Skin diseases in Norway and cutaneous squamous cell carcinoma in four Nordic countries:

The role of occupation and occupational exposures

A population-based study

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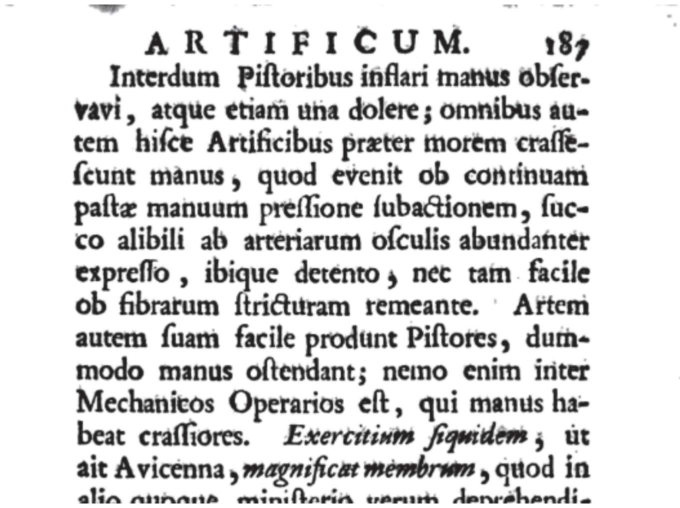

ARTIFICUM. 187

Interdum Piſtoribus inflari manus obſervavi, atque etiam una dolere; omnibus autem hiſce Artificibus præter morem craſſeſcunt manus, quod evenit ob continuam paſtæ manuum preſſione ſubactionem, ſucco alibili ab arteriarum oſculis abundanter expreſſo, ibique detento, nec tam facile ob fibrarum ſtricturam remeante. Artem autem ſuam facile produnt Piſtores, dummodo manus oſtendant; nemo enim inter Mechanicos Operarios eſt, qui manus habeat craſſiores. *Exercitium ſiquidem*, ut ait Avicenna, *magnificat membrum*, quod in alio quoque miniſterio verum deprehendi-

"...Now and then I have noticed that bakers have swollen, aching hands. Everyone in this trade gets rough hands by kneading the dough. A baker just has to show his hands to reveal this trade. No other tradesman has similar hands".

"De Morbis Artificum"
Bernardo Ramazzini (1633-1744)

This photography of a baker´s hand was a courtesy from Dr. M.N. Crepy. Available at: http://www.atlasdedermatologieprofessionnelle.com/index.php/Boulanger

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ACKNOWLEDGEMENTS

When I was a 6-year-old boy, I dreamt about becoming a researcher. I was lucky to have been inspired by my dedicated and hardworking parents -**Mirtha & José**- who not only taught me how to count red and white cells in the optical microscope, but also made an enormous effort to afford my education.

Several years later, at the age of 21, I started to volunteer as a research assistant at the Institute of Immunology, Faculty of Medicine, Universidad Nacional de Rosario, Argentina. Isolating white cells from patients with rheumatoid arthritis and lung tuberculosis, ”exposing” the cells to different hormone concentrations, and checking cell growth and measuring cytokines were my main tasks. I am deeply indebted to **Dr María Luisa Bay** and **Dr Oscar Bottasso** for initiating me into the fascinating world of research. Although I loved working with cell culture, part of my dream was to combine research with clinical work, something that was not feasible in my beloved Argentina.

Dream, dream, dream. Reach for the stars told me **Desmond Tutu** in February 2009, when I represented Argentina at the world´s largest student festival in Trondheim. From that moment on, it was clear to me that I will be willing to work hard to make the researcher dream a reality.

Several months later, I went back to Norway, learned Norwegian and started my specialisation into Occupational and Environmental Medicine. I would like to express my deepest gratitude to **Tor Erik Danielsen** who not only shared his contagious commitment for Occupational Medicine, but also introduced me to STANDERM, an international research network aimed at developing standards for a healthy skin at healthy workplaces. My special thanks go to **Prof. Jeanne Duus Johansen**, **Prof. Swen Malte John**, and my colleagues from **STANDERM** who encouraged me to re-activate research within occupational dermatology in Norway.

It has been challenging, but also extremely exciting to do research within occupational dermatology in a country where this discipline was not given enough priority.
I will therefore never forget when my good colleagues **Marit Skogstad** and **Tore Tynes** told me: *“If you want to take a Ph.D. within occupational dermatology, then you will do it. We will support you.”*

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Años mas tardes, cuando tenía 21 años, comencé a trabajar voluntariamente como asistente de investigación en el Instituto de Inmunología de la Facultad de Ciencias Médicas de la Universidad Nacional de Rosario. El trabajo consistía en aislamiento de glóbulos blancos de pacientes con artritis reumatoidea y tuberculosis, para luego exponerlos a diferentes concentraciones de hormonas y finalmente chequear el crecimiento de las células y medir citoquinas. Estoy profundamente agradecido a la **Dra. María Luisa Bay** y al **Dr. Oscar Bottasso** por iniciarme en el fascinante mundo de la investigación. A pesar de que me encantaba trabajar con cultivos celulares, parte de mi sueño fue combinar investigación con trabajo clínico, algo que no era posible realizar en mi amada Argentina.

-"***Sueña, sueña, sueña y alcanza las estrellas"***- me dijo el Premio Nobel de la Paz, **Desmond Tutu** en el 2009, cuando representaba a Argentina en el Encuentro Mundial de estudiantes universitarios mas grande del mundo, en Trondheim. Para mí fue claro desde ese momento, que estaba dispuesto a trabajar duro para convertir el sueño de ser científico en realidad.

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Ha sido desafíante, pero también extremedamente apasionante poder realizar investigación sobre enfermedades cutáneas profesionales, en un país donde la disciplina recibió poca atención. Por esta razón, nunca voy a olvidar aquel día en el que mis buenos colegas **Marit Skogstad** y **Tore Tynes** me dijeron: *"Si queres hacer tu PhD sobre dermatología ocupacional, debes hacerlo. Nosotros estáremos contigo para apoyarte".*

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PREFACE

In clinical medicine, prevention is often linked to early diagnosis, for instance by high sensitive and specific biomarkers. On the other hand, from the perspective of occupational medicine, the conception of prevention is probably larger, and includes preventive actions that can take place at an earlier point where the main goal is not to reduce the damage of the disease by an earlier diagnosis, but rather to preclude the onset of disease by avoiding the exposure that causes it. Epidemiology is concerned with this: conducting research at the population level to provide evidence on whether exposures are associated with health problems and disease. After research is conducted and evidence collected, identification of exposures associated to disease can be utilized to suggest preventive actions with impact on public health.

This is truly the case for dermatologists, occupational physicians, and epidemiologists. Therefore, this thesis attempts to gather approaches from these three disciplines for the purposes of comprehensive prevention of work-related affections of the skin.

Jose Hernán Alfonso

LIST OF PAPERS

The work of the present doctoral thesis includes the following studies, which are referred to in the text by Roman numerals from I to IV:

I. Alfonso, J.H., Løvseth, E.K., Samant, Y., Holm, J.Ø. (2015). **Work-related skin diseases in Norway may be underreported: data from 2000 to 2013.** *Contact Dermatitis, 72,* 409-412. Doi: 10.1111/cod.12355.

II. Alfonso, J.H., Thyssen, J.P., Tynes, T., Mehlum, I.S., Johannessen, H.A. (2015). **Self-reported occupational exposure to chemical and physical factors and risk of skin problems: a 3-year follow-up study of the general working population of Norway.** *Acta Derm Venereol, 95,* 959-62. Doi: 10.2340/00015555-2135.

III. Alfonso, J.H., Tynes, T., Thyssen, J.P., Holm, J.Ø., Johannessen, H.A (2016). **Self-reported occupational skin exposure and risk of physician-certified long-term sick leave: a prospective study of the general working population of Norway.** *Acta Derm Venereol, 96,* 336-40. Doi: 10.2340/00015555-2253.

IV. Alfonso, J.H., Martinsen, J.I., Pukkala, E., Weiderpass, E., Tryggvadottir, L., Nordby, K.C., Kjærheim, K. (2016). **Occupation and relative risk of cutaneous squamous cell carcinoma: a 45-year follow-up study in four Nordic countries**. *J Am Acad Dermatol, In press.* Doi: 10.1016/j.jaad.2016.03.033.

SUMMARY

Background

Skin diseases caused or worsened by occupational exposures –work-related skin diseases- represent up to 30% of occupational diseases in Europe. The chronic course of work-related skin diseases, mostly irritant and allergic contact dermatitis of the hands, is associated with frequent use of health care services, high occurrence of sick leave, job loss, and job change. Therefore, they constitute a top priority public health problem (European Agency for Safety and Health at Work, EU.25 report, 2008).
Furthermore, a growing body of research links exposure to solar UV radiation in outdoor workers to the rapidly increasing incidence of cutaneous squamous cell carcinoma in Europe, which is now recognized as an occupational disease in several European countries.

Work-related skin diseases have a common feature: they are, in fact, highly preventable by reducing exposure to occupational hazards. For instance, prevention strategies are shown to reduce onset and a chronic and relapsing course of these conditions.
Whilst epidemiological studies at the population level are an important tool to determine etiologic and contributing factors of the disease, little is known about the contribution of occupational exposures to the burden of skin problems and diseases in Norway. Moreover, the variation in the relative risk of cutaneous squamous cell carcinoma between occupational categories of the Nordic countries has not yet been described. Therefore, epidemiological studies are needed to identify targets for prevention at the population level.

Main aims

This thesis sought to:

1. Describe the notification trends for work-related skin diseases in Norway for the period 2000-2013.
2. Investigate the contribution of occupational chemical and physical exposures to the burden of skin problems and physician-certified long-term sick leave in the general working population of Norway.
3. Identify the occupational variation in the relative risk of cutaneous squamous cell carcinoma between occupational categories in Finland, Iceland, Sweden, and Norway.

Study population

The first study was based on data from the Norwegian Labour Inspectorate`s Registry of work-related diseases for the period 2000-2013 (n=41,181). The second study was based on Survey information from a random panel sample of the general working-age population (n=6,745) (Survey of Living Conditions – Work Environment 2006 & 2009, conducted by Statistics Norway). The third study was based on the previous Survey for 2009 merged with data from the Norwegian Labour and Welfare Administration's sickness benefit Registry 2009 and 2010 (n=6,182) . Finally, the last study was based on data from the Nordic Occupational Cancer study, which linked demographic census data to diagnosis data from the Nordic Cancer Registries (n=12.9 million).

Design

This thesis used two different designs:
First, a case-series design based on retrospective data in *Study I*.
Second, a prospective cohort-design in *Study II*, *III*, *and IV* with a follow-up up to three-year in *Study II*, one-year in *Study III*, and 45-year in *Study IV*.

Statistical methods

The notification trends of work-related skin diseases, occupations, and occupational exposures for the notified work-related skin diseases were described by frequency statistics and cross-tabulations (*Study I*).

The associations between self-reported occupational exposures with self-reported skin problems (*Study II*), and physician-certified long-term sick leave (*Study III*) were estimated by unconditional logistic regression. Statistical adjustment for other explanatory variables was performed in different models: age, sex, occupation, and other concomitant skin exposures in *Study II*; and age, education, psychosocial, and mechanical exposures at work in *Study III*. The population attributable risk percent attributable to occupational exposures was calculated for both skin problems, and long-term sick leave.

The variation in the relative risk of cutaneous squamous cell carcinoma between occupational categories of four Nordic countries was described by standardised incidence ratios with the incidence rates of cutaneous squamous cell carcinoma for the national population of each country used as reference. Occupational categories were classified according to occupational solar exposure and socioeconomic status.

Main results

Study I reported a decline in the notification of work-related skin diseases from 487 in 2000 to 91 in 2013. Contact dermatitis accounted for 94% of the cases (41% allergic, 43% irritant, 10% unspecified). The five most common occupations with notified work-related skin disease were mechanics, welders and plate-/workshop workers, health personnel, hairdressers, plumber, chefs and kitchen assistant. The five most common occupational exposures consisted of cleaning products, other chemical substances, oils, fuels and solvents, metals, and adhesive and epoxy substances.

Study II reported an association between self-reported occupational exposure to physical factors such as indoor dry air, and skin contact with water and cleaning products with skin problems at follow-up. The population attributable percent risk attributed to these occupational exposures was 15.8%.

In line with the previous findings, *Study III* reported that self-reported occupational skin exposure to cleaning products and waste among men, and occupational skin exposure to water among women predicted physician-certified long-term sick leave. The population attributable percent risk attributed to these occupational exposures was 14.5 %.

Finally, *Study IV* reported a moderate variation of the relative risk of cutaneous squamous cell carcinoma between occupational categories. Excess risk of cutaneous squamous cell carcinoma was found among occupational categories with high socioeconomic status such as physicians and administrators; some with outdoor work such as seamen, public safety workers, Swedish fishermen; and some with potential exposure to chemical substances such as technical workers, printers, public safety workers, and seamen.

Conclusion

Whilst work-related skin diseases seem to be greatly underreported in Norway, this thesis provides evidence of the contribution of occupational skin exposures to the burden of skin problems and physician-certified long-term sick leave in the general working population of Norway.

A potential for primary prevention at the population level is further supported by the population risk attributable to occupational exposures that predicted skin problems and long-term sick leave.

Socioeconomic factors and, to some extent, occupational exposures seem to explain the moderate variation of the relative risk of cutaneous squamous cell carcinoma between occupational categories in Finland, Iceland, Sweden, and Norway.

Overall, this thesis has contributed to the identification of targets for preventive actions and future research within occupational dermatology.

RESUMEN

Antecedentes

Las enfermedades cutáneas causadas o empeoradas por exposiciones laborales (dermatosis profesionales) representan hasta el 30% de las enfermedades ocupacionales en Europa. Por lo tanto, constituyen un considerable problema en el marco de salud pública (European Agency for Safety and Health at Work, EU.25 report, 2008).
Las dermatosis profesionales son fundamentalmente dermatitis de contacto, de tipo irritativo y alérgico con localización frequente en las manos que pueden resultar en consequencias socioeconómicas y psicológicas perjudiciales para el individuo y la sociedad.
Adicionalmente, la incidencia del carcinoma espinocelular de la piel se ha incrementado considerablemente durante las ultimas decadas, comprometiendo fundamentalmente a trabajadores al aire libre expuestos a la radiación ultravioleta solar, como así tambien a aquellos expuestos a sustancias quimicas cancerigenas para la piel como el arsénico y los hidrocarbonos aromáticos policíclicos. En varios países europeos el carcinoma espinocelular de la piel es reconocido como una enfermedad profesional.
Las dermatosis profesionales son evitables si se implementan medidas de prevención adecuadas para reducir las exposiciones ocupacionales que las ocasionan.
En Noruega, poco se conoce acerca del rol de las exposiciones ocupacionales en el desarollo de las dermatosis profesionales. Mundialmente, hasta el día de la fecha, ningún estudio poblacional con un largo seguimiento ha descripto la variación ocupacional en el riesgo de desarrollar carcinoma espinocelular de la piel.
Es así que estudios epidemiológicos a nivel poblacional constituyen una herramienta fundamental para determinar los factores etiológicos de las dermatosis profesionales, e identificar de esta manera prioridades para la prevención.

Objetivos principales

1. Describir la tendencia de notificación de las dermatosis profesionales en Noruega por el periodo 2000-2013.
2. Investigar las asociaciones entre exposiciones laborales y el riesgo de desarrollar problemas cutáneos, como así tambien, su relación con la ausencia laboral prolongada en la población en edad activa de Noruega.
3. Identificar la variación occupacional en el riesgo relativo del carcinoma espinocelular de la piel en cuatro países Nórdicos (Finlandia, Islandia, Suecia y Noruega)

Población de estudio

El primer estudio se halla basado en información del Registro de enfermedades profesionales del Ministerio Noruego de Trabajo (n=41.181). El segundo, en una muestra randomizada de la población en edad activa de Noruega, el Estudio de Condiciones de Vida y Laborales 2006 y 2009. Centro Nacional de Estadisticas de Noruega (n=6.745). El tercero en un enlace entre la base de información del segundo estudio con información del Registro de Ausencia Laboral 2009-2010 de la Administración Noruega de Trabajo y Bienestar Social (n=6.182). Finalmente, el cuarto estudio se halla basado en información de Estudio de Cancer Ocupacional de los países Nórdicos, que ha conectado información demográfica recolectada por censos nacionales a información diagnóstica de los Registros de Cancer de los respectivos países (n=12. 900. 000).

Diseño y métodos estadistícos

Esta tésis ha utilizado dos tipos de diseño:
Primero, una serie de casos fue utilizado en el primer estudio para describir de forma retrospectiva las tendencias en la notificación de dermatosis profesionales.
Un diseño longititudinal fue utilizado para el resto, con un periodo de seguimiento de tres años para el segundo estudio, un año para el tercero y 45 años para el cuarto.
Modelos de regresión logistica incondicional fueron utilizados en el segundo y tercer estudio. También se estimó el riesgo atribuible poblacional para las exposiciones ocupacionales asociadas a los problemas cutáneos y ausencia laboral prolongada.
El riesgo relativo de carcinoma espinocelular entre categorías ocupacionales de cuatro países Nórdicos fue estimado por medio del cálculo de tasas estandarizados de incidencia, con la incidencia específica de carcinoma espinocelular de cada país como referencia.

Resultados principales

El número de notificaciones de dermatosis profesionales declinó de 487 en el 2000 a 91 en el 2013. Dermatitis por contacto representaron el 94% de los casos (41% dermatitis por contacto alérgica, 43% irritativa, 10% inespecifica). Las cinco ocupaciones más comunmente notificadas fueron mecánicos, soldadores y talleristas, personal de la salud, peluqueros, plomeros, y empleados de cocina. Las cinco exposiciones laborales más frequentemente reportadas fueron productos de limpieza, sustancias quimicas, aceites minerales y solventes, metales, adhesivos y sustancias epoxys.

El segundo estudio, reveló que exposiciones ocupacionales a factores fisícos como aire seco, trabajo húmedo, y productos de limpieza estan asociadas al riesgo de reportar problemas cutáneos durante seguimiento. El porcentaje de riesgo poblacional atribuible a estos factores fue del 15,8 %.
En el tercer estudio, la exposición cutánea ocupacional a productos de limpieza y desechos en los hombres; y al trabajo húmedo en las mujeres estuvieron asociados a un mayor riesgo de ausencia laboral prolongada.
El porcentaje de riesgo poblacional atribuible a estos factores fue del 14,5%.

En el cuarto estudio, el riesgo relativo de carcinoma espinocelular fue elevado en ocupaciones de grupos socioeconómico alto como por ejemplo médicos y administradores; algunas ocupaciones con trabajo al aire libre como por ejemplo, marineros, empleados públicos de seguridad, pescadores Suecos, jardineras; y en algunos con potencial exposición laboral a sustancias químicas como por ejemplo empleados técnicos, trabajadores de imprenta, empleados públicos de seguridad y marineros.

Conclusión

A pesar de que las dermatosis profesionales parecerían estar subnotificadas en Noruega, esta tésis doctoral brinda evidencia sobre la contribución de exposiciones laborales al riesgo de desarrollar problemas cutáneos, como así tambien al riesgo de la ausencia laboral prolongada, en la población general en edad activa de Noruega. Adicionalmente, la estimación del riesgo atribuible poblacional indicaría un potencial para la prevención a nivel poblacional.
Factores socioeconómicos y, hasta cierto punto, exposiciones ocupacionales explicarían la variación moderada en el riesgo relativo de desarrollar carcinoma espinocelular de la piel entre categorías ocupacionales de Finlandia, Islandia, Suecia y Noruega.
En general, esta tésis ha contribuido con la identificación de prioridades para la prevención de dermatosis profesionales y futura investigación en el campo de la dermatología ocupacional.

LIST OF ABBREVIATIONS

OSD	Occupational skin diseases
UVR	Ultraviolet radiation
ICD	Irritant contact dermatitis
ACD	Allergic contact dermatitis
CD	Contact dermatitis
AD	Atopic dermatitis
cSCC	Cutaneous squamous cell carcinoma
BCC	Basal cell carcinoma
PAH	Polycyclic aromatic hydrocarbons
LTSL	Physician-certified long-term sick leave
SES	Socioeconomic status
DAGs	Directed acyclic graphs
OR	Odds ratios
95% CI	95% Confidence interval
PAR	Population attributable risk
SIR	Standardised incidence ratio

CHAPTER I: INTRODUCTION

Skin diseases are associated to a substantial burden in the global context of health: they are both widespread and among the most prevalent and disabling diseases, representing a source of considerable loss of healthy life. Collectively, skin diseases were the 4th leading cause of non-fatal burden expressed as years lost due to disability in 2010.[1]
As an example, work-related skin diseases, most of them preventable by reduction of occupational exposures, impose a significant burden to the society. According to the World Health Organization, they represent a challenge for all workers; and the EU Commission has defined insufficient prevention a top priority problem.[2] Moreover, the increasing incidence of cutaneous squamous cell carcinoma[3] and its association to occupational exposures is a matter of big concern.[4-5]
Therefore, epidemiological studies at the population level can contribute to identify potential targets for prevention of work-related skin diseases.
To begin with, this introduction will display the main findings of two systematic literature searches performed for the purposes of this thesis: the first aimed to identify Norwegian studies focusing on work-related skin diseases for the last 35 years, and the second aimed to identify population-based studies with a prospective cohort design focusing on occupational exposures and skin diseases.

1.1 NORWEGIAN STUDIES ON THE TOPIC OF WORK-RELATED SKIN DISEASES

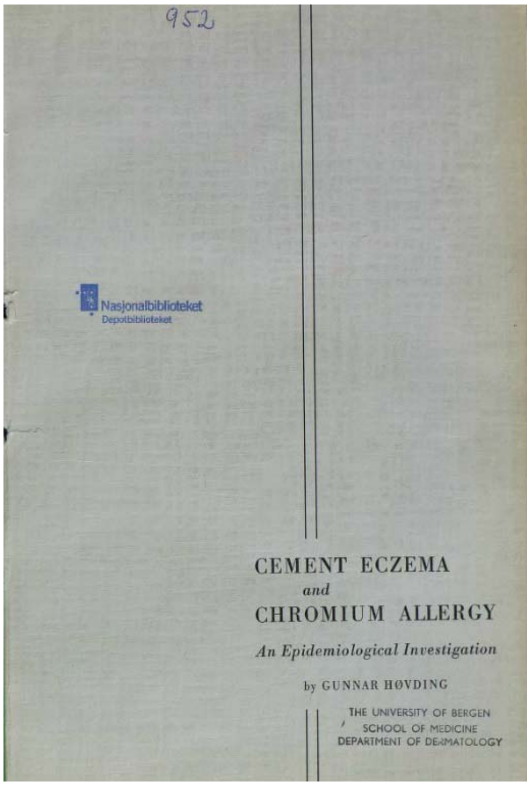
The first studies

Epidemiological studies on work-related skin diseases have been uncommon in Norway.[6] The first reported Norwegian publication seems to be one report on petroleum acne from 1921.[7] The first general overview of dermatitis as a work-related disease was a leaflet made by Professor Niels Danbolt in 1942 (Figure 1, left).[8] The same year, occupation was acknowledged, in the Journal of the Norwegian Medical Association, as a common cause for dermatitis.[7]

Overall, only two Ph.D. studies about occupational dermatology were performed. Gunnar Høvding (1970) performed the first one, focusing on cement dermatitis caused by chromates (Figure 1, right).[9] From that point, cement dermatitis has been identified as one of the most serious occupational health problems in building trades and industries.[10] In 1986, Petter Kristensen described the occurrence of hand dermatitis among a group of Norwegian hairdresser apprentices.[11] Several years later, Jan-Øivind Holm (1994) performed an epidemiological study of hand dermatitis and atopy among hairdressers and trainees.[12]

The single population-based study that took into account occupation as a risk factor for hand dermatoses and sick leave was performed for more than 30 years in the county of Troms.[13]

Figure 1. First Norwegian studies on work-related skin diseases.



On the left: picture of the first Norwegian leaflet about dermatitis as a work-related disease prepared by Prof N. C. Gauslaa Danbolt (1900 – 1984).[8] On the right: the first Norwegian Ph.D. about occupational dermatology by G.Høvding (1970).[9] Source: National Library of Norway. Free to use without restriction.

Systematic literature search

A systematic literature search was conducted in the database OVID Medline to investigate the number of Norwegian studies on work-related skin diseases, the study design and population sample for the period 1980-2015, with the last search on 19 November 2015. This search yielded 49 articles. Additionally, 5 additional articles known by the author, but not retrieved by the search were included. The already published articles of this thesis were excluded. All articles were full read, and classified according to the design, population sample, and level of evidence (Table 1).

Table 1. Overview of Norwegian studies on work-related skin diseases (1980 – 2015).

Observational studies		
Study design (number)	**Population (Author/s and year/s)**	**Level of evidence[1]**
Cohort (3)	Industrial painters: Romyhr et al. 2006.[14] Farmers: Nordby et al. 2004.[15] Hairdressers: Holm, study VI 1994.[12]	**II-2**
Cross-sectional (24)	Aquaculture farm: Granslo et al. 2009.[16] Seafood industry: Aasmo et al. 2005,[17] Bang et al. 2005,[18] Kavli & Moseng 1987,[19] Beck et al. 1983.[20] Dental health personnel: Jacobsen et al. 2003,[21] Morken et al. 1999,[22] Jacobsen & Hensten-Pettersen 1995,[23] Jacobsen & Pettersen 1993,[24] Jacobsen et al. 1991,[25] Jacobsen & Pettersen 1989.[26] Health personnel: Holter et al. 2002,[27] Holm 1995,[28] Kavli et al. 1987.[29] Ship's engineers: Svendsen & Hilt 1997.[30] Mechanics: Moen et al. 1995.[31] Car painters: Grønberg et al. 1994.[32] Hairdressers: Holm & Veierød, study I to V, 1994.[12] General population: Kavli 1984.[13] Shrimp peelers: Kavli 1985.[33] Wood workers: Efskind 1980.[34]	**II-2**
Case-series (14)	Incidence of occupational skin diseases as compared to other European countries 2000–2012 Stocks et al. 2015.[35] Health personnel: Dahlin et al. 2014,[36] Steinkjer 1998.[37] Reporting of work-related diseases in 2006: Samant et al. 2008.[38] Divers: Ahlén et al. 2003.[39] Genotypes of Pseudomonas aeruginosa on skin infections in occupational saturation diving systems: Ahlén et al. 2001.[40] Registration of patients with work-related contact dermatitis: Holm & Engesland (1994)[41] Military personnel: Selvaag 2000.[42] Beauticians: Selvaag & Holm 1995.[43] Construction workers: Skogstad & Levy 1994.[44] Electromechanic workers: Leira et al. 1992.[45] Electrical workers: Skyberg & Ronneberg 1986.[46] Wood workers: Johnsson et al. 1983.[47] Office workers: Nilsen 1982.[48]	**II-3**
Case-report (2)	Construction workers: Tindholdt et al. 2005.[49] Beauticians: Selvaag et al. 1995.[50]	III
Review (3)	Chemical hazards in offshore work: Moen et al. 2004.[51] Prevention of work-related latex allergy: Mehlum 1998.[52] Delayed allergy against rubber gloves. An occupational dermatitis among health personnel Holm et al. 1993.[53]	
Letter to editor (2)	Little research activity in occupational dermatology in Norway: Alfonso et al. 2015.[6] Health personnel: Holm 1992.[54]	
Unclassified (3)	Surveys in occupational dermatology: Nyfors 1994.[55] Occupational dermatitis among fishermen: Tellnes 1997.[56] Occupational eczema: diagnosis and treatment: Kavli & Kristensen 1985.[57]	

1. US Preventive Services Task Force (1989). Guide to clinical preventive services report of the U.S. Preventive Services Task Force. Washington, DC: The Task Force.

As Table 1 shows, the most frequent study design was cross-sectional, followed by case-series, both focusing on specific risk groups and on information from reporting systems.

Dental health personnel and hairdressers were the risk groups investigated most frequently. However, most of these studies were performed during the 1990 and exposure scenarios may be different today.

The studies with a prospective cohort design were performed among hairdressers,[12] industrial painters,[14] and male farmers.[15]

Whilst Norway has a great part of the working population employed in the offshore sector, this search did not retrieve many study with special focus on this group. For instance, only one review described that skin problems due to occupational exposure to chemical hazards are frequent among offshore workers.[51]

In brief, most of the studies focused on contact dermatitis, two on skin infections caused by *Pseudomonas aeruginosa* among divers,[39,40] and one on cutaneous squamous cell carcinoma of the lips among farmers.[14]

This search did not retrieve any intervention study.

1.2 POPULATION-BASED STUDIES ON OCCUPATION AND SKIN DISEASES

A systematic literature search aimed to identify population-based studies with a prospective cohort design focusing on occupational exposures and skin diseases was conducted in the database OVID Medline, with the last search on 10 October 2015. Keratinocyte carcinomas were not included, as metanalyses focusing on associations between occupational exposure to solar UVR and cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are available.[4,58]
The search strategy included a combination of free text terms indexed by a hierarchical controlled vocabulary (MeSH and Emtree) adapted for OVID Medline (Appendix I).
Table 2 shows the inclusion criteria.

Table 2. Inclusion criteria for the systematic literature search.

Study subjects	Population-based
Design	Prospective cohort
Exposure	Occupational exposures
Outcome	Work-related/Occupational dermatitis, skin disease, skin problems, skin complaints, skin conditions, dermatoses
Language	English, Norwegian, Danish, Swedish, Spanish
Period	1980 – 10/10/2015

The search yielded 297 articles. All titles and abstracts were assessed against the inclusion criteria for possible relevance (Table 2).
At this point, only population-based studies dealing with occupational exposures and skin diseases were included. Three additional articles identified in references lists, but not retrieved by the search were also included.
From 26 eligible articles, which were reviewed two times, 15 studies still lacked a population-based sample (Figure 2).
After the qualitative assessment, two studies with a prospective cohort design[59,61] were identified from the 11 population-based studies (Figure 2).

In brief, most of the population-based studies had a cross-sectional design. Among the studies with a prospective design, one single study assessed associations between occupational exposure and risk of hand dermatitis. However, the focus was merely on frequent hand washing at work.[61]
Table 3 shows an overview of the 11 population-based studies included in the qualitative synthesis.

Figure 2. Prisma flow diagram.

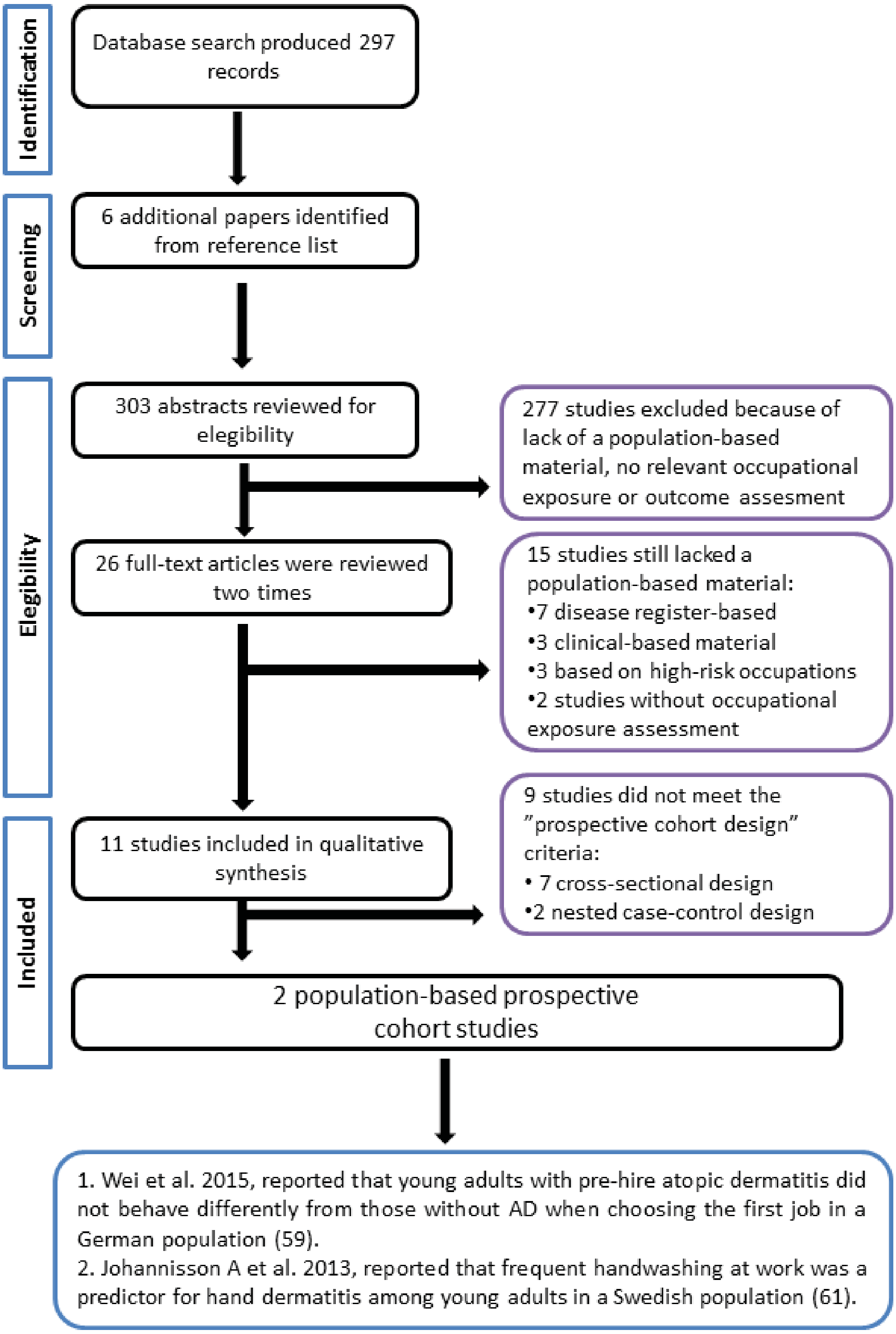


Table 3. Overview of population-based studies regarding occupation and skin diseases.

First author	Year	Country	Study population	Study design	Methods	Conclusions
Wei[59]	2015	Germany	2,051 subjects aged 19-24 years were followed-up from childhood.	Prospective cohort study.	Survey data. Exposure variable: atopic dermatitis. Job counselling Adjustment for potential confounders: parental history of asthma, allergic rhinitis, atopic dermatitis. Socioeconomic status Smoking. Outcome variable: type of occupation (high risk job for hand eczema vs. low risk job for hand eczema). Use of protective measures and skin care. Only complete cases (participants with no missing data on exposures, outcomes, and confounders were included for descriptive analyses) Univariate logistic regression models. Multiple logistic regression models. (Imputation methods were used for missing data)	Young adults with pre-hire AD did not behave differently from those without AD in terms of choosing their first job. Subjects with AD were not significantly more likely to use secondary preventive measures than healthy subjects when they were under high-risk exposures for hand eczema. Subjects with parental history of AD or pre-employment counselling seemed to have increased use of secondary preventive measures. Main limitation: The outcome measure was based on the first job choice at the very beginning and the subject´s careers and might represent only temporary or short-term part time jobs.
St. Louis[60]	2014	USA	A random sample of the general adult population of three states: Connecticut, Kentucky, and Michigan.	Cross-sectional population based study	One-year prevalence for self-reported dermatitis. Received medical attention due to skin conditions. Work-related dermatitis diagnosed by a medical doctor. Personal perceptions of work-relatedness, Job changes associated with dermatitis.	The overall one-year prevalence for dermatitis was between 7.9 to 15.6%. Female responders were more likely to report dermatitis. Between 13 to 18% of all dermatitis were related to work by using a definition of work-related dermatitis that included both clinician supported opinions, and the opinions of individuals themselves. Including patient´s perceptions of work-relatedness produced a larger prevalence estimate for work-related dermatitis than the previously published estimate of 5.6% which included only those cases of dermatitis attributed to work by healthcare professionals.

Johannisson [61]	2013		2,403 young adults, 16 – 19 years old in (1995) and aged 29 – 32 years, 13 years later (2008).	Prospective cohort study (13-year follow-up)	Survey data regarding one-year prevalence of hand eczema, childhood eczema, asthma and rhinoconjunctivitis, household size and family structure, occupation and everyday activities, hand washing, and skin care.	Incidence of hand eczema in early adulthood tends to be associated with factors in everyday life such as frequent hand-washing. The early onset of hand eczema seemed to be related to endogenous risk factors such as a history of childhood eczema. The higher frequency of hand eczema among women depended on exogenous factors.
Meding[62]	2013	Sweden	A random sample of the general population of Sweden. (Nationwide Environmental Health Survey 2007)	Cross-sectional population based study	Self-reported data regarding occupational and non-occupational exposure to water from two Swedish health surveys (Nationwide Environ-mental Health Survey 2007: non occupational exposure to water) and Stockholm Public Health Survey 2006 (occupational exposure to water) Chi-square tests to test differences between women and men. Prevalence proportion ratios to analyse associations between reported exposure to water and sex, age, children < 6 years, daily smoking, general health, and hand eczema.	More than 20% of the population reported water exposure more than 20 times during an entire day, and 6% of the population reported occupational exposure to water. Women reported higher exposure than men both during an entire day and at work. High water exposure over the entire day was found to be considerably more frequent than exposure at work. Thus, a significant proportion of water exposure seems to occur outside work.
Anveden[63]	2006	Sweden	A random sample of 3,000 individuals aged 20-65 years was drawn from the population Registry in Göteborg. Response frequency: 74%	Population-based, retrospective nested case-control study.	Postal questionnaire for self-reported hand eczema during the last 12 months. (Hole population sample) Telephone standardised questionnaire regarding skin exposures and use of protective gloves at work, and during activities off work. (Retrospective assessment of skin exposures). Matched analysis comparing	Individuals with or without hand eczema seemed to have similar exposure to skin irritants. Women reported more wet exposure than men at work as well as in leisure time. Women and men with high wet exposure at work also tended to have high wet exposure at leisure time. Using job titles as a proxy for exposure gives misclassification, which may result in underestimation of hand eczema risk.

					exposure in cases and controls, and changes of exposure over time was performed using sign test. For comparison of prevalence in male and females X^2 statistics or Fisher´s exact test.	
Nyren[64]	2005	Sweden	Medical records of the compulsory school health services in Stockholm were reviewed for people born 1960 and 1969. 600 cases with signs of atopic dermatitis and 600 controls matched for age and sex were identified. Response frequency: 71%	Population-based nested case-control study -Case-control design limits its interpretation)	A postal questionnaire assessed occupational exposure to water, detergents, chemicals and frequency of hand washing, choice of job, past and present skin disease, sick leave, and change of job due to eczema. Chi-square test was used for comparisons of the proportions. Means were compared with Student T-test.	A history of atopic dermatitis in childhood did not seem to influence the choice of job nor hazardous occupational skin exposure (the proportions of cases and controls in jobs with high risk of hand eczema were similar, as was the exposure to water, detergents, chemicals and hand washing). The self-reported cumulative prevalence of hand eczema was 42% for the cases and 13% for the controls. A history of atopic dermatitis is associated to an increased risk of job change, sick leave, and medical consultations due to the increased risk of hand eczema (Among the cases 9% reported job change due to eczema compared with 2% of the controls. The corresponding proportion of sick leave were 10% and 2%)
Montnémery [65]	2005	Sweden	Random sample of the general population. Response frequency: 78.1%	Cross-sectional population based study	Postal questionnaire regarding: respiratory symptoms, smoking, hand eczema	Lifetime prevalence varied between 5.7% and 16.7% among women and between 5.2% and 9.5% among men. Female sex and smoking were independent risk factors for reporting 1-year prevalence of hand eczema, age was inversely related. Aggregated risk occupation or categorized occupations such as medical and nursing work, production or service were not significantly associated with 1-year prevalence of hand eczema.
Montnémery [66]	2003	Sweden	Random sample of the general adult population. (12,071 adults, aged 20–59 years, living in southern Sweden) Response frequency: 70.1%	Cross-sectional population based study	Postal questionnaire. Self-reported eczema, upper and lower respiratory symptoms, asthma and Chronic Bronchitis Emphysema (CBE). Multiple logistic regression analysis was applied to estimate the association between the risk factors (heredity, self-reported asthma	Self-reported eczema is a common disease in an adult population especially among women. Eczema seems to be linked to environment factors, obstructive pulmonary diseases and rhinitis. The prevalence of self-reported eczema among the economically active population varied from 17.1% to 8.2% with the highest rates among assistant non-manual employees.

					and CBE, nasal symptoms, socioeconomic group, environmental factors, age, gender and smoking habits) and self-reported eczema.	
Meding[67]	2002	Sweden	Random sample of the general working-age population in 1983 and 1996	Cross-sectional population based study	Postal questionnaire regarding: skin atopy, hand eczema during the last 12 months, previous history of hay fever, asthma. Occupational exposure of the hands (solvents, oils, paint). Occupation. Response frequency: 83.5% in 1983 and 73.9 % in 1996. Univariate comparison of prevalence by X^2 statistics. In the analysis of logistic regression, the PROC LOGIST procedure of SAS was used and the confidence intervals were calculated using Student's t distribution	Hand eczema in Swedish adults decreased between 1983 and 1996 despite an increasing prevalence of childhood eczema. Secular changes in reporting hand eczema in childhood eczema may explain some of the changes, but a decreased occupational exposure to skin irritants is a probable cause, implying that occupational factors may be important predictors of hand eczema.
Behrens[68]	1994	USA	General working population	Cross-sectional population based-study	Prevalence estimates based on self-reported data from a National Survey	Prevalence of dermatitis among people recently working was 11.2%, which represents 13.7 million workers. Three occupational groups had the highest prevalence due to contact with substances at work: physicians, dentists, nurses, pharmacists, and dietitians, workers in service occupations, and health care therapists, technologists, technicians, and assistants.
Meding[69]	1990	Sweden	A random sample of 20,000 individuals aged 20-65 years old the general population of Gothenburg. Response frequency: 82.9%	Cross-sectional population based-study	Postal questionnaire, and a random sample of the answers were invited to dermatological examination	1-year prevalence of hand eczema: 11%. Point-prevalence: 5.4%. Most common diagnosis; ICD (35%), atopic hand eczema (22%), ACD (19%). Hand eczema was twice as common in females as in males. A higher period prevalence for hand eczema was found for exposure to water and detergents, dust and dry dirt, and unspecified chemicals. 8% of the individuals with hand eczema changed occupation because their hand eczema. Regular or frequent glove use was more common among people with hand eczema.

		69% of the individuals reported medical consultation for their hand eczema. 21.4% reported a sick leave period for minimum 7 days. The mean total sick leave time was 4.0 weeks for all hand eczema patients. The number of sick-leave periods was larger for service workers. Predictive factors for hand eczema: childhood eczema, sex, occupational exposure, hay fever/asthma, service occupation, exposure: water, detergent. Foodstuffs and age were negative correlated. Severity of hand eczema: Mean duration years: 12.0 (ACD), 9.9 (ICD), 16.3 (atopic hand eczema). Change of occupation (%): 14.4 (ACD), 7.0 (ICD), 5.9 (atopic hand eczema).

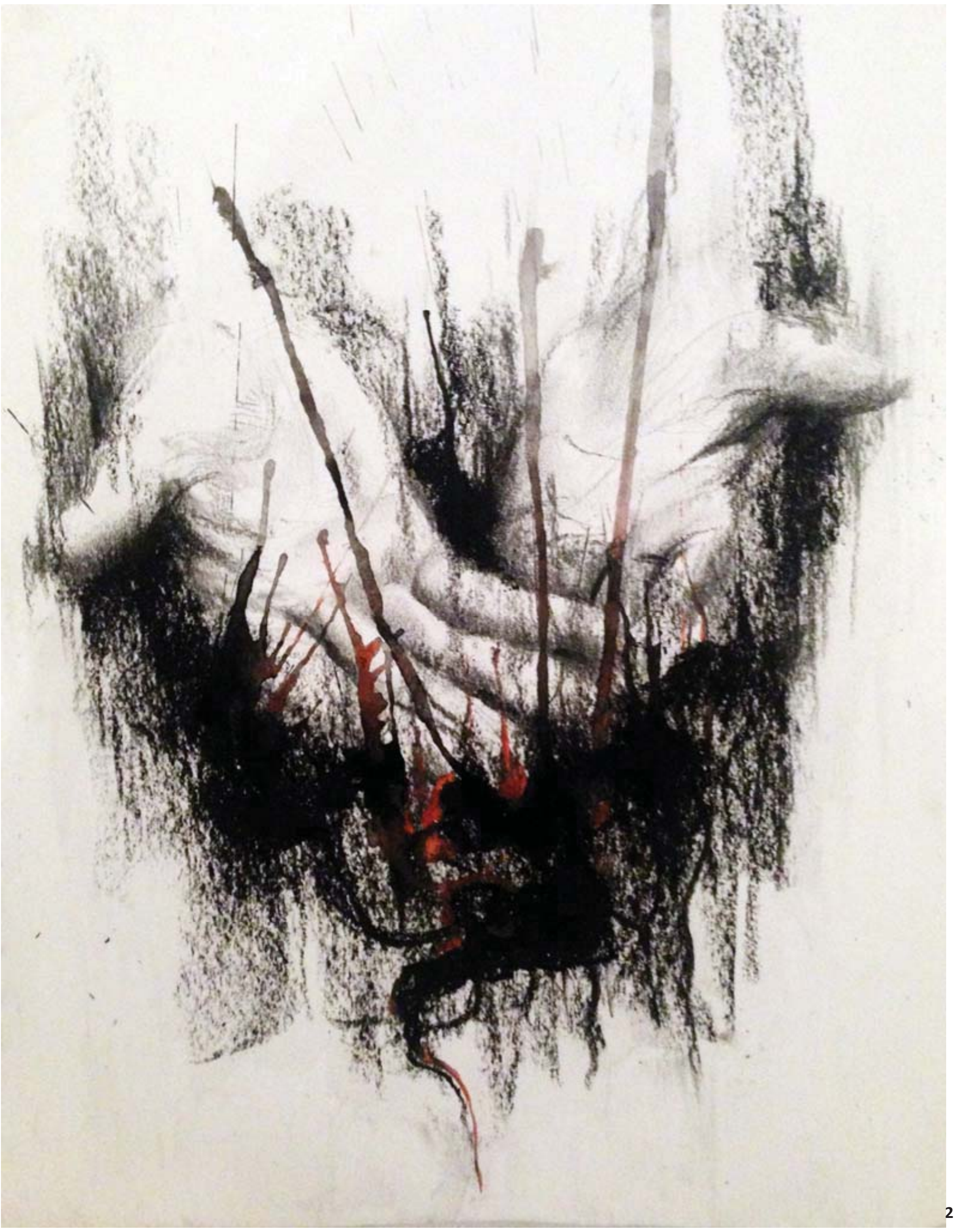
1.3 CONCLUSION OF THE SYSTEMATIC LITERATURE SEARCH

1. Scarce research on the topic of work-related skin disease has been performed in Norway during the last 35 years. This is in line with the findings of a bibliometric study performed by Gjersvik et al. 2010,[70] which reported that Norway has performed poorest within dermatological research for the period 1989-2008 in comparison to other Nordic countries.
2. Most of the population-based studies focusing on occupation and skin conditions have a cross-sectional design. Such a design is more prone to healthy worker survivor bias because individuals with severe disease may have left the workforce.
3. The search did not retrieve any prospective cohort study that investigated associations between a range of occupational exposures and skin problems plus its consequences in terms of long-term sick leave in a general working population.
4. Though, increasing evidence of an association between occupation and the risk of developing cutaneous squamous cell carcinoma and basal cell carcinoma is available,[4] the metanalyses did not include any population-based study with a long follow-up.

Overall, the results of the systematic literature search demonstrate that evidence about the epidemiology of work-related skin diseases in Norway is limited, and that population-based studies with a prospective cohort design focusing on occupational exposures and skin diseases are scarce.
Indeed, the paucity of population-based studies in occupational dermatology has recently been highlighted as an unmet need by a group of dermatologists and occupational physicians.[71]

1.4 THESIS OUTLINE

The research questions and aims are presented in Chapter II.
Chapter III provides theoretical background of relevance for *Study I* to *IV*. Given that part of this thesis is based on self-reported data (*Study II* & *III*), this chapter will also revise the pathophysiology of work-related skin diseases.
The material and methods are described in Chapter IV. The main findings of *Study I* to *IV* are summarised in Chapter V. Additionally results of supplementary analysis are also presented in this chapter. Chapter VI contains a discussion of the results in the light of validity issues. Lastly, conclusions and practical implications are presented in Chapter VII.



