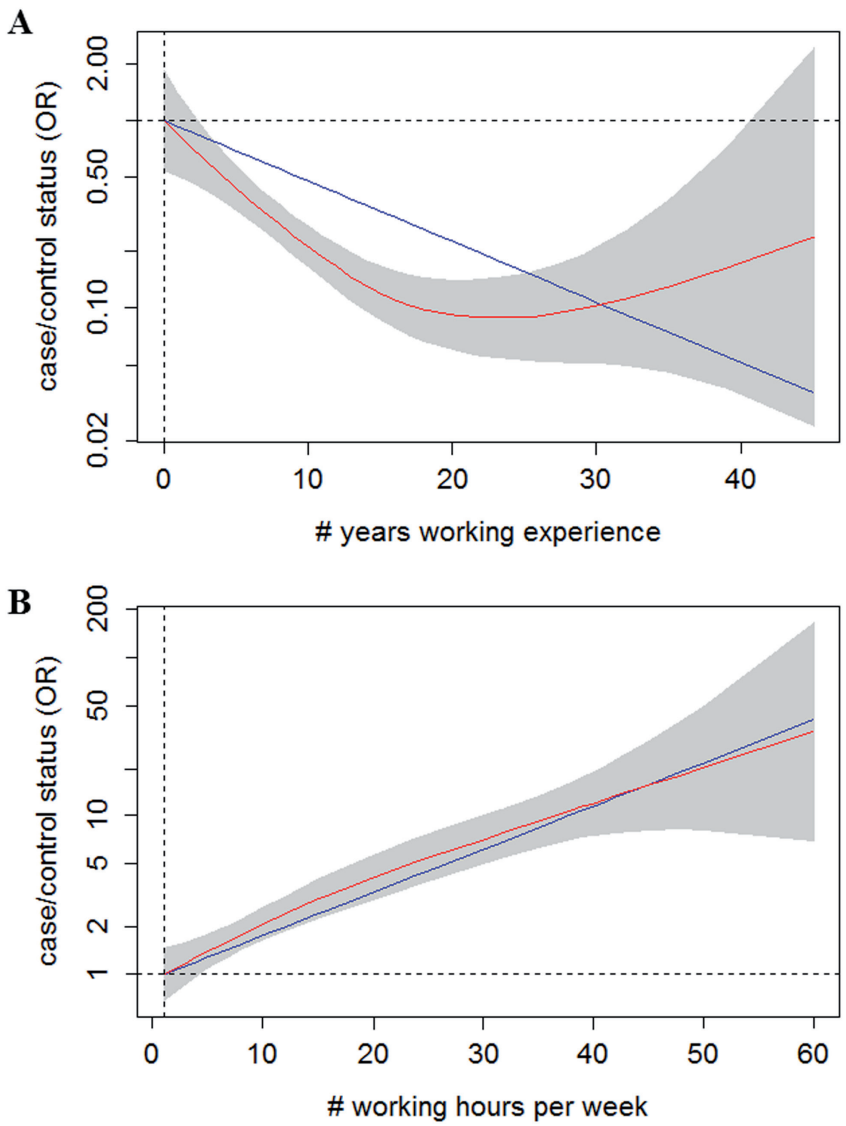
	N	%[c]	N	%[c]
Possible dermatitis according to symptom-based questionnaire[d]	159	88.8%	12	8.0%
Dermatitis according to symptom-based questionnaire[d]	100	55.9%	2	1.3%
Symptoms according to photo-questionnaire	150	83.8%	23	15.2%
Mild symptoms	26	14.5%	9	6.0%
Severe symptoms	124	69.3%	14	9.3%

[(a)] At the time of epoxy allergy diagnosis
[(b)] At the time of completing the questionnaire
[(c)] Percentages of the total number of cases/controls
[(d)] According to Jungbauer *et al.*[11]

Determinants of epoxy allergy

Results of the univariate and multiple logistic regression analysis are shown in Table 3. After adjustment, positive and statistically significant associations were found between epoxy allergy and intensity of exposure to epoxy products (hours per week, an unusually high exposure to epoxy products), wearing short sleeves or pants, and not always using the right type of gloves. Working years with epoxy products and not using skin cream were inversely associated with epoxy allergy. Figure 1 shows smoothed plots representing the relation between epoxy allergy and years of working experience and number of working hours per week with epoxy products. Years of working experience show a steep inverse association with epoxy allergy until 20 years, after which the magnitude of the association levels off. Working hours per week shows a log-linear association with epoxy allergy. Upon exclusion of controls with any self-reported skin symptoms (not necessarily epoxy allergy), no major differences in ORs were found. Similar, but less precise, risk estimates were obtained when using only cases who reported severe symptoms (data not shown).

Figure 1 - Associations between working years (A) and working hours with epoxy products per week (B) and epoxy allergy.



Associations corrected for age. Red lines are based on a generalized additive model, blue lines illustrate presumed linearity, as used in the regression analyses.

Table 3 - Determinants of epoxy allergy analyzed in 179 cases and 151 controls.

Variable	N cases	N controls	Crude OR	95% CI	Adjusted OR[a]	95% CI
Age (per 10 years increase)	136	150	1.05[b]	0.86-1.29	1.26	0.95-1.66
Did you ever suffer from hay fever?						
No	126	107	Reference			
Yes/Don't know	32	24	1.21	0.66-2.21		
Do you use a skin cream?						
Yes, more than once a day	49	26	Reference		Reference	
Yes, daily	84	56	0.80	0.44-1.43	0.60	0.28-1.25
Yes, less than daily	15	25	**0.32**	0.14-0.71	**0.32**	0.12-0.86
No	20	32	**0.33**	0.16-0.69	**0.22**	0.08-0.59
Years of working with epoxy (per 10 years increase)	151	138	**0.52**	0.39-0.69	**0.41**	0.27-0.61
Number of working hours a week (per 10 hours increase)	146	117	**1.89**	1.56-2.29	**1.72**	1.39-2.14
Did you ever have an unusually high dermal exposure to epoxy products?						
No	82	98	Reference		Reference	
Yes	38	19	**2.39**	1.28-4.46	**2.13**	1.01-4.51
Don't know	37	18	**2.46**	1.30-4.64	1.50	0.70-3.20
Do you use gloves when working with epoxy products?						
Always	132	119	Reference			
Not always	44	24	1.65	0.95-2.88		

What type of gloves resemble the glove you use when working with epoxy product most?						
Only chemically resistant gloves[c]	35	51	Reference		Reference	
(Also) other types of gloves	143	97	**2.15**	1.30-3.55	**2.12**	1.12-4.01
How often do you change gloves?						
More than once a day	55	39	Reference			
Once a day	35	46	**0.54**	0.30-0.98		
Less than once a day or at irregular moments (e.g. just when dirty/torn)	79	57	0.98	0.58-1.68		
Are your gloves comfortable enough?						
Yes	140	128	Reference			
No	28	14	1.83	0.92-3.63		
Do you change clothes after working with epoxy products?						
Yes, at work	72	59	Reference			
At home / not at all	103	88	0.96	0.61-1.50		
Do you shower after working with epoxy products?						
Yes, at work	15	5	Reference			
At home / not at all	160	136	0.39	0.14-1.11		
Do you wash your hands directly after working with epoxy products?						
Always	77	70	Reference			
Most of the times	65	41	1.44	0.87-2.39		
Sometimes / never	31	26	1.08	0.59-2.00		
Do you wash your hands before eating?						
Always	137	109	Reference			
Most of the times / sometimes / never	38	32	0.94	0.55-1.61		

Table 3 - continued

How often do you wash your hands during a working day?						
At least five times a day	110	77	Reference			
Less than five times a day	60	62	0.68	0.43-1.07		
How do you clean your hands?						
With a special handcleaner	73	66	Reference			
Only with water, water and soap, water and abrasive soap or a solvent	101	75	1.22	0.78-1.90		
During summer, do you wear clothes with short sleeves or pants when working with epoxy products?						
No	50	43	Reference		Reference	
Sometimes	58	58	0.86	0.50-1.49	0.95	0.48-1.89
Yes, always when it was warm	60	26	**1.98**	1.07-3.67	**2.38**	1.03-5.52
Do you wear cuffs or gloves with cuffs when working with epoxy products?						
Always	46	35	Reference			
Sometimes	44	42	0.80	0.43-1.47		
Never	58	59	0.75	0.42-1.32		
Do you wear boots or gaiters when working with epoxy products?						
Always	18	13	Reference			
Sometimes	23	24	0.69	0.28-1.73		
Never	116	86	0.97	0.45-2.10		
Do you wear knee protection when working on your knees with epoxy products?						
Yes, always	90	62	Reference			
Yes, most of the times / sometimes / never	19	17	**0.56**	0.33-0.95		
Not applicable, I never worked on my knees with epoxy products	35	16	1.51	0.77-2.96		

How do you combine the epoxy resin and hardener of the epoxy product you work most with?				
Resin and hardener were in a dosage system / resin and hardener were in a closed system / the hardener was poured into the resin	49	54	Reference	
Only by pouring the hardener into the resin	115	86	1.47	0.91-2.37
How do you mix the epoxy product you work most with?				
Using an electric mixer in an open barrel / using a closed system / using a package that allows kneading without opening	138	113	Reference	
Manually in an open barrel	31	27	0.94	0.53-1.67
How do you clean the tools of the epoxy product you work most with?				
No cleaning, tools were disposed	26	28	Reference	
Dry cleaning with a whipe / with a solvent / by sanding the tools / by other means	142	115	1.33	0.74-2.39

Due to missing answers, not all categories add up to 407 subjects. Complete datasets (n=25) were generated by multiple imputation. Odds ratios were estimated by combination of the results of logistic regression analysis of each multiply imputed data set.

[(a)] Adjusted OR were adjusted for age, years of working experience, number of working hours per week, ever having had an unusually high exposure to epoxy product during work, wearing no other than chemically resistant gloves, wearing short sleeves and using skin cream.

[(b)] Bold type indicates statistically significant associations ($p<0.05$)

[(c)] Chemically resistant are to the cuff dipped tricot gloves or nitryl/butyl rubber gloves

Discussion

The objective of our case-control study was to establish determinants associated with epoxy allergy in construction workers. We found strong associations of hygienic behaviour and personal protection at the workplace with epoxy allergy. Wearing correct gloves and long sleeves and pants even when it is warm seem to protect against epoxy allergy, as does carefully working to avoid accidents like a snapping injection hose and a vigorous exothermic reaction when mixing resin and hardener.

The association with accidental exposure agrees with the findings of Kanerva *et al*., who showed that a single accidental exposure to epoxy compounds may cause skin sensitization.[17] Use of any type of glove, whether chemically resistant or not, shows no association, indicating that gloves made of cotton, leather and latex (household quality) do not adequately protect from skin exposure. In fact, in separate analyses leather gloves, cotton gloves and latex household gloves are positively associated with epoxy allergy (data not shown), which confirms the conclusion of Van Putten *et al*. that inadequate gloves have an adverse effect on skin protection.[3] The association with skin cream may be a matter of reverse causation, in a sense that people start using a skin cream once they observe their skin problems. The inverse association with years of working experience may point to a healthy worker survivor effect. Frequency of changing gloves and wearing knee protection are also inversely associated, but associations attenuated after adjustment. Only two earlier studies investigated determinants of epoxy exposure[6] and epoxy allergy[1,7] in a small number of subjects. Fillenham *et al*. reported results of an observational study in 21 Swedish workers from eight companies, and found uncured epoxy resin on gloves, tools and work areas.[6] They also observed that the gloves used were often inadequate for handling epoxies. In a cross-sectional study in 22 workers from one company in Taipei, Chu *et al*. showed that the development of allergy depends on various determinants such as hygienic behaviour.[7] Workers who washed their hands after using epoxy products seemed to have a lower likelihood of developing epoxy allergy than those who did not wash their hands. In our study, the differences in hand hygiene were small: 43% (n=77) of the cases and 46% (n=70) of the controls always wash their hands directly after working with epoxy products. The association between poor hand hygiene and epoxy allergy was positive, but not significant.

As a part of the control group was recruited at instruction sessions, we were unable to assess the effect of instruction in our study. However, in the group that was recruited directly at companies, we found a strong negative association with both oral and written safety and hygiene instruction (results not shown).

Apart from the simple fact that measures tend to be more successful when people know why and how to apply them, this observation may emphasise the importance of instruction on safe working with epoxies.

The control group has worked more years with epoxies, but the case group was exposed more hours per week, and the cumulative exposure time of the case group is over twice of that of the control group: cases 150, controls 60 hours*year/week. The case group also used more product per week. Thus, epoxy allergy is associated with exposure duration per week, but negatively associated with years of exposure. The strong association between epoxy allergy and unusually high exposure also points to the importance of exposure intensity.

One out of every five epoxy workers develops an allergy against epoxies[3,4] and skin symptoms among the cases upon epoxy exposure are severe. An important advantage of our study is that the cases were very well defined. All cases were tested positively on epoxy allergy by means of a patch test. As expected, prevalence of hand dermatitis among the cases was high: 88.8% had possible hand dermatitis and 55.9% had hand dermatitis according to the symptom based questionnaire. On the photo-questionnaire, 69.3% of the cases reported skin symptoms in the highest of three categories of severity. Based on the symptom-based questionnaire, 9.2% of the controls had possibly hand dermatitis, and 2.2% had hand dermatitis. The prevalence of dermatitis among the controls is remarkably low. In *Chapter 3* of this thesis, we report a self-reported prevalence of contact dermatitis of 46.9% among construction workers. Glove use to prevent epoxy allergy may also help to prevent other skin symptoms. Furthermore, once an epoxy allergy is developed, people tend to leave the job, which may also mask the presence of other skin symptoms. Bangsgaard *et al*. studied the fate of workers who developed an epoxy allergy and found that over 80% of them avoided further exposure (change of work place/tasks, end of job, sick leave). [18] On the other hand, Mascaro *et al*. found that, in the general working population in Spain, 18% of persons with severe hand dermatitis reach the state of permanent disability.[19] Questions in the study in *Chapter 3* were slightly different from those in this chapter, which makes comparison of the results somewhat uncertain. Due to the low prevalence of dermatitis in the control group we decided not to test the control group for epoxy allergy. In the study by Chu *et al*., none of the asymptomatic workers were reactive to the epoxy components in the patch test.[7] Our results did not change when symptomatic controls were excluded, so we believe that it is unlikely for undiagnosed controls to have influenced the current findings. The time lag between first exposure and the development of symptoms is remarkably long. Bangsgaard *et al*. found that among epoxy workers, 62.4% develop a

skin allergy within one year.[18] The explanation for this is that the occupational insurance starts after the vocational training and the probationary period. People who develop an allergy within this time are not registered in the files of BGBAU. As a consequence, people who are most susceptible to sensitization are missed and the number of sensitized people is underestimated.

Potential risk factors were assessed by a self-completed questionnaire. Retrospective data collection by questionnaire has potential limitations, like recall bias, misclassification in answers, and socially desirable answers. To be sure that the questions are clear to the target group, we mainly used questions from validated questionnaires.[8,9] New questions were validated in the field study, described in *Chapter 3*. The response for the control group was relatively low (29%), compared to 50% for the case group. We cannot exclude some degree of selection bias due to overrepresentation of controls with safer working practices, although companies were not specifically selected for good working practices. Therefore, we believe that selection bias is not a major problem in this study. Also, cases and controls showed a similar age distribution, and had working experience in the same industry. However, some overestimation of the effect of control measures cannot be entirely excluded. A longitudinal, prospective study would overcome this limitation, as subjects are included before disease onset. Compared to other questionnaire studies in the construction industry, 29% is not a poor response. Hoonakker *et al*. reported responses varying from 8% to 27% for questionnaire studies in the construction industry.[20]

Conclusions

Skin symptoms associated with epoxy allergy are severe. Poor hygienic behaviour and poor personal protection are strong determinants for epoxy allergy. Especially avoiding accidents, wearing chemical resistant gloves and avoiding bare arms and legs appear to prevent or delay development of epoxy allergy.