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2. Painting made by **Ragnheiður Þorgrímsdóttir** using Charcoal technique. The black represents occupational exposures damaging the skin. The red means blood, wound, and fear.

Ragnheiður Þorgrímsdóttir was born in Iceland. She graduated from Accademia di Belle Arti in Florence, Italy in 2015. She is currently taking a master in Fine Arts at the New York Academy of Arts in New York. http://ragnpaint.com/

CHAPTER II: AIMS

2.1 Research questions

At the beginning of the study, the following research questions were formulated:

1. How has the notification trend for work-related skin diseases been from 2000 to 2013? Which are the most common diagnoses, occupations and occupational exposures for the notified work-related skin diseases in Norway?

2. To what extent is occupational skin exposure to water, chemicals, irritants, and physical factors in 2006 and/or 2009 associated with skin problems in 2009 in the general working population of Norway? Which risk factors are the most important for skin problems in the general working population, evaluated with the population attributable risk (PAR)? To what extent can sex differences to report skin problems be explained by differences in the distribution of exposures?

3. To what extent is occupational skin exposure to water, chemicals, physical, and biological factors in 2009 associated to physician-certified long-term sick leave in the general working population of Norway in 2010?

4. What is the variation of the relative risk of cutaneous squamous cell carcinoma between occupational categories of four Nordic countries? To what extent can sex differences in the relative risk of cSCC in the Nordic countries be explained by sex differences in the distribution of occupational categories?

2.2. Aims

To answer the previous research questions, the following specific aims have been achieved:

1. To describe the frequency of notified work-related skin diseases, occupations, and occupational exposures most commonly reported to the Norwegian Labour Inspectorate´s Registry of work-related skin diseases for the period 2000 – 2013 ***(Study I)***.

2. To investigate associations between self-reported occupational skin exposure to irritants and physical factors with skin problems in the general working population of Norway. To calculate the population attributable risk (PAR) for occupational skin exposures associated to skin problems ***(Study II)***.

3. To investigate associations between self-reported occupational skin exposure to chemical, biological, and physical factors with physician-certified long-term sick leave in the general working population of Norway. To calculate the population attributable risk (PAR) for occupational skin exposures associated to physician-certified long-term sick leave ***(Study III)***.

4. To describe variation in the relative risk of cutaneous squamous cell carcinoma between occupational categories of four Nordic countries (Finland, Iceland, Sweden, and Norway) ***(Study IV)***.

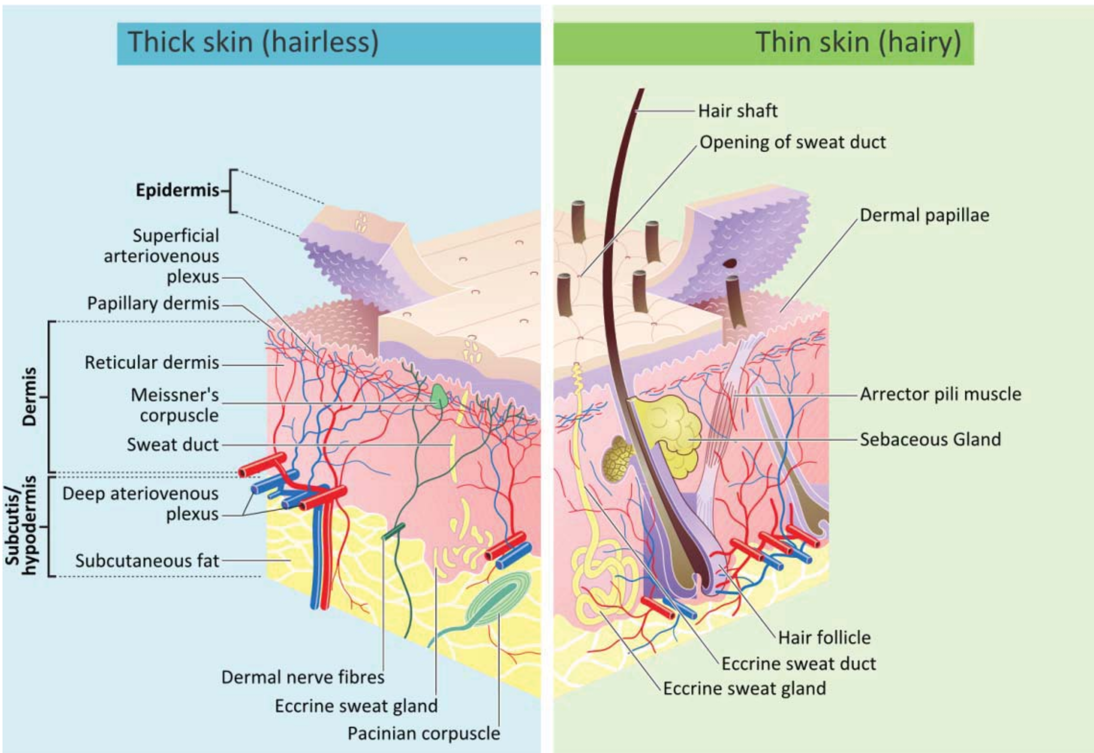
CHAPTER III: THEORETICAL BACKGROUND

I will first provide background information about the structure of healthy skin to better explain how occupational exposures can lead to an alteration of the skin barrier, subsequent skin problems, and disease. After a definition and classification of work-related skin diseases, both endogenous and exogenous risk factors, with special focus on contact dermatitis and cutaneous squamous cell carcinoma, will be explained. The consequences of work-related skin diseases in terms of sick leave will be then illustrated.

3.1 THE HEALTHY SKIN

The skin is human body´s largest organ and consists of the epidermis, the dermis, and subcutis - which is essentially adipose and connective tissue[72] (Fig 3).

Figure 3. Skin structure: thick skin, thin skin, and its adnexa.[73]

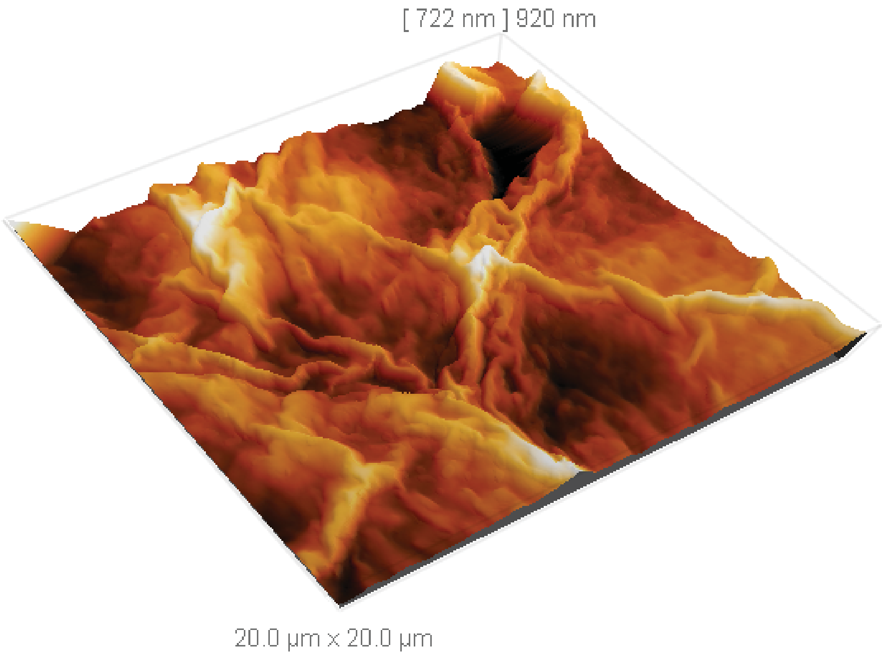


The epidermis comprises a multi-layered epithelium, the interfollicular epidermis, and its adnexa (hair follicles, sebaceous glands, and sweat glands). Both the distribution of adnexal structures and the thickness of the interfollicular epidermis varies in different body sites.[72] Thermoregulation, the most important function of the adnexa, is facilitated by hairs and sweat.

More than 90% of the cells in the epidermis consist of the keratinocytes, which are perpetually renewed from the *stratum basale* to the *stratum corneum* in a differentiation process that takes between three to seven weeks.[74] The keratinocytes suffer biochemical and structural modifications to become to corneocytes, which are anucleated flattened cells containing keratin.

Additionally, a "cement" made of lipids, cholesterol, free saturated fatty acids, and ceramides is secreted into the intercellular spaces, which increases cell cohesion and thereby contributes to making the epidermis an effective barrier. Moreover, corneodesmosomes link corneocytes to each other making this barrier even more effective. The breakdown of these corneodesmosomes provokes the final phenomenon of desquamation of the corneocytes.[74]
Figure 4 shows a topographic picture of corneocytes from the author´s skin taken with Atomic Force Microscopy.[3]

Figure 4. Topographic picture of corneocytes.



3. Atomic Force Microscopy is a method for imaging surfaces with demonstrated resolution on the order or fractions of nanometer. This nanoscale topography can offer multiple advantages i.e. in predicting individual risk for skin diseases. I am indebted to Dr. Nils Anspach DME Nanotechnologie GmbH, Braunschweig, Germany for demonstration and the picture.

All these architectural elements in the *stratum corneum* enable the skin to fulfil its essential function as a "protective interface between the body and the external environment".[72,74]

Between 5 to 10% of the cells of the epidermis consist of melanocytes located in the *stratum basale.* They are derived from neural crest progenitors and are responsible for pigmentation and photoprotection by the production of brown/black eumelanin and red pheomelanin.

Besides the basal production of melanin, which is hormone-regulated, diverse stimuli can also activate its production.[75] For example, the penetration of solar ultraviolet radiation (UVR) in the skin induce DNA damage in the keratinocytes leading to p53 activation and consequently up-regulation of proopiomelanocortin. A post-translational cleavage of propiomelanocortin produces β-endorphin**[4]** and α-MSH which stimulates melanin synthesis and transfer of melanosomes (melanin-containing vesicles) to keratinocytes.[75]

Chronic exposure to UVR results in elevated β-endorphin levels**[4]** associated to analgesia and dependency.[75]

Besides protecting us, the skin is colonized by a dense community of commensal microorganisms including bacteria, viruses, and fungi (microbiota), of which the diversity may be essential for a healthy skin.[76] For instance, a potential association of the microbiota with skin inflammatory disorders such as atopic dermatitis, acne, and psoriasis has been suggested.[76]

The <u>dermis</u> is histologically organized into three layers: the papillary layer, the reticular layer, and the sub-cutis. The main resident cell type is the fibroblast, which density is higher in the papillary dermis, whilst the reticular dermis is made up of fibrillar collagen.[72]

The subcutis, historically termed *hypodermis*, consist of lobules of adipose tissue surrounded by partitions of thin connective tissue which form septae, through which the large arterial and venous blood vessels designated for the skin pass. Lymphatics accompany the blood vessels into the hypodermis and the dermis, but are not visible.[72]

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4. A recent study reported that UVR-induced β-endorphin production in skin mediates addiction to UV light in mice, suggesting the presence of an endogenous opiate-mediated mechanism for primordial UV addiction (G. L. Fell, K. C. Robinson, J. Mao, C. J. Woolf, D. E. Fisher, Cell 157, 1527–1534 (2014). Future skin cancer prevention efforts may benefit from considering UVR-seeking behavior in the context of biological addiction.[75]

Different types of nerve endings within the dermis and epidermis provide the skin with a variety of sensations from pleasure to painful.[72] For example, sensations to cold, heat, vibration, and chemical factors.

Overall, the healthy skin assures protection against physical agents, chemicals, mechanical injuries, impact, light, UV radiation, cold, and heat. Extrinsic factors such as occupational exposure to chemical, physical, and mechanical exposures may threaten skin integrity, leading to the development of work-related skin problems and subsequent disease.

3.2 DEFINITION OF WORK-RELATED/OCCUPATIONAL SKIN DISEASE

Occupational skin diseases (OSD) have been reported since the 18th century (Pott, 1775).[77]
Work-related skin disease/OSD can be defined as skin diseases caused or aggravated by working conditions.[78] A common definition of occupational skin disease (or dermatoses) is still not available in Europe at the moment.[71] Definitions vary according diverging national legal requirements regarding compensation.[71] It has to be mentioned that the lack of a common definition for work-related skin diseases/OSD across Europe represents a challenge for the comparison of epidemiological studies across countries.

The Norwegian Labour Inspectorate defines *work-related diseases* as all conditions that are attributed to, or exacerbated by exposures at the workplace.[38] Despite of work-related and occupational diseases are often used as synonymous, an important distinction between these definitions exists. Only those conditions included in the Norwegian Labour & Welfare Administration's list of compensable work-related diseases are defined as occupational diseases, *sensu strictu,* by the Norwegian Ministry for Health Care Services.[38]

For the purposes of this thesis, the term work-related skin diseases will be preferred. Given that the literature does not always make a clear distinction between these conditions, the term work-related skin disease/OSD can be used indistinctly according to the cited article.

3.3 CLASSIFICATION OF WORK-RELATED SKIN DISEASES

Lachapelle et al. 1992,[79] suggested a classification of skin conditions according to different types of occupational exposure (Table 4). Contact dermatitis of the hands comprises the majority of the cases (between 90-95%) of work-related skin diseases.

In the general population, of mostly European countries, the one-year prevalence of hand dermatitis ranges from 6.5% to 17.5%.[80] For example, Swedish estimates range from 7.5% to 15.8%.[61] Among risk groups for work-related skin disease such as hairdressers, health personnel, cleaners, construction workers, kitchen workers, etc., the prevalence estimates for hand dermatitis range from 22% to 42%.[2]

The draft of the next International Code Diseases (ICD)-11 proposes a comprehensive classification of work-related skin diseases, which also includes exacerbation of constitutional dermatitis due to occupational exposures, occupational-acquired dermatoses due to exposure to cold or heat, and skin cancer due to chemical and physical hazards.[71]

Table 4. Classification of work-related skin diseases (Adapted from Lachapelle et al. 1992).[79]

Occupational exposure	Skin disease
Chemical agents	Chemical skin injury Irritant contact dermatitis Allergic contact dermatitis Protein contact dermatitis Phototoxic dermatitis Urticaria Acne (E.g. oil acne, chloracne) Leucoderma/vitiligo-like skin diseases (phenols, catechol, and hydroquinone causing death of melanocytes and subsequent depigmentation) Scleroderma like diseases (vinyl chloride monomer, silica dust, organic solvents, and epoxy resins have all been reported as associated with scleroderma-like conditions) Cutaneous squamous cell carcinoma Melanoma skin cancer
Physical agents	Irritant contact dermatitis due to physical agents (heat, cold, dry air) Physical urticaria (cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, vibratory angioedema) # Cutaneous squamous cell carcinoma (UVB radiation, ionizing radiation) Melanoma skin cancer (UVB radiation) Raynaud phenomenon (vibration)
Biological agents	Bacteria (E.g. erysipeloid, Querry fever, Borreliose) Virus (E.g. orf –contagious pustular dermatitis) Fungies (E.g. Tinea pedis) Parasites Alga (Protothecosis)

#Zuberbier T, et al. (2014). *Allergy*, *69*, 868–887.

3.4 IRRITANT CONTACT DERMATITIS

It is an inflammation of the skin resulting from exposure to an exogenous agent i.e. chemical, physical, mechanical exposures, or a combination of them, which does not require prior sensitization of the immune system.[81]
Cutaneous responses depend on the type of irritant (detergent, acid, alkali, oil, organic solvent), the concentration at which the irritants comes into contact with the skin, the type of exposure (dose-effect relationship), and individual factors.
Additionally, clinical manifestations are modified by environmental factors such as mechanical pressure, temperature, humidity,[81] and individual characteristics (age, sex, ethnicity, pre-existing skin disease, atopic dermatitis, and anatomic region exposed). Therefore ICD, is not an independent clinical entity, but rather a spectrum of disease. Table 5 shows a classification of ICD, according to Chew & Maibach, 2006.[81]

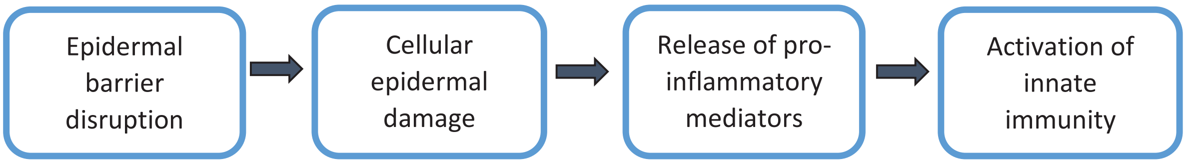
Table 5. Classification of irritant contact dermatitis (ICD) (Adapted from Chew & Maibach 2006).[81]

Type of Irritation	Onset	Example irritants
1. Acute	Acute: often a single exposure	Highly alkaline or highly acidic compounds.
2. Delayed acute ICD	Delayed: 8 – 24 h or longer	Hexanediol, butanediol diacrylates, dithranol, benzalkonium chloride.
3. Irritant reaction	Acute: often multiple exposures	Detergents, soap, water.
4. Chronic ICD	Slowly developing: over weeks to years	Sodium lauryl sulfate, solvents, detergents, water, organic acids.
5. Traumatic ICD	Slowly developing: after trauma	Burns, lacerations with allergen exposure.
6. Acneiform ICD	Slowly developing: weeks to months	Chlorinated aromatic hydrocarbons, metals, mineral oils, greases, tars, metalworking fluids, cutting oils.
7. Non-erythematous irritation	Slowly developing	Cosmetics, textiles.
8. Sensory irritation	Acute: seconds to minutes after exposure	Lactic acid, cosmetics, urticariants.
9. Friction dermatitis	Slowly developing	Associated with paper work.
10. Asteatotic irritant dermatitis	Slowly developing	Environmental (winter, dryness).

Pathogenesis

The major pathophysiological changes of ICD are summarized in Figure 5.

Figure 5. Irritant contact dermatitis: major pathophysiological changes.



The initiating event of ICD is the disruption of the epidermal barrier by irritants which results in increased skin permeability and trans-epidermal water loss.[82]
Repeated and frequent occupational skin exposure to chemical, physical, and mechanical stimuli induces epidermal keratinocytes to release various cytokines and chemoquines. For instance, the cytokine IL-1α is available as a preformed pool and quickly secreted upon keratinocyte damage or activation, being considered "the main switch" in the activation of the skin inflammatory cascade. TNF-α is also secreted by the keratinocytes upon activation.[82] This "alarm signal", a common phase in the skin response to both irritants and allergens, triggers the release of other cytokines and chemoquines such as IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (GM-SCF), and other pro-inflammatory mediators that recruit cells to the damaged skin.[82]

In addition, upon disruption and/or damage of the *stratum corneum,* changes in the gradients of calcium, other ions, the pH, and cytokines release activate restoration of the skin barrier by triggering proliferation of keratinocytes as well as the synthesis and secretion of lipids.[83]
Nevertheless, a chronic increase of these cytokines may lead to the hyperproliferation of the epidermis as seen in chronic dermatitis.

Cumulative irritative contact dermatitis

Repeated skin exposure to single or multiple external agents, especially weak irritants such as water, leads to the development of cumulative chronic ICD,[82] which develops slowly after repeated sub-threshold irritative damages to the skin if the time between the insults is too short for complete restoration of skin barrier function (Malten, 1981).[84] Cumulative and chronic ICD are synonymous, and include clinical symptoms and signs such as itching and pain due to cracking of the hyperkeratotic skin, dryness, erythema, and vesicles.[81,82]

The symptoms and signs will develop after the damage exceeds a certain “manifestation threshold”, which is individually determined, and can take a period from days to weeks or even years.[84] For instance, a decreased threshold or an increased restoration time leading to earlier development of clinical ICD may be characteristic of persons with sensitive skin.

Hardening phenomenon

Repeated skin exposure to irritants leads, in some individuals, to the development of an adaptive skin “tolerance” response, which is known as the *hardening phenomenon.*[85] Despite the underlying mechanism stills unclear, the contributory factors may include: irritant-induced changes in skin morphology (acanthosis and hyperkeratosis), in the lipid composition of the *stratum corneum*, in the permeability of the skin barrier, and/or in the expression of inflammatory mediators.[85,86]

3.5 ALLERGIC CONTACT DERMATITIS (ACD)

ACD is a T-cell-mediated delayed-type hypersensitivity reaction that occurs after skin exposure to a specific hapten in previously sensitised individuals.[87] The major pathophysiological events in ACD include: the induction phase (sensitisation or primary) and elicitation phase (effector or secondary).
The induction phase includes the events following a first contact with the allergen being completed when the individual is sensitised and capable of giving a positive ACD reaction. Elicitation occurs at the secondary encounter with the same allergen, which leads to recruitment and activation of the allergen-specific T cells and a local inflammatory response.
The entire process of the induction phases requires days to several weeks, whereas the elicitation phase reaction is typically fully developed after 1-4 days.[87]

Contact allergy is not the same as allergic contact dermatitis

Contact allergy, the acquired delayed hypersensitivity to an environmental substance, must be distinguished from ACD, which is the skin disease developed from subsequent exposure to the contact allergen. If the patient avoids exposure to the allergen no symptoms from the contact allergy will appear.[87] However, as contact allergy is often a life-long condition, some contact allergens can be easily avoided, but others –many of them in occupational settings– are occurring ubiquitously leading to recurrent or allergic contact dermatitis. For example, in “persistent post-occupational dermatitis” there is incomplete improvement of the contact dermatitis despite removal from occupational exposure.[88]

Irritant or allergic contact dermatitis?

ACD and ICD can be clinically and histologically indistinguishable despite their different pathogenesis challenging both clinicians and researchers.
The gold standard diagnostic method for ACD is epicutaneous patch-testing complemented with prick testing in case of immediate symptoms. An accurate differential diagnosis should be addressed including irritant contact dermatitis (by assessing potential exposure to irritant agents).[87] Concomitant exposure to skin irritants and contact allergens increases the risk of sensitization, imposing a need to identify irritant factors.
A golden standard diagnostic method to differentiate ACD and ICD is not yet available. A recent pilot study, which used high-definition optical coherence tomography to differentiate both conditions,[89] suggested that an increased epidermal thickness, as a probable result of acute regenerative hyper-proliferation and disturbed differentiation expressed by parakeratosis, may be pathgnomonic for ICD (Boone, et al. 2015).[89] These features might contribute to differentiate patch-testing doubtful reactions in real-time by a non-invasive manner.[89]

3.6 SKIN CANCER

Definition and nomenclature

The skin is the most common cancer site in Caucasian populations, but still likely to be among the most preventable through exposure reduction, early detection, and treatment.[75]
The term “skin cancer” is quite unspecific and includes different clinicopathologic entities with different etiologic factors, clinical course, treatment, and prognosis. Classically, skin cancer has been classified as “melanoma skin cancer” and “non-melanoma skin cancer” (which includes a large number of different disorders, especially basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC).[90] Karimkhani et al. 2015,[90] suggested that the term “keratinocyte carcinoma” is a more accurate and appropriate term when referring to cSCC and BCC together (both are carcinomas which histologically resemble epidermal keratinocytes).[90]

Latency period

Whilst the latency period of inflammatory work-related skin diseases, particularly ACD, ICD and urticaria is relatively short, the first manifestation of skin cancer due to occupational exposures is often seen many years after the occupational exposure has ceased (even when the affected individual is not longer occupationally exposed).[91]

Recognition as an occupational disease

In Europe, the legislation of seven out of 11 surveyed countries recognizes cutaneous squamous cell carcinoma as an occupational disease. For basal cell carcinoma (6 of 11), actinic keratosis (5 of 11), and malignant melanoma (5 of 11) (Ullrich et al. 2016).[92]
Due to poor registration practices in many countries, population-based studies on cSCC and BCC incidence are scarce.[5]

Associations between occupation, occupational exposures, and skin cancer

Cutaneous squamous cell carcinoma

Sir Percival Pott described for first time in 1775 the occurrence of occupational cause of cancers when he reported the frequent manifestation of "soot warts" in the scrotum of young boys**[5]** who cleaned the soot and creosote from fireplace chimneys in England[77] (Figure 6). Later, these "soot warts" were identified as cSCC.

A recent metanalysis reported that occupationally UV-exposed workers have almost doubled risk of developing cSCC, with risk increasing at decreasing latitude.[4] Table 6 summarizes the skin carcinogenic agents with sufficient and limited evidence in humans for keratinocyte carcinomas, according to the International Association on Research on Cancer (IARC) Monographs Volume 1 to 114.

Figure 6. Child chimney sweeps.**[93]**

Source: New York Public Library Digital Collections. Free to use without restriction

5. At the age of four and five, boys were sold to clean chimneys, due to their small size. Sweep the chimneys naked so their masters would not have to replace clothing that would have been ruined in the chimneys. They were poorly fed and clothed, rarely bathed, chlidren slept in cellars on bags of the soot that they had swept.

Table 6. Classification of carcinogenic agents for keratinocyte carcinomas* with sufficient or limited evidence in humans. Adapted from Volumes 1 to 114. IARC[6]

Keratinocyte carcinomas	
Carcinogenic agents with sufficient evidence in humans	**Carcinogenic agents with limited evidence in humans**
Arsenic and inorganic arsenic compounds	Creosotes
Azathioprine	Human immunodeficiency virus type 1
Coal-tar distillation	Human papillomavirus types 5 and 8 (in patients with epidermodysplasia verruciformis)
Coal-tar pitch	Hydrochlorothiazide
Cyclosporine	Nitrogen mustard
Methoxsalen plus ultraviolet A	Petroleum refining occupational exposures
Mineral oils, untreated or mildly treated	Ultraviolet-tanning devices
Shale oils	Merkel cell polyomavirus (MCV)
Solar radiation	
Soot	
X-radiation, gamma-radiation	

***** The original expression in the table is: “skin (other neoplasms)”

Basal cell carcinoma

The available evidence indicates that UV exposed outdoor workers are at least at 43% higher risk of BCC compared to non-exposed workers.[58] However, the evidence of the association is not as robust as for cSCC, due to non-differential misclassification of exposures and incomplete registration of BCC (Bauer et al. 2011).[58]

Melanoma skin cancer

Intermittent sun exposure and sunburn history during childhood are suggested as the most important risk factors, but a high occupational sun exposure seems to be inversely associated to melanoma risk.[94] Nevertheless, some studies indicate that exposures in adulthood, e.g. occupational sun exposure, may contribute to an increased risk of developing melanoma skin cancer.[95] Several studies have also suggested that exposure to polycyclic aromatic hydrocarbons, benzene, or other chemicals used in the printing

6. IARC. List of classifications by cancer sites with sufficient or limited evidence in humans, Volumes 1 to 144. Adapted from Cogliano *et al.* (2011) available at: http://jnci.oxfordjournals.org/content/early/2011/12/11/jnci.djr483.full.pdf+html Last update: 4 November 2015.

industry are associated with the development of melanoma. Cohort studies of electrical and electronics workers along with at least one case-control study have also shown elevated risk for melanoma.[95]

Given that this thesis will focus on the occupational variation of the relative risk of cutaneous squamous cell carcinoma between occupational categories in four Nordic countries, more details about its epidemiology and registration in the Nordic countries will be further revised.

Cutaneous squamous cell carcinoma

Invasive cSCC is the most frequent aggressive cancer to the skin and second skin carcinoma in incidence after BCC.[96] An estimate of 50–70% of SCC in fair-skinned people is associated to solar UVR. Thus, the most common localization includes areas of direct exposure to the sun, such as the forehead, face, ears, scalp, neck and dorsum of the hands (Figure 7). The vermilion of the lower lip is another common site.[96]

Between 3% and 23% of cSCC (depending on the anatomical location) recur after treatment, more than half of cases during the first year, but may do so even more than 5 years after the first removal.[97]
The risk of metastasis is 5% for the cSCC from sun-exposed areas, but 38% in the SCC at non sun-exposed areas. [97]

Registration of cutaneous squamous cell carcinoma in Finland, Iceland, Sweden, and Norway

National cancer registration started in 1953 in Finland and Norway, in 1955 in Iceland, and in 1958 in Sweden.[98]

The cancer registries in these Nordic countries receive information on cSCC cases from general and specialist practitioners, hospital departments, pathology departments, and from pathology autopsy notifications. Unlike the other Nordic countries, Sweden does not registry cancer cases from death certificates.[98]

The completeness and high specificity for the registration of cSCC cases in the Nordic countries is guaranteed by multiple sources of information, and validity studies performed.[99] For instance, for the period 2001-2005, 99.8% of the cSCCs in the Cancer Registry of Norway were morphologically verified.[100]

Figure 7. Cutaneous squamous cell carcinoma in the left ear and dorsum of hands.[7]

Incidence of cutaneous squamous cell carcinoma in the Nordic countries

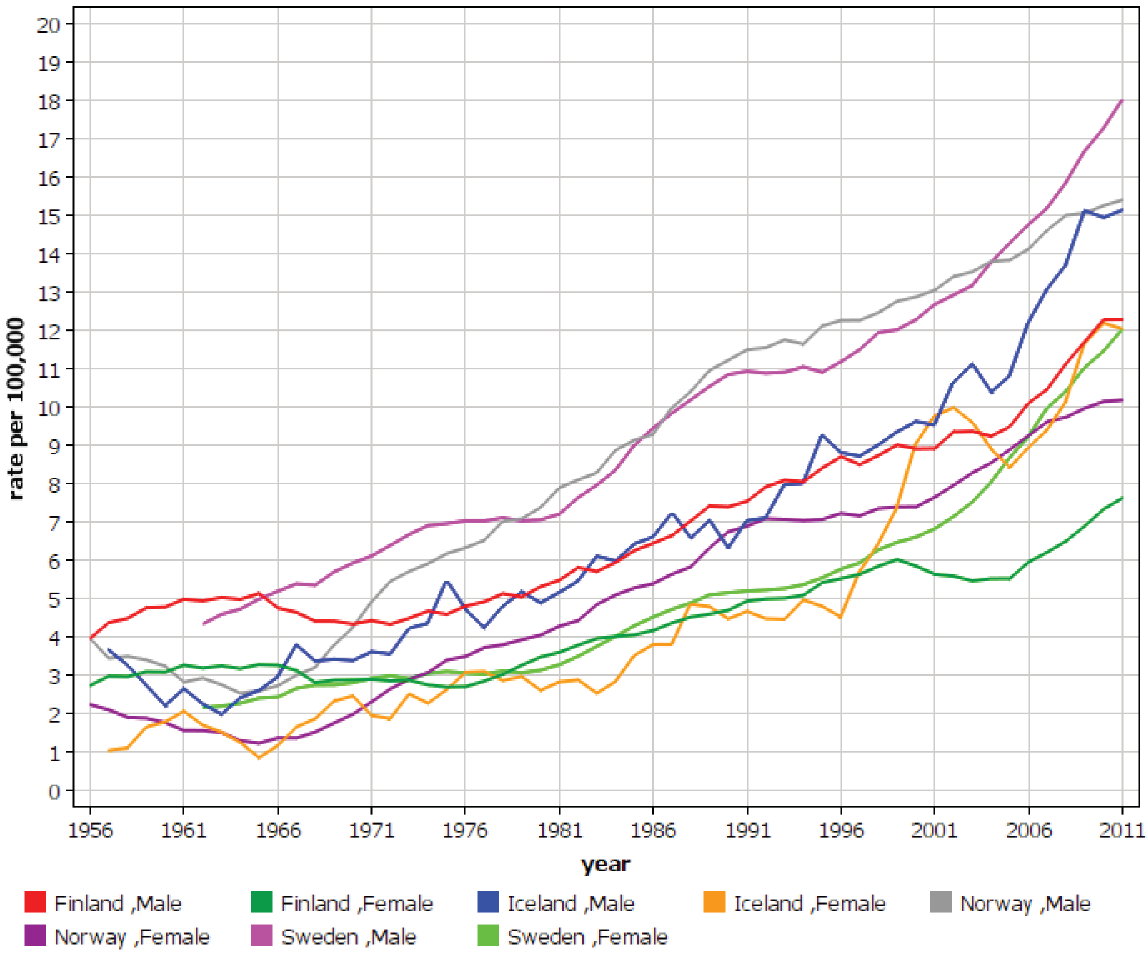
Figure 8 shows that the age-specific incidence rate of cSCC in the Nordic countries has increased about three fold during the latest 60 years, both for women and men. From the early 1970–2011, Norwegian and Swedish males had the highest cSCC incidence rate, and after 2001 also Icelandic males. The trends for Sweden show a fourfold increase in the SCC incidence rate in both sexes from 1960 to 2011.[3]

7. Courtesy from: Dr. M.N Crépy Atlas de Dermatologie Professionnelle. http://www.atlasdedermatologieprofessionnelle.com/index.php/Accueil

The total number of new cases per year (incidence 2009-2013) was 7,110 (3,805 cases for men, 3305 for women), with the highest number of new cases were reported in Sweden.[3] By the end of 2013, 28,611 men and 26,464 women were living with the diagnosis (prevalence).

Due to increasing incidence trend, the identification of occupational variation of relative risk of cSCC between occupational categories in the Nordic countries may have preventive implications.

Figure 8. Cutaneous squamous cell carcinoma: age-specific incidence 1960 -2011 in four Nordic countries, by sex.[3]

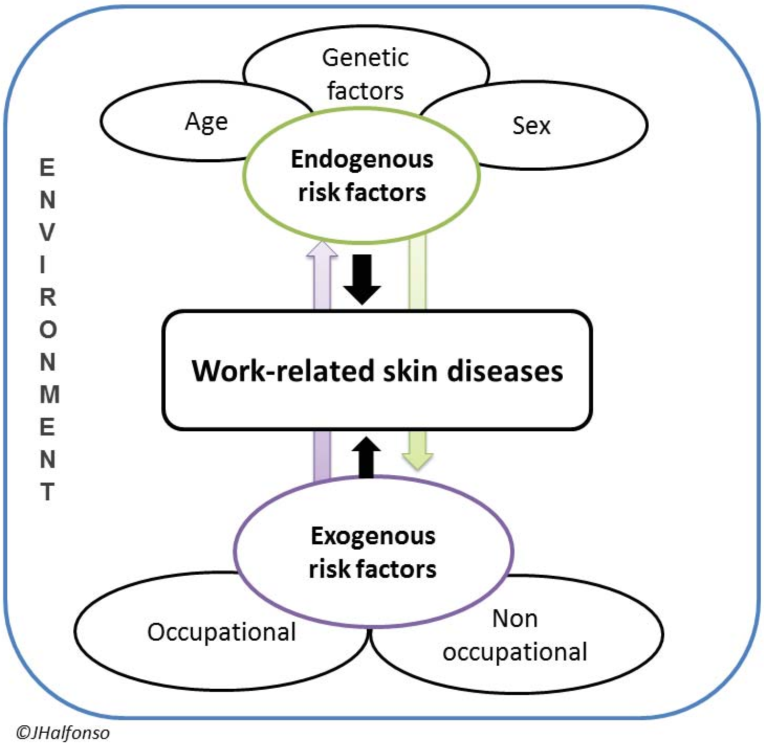


3.7 DETERMINANTS OF WORK-RELATED SKIN PROBLEMS, DISEASES, AND CUTANEOUS SQUAMOUS CELL CARCINOMA

The development of work-related skin problems and diseases is influenced by a combination of endogenous risk factors (individual susceptibility), and exogenous risk factors (environmental exposures) (Figure 9). Environmental exposures can occur at both the workplace and leisure time.

Occupational skin exposure to hazardous substances such as physical factors and chemical factors is a *sine qua non* condition of work-related skin diseases. Moreover, individual susceptibility characteristics may influence the development of these conditions, and make some individuals more prone to develop such diseases.

Figure 9. Factors involved in the pathogenesis of work-related skin disease.



3.7.1 Endogenous factors

Atopic dermatitis (AD)

It is a chronic –non curable- skin disease that generally starts in infancy and affects between 5% and 20% of individuals worldwide.[101] Several studies have suggested that a history of AD in childhood is associated with an increased risk of hand dermatitis in adulthood, in some cases to a three fold risk.[61,64,80] A Danish population-based cohort study with 5-year follow-up reported recently that AD is associated with persistent and incident hand dermatitis (Heede, et al. 2016).[102]

Filaggrin mutations

The integrity in the *stratum corneum* is influenced by one structural protein called filaggrin. Filaggrin loss-of-function mutations are associated to an elevated risk of developing AD.[103] However, whether mutations alone increase the risk of developing ICD is still unclear.

Filaggrin mutations affect between 8–10% of adults from the general population, but the frequency is even higher in individuals with AD.[103,104] For example, a Danish birth cohort study reported a frequency of 17.6% for filaggrin mutations among individuals with AD and 7.9% among individuals without AD.[103]
It has to be highlighted that not all individuals with filaggrin mutations develop dermatitis.[104,105] Nevertheless, several studies have reported that concomitant AD and filaggrin mutations are associated with early onset of disease, severity, and persistency.[103,106-108] For those with occupational ICD, the presence of a mutation and atopy led to poorer clinical and professional outcome.[109] Moreover, Visser et al. 2013[109] reported that the risk of ICD was increased in individuals with filaggrin mutations (OR 1.6), and those with atopy (OR 2.9).

The identification of individual susceptibility markers such as loss of filaggrin mutations is a fascinating research area because of their potential preventive implications. Consequently, workers with elevated individual susceptibility can be identified and theoretically prevented of developing work-related contact dermatitis.
For instance, an association between filaggrin and ICD was reported among high-risk occupations such as health care, metal and construction, hairdressing, food and catering, and cleaning.[110, 111] Recently, a Dutch study among construction workers has reported evidence of a strong association between filaggrin loss-of-function mutations with doctor-diagnosed CD, and to a lesser extent also with self-reported CD (Timmerman et al. 2016).[112]

The link between filaggrin and cSCC is also captivating: filaggrin is degraded to, among other things, trans-Urocanic acid (trans-UCA), which is a chromophore that provides protection against UVR. Accordingly, a deficiency of filaggrin leads to altered endogenous protection against UVR exposure.[113] Recently, a Danish study reported an elevated risk of cSCC in individuals with a complete absence of filaggrin in the skin (Kaee et al. 2014).[114] The pathomechanism is likely explained by a reduction in the amount of trans-UCA in the *stratum corneum*, leading to greater UV penetration into nucleated cell layers and elevated risk of malignant transformation.[114]

Other genetic and individual susceptibility factors

Variations in the genes involved in inflammatory cytokines such as TNF α, IL1-β, IL-6, IL-16[111] have been identified as genetic susceptibility factors for contact dermatitis.

Moreover, variations in genes involved in metabolic enzymes may also have a role for individual susceptibility. For instance, Wang et al. 2007,[115] reported a higher risk of chromate sensitization in the carriers of glutathione S-transferase theta 1 (GST-T1) null genotype. On the other hand, Nacak et al. 2006,[116] reported that polymorphisms in N-acetyltransferase (NAT) are protective for p-phenylendiamine sensitization.

Genetic skin conditions such as Xeroderma pigmentosum, oculocutaneous albinism, epidermodysplasia verruciformis, recessive dystrophic epidemolysis bullosa, Muir-Torre syndrome are associated with an increased risk of developing cSCC.[117]
Organ transplant recipients have a 65-fold higher risk for cSCC and 20-fold higher risk for cSCC in the lips compared to the general population.[117]

Are skin barrier defects associated to increased susceptibility to cutaneous squamous cell carcinoma?

Results from observational studies have been contradictory. Arana et al. 2010[118] reported an elevated risk in individuals with AD (Incidence rate ratio for cSCC: 1.46 (95% CI: 1.27-169). A large Danish cohort study from 1977 to 2006 reported also an association between AD and elevated risk for cSCC.[119]
A Swedish retrospective cohort study reported a non-significant 50% excess risk for keratinocyte carcinomas (SIR: 1.5; 95% CI: 0.8-2.6), seemingly confined to men and to the first 10 years of follow-up.[120] Conversely, a Dutch study has reported recently that AD is not associated with the risk of developing actinic keratosis (Hajdarbegovic et al. 2016).[121]

In general, the positive associations between AD and the risk of keratinocyte carcinomas can be a result of detection bias or the carcinogenic effect of some therapies for severe AD.[122] Future studies should address potential confounding to clarify whether skin barrier defects are associated to increased susceptibility for keratinocyte carcinomas.

Age

Experimental studies reported a decreased sensitivity to cutaneous irritants with increasing age.[123]
Given that the main risk factor for cSCC is cumulative exposure to skin carcinogens, older individuals are at a higher risk to develop cSCC.[124]

Sex

Swedish and Danish studies[125,126] reported that the higher occurrence of work-related contact dermatitis among women can be attributed to differences in exposure patterns at work and leisure time.

The higher occurrence of keratinocyte carcinomas among men has been attributed to sex-related differences in exposure to the sun during occupational and leisure activities, the use of sun protection, and loss of scalp hair.[127]

Ethnicity

The current evidence on ethnicity as an endogenous risk factor for contact dermatitis is controversial.[128] Weak evidence of statistically significant differences in the skin response to irritants between Caucasian and African or Asian groups has been found.[128] On the other hand, ethnicity is a well known risk factor for cSCC with a higher occurrence among Caucasians, which is mainly attributed to the fair skin type.[117]

3.7.2 Exogenous factors: Occupational exposures

Wet work

Wet-work is defined as activities where workers have to immerse their hands in liquids, wear waterproof (occlusive) gloves for more than two hours per shift, or wash their hands more than 20 times per shift.[129]

Frequent exposure to water leads to swelling and shrinking of the *stratum corneum* and subsequent hand dermatitis. For instance, wet work is a well-known risk factor for ICD in hairdressing, nursing, cleaning, food handling, metal working, manufacturing, construction, machine tool operation, food preparation, printing, metal plating, leather work, engine servicing, and floristry.[130]

Duration and frequency of exposure to wet work are the main risk determinants for the development of ICD. For instance, Meding et al. 2016,[131] have reported recently challenging differences in water exposure between occupational groups, and extensive water exposure in service occupations.
Wet work along with the simultaneous effect of cleaning products, disinfectants, solvents, alkalis, and acids lead to additional epidermal barrier disruption which facilitates the penetration of allergens and further transepidermal water loss.[130]

Glove occlusion

Extensive and prolonged glove occlusion may lead to skin barrier disruption and subsequent development of ICD.[132] A recent review reported that occlusion significantly enhances the skin barrier damage following exposure to cleaning products in a dose-response manner (Tiedemann, et al. 2016).[132]

Skin exposure with chemical products

Cleaning products interact with the *stratum corneum* leading to skin barrier disruption due to an increased protease activity, inhibition of the lipid synthesis, delipidation, and denaturation of keratins which results in increased permeability and cytotoxic efects.[133]

Additionally, fragrances and preservatives ingredients may lead to allergic contact sensitisation. The most common used fragrances in cleaning products are limonene, linalolol, butylphenyl methylpropional, hexyl cinnamal, citronella, and geraniol.[134] The most important preservatives include: isothiazolinones, formaldehyde and formaldehyde-releasers, iodopropynyl butylcarbamate, methyldibromoglutaronitrile, and parabens.[135]

Skin contact with organic solvents, besides systemic adverse effects, can lead to skin dryness, whitening, sensory irritation, cumulative irritant contact dermatitis, contact urticaria, skin chemical injuries, and scleroderma.[136] The effects vary according to the chemical structure, concentration, and duration of exposure.

Paints, lacquers, and varnishes[137] may lead to development of both ICD and ACD. A period of irritant dermatitis occurs often prior to skin sensitisation to ingredients such as epoxy resin based compounds, formaldehyde resins, acrilyn resins, and hardeners. Additionally, preservatives are the second most common cause of ACD among workers exposed to these substances.[137]

Cutting fluids can contribute to the development of ICD and ACD. Historically, cutting fluids based on neat insoluble oils were associated to folliculitis/oil-induced acne, and furunculosis in the forearms, thighs, hands, and face. Due to solvent refining of oils, work-related acne and folliculitis are not any longer so frequent. ACD can occur as a consequence of exposure to metals such as nickel, chromate, and cobalt that are released into the cutting fluid from the metal being machined. Additionally, some emulsifiers such as Colophony may cause sensitization.[138]

Coatings, either metallic or non-metallic may lead to ACD and ICD. Metallic coatings containing nickel, chromium, cobalt have contact sensibilisation properties. Direct or airborne contact with specific polymers from plastic resins and paint coatings can also induce ICD, ACD, contact urticaria, mucosal irritation, allergy, and scleroderma.[139]

Skin contact with allergens from thousands of different products may trigger sensitisation resulting in ACD.[140] They include medicines, antioxidants, preservatives, antiseptics, biocides, pesticides, cleaning products, metals, constituents of plastic and rubber materials, oils, pigments and dyes, cosmetics, depilatory waxes, Peru balsam, rosin, turpentine, plant (latex), animal proteins, and enzymes

For instance, contact allergy to at least one allergen of the European baseline series was diagnosed in more than one quarter of the general European population.[141] The highest age-standardised prevalence (≥ 1%) was found for nickel (14.5%; 95% CI 13.2-15.8), thimerosal (5.0%; 95% CI 4.2-5.8), cobalt (2.2%; 95% CI 1.7-2.7), fragrance mix II (1.9%, 95% CI 1.5-2.5), fragrance mix I (1.8% 95% CI 1.4-2.3), hydroxyisohexyl-3-cyclohexene carboxaldehyde (1.4%, 95% CI 1.0-1.9), p-tert-butylphenol- formaldehyde-resin (1.3%; 95% CI 0.9-1.7), and p-phenylenediamine (1.0%; 95% CI 0.6-1.3).[141]

The latest data collected by the European Surveillance System on Contact Allergy network, for 11 European countries from 2002 to 2010, reported that thiuram rubber chemical accelerators, epoxy resin, and the antimicrobials methylchloroisothiazolinone/methylisothiazolinone, methyldibromoglutaronitrile, and formaldehyde are associated with an at least doubled risk of OCD (Pesonen et al. 2015). The highest risk for OCD was reported for occupational categories such as “other personal services workers” (include hairdressers), nursing and other healthcare professionals, precision workers in metal and related materials, and blacksmiths, tool-makers, and related trades workers.[142]

Polycyclic aromatic hydrocarbons (PAH),[143] consist of a family of multiple rings hydrocarbon compounds that are produced under conditions of incomplete combustion, and are therefore common in cigarette smoke, coal tar, smoke from fires, burnt food, particulate air pollution, and organic chemical processes. For instance, mixtures of them are found in coal tar, pitch, asphalt, soot, creosotes, anthracenes, paraffin waxes, lubricants, and cutting oils.
These hydrocarbon compounds include benzo(a)pyrene, chrysene, benzo(a)anthracene, benzo(b)fluoranthene, dibenzo(a,h)anthracene, dibenzopyrene, and 5-methylchrysene. They occur naturally in mixtures, never as individual compounds, and are often monitored and quantified by the concentration of benzo(a)pyrene.
Several of them are known to be pro-carcinogens, presenting a cancer risk after absorption and metabolism, acting as both mutagenic initiators (interacting directly with DNA) and potent promoters. Moreover, they are potent inducers of the mixed function oxidase in all tissues, and therefore may accelerate the Phase I metabolism and activation of other carcinogens.
Because of their ultraviolet absorption characteristics, they are photosensitizing, increasing sun damage in sunlight, and causing dermatitis among exposed workers such as roofers.[143]

Skin exposures to untreated or mildly treated mineral oil containing PAHs have been linked to skin and scrotal cancers among mule spinners, wax pressmen, metal workers exposed to poorly refined cutting oils, and machine operators using lubricant oils.

The latent periods between exposure to PAHs and skin cancer vary from about 20 (coal tar) to 50 years or more (mineral oil).[143]

Arsenic, carcinogenic in humans, is used in the industry as an alloying agent, in the semiconductor and microchip industry, processing glass, pigments, textiles, paper, metal adhesives, wood preservatives, ammunition, tanning process and, in more limited extent, in the manufacture of pesticides and pharmaceuticals.[144] The premalignant skin tumours are punctuate keratosis on the palms of the hands and soles of the feet in subjects exposed to arsenic, which are considered pathgnomonic for chronic arsenic exposure. They are usually multiple and may progress to cSCC.[145] Superficial basaliomas are also associated to a chronic arsenic exposure.[145]

Skin exposure to biological agents

Vegetables and fruits may lead to ICD, ACD, photoallergic CD, contact urticaria, and protein contact dermatitis.[146]
Common fruits and vegetables responsible for ICD comprise: garlic, onion, potatoes, citrus fruits, pineapple, radish, cauliflower, broccoli, and carrots.
Lettuce, endive, artichoke, citrus fruit, mango, tomato, and others have ingredients that can lead to skin sensitisation and ACD. Psoralens (furocoumarins) in lime, lemon, orange, bitter, bergamot orange, grapefruit, fennel, carrot may induce phototoxic dermatitis after UV exposure.[146]
Protein contact dermatitis includes an eczematous reaction occurring after skin contact to high molecular weight proteins from plants and animals. The proteins may easily penetrate through a damaged skin barrier, due to for example wet work and elicit urticarial and vesicular reactions (type I) followed by a delayed (type IV) allergic reaction.

Plants can also cause ICD, ACD, urticarial, and phototoxic reactions. Most allergic reactions are caused by a small number of plant families such as *Anacardiaceae* (e.g. poison ivy) and *Compositae* or *Asteraceae* (e g. *chrysanthemum*).[146] Phototoxic reactions are restricted to areas exposed to plant material and solar UVR.

Animal contact can lead to ACD, ICD, protein contact dermatitis, parasite infestations, and zoonoses.[146]

Woods, mainly raw wood, can cause ACD and ICD often with an airborne pattern. Other skin problems such as contact urticaria, photocontact dermatitis, and erythema multiform are uncommon. The chemical substances responsible for allergic reactions are mostly benzo-, naphto-, furano, and phenantrene quinones, stilbenes, phenolic compounds, and terpenes. The chemical substances responsible for the majority of irritative reactions are alkaloids, glycosides, anthraquinones, saponins, phenols, and flavonoids.[146]

Infections and infestations by virus, bacteria, and fungi can be of occupational origin.[146] The most classical virus includes orf, milker's nodule, herpes simplex, butcher warts, and hepatitis B. Infection for human immunodeficiency virus type 1, human papillomavirus types 5 and 8 in patients with epidermodysplasia verruciformis may also be associated to cSCC, (limited evidence, IARC Vol 11-14).[147]
Examples of bacterial skin infections of occupational origin are staphylococcal, streptococcal, erysipeloid, and brucellosis.[146]
Mycoses can also be related to occupational activities. They include: dermatophytes, candidiasis, subcutaneous and deep mycoses.
Protothecosis is the only work-related disease due to an algae: Prototheca, mainly in tropical and subtropical countries.[146]

Skin exposure to mechanical factors

Mechanical injuries to the skin, such as friction, pressure, and contact with abrasive material can affect the skin from the *stratum corneum* until the subcutaneous tissue.[148] Modifications occur mainly on the hands, feet, knees, elbows, lips, and neck. The skin manifestations include hyperkeratosis, fissures, lichenification, fingertip dermatitis (pulpitis), Raynaud phenomenon from vibration, pressure urticaria.
Additionally, the effects of the mechanical factors are modified by humidity, sweating, age, sex, nutritional status, infection, pre-existing diseases, genetic, and racial factors. Psoriasis, a high prevalent skin condition in Norway,[149] can be worsened by mechanical factors at work.[148] For example, isomorphic Koebner phenomenon is common among workers with psoriasis exposed to mechanical traumas.[148]

An industrial injury leading to burn injuries and scars can be premalignant conditions for skin cancer. Cutaneous squamous cell carcinoma occurs more frequently, but other forms of skin cancer such as BCC and malignant melanoma may also occur. The mean latency interval for development of cSCC after an injury is approximately 31 years.[150]

Skin exposure to physical factors

The role of environmental physical factors such as heat, cold, and low humidity (dry air) to occupational dermatoses is often dismissed.[151]

A systematic literature review have concluded recently that exposure to low humidity and temperature lead to skin barrier impairment and increased susceptibility towards mechanical stress (Engebretsen et al. 2015).[152] Consequently, the keratinocytes release pro-inflammatory cytokines and cortisol, the number of dermal mast cells increases, and the skin becomes more reactive towards skin irritants and allergens.[152]

Heat stress has been suggested as a risk factor for skin carcinogenesis by a cellular mechanism that involves heat shock proteins, chaperone proteins, which prevent cells from undergoing apoptosis- and oncogenic mutant proteins.[153]

Solar ultraviolet radiation is the main risk factor for development of skin cancer.[147]
UVB radiation (280–315 nm) acts directly through specific changes in oncogenes and p53 tumour suppressor genes, for example the formation of pyrimidine dimmers in DNA and RNA, which leads to mutations in keratinocytes and to neoplastic transformation.
UVA (315–400 nm) causes indirect DNA damage via a photo-oxidative stress-mediated mechanism, resulting in formation of reactive oxygen species, which interact with lipids, proteins and DNA to generate intermediates that combine with DNA to form adducts.[154]
Several complex DNA repair systems are needed to prevent the harmful effects of these pre-mutagenic adducts. UVA radiation penetrates deeper into the skin, reinforces the carcinogenic effects of UVB rays and leads to additional aging and immunosuppression.[154]
Individual exposure to solar UVR can be classified as intermittent (short, intense sun exposure through activities such as sunbathing, outdoor recreations, and holidays in sunny climates), chronic (more continuous, primarily occupational exposure), and total sun exposure (the sum of intermittent and chronic exposure).[95] According to IARC, outdoor workers are exposed to 2-3 times higher solar UVR than indoor workers.[155]

Ionizing radiation consists of particles (alpha and beta particles, and neutrons) or electromagnetic waves (gamma rays with wavelengths less than 0.01 nm, which is less than the diameter of an atom, and X-rays with wavelengths from 0.01 to 10nm. High acute radiation exposure (1 Sv and above) may lead to the development of acute radiation dermatitis with redness, itching, and infiltration of the skin.[156]
Higher doses can even cause bleeding into the skin, blisters and necrosis. The final stage can be a chronic dermatitis (radiodermatitis) with radio atrophy of the skin, sclerosis, keratinisation disorders, pigmentary changes, loss of sebaceous glands, hair loss and telangiectasia.[156] Nowadays, radiation-induced dermatitis is mostly caused by radiotherapy for underlying malignancies.
Exposure to ionizing radiation can lead to the development of cSCC and BCC, and less often sarcomas. Actinic keratosis caused by exposure to X-rays were common to observe in the hands of radiologists and surgeons previously, but due to the current radiation

limits occupational groups exposed to ionizing radiations do not longer have a higher incidence of radiation induced diseases.[156]

Some remarks

In general, sufficient experimental and clinical evidence regarding occupational chemical, biological, physical, and mechanical exposures leading to the development of skin problems and diseases is available (Figure 10).

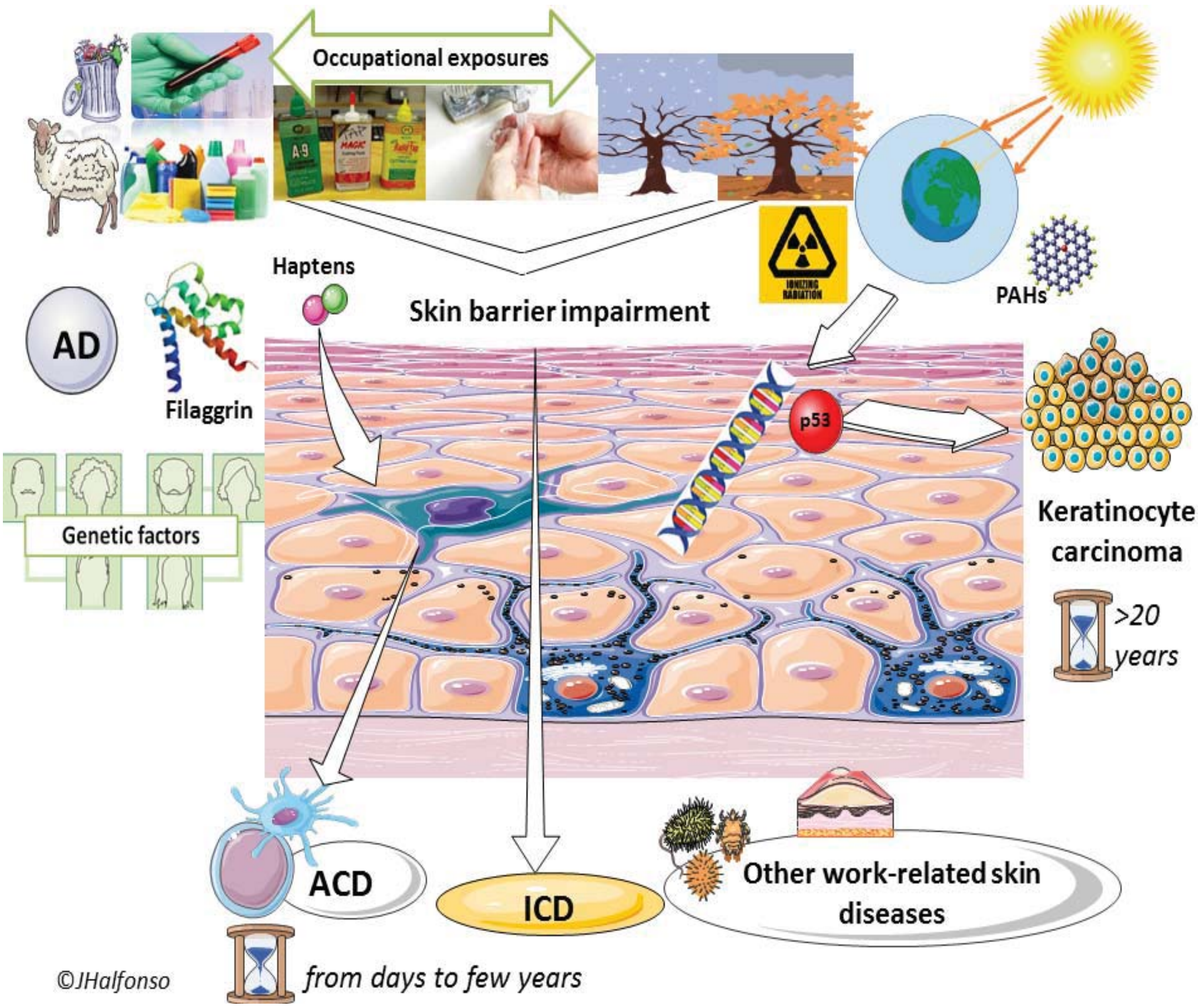
Furthermore, some population-based studies reporting associations between occupational exposure to water, skin allergens and higher risk for developing of hand dermatitis,[61-64,69] have also been performed.
However, according to the systematic literature search displayed in Chapter I, the role of other occupational exposures such as cleaning products, oil and cutting fluids, physical factors, and the effect of concomitant exposures on the risk of skin conditions have not been sufficiently addressed in population-based studies with a prospective design.

Additionally, the evidence of the role of occupation and occupational exposures on the burden of skin conditions in the general working population of Norway is insufficient.

Whilst National registries of work-related diseases can be a source to investigate the role of occupational exposures on the burden of skin diseases, the Norwegian registry is far from complete.[38]

Population surveys and linking with other national comprehensive registries such as the Norwegian Labour and Welfare Administration's sickness benefit registry,[157] and the Cancer Registry[98] can provide with valuable information to investigate the role of occupation and occupational exposures on the burden of skin problems and diseases.

Figure 10. Exogenous, endogenous risk factors related to the development of work-related skin disease.



Servier Medical Art kindly provided images for the design of this figure.

3.8 SKIN EXPOSURES AND SKIN PROBLEMS IN THE GENERAL WORKING POPULATION OF NORWAY

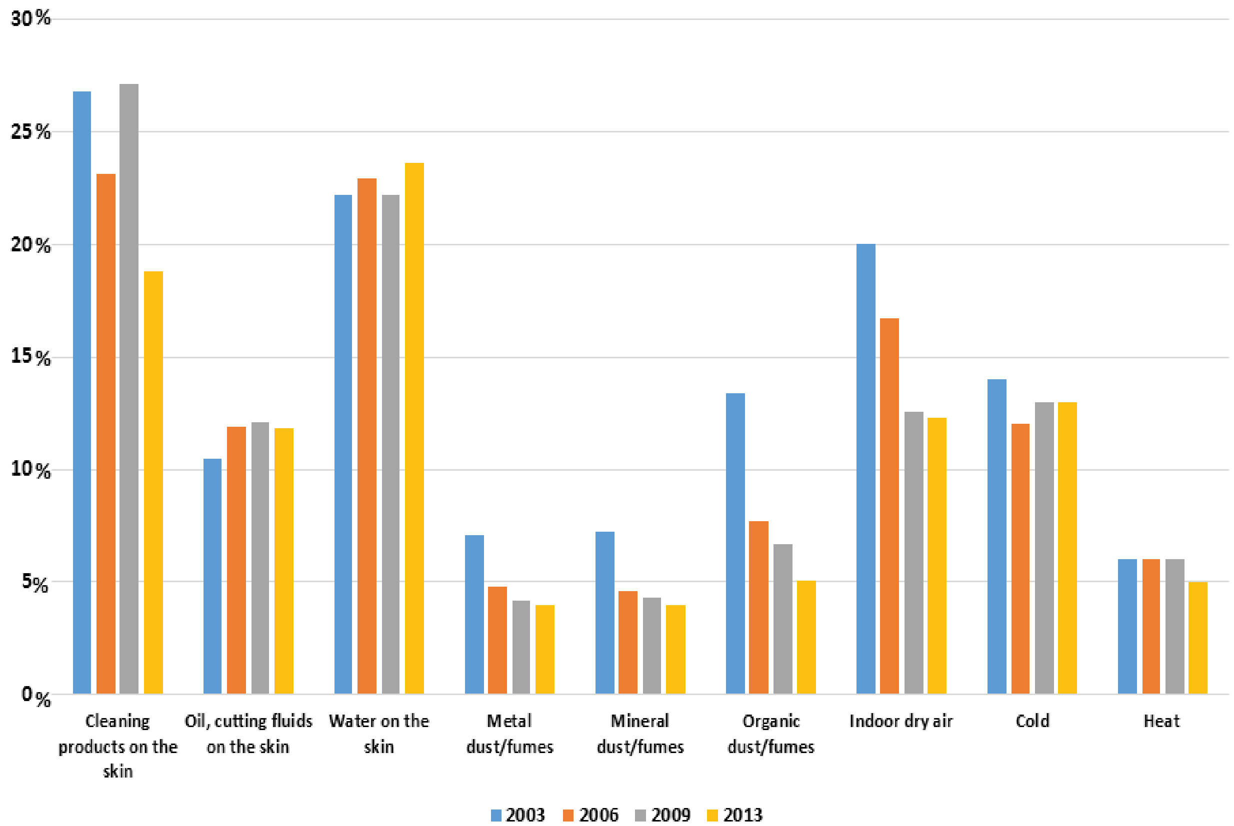
Statistics Norway conducts a Survey on Living and Working conditions every three years, which gathers data for work environment surveillance from a random sample of Norwegian residents aged 18–66, and includes questions regarding occupational skin exposure and skin problems.[157]

Once the National Surveillance System for Work Environment and Occupational Health (NOA) was established in 2006, the sample size was increased from a net sample of approximately 2,500 to 10,000 workers. In addition, the Survey has been based on responses from a panel of interviewees, where the most recent survey was performed in 2013.[157] Figure 11 shows the figures for self-reported occupational chemical and physical exposures for the period 2003-2013 in a random sample of the general working population of Norway.

By 2013, women were slightly more likely to report skin exposure to cleaning products and twice as likely to report skin contact with water for a quarter of the working day or longer. Men reported four times as much skin contact with oil/cutting fluids as women, and almost seven times more contact with oils and lubricants. Occupational exposure to other chemical hazards and physical factors were also reported more frequently among men. The sex differences have been quite stable from 2003 to 2013.

In general, occupational skin exposure declines with age and higher levels of education.[157]

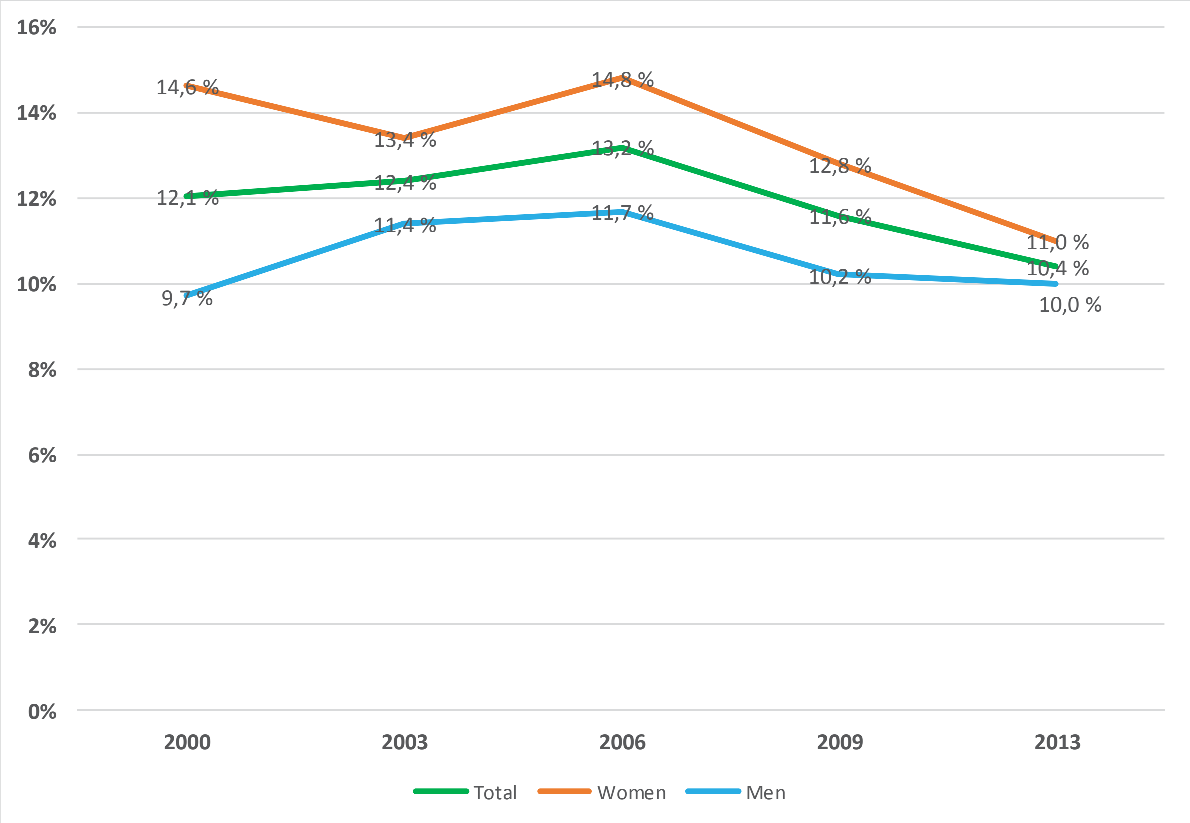
Figure 11. Self-reported chemical and physical exposures in the general working population of Norway (2003-2013)



Data source: STAMI, NOA (Statistics Norway)

Figure 12 shows a slight decline in the occurrence of self-reported skin problems from 2000 to 2013, which should be interpreted with caution due to the panel design of the survey.

Figure 12. Trends in self-reported skin problems in the general working population of Norway (2000-2013).



Data source: STAMI, NOA (Statistics Norway)

3.9 SOCIOECONOMIC IMPACT OF WORK-RELATED SKIN DISEASES

Work-related skin diseases, especially occupational contact dermatitis, are associated to considerable occupational, domestic, social, and psychological consequences.[158]
Due to the rising incidence, high recurrence rate, and occurrence of multiple cSCC, they represent one of the most costly cancers for the society not only for the Nordic countries, but also worldwide.[159]

Work-related skin diseases are usually localized on visible parts of the body which may lead to social impairment. For instance, a Norwegian study has recently reported that dermatological outpatients with keratinocyte carcinomas and dermatitis had more often psychological problems than controls. However, this study did not specifically addressed the psychological comorbidities of work-related skin conditions (Balieva et al. 2016).[160]

The wide-ranging socioeconomic consequences of work-related skin diseases underline the relevance of prioritizing research and prevention of these conditions.

Sick leave due to work-related skin diseases -mainly contact dermatitis-

Costs related to sick leave and intense use of healthcare services constitute the major part of the economic burden of work-related skin diseases.[161] Occupational contact dermatitis becomes often chronic, have a poor long-term prognosis, and imposes a significant impact on workers and their employers in terms of sick leave and loss of productivity.[2,161,162]

According to the severity and impact on the work, the annual costs may be in the same range or even exceed those for chronic inflammatory skin disease like psoriasis and atopic dermatitis.[161-163] The related costs due to loss of productivity exceed 5 billion €/ year, only in the European Union.[2]

An Australian follow-up study of patients with OSD reported that the average time lost from work was 16 days each year (Rosen & Freeman, 1992).[164] Burnett et al. (1998)[165] reported that 14% of the cases of OSD in the American private industry resulted in sick leave periods of ten days or more.

A Swedish 12-year follow-up study reported that 48% of the OSD patients had at least one sick leave period of seven days on any occasion (Meding et al. 2005).[166] Moreover, 82% of all the participants changed their work situation in some way because of the skin condition, and 44% changed job.[166]

A Danish 1-year follow-up study revealed similar trends: 57% of the OSD patients had a sick-leave due to hand dermatitis in the past 12 months, 44% reported job change, 15% was on early retirement, and 72% suffered impairment of quality of life (Cvetkovski et al. 2009).[167] Furthermore, severe occupational hand dermatitis, age 40 years or greater, and severe impairment of life at baseline appeared to be important predictors for long-term sick leave and unemployment.[167]

A Finnish 6-month follow-up study reported that 26% of the 1,048 OSD patients had a sick-leave period, but duration was not specified (Mälkönen et al. 2009).[168]
Only one Norwegian study from 1984, reported that sick leave due to hand dermatoses was more frequent among women with housework as their main occupation, workers with lower educational level, and in men and women with physically active jobs.[13] ICD and ACD were found in 78.4%, psoriasis in 9.5%, and atopic dermatitis in 8% of the participants.[13]

Whereas several studies, mostly from clinical populations, reported associations between OSD and sick-leave, few prospective studies assessed associations between occupational skin exposures and long-term sick leave in a general working population.

Physician-certified sick leave in Norway

Norway is the Scandinavian country with the highest expenditure due to sick leave.[169] For instance, in 2015, the estimated costs staggered to about 39.6 billion NOK, which accounts to 9.5 % of the estimated social insurance costs.[170] Since employers pay for the first 16 consecutive days of a given sick leave period, the cost are even higher for the private sector, where the annual cost is also estimated to be in the billions.[171]

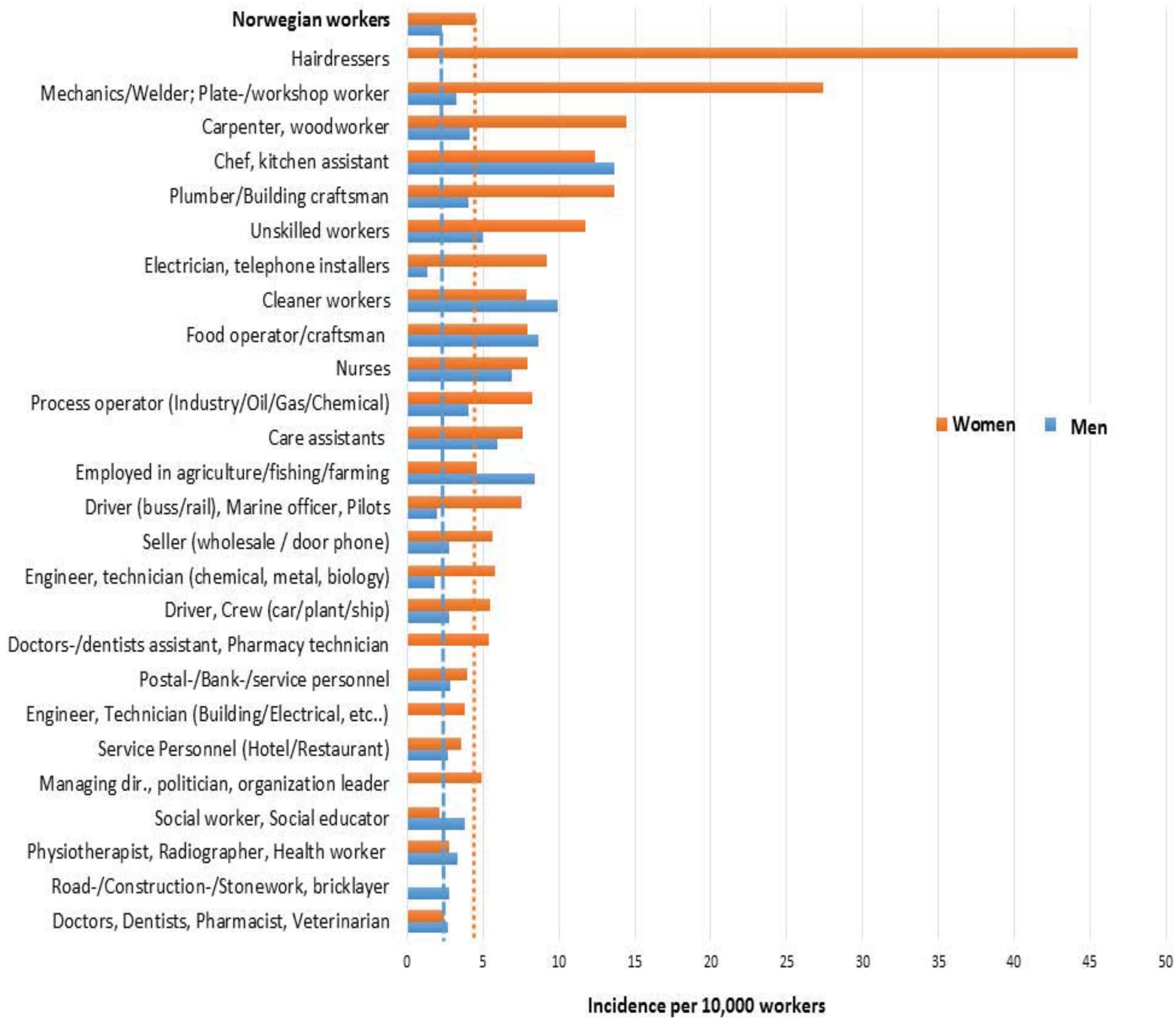
Approximately 60% of physician-certified sick leave consists of musculoskeletal disorders and mental health complaints. This prevalence has remained steady for the past 20 years.[157]

For the period 2010-2013, the annual incidence for physician-certified long-term sick leave due to skin diseases (both contact dermatitis and other skin diseases) was 45 per 10,000 workers (47 and 44 per 10,000 for women and men).[172]
In 2010, most of the occupations with wet work and occupational skin exposure to chemical and biological substances had a higher incidence for long-term physician certified sick leave due to contact dermatitis and other skin diseases than the average incidence in Norwegian workers (Figure 13 and 14).

Whilst associations between mechanical and psychosocial exposures at work and long-term sick leave have been previously reported for the general working population of Norway,[173,174] associations between occupational skin exposure and physician-certified long-term sick leave have not yet been investigated.

Such an assessment may have preventive implications not only to reduce the burden related to occupational skin exposures, but also to reduce long-term sick leave in the general working population of Norway.

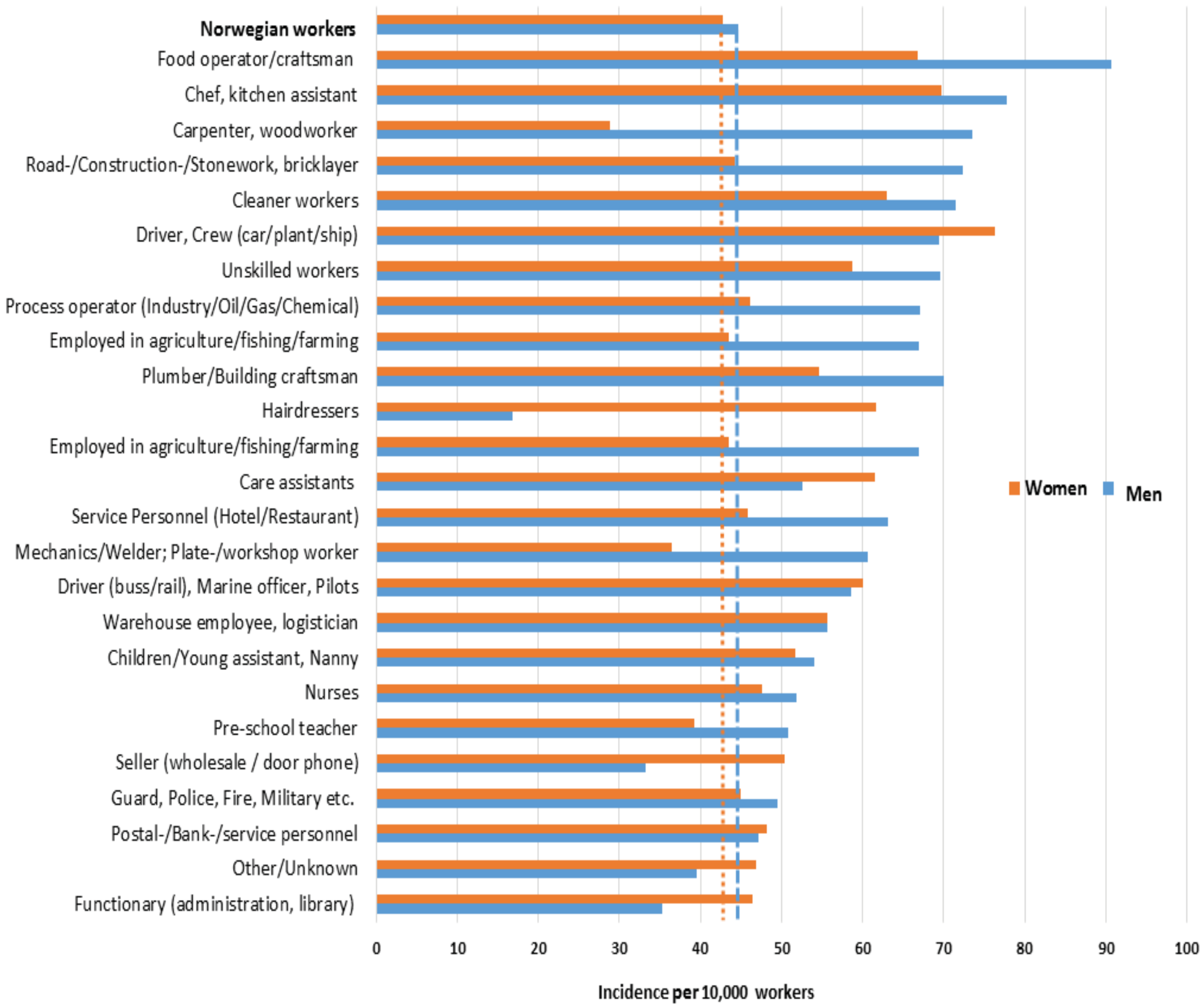
Figure 13. One-year incidence for long-term sickness absence due to contact dermatitis among Norwegian workers[8] in 2010.



Data Source: STAMI, NOA (NAV 2010-13)

8. Information for self-employed workers not available

Figure 14. One-year incidence for long-term sickness absence due to "other skin diseases" among Norwegian workers[9] in 2010.



Data Source: STAMI, NOA (NAV 2010-13)

9. Information for self-employed workers not available

CHAPTER IV: MATERIAL AND METHODS

Table 7 gives an overview of the aims and material and methods for each study.

Table 7. Summary of the aims and methods of Studies I to IV.

Study	I	II	III	IV
Main aim	To describe the frequency of notified work-related skin diseases, occupations and occupational exposures to the Norwegian Labour Inspectorate´s Registry for work-related diseases	To investigate the associations between occupational exposures and skin problems in the general working population of Norway	To investigate the associations between occupational skin exposure and physician-certified long-term sick leave in the general working population of Norway	To describe occupational variation in the relative risk of cSCC between occupational categories of four Nordic countries
Study design	Retrospective case-series	Prospective cohort		Historical prospective cohort
Source population	General working population			General adult population of Finland, Iceland, Sweden, and Norway
Data source	Norwegian Labour Inspectorate´s Registry for work-related diseases	Survey of Level of Living – Working Conditions (Statistics Norway)	Survey of Level of Living – Working Conditions (Statistics Norway) and the Norwegian Labour and Welfare Administration's sickness benefit registry.	Nordic Occupational Cancer study
Time period	2000 - 2013	2006 - 2009	2009 - 2010	1961 – 2003/2005
Variables	Diagnosis of skin disease (ICD-10) Occupation Occupational exposures Age Sex	Occupational exposure to chemical and physical factors. Self-reported skin problems Age Sex Occupation	Occupational exposure to chemical and physical factors Physician-certified sick leave (>16 days) Age Sex Occupation Education	Occupation Diagnosis of cSCC (ICD-7) Age Sex
Statistical analysis	Descriptive statistics	Unconditional logistic regression Population attributable risk		Standardised incidence ratio

4.1 STUDY DESIGN

Retrospective case-series (*Study I*): includes the report of multiple clinical cases or subjects with a specific finding.[175] For the purposes of *Study I*: subjects with notified work-related skin diseases.

Prospective cohort (*Study II & III*): investigators conceive and design the study, recruit cohort members, and collect baseline exposure data on all subjects. The cohort members are then followed-up prospectively to record the development of the outcome of interest (skin problems for *Study II*, and physician-certified long-term sick leave for *Study III*). Data, at follow-up, can be collected by mail or internet questionnaires, by phone or personal interviews, physical examinations, and laboratory or imaging tests.[176]

Historical prospective cohort (*Study IV*): the identification of cohort members is based on records of previous exposure. A good quality of records to ascertain disease is essential because the follow-up until the occurrence of the disease is wholly or partially in the past.[176]

4.2. DATA SOURCES AND STUDY POPULATIONS

Study I

The *Norwegian Labour Inspectorate´s registry for work-related diseases* was established in 1920, based on the principle of sentinel health events to prevent ongoing hazardous exposures in the workplaces.[38] Notification of confirmed or suspected work-related diseases is mandatory for all physicians according to The Work Environment Act of 1977.[38]

Study II

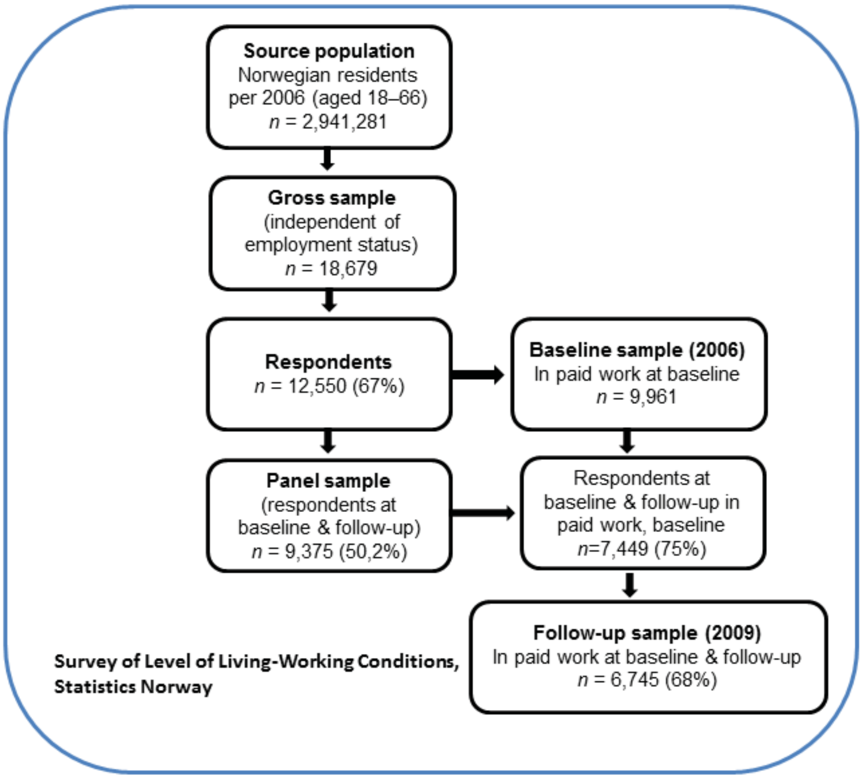
The *Survey of Level of Living – Working Conditions (Statistics Norway)* 2006 and 2009 included a population panel sample of the general working population followed up from 2006 to 2009 (only originally identified members are followed-up to the end of study period). Table 8 shows details of this Survey for 2006 and 2009.[177,178]

The eligible responders were Norwegian residents aged 18–66 years. The panel data comprised responders participating in both surveys and consisted of 9,375 persons (response frequency: 50.2% of the gross sample; 74.4% of the baseline cross-sectional sample). Responders in the panel dataset who were enrolled in paid work both at baseline and follow-up (n = 6,745) constituted the study population (Figure 15).

Table 8. Survey of Level of Living-Working conditions 2006 and 2009: details of the population.[175-176]

Survey of Level of Living – Working Conditions (Statistics Norway)		
Year	**2006**	**2009**
Gross sample	18,679 individuals	20,136 individuals
Responders	12,550 individuals	12,555 individuals
Response frequency	67.2%	61%
Data collection	18/09/2006 – 24/02/2007	22/06/2009 – 9/01/2010
Method for data collection	Telephone interviews (Computer Assisted Telephone Interview CATI), with the exception of 0.5% of the interviews which were conducted face-to-face (Computer Assisted Personal Interview CAPI). The interviews took an average of 24 minutes	

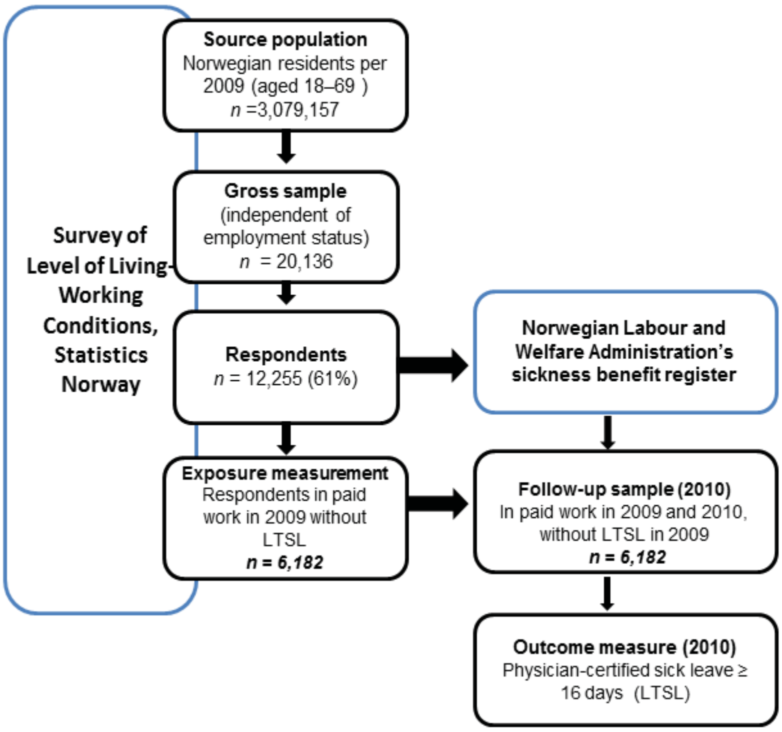
Figure 15. Flow chart: population sample for Study *II.*



Study III

The data was merged between the nationwide Survey of Level of Living – Working Conditions (Statistics Norway) 2009 (Table 8) and the Norwegian Labour and Welfare Administration's sickness benefit Registry 2009 and 2010, which records information on sick-leave diagnoses and disability pension. The linkage, at the individual level, was performed using the Norwegian unique personal identification number (Fig. 16).

Figure 16. Flow chart: population sample for *Study III*. LTSL: physician-certified long-term sick leave > 16 days.



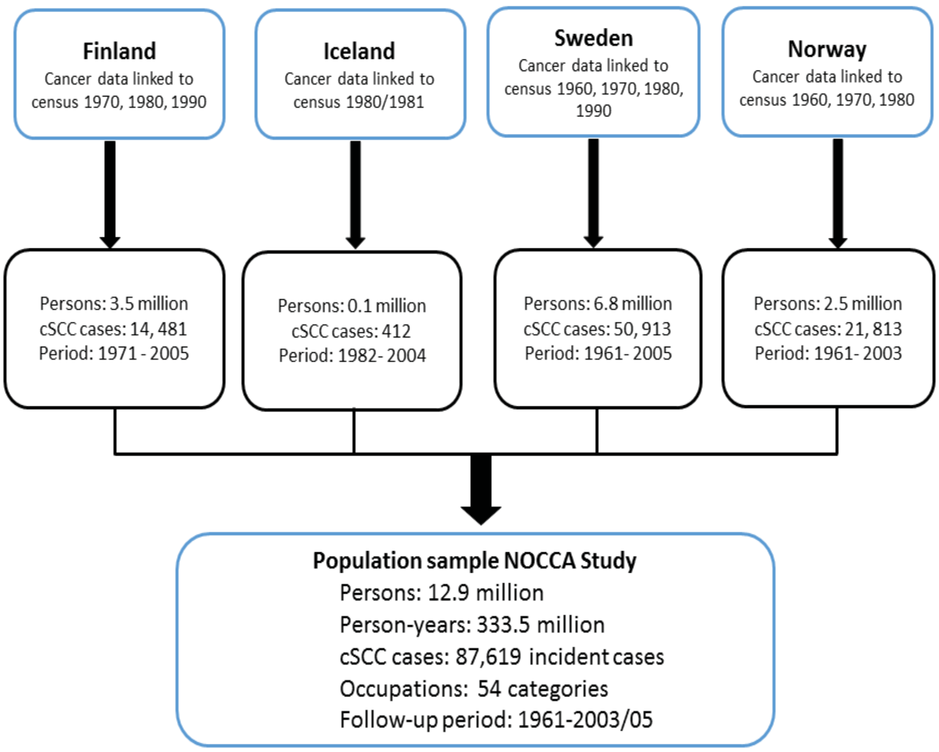
The eligible responders were Norwegian residents aged 18–69 years. In 2009, this population consisted of 3,079,157 persons (source population), whereof a gross sample of 20,136 individuals was randomly drawn. Of these, 7881 did not respond at baseline, and the most important reason was that the interviewer was unable to get in touch with the responders despite several attempts (19%), 16% did not want to participate, and 3% were prevented from participation. A total of 12,255 (61%) persons were then interviewed (Fig. 14). The baseline sample was compared with the gross sample according to the benchmarks of age, sex and region; and no major differences were detected.[177.178]

Responders who were enrolled in paid work for at least 1 hour during a reference week both in 2009 and 2010 constituted the follow-up sample (n= 6,758). Of the 6,758 subjects, 576 had physician-certified long-term sick leave (LTSL) in 2009 and where thus excluded. Hence, 6,182 employees were eligible for the prospective analyses and individually followed-up for medically confirmed LTSL incidence until the end of 2010 (Fig. 16).

Study IV

Data was obtained from the Nordic Occupational Cancer (NOCCA) project (http://astra.cancer.fi/NOCCA) which linked occupational information from censuses in the five Nordic countries to information on cancer diagnoses from the respective cancer registries, by using the unique personal identity codes[98]. Briefly, the study base consisted of approximately 12.9 million persons, born between 1896 and 1960 (Figure 17). Census questionnaires, centrally coded and computerized in the national statistical offices included questions related to economic activity, occupation, and industry.[98]

Figure 17. Population sample of the Nordic occupational cancer study for *Study IV.*



4.3 POWER ANALYSIS

During the design-phase, power analysis were performed to assess whether the sample size in *Study II* & *III* was adequate to detect the effect of skin exposure on skin problems, and on physician-certified long-term sick leave. The computations were performed using the *power* command in STATA version 13.0. The sample size calculations assumed a power of 0.8 and a significance level of 0.05.

Study I did not include power analysis because it was a descriptive study without hypothesis testing.
The large size of the NOCCA database, virtually including the total adult Nordic population during the follow-up, allows to investigate associations between a wide range of occupations and cancer types.[98]

4.4. EXPOSURE AND OUTCOME VARIABLES

Study I

The notification of suspected or confirmed work-related skin disease was based on the medical reports sent by general practitioners, occupational physicians or dermatologists to the Norwegian Labour Inspectorate´s Registry for work-related diseases. Demographic information included sex, age, diagnose coded using the International Classification of Diseases (ICD-10), occupation/industry of employment, and information on occupational exposure (coded based on European occupational disease schedules exposure codes).[179] Data on pre-existing non-occupational contact allergy, AD, localization and severity were not available.

Study II

Figure 18 shows an overview of *Study II* with the exposure and outcome assessment at both baseline (2006) and follow-up (2009).

Exposure variable: Occupational exposures

Self-reported occupational exposure at baseline and follow-up was assessed based on nine items developed by an expert group from a Nordic cooperation project (Table 9). The questions have been applied in regular surveys of living conditions since 1989.[180]

Figure 18. *Study II*: design, exposure, and outcome assessment.

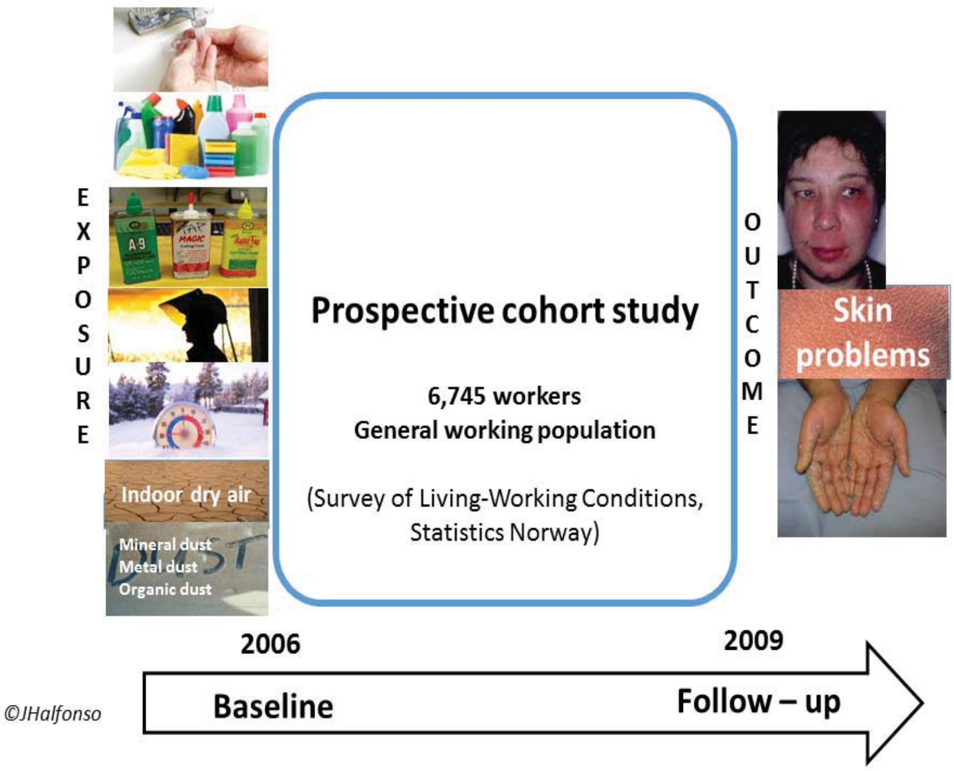


Table 9. Assessment of occupational exposure at baseline (2006) and follow-up (2009).

Occupational exposure		Question
Skin contact	Water	*Do you get water on your skin several times per hour in your day-to-day work? Including washing your hands.*
	Cleaning products	*Are you, in your day-to-day work, exposed to skin contact with cleaning products, disinfectants, solvents or other degreasing agents?*
	Oil, cutting fluids	*Are you, in your day-to-day work, exposed to skin contact with oils, lubricants or cutting fluids?*
Physical exposures	Heat	*Are you, in your day-to-day work, exposed to heat, i.e. temperatures of approx. 28 degrees Celsius or higher?*
	Cold	*Are you, in your day-to-day work, exposed to cold, i.e. working outdoors in the winter, or working in cold rooms, etc.?*
	Indoor dry air	*Are you, in your day-to-day work, exposed to indoor dry air?*
Chemical exposures	Mineral dust/fumes	*From where you work, can you clearly see in the air, or smell mineral dust? E.g. from stone, quartz, cement, asbestos or mineral wool?*
	Metal dust/fumes	*From where you work, can you clearly see in the air, or smell metal dust? E.g. from weld fumes, lead, chrome, nickel, zinc, aluminium, cobber or tin dust?*
	Organic dust/fumes	*From where you work, can you clearly see in the air, or smell organic dust? E.g. from textiles, wood, flour, clothes or animals?*

The response categories were “Yes” and “No”. “Yes” responders were asked to estimate the proportion of the working day during which they were exposed (response categories: “almost all the time”, “three-quarters of the working day”, “half of the working day”, “a quarter of the working day” and “very little of the working day”). Scores were then categorized into two categories: “non-exposed” (none exposed and exposed a very little of the working day) and “exposed” (a quarter of the working day or more).
For the prospective analyses with exposure assessed at both baseline (2006) and follow-up (2009), exposure categories were classified into four categories: “not exposed”, “exposed only at baseline”, “exposed only at follow-up”, and “exposed at both baseline and follow-up”.