Acknowledgements

The authors thank mrs. Katrin Schäfer for many phone calls to subjects and Mrs. Yvonne Schäfer for organising the sessions on epoxies. Permission of Dr. Harma Stenveld from the Dutch Centre for Occupational Skin Diseases to use the photo-questionnaire is gratefully acknowledged.

References

1 Anveden Berglind I, Lind ML, Liden C. Epoxy pipe relining - an emerging contact allergy risk for workers. *Contact Dermatitis* 2012; **67**:59-65.
2 Geier J, Krautheim A, Uter W, et al. Occupational contact allergy in the building trade in Germany: influence of preventive measures and changing exposure. *Int Arch Occup Environ Health* 2011; **84**:403-411.
3 van Putten PB, Coenraads PJ, Nater JP. Hand dermatoses and contact allergic reactions in construction workers exposed to epoxy resins. *Contact Dermatitis* 1984; **10**:146-150.
4 Romyhr O, Nyfors A, Leira HL, Smedbold HT. Allergic contact dermatitis caused by epoxy resin systems in industrial painters. *Contact Dermatitis* 2006; **55**:167-172.
5 Ruhl R, Wriedt H. Some economic benefits of REACH. *Ann Occup Hyg* 2006; **50**:541-544.
6 Fillenham G, Liden C, Anveden Berglind I. Skin exposure to epoxy in the pipe relining trade - an observational study. *Contact Dermatitis* 2012; **67**:66-72.
7 Chu CY, Ponten A, Sun CC, Jee SH. Concomitant contact allergy to the resins, reactive diluents and hardener of a bisphenol A/F-based epoxy resin in subway construction workers. *Contact Dermatitis* 2006; **54**:131-139.
8 Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994; **7**:954-960.
9 Smit HA, Coenraads PJ, Lavrijsen AP, Nater JP. Evaluation of a self-administered questionnaire on hand dermatitis. *Contact Dermatitis* 1992; **26**:11-16.
10 Timmerman JG, Zilaout H, Heederik D, et al. Validation of a questionnaire on hand hygiene in the construction industry. *Ann Occup Hyg* 2014; **58**:1046-1056.
11 Jungbauer FH, Piebenga WP, ten Berge EE, et al. NVAB-richtlijn: Preventie Contacteczeem (NVAB guideline: Prevention of Contact Dermatitis). Available at: https://www.nvab-online.nl/sites/default/files/bestanden-webpaginas/Contacteczeem%20RL.pdf (last accessed 7 april 2015).
12 Van der Walle HB, Piebenga WP. In: *Skin and Occupation*(Anonymous) Arnhem: Centre for Skin and Occupation, 2004; 75-76,77.
13 van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res* 2007; **16**:219-242.
14 Eide GE, Gefeller O. Sequential and average attributable fractions as aids in the selection of preventive strategies. *J Clin Epidemiol* 1995; **48**:645-655.
15 Ruckinger S, von Kries R, Toschke AM. An illustration of and programs estimating attributable fractions in large scale surveys considering multiple risk factors. *BMC Med Res Methodol* 2009; **9**:7-2288-9-7.
16 Federatie van Medisch Wetenschappelijke Verenigingen (Federa). The Code of Conduct for the Use of Data in Health Research. Available at: https://www.federa.org/codes-conduct (last accessed 11/1 2016).
17 Kanerva L, Tarvainen K, Pinola A, et al. A single accidental exposure may result in a chemical burn, primary sensitization and allergic contact dermatitis. *Contact Dermatitis* 1994; **31**:229-235.
18 Bangsgaard N, Thyssen JP, Menne T, et al. Contact allergy to epoxy resin: risk occupations and consequences. *Contact Dermatitis* 2012; **67**:73-77.
19 Mascaro JM, Querol I, Lindner L, et al. Costs of patients with occupational severe chronic

hand eczema refractory to topical corticosteroids for employer's mutual insurance companies in Spain. *Value Helath* 2009; **12**:A453-A454.
20 Hoonakker P, Carayon P, Loushine T. Barriers and benefits of quality management in the construction industry: an empirical study. *Total Quality Management* 2010; **21**:953-969.

CHAPTER 7
General discussion

Improving occupational health care for construction workers with contact dermatitis

7

This thesis aimed to investigate the prevalence of contact dermatitis (CD) among Dutch construction workers and its occupational determinants. The eventual goal was to develop, based on these determinants, a triage tool to be used by occupational physicians to discriminate construction workers with a high risk of having CD from workers with a lower risk.

Main findings

In *Chapter 2*, we present a high self-reported prevalence of skin symptoms (25.4%) in 152,200 male construction yard workers who visited a routine medical check-up. Skin symptoms were positively associated with reported nuisance due to occupational exposure to dust (prevalence ratio (PR): 1.59, 95% confidence interval (CI): 1.55–1.63) and chemicals (PR: 1.09, 95% CI: 1.06-1.14). These cross-sectional findings were supported by longitudinal analyses in a study population subset.

Chapter 3 describes the validation of a questionnaire on hand hygiene. Observations of hand contamination, glove use and glove types agreed well with self-reported questionnaire items (Cohen's kappa 0.75, 0.97 and 0.88). Self-reported one-year CD prevalence was 46.9%. Dirty hands (PR 2.30, 95% CI: 1.14–4.65) and difficulty with cleaning the hands (PR: 1.26, 95% CI: 1.05–1.52) at the end of the working day were positively associated with reporting CD.

In C*hapter 4,* dermatological evaluations were performed by an expert team consisting of a dermatologist and an occupational physician specialized in dermatology. CD prevalence in a subset of the study population was high (mild CD: 34.0%, severe CD: 24.3%). In addition, a strong association between diagnosed CD and loss-of-function mutations in the filaggrin (*FLG*) gene was found (odds ratio (OR) mild CD: 5.71, 95% CI: 1.63–20.06; OR severe CD: 8.26, 95% CI: 2.32–29.39). The association between *FLG* loss-of-function mutations and self-reported 'possible CD' was less strong: OR 2.74 (95% CI: 1.27-5.91) whereas self-reported 'CD' was not significantly associated with FLG mutations (OR: 2.47, 95% CI: 0.77-7.90).

Chapter 5 describes the capability of two occupational physicians to detect symptoms of CD. Their diagnoses were compared with the diagnoses of the expert panel. Agreement between occupational physicians and the expert panel was low (Cohens kappa ranging from 0.12 to 0.40) and increased to moderate after training (0.25 to 0.55). CD prevalence in the total study population was comparable to the prevalence in the subset analyzed in *Chapter 4* (mild CD:

38.2%, severe CD: 23.2%). No major specific occupational determinants of CD were found, but weak positive associations were found with washing the hands with solvents (PR: 1.17, 95% CI: 1.03-1.34) and performing job-related tasks at home for more than 4h/week (PR: 1.14, 95% CI: 1.04-1.26).

Chapter 6 describes a case-control study that identified several determinants of skin allergy to epoxy products in a sample of German construction workers. Wearing short sleeves or short trousers during work (OR: 2.38, 95% CI: 1.03–5.52), not always using the correct type of gloves (OR: 2.12, 95% CI: 1.12–4.01) and having had an unusually high level of exposure to epoxy products (OR: 2.13, 95% CI: 1.01-4.51) were associated with epoxy allergy. In addition, increased risk was found with increasing exposure hours per week (OR per ten hours: 1.72, 95% CI: 1.39–2.14).

Prevalence of CD

The prevalence of CD in Dutch construction workers in our study was high, considerably higher than the point prevalence of 7.8% Coenraads *et al.* reported in Dutch construction workers in 1984:[1] we found a doctor-diagnosed point prevalence of 61.4%, see *Chapter 5*. In studies in other countries, the prevalence of CD amongst construction workers ranged from 4% to 13%,[2-4] with a higher prevalence of 67% in cement workers.[5] The prevalence in our study was also high compared to health care workers in The Netherlands, where self-reported one-year prevalence was reported to be between 12%[6] and approximately 30%[7] to 48%.[8] In Dutch manual workers, self-reported point prevalence was around 13%.[9] International studies also reported a significant occurrence of CD in other high risk occupations: workers exposed to metal cutting fluids (incidence of 50% in a group of 24 new machinists after 9 weeks of work,[10] florists (30% self-reported point prevalence),[11] metal workers (27% doctor-diagnosed point prevalence, irritant contact dermatitis; ICD),[12] and hairdressers (22% self-reported one-year prevalence).[13] Altogether, CD appears to be a common condition in high risk occupations, but differences in prevalence between studies are quite difficult to interpret due to variation in study design and methods of diagnosis.

In a number of the above mentioned studies, also the prevalence of less severe skin damage was reported. In one study in Indian construction workers, CD prevalence was 4% but an additional 19.6% was diagnosed with frictional callosities and 10.9% with fissures.[3] In another Indian study in construction workers, 30.9% reported itchy rash.[4] Rough skin and erythema were reported in 31% in the above mentioned study on metal workers[12] and 72.6% of Portuguese

florists reported minor symptoms of hand dermatitis.[11] A possible explanation for the high CD prevalence we found is that our dermatological expert team might have used a more sensitive diagnosis of dermatitis than dermatologists did in other studies. In our study, severe CD was diagnosed in 23.2%, which is comparable to overall CD prevalence in other high-risk occupations. Interestingly, in our study, the self-reported one-year CD prevalence was much lower than the doctor-diagnosed point prevalence, whereas in the study in Dutch nurses, self-reported prevalence was much higher than doctor diagnosed prevalence (48% vs. 18%).[8] It should be noted, however, that the self-administered symptom-based questionnaire was originally developed and validated in that particular population of Dutch nurses and was already reported to be less accurate in an industrial population.[14] In our pilot study on the construction yard, see *Chapter 3*, we found a high self-reported one-year CD prevalence of 47%, which was comparable with the self-reported one-year prevalence in nurses (48%). In our main study, *Chapter 5*, the self-reported one-year prevalence was lower: 32.9%. Contrary to nurses, construction workers under-report dermatitis symptoms and may not consider them to be a problem, a phenomenon which was also seen in the general population.[15] However, our expert panel did classify the symptoms that were not reported by the construction workers themselves as (mild) CD. It is known that minor symptoms of dermatitis can be precursors for more severe dermatitis. In a Danish study, it was shown that subjects with dermatitis symptoms who did not consult a medical doctor generally had long-lasting symptoms.[15] This stresses the need for a good surveillance system in construction workers, in which the occupational physician detects CD symptoms at an early stage before they aggravate.

Occupational health care: how successful are occupational physicians in detecting (early) CD symptoms?

The high prevalence of CD and the vast majority of it being occupational (95%) suggest that the Dutch occupational health care system fails at both preventing and recognizing CD. In *Chapter 5*, we investigated the ability of two occupational physicians with years of experience in the construction industry to recognize (early) CD.

Mild CD was poorly recognized by the two occupational physicians: they made a diagnosis of mild CD in only 8.0% and 16.0% of all subjects, compared to 38.2% by the expert panel. After a dermatological training by the expert panel, the percentage diagnosed with mild CD by the occupational physicians increased to 21.3% and 25.3%, respectively. Before training they diagnosed 32.0% and 36.0% of all subjects with severe CD, compared to 23.2% by

the expert panel. After training, percentages dropped to 18.7% and 34.7%, respectively. Mutual agreement between the two occupational physicians could not be improved by training, but the poor agreement with the expert panel improved for both occupational physicians after training, both for mild CD and severe CD. These results do not only underpin the need for a dermatological training for occupational physicians, but also show the potential effects resulting from training. This is also demonstrated by the increase of the negative and positive predictive values of the occupational physicians' diagnoses compared to the expert panel's diagnosis. It must be noted however, that, although the positive predictive value of the occupational physicians' diagnoses after training was high (84-97%), negative predictive value remained rather low (53-60%). For severe CD, negative predictive values were high (82-85%) but positive predictive values were lower (42-79%).

How can detection of (early) CD symptoms by occupational physicians be improved?

Based on the comparison of the diagnoses of the occupational physicians and the expert panel, we conclude that a dermatological training can help the occupational physician to recognize and detect (early) CD. Nonetheless, a triage tool could still help them to detect workers with high risk of having CD. Unfortunately, the high CD prevalence, the lack of clear associations with potential occupational determinants and the large discrepancy between self-reported CD and doctor-diagnosed CD (*Chapter 5*), seriously hamper development of a triage tool. Therefore, we decided not to develop a triage tool as, based on the present study population, more than half of all construction workers would be identified as possibly having CD. Still, self-reported questionnaire-derived symptom data could be helpful to support the occupational physician in discriminating workers with high risk of (early) CD from workers with a lower risk. Theoretically, the full set of items on symptom in our questionnaire could be implemented in the questionnaire construction workers receive and fill-in before visiting their regular check-up. This, however, would require workers to fill in eight questions, and the occupational physician to calculate a score to assess the probability of CD. Alternatively, only the question on fissures could be included: sensitivity, specificity and predictive values for this single question were about as high as for the complete set of questions (*Chapter 5*). Therefore, the question on fissures could be a useful trigger for the occupational physician to physically examine the worker's hands, rather than screening the hands of all construction workers. As discussed earlier, a dermatological training should be given to the occupational physicians in order to correctly diagnose skin conditions of the workers' hands.

The very strong association we found between *FLG* loss-of-function mutations and CD in *Chapter 4* could theoretically be used to improve health care. After genetic testing, susceptible workers could be provided with additional protection, personalized education and supervision by an occupational physician. However, CD is a so-called complex disease, which means that multiple genetic and environmental factors determine its incidence and prevalence. Due to the relatively low frequency of *FLG* loss-of-function mutations, and limited penetrance in individuals with one mutation,[16] the attributable fraction is only 8.5%. In addition, there is an ongoing debate whether it is ethical to perform genetic screening for identifying susceptible individuals, in particular in the context of the work environment.[17-19] Appropriate genetic tests need to have high sensitivity and specificity for the prediction of disease risk to prevent employees from incorrectly being considered susceptible. Moreover, although identification of genetically susceptible employees could give opportunities to protect them from developing contact dermatitis, genetic testing could also give an employer a reason to refuse a job to a susceptible employee. Therefore, genetic screening to detect susceptible workers is not advisable within the near future.

Recommendations for future research

This study showed a high prevalence of CD in Dutch construction workers. Unfortunately, in our construction industry-wide, cross-sectional study, we were not able to identify major occupational determinants, like exposure to cement[20] and epoxy resins,[21] which are well-known risk factors for CD. The questionnaire included questions on the use of many different materials and products. However, probably due to the large variety in jobs and tasks, no particular material or product was significantly associated with CD. We did, however, find some more generic determinants: self-reported dirty hands which are difficult to clean at the end of the working day (*Chapter 3*) and cleaning the hands with solvents (*Chapter 5*). Together with not using gloves and hand cream, these determinants point to sub-optimal hand care. Improving the way construction workers care for the skin of their hands could lower the CD prevalence, and might help to elucidate specific work-related determinants.

A number of challenges remain at this point: first of all, we do not have a clear view on actual hand care, as use of hand cream and gloves only give a broad indication of hand care. Although adjusting for glove use and hand cream use in our analyses did not unveil relations between CD and occupational determinants, there might still be residual confounding by hand care. However, we have no clear view on the relations between hand care, occupational determinants of CD and CD. The rationale behind the way subjects care for their hands might influence their

exposure to occupational determinants and vice versa. For example, we presume that subjects with CD tend to use hand cream more often but they also might use specific products less or adapt their working methods if they have the opportunity to do so.

Closer investigation of occupational determinants can be performed by carrying out a series of smaller studies on specific agents in specific subgroups within the construction industry, like our study in epoxy workers, described in *Chapter 6*. This could provide enough statistical power to identify both known and unknown determinants in those subgroups. This, in turn, could be input for focused prevention and development of a triage tool for use within that job title. However, to develop a construction industry-wide triage tool, knowledge about generic determinants is needed, rather than only in specific subgroups. To gain more insight into the possible occupational determinants of CD, a construction industry-wide longitudinal study could be carried out. Although costly and time consuming, selecting a population of apprentice-construction workers and following them over time would give more certainty about causal relations between possible determinants and CD than a cross-sectional study. Although, as discussed in *Chapter 1*, exposure assessment remains difficult and will probably still rely on self-reported exposures, a longitudinal study design could facilitate identification of particular occupational determinants, like used materials or products. This, in turn, could help to develop a triage tool based on occupational determinants, aiding occupational physicians in discriminating construction workers with a high risk of developing CD from those with a lower risk.

In addition to more research on determinants of CD, it might be interesting to assess how our expert panel performed compared to other dermatologists. This could be done by taking a subgroup of our study population and let them be diagnosed by dermatologists who performed physical examinations in other studies. This way, we can assess whether our expert panel used a more sensitive definition of CD than other experienced dermatologists did.[1-4,8]

Practical recommendations

We recommend that awareness of the risk on CD in the construction industry should be increased, among occupational physicians as well as among employers and employees. Education of occupational physicians, including a dermatological training to improve detection of (early) CD, is recommended. It is known that the treatment of dermatitis, with its dynamic but chronic course, requires a lot of time and extensive education which is not always available in regular health care.[22-24] A Danish study showed that many dermatitis patients are never referred to a dermatologist by

their general practitioner (GP)[15] and also in our study, the occupational physicians reported they almost never referred workers to a dermatologist. Cooperation of GP's and occupational physicians with dermatologists could help making treatment of dermatitis more effective. Interestingly, in a Dutch trial, an integrated care program for hand dermatitis patients was more effective than regular care after six months therapy but not after twelve months.[25]

Employers and employees should realize that the risk of developing CD in the construction industry is high. The importance of personal protective equipment like correct gloves should be promoted, as well as the use of hand cream.[26,27] Long-lasting exposure to irritants may first lead to mild symptoms like redness and scaling but impaired skin barrier function is prone to aggravate the skin problems and fissures may develop. Keeping the skin flexible and hydrated will reduce the chance of developing severe symptoms of CD. Awareness of skin care and hand hygiene may in general, however, be limited among construction workers. Interestingly, we found and inverse association between CD and hand cream use in *Chapters 3* and *5*. This might mean that construction workers start using hand cream only after (noticeable) symptoms have developed. If they can be convinced to use skin cream *before* symptoms develop, and thereby help to prevent development of symptoms, prevalence of CD might drop. One way to achieve this could be the distribution of hand cream to employees who visit the check-up and report symptoms. If their symptoms abate after starting to use hand cream, they might also convince their colleagues to use hand cream. This also might stimulate construction workers to start using hand cream well before symptoms develop. In the ideal situation, as early as during their vocational training, construction workers should become familiar with the risk of skin problems and methods to prevent development of CD.

Conclusions

This thesis shows that the prevalence of CD among Dutch construction workers is high, both self-reported and doctor-diagnosed. The most probable cause of CD among construction workers is cumulative exposures to multiple mildly irritant factors. A strong relation was found between loss-of-function mutations in the filaggrin gene and CD in construction workers, but the attributable fraction was relatively small. Not only workers and employers should be educated on the risk of occupational CD in the construction industry but also occupational physicians as current occupational health care fails to successfully detect (early) CD. Therefore, occupational physicians should develop skills to recognize and diagnose CD at an early stage.

References

1 Coenraads PJ, Nater JP, Jansen HA, Lantinga H. Prevalence of eczema and other dermatoses of the hands and forearms in construction workers in the Netherlands. *Clin Exp Dermatol* 1984; **9**:149-158.

2 Kuruvila M, Dubey S, Gahalaut P. Pattern of skin diseases among migrant construction workers in Mangalore. *Indian J Dermatol Venereol Leprol* 2006; **72**:129-132.

3 Shah KR, Tiwari RR. Occupational skin problems in construction workers. *Indian J Dermatol* 2010; **55**:348-351.

4 Banerjee M, Kamath R, Tiwari RR, Nair NP. Dermatological and respiratory problems in migrant construction workers of Udupi, Karnataka. *Indian J Occup Environ Med* 2015; **19**:125-128.

5 Wang BJ, Wu JD, Sheu SC, et al. Occupational hand dermatitis among cement workers in Taiwan. *J Formos Med Assoc* 2011; **110**:775-779.

6 van der Meer EW, Boot CR, van der Gulden JW, et al. Hand eczema among healthcare professionals in the Netherlands: prevalence, absenteeism, and presenteeism. *Contact Dermatitis* 2013; **69**:164-171.

7 Visser MJ, Verberk MM, van Dijk FJ, et al. Wet work and hand eczema in apprentice nurses; part I of a prospective cohort study. *Contact Dermatitis* 2014; **70**:44-55.

8 Smit HA, Coenraads PJ, Lavrijsen AP, Nater JP. Evaluation of a self-administered questionnaire on hand dermatitis. *Contact Dermatitis* 1992; **26**:11-16.

9 Smit HA, Burdorf A, Coenraads PJ. Prevalence of hand dermatitis in different occupations. *Int J Epidemiol* 1993; **22**:288-293.

10 Goh CL, Gan SL. The incidence of cutting fluid dermatitis among metalworkers in a metal fabrication factory: a prospective study. *Contact Dermatitis* 1994; **31**:111-115.

11 Pereira F. Hand dermatitis in florists. *Contact Dermatitis* 1996; **34**:144-145.

12 de Boer EM, van Ketel WG, Bruynzeel DP. Dermatoses in metal workers. (I). Irritant contact dermatitis. *Contact Dermatitis* 1989; **20**:212-218.

13 Steengaard SS, Bregnhoj A, Johansen JD. Hand eczema among hairdressing apprentices in Denmark following a nationwide prospective intervention programme: 6-year follow-up. *Contact Dermatitis* 2016; **75**:32-40.

14 Vermeulen R, Kromhout H, Bruynzeel DP, de Boer EM. Ascertainment of hand dermatitis using a symptom-based questionnaire; applicability in an industrial population. *Contact Dermatitis* 2000; **42**:202-206.

15 Hald M, Berg ND, Elberling J, Johansen JD. Medical consultations in relation to severity of hand eczema in the general population. *Br J Dermatol* 2008; **158**:773-777.

16 Brown SJ, Relton CL, Liao H, et al. Filaggrin haploinsufficiency is highly penetrant and is associated with increased severity of eczema: further delineation of the skin phenotype in a prospective epidemiological study of 792 school children. *Br J Dermatol* 2009; **161**:884-889.

17 Landeck L, Visser M, Kezic S, John SM. Genotype-phenotype associations in filaggrin loss-of-function mutation carriers. *Contact Dermatitis* 2013; **68**:149-155.

18 Schulte P, Howard J. Genetic susceptibility and the setting of occupational health standards. *Annu Rev Public Health* 2011; **32**:149-159.

19 Visser MJ, Rhebergen MD, Kezic S, et al. Ethical issues of genetic susceptibility testing for occupational diseases: opinions of trainees in a high-risk job. *Int Arch Occup Environ*

Health 2013; **86**:827-836.
20 Winder C, Carmody M. The dermal toxicity of cement. *Toxicol Ind Health* 2002; **18**:321-331.
21 Geraut C, Tripodi D, Brunet-Courtois B, et al. Occupational dermatitis to epoxydic and phenolic resins. *Eur J Dermatol* 2009; **19**:205-213.
22 Courtenay M, Carey N. Nurse-led care in dermatology: a review of the literature. *Br J Dermatol* 2006; **154**:1-6.
23 Weisshaar E, Radulescu M, Soder S, et al. Secondary individual prevention of occupational skin diseases in health care workers, cleaners and kitchen employees: aims, experiences and descriptive results. *Int Arch Occup Environ Health* 2007; **80**:477-484.
24 van Gils RF, van der Valk PG, Bruynzeel D, et al. Integrated, multidisciplinary care for hand eczema: design of a randomized controlled trial and cost-effectiveness study. *BMC Public Health* 2009; **9**:438-2458-9-438.
25 van Gils RF, Bosmans JE, Boot CR, et al. Economic evaluation of an integrated care programme for patients with hand dermatitis. *Contact Dermatitis* 2013; **69**:144-152.
26 Winker R, Salameh B, Stolkovich S, et al. Effectiveness of skin protection creams in the prevention of occupational dermatitis: results of a randomized, controlled trial. *Int Arch Occup Environ Health* 2009; **82**:653-662.
27 Mostosi C, Simonart T. Effectiveness of Barrier Creams against Irritant Contact Dermatitis. *Dermatology* 2016; **232**:353-362.

SUPPLEMENTS

S

Supplement 1 – Questionnaire used in *Chapter 3*.

QUESTIONNAIRE

Gender

1- What is your gender?

□ Male □ Female

Birth date

2- What is your birth date? ……-……-……

Job title

3- What is your job title? ……

Symptoms

4- Did you have one of the following symptoms on your hands of fingers in the past 12 months (Please select all answers that apply, several answers are possible)

□ Red or swollen hands or fingers
□ Scaled hands or fingers
□ Itchy hands or fingers
□ Fissured hands or fingers
□ Vesicles in hands or fingers
□ Red bumps on hands or fingers
□ None of the above symptoms (-> go to question **7**)

Occurrence of Symptoms

5- Did one or more of these symptoms last for more than three weeks?

□ Yes □ No

Recurrence of Symptoms

6- Did one or more of these symptoms occur more than once the past 12 months?

□ Yes □ No

Dirty hands

7- How dirty are your hands at the end of a working day?

□ Not dirty (for example because you carry good protection)
□ A bit dirty
□ Very dirty (more than half of your skin surface is dirty)

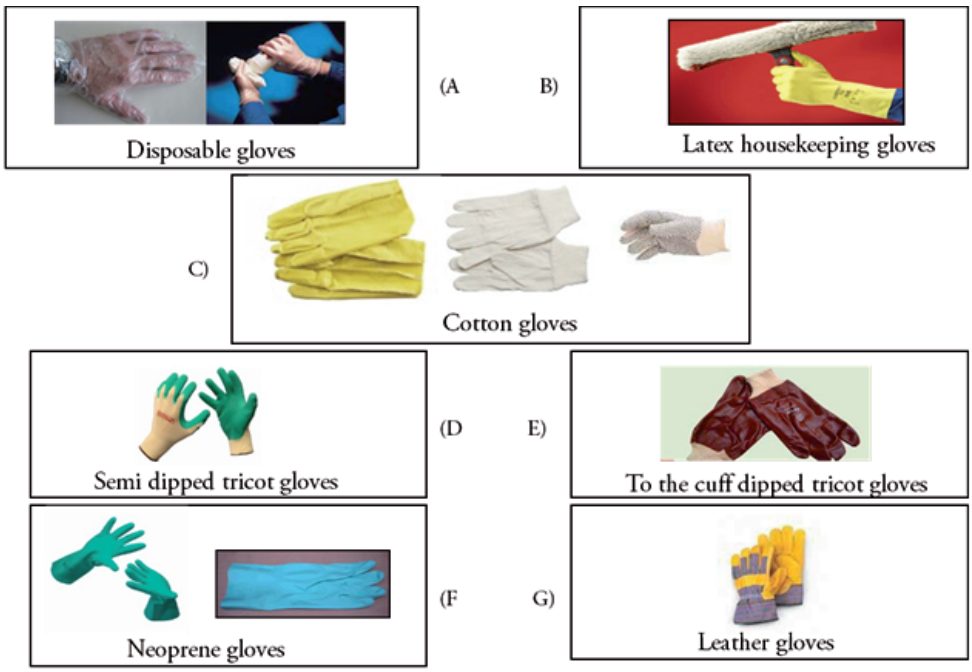
Protective glove use

8- How often do you wear gloves while working?

□ (Almost) always □ Mostly
□ Sometimes □ (Almost) never

Glove types

9- If you use hand gloves during the work, what type of gloves do you usually use? (Please select all that apply, there are several answers possible)



Difficulty of hand cleaning

10- If your hands are dirty, how difficult is it to clean them?

- □ Easy
- □ Not easy, but not difficult
- □ Difficult

Hand washing frequency

11- How often do you wash your hands during a working day?

□ Less than 5 times □ Five to ten times □ More than 10 times

Hand washing detergents

12- How do you mostly wash your hands?
(Please select all that apply, there are several answers possible)

- □ With water only
- □ With water and soap (without abrasive)
- □ With water and soap with abrasive
- □ With a solvent (white spirit, thinner etc.)
- □ With a special hand cleaner
- □ With a clean rag
- □ Else, namely ……

Waterproof gloves

13- Do you wear waterproof gloves during your work often longer than a total of two hours?

□ Yes □ No

Glove changing

14- How often do you use clean gloves?

□ Not at a fixed time, but if they are dirty / coarse □ Weekly
□ Two times a week □ Daily □ Several times a day

Hand cream use

15- Do you use hand cream?

□ No
□ Yes, once a week
□ Yes, every other day
□ Yes, every day
□ Yes, several times a day

Reasons for wearing gloves

16- What are the main reasons why you are wearing gloves?

□ I had information about it in the past
□ That is an occupational safety standard
□ That is a habit
□ Because in the past I've had skin problems
□ Because at the moment I have skin problems
□ Because I do not want to take risks
□ Because the materials I work with are dirty/coarse
□ Because otherwise I get cold hands

Supplement 2 - Frequencies of questionnaire items not validated in *Chapter 3*.

Questionnaire item	**N**	**%**
Difficulties with hand cleaning		
If your hands are dirty, how difficult is it to get them clean?		
- Easy	130	73.5
- Not easy, but not difficult	36	20.3
- Difficult	11	6.2
Hand washing frequency		
How often do you wash your hands during a working day?		
- Less than 5 times	127	71.8
- 5 to 10 times	48	27.1
- More than 10 times	2	1.1
Hand washing detergents		
How do you mostly wash your hands?		
(Please select all that apply, there are several answers possible)		
- With water only	18	10.2

- With water and soap (without abrasive)	40	22.6
- With water and soap with abrasive	125	70.1
- With a solvent (terpentine, thinner etc.)	3	1.7
- With a special hand cleaner	3	1.7
- With a cleaning rag	1	0.6
- Else, namely…	0	0.0

Waterproof gloves

Do you wear waterproof gloves during your work often longer than a total of two hours?

- Yes	27	15.3
- No	150	84.8

Glove changing

How often do you use clean gloves?

- Not at a fixed time, but if they are dirty /coarse	138	87.9
- Weekly	14	14.9
- Two times a week	3	1.9
- Daily	2	1.3
- Several times a day	0	0.0

Hand cream use

Do you use hand cream?