Outcome: skin problems

At baseline and follow-up, the outcome was assessed using the following question: *“Have you over the past month been afflicted by eczema, itchy skin or rash?”.*
Responders who gave an affirmative answer were further asked: “*Have you been severely afflicted, somewhat afflicted or little afflicted?”*
Cases were defined as responders who reported being afflicted a little or more at follow-up.

Study III

Figure 19 shows an overview of *Study III* with the exposure assessment at baseline (2009) and outcome at both baseline and follow-up (2010).

Exposure variable: Occupational skin exposure

Self-reported occupational skin exposure at baseline was assessed based on the same items described in Table 9. Additionally, self-reported occupational exposure to biological factors such as waste and biological samples were measured based on the items described in Table 10 (these questions have been included in the Survey since 2009).

Outcome variable: physician- certified long-term sick leave (LTSL)

The outcome variable at follow-up (2010) in *Study III* was incident cases of physician-certified sick leave for a period of 16 or more working days (LTSL). Data at the individual level was obtained from the Norwegian Labour and Welfare Administration’s sickness benefit Registry.

Figure 19. *Study III*: design, exposure, and outcome assessment.

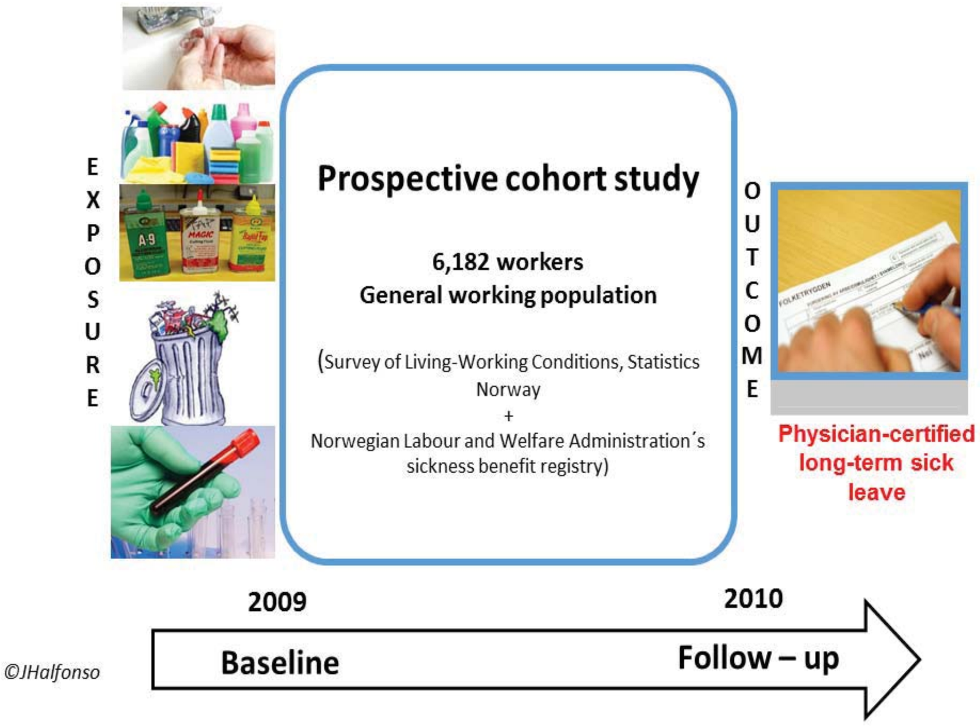


Table 10. Assessment of occupational exposure to biological factors at baseline (2009) (Study III)

Exposure measurement		Question
Biological exposures	Waste	*Are you, in your day-to-day work, exposed to waste, e.g. garbage, offal, sewage or used disposable equipment.*
	Biological samples	*Are you, in your day-to-day work, exposed to biological samples such as body fluids (e.g. blood, saliva, faeces or urine), or laboratory materials (e.g. biological samples from patients or animals?).*

Rationale of the cut-off limit for physician-certified long-term sick leave

In Norway, employees are entitled to use a personal declaration for sick leave of up to three days or a total of eight days spread over four different occasions during a 12-month period. In addition, if the employee´s child is sick, the employee can stay at home for 10–15 days, depending on the number of children. Thus, a sick leave period shorter than 16 days may include sick leave due to minor health problems such as common cold and the ability to stay at home with sick children. If the employee is sick beyond the personal declaration days, or if the severity of the illness requires it, then physician-certified sick leave is required. Therefore, this cut-off limit is likely to capture sickness that is more serious.

Study IV

Occupation

Occupational classification was based on the occupation recorded in the first available census in which the person participated in the age range of 30–64 years.[98] In Finland, Norway, and Sweden occupation was coded according to national adaptations of the Nordic Occupational Classification,[181] which is a Nordic adaptation of the International Standard Classification of Occupations (ISCO-58).[182] In Iceland occupation was coded according to a national adaptation of ISCO established in 1968 (ISCO-68).[183]

The original national occupational codes were converted to a common classification with 53 occupational categories, and an additional category of economically inactive persons. Detailed description of each occupational category is available in the Appendix 2.

For the purposes of this study, occupational categories were further classified as regards to outdoor/indoor work according to Radespiel-Tröger et al. 2009[184] (Table 11), and also merged into socioeconomic groups as previously done by Lynge et al. 2015[185] (Table 12).

Table 11. Classification of occupational categories according to outdoor/indoor work.[184]

Outdoor work	Seamen, farmers, fishermen, forestry workers, gardeners, bricklayers, other construction workers.
Mixed outdoor/ indoor work	Mechanics, wood workers, waiters, food workers, chimney sweeps, technical workers, electrical workers, painters, teachers, plumbers, public safety workers, postal workers, building caretakers, military personnel, drivers, transport workers, welders.
Indoor work	All remaining occupational categories.

Table 12. Coding of socioeconomic groups.[185]

Socioeconomic group	Occupational categories
Managers	Technical workers, physicians, dentists, teachers, administrators.
Lower administrative	Laboratory assistants, nurses, religious workers, artistic workers, journalists, clerical workers, sales agents, shop workers, transport workers, drivers, postal workers, public safety workers.
Skilled and specialized workers	Assistant nurses, other health workers, miners and quarry workers, seamen, textile workers, shoe and leather workers, smelting workers, mechanics, plumbers, welders, electrical workers, wood workers, painters, bricklayers, printers, chemical process workers, food workers, beverage workers, tobacco workers, glass makers, engine operators, cooks and stewards, waiters, chimney sweeps, hairdressers, launderers.
Unskilled workers	Other construction workers, packers, domestic assistants, building caretakers.
Farmers/forestry/fishing	Farmers, gardeners, fishermen, forestry workers.
Inactive	Economically inactive.
Not classified	Military personnel, “other workers”.

Cancer data

For the period 1960 – 2005, skin cancer was classified according to the International Classification of Diseases 7 (ICD 7) in “melanoma skin-cancer” and “other skin cancers/non-melanoma skin cancer”. Denmark was excluded because cases of BCC were also included from 1945 to 1977.

Data regarding cSCC topography, morphology, and date of diagnosis were registered. For all countries, only the first incident case of cSCC (primary cSCC) was included. Multiple cSCC at the time of diagnosis were counted as one incident case, and subjects were censored after the initial diagnosis.

Time windows of follow-up: capture period for cancer cases

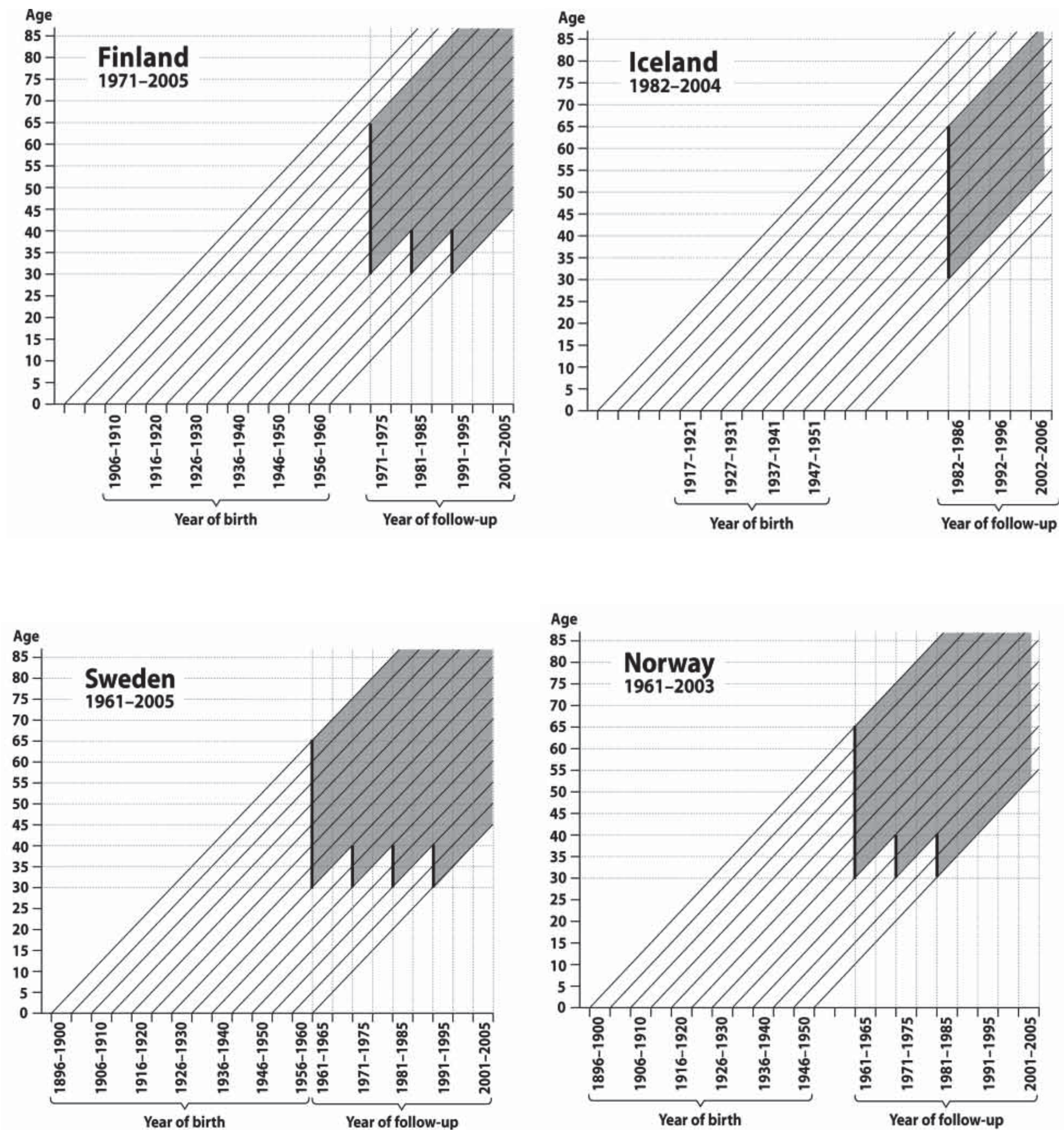
A person entered the cohort on January 1 of the year after the first available census where s/he participated, provided that s/he was 30-64 years old.

Person-years were then counted until the date of diagnosis, emigration, death or to December 31 of the following years: 2003 in Norway, 2004 in Iceland, and 2005 in Finland and Sweden.

The unique personal identity code used in all four countries allows the linkage between the census data, the mortality, emigration data and the cancer incidence data.[98]

Figure 20 shows time windows of follow-up of the cohort defined by year of birth and age, per country The initial years of the study capture the cases of those subjects aged 50 years old or more. These subjects were born before 1911 in Sweden and Norway; before 1921 in Finland; and before 1932 in Iceland.

Figure 20. Time windows of follow-up of the cohort. Bold vertical lines indicate time of baseline census used for allocation of the occupational category (from Pukkala et al. 2009).[98]



4.5 COVARIATES

- Sex: based on information from Registry *(Study I & IV)* and Survey data *(Study II & III).*

- Age: based on information from Registry and Survey data. Responders are grouped by age at year-end for the completion of the interview (*Study II & III),* and for the age at diagnosis (*Study I & IV).*
- Occupation: based on information from an open questionnaire, coded by Statistics Norway into a professional title in accordance with the International Standard Classification of Occupations (ISCO 1988) and recoded into 10 major occupational groups (Legislators, senior officials and managers, professionals, technicians and associate professionals, clerks, service workers and shop sale workers, skilled agricultural and fishery workers, craft-related trade workers, plant-machine operators and assemblers, elementary occupations, other occupations) *(Study II & III).*
- Education: based on information from Survey data (*Study III*).

4.6 STATISTICAL METHODS

Data analyses were performed with the Statistical Package for Social Sciences version 16.0 for Windows (SPSS Inc., Chicago, USA) (*Study I, II,* and *III*), Stata SE version 12 and 13 (*Study IV*).

Analyses were carried out separately for men and women.

Study I

Frequency statistics and cross tabulations were used to describe the trend for notifications of work-related skin diseases from 2000 to 2013, type of notified work-related skin disease by sex, age, occupation, and occupational exposures.

Study II

Associations between self-reported occupational exposures and skin problems were assessed by unconditional logistic regression using the following designs:

(i) Prospective analyses with exposure measured at baseline (2006)

(ii) Prospective analyses with exposure measured at both baseline (2006) and follow-up (2009).

The associations were estimated as odds ratios (ORs) with 95% confidence intervals (95% CIs).

Study III

Associations between self-reported occupational exposures and physician-certified long-term sick leave were assessed by unconditional logistic regression obtaining odds ratios with 95% CI.

Study IV

The relative risk of the cancer incidence of each occupational category was described by the standardised incidence ratio (SIR), which was calculated as the ratio of the observed to the expected number of cancer cases, using the cSCC incidence rates for the entire national study populations of each country as reference. For a given sex (g), the SIR for a given occupational category (o) in a given country (c) was calculated as:

$$\mathrm{SIR}_{goc} = \frac{\sum_a \sum_p Obs_{gocap}}{\left\{ \sum_a \sum_p PY_{gocap} \frac{\sum_o Obs_{gocap}}{\sum_o PY_{gocap}} \right\}}$$

Where Obs= observed number of cases; PY: person years; a=age; p= calendar period. The denominator in the equation is the expected number of cancer cases for the given sex category, occupational category, age, period, and country. This means that to describe relative risks related to occupation we compared the incidence of cancer in a given occupation, in a given country with the general population in the same country.

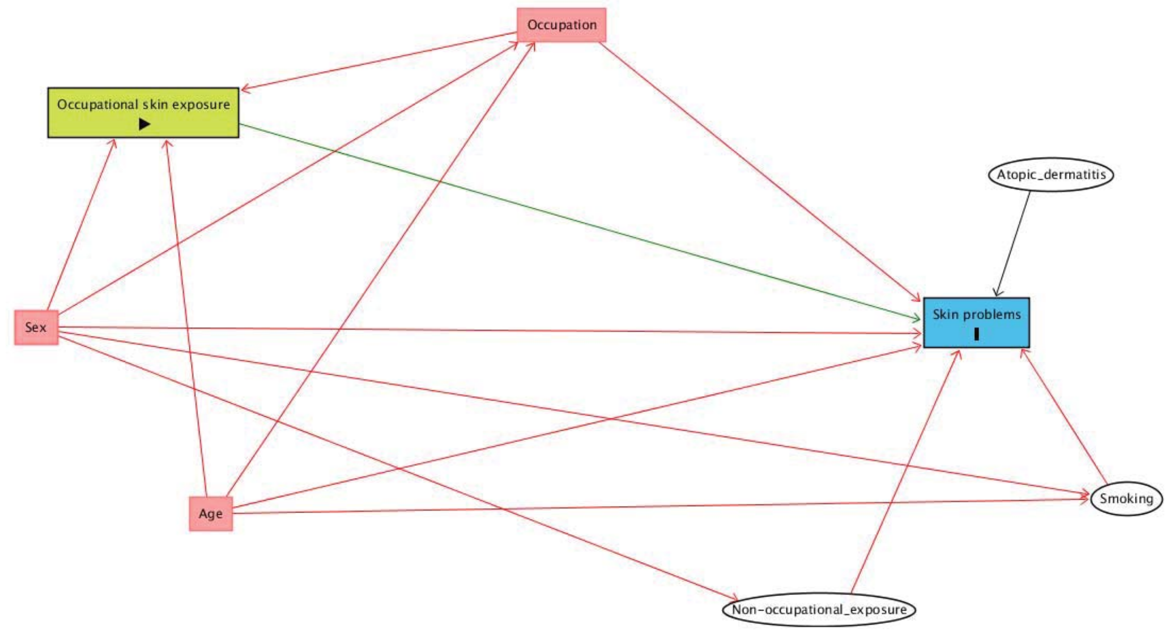
The observed number of cancer cases and person-years were stratified into two sex categories, eight 5-year attained age categories (30–34; 35–39; … 85+ years), and 5-year calendar periods (1961–1975; 1976–1980; …; 2001–2005). The expected number of cancer cases was based on number of person-years in each stratum (country, sex, age, and calendar period), and the respective incidence rates of each country. The same criteria were used for both the denominator (the population) in calculating the standard population rate and the person-years of the at-risk population for each occupational category-age-sex strata.

For each SIR the exact 95% CI was determined by assuming a Poisson distribution of the observed number of cases. The SIR was regarded as statistically significant if the 95% CI did not include 1.0.

4.7 Directed Acyclic Graphs (DAGs)

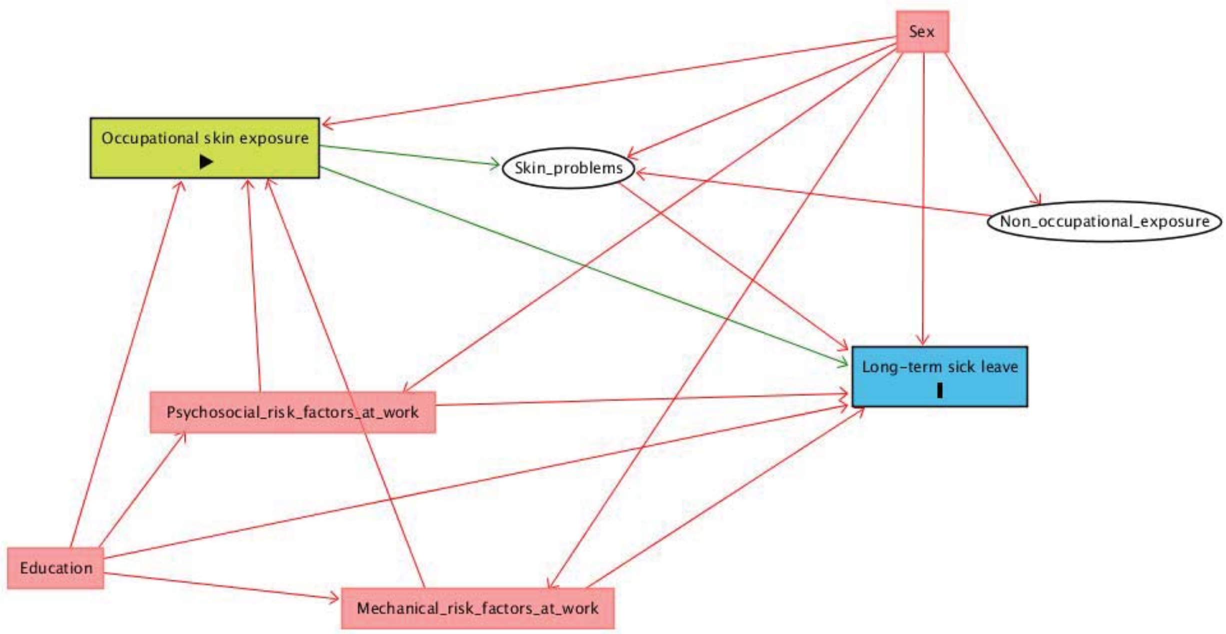
The web-based software DAGitty version 2.3 (available at dagitty.net) was used to draw and analyse DAGs, also known as causal diagrams, during the design-phase of statistical analysis. [186] Figure 21 and 22 show the DAGs for *Study II* & III.

Figure 21. Directed acyclic graph for *Study II.*



Exposure outcome ancestor of exposure and outcome unmeasured variable causal path biasing path

Figure 22. Directed acyclic graph for *Study III.*



Exposure outcome ancestor of exposure and outcome unmeasured variable causal path biasing path

4.8 ADJUSTMENT FOR POTENTIAL CONFOUNDING

Based on the DAGs analysis, *Study II* & *III* included different models with adjustment for potential confounders.
Figure 23 shows an overview of models for statistical adjustments in Study *II.*
Each new model included n + 1 the variables adjusted for in the previous model. Model #2 included adjustments for skin problems at baseline. Model #3 included further adjustments for sex, age, and occupation.

To limit the potential of over-adjustment, in model #4, each occupational exposure was adjusted only for other occupational exposures that were first estimated to exert an influence above a certain threshold. This estimation was made *à priori* based on the following procedure suggested by Rothman.[187] In the first step, crude ORs were estimated separately for each occupational exposure. In the second step, each of the other occupational exposure variables were entered one at a time. If the inclusion of a potential confounder resulted in a change in the OR of 10% or more, that variable was treated as a confounder in the multiple regression models.

Figure 23. Models for statistical adjustments in *Study II.*

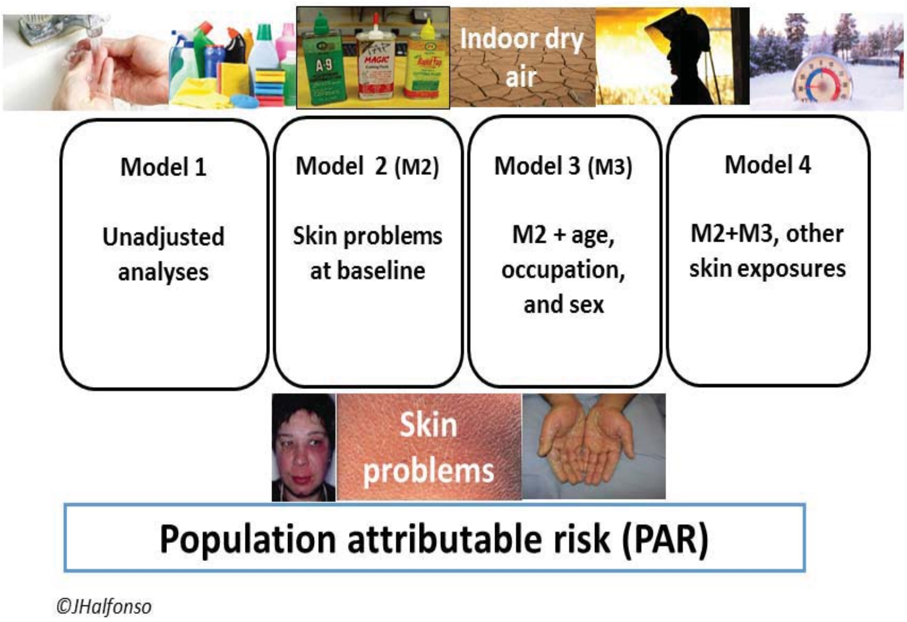
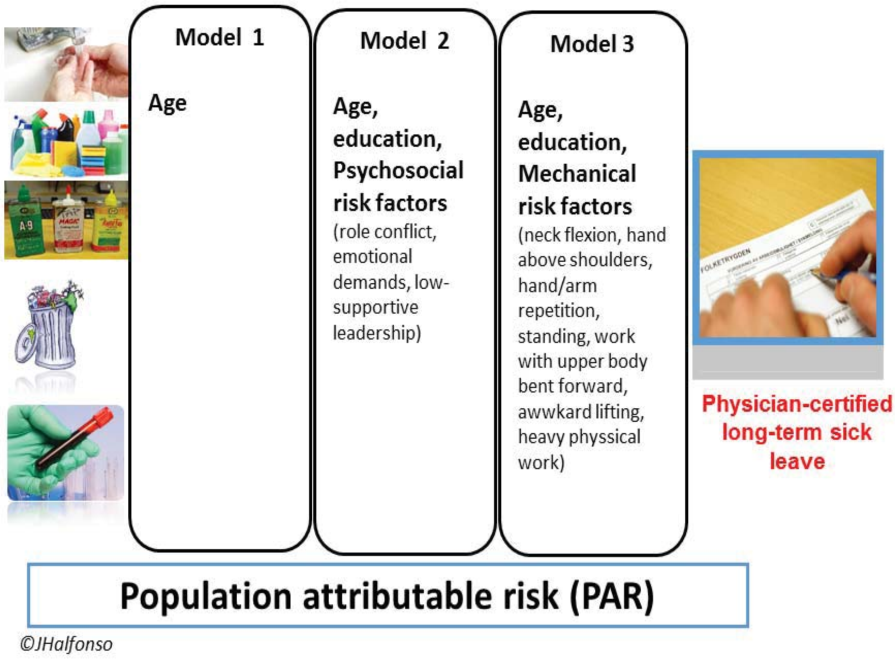


Figure 24 shows an overview of models for statistical adjustments in Study *III.*
Model #1 included adjustment for age.
Model #2 included further adjustments for education and psychosocial exposures at work shown to predict physician-certified sick leave in the general working population of Norway.[173] Role conflict, emotional demands and low supportive leadership have been reported as the most important psychosocial predictors of long-term sick leave.[173]
Finally, model #3, included adjustment for age, education and mechanical exposures at work shown to predict sick leave in the general working population of Norway.[174] Neck flexion, hand above shoulders, hand/arm repetition, standing, work with upper body bent forward, awkward lifting and heavy physical work have been reported as the most important mechanical predictors for long-term sick leave.[174]

Figure 24. Models for statistical adjustments in *Study III.*



4.9 POPULATION ATTRIBUTABLE RISK (PAR)

It is defined as the reduction in incidence that would be achieved if the population had been entirely unexposed, compared with the current exposure pattern. It is a measure of population impact that answers to the question: How many cases of the health problem observed in the study population are attributable to a specific exposure?[188]

PAR combines information on prevalence and a measure of association to provide a quantitative estimate of the proportion of disease in the population that is directly attributable to a particular exposure. PAR estimates the public health impact of a particular exposure and is used to estimate the proportion of disease that can be prevented if that exposure were eliminated.[189] The PAR with 95% CIs was calculated for the statistically significant occupational exposures in the adjusted regression analyses, both in *Study II* & *III*, based on the method described by Natarajan et al. [190]

4.10 REPORTING AND SUBMISSION OF RESULTS

As suggested by Langan et al. 2011,[191] the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations were followed for reporting and submission of the findings of the observational studies of this doctoral thesis.

4.11 ADDITIONAL ANALYSIS

Some additional analyses are included to supplement the information provided for *Study I* & *II*.

For *Study I*, the frequency of work-related skin diseases notified to the Norwegian Petroleum Safety Authority was analysed, given that the Norwegian Labour Inspectorate Registry does not include data from the Norwegian offshore sector.

For *Study II*, attrition analysis was performed to assess whether a potential healthy worker effect influenced the response frequency at follow-up. Attrition bias can be a source of bias if the loss to follow-up is attributed to the study outcome measure.[192] With other words, the occurrence of skin problems at baseline could have influenced an eventual loss to follow-up with impact on the external and internal validity of the follow-up assessment. Thus, associations between socioeconomic variables and skin problems at baseline and frequency response at follow-up were determined by Pearson´s Chi-square tests and unconditional logistic regression (Table 13, Chapter V). The level for significance was set to $p < .05$ (95% CI).

The Pearson´s chi-square test, also known as the chi-square goodness- of-fit test or chi-square test for independence, is useful to determine whether there is a significant difference between the expected frequencies and the observed frequencies in one or more categories.

Moreover, to assess whether the occurrence of skin problems at baseline could have led to changes in exposure patterns at follow up, we further analysed by unconditional logistic regression associations between skin problems at baseline and occupational exposures at follow-up (Table 14, Chapter V).

4.12 ETHICAL CONSIDERATIONS

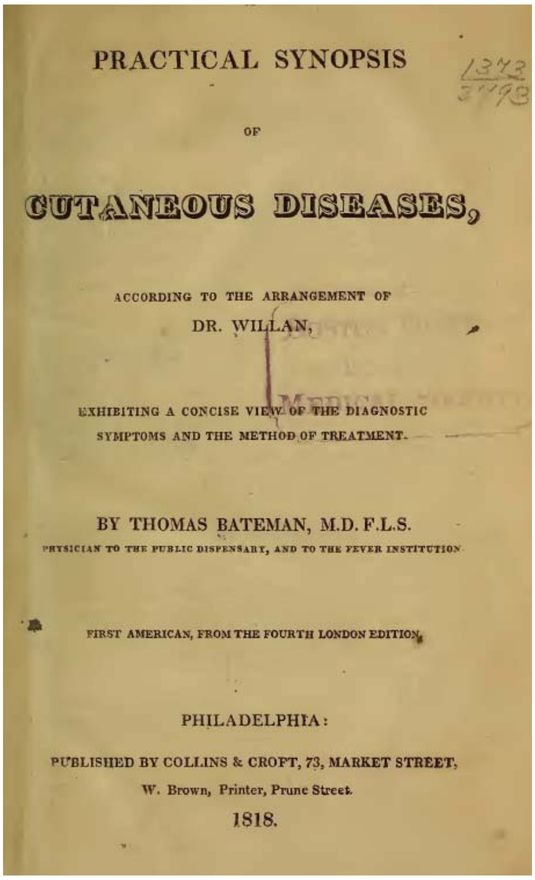
Use of data for *Study I* did not require Ethical approval from the Region Committee for Research Ethics, Oslo.

For *Study II* & *III*, Statistics Norway carried out the survey according to statutory rules. Statistics Norway has appointed its own privacy ombudsman, approved by the Norwegian Data Inspectorate. All persons gave their informed consent prior to their inclusion in the study.

For *Study IV*, study approval was obtained from the National Review Board of each participating country.

"…Eczema rubrum: the disease is preceded by a sense of stiffness, burning, heat and itching, in the part where it commences... These sensations are soon followed by an appearance of redness, and the surface is somewhat rough to the touch…"[10]

The first definition of eczema from «A practical synopsis of Cutaneous Diseases. 1814
Thomas Bateman (1778-1821)


PRACTICAL SYNOPSIS

OF

CUTANEOUS DISEASES,

ACCORDING TO THE ARRANGEMENT OF
DR. WILLAN,

EXHIBITING A CONCISE VIEW OF THE DIAGNOSTIC
SYMPTOMS AND THE METHOD OF TREATMENT.

BY THOMAS BATEMAN, M.D. F.L.S.
PHYSICIAN TO THE PUBLIC DISPENSARY, AND TO THE FEVER INSTITUTION

FIRST AMERICAN, FROM THE FOURTH LONDON EDITION.

PHILADELPHIA:
PUBLISHED BY COLLINS & CROFT, 73, MARKET STREET,
W. Brown, Printer, Prune Street.
1818.

10. It is worthy of remark that Dr. Bateman defined "*eczema rubrum*" by giving an example of skin irritation following mercury exposure, and considering the effect of cold and heat on the skin. His description of "*eczema impetiginodes*" as *"the irritation of various substances; and, when these are habitually applied, it is constantly kept up in a chronic form*" reminds me on the pathophysiology of cumulative irritative contact dermatitis.
Dr. Bateman actually described examples of occupational affections of the skin. He called "impetigo sparsa" to eruptions in the fingers and hands of sugar workers and bricklayers. He stressed that, *"neither case are contagious, as the popular appellation might lead us to suppose*»
He mentioned that Dr. Willan described a topical variety of "ecthyma", occurring on the hands and fingers of workmen employed among metallic powders, *"As it commences in a vesicular form, and though afterwards purulent, produces irregular patches of thin scabs, it should perhaps have been referred to eczema".* I wonder if these cases corresponded to allergic contact dermatitis.

CHAPTER V: SUMMARY OF RESULTS

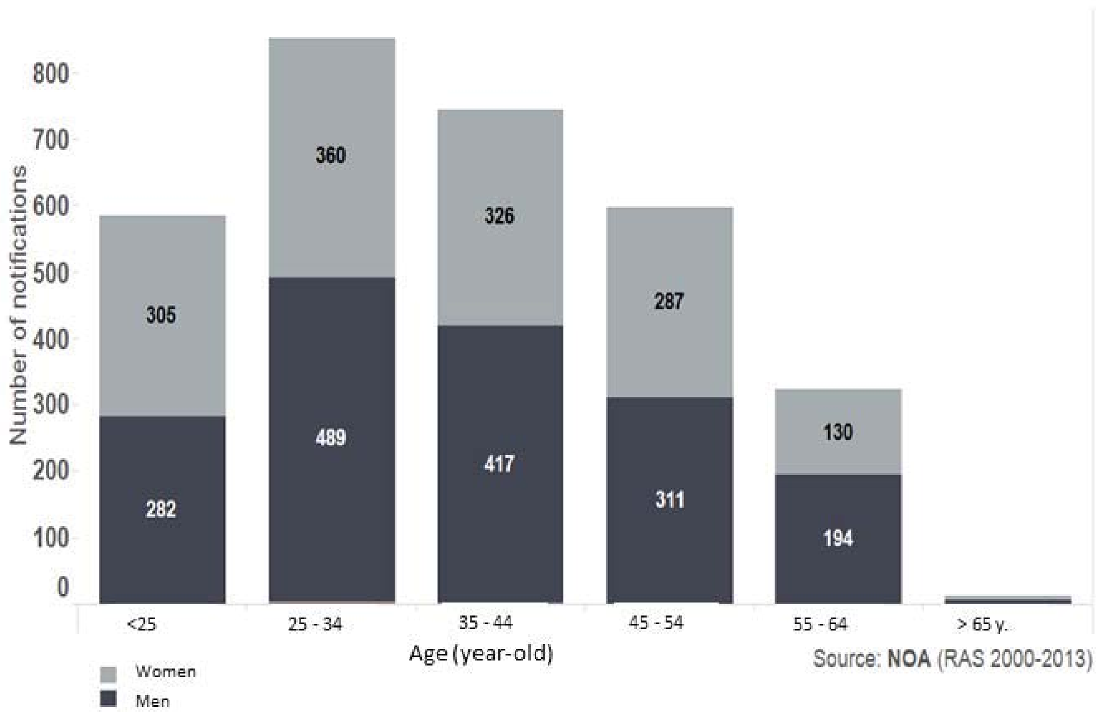
5.1. Notified work-related skin diseases in Norway, 2000 – 2013 (*Study I*)

Skin diseases, with 3,142 cases out of 41,181 notifications, ranked in third place after diseases of the ear and the respiratory system.

The number of notifications declined dramatically from 487 in 2000 to 91 in 2013, but a similar trend was observed for other diseases. Contact dermatitis accounted for 94% of all the notified skin diseases (43% irritant CD, 41% allergic CD, and 10% unspecified CD).

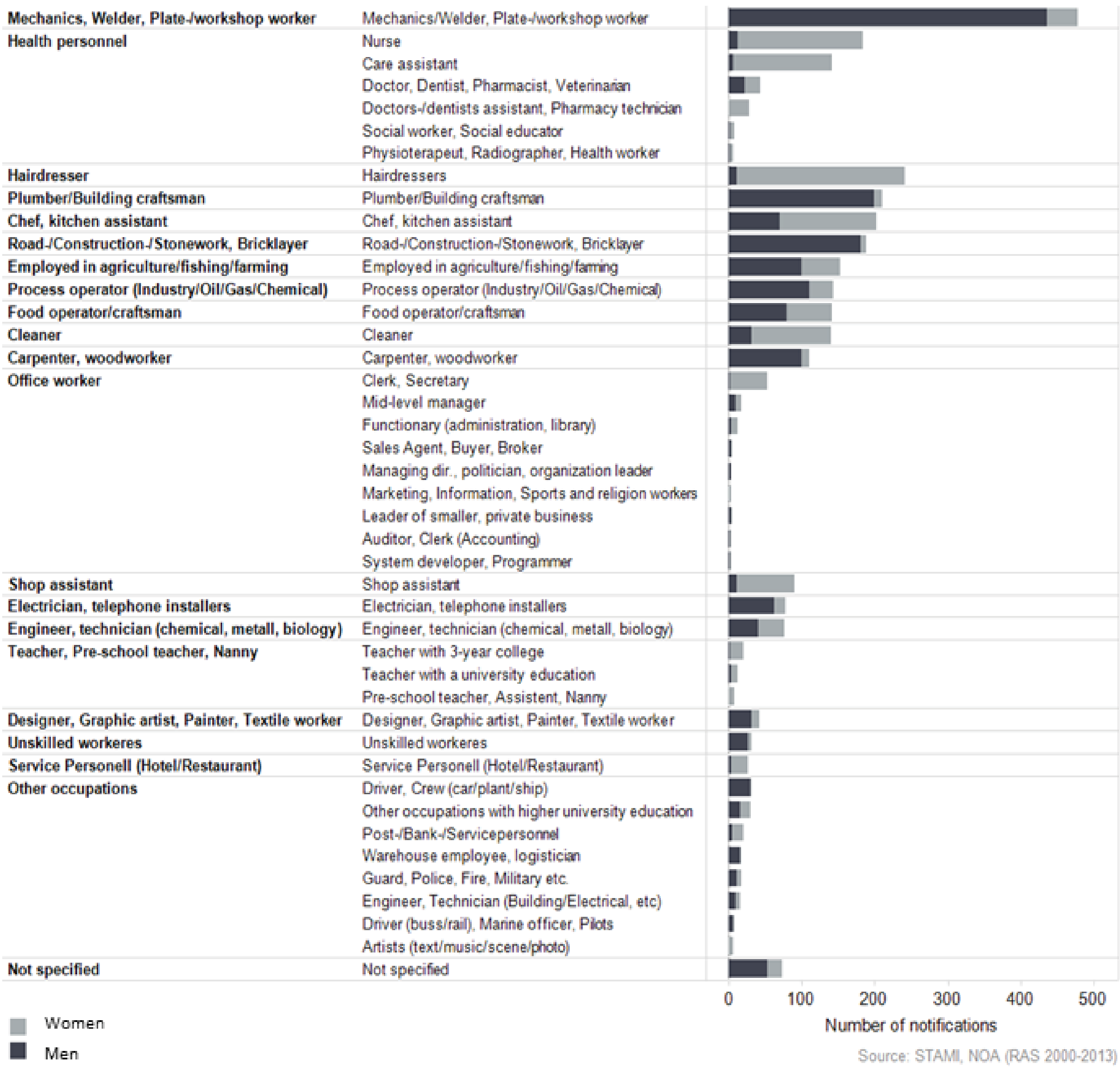
Figure 25 shows the distribution of notified cases by age and sex.

Figure 25. Number of notified work-related skin diseases by sex and age, 2000 – 2013.



The detail of occupations with notified work-related skin diseases are shown in Fig. 26.

Figure 26. Number of notified work-related skin diseases by occupation and sex, 2000 – 2013.

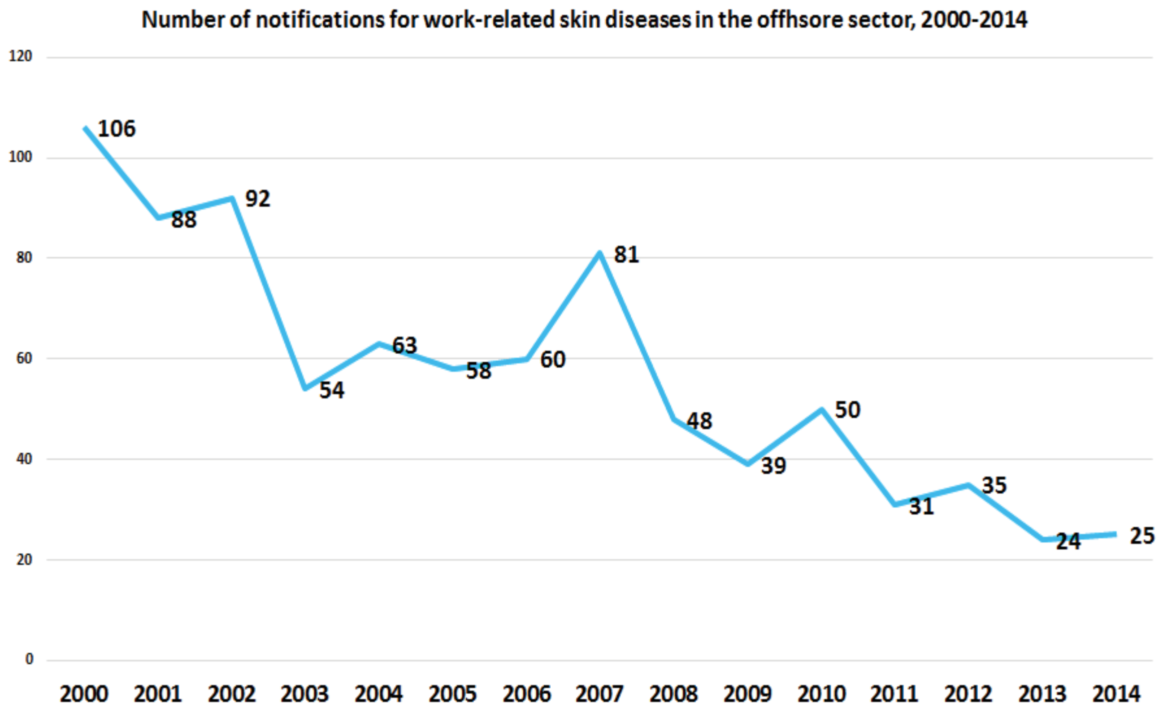


The most common occupational exposures were skin contact with cleaning products, other chemical substances, oils, fuels and solvents, metals, adhesive and epoxy substances, plastic and rubber products.

5.2. Notified work-related skin diseases in the Norwegian offshore sector 2000 – 2014.

For the period 2000-2014, 854 cases of work-related skin diseases were reported to the Petroleum Safety Authority Registry for work-related diseases. The number of notifications declined dramatically from 106 in 2000 to 25 in 2014 (Figure 27).

Figure 27. Notified work-related skin diseases in the Norwegian offshore sector for the period 2000 – 2014.



Contact dermatitis accounted for 97% of all the skin diseases, followed by skin infections. The majority of the cases were among male workers (89.2%).

Chemical exposures were the most frequent notified occupational exposure (95%), followed by physical exposures (4.1 %), whereof dry air was the most common. Skin contact with mineral oils and paraffin accounted for 45% of the total number of cases, 16% of the notifications lacked specific information about the chemical exposure, and epoxy-based substances accounted for 7.2% of the cases.

The occupational group with most notifications was oil workers (ca. 75%), followed by cleaners and kitchen workers (ca. 12%).

5.3. Association between self-reported occupational exposures and skin problems (*Study II*)

The one-month prevalence of skin problems was 13.2% at baseline (2006), 11.7% at follow-up (2009), and 5.9% at both time-points. These percentages correspond to approximately 304,000 individuals of the general working population at baseline, 287,500 at follow-up, and 143,400 at both time-points. Women reported skin problems more frequently than men.

In the prospective analyses with exposures measured at baseline, self-reported exposure to indoor dry air was the most consistent risk factor for the 1-month prevalence of skin problems at follow-up with odds ratios of 1.3.

We found evidence of an association between self-reported skin exposure to water, cleaning products, and organic dust/fumes with skin problems at follow-up. However, the strength of these associations was less evident after adjustments for sex, age, and occupation. Self-reported skin exposure to oil and cutting fluids was a predictor for skin problems at follow-up only in this model. The strength of the association became weaker in the model that included further adjustment for skin exposure to cleaning products, which may suggest that skin exposure to cleaning products mediates the prejudicial effects of skin exposure to oil and cutting fluids on the risk of reporting skin problems at follow-up.

In the prospective analyses with exposure measured at both baseline and follow-up, self-reported skin exposure to water, cleaning products, and indoor dry air at both time-points were the most consistent predictors associated to skin problems at follow-up. Self-reported skin exposure to heat and organic dust/fumes only at follow-up were also predictors for skin problems.

Self-reported skin exposure to oil/cutting fluids at follow-up and at both-time points was associated to skin problems only in the model which included adjustments for sex, age, and occupation. However, this effect became less evident in the model that included further adjustment for skin exposure to cleaning products. Overall, we found weak evidence of an association between self-reported skin exposures only at baseline with skin problems at follow-up.

The total combined PAR for occupational exposures was 15.8%, whereof skin exposure to cleaning products and water had by far the highest impact (7.3% and 4.4%)

Stratification by sex showed that the association between occupational exposure to water at both time-points and skin problems was stronger among women only. The effect of occupational exposure to indoor dry air at both time points was stronger among men. No major sex differences were found as regards as other occupational exposure factors.

5.4. Attrition analysis

Table 13 shows results of the attrition analysis (additional analysis for *Study II*).

Table 13. Survey response at baseline (2006) and differences in survey response at follow-up (2009) for baseline predictors.

Baseline predictors	Responders at baseline	Response frequency at follow-up (%)	Group difference Response frequency (x^2)	OR
Sex				
Male	5,236	74.8	7.006 (p:0.008)	(Ref)
Female	4,725	77.1		0.88 (0.80-097)
Age (years)				
17-24	987	58.9	231.390 (p:0.000)	(Ref)
25-34	2,003	70.8		0.59 (0.50–0.69)
35-44	2,655	79.1		0.38 (0.32–0.44)
45-54	2,412	78.8		0.38 (0.33–0.45)
55-66	1,904	81.8		0.31 (0.26–0.37)
Education				
Basic school level	683	67.9	171.234 (p:0.000)	(Ref)
Upper secondary education, not finished	2,385	70.5		0.89 (0.74–1.07)
Upper secondary education	3,132	74.8		0.71 (0.56–0.85)
University/college 4 years	2,701	82.7		0.44 (0.37–0.53)
University/college 4 years +	880	84.3		0.39 (0.30–0.50)
Occupation				
Legislators, senior officials and managers	952	77.7	200.310 (p:0.000)	(Ref)
Professionals	1,411	81.9		0.77 (0.63-0.95)
Technicians and associate professionals	2,547	81.7		0.78 (0.65–0.94)
Clerks	646	76.2		1.09 (0.86-1.38)
Service workers and shop sale workers	2,026	71.3		1.40 (1.17-1.68)
Skilled agricultural and fishery workers	220	83.2		0.71 (0.48-1.04)
Craft-related trade workers	1,002	71.0		1.43 (1.16-1.75)
Plant-machine operators and assemblers	642	65.3		1.86 (1.49-2.32)
Elementary occupations	343	61.5		2.18 (1.67-2.85)
Other occupations	170	71.2		1.41 (0.98-2.04)
Skin problems				
Yes	8,643	76.0	0.182 (p:0.670)	(Ref)
No	1,311	75.4		1.03 (0.90–1.18)

Whilst the occurrence of skin problems did not predict frequency response at follow-up, age, sex, education, and occupation were the most important predictors.

The response frequency for women was higher at follow-up. For both age and education, the findings showed that survey response at follow-up increased incrementally with older ages and higher levels of education.
Table 14 displays the odds ratio for associations between skin problems at baseline (2006), and occupational exposures at follow-up (2009).

The occurrence of skin problems at baseline did not seem to have an effect on the follow-up exposure to cleaning products, organic, and mineral dust.

On the other hand, reporting skin problems at baseline seemed to have an inverse effect on follow-up exposure to water, oil and cutting fluids, dry indoor air, cold, heat, and metallic dust.

Table 14. Association between skin problems at baseline (2006) and skin exposure at follow-up (2009). Adjustments were made for skin exposures at baseline (2006).