- No	88	49.7
- Yes, once a week	18	10.2
- Yes, every other day	10	5.7
- Yes, every day	43	24.3
- Yes, several times a day	18	10.2

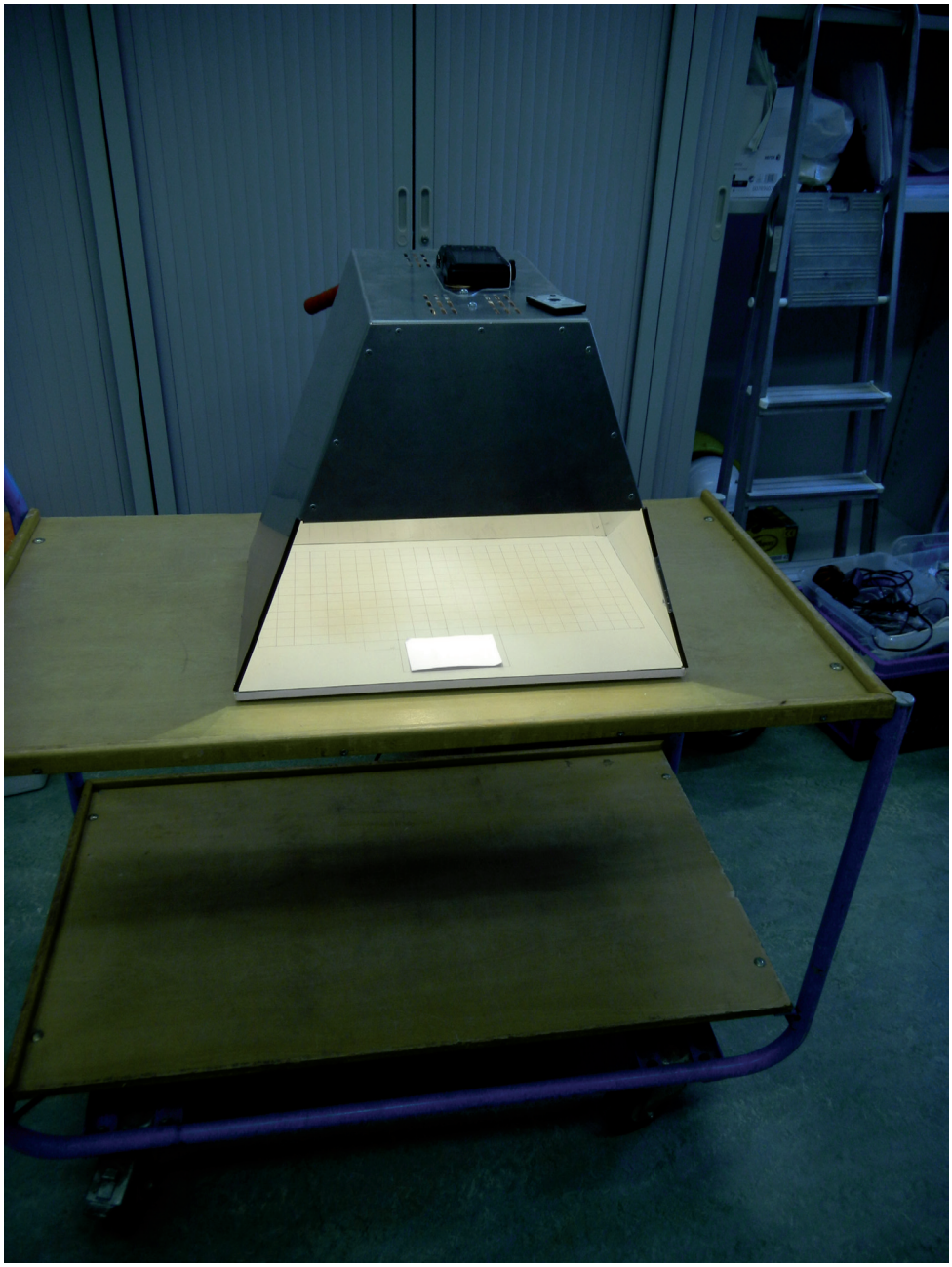
Reasons for wearing gloves

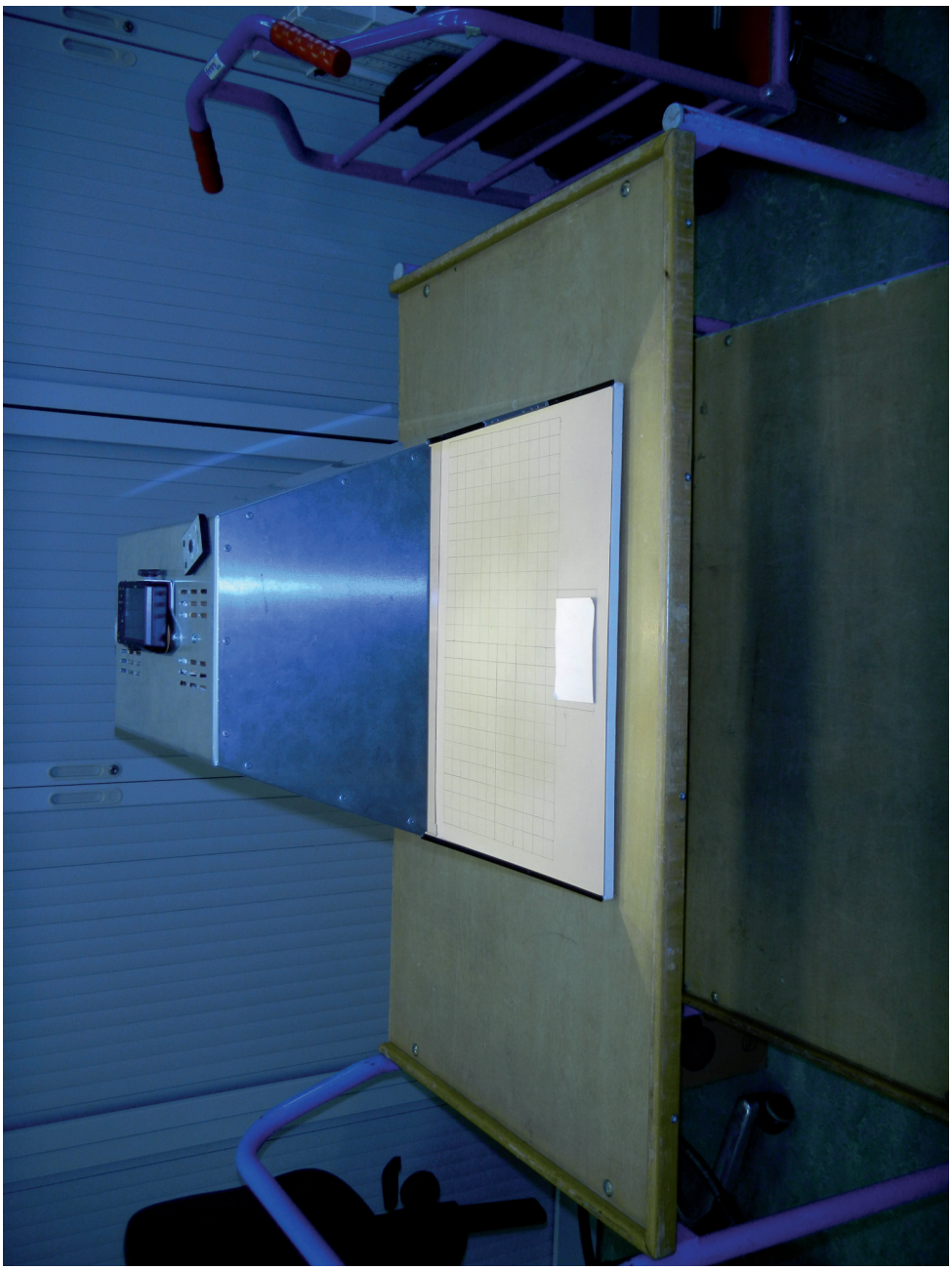
(several answers possible)

What are the main reasons why you are wearing gloves?

- I had information about it in the past	2	1.1
- That is an occupational safety standard	18	10.2
- That is a habit	17	9.6
- Because in the past I have had skin problems	3	1.7
- Because at the moment I have skin problems	2	1.1
- Because I do not want to take risks	90	50.9
- Because the materials I work with are dirty/coarse	127	71.8
- Because otherwise I get cold hands	61	34.5

Supplement 3 - The lighting chamber.





Supplement 4 – Photographic examples of symptoms of contact dermatitis in our study population.

Erythema (redness)

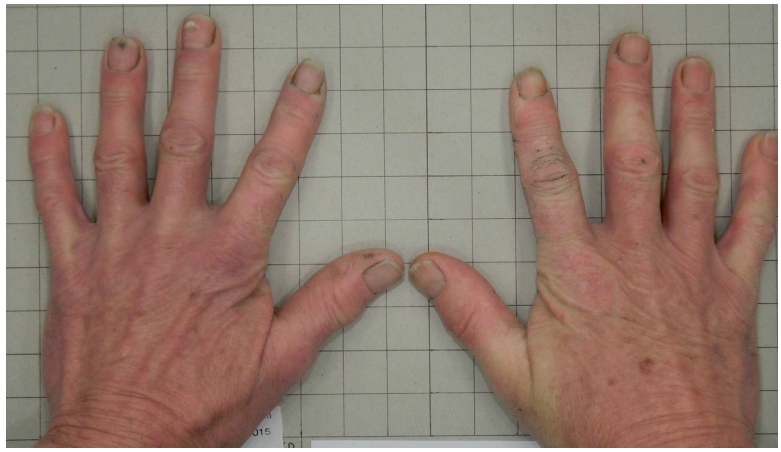


Figure 1a - Example of redness (erythema), also visible are: scaling (squamae) and fissures.

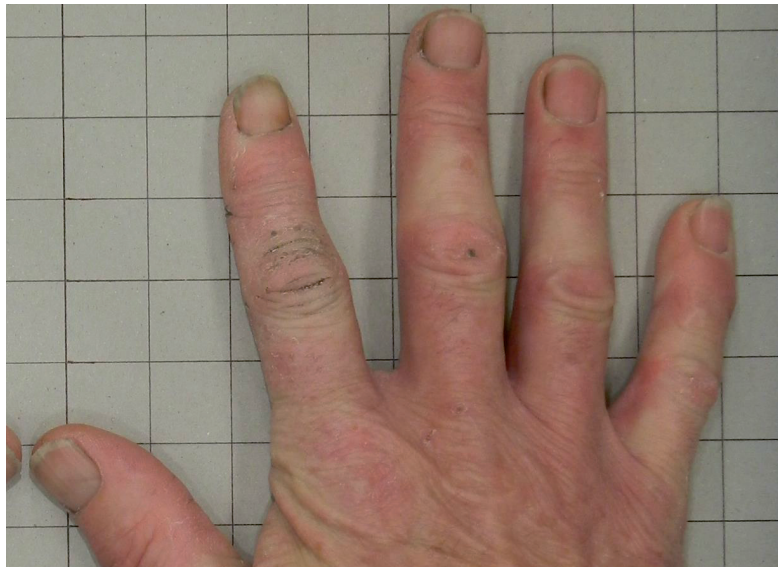


Figure 1b - High resolution example of redness (erythema), also visible are: scaling (squamae) and fissures.

Erythema (redness)

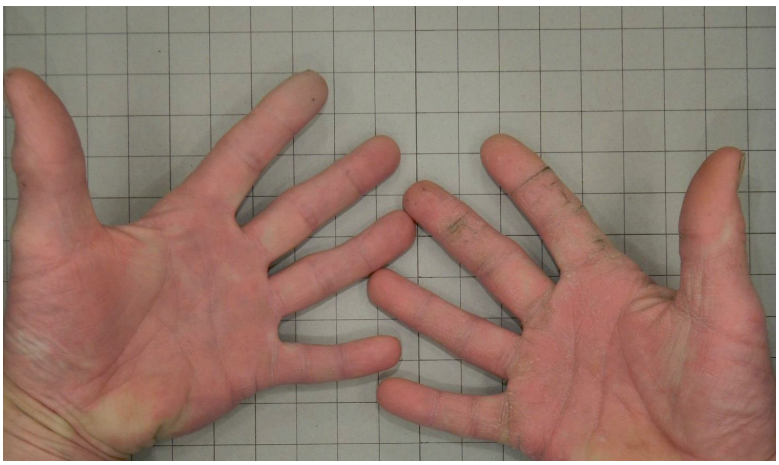


Figure 2 - Example of redness (erythema), also visible are: scaling (squamae) and fissures.

Papulae (bumps)

Figure 3a - Example of bumps, also visible are: redness (erythema), scaling (squamae) and fissures.

Figure 3b - High resolution example of bumps, also visible are: redness (erythema), scaling (squamae) and fissures.

Squamae (scalyness)

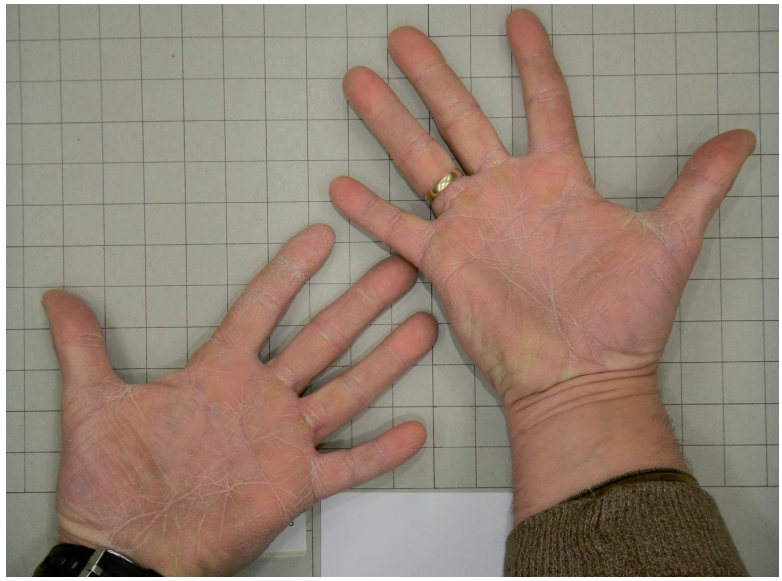


Figure 4a - Example of scaling (squamae), also visible are: redness (erythema).

Figure 4b - High resolution example of scaling (squamae).

Squamae (Scalyness)

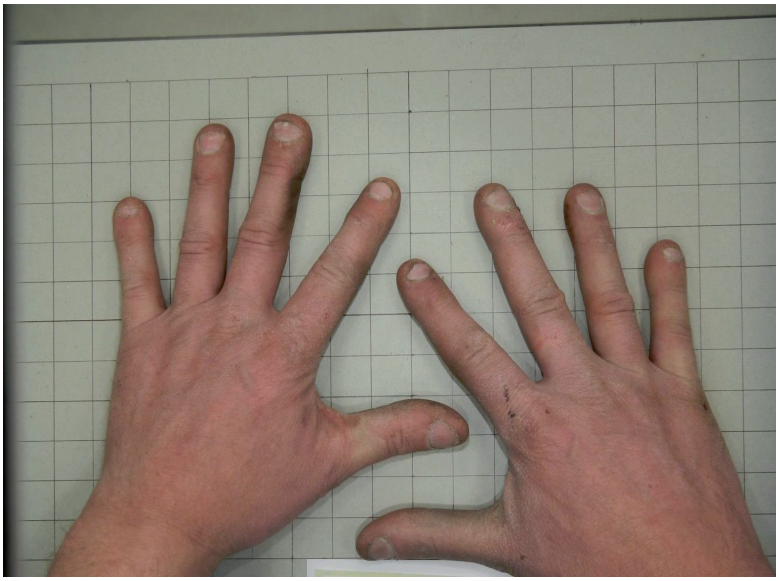


Figure 5a - Example of scaling (squamae), also visible is: redness (erythema).