Skin exposure at follow-up	OR (95% CI)
Cleaning products	1.33 (1.05-1.68)
Water	1.05 (0.85-1.30)
Oil and cutting fluids	1.04 (0.71-1.52)
Dry indoor air	1.06 (0.86-1.31)
Cold	0.93 (0.72-1.20)
Heat	0.73 (0.49-1.09)
Organic dust	1.66 (1.08-2.53)
Mineral dust	1.64 (1.05-2.55)
Metallic dust	0.68 (0.38-1.22)

5.5. Association between self-reported occupational skin exposure in 2009 and physician-certified long-term sick leave (>16 days) in 2010 (*Study III*)

At follow-up, 13.7% out of the 6,182 participants were on physician-certified long-term sick leave (LTSL), after restricting for responders with an active employee relationship for 100 days or more in both 2009 and 2010 and without LTSL in 2009. These percentages correspond to approximately 336,609 individuals of the general working population of Norway in 2010.

The frequency of LTSL was higher among women, skilled agricultural and fishery workers, other occupations, elementary occupations, service workers and shop sale workers; also in responders with the lowest educational level.

Among women, after adjustments for age, education, and the effect of psychosocial risk factors at work, responders reporting skin exposure to cleaning products had 1.5 higher odds of being on LTSL. Women reporting skin exposure to water had 1.6 higher odds of being on LTSL, and those reporting exposure to biological samples had 1.4 higher odds of being on LTSL (Model II). In the model that considered mechanical risk factors at work, evidence of an association between occupational skin exposure to water and LTSL was found (Model III).

Among men, after adjustments for age, education, and the effect of psychosocial risk factors at work responders reporting skin exposure to cleaning products had 2.1 higher odds of being on LTSL (Model II). Men reporting skin exposure to water had 1.4 higher odds of being on LTSL, those reporting skin exposure to oil/cutting fluids had 1.5 higher odds of being on LTSL, and those reporting exposure to waste had 2.3 higher odds of being on LTSL (Model II). In the model that considered mechanical risk factors at work, evidence of an association between occupational skin exposure to cleaning products and waste with LTSL was found (Model III).

Both for women and men, occupational exposure to physical factors such as indoor dry air, heat, and cold; and to chemical exposures such as organic, mineral, and metallic dust did not predict LTSL at follow-up (Results are shown in Appendix 3). However, we found an association between self-reported exposure to indoor dry and short-term sick leave (duration less than 16 days) for both sexes female OR 1.4 (95% CI: 1.2 – 1.7); male OR 1.3 (95% CI: 1.1 – 1.7) in Model II and III.

The PAR estimation showed that 14.5% of the new cases with LTSL were attributable to occupational skin exposure associated with long-term sick leave.

5.6 Occupation and relative risk of cSCC in four Nordic countries (*Study IV*)

In the follow-up period from 1961 to 2003/05, 87,619 incident cases of first primary cSCC were reported to the cancer registries.

Table 15 and 16 shows elevated SIRs among men and women stratified by age groups for different occupational categories. The non-elevated SIRs for both sexes are shown in Appendix 4.

Table 15. Standardised incidence ratios (SIR) and 95% confidence intervals (95% CI) for cutaneous squamous cell carcinoma among men, according to age groups in Finland, Iceland, Norway, and Sweden.

	30-49 years			**>50 years**		
Occupational categories	**Obs***	**SIR**	**95% CI**	**Obs***	**SIR**	**95% CI**
Seamen	21	1.19	0.74 – 1.83	683	**1.23**	1.14 – 1.32
Military personnel	21	1.47	0.91 – 2.25	479	**1.29**	1.17 – 1.41
Public safety workers	31	1.20	0.82 – 1.71	757	**1.25**	1.16 – 1.34
Teachers	67	1.15	0.89 – 1.46	1,323	**1.20**	1.13 – 1.26
Technical workers, etc.	150	0.97	0.82 – 1.14	3,775	**1.13**	1.09 – 1.16
Transport workers	23	1.02	0.65 – 1.53	987	**1.10**	1.03 – 1.16
Physicians	23	**2.15**	1.36 – 3.22	341	**1.75**	1.57 - 1.95
Dentists	3	0.85	0.18 – 2.50	117	**1.30**	1.08 – 1.56
Nurses	8	**3.44**	1.48 – 6.77	5	1.06	0.34 – 2.49
Assistant nurses	8	1.89	0.82 – 3.72	62	**1.36**	1.04 – 1.75
"Other health workers"	3	0.40	0.08 – 1.15	163	**1.16**	1.00 – 1.35
Clerical workers	75	**1.36**	1.07 – 1.70	2,024	**1.18**	1.13 – 1.23
Religious workers etc.	71	**1.41**	1.10 – 1.78	913	**1.27**	1.19 – 1.36
Administrators	79	**1.31**	1.03 – 1.63	2,567	**1.32**	1.27 – 1.37
Sales agents	67	0.81	0.63 – 1.03	2,676	**1.16**	1.11 – 1.20
Printers	19	1.26	0.76 – 1.97	397	**1.13**	1.02 – 1.24
Artistic workers	21	**1.95**	1.20 – 2.98	234	1.01	0.88 – 1.15
All categories	**1,566**	**1.00**	**Ref.**	**48,724**	**1.00**	**Ref.**

*Obs: observed cases. Occupational categories with outdoor work Occupational categories with mixed outdoor/indoor work Occupational categories with indoor work.

Table 16. Standardised incidence ratios (SIR) and 95% confidence intervals (95% CI) for cutaneous squamous cell carcinoma among women, according to age groups in Finland, Iceland, Norway, and Sweden.

	30-49 years			>50 years		
Occupational categories	**Obs***	**SIR**	**95% CI**	**Obs***	**SIR**	**95% CI**
Gardeners	23	1.16	0.73 – 1.73	1,261	**1.04**	1.00 – 1.10
Teachers	75	1.02	0.80 – 1.28	992	**1.18**	1.10 – 1.25
Physicians	7	1.80	0.72 – 3.71	43	**1.76**	1.28 – 2.37
Dentists	1	0.51	0.01 – 2.83	40	**1.41**	1.00 – 1.91
Nurses	41	1.13	0.81 – 1.53	452	**1.11**	1.01 – 1.22
"Other health workers"	26	0.94	0.61 – 1.37	328	**1.13**	1.01 – 1.26
Clerical workers	186	1.06	0.91 – 1.22	2,637	**1.11**	1.07 – 1.15
Administrators	27	**2.01**	1.32 – 2.92	175	**1.16**	1.00 – 1.34
Journalists	2	0.74	0.09 – 2.66	36	**1.41**	1.00 – 1.95
All categories	**1,218**	**1.00**	**Ref**	**36,111**	**1.00**	**Ref.**

*Obs: observed cases. Occupational categories with outdoor work Occupational categories with mixed outdoor/indoor work Occupational categories with indoor work.

Figure 28 shows the stratified SIRs by period in occupational categories with outdoor work among men. Seamen were the only occupational category with elevated SIRs in the three periods. Elevated SIRs were found among farmers only for the period 1961 -1975.
A consistent tendency of decreasing SIRs from the 1960s was observed for all occupational categories with outdoor work.

Occupational categories with “mixed indoor/outdoor work” and with “indoor work” did not show any consistent trend across periods.
Among women, no consistent trend across periods was observed for the occupational categories stratified according to outdoor/indoor work.

Stratification by socioeconomic groups showed a tendency of increasing SIRs across periods for occupational categories at the top of the socioeconomic hierarchy (“managers” and “lower administrative”, and a consistent tendency of decreasing SIRs among the group of farmers/forestry workers/fishermen (Figure 29). A similar pattern was found for both sexes.

Figure 28. Standardised incidence ratios (SIR) for cutaneous squamous cell carcinoma among men in occupational categories with outdoor work by period, in four Nordic countries 1961 – 2005. X axis is in logarithmic scale.

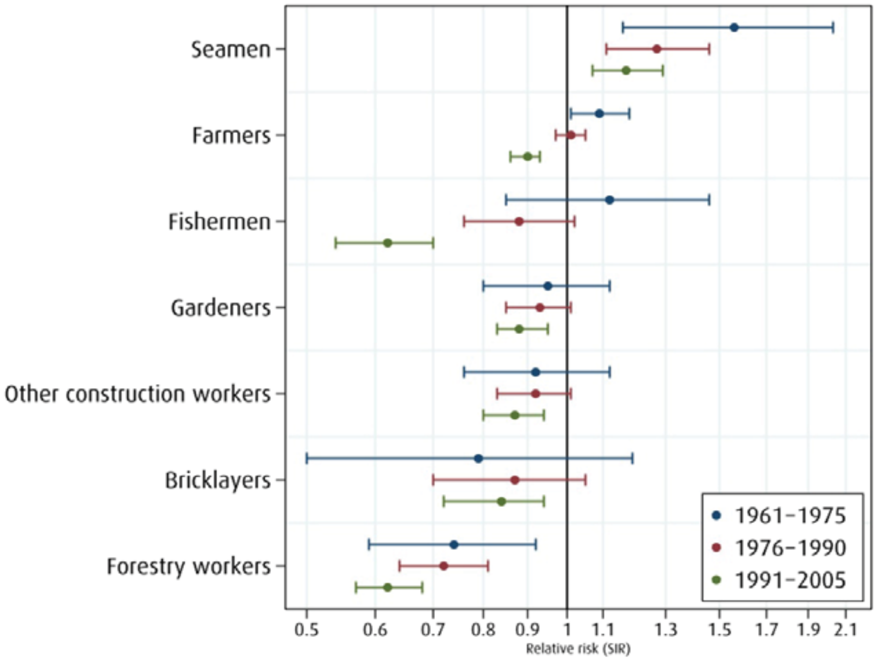


Figure 29. Standardised incidence ratios (SIR), by socioeconomic group and period, among men and women in four Nordic countries. 1961- 2005. X axis is in logarithmic scale

"…its origin from a lodgement of soot in the rugae of the scrotum, and at first not to be a disease of the habit…, but here the subjects are young, in general in good health, at least at first; the disease brought on them by their occupation…"

Chirurgical observations: "Cancer scroti." Page 67. 1775
Sir. Percival Pott (1714-1788)

11

11. **Ragnheiður Þorgrímsdóttir** made this painting from charcoal and ink after I told her about the first descriptions of skin cancer due to occupational exposures among chimney sweeps.

Ragnheiður Þorgrímsdóttir is from Iceland, graduated from Accademia di Belle Arti in Florence, Italy 2015. She is currently taking a master in Fine Arts at the New York Academy of Arts in New York. http://ragnpaint.com/

CHAPTER VI: DISCUSSION

6.1 THE MAIN FINDINGS AND COMPARISONS WITH OTHER STUDIES

Given that scarce research within occupational dermatology has been performed in Norway, this thesis sought to investigate the notification trends of work-related skin diseases, the contribution of occupational skin exposures to the risk of skin problems and physician-certified long-term sick leave in the general working population of Norway. Furthermore, to describe the variation in the relative risk of cSCC between occupational categories of four Nordic countries.

Hence, this is the first Norwegian population-based study with focus on occupation, occupational exposures and skin conditions.

Study I

To start with, this study has described a steep decline in the notifications of work-related skin diseases from 2000 to 2013. Such a decline should be interpreted with cautious, as this study did not adjust for changes in the population at risk; a decline in the population at risk without the appropriate adjustment will bias the trend toward a decline.[193] However, few studies adjusted appropriately for changes in the population at risk.[194,195] For instance, one of the most robust studies with such an adjustment reported that Norway was one of the few European countries with an increasing trend in the incidence of occupational allergic contact dermatitis compared to other European countries.[195] Moreover, a simplified reporting system with regular follow-up for a 2-year-period (1994–1995) in Oslo reported that only 24% of the work-related skin diseases notified in the reporting system were also notified to the Norwegian Labour Inspectorate registry.[196]

Therefore, *Study I* has defined underreporting of work-related skin diseases as a challenge that may hamper research and prevention on these conditions, in that they will not be highly prioritized by work and health authorities.[197]
Indeed, underreporting of work-related skin diseases is a common challenge for all European countries,[198-202] and the level of underreporting is even higher in countries of East Europe such as Romania where during 2013 only three cases of work-related skin disease were notified.[71] Moreover, underreporting is acknowledged even in countries with more comprehensive notifications systems e.g. Great Britain, which combines information from dermatologists, occupational physicians, and general physicians. For instance, a decline in notifications was also reported for the period 1996 - 2014.[203]

The occupations with most notifications comprised: mechanics, welders and plate-/workshop workers, health personnel, hairdressers, plumber, chefs, and kitchen assistants. The most common exposures consisted of cleaning products, other chemical substances, oils, fuels and solvents, metals, and adhesive and epoxy substances.
The incompleteness of this Registry undermines the findings of this study, nevertheless, it should be noted that the most frequently reported exposure factors and occupations were similar to those from more complete notifications systems i.e. Great Britain,[203] Denmark,[204] and Finland.[205]

Study II

This study reported that the one-month prevalence of skin problems ranged from 13.2% at baseline to 11.7% at follow-up. The prevalence estimates are in line with data from a Norwegian Survey study that applied a validated questionnaire for health problems.[206]

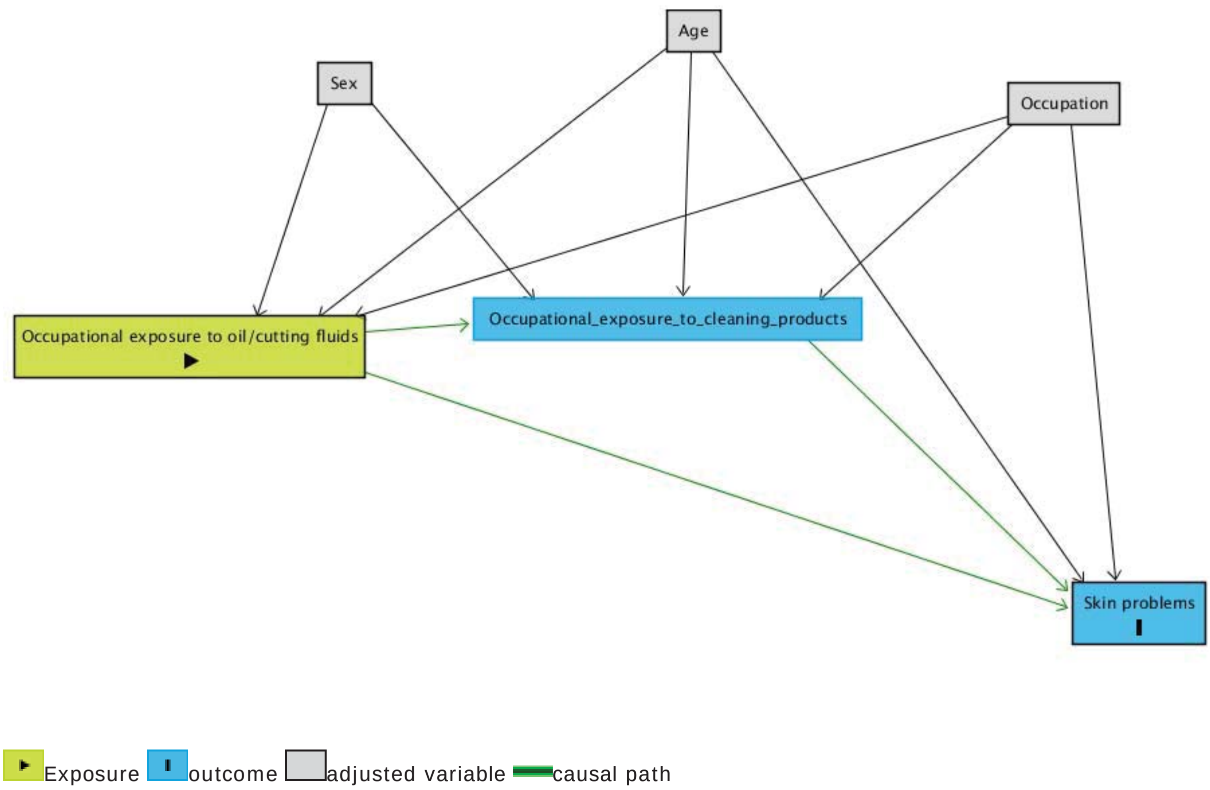
Incidence estimates are usually preferred for analysing risk factors, but they do not provide information on the number of workers with a health problem at any one time (point prevalence) or over a defined period of time (period prevalence). Because work-related skin diseases develop chronically as relapsing conditions, the incidence and point prevalence may be less informative than the period-prevalence, which includes subjects with long-lasting disease and relatively recent cases.

In line with the findings of *Study I*, as regard the most common exposures for the notified work-related skin diseases, *Study II* reported that skin exposure to cleaning products, water, oil and cutting fluids, and physical factors such as indoor dry air were the most consistent risk factors for skin problems in the general working population of Norway.[207] In view of the systematic literature search performed for the purposes of this thesis (Chapter I), this was the first study to report such an association between self-reported occupational exposures and skin problems in a prospective cohort of the general working population. For instance, Thyssen et al.[80] suggested previously that general population studies may be suboptimal when one investigates the risk of, for example, wet work and occupational exposures as an effect can be diluted due to low statistical power.

Overall, our findings regarding exposure to water and cleaning products as risk factors for skin problems are consistent with the evidence available from cross-sectional population-based studies, [69] and studies performed in risk proffesions.[130]

We found evidence of the injurious effects of oil and cutting fluids may be mediated by skin exposure to cleaning products (Fig. 30). This is a novel finding in a general working population, which accords well with current evidence from experimental and clinical studies.[133,136,138,140] Not only do the irritant effects of oil and cutting fluids damage the skin barrier, but also facilitate the penetration of potential allergens from cleaning products.[138] In fact, cleaning products degrease the skin, denaturise keratin and lowers the hydration, which additionally contribute to cumulative irritation.[133]

Figure 30. The effect of occupational exposure to oil/cutting fluids on skin problems may be mediated via skin exposure to cleaning products.



Minimal sufficient adjustment sets for estimating the total effect of Occupational exposure to oil/cutting fluids on Skin problems: age, occupation, and sex.
Minimal sufficient adjustment sets for estimating the direct effect of Occupational exposure to oil/cutting fluids on Skin problems: Age, Occupation, Occupational_exposure_to_cleaning

Self-reported exposure to indoor dry air at baseline was a consistent predictor for skin problems at follow-up, which is in line with the current evidence regarding negative effects of low humidity on the skin barrier, as recently reported in a systematic review by Engebretsen et al. (2015).[152]

Moreover, occupational exposure to water and cleaning products may lead to xerosis induced by frequent washing.[208] Exposure to dry air and dramatic temperature shifts between cold outdoor and the warm, arid, centrally heated indoor environments can contribute to the development of winter xerosis.[208]

It can also be hypothesised that biological variations of the skin barrier leading to "dry skin conditions" such as atopic dermatitis, atopic xerosis, nonatopic xerosis, winter xerosis, and asteatotic dermatitis[208] may explain that some subjects are more susceptible to develop skin problems, or that responders with established skin problems are more prone to report exposure to indoor dry air (reverse causality). Nevertheless, we found weak evidence of an association between skin problems at baseline and self-reported skin exposure to indoor dry air at follow-up (Table 14).

The population attributable risk of 15.8 % suggests a prevention potential for skin problems through the reduction of known occupational risk factors.

Study III

This study reported that occupational skin exposure to water among women, and to cleaning products and waste among men were risk factors for physician-certified long-term sick leave in the general working population of Norway. These findings are in line not only with the most common occupational exposures for work-related skin diseases notified for the period 2000 to 2013 in Norway (*Study I*), but also with occupational skin exposures shown to predict skin problems in *Study II*. Furthermore, many of the occupations with wet work and occupational exposure to chemical, biological, and physical factors were on the top regarding long-term sick leave due skin diseases in 2010 (Figure 13 & 14, Chapter III).

Whilst *Study II* reported that self-reported exposure to indoor dry air was a consistent risk factor for skin problems, this exposure did not predict LTSL in 2010. However, separate analyses showed that self-reported exposure to indoor dry air predicted short-term physician-certified sick leave (< 16 days).

To our knowledge, this was the first study to show an association between occupational skin exposure and physician-certified long-term sick leave in the general working population of Norway. Although the study design is not wholly comparable, a Danish study of the general working population, which used the same questions to assess exposure, reported that occupational self-reported skin exposure to cleaning agents was a risk factor for disability pension among women.[209]

The population attributable risk of LTSL of 14.5% not only underlines the contribution of occupational skin exposure as an important risk factor for LTSL, but also suggest a potential for prevention in the general working population of Norway in line with the findings of *Study II*.

Both the Norwegian Labour Inspectorate´s registry for work-related diseases and the Survey of Level of Living – Working Conditions (Statistics Norway) are not adequate data sources to investigate the relative risk of cSCC between occupational categories. The Nordic Occupational Cancer Study provides with high-quality data to describe the variation of the relative risk of cSCC between occupational categories not only for Norway, but also for Finland, Iceland, and Sweden.

Study IV

This study reported a moderate variation of the SIR estimates for cutaneous squamous cell carcinoma between occupational categories in Finland, Iceland, Sweden, and Norway.

Elevated relative risk was found in occupational categories with high socioeconomic status such as medical doctors and administrators, some occupational categories with outdoor work such as seamen, public safety workers, Swedish fishermen, and female gardeners; and some occupational categories with potential exposure to chemical products such as printers, technical workers, seamen, and public safety workers. Overall, such an occupational variation of the relative risk of cSCC seems to be associated with socioeconomic factors, and to some extent to occupational exposures.

To our knowledge, this was the first population-based study with a 45-year follow-up that investigated the occupational variation of cSCC between occupational categories in such a large population.

It was surprising that occupational categories with high socioeconomic status had the highest relative risk for developing cSCC; however, many of these groups showed high SIRs also in young ages, which support our hypothesis regarding a higher sun exposure during leisure time.

A study comparing amount of leisure time between OECD (Organization for Economic Cooperation and Development) countries reported that Norway had the highest proportion of leisure time, but also Finland and Sweden were above the average for OECD countries. The same study reported that the share of time spent in leisure was broadly unchanged from 1980-2000 in Norway (data available for Norway).[210]

Occupational categories with outdoor work such as seamen, female gardeners, Swedish fishermen, and Finnish female wood workers had elevated relative risk of cSCC, but the fact that a consistent elevated SIR was not found among all occupational categories with outdoor work should not be interpreted as a contradiction of the available evidence.[4] In fact, this finding may be attributable to several factors:

- Firstly, the about two-fold increase in the reference incidence rate from 1960 to 2005.

- Secondly, the skin of outdoor workers is often quite covered due to climatic conditions in the Nordic countries. For instance occupational categories with outdoor work had an average relative risk of 1.50 for lip cancer,[98] (approximately 90% consist of cSCC), not so easy to cover mouth and lips whilst working.
- Thirdly, several studies reported that outdoor workers are more likely to employ sun safety practices such as wearing a hat or protective clothes.[211-213]
- Furthermore, a higher occupational mobility among some occupational categories with outdoor work may have contributed to the lower relative risks observed. In fact, the proportion of the population working in the primary sector (agriculture, fishing, forestry, hunting, and fishing) has decreased dramatically since 1960. Thus, only 2 - 6% of the working population in each Nordic country were occupied in this sector by the end of follow-up in 2005.[214]
- Lastly, the use of occupational title as a *proxy* for outdoor exposure to solar UVR, may lead to an underestimation of the real associations due to non-differential misclassification.[4]

Overall, the findings of *Study IV* are, to some extent, in line with a population based nested case-control study,[215] which reported low risk among male farmers, and elevated risk among some indoor occupations.

6.2 ADVANTAGES AND LIMITATIONS

The main advantages of the studies are:

- The observation period of 13 years in *Study I*.
- The prospective cohort design for *Study II* to *IV*.
- The large population samples.
- The 3-year follow-up in *Study II*, and the 45-year follow-up in *Study IV*.
- *Study II* & *III* focused on occupational exposures rather than on job titles. Anvenden et al.[63] suggested that using job titles as a proxy for occupational skin exposure underestimates not only variations in exposure within occupations or over time in the same job, but also associations with the outcome measure.
- *Study II* to *IV* included linkage at the individual level between the registries withfollow-up outcome data by the use of unique personal identification numbers.
- The high quality of the outcome data (LTSL) in *Study III*, and cancer data in *Study IV*.
- The assessment and control for confounding during the design and analysis (*Study II* & *III*).

Nevertheless, the findings of this doctoral thesis have to be interpreted in the light of the following limitations:

- Firstly, the use of an incomplete Registry to describe trends of reporting of WRSD, as well as the lack of adjustment for changes in the population at risk (*Study I*).
- Secondly, the use of self-reported data in *Study II* & *III* such as the use of non-validated questionnaires to assess exposure (*Study II* & *III*), and partially the outcome measure (*Study II*). For this reason, Chapter III revised how occupational skin exposure can alter skin homeostasis, with the subsequent development of skin problems and disease. Moreover, Appendix 5 provides an overview of available validated questionnaires in occupational dermatology.
- Thirdly, it was not possible to assess whether the incident cases of LTSL in 2010 were in fact due to dermatological problems (*Study III*). For this reason, Figure 13 & 14 in Chapter III showed the incidence of long-term sick leave due to contact dermatitis and other skin diseases among Norwegian workers in 2010.
- Finally, the lack of complete occupational history information was a limitation of *Study IV*. For this reason, Appendix 6 provides an overview of the proportion of individuals who reported the same occupational category at two subsequent censuses.

6.3 METHODOLOGICAL CONSIDERATIONS

The next sections will discuss validity issues with focus on interpretation of the main findings and implications of the limitations:

To what extent do random variation or systematic errors such as selection bias, information bias, and confounding influence the associations and findings reported by this doctoral thesis? If so, which are the implications and how should results be interpreted?

Validity of occupational epidemiology studies

"With careful and prolonged planning, we may reduce or eliminate many potential sources of bias, but seldom will we be able to eliminate all of them. Accept bias as inevitable and then endeavour to recognize and report all exceptions that do slip thought the cracks."[12]

Good and Hardin (2006)

"*Unlike error related to random variability, bias cannot be assessed without external knowledge of the world"*[13]

Herbert I. Weisberg (2010)

An epidemiologic study aims to obtain a valid and precise estimate of the effect size or measure of disease occurrence (absence of systematic bias and random error) in the source population of the study.[216] Thus, the validity of a study can be divided into internal validity (violated by systematic bias), and external validity (generalisability).[216]

In general, systematic bias can be distinguished from random error, as the latter can be reduced by increasing the size of the study, whereas systematic bias can only be reduced by changing the study design.[217]

Study design

Which are the practical implications and limitations of the study designs used?

In this thesis, two different study designs are of relevance: for *Study I*, a retrospective case-series design; for *Study II to IV*, a prospective cohort design, whereof *Study IV* was a historical prospective cohort.

A retrospective case-series design is inexpensive, but unable to show temporal associations and determine the incidence of an outcome. Thus, it provides a low level of evidence.[175] However, in *Study I*, the selected design was adequate to answer the

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12. Common Errors in Statistics (and How to Avoid Them), p. 113
13. Bias and Causation: Models and Judgment for Valid Comparisons, p. 26

research question I: *to describe notification trends of work-related skin diseases for the period 2000 - 2013, the occupations, and occupational exposures most frequently notified.* Additionally, the overall findings generated the hypothesis further evaluated in *Study II* & *III*.

A prospective cohort design (*Study II* & *III*) is expensive and time-consuming (except for a historical prospective cohort: *Study IV*), but is advantageous to assess the effects of exposure on a specific health outcome with a greater accuracy since the individuals serve as their own controls and consequently between-worker variation is removed.[175] Moreover, it provides more reliable information on the directionality of a temporal association between an exposure and a health outcome. For example, in the case of *Study II:* associations between occupational chemical and physical exposures with skin problems in the general working population of Norway; and in the case of *Study III*: associations between occupational skin exposure and the risk of physician-certified long-term sick leave. Additionally, a prospective cohort is also adequate to determine the incidence of an outcome. [175,176] For example, in the case of *Study IV*, the main goal was to describe the variation in the relative risk of cSCC between occupational categories of four Nordic countries by the estimation of the standardised incidence ratio.

Due to the high costs of a prospective cohort design, *"funding bias"* towards studies with commercial interests may be an issue.[175] Nevertheless, this project was investigator-initiated, and founded by National funds.

Duration of follow-up

Which are the practical implications of the follow-up for the different studies?

Bearing in mind the pathophysiology of some work-related skin conditions, the three-year follow-up of *Study II* may be prone to underestimate plausible associations between occupational exposures and skin problems attributable to skin conditions with an acute and subacute onset such as chemical skin injury, contact urticaria, acute ICD, delayed acute ICD, irritant reactions, and sensory irritation. On the other hand, a three-year follow-up is more prone to capture skin problems attributable to slowly developing skin conditions such as chronic ICD, traumatic ICD, acneiform ICD, friction dermatitis, or asteatotic irritant dermatitis. However, it is reasonable to assume that workers with skin problems attributed to occupational exposure could be already on sick leave or have changed their occupations. Therefore, the follow-up in *Study III* was limited only to one year and restricted to individuals without long-term sick leave in 2009.

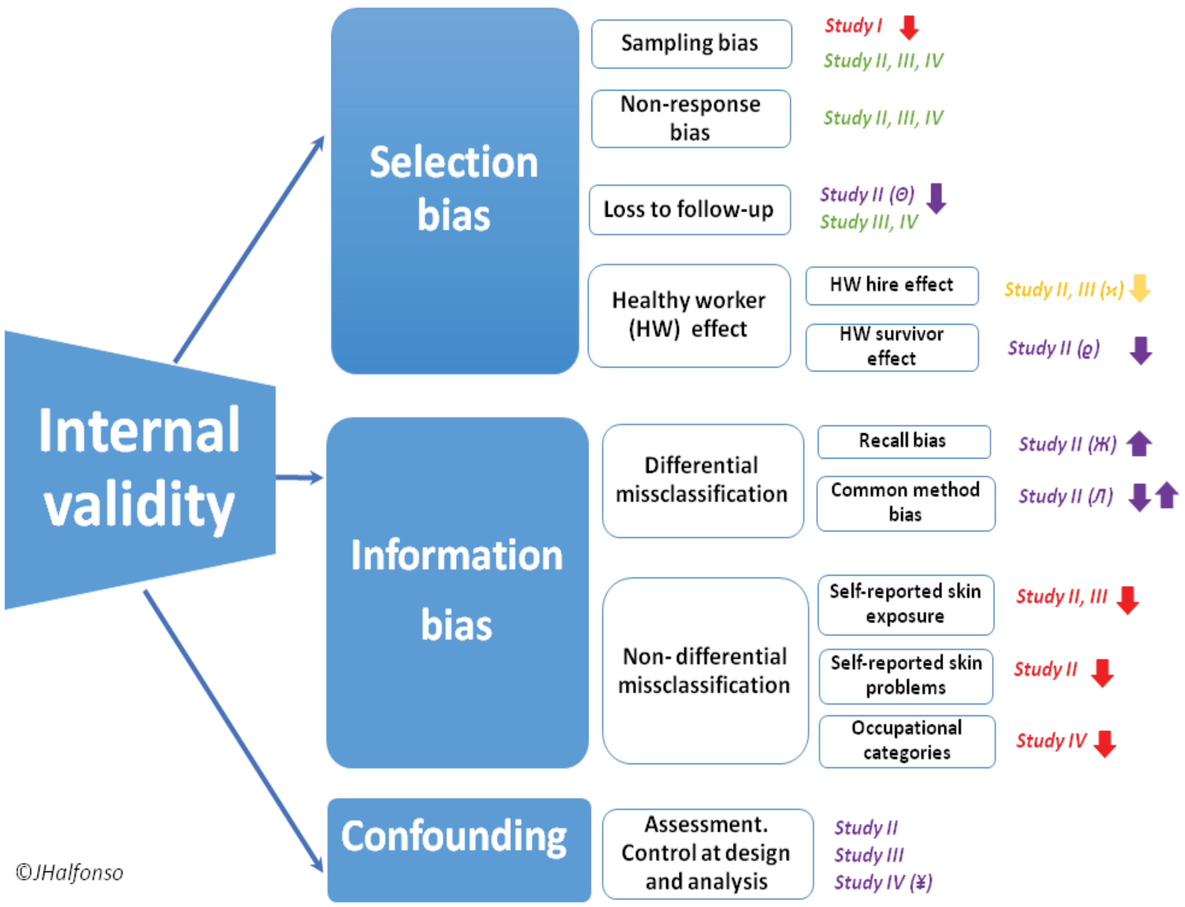
Given that cumulative exposure to carcinogens is the main environmental risk factor for cSCC, the 45-year follow-up of *Study IV* is prone to capture incident cases of cSCC attributed to cumulative occupational exposure.

6.4 INTERNAL VALIDITY

The lack of internal validity may create systematic bias in the exposure-outcome association, leading to an erroneous association.[216] Thus, systematic bias is not predictable and can lead to over or underestimation of the effects.

Figure 31 shows an overview of the different type of systematic errors of the different studies and their potential effect on the exposure-outcome associations.

Figure 31. Internal validity at a glance



The bias was an issue in the Study. The bias was not an issue in the Study. The potential bias was taken into account during the design, statistical analysis, or additional analysis. It was not possible to assess the effect of the potential bias. The arrows indicate in which direction the bias eventually would have affected the estimates. (Θ) Loss to follow-up: 24%. Attrition analyses showed weak evidence that loss to follow-up was attributed to the occurrence of skin problems. A potential healthy worker hire effect cannot be excluded. If present, it may lead to an underestimation of the effect estimates. (ϱ) Weak evidence of a healthy worker survivor effect attributed to the occurrence of skin problems. (Ж) To limit the impact of a potential recall bias (overestimation of the effect estimates) statistical analysis included adjustment for skin problems at baseline. (Л) To limit the impact of potential common method bias, questions regarding exposure were performed before questions regarding skin problems. The included response categories were different. (¥) Study IV did not include control for confounding.

6.4.1 SELECTION BIAS

The procedures by which the study participants are selected from the source population, or select themselves by agreeing to participate may lead to selection bias.[216]

It occurs when the selected participants are systematically different from non-participants. Consequently, the exposure-outcome association is different among participants and non-participants. Different examples of selection bias such as sampling bias, non-response bias, loss to follow-up, and healthy worker effect will be further discussed. [216,217]

Sampling bias

If information from a population sample is collected in such a way that some members of the intended population are less likely to be included than others, such a selection process will result in a biased sample. In fact, this is an important limitation of *Study I* as only notified cases of work-related skin diseases were included. Thus, it is plausible that only severe cases of skin diseases get notified.

Given that *Study II* & *III* included a random sample of the general population, and *Study IV* the whole adult population sampling bias is not a limitation.

Non-response bias

In prospective cohort studies, non-response bias is an issue if non-participation is associated with the exposure and the outcome.[216, 217]
Study II & *III* had a non-response frequency at baseline of 33% and 39%. However, Statistics Norway did not find systematic differences across the benchmarks of age, sex, and region between responders and non-responders.[177,178]
For this reason, it seems little plausible that non-response bias could have affected the estimates of *Study II* & *III*. Furthermore, previous studies have reported that health problems do not necessarily differ between responders and non-responders and that some differences do not necessarily produce biased risk estimates.[218, 219]

In *Study IV*, non-response bias is not an issue as it included census data for the adult population of Finland, Iceland, Sweden, and Norway.

Loss to follow-up

Loss to follow-up can be problematic in prospective cohort studies leading to bias, low statistical power and limiting the validity of exposure-outcome associations.[216]
The loss to follow-up in *Study II* was 24 %. *To what extent could the loss to follow-up have affected the associations reported?*

Different mechanisms of loss to follow-up have been described; the most problematic occurs if dropouts are related to the outcome of the study.[220] In the case of *Study II,* if loss to follow-up were related to the occurrence of skin problems**[14]** even a loss to follow of 24% would bias the association between occupational skin exposure and skin problems towards the null value (underestimation of the true association). Therefore, to examine whether loss to follow-up was related to the occurrence of skin problems, attrition analysis were performed. The implications of these results are further discussed in the next section.

On the other hand, *Study III* included linkage between exposure data from a Survey and registered physician-certified sick leave data at the individual level, without loss to follow-up.

Likewise, *Study IV* included linkage between the census, mortality, and emigration data with the cancer incidence data by the unique personal identity code, which additionally led to precise person- year calculations.

Healthy worker effect

It is an example of selection bias that underestimates the mortality/morbidity related to occupational exposures (underestimation of the exposure-outcome association).[216] This bias reflects the healthier status of the working population compared to the general population (which includes people who are too sick to work).

Two components of healthy worker effect bias have been suggested:[221]

1) Healthy worker hire effect: which includes the selection of healthier workers at hire, either due to self-selection (e.g. perceived health status) or employer selection (e.g. healthier subjects at lower risk of disease being employed preferentially).
2) Healthy worker survivor effect: once hired, less healthy workers are more likely than healthy co-workers to leave high-exposure jobs, either by ending employment or being transferred out. This selection away from exposed jobs may reduce the impact of exposure in a given person (protecting that participant´s health), but on the other hand it may lead to the biased conclusion that the occupational exposure is not associated to the health problem or disease.

As an example, *Study II* hypothesized that a potential healthy worker survivor effect could have explained the weak associations between skin exposure to water, cleaning products, oil/cutting fluids and organic dust/fumes at baseline with the risk of skin problems at

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14. The probability of being lost at follow-up which depends on the outcome to be measured and cannot be completely explained by other variable is defined as loss to follow-up missing not at random (MNAR), or non-ignorable. According to statistical modelling, a merely 20% loss to follow-up underestimates the true OR by approximately half its value.[220]

follow-up (Table SII, Study II). Several studies suggested that people change or lose their jobs because of skin problems early in the course of the disease.[222,223] However, the attrition analysis showed weak evidence of an association between the occurrence of skin problems at baseline and a lower frequency response at follow-up (Table 13). Hence, it seems reasonable to assume that a healthy worker survivor effect attributable to skin problems at baseline was not necessarily a substantial bias in *Study II.*

As we do not know whether participants with chronic skin conditions such as severe contact dermatitis or psoriasis[224,225] were less likely to respond at baseline, it must be emphasized that weak evidence for a *healthy worker survivor effect*, does not exclude a plausible *healthy worker hire effect* (healthy worker effect before recruitment). Firstly, individual susceptibility factors, such as atopic dermatitis, could have led to more susceptible individuals to avoid occupations with hazardous skin exposures. For example, Holm & Veierød 1994,[12] reported that the occurrence of atopic dermatitis was 50% lower among Norwegian hairdressers compared with teachers.[12] More recently, Bandier et al. 2013[225] found that filaggrin mutation carriers who reported hand dermatitis before 15 years of age avoided occupational exposure to irritants.[225]

Other plausible explanations include a hardening phenomenon,[85,86] or that responders with skin problems may change their work or avoid certain exposures as a result of preventive measures at the workplace. For instance, this last hypothesis is partly supported by the fact that responders with skin problems at baseline reported less occupational exposure to water, oil and cutting fluids, indoor dry air, heat, cold, and metallic dust at follow-up (Table 14). The findings give indication that occupational exposure to cleaning products, organic dust, and mineral dust may be more difficult to avoid.

On the other hand, it should be remarked that a German prospective cohort study[59] and a Swedish nested case-control study[64] (both population-based) did not find strong evidence of an association between atopic dermatitis and the subsequent choice of first job,[59] or avoidance of occupations with hazardous skin exposures.[64]

6.4.2 INFORMATION BIAS

This type of systematic error can arise because the information collected about or from study subjects is erroneous regarding exposure or disease status.[216] It can be divided into differential and non-differential misclassification.[216]

Differential misclassification

Differential misclassification of exposure (disease) occurs when the probability of misclassifying the exposure (disease) differs among diseased (exposed) and non-diseased (non-exposed) persons. Bias can go either direction (underestimation or overestimation of the exposure-outcome association).

Recall bias is an example of differential misclassification.[216] It arises partly because those with health problems are more aware of specific exposures than those without, being more prone to report a particular exposure.[216] For example, in *Study II*, the subjects reporting skin problems could have recalled their previous skin exposures better than those without skin problems. However, our analysis included adjustment for skin problems at baseline, which may have reduced the potential problem of *recall bias*. Recall bias was not an issue in *Study III* & *IV*.

Common method bias is a type of differential misclassification that occurs when the participants fill in an exposure level and a health outcome. The bias leads to false strong associations because some individuals tend to report both high (low) exposure and high (low) level of outcome creating a "*bias*ed dependency in the data".[226,227]

Consequently, common method bias could have inflated the associations of particularly *Study II*. Nevertheless, it has to be acknowledged that questions about skin exposures and skin problems were only a small part of the Survey, whereof questions regarding occupational exposures were administrated before questions on health problems and with different types of response categories. These factors may have reduced the effect of *common method bias.*[227,228]

The best way to limit the effect of such a bias is to measure the exposure or outcome objectively or from different sources.[228] For instance, *Study III* included two different data sources for assessment of occupational exposure and health outcome (LTSL). Furthermore, *Study IV* also included two independent data sources for information on occupation and incident cases of cSCC. For these reasons, *common method bias* is not an issue for *Study III* & *IV*.

Non-differential misclassification

If misclassification of exposure (or disease) is unrelated to disease (or exposure) then the misclassification is non-differential,[216] leading to an underestimation of the real effect estimate.

The assessments that are most prone to non-differential misclassification comprise self-reported occupational skin exposures in *Study II* & *III*, self-reported skin problems in *Study II*, and the classification of occupational categories in *Study IV.*

Self-report of occupational skin exposure and skin problems

Self-report of occupational skin exposure and skin conditions is widely used in occupational dermatology (Table 3, Chapter I), as it is often the only feasible method for collecting information at the population level.[229]

Self-reported occupational skin exposure

In *Study II* & *III*, exposure data were based only on self-report.
Fritschi et al. 1996,[230] suggested that self-respondents may have the advantage of having personally experienced the working environments. Moreover, Teschke et al. 2002[231] reported, in a systematic review, that subjects can reliably and accurately report exposures to hazards which they can easily sense if the agents are presented in predefined questions regarding broad classes of exposure, for example “oil and greases”, “degreasers” rather than about specific chemical exposures, for example, “chromium”. For instance, questions used by The Survey of Living-Working conditions 2006 and 2009 to assess occupational exposures are examples of wording that included broad classes of exposure to agents that can easily be sensed by the skin (“water”, “cleaning products”, “oil and cutting fluids”, Table 9 & 10, Chapter IV).

Validated questionnaires to measure occupational skin exposures are available (Appendix 5). For instance, Anvenden et al. 2006[64] found strong correlation between self-reports by questionnaires and observations regarding total time of skin exposure to water, occlusive gloves, and foodstuffs, and a moderate correlation regarding frequency of hand washing.

Future studies in Norway should use validated questions to assess skin exposure (Appendix 5).

Self-reported skin problems

Previous studies have suggested that self-reporting of skin problems underestimates the real prevalence of skin conditions.[229, 232-234]

Given that many skin conditions have a fluctuating progress, it is reasonable to assume that the one-month prevalence of skin problems reported in *Study II* is even more likely to underestimate than overestimate the true prevalence of skin problems in the general working population of Norway.

As regards the validation of the question used to assess the one month prevalence of skin problems it is, actually, not completely true that this question was not validated previously.

Mehlum et al. 2005[235] compared self-reported work-relatedness of skin problems with expert assessment, based on specific criteria, in a population of young adults of the Oslo Health Study.[235] An agreement of 85% between self-reported skin problems and expert assessment was reported.[235] Although this study focused on the work-relatedness of self-reporting, the question used to assess the one-month prevalence of skin problems was the same as in *Study II*. Moreover, the disagreement in the majority of the cases was because the responder did not consider the problem as work-related.[235]

Is the prevalence of skin problems a valid measure to assess plausible associations with occupational exposures?

Table 3 (Chapter I) showed that the majority of the population-based studies within occupational dermatology use hand dermatitis as a surrogate for work-related skin diseases. This is, in fact, supported by Meding´s studies on the prevalence of hand dermatitis in the general population of Gothenburg, Sweden (1-year prevalence of 10.6%)[236] versus the 1-year prevalence of occupational hand dermatitis in this same population of 11.8%.[69]

Study II used a symptom-based question. According to Svensson et al. 2002[237] a symptom-based diagnosis with reported skin signs is not appropriate for population studies assessing the prevalence of hand dermatitis.

Nevertheless, it is important to emphasize that *Study II* did not aim to assess the prevalence of hand dermatitis in the general working population of Norway, but rather the contribution of occupational exposures on skin problems. Accordingly, a symptom-based question may facilitate the reporting of minor symptoms and consequently the identification of associations between occupational exposures and skin problems.

Given that the overall associations reported for *Study II* & *III* are consistent with the current evidence, self-report data and the lack of a validated instrument to measure exposure do not necessarily undermine the reported findings.

Classification of occupational categories in Study IV

Whilst the classification of occupational categories is heterogeneous (Appendix 2), validation studies reported that it is reasonably accurate in the Nordic censuses.[98]

For the purposes of *Study IV*, occupational categories were classified according to outdoor/indoor work. Schmitt et al.[4] reported that the use of occupation title as a *proxy* for outdoor exposure to solar UVR leads to an underestimation of the real associations due to non-differential misclassification. For instance, stronger evidence of an association between occupational outdoor UVR exposure and cSCC risk was reported for studies that directly assessed individual outdoor UV exposure compared to studies that used occupation title as a *proxy.*

What about occupational mobility in Study IV?

The lack of a complete occupational history was a limitation of *Study IV*, especially for occupational categories with a high occupational mobility. The occupational classification was based on the occupation recorded in the first census the person participated in the age of 30-64 years. The proportion of individuals who had the same occupational category in the first and second census available, i.e., 1960 and 1970 censuses in Norway and Sweden; 1970 and 1980 censuses in Finland is shown in Appendix 6. Generally, stability was highest among men and in occupational categories where a long education was required such as physicians, dentists, and teachers.

Occupational stability was lower for occupational categories with outdoor work, (from 21.5% for male gardeners in Norway to 77.8% for male farmers in Finland). Bearing in mind that cSCC may arise after discontinuation of exposure it is reasonable to assume that outdoor workers with a higher occupational mobility may have contributed to a lower cumulative exposure to solar UVR, and to the lower SIRs among several occupational categories with outdoor work.

Additionally, individual career development may have moved workers to leading position. Thus, to avoid the occupational misclassification related to the beginning of the work career, the follow-up started with the occupation hold at the age of 30 years or older.

6.4.3 CONFOUNDING

Confounding is a phenomenon leading to spurious exposure-outcome associations. With other words, it arises when the association between an exposure and outcome is partially or totally explained by a third variable, a common determinant of both exposure and outcome. Confounding may result in an over- or underestimation of the effect.[216]

This third variable, the confounder, is associated with both the exposure (condition 1) and the outcome (condition 2), but it is not an intermediate variable (condition 3).[216]

Therefore, control for confounding is necessary to avoid spurious exposure-outcome associations, and requires an *"à priori"* assessment based on previous biological and epidemiological evidence, assessment of the extent to which the effect estimate changes when the factor is controlled in the analysis, or both.[216]

Causal diagrams e.g. directed acyclic graphs are also useful to assess for confounding (Chapter IV).[238] The three approaches were used for the purposes of this thesis.

After assessment, confounding can be controlled in the study design, in the analysis, or in both.

Controlling for confounding in the design of the study

Three methods to prevent confounding can be used through the design of the study: randomisation, restriction, or matching study subjects on potential confounders.[216]

Randomisation is the most powerful technique to control for both known and unknown confounders, [216] but it can only be used in intervention studies such as a "randomised controlled trial".[239]

Restriction involves the selection of subjects under the assumption that they have the same (or nearly the same) value for a potential confounder. For instance, in *Study II* to *IV* we restricted the analysis to the working-age population. Moreover, for the purposes of *Study II* we restricted the analysis to those being in paid work. In *Study III*, the analysis were further restricted to those subjects that worked 100 days or more both at baseline and follow-up, but without long-term sick leave at baseline.

These restrictions are examples of *"à priori"* decisions to better identify and estimate the contribution of occupational exposures to the burden of skin problems.

It should be remarked that such an approach may, in fact, reduce the efficiency of a study. For instance, in the case of *Study II* & *III*, it may have led to an underestimation of the real associations.

The third method involves *matching* study subjects on potential confounders, but this is more common for case-control studies and may lead to high costs.[217]

Controlling for confounding in the data analysis

Confounding can also be controlled in the data analysis, which requires adequate information about the potential confounding factors.

The two main methods consist of stratification and adjustment by multivariate regression models.[216] For instance, all studies included stratification: by sex and age in *Study I* to *IV*, by period and occupational categories according to outdoor, indoor and mixed outdoor/ indoor work, and socioeconomic status in *Study IV*.