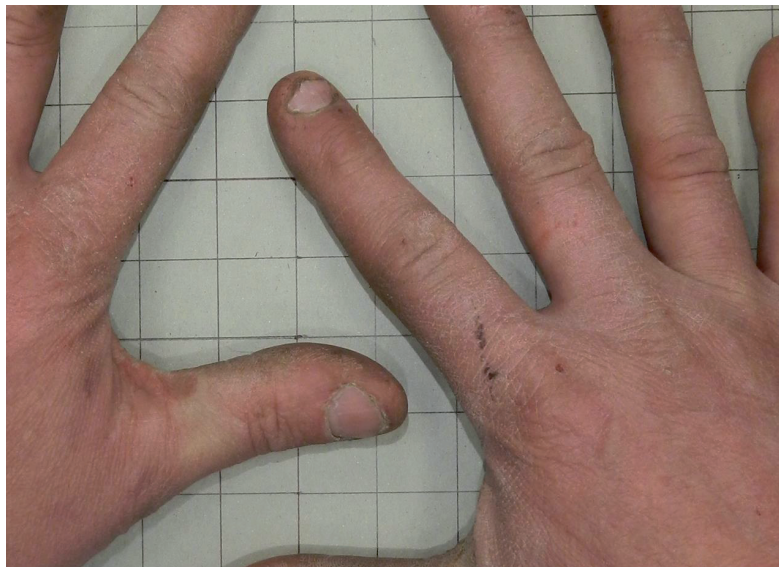


Figure 5b - High resolution example of scaling (squamae), also visible is: redness (erythema).

Crusts

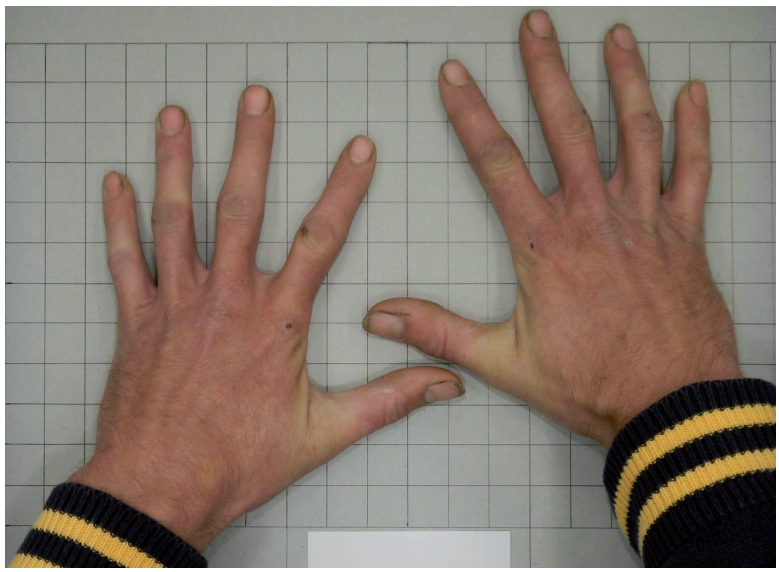


Figure 6a - Example of crusts, also visible is: redness (erythema), scaling (squamae) and fissures.

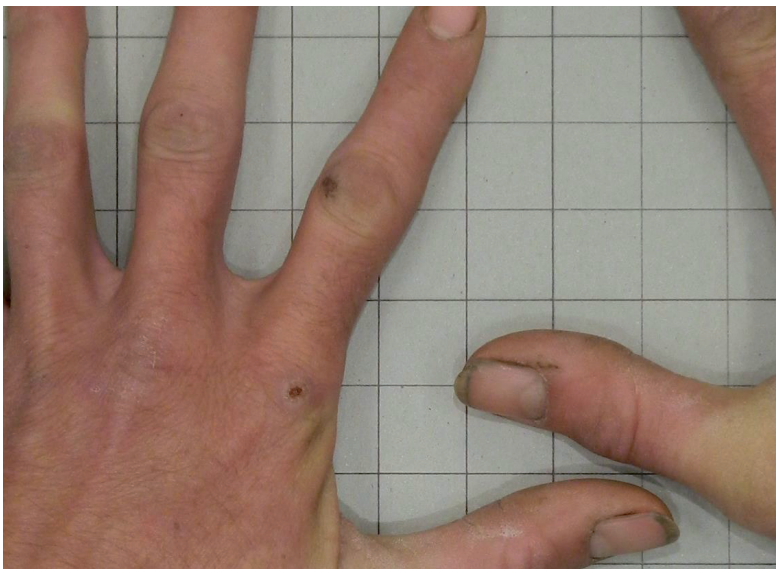


Figure 6b - High resolution example of crusts, also visible are: redness (erythema), scaling (squamae) and fissures.

Pigment

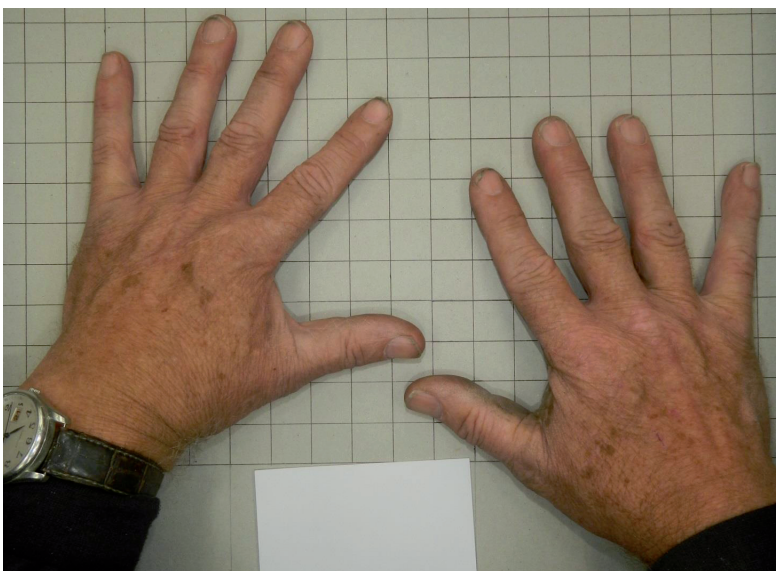


Figure 7a - Example of pigment changes, also visible is: scaling (squamae).

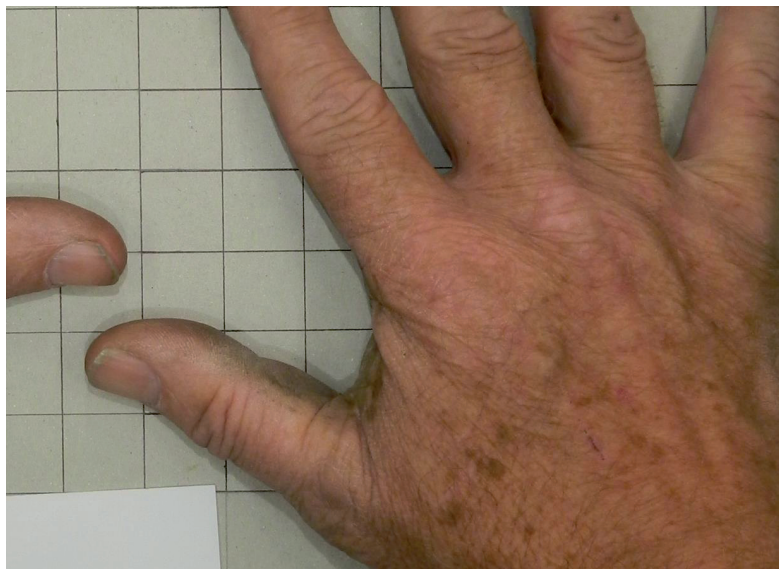


Figure 7b - High resolution example of pigment changes, also visible is: scaling (squamae).

Atrophy

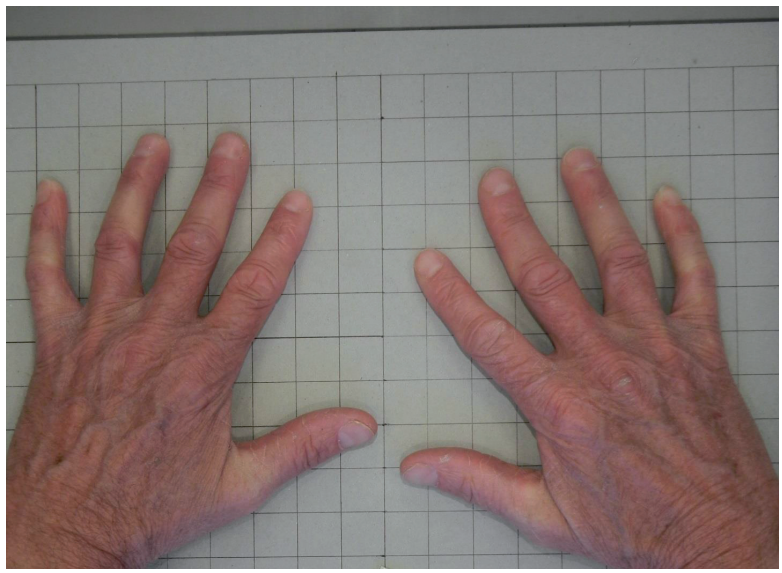


Figure 8a - Example of atrophy, also visible are: redness (erythema) and scaling (squamae).

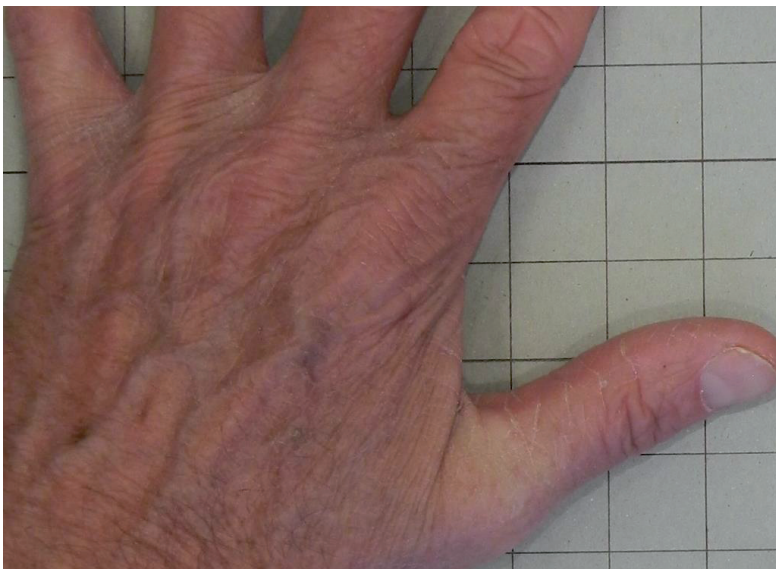


Figure 8b - High resolution example of atrophy, also visible are: redness (erythema) and scaling (squamae).

Fissures

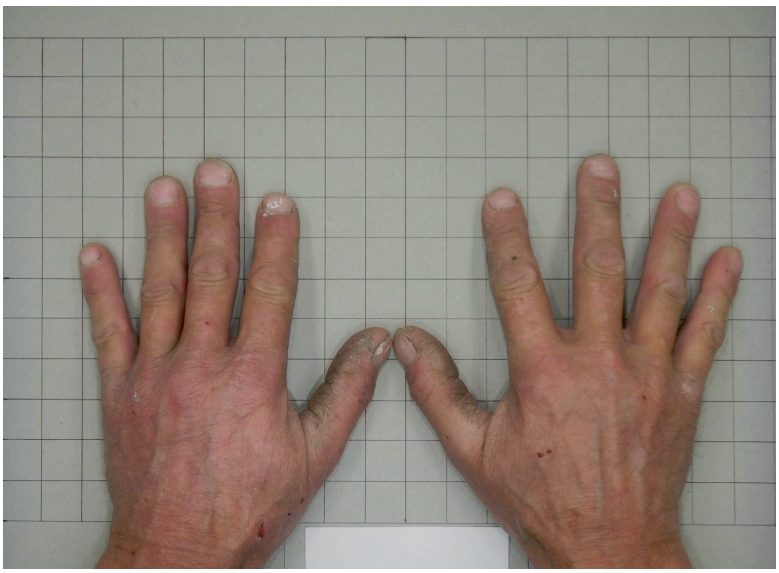


Figure 9a - Example of fissures, also visible are: redness (erythema), scaling (squamae) and crusts.

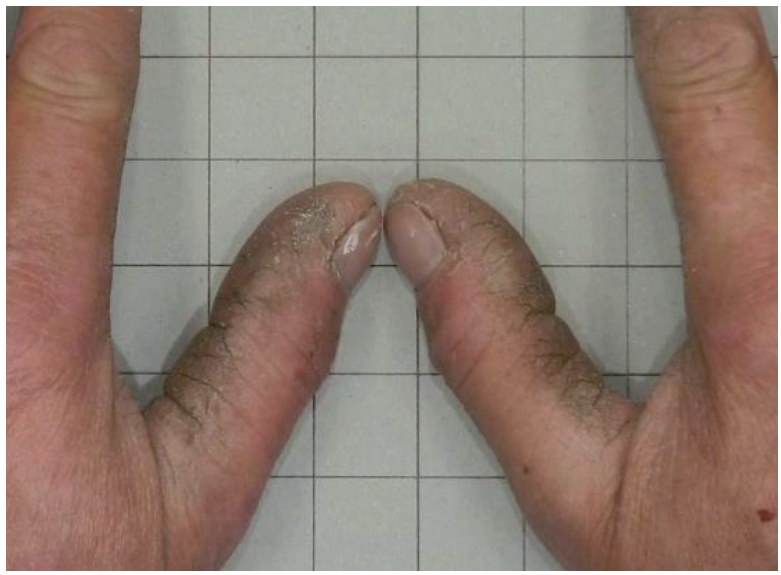


Figure 9b - High resolution example fissures, also visible are: redness (erythema), scaling (squamae) and crusts.

Fissures

Figure 10a - Example of fissures, also visible are: redness (erythema) and scaling (squamae).

Figure 10b - High resolution example of fissures, also visible are: redness (erythema) and scaling (squamae).

Ulcers

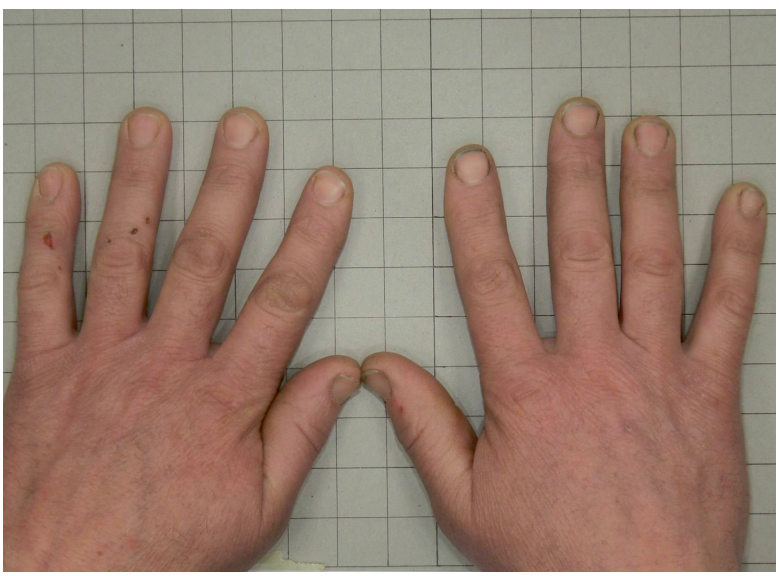


Figure 11a - Example of ulceration, also visible are: redness (erythema), scaling (squamae) and crusts (traumatic). NOTE: this is the only example of ulceration in our study population.

Figure 11b - High resolution example of ulcering, also visible is: redness (erythema), scaling (squamae) and crusts (traumatic).

Vesicles and bullae were not seen in our study population.

Supplement 5 – Questionnaire items relevant for *Chapter 4* and *Chapter 5*. Questions used for assessing atopic predisposition are marked with an asterisk (*).

GENERAL QUESTIONS

0.1 What is your gender?

(1) □ male
(2) □ female

0.2 What is your date of birth?

__ __ - __ __ __ - __ __ __ __
day month year

0.3 What is your main jobtitle?

.....

QUESTIONS ON YOUR HEALTH - SKIN

*** 1.1** Have you **ever** had an itchy rash?

(1) □ yes (2) □ no

If yes, ...

*** 1.1.1** Has this rash begun before you were 2 years of age?

(1) □ yes (2) □ no

*** 1.2** Have you ever had eczema in the folds of the elbows, knees, ankles or around the neck?

(1) □ yes (2) □ no (***if no****, continue with question 1.3*)

Zo ja, ...

*** 1.2.1** Do you currently have eczema in skin folds or elsewhere on your body?

(1) □ yes (2) □ no

*** 1.3** Did you suffer from a dry skin in the **last 12 months?**

(1) □ yes (2) □ no

1.4/1.5 Did you have one of the following symptoms on your hands or fingers **in the past 12 months**? (*multiple answers possible*)

(1) □ red and swollen hands or fingers
(2) □ scaly hands or fingers
(3) □ itchy hands or fingers
(4) □ hands or fingers with fissures

(5) □ vesicles on the hands or between the fingers
(6) □ red bumps on hands or fingers
(7) □ none of the above mentioned symptoms (*continue to question 1.13*)

If you selected one ore more of the above mentioned symptoms,...

1.6 Did one or more of these symptoms last for more than three weeks?

(1) □ yes (2) □ no

1.7 Did one or more of these symptoms occur more than once the past 12 months?

(1) □ ja (2) □ nee

1.8 Do the symptoms decrease during free days or sickness leave or increase when working?

(1) □ yes (2) □ no

1.9 Do you think your current or earlier symptoms are related to your work?

(1) □ yes (2) □ no (***if no***, *continue with question 1.10)*

If yes, ...

1.9.1 What do you think is the cause of your symptoms?

(1) .....

1.10 Do you have colleagues with comparable symptoms?

(1) □ yes (2) □ no

1.11 Are your symptoms known to your occupational physician?

(1) □ yes (2) □ no

*** 1.12** Are you currently being treated for skin or airway symptoms?

(1) □ yes (2) □ no (***if no***, *continue to question 1.13)*

If yes, ...

*** 1.12.1** Which medicines do you take for this?

(1) .....

1.13 Did any of your (grand)parents and/or siblings suffer from eczema?

(1) □ yes (2) □ no

QUESTIONS ON YOUR HEALTH – RESPIRATORY TRACT

3.1 Have you had whistling in your chest at any time **in the last 12 months**?

(1) □ yes (2) □ no

3.2 Have you been woken by an attack of shortness of breath at any time **in the last 12 months**?

(1) □ yes (2) □ no

3.3 Have you **ever** had asthma?

(1) □ yes (2) □ no (***if no****, continue with question 3.4*)

If yes, ...

3.3.1 Was your asthma confirmed by a doctor?

(1) □ yes (2) □ no (***if no****, continue with question 3.3.2*)

If yes, ...

3.3.1.1 In which year was your asthma confirmed?

|__|__|__|__| (year)

3.3.2 Have you had an attack of asthma **in the last 12 months**?

(1) □ yes (2) □ no

3.3.3 Are you currently taking any medicines for asthma?

(1) □ yes (2) □ no

3.4 Do you have any form of nasal allergy, including 'hay fever'?

(1) □ yes (2) □ no

*** 3.5** Are you hypersensitive ("allergic") to certain substances?

(1) □ yes (2) □ no (*if no, continue to question 4.1*)

If yes, ...

*** 3.5.1** Which substances are you hypersensitive to?
(*you can fill in more than one substance*)

(1) .....
(2) .....
(3) .....

QUESTIONS ON YOUR WORK – GENERAL

6.6 What are your main hobbies?
(*You can give more than one answer.*)

(1) .....
(2) .....
(3) .....

Supplement 6 - Prevalences of the different skin changes and their associations with *FLG* status.

	***FLG* variants (n=32)**		***FLG* wildtype (n=474)**			
	N	%	N	%	OR	95% CI
Doctor-diagnosed						
Atrophy	2	6.3	2	0.4	**15.73**	2.14-115.61
Scaling skin	29	90.6	281	59.3	**6.64**	1.99-22.10
Bumps	2	6.3	5	1.1	**6.26**	1.17-33.60
Redness	29	90.6	309	65.2	**5.16**	1.55-17.20
Fissures	14	43.8	109	23.0	**2.61**	1.26-5.41
Crusts	2	6.3	15	3.2	2.04	0.45-9.34
Pigment	1	3.1	19	4.0	0.77	0.10-5.96
Ulcer	-	-	1	0.2	-	-
Vesicles	-	-	-	-	-	-
Bullae	-	-	-	-	-	-
Self-reported						
Fissures	18	56.3	143	30.2	**2.98**	1.44-6.15
Itchy skin	9	28.1	61	12.9	**2.65**	1.17-5.99
Scaly skin	5	15.6	51	10.8	1.54	0.57-4.17
Swellings	1	3.1	17	3.6	0.87	0.11-6.73
Vesicles	-	-	20	4.2	-	-
Red skin	-	-	21	4.4	-	-

Supplement 7 - Results of sensitivity analyses with mild CD and severe CD as health endpoint.

			Mild + severe CD		Mild CD		Severe CD	
	N	%	PR	95% CI	PR	95% CI	PR	95% CI
General variables								
Age per 10y increase	-	-	**1.04**	**1.01-1.09**	1.00	0.96-1.05	**1.16**	**1.05-1.28**
Recruited at company	426	56.7	**1.25**	**1.09-1.43**	**1.66**	**1.39-1.97**	1.04	0.79-1.37
Recruited during “eczema season”	510	67.9	1.01	0.87-1.16	1.02	0.85-1.21	1.10	0.84-1.45
Family history of eczema	171	23.3	1.01	0.91-1.12	1.00	0.88-1.14	1.01	0.80-1.29
Uses hand cream	315	42.1	**1.21**	**1.10-1.34**	**1.16**	**1.05-1.29**	**1.63**	**1.30-2.04**
General occupational variables								
Job title:								
Painter	100	13.3	(reference)		(reference)		(reference)	
Carpenter	340	45.3	**1.92**	**1.45-2.54**	**2.17**	**1.58-2.99**	**3.42**	**1.74-6.70**
Bricklayer	68	9.1	**2.05**	**1.50-2.81**	**2.50**	**1.78-3.53**	**3.02**	**1.43-6.37**
Other	211	28.1	**1.93**	**1.45-2.58**	**2.18**	**1.58-3.02**	**3.53**	**1.79-6.99**
Had information on CD in the past	78	10.4	0.96	0.83-1.11	0.92	0.76-1.11	1.01	0.73-1.38
Changed working methods after receiving information on CD	56	7.5	1.00	0.83-1.19	0.94	0.75-1.19	1.14	0.78-1.68
Uses gloves	349	46.5	0.92	0.83-1.01	0.80	0.62-1.04	0.82	0.65-1.03
Does not change gloves at regular moments	570	79.5	1.10	0.97-1.25	1.28	0.91-1.78	1.02	0.78-1.35
Uses waterproof gloves	74	9.9	1.03	0.87-1.22	0.99	0.79-1.25	1.14	0.81-1.60
Reports very dirty hands after work	113	15.1	1.07	0.96-1.20	1.03	0.94-1.13	1.37	0.98-1.90
Reports cleaning hands after work not easy	305	40.8	**1.13**	**1.04-1.24**	1.26	0.96-1.64	**1.84**	**1.31-2.60**
Washes hands more than five times/day	197	26.3	0.96	0.87-1.08	0.91	0.79-1.04	1.01	0.80-1.27
Washes hands with solvents	46	6.2	**1.17**	**1.03-1.34**	1.60	0.95-2.72	0.90	0.35-2.30
Washes hands using abrasive soap	221	29.6	0.98	0.88-1.09	0.97	0.85-1.10	0.94	0.72-1.21
Works more than 4h/week at home performing job-related tasks	351	47.0	**1.14**	**1.04-1.26**	1.11	1.00-1.24	**1.42**	**1.12-1.80**

PR: Prevalence Ratio, 95% CI: 95% Confidence Interval
All PR are adjusted for age, method of recruitment, eczema season, hand cream use, job title and performing job-related task at home for more than four hours a week.

Supplement 8 - Results of sensitivity analyses: determinants of CD in the Dutch construction industry per jobtitle.

	Carpenters		Bricklayers		Painters		Other job titles	
	PR	95% CI	PR	95% CI	PR	95% CI	PR	95% CI
General variables								
Age per 10y increase	1.04	0.98-1.10	1.02	0.90-1.16	**1.34**	**1.01-1.79**	1.04	0.93-1.17
Recruited at company	1.21	0.99-1.49	1.16	0.90-1.50	1.57	0.71-3.47	1.38	0.95-2.01
Recruited during "eczema season"	0.93	0.75-1.16	1.12	0.86-1.46	1.35	0.72-2.52	1.03	0.68-1.56
Uses hand cream	**1.22**	**1.06-1.40**	1.07	0.77-1.49	**1.92**	**1.09-3.37**	**1.34**	**1.08-1.66**
General occupational variables								
Washes hands with solvents	1.19	1.01-1.40	1.16	1.16-1.16	**1.27**	**0.60-2.68**		*n.e.*
Works more than 4h/ week at home performing job-related tasks	**1.18**	**1.02-1.37**	0.94	0.74-1.20	1.13	0.64-1.99	**1.26**	**1.02-1.56**
Handled products and materials at work								
Works with stones or blocks	1.12	0.88-1.43	0.95	0.52-1.75	1.31	0.75-2.29	1.03	0.88-1.21
Works with cement	0.93	0.73-1.18		*n.e.*	1.46	0.88-2.43	1.02	0.84-1.24
Works with anhydrite or gypsum	1.03	0.85-1.24	0.99	0.71-1.39	0.89	0.50-1.57	1.05	0.89-1.23
Works with releasing agent	1.11	0.97-1.27	0.96	0.73-1.27	0.58	0.17-1.95	1.03	0.81-1.30
Works with wood		*n.e.*	1.05	0.68-1.62	1.24	0.60-2.55	0.95	0.77-1.18
Works with board		*n.e.*	1.03	0.72-1.49	1.23	0.72-2.08	0.98	0.77-1.24
Works with insulation materials	1.00	0.59-1.69	0.99	0.59-1.67	1.12	0.58-2.15	0.97	0.77-1.21
Works with paints	1.13	0.81-1.58	0.99	0.70-1.41		*n.e.*	0.93	0.81-1.06
Works with fillings	0.97	0.81-1.17	0.96	0.66-1.40		*n.e.*	0.96	0.81-1.13
Works with caulk	0.70	0.45-1.07	1.00	0.71-1.40		*n.e.*	0.98	0.77-1.25
Works with cleansers	0.97	0.77-1.22	1.00	0.73-1.37	2.01	0.48-8.50	0.96	0.78-1.20
Works with glues	0.97	0.78-1.20	1.01	0.64-1.61	1.22	0.73-2.02	0.96	0.81-1.15
Works with roofing materials	1.06	0.92-1.23	0.98	0.67-1.42	1.04	0.21-5.07	0.97	0.76-1.23

Works with bituminous road materials	1.02	0.86-1.21	0.97	0.71-1.32		*n.e.*	0.81	0.57-1.14
Is frequently exposed to rubber during work	1.03	0.88-1.21	0.97	0.69-1.38	1.23	0.68-2.23	0.96	0.82-1.13
Is frequently exposed to leather during work	1.13	0.99-1.29	0.92	0.56-1.50	0.73	0.27-1.98	1.01	0.80-1.27
Is frequently exposed to latex during work	0.99	0.87-1.13	0.92	0.66-1.28	1.05	0.51-2.14	1.01	0.82-1.23
Is frequently exposed to abrasive materials during work	0.97	0.71-1.33	1.00	0.65-1.52		*n.e.*	0.95	0.77-1.18
Handled materials at home								
Works with 2-component products at home	0.99	0.86-1.13	0.95	0.60-1.49	0.94	0.47-1.87	0.95	0.75-1.20
Works with solvents at home	1.00	0.84-1.17	0.95	0.59-1.53	0.86	0.45-1.65	1.01	0.78-1.30
Works with paint at home	1.05	0.87-1.27	0.97	0.69-1.36	1.09	0.53-2.24	0.93	0.80-1.08
Works with abrasive products at home	1.05	0.85-1.30	1.01	0.57-1.80	0.99	0.52-1.89	0.76	0.57-1.00
Performs wet work at home	1.02	0.89-1.17	1.10	0.75-1.60	0.84	0.47-1.52	1.04	0.88-1.22

All PR are adjusted for age, method of recruitment, eczema season, hand cream use and performing job-related task at home for more than four hours a week.
PR: Prevalence Ratio, 95% CI: 95% Confidence Interval, n.e.: not estimable.

SUMMARY

General introduction

Construction workers are employed in a large and dynamic occupational sector. Numerous job titles can be distinguished within the construction industry and all have their own specific characteristics. Almost all construction yard job titles, however, have in common that the workers are exposed to hazardous substances during their work.

Contact dermatitis (CD) is one of the most prevalent occupational diseases in many countries. In the general population, the one year prevalence of hand dermatitis, the main proxy for CD, varies between 5% and 11%. CD is an inflammation of the skin which is caused or worsened by contact with an exogenous agent. CD can occur in reaction to an irritant agent (Irritant CD, ICD) or after contact with an allergenic agent (Allergic CD, ACD). External environmental agents form one main category of risk factors for CD, the other category is formed by endogenous risk factors, which originate from inside the body. The most important endogenous risk factor is an atopic predisposition, which is a risk factor for development of CD but also for atopic asthma and allergic rhinitis. Carriage of loss-of-function mutations in the filaggrin gene (*FLG*) is another well-studied endogenous risk factor. Filaggrin deficiency leads to a drier and more permeable skin, thus increasing the risk for CD.

When the exposure to the agent which causes CD occurs in the workplace, CD is considered occupational CD (OCD). In 1984, hand dermatitis prevalence was reported to be 7.8% in the Dutch construction industry, compared to 4.6% in the general population. Since then, no studies on CD have been performed in Dutch construction workers. In other countries, CD prevalence between 4% and 20% was reported in construction workers, with a higher prevalence of 67% in one study among cement workers. Cement is a well-known irritant and may contain allergenic substances, but also other substances at work may cause OCD, including abrasive materials, solvents, epoxy resins and water (“wet work”). Gloves are recommended to protect workers’ hands, but workers may not know how to choose the correct protective gloves for each task.