It should be mentioned that several of the explanatory variables were not suitable for stratification, as this would have reduced the statistical power and produced complex results difficult to interpret. Therefore*, Study II to IV* included multivariable regression analysis which allowed controlling for several variables in different models simultaneously (Chapter IV).

For example, in *Study III*, psychosocial exposures at work did not act as major confounders for any of the analysed association between skin exposure and LTSL (Model II). However, adjustment for mechanical exposures at work slightly attenuated the majority of the odds ratios (Model III). Given that the most frequent reasons of long-term sick leave in the general working population of Norway are musculoskeletal disorders and mental health complaints these findings were not surprising.

Lack of control of confounding in the analysis for relevant risk factors such as atopic dermatitis, smoking, and exposures during leisure time e.g. hobbies (*Studies II & III*) and having small children under the age of four years (*Study II & III*) has to be considered as limitations.

In *Study IV*, socioeconomic status was used as a *proxy* for exposures during leisure time, under the assumption that those with higher socioeconomic status had more time and money available for vacations in lower latitudes and recreational outdoor activities.

6.5 RANDOM ERROR AND PRECISION

Random error is often equated with "chance" or "random variation"[240] and occur in any epidemiologic study, unless the study is infinitely large, but this is not realistic. Therefore, the most effective way to reduce random error is by increasing the study size, so the precision of the effect estimate will be consequently improved.[240] For instance, although *Study II* & *III* included a large population sample and *Study IV* included the whole adult population of four Nordic countries, random error may have occurred.

In order to assess whether our population sample was large enough to be informative and detect associations, power analysis were performed during the design phase (Chapter IV). Still, such power calculations should be considered as a rough guide as to whether a feasible study is large enough to be worthwhile.

The probability that an observed association occurred as a result of random variability (chance) was evaluated in *Study II* & *III* by the *p-test* or test of statistical significance. The *p-value* expresses the probability that an association, at least as strong as the observed association, could be caused by chance alone. [15] If the p-value is low (typically below the chosen value of 5% in medical research), it is claimed that evidence against the null hypothesis (no association between exposure and outcome) is present, concluding that evidence of an association is more likely than no association. Accordingly, the test of statistical significance is a qualitative test and t the *p-value* does not reflect the precision of an estimate or the strength of an association. Nowadays, both clinical and epidemiological researchers criticize to the use of this test.[241,242]

15. This knowldege may sound trivial for many, but I have often experienced too much focus on the "significance" of p-values in clinical forums.

Thus, I would like to emphasize that the “significant” findings of this thesis should not be interpreted as a “proof” of an association, as well as the “non-significant” findings should not be equalled to a “proof” for lack of an association. Whereas a significant finding indicates that chance is an unlikely explanation of the results, it does not exclude that results may be attributed to bias or confounding.

For that reason, the confidence intervals (CIs) around the point estimate are a preferable way to express and assess the random error that underlies the estimates reported. Hence, a wide CI reflects more random error and lower precision than a narrow CI.[240] The confidence level was, for the purposes of this thesis, sat to 95% indicating that the frequency with which the CI will contain the true parameter value will be at least 95% if the data collection and analysis could be repeated many times, given that the statistical model is correct and without systematic error.
For example, in *Study IV* the uncertainty of the SIRs was expressed by deriving ninety-five percent confidence intervals (CIs), assuming a Poisson distribution of the observed cases. For some occupational categories few cases were observed, which led to wide CIs

With other words, when interpreting the point estimates of the different studies of this thesis, CI should not be considered as a literal measure of statistical variability or precision, but rather as a general estimate of the uncertainty due to random error alone.

More modern approaches to random error include the use of Likelihood intervals and Bayesian intervals.[240]

6.6 EXTERNAL VALIDITY

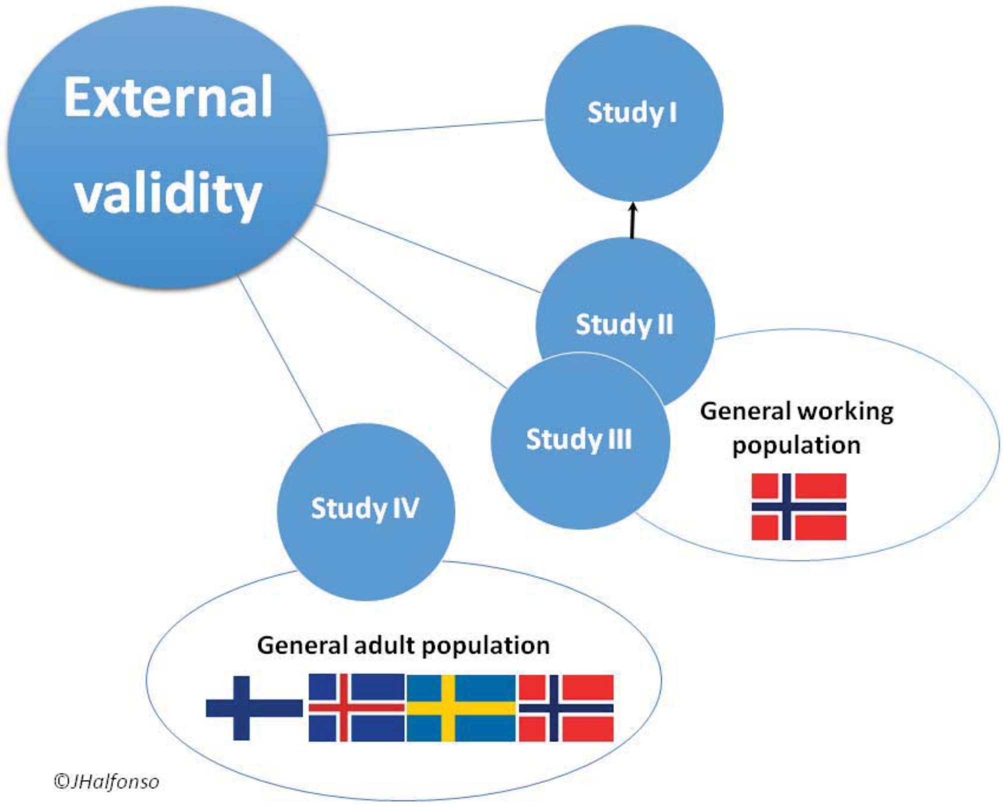
To what extent can the findings of this thesis be generalized to the Norwegian population or other populations?

Biological effects can differ across different populations,[216] and for the purposes of this thesis, not only the effect of occupational skin exposures on the skin may vary among different populations, but also the distribution of such exposures.

Therefore, the issue of external validity (also known as generalisability) can be defined as the degree to which results of the study may apply, be relevant, or be generalized to populations or groups that did not participate in the study.[243.]

Figure 32 shows a schematic overview for the external validity of the studies comprising this thesis.

Figure 32. External validity at a glance.



Given that a majority in the population samples are Caucasian, it seems reasonable to assume, in general terms, that the reported results can be generalisable to Caucasians of the general working population of Norway (*Study I* to *III*), and of the general adult population of Finland, Iceland, Sweden, and Norway (*Study IV*).

Nevertheless, different countries have different industries and different work-related exposures making the epidemiology of work-related skin diseases difficult to generalise across borders.

Additionally, work-related exposures change over time and affected workers may continue to suffer skin problems and disease induced by occupational exposures to which he or she is no longer exposed (e.g. persistent post-occupational dermatitis, recurrent cSCC).

Study I

Despite of notification of work-related diseases is mandatory by law, only between 3 and 5% of general physicians and 36% of occupational physicians report to the Registry of Work-related diseases of the Norwegian Labour Inspectorate.[38]

Therefore, the number of notified cases may not reflect the true number of workers with work-related skin diseases.

It should be mentioned that the occupations with most notifications in *Study I* are consistent with the occupations of patients that got diagnosed and treated for contact dermatitis by dermatologists for the period 2008-2010 in a cohort of 626,928 Norwegian born during 1967-1976.[172]

Moreover, the most frequent occupational exposures related to the notified work-related skin diseases are consistent with occupational skin exposures shown to predict skin problems and LTSL in the general working population of Norway (*Study II* & *III*).

Study II & III

Given that a random sample of the Norwegian general working population aged 18–66 years was included, it seems reasonable to assume that the findings regarding associations between self-reported occupational exposures with skin problems, and the associations between occupational skin exposures with physician-certified long term sick leave can be generalized to the general working population of Norway.

It should be remarked that the Survey of Living-Working Conditions, Statistics Norway covers only people included in the National Population Registry, and migrant workers on short-term contracts are not included. Most of them are employed in blue-collar occupations where exposure to chemical, physical and mechanical factors is greater. However, by 2013, migrant workers constituted about 3% of the working population in Norway.[157]

Study IV

The findings ought to be valid for the adult population participating in any computerised population census of four Nordic countries: Sweden (1960, 1970, 1980, 1990); Finland (1970, 1980, and 1990); Norway (1960, 1970, and 1980), and Iceland (1981) and followed up to 2003-2005.

6.7 SEX DIFFERENCES

This thesis included stratification by sex, which has to be considered as an additional advantage, since stratification not only allows control for potential confounding, but also provides evidence of whether the relationship exposure-skin problems/disease differ between sexes or not.[244]

In general, women had higher odds ratios for reporting skin problems, and for being on physician-certified long-term sick leave.

Men had a higher frequency of notified work-related skin diseases to the Registry of work-related diseases of the Norwegian Labour Inspectorate, and to the Petroleum Safety Authority Registry, and a higher variation in the relative risk of cSCC between occupational categories.

In general, the sex differences observed can be attributed to sex differences in the distribution of occupation and exposures, which is consistent with the current scientific evidence.[61,125-127,245]

On the other hand, it has also been reported an increased severity of skin conditions among men, minor knowledge about skin care, and lower use of moisturizers,[125, 126, 245,246] and suncream,[127] which to some extent, may explain the sex differences reported in *Study I* & *IV,* and some of the stronger associations among men reported in *Study II* & *III*.

It should be mentioned that *Study I* to *IV* did not include data regarding domestic and leisure activities, but, it is well known that women use more jewellery, hair dyes, cosmetics, and other skin care products than the average man, and these substances may cause skin irritation and/or contact allergies.[245] In addition, women are more observant of skin problems than the average man.[245] Women taking care of small children may be also more exposed to wet work than men.[62]

6.8 CAUSATION OR ASSOCIATION?

"Health sciences infer causal relations from mixed evidence: on one hand, mechanisms and theoretical knowledge and, on the other, statistics and probabilities".[16]

Russo & Williamson, 2007

To what extent do the reported findings of this doctoral thesis provide evidence of a causal association between occupational exposures with skin problems and LTSL? To what extent do the findings of Study IV provide evidence of a causal association between occupational categories with the relative risk of cSCC? In other words, is it possible to infer causality from any of the observations and associations reported?

16. Russo F & Williamson J. Interpreting Causality in the Health Sciences (2007). International Studies in the Philosophy of Science Vol. 21, No. 2, pp. 157–170. Available: https://blogs.kent.ac.uk/federica/files/2009/11/Interpreting_causality_ISPS.pdf Accessed on 25/02/2016.

In the last section of the discussion, I would like to discuss the overall findings in the view of different theoretical conceptions of causality.

Austin Bradford Hill: "viewpoints for causation"

Austin Bradford Hill outlined, in a paper from 1965, nine principles to determine whether associations from observational studies can be interpreted as an indication for causation.[247] It must be emphasized that Hill denominated these principles as "viewpoints for causation", and not as "criteria for causation". He even stated that these "viewpoints" are not intended to be "hard and fast rules".[247]
As an example, I will attempt to discuss the main findings of this thesis, when applicable, in the light of Hill´s viewpoints for causation:

1) *Strength of association: how strong is the association?*

   Study II reports evidence that occupational skin exposures to water, cleaning products, and indoor dry air are associated with skin problems.[207] Moreover, *Study III* reports evidence that LTSL is associated with occupational skin exposure to water among women, and with occupational skin exposure to cleaning products and waste among men.[248] In both studies the odds ratio are relative small.[207,248]

   Although, *Study IV* is a descriptive study, a plausible association between socioeconomic group and a higher cumulative sun exposure driven by major levels of exposure during leisure time can, to some extent, explain the higher SIRs among occupational categories with high socioeconomic status.[249]
   The findings also suggest that occupational exposure to UVR and skin carcinogens may contribute to the increased SIRs in some occupational categories with outdoor work and potential exposure to skin carcinogens.

   Hill advised to be careful when interpreting no associations or weak associations. For instance, weak associations may be causal if a trustworthy hypothesis is behind and the study design is appropriate.[247]

2) *Temporality: Did the exposure precede the disease?*

   As previously discussed, *Study II to IV* used a prospective cohort design which is better suited in order to capture the temporal relation between a putative cause (exposure) and effect (health problem/disease).[175]

   Furthermore, *Study II* included, by design, statistical analysis with adjustment for skin problems at baseline, and *Study III* included analysis restricted to subjects without LTSL in 2009. Therefore, it is reasonable to assume the directionality exposure-health problem/disease in the associations reported.

3) *Consistency: Is the association found consistent with other studies using different methods?*

   Study II & III report associations that are consistent with the exposures more frequently reported for the notified work-related skin diseases in Norway for the period 2010-2013 (*Study I*).[197] Moreover, our findings are also consistent with population-based cross-sectional studies that assessed associations between occupational skin exposure and hand dermatitis.

   The elevated relative risk of cutaneous squamous cell carcinoma for some outdoor workers, such as seamen, female gardeners, and Swedish fishermen, is consistent with findings from the meta-analysis performed by Schmitt et al. 2011.[4]
   On the other hand, the lower relative risk reported for some outdoor workers such as farmers is consistent with the findings from Marehbian et al. 2007.[215]

4) *Theoretical plausibility: Is the association consistent with other biological evidence?*

   Study I & II report consistent associations with the biological evidence regarding occupational exposures leading to structural changes in the skin barrier and *à posteriori* development of skin problems and disease.

   Study III did not include, due to confidentiality issues, information about whether the sick leave episodes were related to dermatological health problems. However, the highest incidence of LTSL due to contact dermatitis and other skin diseases in 2010 was among occupations with occupational exposure to wet work, and other chemical and biological hazards (Figure 13 & 14, Chapter III).

   The strength of association between solar UVR and cSCC risk decreases with increasing latitude.[250,251] Accordingly, the annual exposure to carcinogenic solar UVR at sea level in the southernmost part of the Nordic countries included in *Study IV* (Skåne, Sweden, latitude 55 N) and in the northernmost parts of the Nordic countries (latitude about 70 N) is between 25% and 20% of the respective exposure at the equator.[252]
   Study IV did not include analyses stratified according to geographical localization for the incident cSCC cases, however, it is biologically plausible that the Northern latitude had an inverse effect on the cumulative exposure to solar UVR and, consequently, on the relative risks of cSCC among occupational categories with outdoor work.

5) *Coherence: Is the association coherent across different studies?*

   The conclusion of an association between occupational skin exposure to water, cleaning products and indoor dry air with skin problems is aligned with knowledge about the pathogenesis of work-related skin problems and diseases (Chapter III). Moreover, the associations reported in *Study III* are aligned with the results of *Study I & II*.

At first sight, the lower relative risk estimates among occupational categories with outdoor work as compared with the rest of the population, seem to be incongruent with the current evidence.[4] However, the reported relative risk estimates are aligned with the about two-fold increase in the reference cSCC incidence rate, the higher occupational mobility among outdoor workers, and the underestimation of the relative risk estimates attributable to non-differential misclassification.

6) *Specificity in the causes: Is the association specific?*

This is, in my opinion, the most problematic viewpoint for causation, as work-related skin problems and diseases do not develop because of merely one risk factor, but rather several factors involved in the pathogenesis (Figure 9, chapter III).
For example, in the case of cSCC, where cumulative exposure to solar UVR is the main risk factor, the total cumulative exposure in an individual is comprised by both occupational and non-occupational exposures.

7) *Dose-response relationship: Does the association become stronger with increasing exposure?*

The studies of this thesis have not specifically assessed dose-response relationship. However, some findings of *Study II* & *IV* may suggest some indication of stronger associations with cumulative exposures.

Firstly, *Study II* reported a higher odds ratio of skin problems among those reporting occupational skin exposure to water, cleaning products, and indoor dry air at both baseline and follow-up, compared to those reporting at baseline only.

Secondly, *Study IV* reported high relative risk estimates among seamen and public safety workers; these occupational categories are exposed not only to outdoor solar UVR, but also to other skin carcinogens such as PAHs and arsenic.

8) *Experimental evidence:*

Most of the previously discussed findings are also in line with the available experimental evidence for development of skin problems, disease, including cSCC as explained in Chapter III.

9) *Analogy: Does the association have any analogue?*

This viewpoint of causality is somewhat contradictory to *specificity,* given that the more suitable the analogy, the less specific are the effects of a cause or less specific the causes of an effect.

According to Hill,[247] a positive answer to the question of temporality (question 2) is *sine qua non* for an exposure-disease association to be interpreted as an indication for causation.[247]

According to Saracci,[253] a positive answer to the question of coherence (number 5) provides, additionally, the strongest support to this interpretation. Furthermore, a positive answer to each of the other questions increases the likelihood of an association to be interpreted as indication for causation.[253]

Overall, the odds ratio in *Study II* & *III* and the SIRs in *Study IV*, based on large population samples, are certainly small, but the totality of the evidence as regards as biological plausibility, consistency, coherence among findings from other studies with different designs seems to be robust.

Kenneth Rothman: "model of sufficient-component causes"

Rothman suggested "a model of sufficient-component causes"[254] to interpret causality. The cause of a specific disease is defined as an antecedent event, condition, or characteristic that was necessary for the occurrence of the disease at the moment, given that other conditions are fixed. *Sufficient cause* is meant as a complete causal mechanism, a minimal set of conditions and events that are sufficient for the outcome to occur. The term *necessary cause* is reserved for a particular type of component cause under the sufficient - cause model that also operates to produce the effect.[254]

In view of this model, I would like to emphasize that our findings are not attempting to describe a complete "causal" mechanism, but rather a component of it: the contribution of occupational skin exposure to the risk of skin problems in *Study II*, and to the risk of LTSL in *Study III*. Moreover, the findings of *Study IV* are describing the variation of the relative risk of cSCC between different occupational categories.

The model of sufficient-component causes is useful for consideration of interaction between different component causes, but not so convenient when assessing temporality or dose-response relationships.[254]

Miguel Hernan: "counterfactual perspective"

In the light of Miguel Hernan's counterfactual perspective on causality,[239] our findings of evidence of an association should not be interpreted as equivalent for causation. The gold standard design to answer such a question is a randomised controlled experiment (intervention study), which is not feasible to perform with observational data. Nevertheless, Hernan[239] suggests that observational data can be used to infer causality if some comprehensive conditions[17] are accomplished under the assumption that all

17. Exchangeability, positivity, consistency, no model misspecification.

confounding is properly measured, something that, from my point of view, sounds unachievable.

Causal diagrams: "directed acyclic graphs"

Methods that are more modern also include the use of causal diagrams (DAGs).[238]

Study II & III included DAGs, especially at planning statistical analysis, assessing for confounding, and interpreting the results. The use of DAGs is helpful to clarify the limitations and possibilities of what can be estimated from the measured data.[254] However, several epidemiologists criticize the use of DAGs and consider that DAGs simplify the real scenarios of relationships between exposure, outcome, and other explanatory variables.[255] For instance, Greenland stated, "causal inference from observational data using formal causal models remains a theoretical and largely speculative exercise".[256]

We need a pluralistic view of causality in epidemiology

In general, it seems that universal and objective causal criteria to assess causality do not exist, and we still need to sharpen our thinking as regards to causality. As emphasized by Rothman, "universal and objective causal criteria, if they exist, have yet to be identified".[254]

It has to be acknowledged that the "populations" epidemiologists study are not just collections of individuals conveniently grouped for the purposes of the study, but are instead historical entities. Hence, every population´s history, culture, organisation, economic and social divisions influences not only how and why people are exposed to particular factors, but also how they respond, and report their exposures and health problems. For this reason, a multilevel approach is necessary, and studies at population level should be complementary to studies at the individual and micro-levels.

As Neil Pierce claims, "epidemiology in a changing world requires not just multi-level analysis, but rather multi-level thinking".[257]

In my opinion, this "multi-level thinking" should apply not only when assessing and interpreting associations from observational studies, but also when planning and implementing prevention actions.

Final remarks

Sir Richard Doll claimed that weak associations –less than three to one- might offer opportunities for the improvement of public health, if they are observed among exposures that are common and prevalent diseases in the community.[258]

Given that occupational skin exposures are common and skin problems and diseases are prevalent, this thesis adds to the evidence that occupational skin exposures contribute to the burden of skin problems and long-term sick leave in the general working population of Norway. Moreover, the estimated population attributable risks provide a bridge by which the results of this epidemiologic study can be made relevant to public health policy by the reduction of known risk factors at the population level.

Finally, by the description of occupational variance in the relative risk of cutaneous squamous cell carcinoma in the adult population of four Nordic countries, this thesis has contributed to the identification of targets for prevention and future research of one of the most prevalent and preventable cancers of the human body.

I wish that policy makers, employers, workers, and occupational health personnel acknowledged that the skin is the most important 2m^2 of a worker´s life.

YOUR SKIN. THE MOST IMPORTANT 2m^2 OF YOUR LIFE.
EADV - EUROPREVENTION
CAMPAIGN: HEALTHY SKIN@WORK [18]

HUDEN. DE VIKTIGSTE 2m^2 I DITT LIV
EADV - EUROPREVENTION
CAMPAIGN: HEALTHY SKIN@WORK

TU PIEL. LOS MÁS IMPORTANTES 2m^2 DE TU VIDA
EADV - EUROPREVENTION
CAMPAIGN: HEALTHY SKIN@WORK

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18. This logo was designed by the European Academy of Dermatology and Venearology to be used in preventive campaigns. In April 2015, after a request the logo was translated and adapted to Norwegian and Spanish to be used in preventive campaigns in Norway, Argentina, and Spain. (Rights to reproduce this logo from European Academy of Dermatology and Venearology).

"…If there be any chance of putting a stop to, or preventing this mischief, it must be by the immediate removal of the part affected; I mean that part of the scrotum where the sore is, for if it be suffered to remain until the virus has seized the testicle, it is generally too late even for castration…"

Chirurgical observations: "Cancer scroti." Page 67. 1775
Sir. Percival Pott (1714-1788)

CHAPTER VII: CONCLUSION AND IMPLICATIONS

7.1. CONCLUSION

Whilst work-related skin diseases seem to be greatly underreported, occupational skin exposures contribute to the burden of skin problems and physician-certified long-term sick leave in the general working population of Norway. A potential for primary prevention at the population level is supported by the population risk attributable to occupational exposures.

Socioeconomic factors and to some extent occupational exposures seem to explain the moderate variation of the relative risk of cutaneous squamous cell carcinoma between occupational categories in Finland, Iceland, Sweden, and Norway.

As a whole, this thesis has not only contributed to identify targets for primary prevention of skin problems and work-related skin diseases in Norway, but also for the prevention of cutaneous squamous cell carcinoma in four Nordic countries.
Research and prevention efforts within occupational dermatology have to be continued.

7.2 IMPLICATIONS

Implications for prevention

1. A surveillance system for work-related skin diseases that provides comprehensive and reliable data is necessary to identify targets for prevention of onset and chronification of work-related skin diseases. Such a system can be achievable by, for example:

   - A capture-recapture method combining information from different registries. For instance, such an approach has been used to study the occurrence of work-related injuries in Norway.[259]
   - A specific surveillance system for work-related skin diseases. For example, in Great Britain, THOR and EPIDERM combine information from dermatologists, occupational physicians and general practitioners.[203] In Norway a specific notification system for work-related skin diseases could combine information from different sources such as the Norwegian Labour Inspectorate, the Norwegian Petroleum Authority, and the Norwegian Patient Registry.
   - The German "Dermatologist's procedure" may also serve as a model on how to identify early work related skin problems and prevent social, psychological and economic consequences of work-related skin diseases.[260]

2. In the planning and implementation of measures aimed at primary prevention of work-related skin diseases, the focus should be on high-risk occupations and the most common occupational exposures.
    - Although the notified work-related skin diseases may represent only the tip of the iceberg, the findings of this thesis suggest that prevention and surveillance efforts should be directed to specific occupations such as mechanics, welders, health personnel, hairdressers, plumbers/building craftsmen, kitchen workers, and cleaners.[172,197] The fact that exposure to cleaning products, chemical substances, oils and solvents, metals, and epoxy substances were the most frequent notified exposures illustrates that prevention should focus on wet work occupations and those with skin contact with chemical substances.[197]

    - The population attributable risk of 15.8% found in *Study II* suggests a potential for prevention via the reduction of occupational skin exposures associated to skin problems.[207] Thus, prevention strategies should aim at reducing occupational exposures to water, cleaning products, oil and cutting fluids, indoor dry air, and the effect of concomitant occupational exposures on the skin.

    - The population attributable risk of 14.5% found in *Study III* highlights that prevention strategies aimed to reduce skin exposure to water among women, and skin exposure to cleaning products and waste among men can contribute to reduce physician certified long-term sick leave.[248]

    - Our findings emphasize the need of targeting occupational categories with elevated relative risk of cutaneous squamous cell carcinoma in prevention strategies, for instance occupations with high socioeconomic status, and not only occupational categories with outdoor work.[249]

A practical approach to prevention and skin protection

- Primary prevention strategies aimed at maintaining a healthy skin at healthy workplaces should follow the **S**TOP concept (**S**ubstitution, **T**echnical measures, **O**rganizational measures, and **P**ersonal protection).[261]

- When technical and organizational prevention measures are not sufficient, personal protective equipment (e.g. gloves, moisturizers, clothing, sunglasses, and suncream) must be provided and the correct application/use must be trained regularly. Several studies have shown that protective strategies are applied insufficiently; therefore regular instructions on use and application are necessary.[262,263]

- Appendix 7 summarises practical examples of preventive measures for work-related hand dermatitis and skin cancer.

7.3 PERSPECTIVES FOR FUTURE RESEARCH

"It is only by looking for associations that epidemiologists can produce new hypothesis worthy of further investigation and some associations that have, at first glance, seemed to be the least attractive may prove to be very productive."

Sir Richard Doll, J Epidemiol 1996, page 12[19]

- Future research within occupational dermatology in Norway should use validated questionnaires (Appendix 5), and include analytical tests for assessment of exposure and skin barrier function such as tape stripping, transepidermal water loss, or others.[264] Moreover, information about other explanatory variables such as atopic dermatitis, smoking, and leisure time exposures should be included.

  Norway is known for the high quality of several health registries and a birth-cohort.[265] These data sources can be an important basis for further population-based studies within occupational dermatology.

- Future population-based studies should take into account the effect of concomitant exposures, including the effect of physical factors such as dry air, cold, and heat on the skin barrier.
- Associations between occupational skin exposures and risk of cutaneous squamous cell carcinoma should be further investigated at the population level with reliable exposure measures to ascertain the specific contribution of occupational exposures.
- Future population-based studies should describe the variation of relative risk of malignant melanoma between occupational categories.
- More knowledge on the epidemiology of work-related skin diseases among Norwegian offshore workers is needed.

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19. Weak associations in Epidemiology: Importance, Detection, and Interpretation. Journal of Epidemiology. Vol. 6, No.4 (Supplement) December 1996.

Book Reviews.

Occupational Affections of the Skin. By R. PROSSER WHITE, M.D., Edin.; M.R.C.S., Lond. New York: Paul B. Hoeber. 1915.

The author of this brochure states that his own requirements prompted the compilation of the facts contained in it, and that he claims for it only a needed assistance for the English enquirer. He justly says that complete data are difficult of access, as they are very much scattered in foreign and English periodicals. The book will be, as its author intended, a help. It is not the last word on this subject, but besides the partial aid it will afford to dermatologists and general practitioners, it will serve as a help to future compilers of the data of this subject. The few illustrations are hardly worthy, either in execution or importance, of the general merits of the book.

Book review about the first book on Occupational dermatology titled: "Occupational Affections of the skin", which was written by Robert Prosser White. First published in 1915.

This book review was published in the Boston Medical and Surgical Journal, in 1915.

REFERENCE LIST

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APPENDIX 1

Strategy for systematic literature search regarding population-based studies on occupation and skin conditions.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present (Lagret i Expertsearch som Work-related skin disease in Norway+study design)

1	exp occupational groups/	456,271
2	exp work/	14,947
3	exp workplace/	15,118
4	exp occupations/	27,884
5	exp industry/	258,978
6	exp employment/	58,720
7	industry.mp.	140,671
8	occupation$.mp.	277,708
9	employment.mp.	69,960
10	(working not working group).ti.	30,846
11	worker?.tw.	138,436
12	personnel.mp.	282,326
13	staff.mp.	185,159
14	employee?.mp.	50,587
15	employment.mp.	69,960
16	workplace?.tw.	27,677
17	worksite?.tw.	2,751
18	at work.tw.	13,284
19	work.ti,hw.	104,519
20	job?.tw.	45,489
21	((work or job) adj2 (site? or place? or location? or environment$ or related or condition? or health or capacity or disability)).tw.	39,668
22	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	1,375,567
23	exp Dermatitis, Allergic Contact/ep [Epidemiology]	1,164
24	exp Dermatitis, Allergic Contact/et [Etiology]	6,847
25	exp Dermatitis, Atopic/ep, et [Epidemiology, Etiology]	3,271

26	exp Dermatitis, Irritant/ep, et [Epidemiology, Etiology]	1,402
27	exp Dermatitis, Occupational/ep, et [Epidemiology, Etiology]	4,369
28	exp Dermatitis, Contact/ep, et [Epidemiology, Etiology]	17,897
29	23 or 24 or 25 or 26 or 27 or 28	20,838
30	22 and 29	6,618
31	limit 30 to yr="1980 -Current"	5,536
32	limit 31 to (english or spanish or norwegian or danish or swedish)	4,709
33	limit 32 to "all adult (19 plus years)"	3,037
34	((Occupation* or work*) adj3 (skin* or disease* or dermatitis*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	97,978
35	33 and 34	2,649
36	(occupat* adj3 relat* adj3 skin* adj3 disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	22
37	35 or 36	2,660
38	exp Prospective Studies/	406,935
39	population-based study.mp.	19,956
40	exp Cohort Studies/	1,500,770
41	exp Follow-Up Studies/	537,593
42	population attributable risk.mp.	1,475
43	surveillance.mp.	160,488
44	exp Epidemiology/	23,015
45	38 or 39 or 40 or 41 or 42 or 43 or 44	1,665,533
46	37 and 45	298
47	from 46 keep 1-298	298

APPENDIX 2

Description of the occupational categories of the NOCCA study[98]

Technical, chemical, physical and biological workers include engineers, physicists, architects, chemists, geologists, biologists, meteorologists and related professionals.

Laboratory assistants include life science technicians, pharmaceutical assistants, laboratory technicians, and other health professional assistants.

Physicians include medical doctors.

Dentists include all types of specialists and researchers in the field of odontology.

Nurses include nurses in somatic and psychiatric hospitals, and in the field of health prevention.

Assistant nurses include workers assisting physicians, nurses and midwives in their practical application of preventive and curative measures. They provide caring services for the sick and injured.

Other health and medical workers include veterinarians, pharmacists, physiotherapists, and other types of health professionals not included in the occupational categories 05 or 06. Some of them perform technical tasks related to research and practical application and operational methods in the field of medicine, veterinary medicine, dentistry, pharmacy, sanitation. Pharmacists prepare and handle medicaments.

Teachers include teachers at pre-school, primary and secondary schools, college, university, and special education professionals. The majority works at primary schools.

Religious, juridical and other social science related workers include religious and legal professionals, archivists, librarians, economists, sociologists, psychologists and social work professionals.

Artistic workers include authors (excluding journalists, cf. occupational category 11), sculptors, painters and related artists, painting restorers, composers, singers, musicians, dancers and other types of artists.

Journalists include all types of journalistic work. The tasks include collecting, reporting and commenting on news and current affairs for publication in newspapers and periodicals, or for broadcasting by radio or television.

Administrators and managers include senior officials, managers and legislators working on behalf of governments, regional or local administrators, political parties, trade unions, and other organisations and enterprises.

Clerical workers include secretaries and clerical workers in banks and insurance companies, accounting and bookkeeping clerks, keyboard-operating clerks, and other types of office workers.

Sale and agents include finance and sales associate professionals and business service agents and trade brokers. They sell insurances, real estate, travel services and other business services, and they act as wholesale representatives.

Shop managers and assistants include shop managers and shop sale persons, who sell goods in retail establishments and explain functions of these goods.

Farmers: include field crop and vegetable growers, market oriented animal producers and related workers.

Gardeners and related workers: include gardeners, horticultural and nursery growers.

Fishermen, whalers and sealers: include fishermen, whale and seal hunters: they catch fish and gather other forms of aquatic life for sale or delivery to wholesale buyers or at markets. Whale and seal hunters are present only in Iceland and in Norway. They catch animals for meat, skin and other products for sale.

Forestry workers: include forestry workers and loggers.

Miners and quarries: include miners and quarry workers who extract coal and solid minerals from underground or surface mines and granite, limestone and other kinds of rocks from quarries. They set up and operate machines which cut channels or drill blasting holes into the open face of mines and quarries.

Seamen: include all types of seamen, both sailors working on deck and in engine rooms.

Transport workers: include railway staff, buss and train staff, except drivers, and aircraft pilots, traffic supervisors and other transport and communication workers.

Drivers: include car, taxi, van, bus, motor-cycle, tram, heavy truck and lorry drivers. Their tasks include driving and tending their vehicles in order to transport materials, goods, and passengers.

Post and communication workers: include postal workers such as mail carriers, sorting clerks and telephone switchboard operators.

Textile workers: include textile work such as operators of fibre preparing, spinning, winding, weaving, knitting, sewing, bleaching, dyeing, and fur preparing machines.

Shoe and leather workers: include shoe and leather workers who produce and repair footwear, handbags, etc. Leather workers treat hides and skins in solutions and apply finishing product to convert them into leather.

Smelters and metal foundry workers ore and metal furnace operators, metal smelters, casters and rolling mill operators, metal heat treating plant operators and metal drawers and extruders. Their tasks include operating and monitoring furnaces for ore smelting, refining, converting or reheating metal.

Mechanics, iron and metal ware workers: make products of metal, and assemble and repair machines and motors.

Plumbers workers in this category assemble, fit, install and repair pipes and pipeline systems for drainage, heating, water supply, and sanitary systems.

Welders cut metal parts using flame, electric arc and other sources of heat to melt and cut or fuse metal.

Electrical workers fit, assemble, install, maintain and repair electrical and electronic equipment such as electrical motors, generators, instruments, signal transmitters and receivers, domestic appliances, switchgear, and control apparatus.

Wood workers prepare and treat wood, and make, assemble and repair constructions and products of wood.

Painters and wall paperhangers prepare structural surfaces for painting and apply decorative and protective coatings to buildings, ships, motor vehicles and articles of wood, metal, textile and other materials. Wall paperhangers cover interior walls and ceilings.

Other construction workers include workers in the building and construction industry who do not constitute separate occupational categories in this study. Included here are reinforced concreters, cement finishers, terrazzo workers, insulators, glaziers, underwater workers, and other unspecified building and construction workers.

Bricklayers erect and repair foundations, walls and complete structures of brick, stone and similar materials and cover and decorate walls, ceilings and floors of buildings with tiles and mosaic panels.

Printers and related workers include type setters, printers (not textile printers) and book binders.

Chemical process workers category distil, refine, cook, roast and grind chemicals, prepare pulp for paper production, and make paper.

Food manufacture workers prepare food products of all kind for human and animal consumption. Include occupations such as grain millers, butchers and meat preparers, food preservers, dairy product processors, fish plant workers, bakers, pastry cooks and confectionery makers.

Beverage manufacture workers produce liquor, wine, beer, soft drinks and mineral water.

Tobacco manufacture workers prepare and treat tobacco leaves and make cigarettes, cigars, and other tobacco products.

Glass, ceramic, and tile workers include glass formers and cutters, potters, glass and ceramics kiln men, glass engravers and etchers, glass painters and decorators, rubber and plastic product makers, tanners, fellmongers and pelt dressers, musical instrument makers and tuners, stonecutters and carvers, paper and paperboard products makers, and other small categories.

Packers loaders and warehouse workers perform freight handling tasks, such as loading and unloading ship, aircraft and train cargoes and other freight, wrapping objects, packing liquids, materials and objects in containers, affixing labels on containers, rigging cables, wires and ropes for lifting, hauling and other purposes, and operating specialised vehicles to lift, move, dump and stack materials in warehouses.

Engine and motor operator workers include stationary engine operators, crane and hoist operators, earth moving and related operators, truck drivers and motor vehicle operators.

Public safety and protection workers protect individuals and property against hazards and enforce law and order. Fire-fighters, policemen and detectives, customs officers, guards, and watchmen are included.

Cooks and stewards prepare and cook in hotels, restaurants, other public eating places, aboard ships, aeroplanes and on railway trains.

Domestic assistants' clean rooms, wash dishes, do laundry and ironing, and perform additional domestic duties in private homes.

Waiters include waiters, bartenders and related workers who serve food and beverages in dining and drinking places, clubs, institutions and canteens, on board on ships and on railway trains.

Building caretakers and cleaners: this category take care of apartment houses, office buildings and other buildings and maintain them in an orderly and clean condition. Tasks may include operating furnaces or boilers to provide heat and hot water for tenants.

Chimney sweeps remove soot from flues, chimneys and connecting pipes, and may also clean furnaces and boilers.

Hairdressers include hairdressers, barbers, beauticians and others.

Launders and dry-cleaners workers this category launder, dry clean and press clothing, textile fabrics and similar products.

Military personnel include professional military personnel who lead, plan, organise and execute military work.

Other economically active persons occupational titles not included in previous occupational categories such as precision mechanic workers, athletes and sportsmen, photographers, bath attendants, and several subcategories of service workers.

E**conomically inactive persons** include housewives, early pensioners, students and persons on social support.

APPENDIX 3

Association between self-reported occupational exposure to physical and chemical factors with physician-certified long term sick-leave among women and men.

Table 1

WOMEN				Model #1	Model #2	Model #3
	N	Cases	n (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Physical exposure						
Cold						
Unexposed	2,585	453	17.5	1 (reference)	1 (reference)	1 (reference)
Exposed	160	39	24.4	1.5 (1.0 — 2.2)*	1.3 (0.9 – 1.9)	1.1 (0.7– 1.6)
Heat						
Unexposed	2,646	467	17.6	1 (reference)	1 (reference)	1 (reference)
Exposed	95	24	25.3	1.6 (0.9—2.5)	1.5 (0.9 -2.4)	1.3 (0.8– 2.1)
Indoor dry air						
Unexposed	1,704	283	16.6	1 (reference)	1 (reference)	1 (reference)
Exposed	1039	208	20.0	1.3 (1.0—1.5)*	1.2 (0.9 – 1.5)	1.2 (0.9—1.5)
Chemical exposures						
Metal dust/fumes						
Unexposed	2,730	488	17.9	1 (reference)	1 (reference)	1 (reference)
Exposed	14	3	21.4	1.2 (0.3—4.5)	1.1 (0.3 – 4.1)	1.0 (0.3 - 3.9)
Mineral dust/fumes						
Unexposed	2,733	488	17.9	1 (reference)	1 (reference)	1 (reference)
Exposed	11	3	27.3	1.7 (0.4—6.4)	1.6 (0.4 – 6.2)	1.8 (0.4 - 6.9)
Organic dust/fumes						
Unexposed	2,638	473	17.9	1 (reference)	1 (reference)	1 (reference)
Exposed	103	19	18.4	1.0 (0.6—1.7)	1.0 (0.6 – 1.6)	0.9 (0.5—1.5)

CI, confidence interval; OR, odds ratio *P≤ .05; **P≤ .01. In all models, responders with physician-certified long-term sick leave were excluded. Model #1: adjusted for age. Model # 2: adjusted for age and psychosocial risk factors at work only (role conflict, emotional demands and low supportive leadership), and education. Model # 3: adjusted for age and mechanical risk factors at work only (neck flexion, hand-/arm repetition, hands above shoulders, squatting/kneeling, standing, upper forward bend, awkward lifting, and heavy physical work) and education.

Table 2

MEN				Model #1	Model #2	Model #3
	N	Cases	n (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Physical exposures						
Cold						
Unexposed	2,943	284	9.7	1 (reference)	1 (reference)	1 (reference)
Exposed	481	66	13.7	1.6 (1.2—2.1) **	1.3 (0.9 – 1.7)	0.8 (0.6– 1.2)
Heat						
Unexposed	3,202	314	9.8	1 (reference)	1 (reference)	1 (reference)
Exposed	227	35	15.4	1.8 (1.2—2.6) **	1.5 (1.0 -2.2) *	1.2 (0.8– 1.8)
Indoor dry air						
Unexposed	2,683	260	9.7	1 (reference)	1 (reference)	1 (reference)
Exposed	750	92	12.3%	1.3 (1.0 – 1.7))*	1.1 (0.9 – 1.5)	1.1 (0.8 – 1.4)
Chemical exposures						
Metal dust/fumes						
Unexposed	3,311	328	9.9	1 (reference)	1 (reference)	1 (reference)
Exposed	119	21	17.6	2.1 (1.3– 3.5)**	1.6 (0.9 – 2.6)	1.1(0.6 – 1.9)
Mineral dust/fumes						
Unexposed	3,309	326	9.9	1 (reference)	1 (reference)	1 (reference)
Exposed	119	22	18.5	2.2 (1.4 —3.5)**	1.5 (0.9 – 2.6)	1.0 (0.6 - 1.8)
Organic dust/fumes						
Unexposed	3,302	327	9.9	1 (reference)	1 (reference)	1 (reference)
Exposed	128	21	16.4	1.9 (1.1 – 3.0)*	1.2 (0.7 – 2.0)	1.2 (0.7—2.1)

CI, confidence interval; OR, odds ratio *P≤ .05; **P≤ .01. In all models, responders with physician-certified long-term sick leave were excluded. Model #1: adjusted for age. Model # 2: adjusted for age and psychosocial risk factors at work only (role conflict, emotional demands and low supportive leadership), and education. Model # 3: adjusted for age and mechanical risk factors at work only (neck flexion, hand-/arm repetition, hands above shoulders, squatting/kneeling, standing, upper forward bend, awkward lifting, and heavy physical work) and education.

APPENDIX 4

Standardised incidence ratios (SIR) and 95% confidence intervals (95% CI) for cutaneous squamous cell carcinoma among men, according to age groups in Finland, Iceland, Norway, and Sweden. Only non-significant SIRs are shown here.

	30-49 years			>50 years		
Occupational categories	Obs*	SIR	95% CI	Obs*	SIR	95% CI
Farmers	56	0.80	0.61 – 1.04	5746	0.96	0.93 – 0.98
Gardeners	26	0.94	0.61 – 1.37	1444	0.90	0.86 - 0.95
Fishermen	8	0.82	0.35 – 1.61	461	0.75	0.68 – 0.82
Forestry workers	22	0.94	0.59 – 1.43	808	0.66	0.61 – 0.70
"Other construction workers"	35	0.94	0.65 – 1.30	1146	0.89	0.83 – 0.94
Bricklayers	7	0.97	0.39 – 1.99	292	0.84	0.75 – 0.95
Postal workers	14	0.80	0.44 – 1.34	465	1.06	0.96 – 1.15
Electrical workers	49	0.84	0.62 – 1.11	1242	1.02	0.96 – 1.07
Waiters	6	1.65	0.61 – 3.59	60	1.01	0.77 – 1.29
Plumbers	17	1.03	0.60 – 1.66	385	0.97	0.87 – 1.06
Welders	21	0.94	0.58 – 1.44	382	0.90	0.81 – 1.00
Building caretakers	22	1.21	0.76 – 1.83	437	0.96	0.87 – 1.05
Drivers	73	0.84	0.66 – 1.06	1962	0.93	0.88 – 0-97
Mechanics	119	0.90	0.75 – 1.08	3041	0.90	0.87 – 0.93
Wood workers	59	0.83	0.63 – 1.07	2626	0.87	0.84 – 0.91
Painters	14	0.72	0.39 – 1.20	596	0.85	0.79 – 0.92
Food workers	11	0.67	0.33 – 1.20	624	0.93	0.86 – 1.01
Chimney sweeps	2	1.57	0.19 – 5.68	33	1.00	0.69 – 1.40
Laboratory assistants	2	0.65	0.08 – 2.34	43	1.15	0.83 – 1.55
Journalists	2	0.36	0.04 – 1.31	111	1.06	0.87 – 1.28
Shop workers	27	0.87	0.57 – 1.26	791	1.01	0.94 – 1.08
Miners and quarry workers	9	1.23	0.56 – 2.33	253	0.91	0.80 – 1.03
Glass makers etc	10	0.53	0.26 – 0.98	577	0.98	0.90 – 1.07
Textile workers	9	1.11	0.51 – 2.12	477	0.95	0.86 – 1.05
Shoe and leather workers	2	0.82	1.10 – 2.95	197	0.96	0.84 – 1.11
Smelting workers	12	0.70	0.36 – 1.23	563	0.77	0.71 – 0.84
Chemical process workers	8	0.50	0.22 – 0.99	581	0.91	0.84 – 0.99
Beverage workers	0	0	0.0 – 4.37	23	0.88	0.56 – 1.32
Tobacco workers	0	0	0.0 – 27.86	8	5.41	0.63 – 2.91
Packers	25	0.78	0.51 – 1.16	1133	0.93	0.87 – 0.98
Engine operators	40	0.95	0.68 – 1.30	929	0.98	0.92 – 1.04
Hairdressers	2	1.01	0.12 – 3.64	106	1.03	0.84 – 1.25
Launderers	2	1.44	0.17 – 5.20	76	1.07	0.84 – 1.34
Cooks and stewards	5	0.64	0.21 – 4.31	90	0.73	0.59 – 0.90
Domestic assistants	1	0.77	0.02 – 4.31	3	0.69	0.14 – 2.02
"Other workers"	35	0.93	0.65 – 1.29	1628	0.96	0.92 – 1.01
Economically inactive	124	1.28	1.06 – 1.52	1882	0.89	0.85 – 0.93
All categories	**1,566**	**1.00**	**Ref.**	**48,724**	**1.00**	**Ref.**

*Obs: observed cases. Occupational categories with outdoor work Occupational categories with mixed outdoor/indoor work Occupational categories with indoor work.