To ensure healthy and durable working conditions in the construction industry, good prevention is required. In the Netherlands, employers are responsible to create working conditions which are as good as reasonably possible. Because of the physically demanding work and the many hazardous substances construction workers are exposed to, a regular medical checkup is part of the collective labor agreement in the Dutch construction industry. Workers are entitled to this voluntary checkup every four or every two years, depending on

their age and job title, in order to detect work-related health effects at an early stage.

To decrease the burden of skin disease in the Dutch construction industry, Arbouw, the foundation established by employers' and employees' organizations in the construction industry to improve workers' health and reduce sick leave, initiated the study described in this thesis. The main objectives are to assess the current prevalence of CD in the Dutch construction industry and to discover risk factors of CD in Dutch construction workers. The ultimate goal is to develop a prognostic tool for occupational physicians to detect CD in an early, preferably preclinical, stage.

Contact dermatitis in the Dutch construction industry

In *Chapter 2*, the prevalence of skin symptoms and their associations with occupational risk factors were assessed using data from 152,200 male construction workers. As part of the regular program of voluntary medical check-ups, a questionnaire including items on symptoms and working circumstances is administered to construction industry personnel. Hand eczema symptoms were reported by 25.4% of the construction yard workers and 14.6% of office personnel. Using log-binomial regression analysis, associations between possible risk factors and self-reported hand eczema symptoms and skin hypersensitivity were assessed. The main occupational determinant for hand eczema symptoms was nuisance due to dust exposure (Prevalence Ratio (PR): 1.59, 95% confidence interval (95% CI): 1.55-1.63), followed by nuisance due to exposure to chemicals (PR: 1.09, 95% CI: 1.06-1.14). These cross-sectional findings were supported by longitudinal analyses in a subset of workers for whom data of subsequent check-ups were available.

Due to the large number of different substances used in the construction industry, dermal exposure assessment is complicated. Therefore, questionnaire-based data are of great importance in assessing dermal exposures and their associations with CD. To gain more insight into the occupational determinants of CD, we developed a more detailed questionnaire than the questionnaire which is used in the regular health check-ups. In *Chapter 3*, a number of questionnaire items on hand hygiene were validated in a cross-sectional study amongst 177 construction workers who were observed and interviewed on the construction yard. The observed level of hand contamination, glove use and glove types used were found to agree well with self-reported data from the questionnaire (Cohen's kappa values 0.75, 0.97 and 0.88). Using a validated set of questions, the one-year prevalence of self-reported CD was found to be 46.9%. Log-

binomial regression analysis revealed positive associations between self-reported CD and difficulties with hand cleaning (PR: 1.26, 95% CI: 1.05-1.52), hand contamination at the end of the working day (PR: 2.30, 95% CI: 1.14-4.65) and intensive hand cream use (PR: 2.07, 95% CI: 1.42-3.01).

In *Chapter 4*, the prevalence of doctor-diagnosed CD was analyzed in a larger sample of 506 subjects, which was a subset of our main study population described in *Chapter 5*. From these 506 subjects, blood samples were available, making investigation of the association between CD and *FLG* loss-of-function mutations possible. Four *FLG* loss-of-function mutations were genotyped. In addition, total and specific serum IgE was analyzed by enzyme immunoassays. Diagnosis of CD was performed by a panel consisting of a dermatologist and a clinical occupational medicine specialist using photographs of the subjects' hands, supplemented with self-reported questionnaire data. *FLG* mutations were detected in 6.3% of the study population. Mild CD was diagnosed by the specialists in 34.0%, severe CD in an additional 24.3%. Self-reported CD prevalence was 34.0%. Almost all cases of CD were considered work-related (95.6%). The risk of CD was increased in carriers of at least one *FLG* variant (odds ratio (OR) mild CD: 5.71, 95% CI: 1.63-20.06; OR severe CD: 8.26, 95% CI: 2.32-29.39). Respiratory symptoms and atopic predisposition were not associated with *FLG* variants and CD. Despite the strong associations, the attributable fraction for CD of the four *FLG* loss-of-function mutations was only 8.5%.

The high prevalence of CD in the construction industry has not resulted in a coordinated response from occupational health care services. In the study described in *Chapter 5*, the prevalence and determinants of CD in Dutch construction workers were analyzed in 751 subjects. The CD prevalence was comparable to the study population subset described in *Chapter 4*: 38.2% mild CD and 23.2% severe CD (expert panel's diagnosis) and 32.9% self-reported CD. In addition to assessing the CD prevalence, in this study, the ability of occupational physicians (OPs) to recognize CD symptoms was tested as the photographs of a subset of the study population was evaluated by two OPs. Their diagnoses were compared to the diagnoses of the expert panel. Agreement between OPs' and the expert panel's diagnoses was low but increased after training. From the occupational determinants of CD we studied, only washing the hands with solvents (PR: 1.17, 95% CI: 1.03-1.34) and performing job-related tasks at home were associated with CD (PR: 1.14, 95% CI: 1.04-1.26). In addition, self-reported difficulties with cleaning the hands at the end of the

working day was positively related to CD (PR: 1.13, 95% CI: 1.04-1.24). The lack of specific occupational determinants (e.g. materials like cement) and the fact that performing job-related tasks at home and difficulties with cleaning the hands at the end of the working day were significant determinants, might mean that cumulative exposure to irritants is a key factor in the development of CD in construction workers.

Chapter 6 describes a study which aims to identify occupational determinants of skin allergy to epoxy products in a case-control sample of German construction workers. Cases were ascertained from the files of the German statutory accident insurance of the construction sector (Berufsgenossenschaft für die Bauwirtschaft; BGBAU). For recognition as an occupational disease, epoxy allergy has to be confirmed by means of a patch test. Determinants of epoxy allergy were investigated by comparing 179 workers with and 151 workers without skin allergy against epoxy resins, hardeners and/or reactive diluents. Epoxy allergy was positively associated with an unusually high exposure to epoxy products (OR: 2.13, 95% CI: 1.01-4.51), wearing short sleeves or pants (OR: 2.38, 95% CI: 1.03-5.52), and not always using the right type of gloves (OR: 2.12, 95% CI: 1.12-4.01). In addition, increased risk was found with increasing exposure hours per week (OR per ten hours increase: 1.72, 95% CI: 1.39–2.14). Not using skin cream (OR: 0.22, 95% CI: (0.08-0.59) and working years with epoxy products (OR: 0.41, 95% CI: 0.27-0.61 per 10 years increase), were inversely associated with epoxy allergy suggesting a healthy worker survivor effect.

Conclusions and recommendations

This thesis shows that both the self-reported and doctor-diagnosed prevalence of CD among Dutch construction workers is high. A dermatological expert panel diagnosed mild CD in 38% and severe CD in an additional 23% of 751 investigated construction workers. We attempted to recruit a random sample of workers, and a high response was achieved (74.3%). Distribution of job titles in this study sample was comparable to the Dutch construction industry as a whole.

The most probable cause of CD is cumulative exposure to multiple mildly irritant factors. A strong relation was found between loss-of-function mutations in the filaggrin gene and CD, but the attributable fraction was relatively small. Moreover, ethical and practical issues preclude implementation of genetic testing in occupational health care. Based on the high CD prevalence and the low agreement between the diagnoses of two occupational physicians and

those of a dermatological expert panel, we conclude that occupational health care fails to successfully detect (early) CD.

We recommend that awareness of the risk to develop CD in the construction industry should be increased, among occupational physicians as well as among employers and employees. Education of occupational physicians, including a dermatological training to improve detection of (early) CD, is recommended. Amongst employers and employees, the importance of the correct use of personal protective equipment like gloves should be promoted, as well as the use of hand cream. In the ideal situation, as early as during their vocational training, construction workers should become familiar with the risk of skin problems and methods to prevent development of CD.

SAMENVATTING

Algemene introductie

Bouwvakkers werken in een grote en dynamische bedrijfstak. Binnen de bouw zijn er talloze beroepen te onderscheiden die elk hun eigen, specifieke eigenschappen hebben. Echter, bijna alle bouwplaatsberoepen hebben met elkaar gemeen dat de werknemers zijn blootgesteld aan gevaarlijke stoffen tijdens hun werk.

Contacteczeem (Engels: Contact Dermatitis, CD) is in veel landen één van de meest voorkomende beroepsziekten. In de algemene bevolking variëren schattingen van de prevalentie van handeczeem, de belangrijkste indicator voor de prevalentie van contacteczeem, tussen 5% en 11%. Contacteczeem kan worden gedefinieerd als een huidontsteking die wordt veroorzaakt of verergerd door contact met een stof of door een andere externe invloed. Contacteczeem kan optreden na contact met een irritatieve stof, bijvoorbeeld een oplosmiddel, of irritatieve invloed, bijvoorbeeld koude, droge lucht. Het als gevolg daarvan ontstane eczeem wordt ortho-ergisch of irritatief contacteczeem genoemd (Engels: Irritant Contact Dermatitis, ICD). Contacteczeem kan ook ontstaan na contact met een allergene stof, dan is er sprake van allergisch contacteczeem (Engels: Allergic Contact Dermatitis, ACD). Naast invloeden van buitenaf zijn er ook invloeden die van binnenuit het lichaam komen, de zogenaamde endogene risicofactoren. De belangrijkste van deze endogene risicofactoren is een atopische aanleg, wat behalve voor contacteczeem ook een risicofactor is voor het ontwikkelen van atopische astma en allergische rhinitis. Een andere goed bestudeerde endogene risicofactor is dragerschap van één of meerdere mutaties in het filaggrine gen. Deze mutaties veroorzaken een drogere en meer doorlaatbare huid, waardoor het risico op contacteczeem sterk wordt vergroot.

Als de blootstelling die het contacteczeem veroorzaakt plaatsvindt in de werksfeer dan is er sprake van werkgebonden contacteczeem (Engels: Occupational Contact Dermatitis, OCD). In 1984 bleek uit een onderzoek dat de prevalentie van handeczeem in de Nederlandse bouwsector 7,8% was, tegenover 4,6% in de algemene bevolking. Sindsdien zijn er geen onderzoeken naar contacteczeem in de Nederlandse bouwsector meer uitgevoerd. In studies in andere landen werden prevalenties tussen 4% en 20% gevonden, met een uitschieter van 67% in een onderzoek onder cementwerkers. Cement is een voorbeeld van een bekende irritatieve stof die daarnaast ook allergene bestanddelen kan bevatten maar bijvoorbeeld ook schurende materialen, oplosmiddelen, epoxyharsen en water (nat werk) kunnen werkgebonden contacteczeem veroorzaken. Om de handen van werknemers te beschermen wordt het aangeraden om handschoenen te gebruiken maar het kiezen van de juiste soort handschoenen voor iedere taak kan moeilijk zijn.

Om gezonde en duurzame werkomstandigheden te garanderen is een goed preventiebeleid noodzakelijk. In Nederland zijn alle werkgevers via de Arbowet verantwoordelijk voor het creëren van zo goed mogelijke werkomstandigheden. Vanwege het fysiek veeleisende werk en de mogelijke blootstelling aan veel gevaarlijke stoffen is er in de cao van de Nederlandse bouwnijverheid opgenomen dat bouwvakkers recht hebben op een periodiek arbeidsgeneeskundig onderzoek (PAGO). Om werkgerelateerde aandoeningen vroegtijdig op te sporen worden bouwvakkers hiervoor iedere vier of twee jaar uitgenodigd, afhankelijk van hun leeftijd en beroep.

Om de ziektelast van contacteczeem in de Nederlandse bouwsector terug te dringen heeft Arbouw het onderzoek geïnitieerd dat in dit proefschrift beschreven wordt. Arbouw was een door werkgeversorganisaties en vakbonden opgerichte stichting met als doel het verbeteren van werkomstandigheden in de bouw. De belangrijkste doelen van het onderzoek dat in dit proefschrift beschreven is, waren het vaststellen van de huidige prevalentie van contacteczeem in de Nederlandse bouwsector en het ontdekken van risicofactoren voor bouwvakkers voor het hebben van contacteczeem. Het uiteindelijke doel was om een *triage tool* te ontwikkelen waarmee bedrijfsartsen contacteczeem in een vroeg, bij voorkeur preklinisch, stadium kunnen ontdekken.

Contacteczeem in de Nederlandse bouwsector

In *Hoofdstuk 2* worden de prevalentie van huidklachten en de associaties met werkgerelateerde risicofactoren gepresenteerd uit een onderzoek met data van 152.000 mannelijke bouwvakkers. De data is afkomstig uit het PAGO, waarbij door bouwvakkers een vragenlijst wordt ingevuld met vragen over gezondheidsklachten en werkomstandigheden. Een kwart van het bouwplaatspersoneel gaf aan huidklachten te hebben (25,4%), voor kantoorpersoneel lag het percentage op 14,6%. Met behulp van log-binomiale regressieanalyse werden de associaties tussen huidklachten en werkgerelateerde determinanten berekend. De belangrijkste werkgerelateerde determinant was hinder vanwege stofblootstelling (prevalentie ratio (PR): 1,59; 95% betrouwbaarheidsinterval (95% BI): 1,55-1,63), gevolgd door hinder vanwege blootstelling aan chemische stoffen (PR: 1,09; 95% CI: 1,06-1,14). Deze resultaten uit het dwarsdoorsnedeonderzoek werden ondersteund door een longitudinale analyse in een kleiner gedeelte van de dataset met werknemers van wie data van meerdere, opeenvolgende PAGOs beschikbaar was.

Vanwege het grote aantal verschillende stoffen dat gebruikt wordt in de bouwsector is het schatten van huidblootstelling erg gecompliceerd. Data afkomstig van vragenlijstenonderzoeken zijn daarom van groot belang om de relaties tussen blootstelling aan stoffen en contacteczeem te kunnen ontdekken. Om meer inzicht te krijgen in de werkgerelateerde risicofactoren van contacteczeem werd er een meer gedetailleerde vragenlijst ontwikkeld dan de vragenlijst die bij de PAGOs wordt gebruikt. In *Hoofdstuk 3* wordt een aantal vragen over handhygiëne gevalideerd in een dwarsdoorsnedestudie onder 177 bouwvakkers die werden geobserveerd en geïnterviewd op de bouwplaats. De waargenomen mate van vervuiling van de handen, handschoengebruik en type gebruikte handschoen kwamen goed overeen met de antwoorden die de deelnemers aangaven in de vragenlijst (waarden Cohen's kappa: 0,75; 0,97 en 0,88). Middels een algemeen gebruikte vragenlijst werd de eenjaarsprevalentie van contacteczeem in deze groep bouwvakkers geschat op 46,9%. Met behulp van log-binomiale regressieanalyse werden positieve verbanden aangetoond tussen contacteczeem en moeite met het schoonmaken van de handen aan het einde van de werkdag (PR: 1,26; 95% BI: 1,05-1,52), vieze handen aan het einde van de werkdag (PR: 2,30; 95% BI: 1,14-4,65) en intensief handcrèmegebruik (PR: 2,07; 95% BI: 1,42-3,01).