Standardised incidence ratios (SIR) and 95% confidence intervals (95% CI) for cutaneous squamous cell carcinoma among women, according to age groups in Finland, Iceland, Norway, and Sweden. Only non-significant SIRs are shown

	30-49 years			>50 years		
Occupational categories	Obs*	SIR	95% CI	Obs*	SIR	95% CI
Seamen	0	0	0.0 – 37.16	1	1.09	0.03 – 6.05
Farmers	9	0.54	0.25 – 1.03	723	0.86	0.80 – 0.93
Fishermen	0	0	0.0 – 14.07	1	0.18	0.00 – 1.02
Forestry workers	0	0	0.0 – 8.70	11	0.88	0.44 – 1.58
"Other construction workers"	0	0	0.0 – 7.02	24	0.86	0.55 – 1.28
Bricklayers	0	0	0.0 – 126.42	0	0	0.0 – 3.92
Military personnel	0	0	0.0 – 29.77	0	0	0.0 – 0.38
Public safety workers	1	0.42	0.01 – 2.34	24	1.00	0.64 – 1.48
Technical workers, etc	16	1.25	0.71 – 2.02	98	0.95	0.77 – 1.16
Transport workers	2	1.08	0.13 – 3.89	23	0.70	0.45 – 1.05
Postal workers	20	0.94	0.57 – 1.45	486	1.04	0.95 – 1.14
Electrical workers	6	0.93	0.34 – 2.03	75	0.90	0.71 – 1.13
Waiters	19	1.40	0.84 – 2.18	382	0.85	0.77 – 0.94
Plumbers	0	0	0.0 – 92.97	0	0	0.0 – 16.00
Welders	1	1.35	0.33 – 7.52	3	0.56	0.12 – 1.65
Building caretakers	47	0.92	0.68 – 1.23	1317	0.86	0.81 – 0.91
Drivers	6	1.53	0.56 – 3.33	47	1.07	0.79 – 1.43
Mechanics	7	0.82	0.33 – 1.69	117	0.85	0.71 – 1.02
Wood workers	7	2.12	0.85 – 4.38	93	1.17	0.94 – 1.43
Painters	1	1.59	0.04 – 8.87	13	1.08	0.58 – 1.85
Food workers	6	0.66	0.24 – 1.45	281	0.87	0.77 – 0.98
Chimney sweeps	0	0	0.0 – 482.62	0	0	0.0 – 15.37
Assistant nurses	45	0.82	0.60 – 1.10	526	0.95	0.87 – 1.04
Laboratory assistants	7	0.97	0.39 – 1.99	38	0.98	0.70 – 1.36
Religious workers etc	40	1.04	0.74 – 1.42	265	1.09	0.96 – 1.23
Sales agents	18	0.99	0.58 – 1.56	400	1.03	0.91 – 1.10
Printers	6	1.33	0.49 – 2.89	69	0.80	0.63 – 1.01
Shop workers	64	1.04	0.80 – 1.33	1875	1.03	0.98 – 1.07
Artistic workers	5	0.88	0.29 – 2.05	57	0.97	0.74 – 1.26
Miners and quarry workers	0	0	0.0 – 33.11	4	1.67	0.45 – 4.27
Glass makers etc	8	1.14	0.49 – 2.24	171	0.95	0.82 – 1.11
Textile workers	25	1.15	0.75 – 1.70	997	0.95	0.89 – 1.01
Shoe and leather workers	3	1.46	0.30 – 4.27	80	0.92	0.73 – 1.14
Smelting workers	3	2.94	0.61 – 8.60	12	0.72	0.37 – 1.25
Chemical process workers	5	2.09	0.68 – 4.88	70	1.05	0.82 – 1.33
Beverage workers	0	0	0.0 – 12.88	8	0.63	0.27 – 1.24
Tobacco workers	0	0	0.0 – 13.21	11	1.06	0.53 – 1.90
Packers	10	0.91	0.44 – 1.68	319	0.98	0.87 – 1.09
Engine operators	1	0.63	0.02 – 3.50	15	0.71	0.40 – 1.17
Hairdressers	14	1.63	0.89 – 2.73	154	1.03	0.88 – 1.21
Launderers	6	1.78	0.65 – 3.87	193	0.90	0.85 – 1.03
Cooks and stewards	11	0.87	0.43 – 1.56	449	0.93	0.85 – 1.03
Domestic assistants	41	0.79	0.57 – 1.07	844	0.91	0.84 – 0.97
"Other workers"	22	0.78	0.49 – 1.18	604	0.92	0.84 – 0.99
Economically inactive	348	0.95	0.85 – 1.05	19267	1.00	0.98 – 1.02
All categories	**1,218**	**1.00**	Ref	**36,111**	**1.00**	**Ref.**

APPENDIX 5

Validated questionnaries and methods to assess occupational exposures and prevalence/severity of hand dermatitis (HD)

Assessment of occupational exposures	Assessment by		Advantages	Disadvantages	Languages
	Self-reporting	Physician			
NOSQ-2002[1-4]	X				Danish, Swedish, Norwegian, Finnish, Icelandic, English, Catalan, Spanish, German.
Assessment of prevalence of hand dermatitis					
NOSQ-2002[1-6] *Have you ever had hand eczema?* *Have you ever had eczema on your wrists or forearms?* *When did you last have eczema on your hands, wrists or forearms? (now, within the last 3 months, between 3 and 12 months ago, > 12 months ago)*	x		Good agreement between self-reporting of HD and clinical examination.	Assessment of occupational exposures in the same questionnaire: Common method bias Self-reporting may underestimate the true prevalence.	Danish, Swedish, Norwegian, Finnish, Icelandic, English, Catalan, Spanish, German.

Dutch Guideline[7,8] *Did you have one of the following symptoms on your hands or fingers in the past 12 months?* *Did one or more of these symptoms last for more than 3 weeks?* *Did one or more of these symptoms occur more than once the past 12 months?*	X			Self-reporting. Symptom-based.	Dutch, English.

Assessment of prevalence and severity of hand dermatitis (HD)					
	Assessment by		**Advantages**	**Disadvantages**	**Languages**
	Self-report	**Physician**			
Osnabruck Hand Eczema Severity Index (OHSI)[9-15,27]		x	Easy to use and fast. Validated also in non dermatologists. No subjective assessment of intensity. High reproducibility. No consideration of subjective symptoms. Validated for inter- and intraobserver reliability.	Possibly less useful in early dermatitis. Problematic to assess changes if affected area remains the same.	German, English.
Photographic guide[16-,19,2,27]	x	x	Self-evaluation is possible.	Potentially not good enough for all types of HD. No validated for inter and intraobserver reliability.	English.
Occupational contact dermatitis disease severity index (ODDI)[20,21,27]		x	Comprises clinical course (including reported history) and information on treatment, clinical	Includes subjective factors.	English, German.

		signs and work-related activities (functional impairment).		
Hand eczema Area and Severity Index (HEAS)[22-24,27]	x	Assessment of left and right hand separately. Both extent and intensity. No consideration of subjective symptoms	Not validated for inter and intraobserver reliability. Measurement of intensity adds a subjective element affecting reproducibility	Dutch, English.
Hand eczema score for occupational screenings (HEROS)[25-27]	x	Both extent and intensity • no subjective symptoms • in particular useful for early dermatitis • validated for inter- and intraobserver reliability	Very detailed. Time consuming in severe HD.	German, English

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APPENDIX 6

Occupational mobility over time: number and proportion of individuals who reported the same occupational category at two subsequent censuses, in Finland 1970-1980 census, in Norway and Sweden 1960-1970 censuses, by sex and occupational category (From Pukkala et al. 2009)[98]

		Men						Women					
		Finland		Norway		Sweden		Finland		Norway		Sweden	
No	Occupational category	N	%	N	%	N	%	N	%	N	%	N	%
1	Technical workers, etc.	32190	64.1	15 823	66.9	97 410	70.2	2595	65.9	264	65.2	3479	37.6
2	Laboratory assistants	760	55.3	964	50.9	–	–	1875	65.1	299	43.8	–	–
3	Physicians	1930	90.2	2 077	91.5	3 664	95.0	665	97.0	220	92.7	605	96.2
4	Dentists	310	85.5	854	93.3	2 062	93.6	845	94.1	209	91.9	707	94.3
5	Nurses	70	50.0	18	61.1	–	–	9335	89.8	774	88.4	10223	75.3
6	Assistant nurses	65	15.4	445	34.2	1 133	53.7	11460	43.7	223	33.6	14902	74.6
7	"Other health workers"	1545	72.8	839	53.9	3 487	71.5	8125	68.7	2 425	31.8	4934	77.6
8	Teachers	15130	86.1	9 602	90.6	20 677	83.0	18270	89.8	5 013	90.7	18860	92.5
9	Religious workers etc.	5695	59.0	6 010	64.3	14 684	66.8	5060	66.0	1 125	50.8	5243	64.2
10	Artistic workers	2570	70.6	1 968	53.9	5 706	66.0	1120	55.8	385	60.8	1265	66.1
11	Journalists	1260	65.1	864	71.1	2 768	69.9	935	42.8	93	68.8	574	65.9
12	Administrators	18215	68.6	23 412	53.2	38 193	50.9	2110	49.8	1 187	30.8	2637	40.2
13	Clerical workers	12445	42.9	19 922	54.2	42 817	48.8	55810	78.9	17 651	82.0	60234	79.4
14	Sales agents	19185	52.2	22 599	55.5	60 874	57.1	7135	47.1	2 527	51.4	7726	44.0
15	Shop workers	8900	48.4	8 603	49.3	21 826	45.0	34585	64.1	8 906	68.7	44687	62.0
16	Farmers	72600	77.8	57 683	72.8	97 276	70.3	8075	44.8	1 353	64.3	1649	50.0
17	Gardeners	13260	41.4	17 494	21.1	39 581	44.4	48250	67.6	790	34.9	7855	55.7
18	Fishermen	845	60.9	21 857	50.1	4 009	63.7	90	72.2	17	5.9	21	66.7
19	Forestry workers	14820	45.8	12 056	35.2	26 533	48.7	195	10.3	–	–	134	14.2
20	Miners and quarry workers	2440	40.4	3 490	44.3	7 602	44.0	90	50.0	–	–	30	0.0
21	Seamen	3085	68.1	16 765	50.0	6 290	57.2	40	0.0	–	–	–	–
22	Transport workers	8520	76.5	9 537	76.8	25 728	70.7	1355	42.4	87	33.3	719	41.3
23	Drivers	35755	73.6	25 905	64.8	54 010	60.2	610	54.1	43	18.6	922	37.0
24	Postal workers	4675	77.9	4 204	70.1	10 596	70.2	9760	73.5	3 619	71.5	12557	68.9
25	Textile workers	2950	50.3	5 600	55.2	13 194	57.5	18900	59.4	6 572	59.3	27369	57.2
26	Shoe and leather workers	1240	51.6	2 278	45.4	4 826	51.2	2560	58.2	489	41.7	2249	39.8
27	Smelting workers	4265	42.8	7 157	50.8	21 270	51.5	570	17.5	–	–	348	34.5
28	Mechanics	29755	58.6	33 571	55.8	96 054	61.4	2345	43.9	500	38.4	4422	44.3
29	Plumbers	5455	65.8	3 881	72.2	11 441	66.6	–	–	–	–	–	–
30	Welders	5120	52.4	4 102	52.3	12 707	52.8	180	36.1	–	–	78	16.7
31	Electrical workers	13135	70.2	14 279	64.3	31 654	65.2	1645	46.8	602	46.3	2615	42.3
32	Wood workers	27735	65.8	38 736	69.1	56 689	71.4	4885	53.7	60	23.3	579	44.0
33	Painters	6980	72.6	6 489	69.6	17 940	80.8	680	26.5	15	20.0	170	29.4
34	"Other construction workers"	17630	45.4	6 664	22.9	31 696	56.7	1660	22.0	–	–	–	–
35	Bricklayers	3060	74.3	4 091	63.9	8 075	75.8	75	0.0	–	–	–	–
36	Printers	3475	71.5	3 665	76.0	9 560	75.8	2675	62.1	525	65.3	2186	54.5
37	Chemical process workers	5340	53.4	8 993	46.1	14 740	44.4	1210	44.6	467	28.5	1819	45.4
38	Food workers	4185	53.4	10 242	55.4	16 291	59.4	7080	57.0	1 922	42.1	5231	43.3
39	Beverage workers	195	48.7	–	–	767	43.2	365	34.2	–	–	298	49.0
40	Tobacco workers	45	22.2	148	44.6	72	50.0	230	54.3	171	43.3	222	41.4
41	Glass makers etc.	5380	34.3	4 429	44.8	15 663	46.7	4750	41.5	876	39.5	4683	40.8
42	Packers	10500	41.4	15 069	42.6	29 180	44.2	9010	43.5	1 508	44.3	6960	32.4
43	Engine operators	16655	45.9	7 388	38.6	23 880	42.2	1340	44.0	–	–	199	52.3
44	Public safety workers	7225	80.3	6 545	75.0	13 277	74.4	175	48.6	68	36.8	246	35.8
45	Cooks and stewards	425	35.3	2 560	48.3	2 111	54.2	8620	63.1	2 830	45.5	9994	60.4
46	Home helpers	15	0.0	–	–	46	8.7	5410	44.8	6 749	30.7	14210	47.8
47	Waiters	320	28.1	1 254	43.5	1 412	55.5	8350	44.1	2 507	46.7	12154	46.7
48	Building caretakers	6310	65.9	2 385	69.6	8 835	59.5	27275	65.3	4 242	70.1	20890	56.3
49	Chimney sweeps	520	63.5	348	78.2	914	79.8	25	0.0	–	–	–	–
50	Hairdressers	115	78.3	1 078	89.2	3 452	88.3	2745	78.0	1 188	84.5	4336	78.4
51	Launderers	155	58.1	611	39.4	2 422	52.8	2440	48.8	1 146	40.2	5878	40.9
52	Military personnel	2940	62.6	5 847	72.3	9 200	68.0	–	–	–	–	–	–
53	"Other workers"	7140	38.6	28 164	6.6	33 457	38.8	9170	42.6	7 104	9.1	10311	41.4
1–53	All categories	464535	62.8	508 573	55.5	1 077 756	60.4	352770	64.3	86 774	57.9	337420	62.5

APPENDIX 7

Examples of preventive strategies for work-related hand dermatitis and skin cancer

Prevention strategy	Work-related hand dermatitis	Work-related skin cancer
Substitution	Replacement, modification, or inactivation of hazardous substances, e.g. allergens, and skin carcinogens.[1-3] E.g.: Regulation of allergen and skin carcinogens exposure by legislation on threshold values.	
Technical measures	Proper labelling and storage of chemicals and regular maintenance of tools.	Roofing of permanent outdoor working places (e.g. pay kiosks in parking areas). Use of mobile sun panels or sun shades on construction sites for roadmen and construction workers or in kindergartens/school. Use of UV absorbing window glass for vehicles (e.g. buses, trams, trains, diggers, tractors, cranes, aircrafts) Provision of shaded places for breaks or indoor break rooms.[10-14]
Organizational measures	Skin protection programmes[4]	Avoidance of UV-exposure during midday by early start of work and prolonged lunch break.[10-14]
Protective elements (If organizational and technical prevention measures do not work, personal protective equipment must be provided).	Educational programs:[ʃ] should focus on risk factors and the use of protective elements. To be implemented in the curriculum of vocational school, and to be provided regularly at the workplaces.	
	Regular use of moisturizers: to prevent irritant hand dermatitis and support the treatment of irritant hand dermatitis. They should be applied all over the hands including the fingerwebs, fingertips and back of the hand. Products should not contain fragrances, colouring agents, and preservatives. [5-9] Good hand hygiene regimes should include alcohol hand rubs (fewer irritants than full hand washing procedures). Hand washing should be performed with lukewarm water. The liquid soap must be rinsed off thoroughly and hands must be dried carefully with single use paper towels.[5-9] Protective gloves should be worn with dry and clean hands for wet	Appropriate sunglasses for occupational use must fulfil the requirements of DIN EN 172. Appropriate clothing is long-sleeved shirts and trousers from light-proof fabrics (cotton wool or synthetic fibres) with UPF 50 at least in the shoulder area. [10-14] Appropriate headgears are broad-brimmed helmets or broad-brimmed hats supplied with sun shields and neck guard. The standard safety helmet provides no sufficient sun protection for the face, ears and neck.[10-14] Sunscreens must be applied on all uncovered skin areas.

work and to protect contact to irritants, allergens and hazardous substances for as short a time as possible. Cotton glove liners should be used if gloves have to be worn longer than 10 min, single use glove should be worn only once, and defect gloves must be removed immediately. Only powder-free gloves should be used in all skin risk occupations.[5-9]	Appropriate sunscreens must contain very high, broad-spectrum, photostable filters for both UVB and UVA (SPF 50+, UVA-PF > 1/3 SPF).They must be easy to apply and sweat resistant and, finally, should not irritate the eyes and the skin.[10-14]

[ʃ]Educational programs: at workplaces have been proved to be effective,[15] but several studies showed that protective strategies are applied insufficiently. Therefore regular instructions on use and application as well as increasing workers' compliance to apply the protective measures are essential (10–12,14). Also useful in secondary and tertiary prevention for behavioural change.

Access to experts: occupational physicians, dermatologists or other specialists trained in OSD) should be available for pre-employment and pre-school examination and counselling of high-risk groups for prevention of OSD development, as well as for employees suffering from chronic hand dermatitis for early diagnosis and treatment.

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STUDY I

Work-related skin diseases in Norway may be underreported: data from 2000 to 2013

Alfonso, J.H., Løvseth, E.K., Samant, Y., Holm, J.Ø. (2015)

Contact Dermatitis, 72, 409-412. Doi: 10.1111/cod.12355.

STUDY II

Self-reported occupational exposure to chemical and physical factors and risk of skin problems: a 3-year follow-up study of the general working population of Norway.

Alfonso, J.H., Thyssen, J.P., Tynes, T., Mehlum, I.S., Johannessen, H.A. (2015).

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Acta Derm Venereol 2015; 95: 959–962

INVESTIGATIVE REPORT

Self-reported Occupational Exposure to Chemical and Physical Factors and Risk of Skin Problems: A 3-year Follow-up Study of the General Working Population of Norway

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Prospective studies on occupational dermatoses in the general working population are sparse. This study investigated prospectively the impact of self-reported occupational exposure to chemicals and physical factors on the risk of skin problems. The cohort comprised respondents drawn randomly from the general population in Norway, who were registered employed in 2006 and 2009 ($n=6,745$). Indoor dry air (odds ratio (OR) 1.3; 95% confidence interval (95% CI) 1.1–1.6) was a significant baseline predictor of skin problems at follow-up, whereas exposure to cleaning products (OR 1.7; 95% CI 1.2–2.5), water (OR 1.4; 95% CI 1.1–1.9) and indoor dry air (OR 1.6; 95% CI 1.1–2.1) at both measurement time-points was significantly associated with skin problems. The population risk attributable to these factors was 16%. This study quantified the contribution of occupational exposure factors to skin problems in the general working population of Norway. ***Key words: general working population; skin problems; occupational factors; population – attributable risk; epidemiology; prevention.***

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Skin problems caused or worsened by factors present in the work environment impose a significant burden on affected individuals and society (1). Occupational dermatoses, mostly contact dermatitis, represent an inflammatory response of the skin that typically occurs as a result of repeated exposure to irritants or allergens. The most frequent localizations of these conditions are the hands and forearms, and a major cause in the workplace is "wet work", i.e. frequent or long-lasting contact with water, soaps, detergents and disinfectants, and prolonged wearing of occlusive gloves (2). Other occupational substances that cause dermatoses include oils, lubricants and solvents. In both female- and male-dominated occupations, the 1-year prevalence of hand eczema has been estimated at between 20% and 30% (3–6).

Although there is a well-established relationship between certain work-related skin exposures and specific dermatoses, prospective studies addressing the effects of multiple work factors in the general working population are scarce (7). Moreover, the studies that are available focus on specific occupations (3–6); and the contribution of physical factors, such as heat and cold and dry air, is often dismissed (8).

The aim of this study was to investigate the impact of self-reported work-related exposure to skin irritants and physical and chemical factors on the risk of skin problems in a 3-year prospective cohort randomly selected from the general working population of Norway.

MATERIALS AND METHODS (see Appendix S1[1])

RESULTS

The study cohort comprised respondents drawn randomly from the general working-age population in Norway, who were registered as being in an active employee relationship in 2006 and 2009 ($n=6,745$) (Fig. 1).

Exposure to 9 chemical and physical hazards (Table I) at work was regressed on skin problems at follow-up (2009) using the following designs: (*i*) prospective analyses with exposure measured at baseline (2006) and; (*ii*) prospective analyses with exposure measured at both baseline and follow-up.

Table II shows the 1-month prevalence of skin problems at different measurement times. The risk of having skin problems at follow-up (Table SI[1]) decreased with age, except for the oldest age group, and was higher among women compared with men ($p<0.01$).

Estimation of the effect of baseline exposures on skin problems at follow-up using model #2 (adjusted for skin problems at baseline) (Table SII[1]) revealed that water, cleaning products and indoor dry air were significant predictors. However, in the model that included further adjustment (model #3: sex, age, and occupation), the effect of water and cleaning products was not statistically significant. Conversely, exposure to oil/cutting fluids showed a significant effect only in this model, but after

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2135

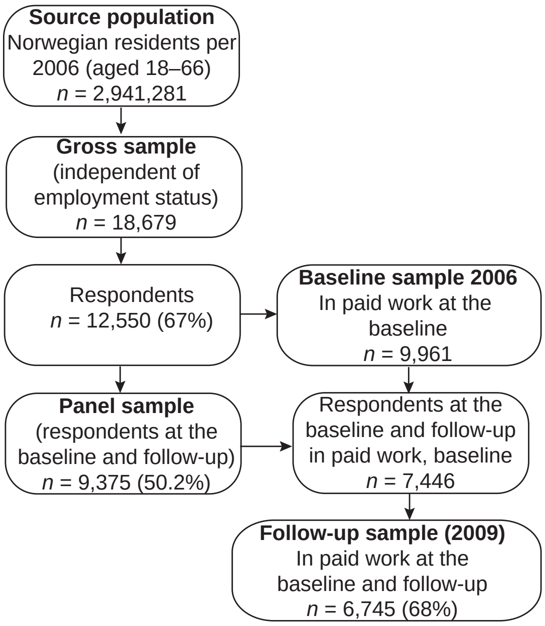

Fig. 1. Source population, random gross sample and panel sample with both baseline (2006) and follow-up (2009) samples included in the study.

adjusting for cleaning products (model #4) this association was no longer statistically significant. Work-related exposure to indoor dry air had a statistically significant effect on skin problems in all models evaluated here.

Statistically significant associations with skin problems were found for respondents exposed to water, cleaning products and indoor air at both baseline and follow-up (Table SIII[1], all models). Exposure to heat and organic dust/fumes at follow-up only significantly predicted skin problems in the different models. Exposure only at follow-up and at both time-points to oil/cutting fluids had a significant effect on skin problems in model #3. However, this effect was not statistically significant after adjusting for cleaning products (model #4).

No statistically significant associations were found regarding exposure to cold, metal or mineral dust/fumes.

The total combined population-attributable risk (PAR) for significant work-related exposure factors was 15.8% (Table SIII[1]). Exposure to cleaning products showed the largest single PAR (7.3%), followed by water (4.4%).

In analyses that were stratified according to sex using model #4 (results not shown), the effect of occupational exposure to water at both time-points was observed in women only (OR 1.6; 95% CI 1.1–2.2 vs. men OR 1.0; 95% CI 0.5–1.9). The effect of work-related exposure to indoor dry air at both time-points was stronger among men (OR 2.0; 95% CI 1.1–3.4) compared with women (OR 1.4; 95% CI 0.9–2.0). No major sex differences were found regarding the effect of other work-related exposure factors.

Table I. *Exposure measurement at baseline (2006) and follow-up (2009)*

Type of work environment exposure
Skin contact
Water
Cleaning products, disinfectants, solvents or other degreasing agents
Oils, lubricants or cutting fluids
Physical factors
Heat, i.e. temperatures of approx. 28°C or higher
Cold, i.e. working outdoors in the winter, or working in cold rooms
Poor indoor environment in terms of dry air
Chemical factors
Mineral dust, e.g. from stone, quartz, cement, asbestos or mineral wool
Metal dust, e.g. from weld fumes, lead, chrome, nickel, zinc, aluminium, cobber or tin dust
Organic dust, e.g. from textiles, wood, flour, clothes or animals

Table II. *Cases of self-reported skin problems at baseline (2006) and at follow-up (2009)*

	Cases, *n*	Cases, % (95% CI)
At baseline	1,311	13.2 (12.5–13.8)
At follow-up	786	11.7 (10.9–12.5)
At both time-points	401	5.9 (5.4–6.5)

DISCUSSION

This study, based on a randomly drawn cohort of the general population of Norway, has demonstrated the contribution of work-environment factors on the risk of subsequent skin problems. To our knowledge, we are the first to have shown this contribution in such a population (7, 9).

The most consistent predictors of skin problems were indoor dry air, water and cleaning products.

The consistent result regarding indoor dry air was unaffected after adjusting for other variables, which indicated that this is a robust finding and that perceived dry air acts as an independent risk factor. To the best of our knowledge, this finding has not been reported previously in a prospective study of the general working population. Therefore, dermatoses due to perceived dry air may be more distressing than their comparative paucity of physical signs might suggest (8, 10). The fact that indoor dry air was the most frequent work exposure reported is in accordance with the large number of Norwegian people working indoors. Although the perceived air "dryness" may be a proxy of actual humidity, in temperate areas such as Scandinavia, the low humidity/high temperature indoor environment is accompanied by low humidity/low temperature outdoor climate during the winter, which also has a drying effect on the stratum corneum (10). However, it is important to emphasize that the sensation of dryness should not always be interpreted as an indicator of low indoor air humidity (11), since different kind of particles and dusts may contribute to this sensation (8, 10). Nevertheless, in our study, the subjects who reported dust exposure exhibited little overlap with those who reported a sensation of indoor dry air. The sex difference observed, with stronger effect among men, may be due to a poor knowledge about skin care (12) and a lower use of moisturizers by men (13).

The finding that cleaning products and water were consistent predictors of skin problems is in agreement with results from a Norwegian register-based study, in which cleaning agents and water were among the most common exposure factors associated with notified work-related skin diseases during the period 2000–2013 (14). The effect of water was found only in women and is probably explained by jobs in which most of the tasks consist of wet work and cleaning (15).

According to our results, the injurious effects of oil and cutting fluids were partly mediated by skin exposure to cleaning products, because the risk of skin problems was lower after adjusting for exposure to cleaning agents. The effect of this occupational exposure has not been assessed previously at the population level and this constitutes a novel finding. Skin exposure to oils, fuels and solvents was the third most common exposure for the work-related skin diseases notified for the period 2000–2013 in Norway (14).

Work-related exposure to heat was a significant predictor of skin problems among workers who were exposed at follow-up only, and this is in accordance with the short-term effects of high temperatures (10). The clinical impression that cold exposure contributes to occupational dermatoses was partially verified in this study, and we speculate that sample characteristics (e.g. sample size) may have affected the significance of our results. As there is evidence of the detrimental effects of cold exposure on the skin (10, 16) further population studies are warranted.

Given that the risk of having skin conditions was increased among workers who were exposed at both time-points, our results demonstrate the harmful effect of long-lasting and cumulative exposure on the risk of having skin problems at the population level. Conversely, the low OR for exposures that occurred only at baseline may be interpreted as a result of people changing their work, or of the hardening or implementation of preventive measures in the workplace. Furthermore, the low OR obtained for subjects who were exposed only at baseline (Table SIII[1]) suggests that exposure reduction leads to a decreased risk of developing skin problems in the general working population.

Several studies have suggested that people change or lose their jobs because of skin problems (17, 18), and that these job changes occur early in the course of the disease (19, 20). Moreover, we do not know whether participants with chronic skin disorders were less likely to respond at baseline. In addition, it is possible that the most vulnerable people had already left their jobs (21) and were thus excluded from this cohort. Both of these selection processes are likely to lead to a healthy worker effect before recruitment and attenuated risk estimates.

This study aimed to estimate the contribution of occupational exposures on skin problems in a general population, and not a complete causal mechanism (22) where individual susceptibility (23, 24) and non-occupational exposures are also of relevance. Thus, it is reasonable that the population risk that was attributable to occupational factors was 16% in our population.

The validity of this longitudinal study was supported by a large representative sample drawn randomly from the general Norwegian working-age population with a high response frequency. The design was prospective and included the measurement of a comprehensive set of exposures and further adjustments.

Despite a non-response frequency of 33%, no systematic differences were found across the benchmarks of age, sex and region between respondents and non-respondents (25). Moreover, previous studies have shown that health problems do not necessarily differ between respondents and non-respondents and that some differences do not necessarily produce biased risk estimates (26).

A particular strength of this study was that we focused on exposure factors rather than on occupations. It has been suggested previously that using job titles as a proxy for occupational skin exposure underestimates variations in exposure within occupations or over time in the same job (27).

The lack of a validated instrument to measure exposures was a limitation of this study. Validated questions on several exposures, in particular to water, exist (27), but they have not been validated in the Norwegian working population. Nevertheless, the occupational exposure factors associated with skin problems in the present study were among the most common occupational exposures for the notified work-related skin diseases in Norway for the period 2000–2013 (14). Future studies should aim at validating self-reports of exposure.

The present study covers mainly subjectively experienced skin problems (illness) (28), where subclinical cases also may be included. Although illness data is usually self-reported (28), the fact that there was no clinically objective measure of the outcome at follow-up was a further limitation. However, our one-month prevalence estimate of 12% at follow-up is in accordance with the results from a Norwegian questionnaire study that applied a validated questionnaire for skin complaints (29).

Although we expect that the vast majority of skin problems represent hand eczema, other conditions, such as psoriasis and urticaria, may be part of our outcome entity.

As all data were collected by self-report, reporting bias and common method bias influencing exposure and outcome measures may have inflated the estimates. However, adjustment for baseline skin problems should have minimized the problem. Moreover, the questions about skin exposures and skin problems were among questions on other topics, and had different types of response categories, and questions regarding occupational exposures were asked before questions about health problems. These factors may have reduced common method bias (30).

In conclusion, the findings of this study indicate the contribution of work-environment factors to the risk of skin problems in a general working population, hence suggesting a potential for prevention via the reduction of known risk factors. Future epidemiological studies and surveillance of occupational dermatoses should include the assessment of physical factors and the effect of concomitant exposures.

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The authors declare no conflicts of interest.

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Appendix S1

MATERIALS AND METHODS

Population

Data were provided by the nationwide Survey of Living Conditions – Work Environment, which was conducted by Statistics Norway (SSB). Data were collected by personal telephone interviews (0.5% of the completed interviews were face-to-face interviews) during 2 periods: from September 2006 to February 2007 (baseline 2006) and from June 2009 to January 2010 (follow-up 2009). Prior to the telephone contact, potential respondents were informed by email about the topic of the study and privacy protection.

The eligible respondents were Norwegian residents aged 18–66 years. In 2006, this population consisted of 2,941,281 persons (source population). A gross sample of 18,679 individuals was randomly drawn from this population, and a total of 12,550 (67%) persons were then interviewed. Among those interviewed (Fig. 1), 9,961 were enrolled in paid work in 2006. The baseline cross-sectional sample was compared with the gross sample according to the benchmarks of age, sex and region; no major differences were detected (25). The panel data comprising the respondents to the survey in 2006 and 2009 consisted of 9,375 persons (response frequency: 50.2% of the gross sample; 74.4% of the baseline cross-sectional sample).

Respondents in the panel dataset who were enrolled in paid work both at baseline and follow-up ($n = 6,745$) constituted the population of the present study.

Work-related exposure measurement

Perceived exposure to work-environment factors was measured based on 9 items (Table I) that were developed by an expert group from a Nordic co-operation project (S1). The questions have been applied in regular surveys of living conditions since 1989.

The response categories were "Yes" and "No". "Yes" respondents were asked to estimate the proportion of the working day during which they were exposed (response categories: "almost all the time", "three-quarters of the working day", "half of the working day", "a quarter of the working day" and "very little of the working day"). Scores were then categorized into 4 categories, "none or very little of the working day", "a quarter of the working day", "half of the working day" and "three-quarters of the working day or more", that were analysed linearly. Score changes from baseline to follow-up were based on the re-coding of the dichotomized scores ("none or very little of the working day" and "a quarter of the working day or more") at baseline and at follow-up into 4 categories: "not exposed", "exposed only at baseline", "exposed only at follow-up" and "exposed at both baseline and follow-up".

Other variables: the assessment of occupation was based on an open questionnaire, coded by SSB into a professional title in accordance with the International Standard Classification of Occupations (ISCO 1988) and re-coded into 10 major occupational groups.

Outcome

At follow-up, the outcome was measured using the following question: "Have you over the past month been afflicted by eczema, itchy skin or rash?" Participants who gave an affirmative answer where further asked: Have you been severely afflicted, somewhat afflicted or little afflicted? Cases were defined as respondents who reported being afflicted a little or more at follow-up.

Statistics

Exposure to chemical and physical hazards at work was regressed on skin problems at follow-up (2009) using the following designs: (*i*) prospective analyses with exposure measured at baseline (2006) and; (*ii*) prospective analyses with exposure measured at both baseline (2006) and follow-up (2009).

The associations were calculated as odds ratios (ORs) with 95% confidence intervals (95% CIs). Adjustments for potential confounders were made by logistic regression analyses in separate models, each model n+1 including the variables adjusted for in the previous model. Model #1 was the crude analysis. In model #2, we made adjustments for skin problems reported at baseline. In model #3, further adjustments were made for sex, age and occupation. To limit the potential of over-adjustment, in model #4, each work-related predictor was adjusted only for other work-related predictors that were first estimated to exert an influence above a certain threshold. This estimation was made *a priori* based on the following procedure suggested by Rothman (S2). In the first step, crude ORs were estimated separately for each work-related factor. In the second step, each of the other work-related variables was entered one at a time. If the inclusion of a potential confounder resulted in a change in the OR of 10% or more, that variable was treated as a real confounder in the multiple regression models.

All statistical analyses were performed using PASW Statistics (formerly SPSS), V.19.0 (IBM, Armonk, New York, USA).

For the statistically significant work-related factors in the adjusted regression analyses (Table SII, model #4), we calculated the PAR with 95% CIs based on the method described by Natarajan et al. (S3, S4).

Ethical considerations

Statistics Norway carried out the survey according to statutory rules. Statistics Norway has appointed its own privacy ombudsman, approved by the Norwegian Data Inspectorate. All persons gave their informed consent prior to their inclusion in the study.

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Table SI. *Distribution of the background variables and their associations with self-reported skin problems at follow-up (2009)*

	N	Cases, *n*	Cases, % (95% CI)
Total	6,729	786	11.7 (10.9 –12.5)
Missing	16		
Age			
17–24 years	458	62	13.5 (10.4–16.7)
25–34 years	1,340	180	13.4 (11.6–15.3)
35–44 years	1,990	233	11.7 (10.3–13.1)
45–54 years	1,822	183	10.0 (8.7–11.4)
55–66 years	1,119	128	11.4 (9.6–13.3)
Sex			
Female	3,195	416	13.0 (11.9–14.2)
Male	3,534	370	10.5 (9.5–11.5)
Occupation			
Legislators, senior officials and managers	687	64	9.3 (7.1–11.5)
Professionals	1,087	102	9.4 (7.6–11.5)
Technicians and associate professionals	1,926	250	13.0 (11.4–14.5)
Clerks	415	52	12.5 (9.3–15.8)
Service workers and shop sale workers	1,220	158	13.0 (11.1–14.9)
Skilled agricultural and fishery workers	155	20	12.9 (7.6–18.2)
Craft-related trades workers	638	62	9.7 (7.4–12.0)
Plant-machine operators and assemblers	360	47	13.1 (9.6–16.6)
Elementary occupations	158	23	14.6 (9.0–20.1)
Other occupations	98	8	8.2 (2.6–13.7)

Table SII. *Multiple logistic regression: self-reported skin problems at follow-up (2009) regressed on self-reported work-related exposures measured at baseline (2006)*

	Total	Cases, *n* (%)	Model #1 OR (95% CI)	Model #2 OR (95% CI)	Model #3 OR (95% CI)	Model #4 OR (95% CI)
1. Water						
Unexposed	5,780	641 (11.1)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Exposed	939	143 (14.0)	1.4 (1.1–1.7)**	1.3 (1.0–1.6)*	1.2 (0.9–1.6)	1.2 (0.9–1.6)
Missing	26	2				
2. Cleaning products						
Unexposed	6,128	694 (11.3)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Exposed	594	91 (15.3)	1.4(1.1–1.8)**	1.3 (1.0–1.7)*	1.3 (0.9–1.7)	1.3 (0.9–1.7)
Missing	23	1				
3. Oil/cutting fluids						
Unexposed	6,276	742 (11.5)	1 (ref)	1 (ref)	1 (ref)	1 (ref)[a]
Exposed	284	43 (15.1)	1.4 (0.9–1.9)	1.4 (0.9–2.0)	1.5 (1.0–2.2)*	1.4 (0.9–2.1)
Missing	21	1				
4. Cold						
Unexposed	5,955	679 (11.4)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Exposed	755	103 (13.6)	1.2 (1.0–1.5)	1.2 (0.9–1.5)	1.2 (0.9–1.5)	1.2 (0.9–1.6)
Missing	35	4				
5. Heat						
Unexposed	6,371	741 (11.6)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Exposed	346	41 (11.8)	1.0 (0.7–1.4)	0.8 (0.6–1.3)	0.8 (0.6–1.2)	0.8 (0.6–1.2)
Missing	28	4				
6. Indoor dry air						
Unexposed	5,581	614 (11.0)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Exposed	1,143	171 (15.0)	1.3 (1.1–1.5)*	1.3 (1.1–1.7)*	1.3 (1.1–1.6)**	1.3 (1.1–1.6)**
Missing	21	1				
7. Metal dust/fumes						
Unexposed	6,567	766 (11.6)	1 (ref)	1 (ref)	1 (ref)	1 (ref)[b]
Exposed	162	20 (12.3)	1.1 (0.7–1.7)	1.0 (0.6–1.7)	1.1 (0.6–1.8)	1.0 (0.6–1.8)
Missing	16	0				
8. Mineral dust/fumes						
Unexposed	6,554	756 (11.5)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Exposed	161	26 (16.1)	1.5 (0.9–2.3)	1.3 (0.8–2.1)	1.4 (0.8–2.4)	1.4 (0.8–2.4)
Missing	30	4				
9. Organic dust/fumes						
Unexposed	6,335	725 (11.4)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Exposed	379	56 (14.8)	1.3 (1.0–1.8)*	1.2 (0.9–1.7)	1.2 (0.9–1.7)	1.2 (0.9–1.7)
Missing	31	5				

Model #1: Crude analysis. Model #2: adjusted for skin problems at baseline. Model # 3: further adjusted for sex, age, and occupation. Model #4: further adjusted for work related exposures yielding a 10% change of OR; [a]further adjusted for cleaning products; [b]further adjusted for cleaning products and indoor dry air.

*$p \leq 0.05$; **$p \leq 0.01$.

CI: confidence interval; OR: odds ratio.

Table SIII. *Multiple logistic regression: self-reported skin problems at follow-up (2009) regressed on changes in self-reported work-related exposures from baseline (2006) to follow-up (2009)*

	Total	Cases, *n* (%)	Model #1 OR (95% CI)	Model #2 OR (95% CI)	Model #3 OR (95% CI)	Model #4 OR (95% CI)	PAR[a] % (95% CI)
1. Water							
Unexposed	5,161	559 (10.8)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	
Exposed only at baseline	340	44 (12.9)	1.2 (0.9–1.7)	1.1 (0.8–1.6)	1.0 (0.7–1.5)	1.0 (0.7–1.5)	
Exposed only at follow-up	614	82 (13.4)	1.3 (1.0–1.6)*	1.3 (1.0–1.7)*	1.3 (1.0–1.9)*	1.3 (1.0–1. 9)	
Exposed at both time-points	595	98 (16.5)	1.6 (1.3–2.0)**	1.5 (1.1–1.9)**	1.4 (1.1–1.9)*	1.4 (1.1–1.9)*	4.4 (0.2–8.9)
Missing	35	3					
2. Cleaning products							
Unexposed	5,703	621 (10.9)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	
Exposed only at baseline	326	39 (12.0)	1.1 (0.8–1.6)	1.1 (0.8–1.7)	1.1 (0.8–1.7)	1.1 (0.8–1.7)	
Exposed only at follow-up	419	73 (17.4)	1.7 (1.3–2.2)**	1.8 (1.3–2.5)**	1.8 (1.3–2.4)**	1.8 (1.3–2.4)**	4.1 (1.4–7.0)
Exposed at both time-points	268	52 (19.5)	2.0 (1.4–2.7)**	1.7 (1.2–2.4)**	1.7 (1.2–2.5)**	1.7 (1.2–2.5)**	3.2 (0.5–6.2)
Missing	29	1					
3. Oil/cutting fluids							
Unexposed	6,276	718 (11.4)	1 (ref)	1 (ref)	1 (ref)	1 (ref)[a]	
Exposed only at baseline	156	20 (12.8)	1.1 (0.7–-1.8)	1.1 (0.7–2.0)	1.3 (0.8–2.2)	1.3 (0.7–2.2)	
Exposed only at follow-up	159	24 (15.1)	1.4 (0.9–2.1)	1.5 (0.9–2.5)	1.6 (1.0–2.7)*	1.4 (0.8–2.3)	
Exposed at both time-points	128	23 (18.0)	1.7 (1.0–2.7)*	1.6 (0.1–2.7)	1.8 (1.1–3.2)*	1.6 (0.9–2.7)	
Missing	26	1					
4. Cold							
Unexposed	5,586	635 (11.4)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	
Exposed only at baseline	393	54 (13.7)	1.2 (0.9–1.7)	1.1 (0.8–1.6)	1.2 (0.8–1.6)	1.2 (0.8–1.6)	
Exposed only at follow-up	362	44 (12.2)	1.1 (0.8–1.5)	1.1 (0.8–1.6)	1.1 (0.8–1.6)	1.1 (0.8–1.6)	
Exposed at both time-points	353	48 (13.6)	1.2 (0.9–1.7)	1.2 (0.9–1.7)	1.3 (0.9–1.9)	1.3 (0.9–1.9)	
Missing	51	5					
5. Heat							
Unexposed	5,980	686 (11.5)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	
Exposed only at baseline	47	4 (8.5)	0.7 (0.3–2.0)	0.5 (0.1–1.4)	0.5 (0.2–0.4)	0.5 (0.2–0.4)	
Exposed only at follow-up	229	36 (15.7)	1.4 (1.0–2.1)*	1.8 (1.2–2.7)**	1.8 (1.2–2.7)**	1.8 (1. 2–2.7)**	2.3 (0.4–4.5)
Exposed at both time-points	114	15 (13.2)	1.2 (0.7–2.0)	1.0 (0.6–1.9)	1.0 (0.5–1.9)	1.0 (0.5–1.9)	
Missing	375	45					
6. Indoor dry air							
Unexposed	5,068	545 (10.8)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	
Exposed only at baseline	757	107 (14.1)	1.4 (1.1–1.7)**	1.3 (1.0–1.6)	1.2 (1.0–1.6)	1.2 (1.0–1.6)	
Exposed only at follow-up	506	69 (13.6)	1.3 (1.0–1.7)*	1.3 (1.0–1.8)	1.3 (0.9–1.7)	1.3 (0.9–1.7)	
Exposed at both time-points	384	64 (16.7)	1.7 (1.2–2.2)**	1.6 (1.2–2.2)**	1.6 (1.1–2.1)**	1.6 (1.1–2.1)**	2.9 (0.4–5.8)
Missing	30	0					
7. Metal dust/fumes							
Unexposed	6,478	752 (11.6)	1 (ref)	1 (ref)	1 (ref)	1 (ref)[b]	
Exposed only at baseline	95	12 (12.6)	1.1 (0.6–2.0)	1.0 (0.5–1.9)	1.0 (0.5–2.1)	1.0 (0.5–2.1)	
Exposed only at follow-up	74	13 (14.9)	1.3 (0.7–2.4)	1.6 (0.8–3.0)	1.6 (0.8–3.1)	1.3 (0.7–2.6)	
Exposed at both time-points	25	4 (13.8)	1.2 (0.4–3.5)	1.0 (0.3–3.4)	1.1 (0.3–3.7)	0.9 (0.3–3.1)	
Missing	56	5					
8. Mineral dust/fumes							
Unexposed	6,449	739 (11.5)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	
Exposed only at baseline	117	18 (15.4)	1.4 (0.8–2.3)	1.6 (0.9–2.7)	1.7 (0.9–3.0)	1.7 (0.9–3.0)	
Exposed only at follow-up	97	15 (15.5)	1.4 (0.8–2.4)	1.3 (0.7–2.5)	1.4 (0.7–2.6)	1.4 (0.7–2.6)	
Exposed at both time-points	43	8 (18.6)	1.8 (0.8–3.8)	1.0 (0.4–2.4)	1.1 (0.5–2.8)	1.1 (0.5–2.8)	
Missing	39	6					
9. Organic dust/fumes							
Unexposed	6,116	687 (11.2)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	
Exposed only at baseline	283	43 (15.2)	1.4 (1.0–1.2)*	1.2 (0.9–1.8)	1.3 (0.9–1.8)	1.3 (0.9–1.8)	
Exposed only at follow-up	212	37 (17.5)	1.7 (1.2–2.4)**	1.6 (1.0–2.4)*	1.6 (1.0–2.4)*	1.6 (1.0–2.4)*	1.9 (–0.1–4.2)
Exposed at both time-points	95	12 (12.6)	1.1 (0.6–2.1)	1.0 (0.5–2.0)	1.0 (0.5–2.3)	1.0 (0.5–2.3)	
Missing	39	7					

[a]PAR based on model #4.

Model #1: crude analysis. Model #2: adjusted for skin problems at baseline. Model #3: further adjusted for sex, age, and occupation. Model #4: further adjusted for work related exposures yielding a 10% change of OR; [a]further adjusted for cleaning products; [b]further adjusted for cleaning products and indoor dry air. CI: confidence interval; OR: odds ratio; PAR: population-attributable risk. *$p \leq 0.05$; **$p \leq 0.01$.

STUDY III

Self-reported occupational skin exposure and risk of physician-certified long-term sick leave: a prospective study of the general working population of Norway.

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INVESTIGATIVE REPORT

Self-reported Occupational Skin Exposure and Risk of Physician-certified Long-term Sick Leave: A Prospective Study of the General Working Population of Norway

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Little is known about the contribution of occupational skin exposure as a risk factor for physician-certified long-term sick leave in the general working population of Norway. This study drew a cohort (*n*=12,255; response at baseline 69.9%) randomly from the general population of Norway. Occupational skin exposure (in 2009) was measured based on 5 items. The outcome of interest was physician-certified long-term sick leave ≥16 days during 2010. Statistical adjustment for psychosocial and mechanical occupational exposures was performed. Long-term sick leave was predicted by occupational skin exposure to cleaning products (odds ratio (OR) 1.7; 95% confidence interval (95% CI) 1.1–2.5) and waste (OR 2.1; 95% CI 1.1–3.7) among men, and occupational skin exposure to water (OR 1.3; 95% CI 1.0–1.6) among women. The estimated population attributable risk for occupational skin exposure was 14.5%, which emphasizes its contribution as an important risk factor for long-term sick leave. ***Key words: sick leave; occupational exposure; skin; risk factors; prospective study.***

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Physician-certified sick leave, a general indicator of poor health and limited functioning, predicts future disability pension (1). Norway is the Scandinavian country with the highest expenditure due to sick leave (2), and the identification of its predictors is essential to plan preventive measures at the population level.

Associations between psychosocial and mechanical work exposures and sick leave have been identified previously (3–5). However, the impact of occupational skin exposure on physician-certified long-term sick leave (LTSL) remains largely unexplored by prospective population-based studies.

Occupational skin exposure to chemical and physical irritants are associated with an excess risk of skin problems in the general working population of Norway (6). Hence, it is of interest to explore further whether occupational skin exposure is also associated with an increased risk of LTSL.

The aim of this prospective study, based on a nationwide cohort of the general working population of Norway, is therefore to quantify the contribution of occupational skin exposure to the risk of physician-certified LTSL. A range of occupational skin exposures was assessed, and statistical adjustments were performed for several explanatory variables, such as psychosocial and mechanical work exposures.

MATERIALS AND METHODS (For more details see Appendix S1[1])

Population

The study population was based on data merged between the nationwide Survey of Level of Living – Working Conditions (Statistics Norway), and the Norwegian Labour and Welfare Administration's sickness benefit register, using the Norwegian unique personal identification number (4, 5). Respondents who were registered as being in an active employee relationship for 100 days or more in both 2009 and 2010, but without LTSL in 2009 were eligible for the prospective analyses (*n*=6,182) (Fig. 1).

Predictors and outcome

Occupational skin exposure was measured at baseline (2009) based on 5 items (Table I) that were developed by an expert group from a Nordic co-operation project (7). The outcome of the study consisted of incident cases of physician-certified sick leave for a period of 16 or more working days (LTSL) at the individual level during follow-up (2010).

Statistical analysis

Associations between occupational skin exposure and LTSL, including statistical adjustments for potential confounders and competing explanatory variables in separate models (Fig. 2), were calculated by logistic regression, obtaining odds ratios (ORs) with 95% confidence intervals (95% CIs). All analyses were carried out separately for men and women. All statistical analyses were performed using PASW Statistics (formerly SPSS), V.19.0 (IBM, Armonk, NY, USA).

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2253

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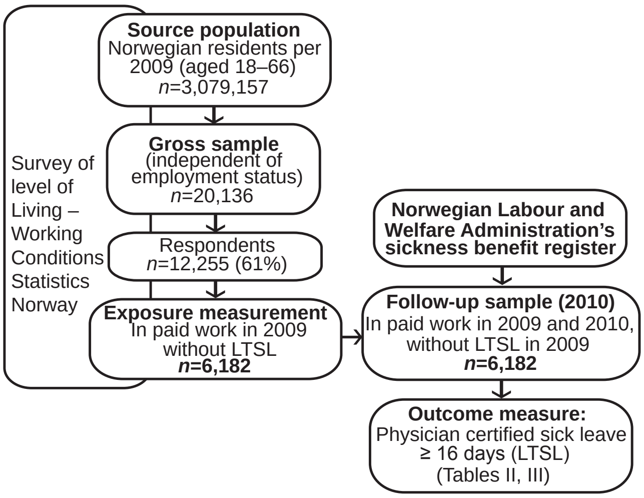

Fig. 1. Source population, random gross sample, response frequency at the baseline, and follow-up sample included in the study.

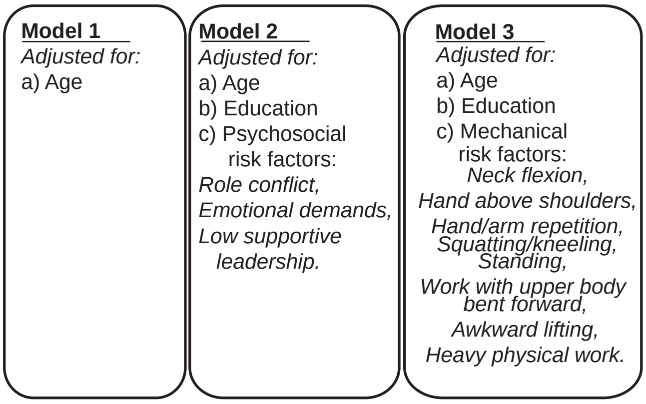

Fig. 2. Models for statistical analysis considering potential confounders and explanatory variables associated with physician-certified long-term sick leave in the general working population of Norway.

The population-attributable risk (PAR) with 95% CIs, based on the method described by Natarajan et al. (8), was calculated for occupational skin exposures that showed an association with LTSL.

RESULTS

During the follow-up 845 (13.7%) of the 6,182 participants were classified with LTSL. The distribution of socio-demographic variables at baseline with the associated risk of LTSL at follow-up is described in Table SI[1]. The risk was highest among workers in the age group 55–66 years, women, agricultural and fishery workers, and among respondents with the lowest educational level (Table SI[1]).

In the crude multiple logistic analyses, self-reported occupational skin exposures at baseline, except for biological samples for men, and oil/cutting fluids for women, were significant risk factors for LTSL at follow-up (results not shown). When adjusting for age only minor changes were observed (Table II, model #1).

Among men, self-reported occupational skin exposure to cleaning products, water, oil/cutting fluids, and waste were significant risk factors for LTSL after statistical adjustments for psychosocial work exposures and education (Table II, model #2). After adjustments for mechanical work exposures and education, skin exposure to cleaning products and waste were significant risk factors for LTSL (Table II, model #3). The risk estimates were reduced only marginally after adjustments for psychosocial and mechanical work exposures at the same time (OR 1.6, CI 95% 1.1–2.6 for cleaning products; OR 1.9, CI 95% 1.1–3.4 for waste).

Among women, self-reported occupational skin exposure to cleaning products, water, and biological samples were significant risk factors for LTSL after statistical adjustments for psychosocial work exposures and education (Table II, model #2). After adjustment for mechanical work exposures and education, water was the only significant risk factor for LTSL, while the risk estimates for cleaning products and biological samples were still elevated but were non-significant (Table II, model #3). Statistical adjustment for both psychosocial, and mechanical work exposures at the same time led to elevated and borderline significant risk estimates for women reporting occupational exposure to water (OR 1.3, 95% CI 0.9–1.7).

Based on model #3, 14.5% of the new cases with LTSL in 2010 were attributable to occupational skin exposures that significantly predicted LTSL (Table III, model #3).

DISCUSSION

This study found strong evidence of an association between self-reported occupational skin exposure to cleaning products and waste among men, and skin exposure to water among women with the risk of phy-

Table I. *Exposure assessment at baseline (2009)*

	Question	Exposures
Skin contact	Do you get water on your skin several times per hour in your day-to-day work? Including washing your hands	Water
	Are you, in your day-to-day work, exposed to skin contact with:	Cleaning products, disinfectants, solvents or other degreasing agents? Oils, lubricants or cutting fluids?
Biological factors	Are you, in your day-to-day work, exposed to biological material, for example:	Waste, e.g. garbage, offal, sewage or used disposable medical equipment? Biological samples, such as body fluids (e.g. blood, saliva, faeces or urine), or laboratory materials (e.g. biological samples from patients or animals?)

Table II. Association between occupational skin exposures measured at baseline (2009) and long-term sick leave (16 days or more) in men and women at follow-up (2010), estimated by multiple logistic regression

	Men					Women				
	N	Cases *n* (%)	Model #1 OR (95% CI)	Model #2 OR (95% CI)	Model #3 OR (95% CI)	*N*	Cases *n* (%)	Model #1 OR (95% CI)	Model #2 OR (95% CI)	Model #3 OR (95% CI)
SKIN CONTACT										
1. Cleaning products										
Unexposed	3,212	311 (9.7)	1 (ref)	1 (ref)	1 (ref)	2,390	400 (16.7)	1 (ref)	1 (ref)	1 (ref)
Exposed	224	41 (18.3)	**2.3 (1.6–3.3)****	**2.1 (1.4–3.0)****	**1.7 (1.1–2.5)***	355	92 (25.9)	**1.7 (1.3–2.2)****	**1.5 (1.1–1.9)****	1.3 (0.9–1.7)
2. Water										
Unexposed	3,084	299 (9.7)	1 (ref)	1 (ref)	1 (ref)	2,064	325 (15.7)	1 (ref)	1 (ref)	1 (ref)
Exposed	345	51 (14.8)	**1.7 (1.2–2.4)****	**1.4 (1.1–2.0)***	1.2 (0.8–1.7)	679	167 (24.6)	**1.7 (1.4–2.1)****	**1.6 (1.3–1.9)****	**1.3 (1.0–1.6)***
3. Oil/cutting fluids										
Unexposed	3,193	315 (9.9)	1 (ref)	1 (ref)	1 (ref)	2,713	487 (18.0)	1 (ref)	1 (ref)	1 (ref)
Exposed	243	37 (15.2)	**1.8 (1.2–2.6)****	**1.5 (1.0–2.2)***	0.9 (0.6–1.4)	32	5 (15.6)	0.8 (0.3–2.1)	0.7 (0.3–1.9)	0.5 (0.2–1.5)
BIOLOGICAL FACTORS										
4. Biological samples										
Unexposed	3,349	340 (10.2)	1 (ref)	1 (ref)	1 (ref)	2,291	386 (16.8)	1 (ref)	1 (ref)	1 (ref)
Exposed	85	12 (14.1)	1.5 (0.8–2.9)	1.5 (0.8–3.0)	1.2 (0.6–2.5)	453	106 (23.4)	**1.5 (1.2–1.9)****	**1.4 (1.1–1.8)****	1.2 (0.8–1.6)
5. Waste										
Unexposed	3,355	333 (9.9)	1 (ref)	1 (ref)	1 (ref)	2,535	443 (17.5)	1 (ref)	1 (ref)	1 (ref)
Exposed	81	19 (23.5)	**2.9 (1.7–5.0)****	**2.3 (1.3–4.0)****	**2.1 (1.1–3.7)***	207	48 (23.2)	**1.4 (1.0–2.0)***	1.3 (0.9–1.8)	1.0 (0.7–1.5)

In all models, respondents registered with physician-certified long-term sick leave in 2009 were excluded. Model #1: adjusted for age. Model # 2: adjusted for age, education and psychosocial risk factors at work (role conflict, emotional demands, and low supportive leadership). Model #3: adjusted for age, education, and mechanical risk factors at work (neck flexion, hands above shoulders, hand-/arm repetition, squatting/kneeling, standing, work with upper-body bent forward, awkward lifting, and heavy physical work). Significant risk estimates in bold.
CI: confidence interval; OR: odds ratio $*p \leq 0.05$; $**p \leq 0.01$.

sician-certified LTSL in the general working population of Norway. These findings are in line not only with the most common occupational exposures for work-related skin diseases notified for the period 2000 to 2013 in Norway (9), but also with occupational skin exposures shown to predict skin problems in a prospective study of the Norwegian general working population (6).

Table III. *Population attributable risk (PAR %) based on the statistically significant odds ratios (OR) from Models #1, #2 and #3 (see Table II)*

Risk factors	Model #1 PAR (95% CI)	Model #2 PAR (95% CI)	Model #3 PAR (95% CI)
SKIN CONTACT			
Cleaning products			
Men	6.5 (2.6–11.0)	6.1 (2.1–10.7)	4.5 (0.4–9.7)
Women	7.8 (3.2–12.9)	6.1 (1.1–11.4)	
Water			
Men	6.1 (1.7–11.3)	4.8 (–0.1–10.7)	
Women	14.3 (4.7–23.3)	12.8 (5.1–19.4)	7.9 (–0.9–16.7)
Oil/cutting fluids			
Men	4.6 (0.9–8.9)	3.5 (–0.3–8.0)	
BIOLOGICAL FACTORS			
Biological samples			
Women	7.1 (2.1–12.7)	6.1 (0.9–12.0)	
Waste			
Men	3.5 (1.0–6.5)	3.0 (0.5–6.2)	2.8 (0.1–6.1)
Women	2.7 (–0.25–6.6)		
Sum			14.5

Model #1: adjusted for age. Model #2: adjusted for age, education and psychosocial risk factors at work (role conflict, emotional demands, and low supportive leadership). Model #3: adjusted for age, education, and mechanical risk factors at work (neck flexion, hands above shoulders, hand-/arm repetition, squatting/kneeling, standing, work with upper body bent forward, awkward lifting, and heavy physical work).

Occupational skin exposure to cleaning products was a consistent and independent risk factor for LTSL among men. Adjustments for both psychosocial and mechanical risk factors at work did not eliminate the observed association. Our findings support results from previous studies: occupational skin exposure to cleaning products was the exposure most frequently associated with work-related skin diseases, in a Norwegian register-based study for the period 2000 to 2013 (9). In addition, occupational skin exposure to cleaning agents was associated with increased risk for skin problems in a prospective study of the Norwegian general working population (6).

Occupational skin exposure to water was an important risk factor for LTSL among women. Occupational skin exposure to water significantly predicted skin problems among women in the general working population of Norway (6) and, as in other Scandinavian countries, this might be explained by the fact that women, to a larger extent than men, hold jobs in which most of the tasks consist of wet work (10, 11).

Occupational exposure to waste for men, and biological samples for women were risk factors for LTSL. After further adjustment for psychosocial and mechanical risk factors at work, the association was observed only among men exposed to waste. To our knowledge, associations between biological work exposures and LTSL have not been reported by earlier studies from Scandinavia (12).

Sex differences regarding self-reported occupational skin exposures were thought to contribute to the higher risk for LTSL among women. However, the associations between occupational exposures and LTSL were stronger for men. For instance, the effect of cleaning products and waste on LTSL was observed only in men, yet more women were exposed. Plausible explanations for the stronger effect among men may include poor knowledge about skin care (13), lower use of moisturizers (10) and increased severity of skin conditions (14). On the other hand, household exposures shown to be risk factors for skin problems among women (11, 15) might contribute to the higher risk among women.

Psychosocial work exposures did not act as major confounders for any of the analysed associations between skin exposures and LTSL. However, adjustment for mechanical work exposures slightly attenuated the majority of the risk estimates. To the best of our knowledge, this was the first study including other occupational risk factors for LTSL when analysing the effect of occupational skin exposure on LTSL.

The validity of this longitudinal, prospectively designed study was supported by a large representative sample drawn randomly from the general Norwegian working-age population. The study included individual linkage to registered sick leave data, without loss to follow-up. The use of different sources of measures excludes the potential for common method bias (16). In addition, our objective assessments of sick leave may have reduced the subjectivity problem and increased the validity of the outcome variable. Given that our analysis included respondents without LTSL in 2009, reverse causality is not a likely explanation for the observed associations. These features lend considerable strength to the study.

The study had a moderately high response rate of 61%. Although no dissimilarities were found between respondents and non-respondents across the benchmarks of age, sex and region (17), we do not know whether people with chronic skin disorders or elevated risk of sick leave were less likely to respond at baseline. In addition, it is possible that the most vulnerable people had already left their jobs (18), and thus were excluded from this cohort. Both of these selection processes may have led to a healthy worker effect before recruitment and attenuated the risk estimates.

A particular strength of this study was the focus on individual exposure factors rather than job titles. The use of job titles as a proxy for occupational exposures may underestimate variations in exposure within occupations, or over time in the same job (19). A limitation was that the questions assessing occupational skin exposures have not been validated in a Scandinavian population, although they have been in use since 1989 (6, 7, 9, 20). For example, a Danish study assessing associations between skin exposure to cleaning agents and disability pension used almost identical questions as our study (20).

A further limitation is that the survey did not include questions on relevant skin exposures outside work. Validated questions on several skin exposures are available (19), for instance skin exposure to water. Moreover, the Nordic Skin Questionnaire is a validated questionnaire for surveying work-related skin diseases, and occupational and non-occupational exposures (21). Therefore, future population-based studies in Norway focusing on work-related skin diseases should aim at validating self-reported skin exposures at work. Nevertheless, even taking into account the risk of over- or under-estimation of reported exposures, the associations we found are in line with other Norwegian studies (6, 9) and previous knowledge (10, 15).

A weakness of our study is that, due to data protection issues, we did not have diagnoses for the physician-certified sick leave, and thus we could not address whether the sick leave episodes were, in fact, due to dermatological health problems. However, workers in wet work occupations, for the period 2010 to 2013, had the highest frequency of LTSL due to contact dermatitis in Norway, which supports the findings of our study (22). Moreover, the precision of the associations found may have been improved by the exclusion of respondents with LTSL in 2009, and adjustment for other explanatory variables shown to predict LTSL in the general working population of Norway, such as psychosocial, and mechanical risk factors at work (4, 5).

Finally, most studies have focused on the relative risk alone, without considering the proportion of employees at risk (23). Hence, the population risk of LTSL attributable to occupational skin exposures of 14.5% underlines the contribution of occupational skin exposure as an important risk factor for LTSL in the general working population of Norway.

In conclusion, this study provides evidence of an association between occupational skin exposure and LTSL for both men and women in the general working population of Norway. In future prospective studies, it would be interesting to investigate whether interventions aimed at reducing LTSL may benefit from reducing occupational skin exposures at the population level.

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The authors declare no conflicts of interest.

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Appendix S1.

MATERIALS AND METHODS

Nationwide survey of level of living: working conditions

Data were collected during the period June 2009 to January 2010 by personal telephone interviews (0.5% of completed interviews were face-to-face). Prior to telephone contact, potential respondents were informed by mail about the topic of the study and privacy protection. The eligible respondents were Norwegian residents aged 18–69 years. In 2009, this population consisted of 3,079,157 persons (source population). A gross sample of 20,136 individuals, independent of employment status, was randomly drawn. Of these, 7,881 did not respond at baseline, and the most important reason (19%) was that the interviewer was unable to get in touch with the respondents despite several attempts, 16% did not want to participate, and 3% were prevented from participation. A total of 12, 255 (61%) persons were then interviewed (Fig. 1). The baseline sample was compared with the gross sample according to the benchmarks of age, sex and region; and no major differences were detected (S1).

Socio-demographic variables

Information regarding sex, age, and educational level was based on administrative registry data. Occupation was based on an open questionnaire and coded by Statistics Norway into a professional title, in accordance with the International Standard Classification of Occupations (ISCO-88).

Predictors

The questions regarding occupational skin exposures (Table I) have been applied in regular surveys of living conditions since 1989. The response categories were "Yes" and "No". "Yes" respondents were asked to estimate the duration of exposure at work (response categories: "almost all the time", "three-quarters of the working day", "half of the working day", "a quarter of the working day" and "very little of the working day"). Scores were re-coded to not exposed ("none or very little of the working day"), and exposed ("a quarter of the working day", "half of the working day" and "three- quarters of the working day or more").

Rationale of the cut-off limit physician-certified long-term sick leave

The rationale of the cut-off limit used is that a sick leave period with a duration shorter than 16 days may include sick leave that is due to minor health problems such as common cold and the ability to stay at home with sick children. In Norway, employees are entitled to use a personal declaration for sick leave of up to three days or a total of eight days spread over four different occasions during a 12-month period. In addition, if the employee´s child is sick, the employee has the right to stay at home for 10–15 days, depending on the number of children. If the employee is sick beyond the personal declaration days, or if the severity of the illness requires it, then physician-certified sick leave is required. Therefore, physician-certified sick leave for 16 days or longer is likely to capture sickness that is more serious.

Models for statistical analysis

In model #1, we adjusted for age. In model #2, further adjustments were made for education and psychosocial work exposures shown to predict physician-certified sick leave in the general working population of Norway (S2). In model #3, effects were adjusted for age, education and mechanical work exposures shown to predict sick leave in the general working population of Norway (S3). Since gender differences in LTSL have been reported (S4) all analyses were carried out separately for men and women.

Population attributable risk (PAR)

The PAR estimate indicates the number (or proportion) of cases that would not occur in a population if the factor were eliminated. The attributable risk in a population depends on the prevalence of the risk factor and the strenght of its association with the disease (S5).

Summary population-attributable risk

The summary attributable risk was calculated according to the formulae: 1 - (1-PARvariable1) X (1-PARvariable2) X (1-PAR variable3), etc (S6).

Ethical considerations

Statistics Norway carried out the survey according to statutory rules. Statistics Norway has appointed its own privacy ombudsman, approved by the Norwegian Data Inspectorate. All persons gave their informed consent prior to their inclusion in the study.

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Table SI. *Socio-demographic variables at baseline (2009) and their associations with long-term sick leave (16 days or more) at follow-up (2010)*

	N	Cases, *n*	Cases, % (95% CI)
Total	6,182	845	13.7 (12.8–14.6)
Age range			
17–24 years	305	43	12.4 (8.7–16.1)
25–34 years	965	166	14.7 (12.5–16.7)
35–44 years	1,545	222	12.6 (10.9–14.2)
45–54 years	1,466	224	13.3 (11.6–15.0)
55–66 years	1,056	190	15.2 (13.0–17.4)
Sex			
Women	2,746	493	18.0 (16.6–19.4)
Men	3,436	352	10.2 (9.2–11.2)
Occupation			
Legislators, senior officials and managers	736	79	10.7 (8.5–12.9)
Professionals	862	70	8.1 (6.3–9.9)
Technicians and associate professionals	724	107	14.8 (12.2–17.4)
Clerks	1,392	158	11.4 (9.7–13.1)
Service workers and shop sales workers	367	59	16.1 (12.3–19.9)
Skilled agricultural and fishery workers	898	181	20.2 (17.6–22.8)
Craft-related trades workers	30	4	13.3 (1.1–25.4)
Plant-machine operators and assemblers	604	87	14.4 (11.6–17.2)
Elementary occupations	343	59	17.2 (13.2–21.2)
Other occupations	122	27	22.1 (14.7–29.5)
Education level			
Basic school level	756	142	18.8 (16.0–21.6)
Upper secondary education	2,534	394	15.5 (14.1–16.9)
University/college	2,763	298	10.8 (9.6–12.0)

STUDY IV

Occupation and relative risk of cutaneous squamous cell carcinoma: a 45-year follow-up study in four Nordic countries.

Alfonso, J.H., Martinsen, J.I., Pukkala, E., Weiderpass, Tryggvadottir, L., Nordby, K.C., Kjærheim, K. (2016).

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The following article is the "uncorrected proof" received on 14.04.2016. The suggested modifications by the Editorial office comprise: confirmation of name spelling and for minor editions that do not affect the scientific content of the article.

Original article

Occupation and relative risk of cutaneous squamous cell carcinoma (cSCC): A 45-year follow-up study in 4 Nordic countries

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Background: The age-adjusted incidence of cutaneous squamous cell carcinoma (cSCC) in the Nordic countries has increased during the last 60 years, and the identification of occupational variation in the relative risk of cSCC may have preventive implications.

Objective: We sought to describe variation in the relative risk of cSCC between occupational categories in Finland, Iceland, Norway, and Sweden.

Methods: This is a historical prospective cohort study based on record linkages between census data for 12.9 million people and cancer registry data from 1961 to 2005. Standardized incidence ratios for cSCC were estimated for 53 occupational categories with the cSCC incidence rates for the national population of each country used as reference.

Results: During follow-up, 87,619 incident cases of cSCC were reported to the national cancer registries. In all countries combined, significant increased standardized incidence ratios were observed among seamen, military personnel, public safety workers, technical workers, teachers, transport workers, physicians, dentists, nurses, other health workers, religious workers, clerical workers, administrators, and sale agents (standardized incidence ratios between 1.08 and 1.77).

Limitations: Information on occupation was based on 1 point in time only.

Conclusion: The occupational variation of the relative risk of cSCC might be associated with socioeconomic factors, and to some extent to occupational exposures. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.03.033.)

Key words: cohort; cutaneous squamous cell carcinoma; epidemiology; general population; occupation; relative risk; socioeconomic position.

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Conflicts of interest: None declared.

Results of Table III were given as an oral presentation at the 24th European Association of Dermatology and Venereology Congress in Copenhagen, Denmark; October 10, 2015.

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In the Nordic countries, the age-adjusted incidence of cutaneous squamous cell carcinoma (cSCC), the second most frequent keratinocyte carcinoma,[1] has increased about 3-fold during the last 60 years.[2] High recurrence rates and occurrence of multiple cSCC impose a significant burden worldwide.[3,4]

Cumulative exposure to solar ultraviolet (UV) radiation is the major risk factor for cSCC.[5] For instance, strong evidence of an association between occupational exposure to solar UV radiation and excess risk of cSCC in outdoor workers has been reported in a meta-analysis by Schmitt et al.[6]

In addition, the excess risk of cSCC previously reported for tar refinery workers,[7] transport workers,[8] and firefighters[9] has been attributed to occupational skin exposure to polycyclic aromatic hydrocarbons, which is carcinogenic after skin absorption and metabolism.[10,11] The excess risk of cSCC found among health workers[12] has been discussed in relation to occupational exposure to artificial UV radiation, ionizing radiation, or both, but no consistent evidence about increased skin cancer risk as a result of these occupational exposures has been found.[13,14]

Although cSCC is one of the few preventable cancers through exposure reduction, few prospective population-based studies with long follow-up have examined occupational variation in the relative risk of cSCC. Therefore, this historical prospective study with 45-year follow-up aimed to describe occupational variation of the relative risk of cSCC in the adult population of 4 Nordic countries, and to discuss findings in light of potential exposure to occupational carcinogens and socioeconomic position.

CAPSULE SUMMARY

- Few population-based studies described relative risk of cutaneous squamous cell carcinoma among occupational categories.
- Occupational categories with high socioeconomic position, some with outdoor work, and some with potential exposure to chemical substances showed increased standardized incidence ratios of cutaneous squamous cell carcinoma.
- These occupational categories should be targeted in prevention strategies.

METHODS

Population

The Nordic Occupational Cancer Study project (http://astra.cancer.fi/NOCCA) linked occupational information from censuses in the 5 Nordic countries to information on cancer diagnoses from the respective cancer registries, by using the unique personal identity codes.[15] Denmark was excluded from the current analysis because it was not possible to separate basal cell carcinoma from cSCC cases before 1978. The details of study materials, coding systems, and analysis were described earlier.[15] Briefly, the study base consisted of approximately 12.9 million persons, born between 1896 and 1960, participating in any computerized population census in 4 Nordic countries: Sweden (1960, 1970, 1980, and 1990); Finland (1970, 1980, and 1990); Norway (1960, 1970, and 1980); and Iceland (1981).

Fig 1 shows an overview of the population sample and the linkage details.

Men and women aged 30 to 64 years who were alive and living in the country on January 1 in the year after the census were included. The choice of this age group aimed to include working-age individuals. The lower age limit was set to 30 years to avoid potential occupational misclassification related to more occupational mobility in the beginning of the work career.[15]

Census questionnaires, centrally coded and computerized in the national statistical offices, included questions related to economic activity and occupation of the whole population. The population registration system on electronic media is daily updated on births, deaths, immigration, and emigration. The linkage among the census data, mortality, and emigration data was based on the unique personal identity codes.

Person-years were then counted until the date of emigration, death, or to December 31 of 2003 in Norway, 2004 in Iceland, and 2005 in Finland and Sweden. Follow-up was done for as long a time as possible in each country, thus the end dates were determined by the timeliness of each cancer registry at the time of linkage.

Study approval was obtained from the national review board of each participating country.

Occupation

Occupational classification was based on the occupation recorded in the first available census in which the person participated in the age range of 30 to 64 years. In Finland, Norway, and Sweden occupation was coded according to national adaptations of the Nordic Occupational Classification,[16] which is a Nordic adaptation of the International Standard Classification of Occcupations-58,[17] and in

Abbreviations used:

CI: confidence interval
cSCC: cutaneous squamous cell carcinoma
SIR: standardized incidence ratio
UV: ultraviolet

Iceland occupation was coded according to a national adaptation of International Standard Classification of Occcupations-68.[18] The original national occupational codes were converted to a common classification with 53 occupational categories, and an additional category of economically inactive persons. Detailed descriptions of each occupational category were previously given (Appendices 1 and 2 of Ref. [15] available at: http://astra.cancer.fi/NOCCA/Incidence/Appendix/appendix-tables.pdf).

Classification of occupational categories

Occupational categories were further classified as regards to outdoor/indoor work according to previously published studies (Table I)[19,20]; and merged into socioeconomic groups as previously done by Lynge et al[21] (Table II).

Cancer data

National cancer registration started in 1953 in Finland and Norway, in 1955 in Iceland, and in 1958 in Sweden. The cancer registries receive information on cancer cases from general and specialist practitioners, hospital departments, pathology departments, and pathology autopsy notifications. Unlike the other Nordic countries, Sweden does not register cancer cases from death certificates.

For this study, cSCC topography, morphology, and date of diagnosis were registered. The cases were classified according to *International Classification of Diseases, Revision* 7. For all countries, only the first incident case of cSCC (primary cSCC) was included. Multiple cSCC at the time of diagnosis were counted as 1 incident case, and patients were censored after the initial diagnosis.

Statistical analysis

The relative risk of the cancer incidence of each occupational category is described by the standardized incidence ratio (SIR), which is calculated as the ratio of the observed to the expected number of cancer cases, using the cSCC incidence rates for the entire national study population of each country as reference. For a given sex (g), the SIR for a given occupational category (o) in a given country (c) was calculated as:

$$\mathrm{SIR}_{goc} = \frac{\sum_a \sum_p Obs_{gocap}}{\left\{ \sum_a \sum_p PY_{gocap} \frac{\sum_o Obs_{gocap}}{\sum_o PY_{gocap}} \right\}}$$

Where Obs = observed number of cases; PY = person years; a = age; and p = period. The denominator in the equation is the expected number of cancer cases for the given sex category, occupational category, age, period, and country.

The observed number of cancer cases and person-years were stratified into 2 sex categories, eight 5-year attained age categories (30-34; 35-39; …; ≥85 years), and 5 calendar periods (1961-1975; 1976-1980; …; 2001-2005). The expected number of cancer cases was based on number of person-years in each stratum (country, sex, age, and calendar period), and the respective reference rates of each country.

The 95% confidence intervals (CI) were determined by assuming a Poisson distribution of the observed number of cases. The SIR was regarded as statistically significant if the 95% CI did not include 1.0.

After this initial calculation, the combined sex-specific occupational SIRs across different countries, age, and period were calculated by the ratio between the sum of all the observed cases and the sum of all the expected cases for each specific strata.

We assume that increased SIRs after 50 years of age may better reflect a plausible occupational association attributable to cumulative exposure to carcinogens.[8] Therefore, we present results stratified by 2 age categories (30-49 and ≥50 years). To evaluate consistency and trends across periods, we present results in 3 calendar periods (1961-1975; 1976-1990; 1991-2005). Analysis were performed with software (STATA, Version 12 and 13; StataCorp LP, College Station, TX).

RESULTS

In total 87,619 incident cases of first primary cSCC were reported to the cancer registries from 1961 to 2005. The number of person-years of follow-up accumulated was 333.5 million.

Table III shows the SIR estimates for cSCC for occupational categories with significant increased SIRs according to age. Among men, at the national level, excess risk after 50 years of age was observed in Swedish fishermen (SIR 1.47; 95% CI 1.25-1.71) and postal workers (SIR 1.13; 95% CI 1.00-1.25); and Norwegian building caretakers (SIR 1.25; 95% CI 1.00-1.54). Among women, at the national level, excess risk after 50 years of age was observed only

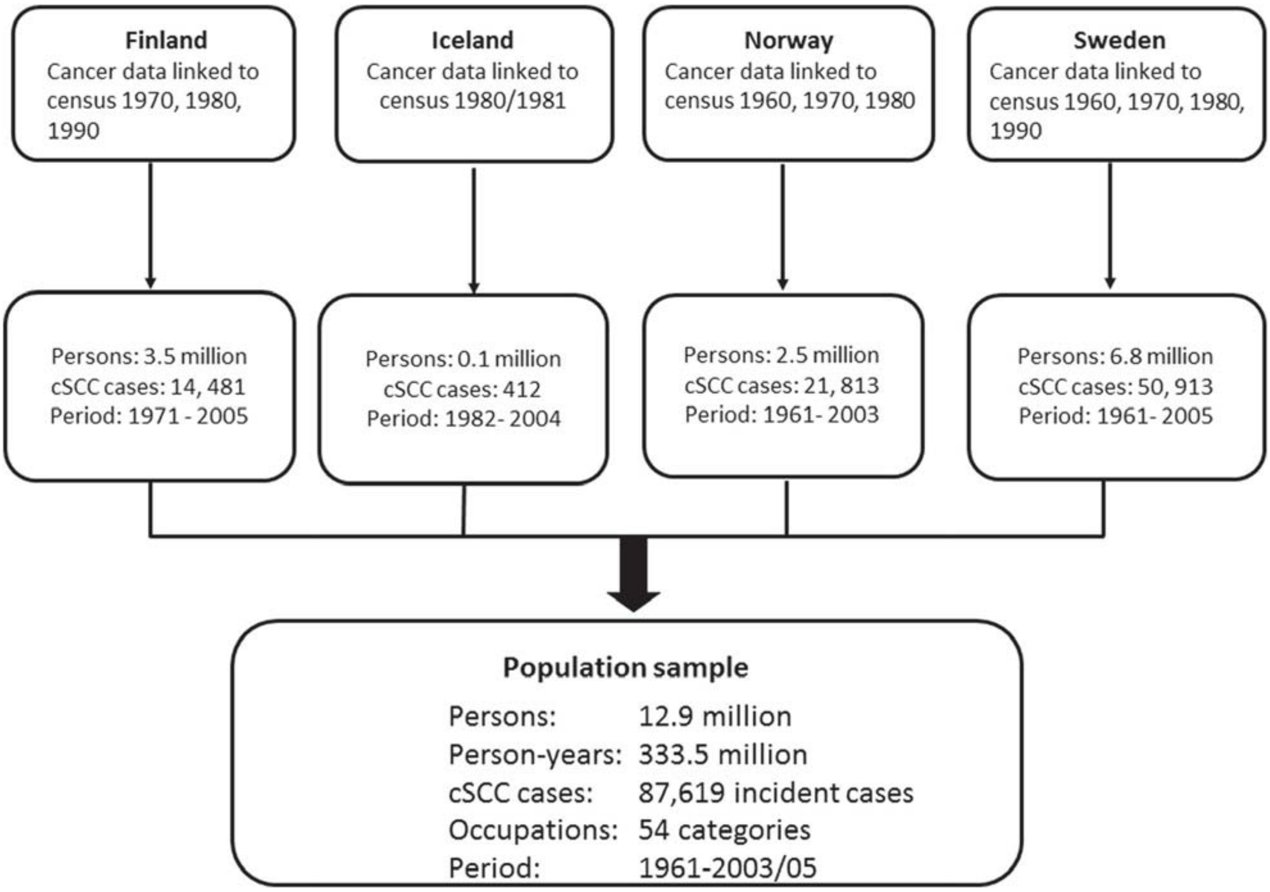

Fig 1. Occupation and relative risk of cutaneous squamous cell carcinoma (*cSCC*) in 4 Nordic countries. Population sample included in the study.

Table I. Classification of occupational categories according to occupational solar exposure

Outdoor work	Seamen, farmers, fishermen, forestry workers, gardeners, bricklayers, other construction workers
Mixed outdoor/ indoor work	Mechanics, woodworkers, waiters, food workers, chimney sweeps, technical workers, electrical workers, painters, teachers, plumbers, public safety workers, postal workers, building caretakers, military personnel, drivers, transport workers, welders
Indoor work	All remaining occupational categories

among Finnish woodworkers (SIR 1.31; 95% CI 1.04-1.64).

Among men, occupational categories with outdoor work had a consistent tendency of decreasing SIRs across periods (Fig 2). Occupational categories with mixed indoor/outdoor work and with indoor work did not show any consistent trend across periods (results not shown).

Among women, no consistent trend across periods was observed for the occupational categories stratified according to outdoor/indoor work (results not shown).

A trend of increasing SIRs across periods for the top of the socioeconomic hierarchy ("managers" and "lower administrative") was observed. Conversely, the group of farmers, forestry workers, and fishers showed a consistent trend of decreasing SIRs (Fig 3). A similar pattern was found for men and women.

DISCUSSION

In general, there was a modest variation of the SIR estimates. Occupational categories with high socioeconomic status, some categories with outdoor work, and some with potential exposure to chemical

Table II. Coding of socioeconomic groups

Socioeconomic group	Occupational categories
Managers	Technical workers, physicians, dentists, teachers, administrators
Lower administrative	Laboratory assistants, nurses, religious workers, artistic workers, journalists, clerical workers, sales agents, shop workers, transport workers, drivers, postal workers, public safety workers
Skilled and specialized workers	Assistant nurses, other health workers, miners and quarry workers, seamen, textile workers, shoe and leather workers, smelting workers, mechanics, plumbers, welders, electrical workers, woodworkers, painters, bricklayers, printers, chemical process workers, food workers, beverage workers, tobacco workers, glass makers, engine operators, cooks and stewards, waiters, chimney sweeps, hairdressers, launderers
Unskilled workers	Other construction workers, packers, domestic assistants, building caretakers
Farmers/forestry/fishing	Farmers, gardeners, fishermen, forestry workers
Inactive	Economically inactive
Not classified	Military personnel, "other workers"

Table III. Increased standardized incidence ratios and 95% confidence intervals for cutaneous squamous cell carcinoma among men and women, according to age groups in Finland, Iceland, Norway, and Sweden

Men	Age 30-49 y	Age >50 y
Occupational categories	SIR (95% CI)	SIR (95% CI)
Seamen	1.19 (0.74-1.83)	1.23 (1.14-1.32)
Military personnel	1.47 (0.91-2.25)	1.29 (1.17-1.41)
Public safety workers	1.20 (0.82-1.71)	1.25 (1.16-1.34)
Teachers	1.15 (0.89-1.46)	1.20 (1.13-1.26)
Technical workers, etc	0.97 (0.82-1.14)	1.13 (1.09-1.16)
Transport workers	1.02 (0.65-1.53)	1.10 (1.03-1.16)
Physicians	2.15 (1.36-3.22)	1.75 (1.57-1.95)
Dentists	0.85 (0.18-2.50)	1.30 (1.08-1.56)
Nurses	3.44 (1.48-6.77)	1.06 (0.34-2.49)
Assistant nurses	1.89 (0.82-3.72)	1.36 (1.04-1.75)
"Other health workers"	0.40 (0.08-1.15)	1.16 (1.00-1.35)
Clerical workers	1.36 (1.07-1.70)	1.18 (1.13-1.23)
Religious workers, etc	1.41 (1.10-1.78)	1.27 (1.19-1.36)
Administrators	1.31 (1.03-1.63)	1.32 (1.27-1.37)
Sales agents	0.81 (0.63-1.03)	1.16 (1.11-1.20)
Printers	1.26 (0.76-1.97)	1.13 (1.02-1.24)
Artistic workers	1.95 (1.20-2.98)	1.01 (0.88-1.15)
All categories	1.00 Ref	1.00 Ref
Women	**Age 30-49 y**	**Age >50 y**
Occupational categories	**SIR (95% CI)**	**SIR (95% CI)**
Gardeners	1.16 (0.73-1.73)	1.04 (1.00-1.10)
Teachers	1.02 (0.80-1.28)	1.18 (1.10-1.25)
Physicians	1.80 (0.72-3.71)	1.76 (1.28-2.37)
Dentists	0.51 (0.01-2.83)	1.41 (1.00-1.91)
Nurses	1.13 (0.81-1.53)	1.11 (1.01-1.22)
"Other health workers"	0.94 (0.61-1.37)	1.13 (1.01-1.26)
Clerical workers	1.06 (0.91-1.22)	1.11 (1.07-1.15)
Administrators	2.01 (1.32-2.92)	1.16 (1.00-1.34)
Journalists	0.74 (0.09-2.66)	1.41 (1.00-1.95)
All categories	1.00 Ref.	1.00 Ref.

CI, Confidence interval; *SIR*, standardized incidence ratio.

substances showed increased SIRs, compared with the general population.

Increased SIRs after 50 years of age, which suggest a plausible occupational association attributable to cumulative exposure to carcinogens,[6] were found among some occupational categories with outdoor work (seamen, female gardeners, Swedish fishermen, and Finnish female woodworkers); some with mixed outdoor/indoor work (military personnel, transport workers, Swedish postal workers, Norwegian male building caretakers); and in occupational categories with potential exposure to polycyclic aromatic hydrocarbon (technical workers, seamen, transport workers, and public safety workers). These findings are in line with previous studies.[6,7,22-24]

Approximately half of public safety workers were firefighters,[15] with potential exposure to human carcinogens such as polycyclic aromatic hydrocarbons and arsenic.[9] In addition, scars are known risk factors for cSCC,[25] and together with long-term chronic heat exposure,[26] may contribute to excess risk of cSCC. The increased SIR in male printers older than 50 years may be explained by exposure to photosensitizing chemicals used in the printing industry, which enhance the association between UV exposure and skin cancer.[12] To our knowledge, excess risk of skin cancer for printers has only been reported for melanoma skin cancer.[27]

It is noteworthy that not all occupational categories with outdoor work showed consistently increased SIRs as compared with the general working-age population. This unexpected finding, which should not be interpreted as a contradiction to the existing evidence,[6] can be explained by several factors. First is the about 2-fold increase in the reference incidence rate from 1960 to 2005.[2] For instance, we observed elevated SIRs in male farmers

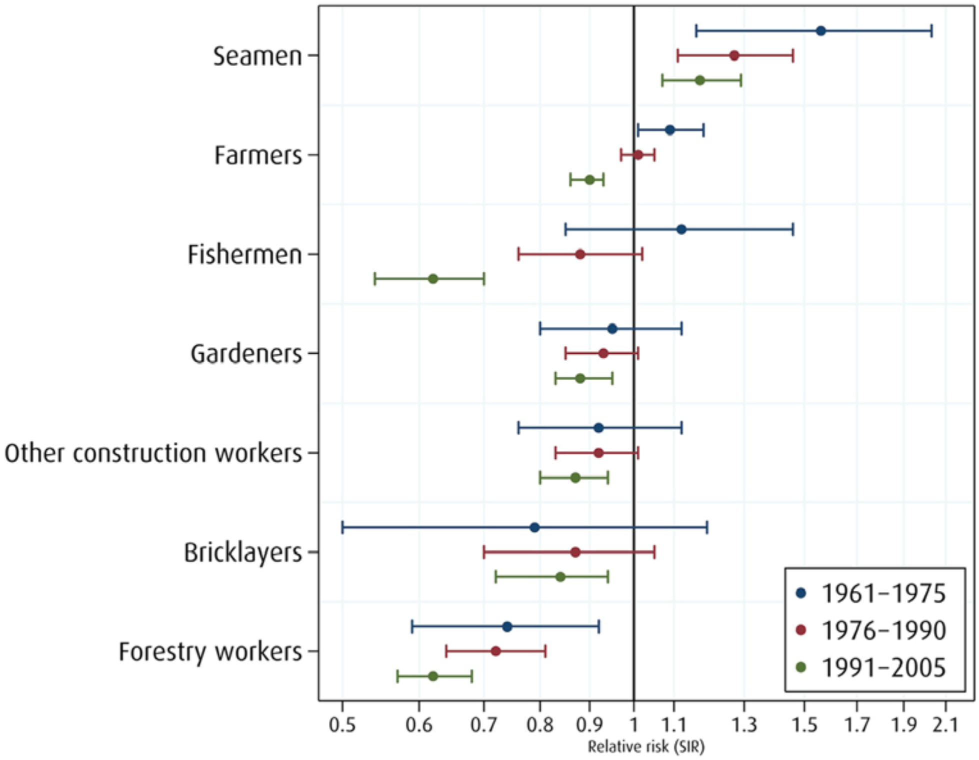

Fig 2. Cutaneous squamous cell carcinoma. Standardized incidence ratios (*SIR*), by period, in occupational categories with outdoor work among men in 4 Nordic countries. 1961 through 2005. X axis is in logarithmic scale.

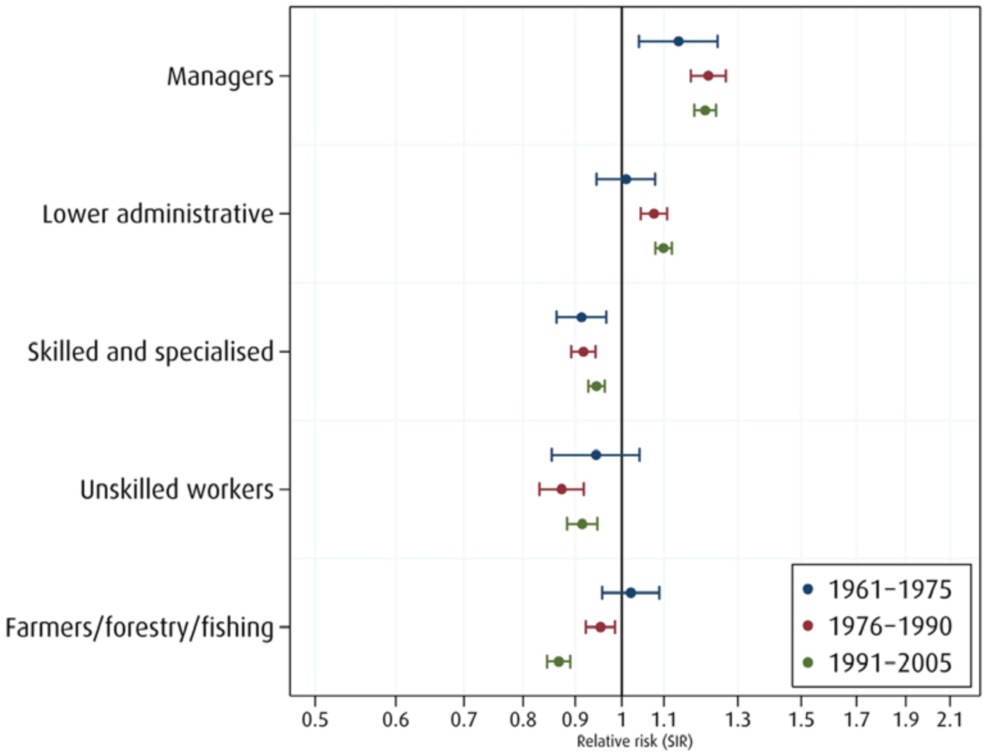

Fig 3. Cutaneous squamous cell carcinoma. Standardized incidence ratios (*SIR*), by socioeconomic group and period, among men and women in 4 Nordic countries. 1961 through 2005. X axis is in logarithmic scale.

only for the period 1961 through 1975 (Fig 2); and a trend of decreasing SIRs for occupational categories of the primary sector (Figs 2 and 3). Secondly, the skin of outdoor workers in the Nordic countries is often quite covered as a result of weather conditions. In fact, outdoor workers have elevated relative risk of lip cancer, which is mainly attributed to UV sun exposure.[15] It is not so easy to cover mouth/lips while working, even when wearing a hat. Moreover, a higher occupational mobility among outdoor workers may contribute to the relative risks observed. For instance, the proportion of the population working in the primary sector (agriculture, fishing, forestry, and hunting) has decreased dramatically since 1960. Thus, only 2% to 6% of the working population in each Nordic country were occupied in this sector by 2005.[28]

Our findings suggest that socioeconomic factors are of relevance when analyzing variation of SIRs across occupational categories. We analyzed socioeconomic position as a proxy for recreational sun exposure, under the assumption that more money for recreational activities, including outdoor activities, and sunny vacations in lower latitudes may contribute to the overall lifetime UV dose.[29] Thus, those employed in occupational categories from the top of the socioeconomic hierarchy may be more prone to excessive sun habits. Another plausible explanation is a greater chance of being given a diagnosis of cSCC, as a result of more awareness, and information leading to more periodic health examinations.[30] Nevertheless, the role of occupational factors cannot be excluded. First, some occupational categories could have included seasonal outdoor work in tropical and subtropical areas. Biological modeling suggested that outdoor seasonal work contributes greatly to the overall lifetime UV dose.[31] Furthermore, growing evidence regarding stressful experiences as potential risk factors for all types of skin cancer is available.[29]

The strengths of this population-based study are its prospective design, the large study population, the long follow-up, and the high quality of the outcome data.[32,33]

Loss to follow-up is common in cohort-based studies.[34] However, the Nordic population register systems offer very accurate data on the vital status of all residents, and the censuses covered the whole population. Thus, no loss to follow-up and precise person-years calculations are additional strengths of this study.

Because it was based on incident cSCC cases and exact person-years, there was no bias attributable to occupational variation in cancer survival and in mortality from competing causes of death.

Few studies have investigated relative risk of cSCC associated to a variety of occupational categories. Validity studies indicate that the occupational classification in the Nordic censuses is reasonably accurate,[15] but the lack of the complete occupational history is a limitation of this study. The proportion of individuals who had the same occupational category in the first and second census available (ie, 1960 and 1970 censuses in Norway and Sweden, and 1970 and 1980 censuses in Finland) was previously described[15]: stability was highest among men, and in occupational categories where a long education is required such as physicians, dentists, and teachers. Occupational stability was lower for occupational categories with outdoor work (from 21.5% for male gardeners in Norway to 77.8% for male farmers in Finland).[15] Accordingly, outdoor workers who switched to a job with less outdoor UV exposure could have contributed to less cumulative UV exposure, and thus to a lower relative risk for cSCC.

Some of the occupational categories used are heterogeneous and potential nondifferential misclassification may underestimate the true associations between specific exposures and cSCC relative risk.[35] For instance, a stronger association between occupational UV sun exposure and cSCC risk was reported for studies that directly assessed individual outdoor UV exposure compared with studies that used the occupation title as a proxy for exposure.[6] Future studies with the inclusion of specific exposure data are warranted.

We were unable to take into account the role of other individual risk factors, such as recreational sun exposure, skin sensitivity,[29] long-term use of immunosuppressive drugs,[30] and smoking, and this is a limitation of the study. However, we analyzed socioeconomic position as a proxy for recreational sun exposure. For factors such as skin phototype or use of immunosuppressants, we do not expect an important variation between occupational categories.

Overall, a high specificity and sensitivity for cSCC is guaranteed by the multiple sources of information, which combine clinical and pathological reports, and validity studies performed in the Nordic countries.[36] Nevertheless, we cannot exclude the possibility that some cases were missed, as cSCC has a low lethal potential and not all cases are necessarily diagnosed or treated, in particular in elderly people with comorbidities.[37] This would, however, introduce a serious bias only if case ascertainment differed between the occupational categories, which is a minor problem in the Nordic countries with generally free and available health care.[15]

As the prevention potential for cSCC is large, our findings are relevant for public health planning, emphasizing the need of targeting occupational categories with increased SIRs in prevention strategies, and not only occupational categories with outdoor work.

Pär Sparen participated in generating and gathering the data from Sweden for the Nordic Occupational Cancer Study.

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Errata list

Cor – correction

Celtf – change of page layout or text format

Side	Linje	Original text	Type of correction	Corrected text
21	2	…(43% allergic, 41% irritant)…	Cor	…(41% allergic, 43 irritant %)…
47	12	β-endorphin level[3]	Cor	β-endorphin level[4]
63	7	interacts	Cor	interact
92	20	Figure 22	Cor	Figure 23
93	14	Figure 23	Cor	Figure 24
99	9	Figure 24	Cor	Figure 25
100	1	Figure 25	Cor	Figure 26
101	7	Figure 26	Cor	Figure 27
108	1	Figure 27	Cor	Figure 28
108	4	Figure 28	Cor	Figure 29
113	3	Figure 29	Cor	Figure 30
120	5	Figure 30	Cor	Figure 31
131	1	Figure 31	Cor	Figure 32