In *Hoofdstuk 4* wordt de prevalentie van door een arts vastgesteld contacteczeem onderzocht bij 506 bouwplaatsmedewerkers, een subpopulatie van de studiepopulatie die wordt beschreven in *Hoofdstuk 5*. Van de genoemde 506 personen waren bloedmonsters aanwezig die het mogelijk maakten om het verband tussen contacteczeem en mutaties in het gen dat codeert voor het eiwit filaggrine (*FLG*) te onderzoeken. Een viertal *FLG* mutaties werd onderzocht. Daarnaast werden ook met behulp van enzym immunoassays (EIA) het totaalgehalte IgE en specifieke IgE antistoffen tegen een vijftal veelvoorkomende allergenen geanalyseerd. De diagnose voor contacteczeem werd, met behulp van foto's van de handen van deelnemers en data uit de vragenlijsten, gesteld door een expertpanel dat bestond uit een dermatoloog en een klinisch arbeidsgeneeskundige. Bij 6,3% van de studiepopulatie werden *FLG* mutaties ontdekt. Mild contacteczeem werd door het expertpanel vastgesteld in 34,0% van de proefpersonen, ernstig contacteczeem in nog eens 24,3%. Het percentage zelf-gerapporteerd contacteczeem lag op 34,0%. Vrijwel alle vastgestelde contacteczeem was werkgerelateerd (95,6%). Het risico op contacteczeem was aanzienlijk hoger in dragers van één of meerdere *FLG* mutaties (odds ratio (OR) mild contacteczeem: 5,71; 95% BI: 1,63-20,06; OR ernstig contacteczeem: 8,26; 95% BI: 2,32-29,39). Luchtwegklachten en atopische aanleg waren niet geassocieerd met *FLG* mutaties en contacteczeem.

De attributieve fractie (de proportie mensen met contacteczeem dat is toe te schrijven aan *FLG* mutaties) was ondanks de sterke associaties beperkt: 8,5%.

Het veelvuldige voorkomen van contacteczeem heeft nog niet tot een gecoördineerde reactie binnen de bedrijfsgezondheidszorg geleid. In de studie die in *Hoofdstuk 5* wordt beschreven, worden de prevalentie en determinanten van contacteczeem in de volledige studiepopulatie van 751 Nederlandse bouwplaatsmedewerkers beschreven. De contacteczeemprevalentie was vergelijkbaar met de prevalentie in de subgroep die werd beschreven in *Hoofdstuk 4*: 38,2% mild contacteczeem en 23,2% ernstig contacteczeem; 32,9% zelfgerapporteerd contacteczeem. In deze studie werd ook getest hoe goed bedrijfsartsen symptomen van contacteczeem kunnen herkennen. Hiervoor werden de foto's van een subpopulatie van 150 personen van de onderzoekspopulatie door een tweetal bedrijfsartsen beoordeeld. Hun diagnosen werden vergeleken met de diagnose van het expertpanel. De overeenstemming tussen de bedrijfsartsen onderling en met het expertpanel was laag maar nam toe nadat ze een dermatologische cursus hadden gevolgd. Van alle werkgerelateerde risicofactoren die onderzocht waren, bleken alleen het wassen van de handen met oplosmiddelen (PR 1,17; 95% BI: 1,03-1,34) en het meer dan vier uur per week thuis uitvoeren van taken die overeenkomen met het werk (PR 1,14; 95% BI: 1,04-1,26) geassocieerd met contacteczeem. Daarnaast werd er ook een verband gevonden tussen het hebben van contacteczeem en het aangeven dat de handen moeilijk schoon worden aan het einde van de werkdag (PR 1,13; 95% BI: 1,04-1,24). Het gebrek aan verbanden met werkgerelateerde oorzaken (bijvoorbeeld materialen zoals cement) en het feit dat het thuis uitvoeren van werkgerelateerde taken en het moeilijk schoonkrijgen van de handen waren geassocieerd met contacteczeem, kan betekenen dat cumulatieve blootstelling aan (meerdere) irritantia bij bouwvakkers een sleutelfactor is in het ontwikkelen van contacteczeem.

In *hoofdstuk 6* wordt een patiënt-controle studie beschreven waarin werkgerelateerde determinanten van huidallergie vanwege epoxyproducten worden onderzocht in een populatie Duitse bouwvakkers. Proefpersonen met vastgestelde epoxyallergie werden vanuit het register van de Duitse sociale ongevallenverzekering van de bouwsector (Berufsgenossenschaft für die Bauwirtschaft, BG BAU) geïdentificeerd, waarbij de allergie bevestigd moet worden door een plaktest om als beroepsziekte erkend te kunnen worden.

In de studie werden 179 werknemers met epoxyallergie vergeleken met 151 werknemers zonder huidallergie. Epoxyallergie was positief geassocieerd met

een ongewoon hoge blootstelling aan epoxyproducten (OR: 2,13; 95% BI: 1,01-4,51), het dragen van korte mouwen of broekspijpen (OR: 2,38; 95% BI: 1,03-5,52), en het niet altijd dragen van de juiste handschoenen (OR: 2,12; 95% BI: 1,12-4,01). Daarnaast werd een verhoogd risico gevonden bij een toenemend aantal uren blootstelling per week (OR per 10 uur toegenomen werktijd: 1,72; 95% BI: 1,39-2,14). Het niet gebruiken van handcrème (OR: 0,22; 95% BI: (0,08-0,59) en het aantal werkjaren met epoxyproducten (OR: 0,41; 95% BI: 0,27-0,61 per toename van 10 jaar), waren negatief geassocieerd met epoxyallergie, wat mogelijk op een *healthy worker effect* wijst.

Conclusies en aanbevelingen

Dit proefschrift toont aan dat zowel zelf-gerapporteerd als door een arts vastgesteld contacteczeem veel voorkomt in de Nederlandse bouwsector. Een dermatologisch expertpanel stelde mild eczeem vast in 38% van de 751 Nederlandse bouwvakkers en ernstig eczeem in nog eens 23%. We hebben getracht een willekeurige doorsnee van bouwvakkers in de studiepopulatie op te nemen, en de respons was hoog (74,3%). De verdeling van beroepen in de studiepopulatie was vergelijkbaar met de Nederlandse bouwsector als geheel.

De meest waarschijnlijk oorzaak van contacteczeem is de cumulatieve blootstelling aan meerdere, mild irritatieve stoffen en factoren. Er werd een sterk verband aangetoond tussen contacteczeem en mutaties in het filaggrinegen maar de attributieve fractie was relatief klein en het implementeren van genetische testen in de bedrijfsgezondheidszorg stuit op zowel ethische als praktische problemen. Gebaseerd op het veelvuldig voorkomen van contacteczeem en de lage overeenstemming van de diagnosen van de bedrijfsartsen met de diagnosen van het expertpanel concluderen we dat de bedrijfsgezondheidszorg er op dit moment niet in slaagt (vroeg) contacteczeem te herkennen.

We bevelen aan om het bewustzijn van het risico op het ontwikkelen van contacteczeem in de bouw te vergroten. Dit zou zowel bij bedrijfsartsen als werknemers en werkgevers gedaan moeten worden. Gedegen opleiding van bedrijfsartsen, inclusief een dermatologische training om (vroege) symptomen van contacteczeem te herkennen, is aan te bevelen. Onder werkgevers en werknemers moet het belang van het gebruiken van de juiste handschoenen en handcrème worden benadrukt. In het ideale geval zouden bouwvakkers al tijdens hun vakopleiding bekend moeten raken met het risico op huidproblemen en maatregelen om contacteczeem te voorkomen.

DANKWOORD

Een periode van ruim zes jaar (gedeeltelijk) aan mijn proefschrift werken ligt inmiddels achter me. Ik ben dankbaar voor de kracht die ik al die jaren gekregen heb om, zeker de laatste anderhalf jaar langzaam maar zeker, door te gaan en zowaar nu een heus proefschrift af te hebben.

In de achterliggende jaren ben ik enorm veel mensen tegengekomen aan wie ik dank verschuldigd ben. Zoveel zelfs dat ik me op voorhand maar vast ga indekken: mocht ik hieronder iemand vergeten: excuses daarvoor!

Om te beginnen, heel veel dank aan mijn copromotoren: Lidwien Smit en Ton Spee. Lidwien, je was er altijd voor me (behalve dan als je zwangerschapsverlof had maar dat zij je vergeven). Je was nooit te beroerd om mee te kijken en mee te denken en dat waardeer ik enorm! Daarnaast probeerde je me altijd vooruit te laten kijken en een planning te maken. Dat was niet mijn sterkste punt maar ook daar heb ik veel van geleerd. Ton, bedankt voor de diepgaande gesprekken waarmee je me inzicht gaf in de wondere wereld van de bouw. Je wist altijd alle resultaten in de context van de praktijk te plaatsen. Dat leverde vaak interessante discussies en nieuwe inzichten op. Veel dank ben ik ook verschuldigd aan mijn promotor: Dick Heederik. Dick, je bezit de bijzondere gave om in een fractie van een ogenblik de essentie van iets te begrijpen. Waarschijnlijk kun je je daarom ook met zoveel dingen tegelijk bezighouden maar toch maakte je altijd tijd vrij als ik met een vraag bij je aanklopte. Dank voor het overzicht en de bijsturing die je op lastige momenten gaf!

Ook mijn andere begeleiders, Frits van Rooy en Esmeralda Krop wil ik hierbij bedanken. Frits, jij was als man van de praktijk voor mij ook van onschatbare waarde, en je nuchtere opmerkingen op door mij geschreven stukken waren altijd nuttig. Esmeralda, jij hebt me grotendeels door het labwerk heengeloodst! Als het over labwerk gaat dan denk ik natuurlijk ook gelijk aan Jack, Siegfried en Nena: dank voor de ondersteuning en gezelligheid in en rond het lab!

De leden van de leescommissie en de opponenten tijdens de verdediging van mijn proefschrift wil ik ook hartelijk danken voor de tijd die ze hieraan besteed hebben.

Thomas en Jan: dank voor het beoordelen van al die foto's en niet minder voor de enorm waardevolle discussies die we gevoerd hebben. Jullie enthousiasme werkte bovendien aanstekelijk! Gerard, dank dat je als medeauteur mee wilde werken aan het artikel over de *FLG* mutaties. Bedankt voor je input! Daan en Paul, jullie hebben ook veel tijd gestoken in de pilotfase van het onderzoek en in

het beoordelen van de foto's. Jullie hebben hiermee een ontzettend belangrijke bijdrage aan mijn proefschrift geleverd: hartelijk dank!

Speciale dank natuurlijk voor mijn kamergenootjes. Wietske, roomie van het eerste uur…jammer dat je op het laatst wel erg ver uit de richting zat maar gelukkig kon ik altijd bij je binnenlopen om het over belangrijke dingen (kinderen) en minder belangrijke dingen (artikelen en proefschriften) te hebben. Floor en Myrna, jullie ook bedankt voor de gezelligheid. Met of zonder hulp van Wietske slaagden jullie er altijd in om me de meest onhandige opmerkingen in de mond te leggen. Ik begrijp dat het nu erg stil is en ik leef daarin met jullie mee. George, ik zou nu een Engelse zin aan je kunnen wijden maar ik vind dat je dit ondertussen wel in het Nederlands moet kunnen lezen. Jij ook bedankt voor de gezelligheid en de handige Engelse taaladviezen! Een speciaal woordje toch voor Hicham: je verbaasde me door als masterstudent stage te willen lopen op uitgerekend mijn onderzoek. Dat deed je fantastisch en ik heb enorm goede herinneringen aan de bouwplaatsbezoeken die we samen afgelegd hebben. Dat we later ook nog eens "echte" collega's werden was helemaal mooi en je was nooit te beroerd om als eerste mijn stukken door te nemen. Bedankt voor je inzet en gezelligheid!

Alle andere IRAS-collega's: bedankt voor de gezellige momenten, jullie vormden een geweldige groep mensen om tussen te kunnen werken. Saskia, jij heel veel dank voor het veldwerk dat je voor me uitgevoerd heb. Het veldwerk was een prachtige maar drukke periode. Een speciaal woord van dank voor Tamara Onos: Tamara, bedankt voor het coördineren van alle bedrijfsbezoeken en het opzetten van de prachtige toolbox. Samen met Jan Snijder, Hans Clemenkowff, Mariska Droog en Hans Bouman wil ik je bedanken voor het geven van de presentaties. Alle mensen van Arbo Unie die hebben meegeholpen bij het opzetten en uitvoeren van het onderzoek: dank voor jullie inzet!

Ook alle ex-collega's van Arbouw wil ik bedanken. Sommigen waren al betrokken bij mijn promotieonderzoek toen we nog geen collega's waren, vooral Jan Golsteijn, Floor de Goede en Frans Meijer hebben veel deuren voor mij ontsloten. Toen ik Frans af mocht lossen bij Arbouw kwam ik in een omgeving van allemaal fijne mensen die me stimuleerden om vooral snel dat boekje af te maken. Toen Arbouw ophield te bestaan en Volandis kwam, was het boekje er nog steeds niet maar de betrokkenheid van de collega's is gelukkig nog steeds. Volandici: bedankt voor jullie steun!

Tot slot, hartelijk dank aan mijn paranimfen. Pa en Hicham, dank dat jullie mijn handje vandaag wilden vasthouden!

Alien, waar zou ik zijn zonder jou? Bedankt voor de steun die je me al die jaren gegeven hebt. Allereerst leerde je me werk en thuis gescheiden te houden en daarvoor ben ik je dankbaar! De avonden dat het eten klaarstond als ik thuis kwam, waren ontelbaar. En wat is er heerlijker dan thuiskomen in een warm, liefdevol nest?

Onvervangbaar onderdeel van dat liefdevolle nest zijn jullie, Hanna en Co-Lise. Jammer dat jullie te jong zijn om mijn paranimfen te mogen zijn…! Jullie hebben samen gretig je best gedaan zoveel mogelijk energie en liefde uit me te trekken. Helaas, dat is niet gelukt want alles wat ik jullie gaf hebben jullie me altijd dubbel en dwars teruggegeven! Thuiskomen is altijd een feest met jullie!

CURRICULUM VITAE CV

Johannes Geertrudes Timmerman wordt op 21 maart 1988 in Buurmalsen geboren. Na het behalen van zijn VWO diploma aan de Gomarus Scholengemeenschap te Gorinchem in 2005 gaat hij Biomedische Wetenschappen studeren aan de Universiteit Utrecht. Tijdens zijn bachelor volgt hij toxicologische vakken bij de studies Biologie en Farmacie en na het behalen van zijn bachelordiploma in 2008 begint hij aan de masteropleiding Toxicology & Environmental Health. Tijdens deze master loopt hij stage bij de afdeling neurotoxicologie van het Institute for Risk Assessment Sciences (IRAS) waar hij meewerkt aan onderzoek naar de effecten van drugs op neurotransmissie. Later loopt hij stage bij het Trimbos Instituut waar hij literatuuronderzoek verricht naar de gevaren van drugsgebruik tijdens de zwangerschap en werkt hij mee aan het vertalen hiervan in begrijpelijke webteksten. Hij rond zijn master af in 2010 na het schrijven van een literatuurscriptie over de rol van perceptie bij onderzoek naar blootstelling aan en gezondheidseffecten van elektromagnetische velden. Dat jaar start hij onder begeleiding van dr. L.A.M. Smit, dr. T. Spee en prof. dr. ir. D.J.J. Heederik met zijn promotieonderzoek aan het IRAS hetgeen geresulteerd heeft in dit proefschrift. Momenteel werkt hij als Specialist Arbeidsepidemiologie bij Volandis.

LIST OF PUBLICATIONS

Timmerman JG, Heederik D, Spee T, Smit LA. Skin symptoms in the construction industry: occurrence and determinants. Am J Ind Med 2014; 57:660-668.

Timmerman JG, Zilaout H, Heederik D, et al. Validation of a questionnaire on hand hygiene in the construction industry. Ann Occup Hyg 2014; 58:1046-1056.

Timmerman JG, Heederik D, Spee T, et al. Contact dermatitis in the construction industry: the role of filaggrin loss-of-function mutations. Br J Dermatol 2015; 174:348-355.

Spee T, Timmerman JG, Rühl R, et al. Determinants of epoxy allergy in the construction industry: a case-control study. Contact dermatitis 2016; 74(5):259-266.